Iron Poisoning

Jeffrey S. Fine, MD

Iron poisoning has always been of particular interest to pediatricians: children are frequently exposed to iron-containing products, and they experience the worst toxicity. The first well-described cases of iron poisoning were published in the 1940s and 1950s, the classic animal experiments were performed in the 1950s and 1960s, and the use of the chelator deferoxamine as an antidote for iron poisoning was introduced in the 1960s.

Most of what we know about the clinical presentation, the pathology, and the pathophysiology of iron poisoning comes from this early work although research continues. What has changed most over the past 50 years is the approach to management. As with many types of poisoning, there is now an emphasis on excellent supportive care with an individualized approach to gastrointestinal decontamination and a selective use of antidotes. With this strategy, the deaths related to iron poisoning have been reduced to only a small number each year. This article reviews the epidemiologic, clinical, animal, and laboratory science related to iron poisoning and its management and focuses on several areas of controversy.

Background

Iron is the fourth most abundant atomic element in the earth’s crust and is found in the minerals hematite, magnetite, and siderite. Biologically, iron is an essential nutrient for most living organisms because it is a component or cofactor of many critical proteins and enzymes such as hemoglobin, myoglobin, catalase, xanthine oxidase, aconitase, reduced nicotinamide adenine dinucleotide, ribonucleotide reductase, peroxidases, and cytochrome oxidase.

Iron is a group-VIII transition metal, with electrons distributed throughout five 3d orbitals. When iron forms chemical compounds or complexes with large proteins such as hemoglobin, these electrons shift between higher and lower energy orbitals and achieve different spin states. With this variable electron distribution, iron can exist in oxidation states between -2 and +6, either donate or receive electrons, and achieve variable redox potentials during electrochemical reactions. This makes iron an ideal mediator of diverse biological redox reactions such as when electrons are transferred down the mitochondrial cytochrome chain. Table 1 lists some basic facts about the physical chemistry and biochemistry of iron.

A typical American diet contains approximately 15 to 40 mg of iron per day most of which is in the ferric form, which is insoluble at physiologic pH and poorly absorbed. This Fe³⁺ is released from food proteins and reduced to the ferrous form by gastric acid. Absorption of dietary iron takes place primarily in the duodenum and upper jejunum and is regulated according to the state of the body’s iron stores. Heme iron is absorbed better than nonheme iron, and different food components may affect iron absorption. For instance, ascorbate increases and phytates decrease absorption; however the overall effect of food is to decrease iron absorption. The body efficiently recycles iron released from senescent red blood cells, so the daily requirement for iron is approximately 1 mg to cover losses of iron in stool, sweat, and urine. Menses accounts for an additional need of 1 mg/d for women. Thus approximately 10% of dietary iron is absorbed.

The intestinal mucosal cell has few barriers to iron uptake, but once inside the cell the transfer of iron to the plasma is highly regulated. The physiology of iron absorption and metabolism is quite complex and out-
TABLE 1. Iron facts

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atomic no.:</td>
<td>26</td>
</tr>
<tr>
<td>Atomic weight:</td>
<td>55.85 g/mol</td>
</tr>
<tr>
<td>Density:</td>
<td>7.794 g/cm³</td>
</tr>
<tr>
<td>Normal serum level:</td>
<td>80-180 µg/dL (14-32 µmol/L)</td>
</tr>
<tr>
<td>Ferrous = Fe²⁺ or Fe(I)</td>
<td></td>
</tr>
<tr>
<td>Ferric = Fe³⁺ or Fe(III)</td>
<td></td>
</tr>
<tr>
<td>Required daily dose:</td>
<td>1 mg/kg per day (maximum 15 mg)</td>
</tr>
</tbody>
</table>

Iron toxicity is related to the generation of free radicals.⁶,⁷ Both normal and pathologic cellular processes produce superoxide (O₂⁻) and hydrogen peroxide (H₂O₂) byproducts, whereas enzymes such as superoxide dismutase, glutathione peroxidase, and catalase normally metabolize and neutralize these free radicals. One of the effects of O₂⁻ is the release of stored iron from ferritin. The free iron reacts with O₂⁻ and H₂O₂ to produce other more reactive and toxic-free radicals such as the hydroxyl radical:⁶,⁷

\[
\begin{align*}
O_2^- + Fe^{3+} & \rightarrow O_2 + Fe^{2+} \\
Fe^{2+} + H_2O_2 & \rightarrow Fe^{3+} + HO^- + OH^- \\
O_2^{••} + H_2O_2 & \rightarrow O_2 + HO^- + OH^- 
\end{align*}
\]

The hydroxyl radical (HO•) formed through this reaction can depolymerize polysaccharides, cause DNA strand breaks, inactivate enzymes, and initiate lipid peroxidation, which is a self-amplifying process that is particularly damaging to cellular and subcellular membranes.⁶,⁷ For example, when lysosomal membranes are destroyed, proteolytic enzymes are released inside the cell, causing further cell damage. If the damage is irreparable, it can also lead to cell death.⁸

The body protects itself from the toxicity of free iron by keeping it chelated during almost all phases of absorption and distribution. From the enterocyte, iron is accepted for transport through the plasma by transferrin, a β1-glycoprotein with 2 high-affinity binding sites for Fe³⁺. One third of the body’s iron is stored as ferritin, a macromolecule capable of binding up to 4500 iron atoms. Sixty percent of this ferritin is in hepatocytes, and 40% is in myocytes and reticuloendothelial cells.

Epidemiology of Iron Poisoning

The American Association of Poison Control Centers (AAPCC) is a consortium of 66 regional poison control and information centers located throughout the United States. Each year the AAPCC collects standardized epidemiologic data about poisonings reported to these centers, and this information is published annually. For 1997, the AAPCC reported 1.5 million poisoning exposures for children and adolescents younger than 20 years.⁹ These pediatric exposures accounted for 67% of all the reported poisoning exposures. Children younger than 6 years accounted for 77% of the pediatric exposures and 50% of all reported exposures.

In 1997, there were 26,544 AAPCC-reported exposures for all types of iron-containing compounds by children and adolescents accounting for 1.7% of all reported pediatric poisoning exposures; 87% were in children younger than 6 years. Sixty-two percent of these childhood exposures were to pediatric multivitamin tablets, which rarely lead to serious toxicity after ingestion. Thirty percent of these exposures were to adult preparations such as iron pills or prenatal vitamins with iron, which are responsible for almost all of the serious toxicity related to iron poisoning.

Iron-containing products are available in many households with young children. Iron pills are prescribed for most pregnant women, and many children are receiving multivitamins with iron. Many of the prenatal vitamins are brightly colored, sugar coated, and resemble popular candies, such as M&M’s or Good & Plenty (Fig 1).¹⁰ Many children’s multivitamins are associated with cartoon characters like the Flintstones. In this regard, the comments of Spencer,¹¹ written in 1954, seem timely:

Now it seems irrational that some things which children are expected to take, such as cod liver oil, remain unpalatable, whereas ferrous sulphate tablets, which are intended mainly for adult use, are made both attractive and sweet.

The reasons that children ingest drugs are multifactorial and include developmental level, inadequate parental knowledge about the toxic potential of individual agents such as iron, access to medications, imitative behavior, lack of supervision, and intrafamilial conflict.¹²,¹³ Almost all deaths from iron poisoning are in children younger than 3 years and follow large exposures to adult iron preparations (30-40 pills), although death after the ingestion of as few as 5 pills has been reported.¹⁴,¹⁵ Early series reported mortality rates of 50% from iron poisoning, which undoubtedly reflected a reporting bias for very sick, hospitalized patients.¹⁶ Despite the extraordinary number of exposures to iron-containing prod-
ucts, deaths rarely occur. For the past 10 years, there has been an average of only 3 to 4 deaths per year reported by the AAPCC, although there are sporadic increases; in 1992, 11 childhood deaths were reported. This number of reported deaths may be an underestimation of the actual incidence, because some deaths are not reported to regional poison control centers.

Although mortality statistics are relatively well maintained, data about poisoning morbidity are difficult to ascertain. The AAPCC reports a significant amount of epidemiologic information related to poisoning, but the annual reports do not stratify all the data according to age. However, the AAPCC did a special review of morbidity and mortality in children younger than 6 years for the period 1985-1990. Eight of 111 deaths during this period were related to iron poisoning; an additional 85 children had "major" life-threatening morbidity. Again, this may be an underestimation of the number of children who experience severe iron poisoning. Several reviews of poisoning hospitalizations suggest that iron poisoning is an infrequent cause of hospitalization; the hospitalization rate for iron poisoning among children aged 0 to 4 years has been estimated at 8.7 per 100,000 children.

Prevention

A representative sample of iron-containing preparations is listed in Table 2. One single 324-mg ferrous sulfate tablet will cause gastrointestinal symptoms in 10% of adults who take iron supplements, and 3 to 4 pills represent a potentially toxic dose in a toddler (Table 3). One way to reduce the frequency of significant poisoning would be to decrease the concentration of iron in each pill. Children's multivitamins contain only 15 to 18 mg of elemental iron per tablet, and this accounts for the lower frequency of severe poisonings related to these products. However, reducing the quantity of iron in adult tablets would require increasing the number of daily doses.

Although many modalities may help to diminish the incidence of childhood poisonings in general and iron poisoning in particular, the surest method is to limit access by keeping children physically separated from iron-containing products. Again, almost 50 years ago Spencer recommended that

the daily dose of three tablets should be wrapped separately in small packets in the same way that sugar is sometimes supplied in hotels in packets containing two lumps.

In 1987, the Consumer Product Safety Commission required that food supplements with more than 250 mg of iron per container be in child-resistant packaging. Unfortunately, child-resistant is not childproof; containers may be left open, the closures may not function correctly, or a sibling may open the container. In 1997 the Food and Drug Administration (FDA) issued a regulation requiring products that contain 30 mg or more of iron per dosage unit to be packaged as individual doses (for example, blister packs).


<table>
<thead>
<tr>
<th>TABLE 2. Iron-containing preparations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preparation</strong></td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Carbonyl Iron</td>
</tr>
<tr>
<td>Ferrous fumarate</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Ferrous gluconate</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Ferrous sulfate</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

*Carbonyl iron is Fe.$^0$.

<table>
<thead>
<tr>
<th>TABLE 3. Liquid preparations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preparation</strong></td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Ferrous fumarate</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Ferrous sulfate</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

*Fe$^{2+}$ in multivitamins ranges from 10 to 200 mg per tablet and 4 to 100 mg/5 ml.
TABLE 3. Guidelines for predicting toxicity and the need for treatment in a 12-kg child

<table>
<thead>
<tr>
<th>Preparation</th>
<th>% Fe²⁺/tablet</th>
<th>mg Fe²⁺/tablet</th>
<th>Evaluation* (20 mg Fe²⁺/kg)</th>
<th>Treatment* (60 mg Fe²⁺/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous sulfate</td>
<td>20</td>
<td>65</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>110</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Ferrous fumarate</td>
<td>33</td>
<td>66</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>110</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

*These are poison center triage guidelines. See Table 6.

TABLE 4. Stages of acute iron toxicity

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Local gastrointestinal effects</td>
</tr>
<tr>
<td>II</td>
<td>Quiescent phase</td>
</tr>
<tr>
<td>III</td>
<td>Systemic toxicity</td>
</tr>
<tr>
<td>IV</td>
<td>Recovery</td>
</tr>
<tr>
<td>V</td>
<td>Gastrointestinal obstruction</td>
</tr>
</tbody>
</table>

Carbonyl iron is another form of iron that has been reintroduced over the past 15 years for the treatment of iron-deficiency anemia, mostly in Europe. Carbonyl iron is produced when iron pentacarbonyl is vaporized and crystallized into submicroscopic spheres of uncharged highly purified metallic iron (Fe⁰). This form of iron must be converted to Fe²⁺ by gastric acid before it can be absorbed, and as a result, carbonyl iron is absorbed more slowly than ferrous sulfate, although the bioavailability of the absorbed iron is high.²⁶

The typical adult dose of carbonyl iron is 100 mg/d, and volunteers have been given up to 10,000 mg/d (140 mg Fe⁰/kg).²⁷,²⁸ The gastrointestinal adverse effects of even the high dose are similar to those of ferrous sulfate, although there is more diarrhea and the carbonyl iron has a funny metallic taste. The highest dose at which no deaths occur in animals (LD₀) is estimated at 10,000 to 15,000 mg Fe⁰/kg, whereas the median lethal dose (LD₅₀) for ferrous sulfate is estimated at 250 mg Fe²⁺/kg.²⁹ These data suggest that limited absorption prevents carbonyl iron toxicity and that unintentional ingestion will not result in serious injury or death. Therefore, the FDA has temporarily exempted carbonyl iron from the unit-dose packaging requirements described above.¹⁵

Pathophysiology of Iron Poisoning

The clinical progression of iron poisoning is usually divided into 5 stages (Table 4). Stage I is gastrointestinal toxicity; nausea, vomiting, and diarrhea have been observed in volunteers at doses as low as 5 mg Fe²⁺/kg.³⁰ Gastrointestinal bleeding may lead to hematemesis or bloody diarrhea. These gastrointestinal effects are attributed to the direct local corrosive effects of iron on the gastric and intestinal mucosa and occur early, usually within several hours. In animal models and in human patients who have required surgery or died, pathologic changes range from mild congestion to hemorrhagic necrosis of the intestinal mucosa, and an iron-filled exudate or coating of the mucosa is often seen.¹¹,³¹-³⁴ Although pathologic effects are concentrated in the stomach and duodenum, areas of small bowel infarction can be observed distally; the colon is rarely affected.³⁵,³⁶ These initial local corrosive changes sometimes lead to the formation of gastric antral and pyloric strictures, which are observed in some patients between 2 and 8 weeks after the initial episode of poisoning (Stage V).³⁶-³⁸

Stage II is a quiescent phase during which there is resolution of gastrointestinal symptoms with apparent clinical improvement. Some of the first reported cases of iron poisoning described children who did not receive any specific therapy, had resolution of gastrointestinal symptoms, and became critically ill after 24 hours and died.³¹,³³ The existence of this phase is controversial because many toxicologists believe that patients who are significantly poisoned will almost always become sick early. From the limited clinical data presented in those early reports, it is difficult to assess what the true clinical status of the children was before and during the quiescent phase or whether death may have been related to another cause, such as aspiration. The possibility of the quiescent phase is important to consider when a child is being managed with observation alone; however, this stage would rarely be seen today because children with significant early gastrointestinal symptoms would receive fluid resuscitation and chelation therapy soon after presentation.

Stage III represents systemic toxicity, which defines true iron poisoning, although a specific dose for this effect has not been defined. Systemic toxicity is clinically manifest as shock with associated signs of hypoperfusion—pallor, cold extremities, tachycardia,
TABLE 5. Serum iron levels after oral doses of iron

<table>
<thead>
<tr>
<th>Study*</th>
<th>Formulation</th>
<th>Dose (mg Fe(^{2+})/kg)</th>
<th>Peak serum iron level (µg/dL)</th>
<th>Time to peak (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Ferrous sulfate chewable multivitamins</td>
<td>5</td>
<td>243</td>
<td>4.2</td>
</tr>
<tr>
<td>B</td>
<td>Ferrous fumarate chewable multivitamins</td>
<td>6</td>
<td>263</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Ferrous fumarate tablets</td>
<td>6</td>
<td>125</td>
<td>6</td>
</tr>
<tr>
<td>A</td>
<td>Ferrous sulfate chewable multivitamins</td>
<td>10</td>
<td>321</td>
<td>4.5</td>
</tr>
<tr>
<td>C</td>
<td>Ferrous sulfate tablets</td>
<td>20</td>
<td>300</td>
<td>2.3</td>
</tr>
</tbody>
</table>

*Studies in adult volunteers

and tachypnea; hypotension may be a late finding.\(^{32,34,39-41}\) Hypovolemic shock and acidosis are the primary determinants of this shock state, but diminished cardiac function contributes (see below). Hypovolemic shock results from the gastrointestinal fluid losses described above as well as increased capillary permeability and possible loss of venous tone.\(^{42}\)

Myocardial dysfunction may be seen in severe iron poisoning. In animal models, decreased heart rate, decreased mean arterial blood pressure, decreased cardiac output, and increased peripheral resistance have been observed even when intravascular volume and pH were corrected.\(^{40,41,43,44}\) Decreased cardiac output is related to decreased myocardial contractility, which is exacerbated by acidosis and hypovolemia.\(^{45,46}\) Although heart failure is frequently seen in chronic iron overload, it has only been rarely reported after acute iron poisoning and may be related to free radical–induced damage.\(^{47}\) In vitro, increased lysosomal enzyme activity has been associated with iron loading of cultured myocytes, and the sarcosomal membrane seems to be particularly susceptible to free radical lipid peroxidation.\(^{45,46}\) In addition, inhibition of cardiac mitochondrial respiratory enzyme activity caused by iron loading contributes to myocardial dysfunction.\(^{48}\)

Systemic iron poisoning is associated with a positive anion-gap metabolic acidosis.\(^{33,34,39-41}\) Several possible explanations for the acidosis have been proposed: (1) conversion of free plasma iron to ferric hydroxide is accompanied by a rise in hydrogen ion concentration;\(^{39}\) (2) free radical damage to mitochondrial membranes prevents normal cellular respiration and electron transport with the subsequent development of lactic acidosis;\(^{49}\) (3) hypovolemia and attendant hypoperfusion contribute to (but are not the primary causes of) acidosis;\(^{44}\) and (4) cardiogenic shock contributes to hypoperfusion.\(^{44,47}\)

In some cases hepatic injury will be evident after 2 to 3 days. Portal blood delivers high concentrations of iron to the liver where it is taken up by both Kupffer’s cells and hepatocytes and exceeds the storage capacity of ferritin. Pathologic changes range from cloudy swelling to periportal hepatic necrosis, and elevated transaminases are observed.\(^{50,51}\) Iron is concentrated within hepatic mitochondria where it destroys mitochondrial membranes through the free radical mechanisms described above and disrupts the electron transport of oxidative phosphorylation.\(^{52-54}\) These effects contribute to both hepatic necrosis and metabolic acidosis.

Abnormalities in coagulation have been observed in animal models and some human patients with iron poisoning.\(^{32,39,55,56-58}\) Increased bleeding may exacerbate hypovolemia. Initially, iron may exert a direct inhibitory effect on clotting factors such as thrombin.\(^{57}\) Later, reduced levels of clotting factors may be an effect of hepatic failure.\(^{58}\)

Stage IV is the period of clinical recovery that will begin soon after the initiation of fluid and antidotal therapy. For severely poisoned patients recovery will be marked by resolution of acidosis and other signs of shock, usually within 3 to 4 days of the acute poisoning, although full recovery may take longer.

Stage V is the late onset of gastric and pyloric strictures, which may occur 2 to 8 weeks after the initial injury. These strictures occur in mucosa in which there was previous damage, and they frequently require surgical therapy.\(^{36-38}\)

Iron Absorption in Overdose

As described above, iron absorption is a highly regulated process. How these processes are affected in overdose is unknown.\(^{59}\) It is clear that there can be rapid absorption through intact intestinal mucosa.\(^{32,34,60}\)

There have been several volunteer studies that examined iron absorption after supratherapeutic oral doses (Table 5).\(^{30,61,62}\) They demonstrate that supratherapeutic doses of iron are well absorbed after ingestion. A peak serum iron level is achieved within several hours of ingestion, and a level measured at 4 hours will be at or near the peak, although the peak level may be delayed.

It is unclear whether very high doses lead to delayed
absorption and peak level; however in many reported cases, children became toxic soon after ingestion. Although the peak level may be delayed, high serum iron levels and the onset of toxicity are seen early. In animals given lethal doses of iron, near-peak levels are observed within an hour.32,34,44

Iron pills can become conglomerated into a mass in the stomach. In many of these cases, despite the observation of a large number of pills at gastrotomy or on a radiograph, the patients are often reported to be relatively asymptomatic. It may be that these iron bezoars reduce the rate of absorption because the iron inside the mass is not readily accessible for absorption. If left untreated, these patients may experience severe delayed toxicity.

**Deferoxamine (Desferrioxamine, Desferal)63-65**

Ferroxamine B is an iron-containing siderophore required by the fungus *Streptomyces pilosus* for normal growth. When the iron is removed, deferoxamine is produced. The straight-chain deferoxamine molecule folds around a single atom of iron to form a very stable octahedral complex, which occupies all of iron's reactive coordination sites (Figs 2 and 3). Deferoxamine has a very high binding constant for iron (10^{31}) and, in vitro, removes iron from transferrin and ferritin but not from hemoglobin. In vivo, deferoxamine cannot remove iron from transferrin and probably chelates iron in transit between transferrin and ferritin. One mole of deferoxamine (100 mg) binds 1 mole of iron (9 mg) to form ferrioxamine, a reddish colored compound.

Deferoxamine is administered through intravenous or intramuscular injection because it has poor oral absorption. The volume of distribution of deferoxamine (0.6-1.2 L/kg) is greater than that of ferrioxamine (0.2 L/kg), which suggests that deferoxamine may distribute to tissues while ferrioxamine is confined to the vascular space. In fact, deferoxamine can remove iron from mitochondria and prevent iron-induced damage in that organelle.66
Deferoxamine was initially advocated for use as a gastric lavage solution despite the fact that huge doses are required to complex a significant oral iron dose: 100 mg Fe\(^{2+}\)/kg in a 10-kg child would require 20 vials of deferoxamine. The first animal models showed that guinea pigs given an LD\(_{50}\) dose of Fe\(^{2+}\) followed by oral deferoxamine had increased survival compared with controls. After this, the use of oral deferoxamine either alone or in combination with parenteral deferoxamine was recommended as therapy for iron poisoning. Several groups reported its use without significant toxicity although not all patients were severely poisoned and most patients received both oral and intravenous deferoxamine. Decreased iron absorption was observed in swine after receiving 60 mg/kg Fe\(^{2+}\) followed by oral deferoxamine; however there was no decrease in iron absorption when human volunteers ingested 5 mg/kg Fe\(^{2+}\) followed by oral deferoxamine.

The use of oral deferoxamine was questioned after an experiment in which 4 dogs were administered near lethal doses of 225 mg Fe\(^{2+}\)/kg as the iron-deferoxamine complex ferrioxamine. The iron was absorbed, and all of the dogs died. In the same study, 9 dogs were given both oral and intravenous deferoxamine as an antidote for induced severe iron poisoning; only 3 of 9 dogs survived. Despite its apparently successful or at least nontoxic use in humans and some animal models, the use of oral deferoxamine is now rarely reported, and most clinicians have abandoned it as a lavage solution.

The use of parenteral deferoxamine as an antidote for iron overdose was derived from the use of deferoxamine as therapy for transfusion-related iron overload. In this setting, intravenous deferoxamine led to increased iron elimination compared with intramuscular administration. The efficacy of deferoxamine as an antidote has never been tested in a human trial. However during those years that deferoxamine was becoming standard therapy, clinical outcomes improved compared with earlier case series. The current recommended dose of 15 mg/kg per hour was determined empirically and has also never been tested.

Limited data suggest that iron remains in the intravascular space for 12 to 24 hours before distribution is complete. It may be during this period that iron is most available for chelation. Therefore, some toxicologists have proposed using higher doses of intravenous deferoxamine during the initial treatment phase, and doses of 25 and 45 mg/kg per hour have been reported. The most common complication seen with intravenous administration of deferoxamine is hypotension. In the early animal models, deferoxamine was given at doses of 40 to 180 mg/kg per hour, or 3 to 10 times higher than the recommended dose, and hypotension was common. Increased levels of histamine measured during periods of hypotension may contribute to the effect although pretreatment with antihistamines does not ameliorate the effect. Hypotension can occur at a dose of 15 mg/kg per hour, and some clinicians recommend starting at a lower dose, for instance 8 mg/kg per hour, and titrating upwards until the desired dose is achieved. Flushing reactions are also associated with deferoxamine administration and are considered an anaphylactoid reaction.

The most concerning possible adverse effect of deferoxamine is the adult respiratory distress syndrome (ARDS), which was observed in 4 cases of iron poisoning in which deferoxamine was used. These adult patients received 15 mg/kg per hour for 32 to 72 hours, had symptoms of respiratory distress, and died. Although this complication was associated with prolonged use of deferoxamine, 10 other patients with deferoxamine infusions greater than 24 hours’ duration and 43 patients with infusions less than 24 hours’ duration did not have symptoms. There is another case report of a child with iron poisoning who had respiratory distress while taking deferoxamine. There are also several case reports of children with hemochromatosis or advanced malignancies in whom ARDS-like syndromes developed while they received deferoxamine infusions for days or weeks. Although a relationship between ARDS and deferoxamine has not been definitely established, an animal model of deferoxamine-induced pulmonary toxicity has been created in hypoxic mice. Lung damage might be the result of inappropriate chelation of intracellular iron with inhibition of key enzymes or of iron-induced free radical damage as described above.

Other adverse effects such as ocular damage and ototoxicity are associated with the chronic use of deferoxamine for transfusion-induced iron overload. In addition, infections with *Yersinia enterocolitica*, *Zygomycetes*, and *Aeromonas hydrophilia* and other organisms are also associated with the chronic use of deferoxamine, although several cases of acute iron poisoning have been complicated by *Y enterocolitica* sepsis. Deferoxamine makes iron available to these organisms for enhanced growth.
TABLE 6. Poison center referral guidelines

<table>
<thead>
<tr>
<th>Estimated dose (mg Fe⁺²/kg)</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>Observe at home</td>
</tr>
<tr>
<td>20-60</td>
<td>Medical evaluation</td>
</tr>
<tr>
<td>&gt;60</td>
<td>Chelation therapy</td>
</tr>
</tbody>
</table>

Deferiprone⁸⁸⁻⁹⁰

Deferiprone (1,2-dimethyl-3-hydroxypyridin-4-one) is a relatively new, orally available iron chelator. Whereas deferoxamine binds iron in a 1:1 molar ratio, 3 molecules of deferiprone are required to bind 1 atom of iron. Thus relatively high doses of deferiprone are required to effectively chelate and remove excess iron. The primary adverse effects of deferiprone are transient agranulocytosis (0%-2%), transient musculoskeletal and joint pains (0%-30%), gastric intolerance (0%-6%), and zinc deficiency (0%-2%). Deferiprone is being evaluated for use in the treatment of iron overload states for patients who cannot tolerate parenteral deferoxamine or for patients who do not have access to parenteral drug administration (eg, patients living in rural areas of developing countries). Its effectiveness for long-term therapy is under investigation.⁹¹,⁹²

Deferiprone has also been considered as a possible therapeutic agent for the treatment of acute iron poisoning and has been tested in animal models. Rats poisoned with an LD₅₀ dose of Fe⁺² had decreased tissue iron accumulation and lower mortality after treatment with intraperitoneal deferiprone.⁹³ However, mice poisoned with Fe⁺² and treated with deferiprone experienced worse toxicity compared with controls.⁹⁴ At this point, deferiprone cannot be recommended for the treatment of acute iron poisoning.

Ancillary Information to Help Predict Toxicity

Considering the high incidence of exposure to iron-containing products among young children, it would be helpful to have some useful tools or guidelines to help management decisions. A number of different evaluation schemes and ancillary tests have been suggested over the years for this purpose. The following sections review the utility of some of these tests.

Does the Estimated Dose Predict Toxicity?

Published cases usually report details about the presumed number of iron pills ingested. In some cases where a small number of pills were reportedly ingested, severe toxicity developed, suggesting that toxicity may not be related to dose. Individual factors related to absorption, iron-binding capacity, or individual susceptibility must play some role in determining toxicity. However, because toddler ingestions are usually not witnessed, the most likely explanation for the discrepancy between the reported iron dose and the severity of illness is inaccurate information about the ingested dose.

Children who ingest large numbers of pills often become sick within 2 hours of ingestion or before parents seek medical attention. It is difficult to understand how a patient with a large number of pills visible on radiograph can have few symptoms, but counting pills on radiograph has never been standardized and may not accurately estimate the ingested dose. Also, large numbers of pills may form an iron bezoar that has a reduced rate of absorption with delayed toxicity.

Because so many children are exposed to iron-containing products and so few have more than mild gastrointestinal irritation, there is a need for guidelines that can be used to decide which children with reported ingestions require medical evaluation. The triage guidelines shown in Table 6 were developed from the case literature and volunteer studies.

The absorption studies described above, in which the ingested dose is accurately known, show that adults with even small ingestions will have at least mild symptoms. Volunteers who ingested 5 to 6 mg/kg of either ferrous sulfate or ferrous fumarate experienced some degree of nausea, diarrhea, or darkened stools.⁶¹ All 6 volunteers who received 20 mg/kg ferrous sulfate had nausea, cramps, and diarrhea; however only one vomited. They all received intravenous fluid therapy and improved.⁶² Although all these volunteers experienced some gastrointestinal symptoms, none had serious systemic clinical toxicity.

Therefore, the action level of 20 mg/kg, which represents the ingestion of only a few pills by a small child, should identify any patient with symptoms requiring medical evaluation (Table 4). It is important to remember that these poison center–based triage guidelines are based on the history of ingestion, which is frequently inaccurate as described above. Therefore, any child with symptoms should also be referred for evaluation, regardless of the estimated ingested iron dose.

Do these triage criteria work? In an early review of
34 patients, 65% of patients believed to have ingested less than 50 mg Fe⁺²/kg had mild symptoms or were asymptomatic, whereas 88% of patients believed to have ingested more than 100 mg Fe⁺²/kg were moderately or severely poisoned. More recently, almost 200 patients were stratified according to their estimated ingested dose. Twenty-two percent of the group who took 20 to 40 mg/kg, 42% of the group who took 40 to 60 mg/kg, and 33% of the group who took more than 60 mg/kg had symptoms, although the highest reported serum iron level in any group was only 539 μg/dL (moderately elevated; see next section). No patient had serious toxicity. According to these results, the authors recommended home observation for patients with an estimated dose of less than 60 mg/kg Fe⁺². Although this management strategy will generally be safe, a low estimated dose does not guarantee a true low dose or a nontoxic ingestion.

Does the Peak Serum Iron Level Predict Toxicity?

The volunteer absorption studies described above suggest that patients with peak serum iron levels between 200 and 300 μg/dL experience gastrointestinal symptoms. Among 32 patients with serum iron levels between 300 and 500 μg/dL, who received various forms of gastrointestinal decontamination but no chelation therapy, 10 patients were asymptomatic, 18 patients were vomiting, 6 patients had diarrhea, and 1 patient was lethargic, and 1 patient had transient hypotension. Although some in this group of patients probably met our criteria for chelation therapy, all recovered without sequelae. In another review, 25% of 13 patients with serum iron levels below 300 μg/dL, 64% of 22 patients with levels between 300 and 500 μg/dL, and 75% of 20 patients with levels greater than 500 μg/dL were moderately or severely poisoned. Very high serum iron levels, generally greater than 1000 μg/dL, are almost always associated with serious toxicity. In the childhood fatalities reported by the AAPCC for the past 10 years, 80% of the patients had serum iron levels greater than 1000 μg/dL, and 40% had levels greater than 5000 μg/dL (Table 7). The reports do not always indicate a time associated with the measured level.

Earlier we discussed why the history of ingestion does not necessarily correlate with the severity of toxicity. Some of the data presented above suggest that the serum iron level may also not correlate with severity of poisoning. There are several possible reasons for the discrepancy.

The ideal serum iron level is a peak level drawn between 2 and 6 hours after ingestion (see “Iron Absorption” above). One of the problems with evaluating whether the serum iron level is a good predictor of toxicity is that for many cases it is not clear when a reported serum iron level was drawn with respect to the time of ingestion. Therefore, it is difficult to know if a reported level represents a peak level. Significant distribution of iron may have occurred by 6 to 12 hours, so an iron level measured many hours after an ingestion may be well below the peak.

Another problem with serum iron measurement occurs during deferoxamine therapy. Deferoxamine interferes with standard assays for iron and leads to a falsely lowered serum iron level. This almost certainly contributes to nearly universal reports of decreased serum iron levels during deferoxamine therapy in clinical case reports. Although accurate serum iron levels can be determined using atomic absorption spectrometry, this is generally not available to the clinician.

One final problem with the serum iron level is that unfortunately, even in the ideal case where the exact dose of ingested iron is known and we can draw a level at the exact peak, we almost never can get the test result back in a timely fashion. Many physicians do not have access to “stat” serum iron levels. At many hospitals, the test is run at an outside reference lab or batched to be run at regularly scheduled intervals. Generally, the clinician will have to make treatment decisions on the basis of the child’s clinical status before a serum iron level is available.

In summary, in spite of factors that may confound the interpretation of serum iron levels, these levels generally correlate with toxicity. Some patients with mild to moderately elevated serum iron levels (300-500 μg/dL) are asymptomatic, most have some symptoms, and a few experience serious toxicity. Patients with levels

<table>
<thead>
<tr>
<th>Serum Fe⁺² (μg/dL)</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;300</td>
<td>2</td>
</tr>
<tr>
<td>300-500</td>
<td>3</td>
</tr>
<tr>
<td>500-1000</td>
<td>2</td>
</tr>
<tr>
<td>1000-5000</td>
<td>15</td>
</tr>
<tr>
<td>&gt;5000</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
</tr>
</tbody>
</table>

between 500 and 1000 µg/dL experience moderate to severe toxicity; however, most recover without sequelae. Patients with levels greater than 1000 µg/dL have severe toxicity and are at risk for death, although even in this group, most recover with therapy.75,76

### Does the Peripheral Leukocyte Count or Serum Glucose Predict Toxicity?

Early clinical descriptions of iron poisoning demonstrated that both the peripheral white blood cell count (WBC) and the serum glucose were elevated in cases of serious iron poisoning.33,95 The utility of these 2 parameters as predictors of iron toxicity has been tested in both children and adults.

One of the first studies in which this question was examined showed that a WBC greater than 15,000 per cubic millimeter or a serum glucose greater than 150 mg/dL each had 100% specificity and positive predictive value when used to identify patients with serum iron levels greater than 300 µg/dL. In other words, the few patients who had an elevated WBC or serum glucose had elevated serum iron levels and a confirmed exposure. Unfortunately, the sensitivity of these tests was only 50%, which means that half of the patients with a serum iron level greater than 300 µg/dL did not have an elevated WBC or serum glucose. In other words, the few patients who had an elevated WBC or serum glucose had elevated serum iron levels and a confirmed exposure. Unfortunately, the sensitivity of these tests was only 50%, which means that half of the patients with a serum iron level greater than 300 µg/dL did not have an elevated WBC or serum glucose. Several other groups repeated these studies in children and adults and showed that both the WBC and the serum glucose were insensitive as screening tests for elevated serum iron levels (Table 8).102-104 In general, vomiting was a more sensitive indicator of elevated serum iron levels than either the WBC or serum glucose, but even vomiting was not 100% sensitive.

The other problem with these criteria is that although they may identify some of the patients with elevated serum iron levels and thus exposure, a positive result from the test does not correlate with a particular serum iron level or level of severity. A level of 300 µg/dL is not associated with significant clinical toxicity, as discussed above.

### Does the Radiograph Predict Toxicity?

A radiograph showing radiopaque pills in the stomach or gastrointestinal tract confirms the ingestion (Fig 4). In many case reports the number of pills seen on radiograph has been counted to predict the likelihood of toxicity.105 The accuracy of counting pills on radiograph has never been tested or standardized. However, it seems reasonable that the appearance of many pills confirms a significant exposure with the potential for toxicity.

However, a “normal” radiograph does not exclude exposure because not all iron preparations are equally visible on radiograph. Chewable multivitamins with iron can be seen on radiograph but may have lower radiopacity than adult iron pills.106 Similarly, the radiopacity of individual iron pills of the same type is not uniform.107,108 The degree of radiopacity is affected by the number and type of pills ingested, the number of pills removed by gastrointestinal decontamination, the state of the pills and the extent of dissolution after mechanical agitation in the stomach, the location of the pills and fragments in the gastrointestinal tract, the degree of absorption, and the formation of any concretions.

Besides confirming exposure and estimating the number of ingested pills, radiographs are also used to

---

**Table 8: Utility of the WBC and serum glucose in predicting iron toxicity**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC &gt;15,000/mm³</td>
<td>A⁵¹</td>
<td>0.47</td>
<td>1.0</td>
<td>1.0</td>
<td>0.57</td>
</tr>
<tr>
<td></td>
<td>B⁵²</td>
<td>0.12</td>
<td>0.94</td>
<td>0.75</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>C⁵³</td>
<td>0.28</td>
<td>0.88</td>
<td>0.89</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>D⁵⁴</td>
<td>0.15</td>
<td>1.0</td>
<td>1.0</td>
<td>0.22</td>
</tr>
<tr>
<td>Glucose &gt;150 mg/dL</td>
<td>A</td>
<td>0.38</td>
<td>1.0</td>
<td>1.0</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>0.07</td>
<td>0.18</td>
<td>0.33</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>0.25</td>
<td>0.80</td>
<td>0.89</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>0.09</td>
<td>1.0</td>
<td>1.0</td>
<td>0.21</td>
</tr>
<tr>
<td>Vomiting</td>
<td>A</td>
<td>0.94</td>
<td>0.25</td>
<td>0.67</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>0.6</td>
<td>0.71</td>
<td>0.75</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>0.66</td>
<td>0.32</td>
<td>0.79</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>0.84</td>
<td>0.5</td>
<td>0.87</td>
<td>0.44</td>
</tr>
<tr>
<td>Radiopacities</td>
<td>A</td>
<td>0.52</td>
<td>0.81</td>
<td>0.83</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>0.15</td>
<td>0.94</td>
<td>0.75</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>0.39</td>
<td>0.66</td>
<td>0.81</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>0.53</td>
<td>0.5</td>
<td>0.81</td>
<td>0.21</td>
</tr>
</tbody>
</table>
assess the success of gastrointestinal decontamination. Several reports demonstrated the inability of various methods of gastrointestinal decontamination to remove iron by obtaining radiographs after emesis, lavage, or catharsis. Again, caution must be exercised. When previously seen pills are no longer seen after gastrointestinal decontamination, this may reflect the physical state of the pill or fragments rather than the success of gastrointestinal decontamination.

**Does the Total Iron-Binding Capacity Predict Toxicity?**

For many years it was thought that a total iron-binding capacity (TIBC) greater than the serum iron level was protective against iron toxicity. Unfortunately the TIBC is not useful in determining the likelihood of toxicity. As an artifact of the techniques used to perform the standard laboratory assay, a rise in the serum iron level leads to an increase in the measured TIBC. Although this artifact can be corrected by modifications to the assay, a technician would have to know the serum iron level first to make the appropriate correction. However, even the corrected value would not be better than the clinical examination at deciding the severity of poisoning. Deferoxamine also interferes with the measurement of TIBC.

**Does the Deferoxamine Challenge Test Predict Toxicity?**

When deferoxamine is administered parenterally, it binds Fe$^{3+}$, and the complex, ferrioxamine, is excreted in the urine. Ferrioxamine is a reddish colored compound and imparts to the urine the famous “vin-rosé” color.

In general, significant iron intoxication treated with deferoxamine will lead to a “positive” urine color change. However, McEnery reported that only 50% of patients with serum iron levels between 500 and 1000 µg/dL had vin-rosé urine after deferoxamine. Villalobos reported that 9 patients with serum iron levels greater than 350 µg/dL had no urine color change after deferoxamine therapy. Freeman and Manoguerra reported an extraordinary case in which a patient had no vin-rosé color change despite a serum iron level of 1989 µg/dL and increased measured urinary iron.

The ability to detect a color change may be related both to the urine level of ferrioxamine as well as the observer’s ability to detect the color change. In fact, this color change may appear only as darker or brownish urine, and the best way to note a color change is to obtain a baseline sample before therapy. It is almost the nature of the change more than the specific color that is important. Placing sequential urine samples in a test-tube rack is a useful method to evaluate the color changes over time.

Once again a positive challenge will confirm exposure, whereas a negative result will not necessarily “rule out” exposure. In addition, no particular serum iron level or severity of toxicity has a correlation with a vin-rosé urine. Therefore, the deferoxamine challenge test is no longer recommended. Intravenous deferoxamine is administered therapeutically to patients with definite or probable systemic iron poisoning.

A variation of the deferoxamine challenge test has been proposed to test gastric fluid for iron. In the deferoxamine “color test,” deferoxamine is added to gastric fluid in the presence of H$_2$O$_2$. A red response indicates a positive result and the presence of iron as ferrioxamine. Although this test is qualitative and not predictive of severity of poisoning, it might confirm exposure quickly in a case of unexplained metabolic acidosis.
Does Gastrointestinal Decontamination Alter the Course of Iron Poisoning?

The general approach to management of the poisoned patient has changed dramatically over the past 25 years. The value of many of the strategies that we advocated not so long ago, such as emesis, gastric lavage, and catharsis, has been questioned. Although each of these therapies was presumed beneficial and was demonstrated (usually in volunteer studies) to cause the return of variable amounts of administered substances and even occasionally to decrease absorption, few studies have shown reduced morbidity or mortality in actually poisoned patients. In addition, there are technical problems associated with performing emesis or lavage, and each is associated with occasional morbidity or mortality.

Pediatricians have been advocates of syrup of ipecac; having syrup of ipecac at home has always been one of the tenets of anticipatory care. However, according to the AAPCC, syrup of ipecac was used in only 1.5% of poisoning cases in 1997, compared with 13.4% in 1983. In general, syrup of ipecac is contraindicated in most cases of serious poisoning and is not necessary in the rest.

The use of ipecac syrup in the setting of iron poisoning is problematic because it interferes with our ability to make a clinical assessment. The patient without vomiting and without other gastrointestinal symptoms is generally presumed to not be poisoned. Once we administer syrup of ipecac and induce emesis, we lose one of our most important clinical indicators.

In the patient with severe iron poisoning who is in shock, syrup of ipecac is contraindicated: the risk of aspiration outweighs the benefit. At least a few of the deaths reported in some of the early cases may have been caused by aspiration. Most patients with moderate or severe toxicity will already have vomited by the time of their initial evaluation. Although there may be some additional recovery of gastric contents, we do not believe that patients benefit significantly from additional gastric emptying after they have vomited spontaneously.

Gastric lavage can also be used for gastric emptying. In the sick patient, endotracheal intubation can be performed with a cuffed endotracheal tube to minimize the risks of aspiration. The main problem with gastric lavage in the small child is technical; even the largest orogastric lavage tube may not allow large iron pills to pass easily, and it is difficult to insert the largest tube in small children. Iron pills tend to conglomerate and congeal, and these sticky masses may also not pass through the lavage tube.

Although gastric lavage is intended to mechanically wash pills out of the stomach, in the case of iron, additional theoretical consideration led to the use of lavage fluids containing bicarbonate, phosphate, and hydroxide ions to complex iron in the gastrointestinal tract to reduce absorption. In the duodenum and small bowel, Fe\(^{2+}\) is absorbed; Fe\(^{3+}\) must be converted to Fe\(^{2+}\) before absorption. Lavage with sodium bicarbonate was expected to convert Fe\(^{2+}\) back to Fe\(^{3+}\) and reduce absorption. The iron-carbonate complex was also expected to be poorly absorbed. There was evidence that noneheme iron was poorly absorbed in the presence of phosphate and calcium, so lavage with Fleet Phospho-Soda was used as a source of phosphate.

In an in vitro model, bicarbonate and phosphate were able to complex a small amount of iron in a simulated gastric environment. However, when rats or pigs were given 60 mg/kg Fe\(^{2+}\) and then lavaged with bicarbonate, phosphate, or distilled water, absorption of iron was similar in all groups. Furthermore, several case reports documented hyperphosphatemia after lavage with Fleet’s Phospho-Soda. As a result of the questioned efficacy and demonstrated toxicity, the use of phosphate lavage was abandoned. Bicarbonate lavage was not criticized for toxicity; however, the experience was that there was little clinical efficacy.

More recently, magnesium hydroxide was demonstrated to complex iron in vitro, and it significantly reduced the absorption of iron in dogs given 60 mg Fe\(^{2+}\)/kg. Magnesium levels were elevated in the dogs, but there was no clinical toxicity. Magnesium hydroxide also reduced absorption in human volunteers given 5 mg Fe\(^{2+}\)/kg. Although magnesium hydroxide was used as standard therapy in some centers and is occasionally recommended, gastric lavage with magnesium hydroxide has not gained a strong foothold in the clinical management of iron poisoning.

Activated charcoal does not have a major role in the treatment of iron poisoning because metallic ions such as iron do not adsorb to it. However, there may be a role for activated charcoal in the patient with a mixed ingestion of a substance such as salicylate, which does adsorb well to charcoal. Interestingly, activated charcoal does bind the deferoxamine-iron complex, so there may be some utility in using oral deferoxamine and charcoal to decontaminate the gastrointestinal tract or charcoal hemoperfusion to increase elimination.
Whole bowel irrigation has been advocated as the ideal procedure for gastrointestinal (as opposed to gastric) lavage. This is a technique whereby the entire gastrointestinal tract is flushed with an isotonic polyelectrolyte solution. It was originally developed as a means of cleansing the gastrointestinal tract before surgery, and it is being used increasingly in poison management. In several animal and volunteer studies in which whole bowel irrigation was used to treat various experimental poisonings there have been mixed results of effectiveness, and none of these studies involved iron. Whole bowel irrigation has been used clinically for iron poisoning and is described in a number of case reports and series. In many of the cases, pills were identified on abdominal radiographs after emesis and/or lavage, and pill fragments were identified in the effluent from whole bowel irrigation. These patients almost always received parenteral deferoxamine therapy in addition to whole bowel irrigation. None of the reported patients had significant complications from the whole bowel irrigation, although it is difficult to know whether they definitely benefited from the therapy. The American Academy of Toxicology concludes that whole bowel irrigation is an unproved therapy, but many clinical toxicologists believe that it is the safest method of gastrointestinal decontamination currently available and that it has the greatest potential for benefit.

A conglomeration of iron pills may form in the stomach after an overdose. Several case reports have detailed the use of gastrotomy to remove these iron bezoars. Although patients did well with surgical therapy, it is unknown whether they would have done as well with traditional therapy alone. Whole bowel irrigation may work well to move such a mass through the gastrointestinal system.

Clinical Management of Iron Poisoning

We have discussed at length many of the controversies in the evaluation and management of iron poisoning. Using this information we can now construct a clinical approach.

1. Clinical evaluation. Serious iron poisoning is not difficult to identify: the patient is lethargic, acido tic, and in shock. A patient in this condition requires immediate attention to airway management and fluid resuscitation, followed by chelation therapy (see below).

   For the patient with a less acute presentation, the most important information with respect to management decisions will be obtained from a thorough history and careful physical examination. Most of our discussion has been focused on younger children. However, when managing an intentional ingestion in a suicidal adolescent, the clinician should be circumspect about any historical information until supportive data are available. For all patients, information about the type and number of pills ingested and the time of ingestion are important; however this information may be inaccurate. The ingestion of almost any amount of iron may lead to gastrointestinal symptoms, and it is also important to elicit these symptoms in the history. It is also important to elicit information about coingested substances, because serious intoxication with other substances may alter the approach to management.

   Subtle presentations require careful attention to accurate measurement of vital signs and identification of early signs of acidosis or shock. Stress, acidosis, gastrointestinal fluid loss from vomiting and diarrhea, third spacing of intravascular volume, and hemoco ncentration may lead to lethargy, coma or altered mental status, tachycardia, tachypnea or hyperpnea, hypotension, pallor, cool skin, or delayed capillary refill.

2. Fluid resuscitation. Most patients with significant intoxication will have some gastrointestinal fluid losses and be in at least the early stages of shock. The initial therapeutic maneuver is to establish intravenous access and administer normal (0.9%) saline at an initial dose of 20 mL/kg followed by a continuous infusion. The total intravenous fluid requirement will be determined by the patient's clinical status.

3. Laboratory evaluation. The focus is on laboratory tests that are easily performed and whose results are available quickly so that they may be used in initial management. A hematocrit or hemoglobin level can be measured at the bedside. If there has been significant fluid loss or third-spacing of fluid, the initial

TABLE 9. Indications for deferoxamine therapy

<table>
<thead>
<tr>
<th>Shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered mental status</td>
</tr>
<tr>
<td>Persistent gastrointestinal symptoms</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td>Pills on radiograph</td>
</tr>
<tr>
<td>Serum iron level &gt;500 μg/dL</td>
</tr>
<tr>
<td>Estimated dose &gt;60 mg Fe²⁺/kg</td>
</tr>
</tbody>
</table>

Curr Probl Pediatr, March 2000
hematocrit may be elevated. Although significant gastrointestinal bleeding can lead to a decreased hematocrit, this is not usually seen. A Hemoccult test of the stool will help to identify occult gastrointestinal bleeding.

A positive anion-gap metabolic acidosis is seen with significant iron poisoning and generally identifies a patient who will require chelation therapy. An arterial blood gas and serum electrolytes can quickly identify the patient with acidosis and an anion gap. An electrocardiogram is helpful to evaluate the possibility of any iron-related myocardial dysfunction and to screen for other potentially cardiotoxic coinfections such as cyclic antidepressant agents.

An acetaminophen level should be obtained for all suicidal adolescents or in the setting of an unknown ingestion. Acetaminophen poisoning may be occult in the early stages but requires therapy to prevent toxicity. In a toddler, when the ingestion has been observed or the child was found playing with iron pills, screening for acetaminophen poisoning is not necessary.

Clotting abnormalities have been seen in some cases of iron poisoning. Abnormalities of liver function will occur with hepatotoxicity, but this is usually a later manifestation of severe poisoning. A serum iron level will be interesting in retrospect but will provide information useful in the early management only if the result can be available relatively soon after it is drawn. Other tests may be ordered at the discretion of the clinician.

4. **Abdominal radiograph.** If the history or physical examination suggests the possibility of significant exposure, an abdominal radiograph is useful. A radiograph showing a large number of pills will confirm the exposure and suggest the need for gastrointestinal decontamination and/or treatment. A radiograph negative for pills may be reassuring, particularly in the setting of minimal clinical symptoms, but does not eliminate the possibility of exposure. There are no clear guidelines about how to interpret a radiograph with only a few pills visible.

5. **Chelation therapy.** If the clinical examination, laboratory evaluation, or radiograph data suggest the possibility of significant exposure or confirm significant toxicity, deferoxamine therapy should be initiated (Table 9). Criteria for initiation of therapy include a history of iron ingestion with (1) any clinical sign of shock; (2) lethargy, coma, or altered mental status; (3) persistent vomiting, diarrhea, hematemesis, hematochezia, or other gastrointestinal symptoms; (4) positive anion-gap metabolic acidosis; (5) a large number of pills on abdominal radiograph; (6) a serum iron level greater than 500 μg/dL; or (7) an estimated dose greater than 60 mg Fe^{2+}/kg.

The recommended dose of deferoxamine is 15 mg/kg per hour as a continuous intravenous infusion. Although this rate of administration is not frequently associated with hypotension, the most common toxicity related to deferoxamine, it is possible to initiate the infusion at a lower rate, for example 8 mg/kg per hour, and incrementally increase the rate every 5 minutes or so until the maximum rate is obtained. If intravenous access is impossible, deferoxamine can be given at a dose of 90 mg/kg intramuscularly. However, intravenous fluid therapy is a critical aspect of management, and intravenous access should be secured as soon as possible.

There are few clear guidelines about the appropriate duration of deferoxamine therapy because there is no well-defined effective dose or end point of therapy. The serum iron level is not helpful because it decreases after 12 to 24 hours naturally and is falsely lowered in the presence of deferoxamine. The manufacturer recommends a total dose of 6 g, but this would only provide 6 hours of therapy for an adult at standard infusion rates.

It was previously recommended to continue therapy until the urine returned to a normal color for 24 hours. This presents the problems of evaluating a vin-rosé urine as previously described. In addition, it leads to protracted courses of therapy that may put the patient at increased risk of pulmonary toxicity. Chelation therapy should continue until there is significant resolution of systemic toxicity, specifically acidosis and shock. Most patients will require chelation for 1 to 2 days, although some may require longer courses.

6. **Gastrointestinal decontamination.** Any patient with probable or confirmed significant exposure should have whole bowel irrigation with the possible exception of a patient who is seen very late (12-24 hours) after exposure. Whole bowel irrigation is initiated with polyethylene glycol-electrolyte solution (Colyte, Golytely) at a rate of 0.5 L/h for children or 2 L/h for adolescents. Young children will generally require administration of the irrigation solution.
through a nasogastric tube, although adolescents may choose to drink it. The typical adverse effects of administration are nausea, bloating, vomiting, and diarrhea, all of which mimic the symptoms of iron poisoning. However, if symptoms seem related to whole bowel irrigation, it is possible to slow the rate of administration to relieve symptoms. Whole bowel irrigation is continued until the effluent is clear. An abdominal radiograph may be used to follow the progress of whole bowel irrigation, remembering the caveats discussed above.

Although there may be a role for administration of magnesium hydroxide to try to reduce absorption, there is little clinical experience with its use. There is no experience to predict the effect of using both whole bowel irrigation and magnesium hydroxide.

7. Disposition. The patient with no history of abdominal pain, nausea, vomiting, or diarrhea and with a normal physical examination is unlikely to have ingested enough iron to lead to serious poisoning. If a patient remains asymptomatic for 6 hours, the patient may be safely discharged.

Patients with minimal gastrointestinal symptoms only but an otherwise normal physical examination should have abdominal radiographs, an arterial blood gas, and electrolytes. If there are no pills visible on an abdominal radiograph and there is no evidence of metabolic acidosis after several hours, the patient is unlikely to develop systemic toxicity. A serum iron level less than 500 μg/dL would support identifying this as a low-risk patient. This patient may be admitted to the hospital for observation or discharged home with close follow-up. Any patient with more than mild gastrointestinal symptoms or with evidence of altered mental status, shock, or acidosis should receive chelation therapy and be admitted to the hospital. Patients with severe toxicity may require intensive care therapy. If a hospital has limited pediatric critical care facilities or does not have access to toxicology consultation, plans to transfer a patient to a tertiary care hospital should be made early, before the patient becomes unstable for transfer.

8. Consultation. The regional poison center should be contacted to report any patient who goes to a health care facility for evaluation of possible poisoning. For patients who have significant toxicity or who are receiving deferoxamine, toxicologic consultation should be requested. If none is available in your area, you can obtain a telephone consultation from the toxicologist on-call at the New York City Poison Control Center by calling 212-POISONS (212-340-4494). To find the phone number or location of a local or regional poison center, one can access the Internet home page of the AAPCC at http://www.aapcc.org.

Is There a Modified Approach to Management in the Pregnant Patient?

Prenatal vitamins with iron are prescribed to almost all pregnant women, and their widespread availability makes iron one of the most common substances ingested by pregnant women attempting suicide. Maternal toxicity is generally greater than fetal toxicity. In 2 reported cases, healthy babies were delivered although the mothers died. In another case, the mother had severe iron toxicity with acidosis, shock, renal failure, and disseminated intravascular coagulation but was not treated with deferoxamine because of concerns about its teratogenic risks. Instead the mother received an exchange transfusion that was followed 45 minutes later by a spontaneous abortion of the 16-week-old fetus. Neonatal and cord blood iron levels were not elevated. In several cases, pregnant women had signs and symptoms of iron poisoning with elevated serum iron levels, were treated with deferoxamine, and delivered healthy infants.

Although the placenta transports iron to the fetus efficiently, it blocks the transfer of large quantities of iron. In a sheep model of iron poisoning, only a small amount of iron was transferred across the placenta despite significantly elevated serum iron levels.

Deferoxamine is reported to be an animal teratogen that causes skeletal deformities and abnormalities of ossification (Class C pregnancy risk according to the FDA). In a recent animal model similar effects were observed, but only with doses of deferoxamine that caused maternal toxicity. Experimentally, there is little transfer of deferoxamine across the placenta. Therefore, the reported fetal effects may be a result of the chelation of essential nutrients (such as trace metals) on the maternal side of the placenta.

In clinical case reports of iron overdose for which deferoxamine was used there have been no adverse effects on the fetus, although most have been second or third trimester poisonings. In 1 case series of 49 patients with iron poisoning during pregnancy, 25 women received deferoxamine. Only 1 woman who received deferoxamine in the first

An approach to evaluation and management of iron poisoning is a clinical one, and ancillary tests have poor sensitivity in the identification of serious toxicity. Most seriously ill patients can be successfully managed by providing excellent supportive care and chelation therapy with deferoxamine. The small number of severe poisonings may be further reduced by decreasing the amount of iron salts available in each pill, packaging high dose iron-containing pills as unit-doses, or changing the type of iron products available to a less toxic form such as carbonyl iron. Future trends in therapy will focus on the use of oral iron chelators as well as new agents being developed to limit and treat free radical–induced organ damage.

Conclusion

In this article we have reviewed the pathophysiology of iron poisoning and suggested an evidence-based approach to evaluation and management. The frequency of exposure to iron-containing products is high; however, most children do not experience serious toxicity. The diagnosis of iron poisoning is a clinical one, and ancillary tests have poor sensitivity in the identification of serious toxicity. Most seriously ill patients can be successfully managed by providing excellent supportive care and chelation therapy with deferoxamine. The small number of severe poisonings may be further reduced by decreasing the amount of iron salts available in each pill, packaging high dose iron-containing pills as unit-doses, or changing the type of iron products available to a less toxic form such as carbonyl iron. Future trends in therapy will focus on the use of oral iron chelators as well as new agents being developed to limit and treat free radical–induced organ damage.

References

25. Nightingale SL. From the food and drug administration. JAMA 1997;277:1343.