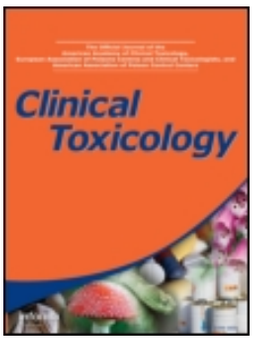

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PRACTICE GUIDELINE

Iron Ingestion: an Evidence-Based Consensus Guideline for Out-of-Hospital Management

Anthony S. Manoguerra, Pharm.D., Andrew R. Erdman, M.D., Lisa L. Booze, Pharm.D., Gwenn Christianson, M.S.N., Paul M. Wax, M.D., Elizabeth J. Scharman, Pharm.D., Alan D. Woolf, M.D., M.P.H., Peter A. Chyka, Pharm.D., Daniel C. Keyes, M.D., M.P.H., Kent R. Olson, M.D., E. Martin Caravati, M.D., M.P.H., and William G. Troutman, Pharm.D.

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From 1983 to 1991, iron caused over 30% of the deaths from accidental ingestion of drug products by children. An evidence-based expert consensus process was used to create this guideline. Relevant articles were abstracted by a trained physician researcher. The first draft of the guideline was created by the primary author. The entire panel discussed and refined the guideline before its distribution to secondary reviewers for comment. The panel then made changes in response to comments received. The objective of this guideline is to assist poison center personnel in the appropriate out-of-hospital triage and initial management of patients with suspected ingestions of iron by 1) describing the manner in which an ingestion of iron might be managed, 2) identifying the key decision elements in managing cases of iron ingestion, 3) providing clear and practical recommendations that reflect the current state of knowledge, and 4) identifying needs for research. This guideline applies to ingestion of iron alone and is based on an assessment of current scientific and clinical information. The expert consensus panel recognizes that specific patient care decisions may be at variance with this guideline and are the prerogative of the patient and the health professionals providing care, considering all of the circumstances involved. The panel's recommendations follow; the grade of recommendation is in parentheses. 1) Patients with stated or suspected self-harm or who are victims of malicious administration of an iron product should be referred to an acute care medical facility immediately. This activity should be guided by local poison center procedures. In general, this should occur regardless of the amount ingested (Grade D). 2) Pediatric or adult patients with a known ingestion of 40 mg/kg or greater of elemental iron in the form of adult ferrous salt formulations or who have severe or persistent symptoms related to iron ingestion should be referred to a healthcare facility for medical evaluation. Patients who have ingested less than 40 mg/kg of elemental iron and who are having mild symptoms can be observed at home. Mild symptoms such as vomiting and diarrhea occur frequently. These mild symptoms should not necessarily prompt referral to a healthcare facility. Patients with more serious symptoms, such as persistent vomiting and diarrhea, alterations in level of consciousness, hematemesis, and bloody diarrhea require referral. The same dose threshold should be used for pregnant women, however, when calculating the mg/kg dose ingested, the pre-pregnancy weight of the woman should be used (Grade C). 3) Patients with ingestions of children's chewable vitamins plus iron should be observed at home with appropriate follow-up. The presence of diarrhea should not be the sole indicator for referral as these products are often sweetened with sorbitol. Children may need referral for the management of dehydration if vomiting or diarrhea is severe or prolonged (Grade C). 4) Patients with unintentional ingestions of carbonyl iron or polysaccharide-iron complex formulations should be observed at home with appropriate follow-up (Grade C). 5) Ipecac syrup, activated charcoal, cathartics, or oral complexing agents, such as bicarbonate or phosphate solutions, should not be used in the out-of-hospital management of iron ingestions (Grade C). 6) Asymptomatic patients are unlikely to develop symptoms if the interval between ingestion and the call to the poison center is greater than 6 hours. These patients should not need referral or prolonged observation. Depending on the specific circumstances, follow-up calls might be indicated (Grade C).

Keywords Iron/poisoning; Ferrous compounds/poisoning; Poison control centers/standards; Practice guidelines

INTRODUCTION

The ingestion of iron, either as tablets of iron salts or as constituents of vitamin and mineral supplements has, for the past few decades, been one of the major causes of poisoning mortality and morbidity in children. From 1983 through 2000, a review of the American Association of Poison Control Centers Toxic Substance Surveillance System showed that at

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least 43 children died from the ingestion of iron supplements (1,2). A review of poisoning deaths reported by US poison centers from 1983 to 1991 found that iron caused over 30% of the deaths from unintentional ingestion of drug products by children (1). The reasons for this high mortality are likely numerous and not entirely understood. Iron supplements might be considered by parents and caretakers to be innocuous dietary supplements, which could lead to careless storage and handling and delays in seeking medical care following ingestions. Ingestions of large numbers of tablets might occur because the bright colors of the tablets could be perceived by children to be candy. Once iron is absorbed from the gastrointestinal tract, the ability to remove it from the body is limited, thus allowing the iron to produce toxicity in spite of optimal treatment.

In January 1997, the US Food and Drug Administration (FDA) issued a final rule requiring that oral dosage forms containing more than 30 mg of elemental iron per dosage unit be packaged in unit-dose packaging with strong warning labels and in compliance with the Poison Prevention Packaging Act (3). Also at that time, many manufacturers voluntarily changed the coatings on tablets, eliminating the sugar coatings in favor of film coatings to further decrease the likelihood of children ingesting large numbers of tablets. These changes were associated with a reduction in the number of poisoning deaths in children from iron ingestions. Following implementation of the rule, from 1998 through 2002, one child was reported to have died from the ingestion of an iron-containing product (2). The National Health Alliance filed a lawsuit against the FDA charging that the agency did not have jurisdiction to enforce packaging of dietary supplements. In October 2003, a court agreed and the FDA removed the final rule requiring unit-dose packaging (4). Iron-containing products reverted to the Consumer Product Safety Commission regulations in effect prior to 1997, which include the use of child-resistant packaging.

Syndrome of Iron Poisoning

Poisoning with iron salts produces a multiphasic syndrome. The first phase, which occurs within a few hours after ingestion, results from the corrosive effects of iron on the gastrointestinal tract and is characterized by vomiting and diarrhea, both of which can become bloody and severe. Acidosis and shock can occur. The gastrointestinal symptoms might subside during the next phase, which can last for 24 hours or more. However, in severe cases, this resolution of symptoms might not be observed (5). During this time, free iron in the blood is depositing in soft tissues and disrupting cellular function. This leads to severe multisystem organ failure, which is the characteristic of the next phase that typically becomes apparent 48–96 hours after ingestion. In severe cases, coma, convulsions, liver and kidney failure, and respiratory distress syndrome are often encountered. Patients who survive severe iron poisoning may be left with scarring of the gastrointestinal tract (6,7). Postmortem examinations of fatal cases show corrosive injury to the gastrointestinal tract, hepatic necrosis, renal tubular necrosis, and deposition of iron in cardiac muscle and the brain (8,9).

Iron Products

Iron is sold as single-ingredient tablets, as prenatal vitamin supplements with iron, and as adult and pediatric vitamin products with iron. Several different iron salts are found in these products in a variety of dosages and dosage forms. The elemental iron content is the standard method of comparing iron salt products. Ferrous fumarate contains 33% elemental iron, ferrous sulfate contains 20% elemental iron, and ferrous gluconate is 12% elemental iron. Children's chewable vitamins with iron typically contain 18 mg of elemental iron or less per tablet.

Carbonyl iron is greater than 98% elemental iron but it cannot be compared directly with the iron salt products. Carbonyl iron is produced by the vaporization of iron pentacarbonyl, leading to the production of uncharged submicroscopic spheres of elemental iron crystals. In order to be absorbed from the gastrointestinal tract, carbonyl iron requires solubilization to ionized iron by stomach acid (10). This dissolution in stomach acid appears to be the rate- and quantity-limiting step in the absorption of the drug. In addition, carbonyl iron has not been reported to cause the corrosive injury to the gastrointestinal tract characteristically seen in iron salt poisoning.

Iron polysaccharide complex is another nonionic form of iron and contains 46% elemental iron by weight. It is produced by neutralization of a ferric chloride-carbohydrate solution. It is sold in products containing 18–150 mg of elemental iron per tablet. It is stated to have an oral LD_{50} in rats of greater than 5000 mg/kg (3). Limited human toxicity information is available but the product appears to have less toxicity than ferrous salts.

The amount of elemental iron present in typical products on the US market used for the same purpose is variable (Table 1).

Substances and Definitions

This guideline is intended to address exposures to iron only. The term ''out-of-hospital'' is defined as the period before a patient reaches a healthcare facility. An acute ingestion is defined as any number of ingestions that occur within a period of less than 8 hours. A child is defined as a person less than 6 years of age.

Intended Users of the Guideline

The intended users of this guideline are personnel in US poison centers. This guideline has been developed for the conditions prevalent in the US While the toxicity of iron is not expected to vary in a clinically significant manner in other nations, the out-of-hospital conditions could be much

TABLE 1
Representative iron products

Iron product	Dosage form(s)	Approximate elemental iron per dosage unit
Ferrous sulfate	250 mg tablets	50 mg/tablet
	325 mg tablets	65 mg/tablet
	Timed-release tablets	65–105 mg/tablet
	Elixir 220 mg/5 mL	44 mg/5 mL
	Drops 75 mg/0.6 mL	15 mg/0.6 mL
Ferrous gluconate	240 mg tablets	28 mg tablet
	300 mg tablets	36 mg/tablet
	325 mg tablets	40 mg/tablet
Ferrous fumarate	100 mg chewable tablets	33 mg/tablet
	Time-release tablets	50–110 mg/tablet
	200 mg tablets	65 mg/tablet
	325 mg tablets	107 mg/tablet
	350 mg tablets	115 mg/tablet
	Suspension 350 mg/5 mL	33 mg/5 mL
Multivitamin hematinic products	Tablet or capsule	65–150 mg/tablet
Prenatal vitamins with iron	Tablet or capsule	9–106 mg/tablet
Adult multiple vitamin plus iron	Tablet or capsule	3–110 mg/tablet
Pediatric multiple vitamin plus iron	Chewable tablet	10–18 mg/tablet
	Drops	10 mg/mL
	Liquid	10 mg/5 mL
Carbonyl iron	Tablets and capsules	50–66 mg/tablet or capsule
	Liquid	15 mg/1.25 mL
Polysaccharide-iron complex	Tablets	50–150 mg/tablet
	Capsules	150 mg/capsule
	Elixir	100 mg/5 mL

From Refs. (11,12).

different. This guideline should not be extrapolated to other settings unless it has been determined that the conditions assumed in this guideline are present.

Objective of the Guideline

The objective of this guideline is to assist poison center personnel in the appropriate out-of-hospital triage and initial management of patients with suspected ingestions of iron by 1) describing the manner in which an ingestion of iron might be managed, 2) identifying the key decision elements in managing cases of iron ingestion, 3) providing clear and practical recommendations that reflect the current state of knowledge, and 4) identifying needs for research. This guideline applies to ingestion of iron alone. Coingestion of additional substances could require different referral and management recommendations depending on the combined toxicities of the substances.

This guideline is based on an assessment of current scientific and clinical information. The expert consensus panel recognizes that specific patient care decisions may be at variance with this guideline and are the prerogative of the patient and the health professionals providing care, considering all of the circumstances involved.

METHODOLOGY

The methodology used for the preparation of this guideline was developed after reviewing the list of key elements of guidelines described by Shaneyfelt et al. (13). An expert consensus panel was established to oversee the guideline development process (Appendix 1). The American Association of Poison Control Centers (AAPCC), the American Academy of Clinical Toxicology (AACT), and the American College of Medical Toxicology (ACMT) appointed members of their organizations to serve as panel members. To serve on the expert consensus panel, an individual had to have an exceptional track record in clinical care and scientific research in toxicology, board certification as a clinical or medical toxicologist, significant US poison center experience, and be an opinion leader with broad esteem. Two Specialists in Poison Information were included as full panel members to provide the viewpoint of the end users of the guideline.

Literature Search

The National Library of Medicine's PubMed database was searched (through November 2003) using iron (poisoning) or iron (toxicity) or ferrous compounds (poisoning) or ferrous compounds (toxicity) as MeSH terms, all limited to humans. The PubMed database was searched again (through November 2003) using iron or ferrous as textwords (title, abstract, MeSH term, CAS number) plus either poison* or overdos* or tox* or intox*, limited to humans. This same process was repeated in International Pharmaceutical Abstracts (1970–November 2003, excluding abstracts of meeting presentations), Science Citation Index (1977–November 2003), Database of Abstracts of Reviews of Effects (accessed November 2003), Cochrane Database of Systematic Reviews (accessed November 2003), and Cochrane Central Register of Controlled Trials (accessed November 2003). Reactions (1980–November 2003), the iron poisoning management in POISINDEX (14), and the bibliographies of recovered articles were reviewed to identify previously undiscovered articles. Furthermore, North American Congress of Clinical Toxicology abstracts published in the Journal of Toxicology-Clinical Toxicology (1995–2003) were reviewed for original human data. The iron chapter bibliographies in four major toxicology textbooks were reviewed for citations of additional articles with original human data (15–18). Finally, The Toxic Exposure Surveillance System (TESS) maintained by the American Association of Poison Control Centers was searched for deaths resulting from iron poisoning (2). These cases were abstracted for use by the panel.

Article Selection

The recovered citations were entered into an EndNote library and duplicate entries were eliminated. The abstracts of the remaining articles were reviewed, looking specifically for those that dealt with estimations of mg/kg or ingested doses with or without subsequent signs or symptoms, time of onset of symptoms, and management techniques that might be suitable for out-of-hospital use (e.g., gastrointestinal decontamination). Articles excluded were those that did not meet either of the preceding criteria, did not add new data (e.g., some reviews, editorials), or that exclusively described inpatient-only procedures (e.g., whole bowel irrigation). Specific animal studies were included only if they were relevant to panel recommendations.

Data Extraction

All articles that were retrieved from the search were reviewed by a single abstractor. Each article was assigned a level of evidence score from 1 to 6 using the rating scheme developed by the Centre for Evidence-Based Medicine at Oxford University (Appendix 2); the complete paper was then reviewed for original human data regarding the toxic effects of iron, or original human data directly relevant to the out-of-hospital management of patients with iron overdose. Relevant data (e.g., dose of iron, resultant effects, time of onset of effects, therapeutic interventions or decontamination measures given, efficacy or results of any interventions, and overall patient outcome) were compiled into a table and a brief summary description of each article was written. This full evidence table is available at http://www.aapcc.org/DiscGuidelines/IronEvidenceTable.pdf. The completed table of all abstracted articles was then forwarded to the panel members for review and consideration in developing the guideline. Every attempt was made to locate significant foreign language articles and have their crucial information extracted, translated, and tabulated. Copies of all of the articles were made available for reading by the panel members on a secure AAPCC website.

Guideline Writing and Review

A guideline draft was prepared by the primary author. The draft was submitted to the expert consensus panel for comment. Using a modified Delphi process, comments from the expert consensus panel members were collected, copied into a table of comments, and submitted to the primary author for response. The primary author responded to each comment in the table and, when appropriate, the guideline draft was modified to incorporate changes suggested by the panel. The revised guideline draft was again reviewed by the panel and, if there was no strong objection by any panelist to any of the changes made by the primary author, the draft was prepared for the external review process. External review of the second draft was conducted by distributing it electronically to AAPCC, AACT, and ACMT members and the secondary review panel. The secondary review panel consisted of representatives from the federal government, public health, emergency services, pediatrics, pharmacy practice, and consumer organizations (Appendix 3). Comments were submitted via a discussion thread on the AAPCC website or privately through e-mail communication to AAPCC staff. All submitted comments were stripped of any information that would identify their sources, copied into a table of comments, and reviewed by the expert consensus panel and the primary author. The primary author responded to each comment in the table and his responses and subsequent changes in the guideline were reviewed and accepted by the panel. Following a meeting of the expert consensus panel, the final revision of the guideline was prepared.

EVALUATION OF THE EVIDENCE ON THE TOXIC DOSE OF IRON

The toxic dose for various iron products was difficult to evaluate from the literature for several reasons:

- Histories of ingestion were often reported as unreliable.
- Many different iron-containing products are or were on the market with varying elemental iron content.

- Patients or their family members or the authors of the articles often failed to identify the exact product or list its elemental iron content.
- The bioavailability of iron varies substantially between products.
- Vomiting and diarrhea often occurred after ingestion and could have resulted in removal of some iron from the gastrointestinal tract.
- In many patients, treatment procedures performed in a hospital might have influenced the outcome.
- Many reports did not provide the doses in a per kilogram basis, making comparisons between reported patients difficult.

These factors were taken into account in evaluating the evidence available for toxic dose.

For the purposes of this guideline, the evidence on dose is divided into three general categories: acute iron exposures in children less than 6 years of age, acute exposures in patients 6 years of age or older, and acute exposures in pregnant women. Acute exposure was defined as a single exposure or multiple exposures occurring within a period of no more than 8 hours. This guideline does not deal with chronic oral exposures or parenteral iron exposures. The term out-of-hospital is defined as the period before a patient reaches a healthcare facility.

When the mg/kg dose or a child's weight was not included in an article, the mg/kg dose was estimated by the use of pediatric growth charts (19). The 95th percentile weight was used for a particular age and sex. When the sex of the child was not stated, the weight for boys was used. This approach errs on the side of estimating a lower mg/kg dose. Estimated mg/kg doses are italicized throughout the guideline whenever they are presented.

Acute Iron Ingestions in Children Less than 6 Years of Age

Adult Formulations of Ferrous Salts

No level 1–3 studies were found that specifically investigated the threshold dose for the development of toxicity in children less than 6 years of age with acute ingestions of adult formulations of ferrous sulfate, ferrous gluconate, or ferrous fumarate. Multiple level 4 articles contained some information on the relationship of dose and clinical effects but establishing a toxic threshold was usually not the primary goal of the articles. Specifically, there were 62 level 4 articles consisting of case reports and case series and two level 6 abstracts with dose and clinical effect information on ferrous sulfate ingestions in children (7,20–82), seven for ferrous gluconate (21–23,27,29,43,58), and three for ferrous fumarate (20,25,83). Unfortunately, one of the case series included children more than 6 years of age in the case pool, raising the possibility that intentional ingestions were included, making interpretation problematic (20). In another article, the age range included children up to 8 years of age (23). In three of the large case series either the precise products or the exact clinical effects were not specified (21–23).

Among the reported cases, the lowest ingested dose of ferrous sulfate associated with the development of significant nausea, vomiting, diarrhea, and stupor was four tablets in a 22-month-old child (24). Similarly, a 20-month-old was reported to be ''drowsy and ill-appearing'' after having ingested fewer than five tablets of ferrous sulfate (56). Both patients were hospitalized, treated with intravenous fluids and supportive care, and did well. In neither case was the amount of elemental iron in the tablets reported by the authors. Two pediatric iron ingestion case series reported that ingestions of fewer than 10 325-mg ferrous sulfate tablets resulted in severe toxicity (20,22). Reynolds and Klein (22) reported the death of a 16-month-old child with the history of ingestion of ''six ferrous sulfate tablets,'' although the authors questioned the accuracy of the history based on a serum iron concentration of greater than 4500 μg/dL (greater than 800 mmol/L). The lowest dose of ferrous sulfate associated with a fatal outcome was a case of a 21-month-old child who, by history, had ingested five to 10 325-mg tablets along with 150–300 mg of phenobarbital and 75–150 mg of methamphetamine (25). The peak serum iron concentration was 2160 μg/dL (387 mmol/L). On autopsy, the child had a subdural hemorrhage, bilateral bronchopneumonia consistent with aspiration, renal tubular necrosis, and gastric erosions, indicating that the death might have been the result of a combination of effects of the ingested drugs.

The lowest ingested dose of ferrous gluconate associated with toxicity was 900 mg elemental iron (the exact dose of ferrous gluconate was not specified) that resulted in vomiting and drowsiness in a 15-month-old child (30). In another report, ingestion of 12–20 tablets of ferrous gluconate (exact dose and elemental iron content not specified) caused the death of an 18-month-old child. A serum iron concentration drawn at least 20 hours after the ingestion was 780 μg/dL (140 mmol/L) (27).

Greenblatt et al. (25) described a 35-month-old child who ingested 6000 mg of ferrous fumarate but they only reported that the child did not become ''seriously ill.'' In another case, a 17-month-old child ingested 43 ferrous fumarate tablets (294 mg/kg of elemental iron), underwent surgical removal of the tablets by gastrotomy, and developed no significant adverse effects (83).

There was one level 2b article and six level 4 articles in which the authors provided information on the dose of elemental iron ingested, but the exact iron preparations were not given or were not known. One article described a large, retrospective review of cases of acute iron ingestion reported to one poison center during a 2-year period (84). Three hundred thirty-nine cases were reported with an age range of 9 months to 33 years. The ingested doses were reported in 199 cases. In the group ingesting 20–40 mg/kg elemental iron, 22% developed abdominal pain, diarrhea, and vomiting while 42% and 33% for the 40–60 mg/kg and greater than 60 mg/kg

groups, respectively, developed these symptoms. The higher dose groups had few patients and there was no statistically significant difference in the development of symptoms between the three groups. No deaths, shock, acidosis, or hepatotoxicity occurred.

Among the level 4 articles was a series of 29 patients in whom elevated serum iron concentrations were measured after ingestion of ferrous sulfate, ferrous gluconate, or unknown iron products, but clinical effects were not reported (21). Another level 4 paper was a retrospective review of 80 children less than 4 years of age with iron ingestions (22). The doses were known in only 23 patients and the authors stated that in four cases of severe toxicity the patients had ingested fewer than 10 tablets but the exact products were not specified. Among the four remaining case reports was a 7-week-old infant who was intentionally given ''a few'' tablets of an unknown iron product by the mother and developed lethargy, persistent acidosis, heme-positive stools, and dehydration. The serum iron concentration 36 hours after admission was 308 g/dL (55 mmol/L) (85). There was a case of lethargy, vomiting, and watery black diarrhea after the ingestion of ''fewer than 15 tablets'' of an unknown iron

TABLE 2
Reported or estimated mg/kg dose ingested for reported fatal iron ingestion cases in patients less than 6 years of age*

Age	Gender	Reported weight (Kg)	Estimated weight (Kg)†	Elemental iron dose ingested (mg)	mg/kg Iron dose ingested	Reference
18 mo	Female		*13.2*	480–800	*36–61*‡	(27)
3 yr	Male		*17.4*	1300 or more	*75 or more*	(27)
3 yr	Female		*17.4*	1300 or more	*75 or more*	(33)
17 mo	Male		*13.9*	1625 or more	*117 or more*	(2)
9 mo	Female		*10.2*	1300 or more	*128 or more*	(2)
3 yr	Male	14.3		1950	136	(2)
18 mo	Male		*14.1*	1950–2600	*138–184*	(38)
16 mo	Male		*13.6*	1950–2775	*143–204*	(38)
2 yr	Male		*15.2*	2275	*150*	(2)
16 mo	Female		*12.7*	1950 or more	*154 or more*	(2)
12 mo	Male		*12.4*	1950	*157*	(38)
11 mo	Female		*11.1*	1950–2275	*176–205*	(37)
12 mo	Male		*12.4*	2275–2600	*183–210*	(2)
18 mo	Male		*14.1*	2600	*184*	(42)
18 mo	Male		*14.1*	2600	*184*	(2)
19 mo	Male	10.8		2275	210	(2)
27 mo	Female		*15.2*	3250	*214*	(22)
18 mo	Male		*14.1*	3250–3900	*230–277*	(46)
16 mo	Male		*13.6*	3250	*239*	(2)
15 mo	Male		*13.4*	3250	*243*	(2)
16 mo	Male	11		3055	278	(47)
11 mo	Female		*11.1*	3250–4550	*293–410*	(2)
2 yr	Female	10		3250	325	(47)
2 yr	Male		*15.2*	5850	*385*	(2)
10 mo	Female		*10.6*	4420	*417*	(2)
22 mo	Male		*14.8*	6240	*422*	(2)
21 mo	Female		*13.8*	5850	*424*	(2)
18 mo	Female		*13.2*	5850	*443*	(50)

*Cases included are only those reported in the literature or to the TESS system where an estimated dose ingested was provided by the author and the only substance ingested was an iron product.

†In those cases where a weight was not reported, estimated weights were derived from the 95th percentile of growth curves for healthy children from the National Center for Health Statistics. In those cases where gender was not reported, male weight for age was used (19). Estimated weights and estimated calculated doses are shown in italics.

‡This child had a serum iron concentration of 780 g/dL drawn at least 20 hours after ingestion. This implies a much larger amount of iron was ingested than what was reported.

product by a 21-month-old child. Although the time of ingestion was not provided, the serum iron concentration on admission was 463 g/dL (83 mmol/L) (59). Death was reported following ingestion of 30 tablets of an unknown iron product by an 11-month-old infant (38).

There were no studies specifically looking at the time to onset of symptoms following the ingestion of ferrous salt formulations. In most case reports, the time of onset of symptoms is not reported. Instead, the authors report the time of presentation for medical care, which can be many hours after the initial onset of symptoms. In a few case reports and series there is evidence that the time to the onset of symptoms, such as drowsiness, abdominal pain, gastrointestinal upset, and vomiting, typically occured within 1–4 hours of ingestion (7,22,26–29,31,33,36,43,44,47,49,55). In only one case report (37) did it appear that the time to onset of symptoms might have been delayed. This case involved a child who ingested 30 tablets of 325 mg ferrous sulfate and was then put down for a nap. The child awoke 10 hours later with vomiting and diarrhea and then soon developed lethargy.

Table 2 provides reported or estimated mg/kg doses for the fatal cases reported in the literature and in TESS for those cases where a dose of iron was reported. As most of the authors failed to report the weight of the children, estimated weights, as previously described, were used to calculate the mg/kg dose ingested.

Multivitamins with Iron

Only one case report (level 4) was found with information on the relationship of dose and clinical effects. In this report, a 2-year-old child ingested 780 mg of elemental iron as a multivitamin with iron product. The iron salt in the product and the weight of the child were not reported. No clinical effects were described and the patient was reported to have done well following treatment with whole bowel irrigation (86).

Chewable Multivitamins with Iron

One case report (level 4) was found with information of the relationship of dose and clinical effects for chewable vitamins with iron (87). In this report, a 2-year-old child ingested 25–50 tablets of a chewable multivitamin with iron product (exact dose and elemental iron content not stated), developed a serum iron concentration of 370 μg/dL (66 mmol/L), and experienced no clinical effects. No case reports were found describing serious or fatal poisonings with these products.

Anderson et al. (88) performed a retrospective review of all pediatric ingestions of iron products reported to the TESS over a 15-year period (level 4). No severe or fatal poisonings were reported in 195,780 reported ingestions of pediatric chewable multivitamin with iron products.

In a swine model in which each animal was given either 60 mg/kg elemental iron as children's chewable iron tablets or ferrous sulfate tablets, Nordt et al. (89) demonstrated that the time to peak serum concentration of iron was shorter and the peak serum iron concentrations were greater in the children's chewable group than in the ferrous sulfate group, although none of the animals achieved a serum iron concentration greater than 500 μg/dL (90 mmol/L). At necropsy 10 hours after iron administration, all animals in the ferrous sulfate group showed extensive esophageal and gastric inflammation and hemorrhage while two animals in the children's chewable vitamin with iron group showed only minimal esophageal inflammation. The other animals in the children's chewable vitamin with iron group showed no gastrointestinal injury.

Liquid Ferrous Salt Products

No case reports of serious or fatal poisoning following ingestion of liquid ferrous salt products were identified. Rodgers et al. (26) reported a 35-month-old child who ingested 76 mg/kg of elemental iron in the form of drops containing 75 mg of ferrous sulfate (15 mg elemental iron) per 0.6 mL (level 4). The child developed vomiting and abdominal pain. The serum iron concentration 3.5 hours following ingestion was 359 μg/dL (64 mmol/L). The child received deferoxamine intravenously for 12 hours and was discharged on the second day following the ingestion.

Carbonyl Iron

One case series (level 4) article described a 2-year retrospective review of carbonyl iron exposures reported to five poison centers (90). Thirty-three cases (ages not specified) were identified but follow-up information was available for only 17 cases. Of these, the ingested dose ranged from 2.2 to 72 mg/kg of elemental iron. One child developed diarrhea and lethargy but these symptoms were attributed to the child's pre-existing viral infection. There were no published reports of serious or fatal poisoning from the ingestion of carbonyl iron products.

Polysaccharide Iron Complex

Klein-Schwartz analyzed TESS data from 1990–1998 for children who had ingested polysaccharide iron complex products (level 4). Six hundred twenty children were identified with none reported as having developed major effects or fatal poisoning (91).

Acute Iron Ingestions in Patients 6 Years of Age or Older

Adult Formulations of Ferrous Salts

No level 1–3 studies were found that specifically investigated the threshold dose for the development of toxicity in patients 6 years of age or older with acute ingestions of adult formulations of ferrous sulfate, gluconate, or fumarate. There were, however, articles that contained some information on the relationship of dose to clinical effects, but establishing a toxic threshold was usually not the primary goal of the studies.

The efficacy of sodium polystyrene sulfate for reducing iron absorption was evaluated in a prospective crossover study in which volunteers were given 10 mg/kg elemental iron as 325 mg ferrous sulfate tablets (92). The volunteers tolerated this dose with only nausea and vomiting as side effects. Another level 1b study gave healthy volunteers 10 mg/kg of elemental iron as ferrous sulfate to test magnesium hydroxide's effect on absorption and found that the subjects developed nausea, vomiting, abdominal pain, and diarrhea that could be related to either the iron ingested or the magnesium hydroxide that was administered (93). Wallace et al. (94) administered 5 mg/kg of elemental iron to volunteers as ferrous sulfate 325 mg tablets and nausea developed in a small number of the subjects (level 1b). Another study (level 2b) compared the effects of ferrous sulfate tablets to carbonyl iron in healthy volunteers. Ingestion of 100 mg of elemental iron as ferrous sulfate resulted in mild effects, primarily gastrointestinal, but also headache and weakness were reported (10). Burkhart et al. (95) administered 20 mg/kg of elemental iron as 200 mg ferrous fumarate tablets to six healthy volunteers to study the effect of an iron overload on total iron binding capacity. All six volunteers developed nausea, abdominal cramps, and diarrhea. One developed vomiting and four were given intravenous fluid replacement. All symptoms resolved within 6 to 12 hours.

There was one level 3b study, a 12-year retrospective review of 113 acute intentional iron ingestions at one institution, that pooled data from ferrous sulfate, fumarate, and gluconate ingestions and stratified the outcomes according to ingested dose in mg/kg of elemental iron. The patients were reported to have ingested a mean of 70 mg/kg of elemental iron with a range of 7 to 350 mg/kg. Twenty patients developed severe toxicity and seven died. The patients who died were said to have ingested between 35 and 110 mg/kg of elemental iron. However, no details of individual cases were provided. Ferrous sulfate was involved in 45 cases (90%), ferrous gluconate in three, and ferrous fumarate in two cases (96).

Fourteen cases of iron poisoning in 13 level 4 articles were identified (8,67,97–107). The lowest dose that resulted in adverse consequences was one tablet, which caused gastrointestinal perforation in three patients, two of whom died (97–99). The lowest dose resulting in systemic toxicity was a case in which the patient reportedly ingested 10 tablets of ferrous sulfate 325 mg and died (104). However, the patient's family noted that as many as 50 tablets were missing from the container and a serum iron measurement drawn 48 hours after the ingestion was 307 μg/dL (55 mmol/L). In another case in an adult, a dose of 3000–4500 mg ferrous sulfate (600–900 mg of elemental iron) ingested along with alcohol resulted in severe toxicity (106).

In a level 2b study assessing the effect of antacids on iron absorption, adult volunteers received 18 mg of elemental iron as ferrous fumarate and experienced no adverse effects (108). In another study, 6 mg/kg of elemental iron given as crushed ferrous fumarate tablets to six adult volunteers resulted in nausea, diarrhea, and dark stools in two subjects (109).

There were three case reports of ingestion of ferrous fumarate (104,110). The lowest ingested dose to cause mild systemic toxic effects from ferrous fumarate tablets was 1650 mg of elemental iron (37.5 mg/kg) that reportedly caused drowsiness and confusion (110).

The lowest ingested dose of ferrous succinate to cause toxicity was 60 tablets (42 mg/kg of elemental iron) that caused mild symptoms of toxicity such as drowsiness and epigastric pain (111).

There were five cases (level 4) reported in two articles in which the ferrous salt was unspecified. Tenenbein (86) reported four adult exposures with ingestions of 35 to 150 mg/kg of elemental iron who were treated with whole bowel irrigation and did well. The second article was a description of a patient who ingested 166 mg/kg of elemental iron and died as a result (112).

There were no studies found specifically examining the time to onset of symptoms in patients of this age group who had ingested ferrous salt formulations. As in the case of ferrous salt poisonings in children, case reports in this older age group also demonstrated that the typical time to onset of symptoms, such as abdominal pain, nausea, and vomiting, was 1 to 4 hours (8,98,101,102,110,116–122). There was one case report found where the time of onset to symptoms might have been delayed, possibly as a result of the treatment the patient received. In this case, a 19-year-old male presented within 1 hour of ingestion of a large number of ferrous sulfate tablets. He was given ipecac syrup, and gastric lavage with sodium bicarbonate solutions was performed. Surgical removal of 60 tablets was performed at 16 hours after ingestion. The only sign or symptom mentioned is a mild metabolic acidosis that was reported at 8 hours following ingestion (125).

Liquid Ferrous Salt Products

Gomez et al. (113) gave 5 mg/kg of ferrous sulfate to healthy adult volunteers for the purpose of testing the efficacy of various decontamination measures (level 1b). The only adverse effect noted with this dose was mild nausea. Jackson et al. (114) gave 5 mg/kg of elemental iron as ferrous sulfate elixir to volunteers to test the efficacy of decontamination regimens. Some of the subjects developed nausea and lightheadedness. One death in an adult was identified (level 4). A young man ''accidentally'' ingested 1/4 pound of a ferrous sulfate suspension. He presented with hematemesis, shock, and cyanosis and died within 3 hours of ingestion (67). No reports were found that described serious or fatal poisonings in adults from the ingestion of pharmaceutical liquid iron preparations.

Chewable Multivitamins with Iron

No level 1–3 studies were found that specifically investigated the threshold dose for the development of toxicity

in adults with acute multiple vitamin with iron exposures. There were, however, two level 2b articles that contained some information on dose and clinical effects but establishing a toxic threshold was not the primary goal of the studies. In the first, 6 mg/kg elemental iron was given as chewable multivitamins plus iron (in the form of ferrous fumarate) to adult volunteers resulting in nausea, diarrhea, and dark stools in two of six subjects (109). In the second study, doses of 5 and 10 mg/kg elemental iron (salt unspecified) were given as chewable multiple vitamins plus iron to adult volunteers, resulting in all five subjects experiencing some degree of nausea, diarrhea, and headaches at both dosages (115).

Polysaccharide Iron Complex

In an analysis of TESS data for 1990–1998, Klein-Schwartz (91) reported 183 adults who ingested polysaccharide-iron complex products (level 4). There were no major effects or fatalities reported. The report concluded that the majority of exposures to these products result in minimal or no toxicity.

Carbonyl Iron

No level 1–3 studies were found that specifically investigated the threshold dose for the development of toxicity in adults with acute carbonyl iron exposures. There was however, one level 2b article that contained some information on the relationship between dose and clinical effects, but establishing a toxic threshold was not the primary goal of the study. In this study, healthy adult volunteers were given oral carbonyl iron in doses ranging from 100 to 10,000 mg. Side effects increased in frequency with increasing dose but were mild and consisted primarily of diarrhea and unpleasant taste, although some experienced headaches and/or weakness (10).

There was also a 2-year retrospective review of all carbonyl iron exposures reported to five poison centers (level 4). Thirty-three cases (age not specified) were identified but follow-up was available for only 17. Three adults were referred to emergency departments. One ingested an unknown amount, one ingested 72 mg/kg, and one ingested 450 mg, but this patient's weight was not reported. All three remained asymptomatic and had serum iron concentrations that were within the reference range (90).

Acute Iron Ingestions in Pregnant Women

Adult Formulations of Ferrous Salts

No level 1–3 studies were found that specifically investigated a threshold dose for the development of toxicity in pregnant women with acute ingestions of adult formulations of ferrous sulfate, gluconate, or fumarate. There were, however, nine case reports (level 4) that contained information on the relationship of dose and clinical effects for adult formulations of ferrous sulfate (8,55,76,116–121) and one case report with an adult formulation of ferrous gluconate (122). The lowest ingested dose of ferrous sulfate to cause maternal effects was 30–50 mg/kg of elemental iron resulting in moderate abdominal distress (116). Six of the eight cases resulted in normal deliveries, one outcome was unreported, and one pregnancy terminated with a spontaneous abortion that occurred following a maternal ingestion of 29,000 mg ferrous sulfate at 16-weeks gestation, after which the mother died (120).

Tran et al. (122) described a patient who was in her 27th week of pregnancy when she ingested 16,200 mg ferrous gluconate (1850 mg or 24 mg/kg elemental iron). She developed vomiting and abdominal pain, a peak serum iron of 603 μg/dL (108 mmol/L), and later delivered a normal, healthy infant (level 4).

There was one level 4 article describing 68 cases of acute overdose of unspecified iron preparations in pregnant women. Follow-up information was available for 51 of the patients and the ingested doses could be estimated in 48 with a range of 470 mg to 10,000 mg elemental iron. The lowest dose associated with symptoms in a mother was 470 mg of elemental iron, which caused nausea. Only two patients developed systemic symptoms. There were 43 live births, three of which were premature, and another three had various abnormalities that the authors did not attribute to iron or deferoxamine therapy. There were two spontaneous abortions and four elective abortions (123).

Dose Requiring Referral to a Healthcare Facility

The only article found that specifically addressed out-of-hospital management of iron exposures was an article examining poison center ''send-in guidelines'' and threshold values for referral to healthcare facilities. The study was a level 2b retrospective analysis of 2921 cases reported to 56 poison centers. Cases were divided into three groups: less than 29 mg/kg, 30–50 mg/kg, and 51–60 mg/kg elemental iron ingested. The study found no difference in the proportion of patients referred to healthcare facilities, the proportion that developed symptoms, and the clinical outcome at poison centers with different send-in threshold doses for elemental iron (124).

Review of TESS Death Reports

All abstracts of iron-related deaths reported to TESS were examined for the years 1985 through 2002. Forty-two cases were found, three in adults and 39 in children. Nineteen cases involved ingestions of ferrous sulfate, 13 involved prenatal vitamins with iron, and 10 involved unspecified iron products. The death reports revealed that in most cases the amount ingested was unknown or very large. The dose was unknown for 23 children and in the range of 20–96 iron salt tablets in the others. In only one case did the history state that a child had ingested as few as four or five tablets. However, the case revealed that after removing a number of tablets from the mouth of the child, the father estimated that the child had

TABLE 3
Summary of iron deaths reported to TESS 1985–2002

Age	Stated iron product ingested	Stated dose	Serum iron concentration μg/dL (mmol/L)	Time serum iron drawn after ingestion
3 yr	Ferrous sulfate 325 mg tablets	Unknown	3805 (681)	3 hr
18 mo	Ferrous sulfate	Unknown	23,000 (4119)	6 hr
10 mo	Ferrous sulfate	22 g	>7000 (>1254)	Unknown
15 mo	Ferrous sulfate 325 mg tablets	Unknown	1200 (215)	1 hr
17 mo	Prenatal iron tablets	Unknown	25,000 (4477)	6 hr
17 mo	Ferrous sulfate 325 mg tablets	Unknown	1400 (251)	4 hr
22 mo	Iron tablets	Unknown	4674 (837)	Unknown
10 mo	Ferrous sulfate tablets	Unknown	18,930 (3390)	Unknown
11 mo	Ferrous sulfate tablets	Unknown	>10,000 (>1790)	2 hr?
14 mo	Ferrous sulfate tablets	Unknown	>10,000 (>1790)	2 hr
15 mo	Iron tablets	Unknown	383 (68)	>10 hr
16 mo	Ferrous sulfate 325 mg tablets	>30 tablets	8500 (1522)	Unknown
9 mo	Ferrous sulfate 325 mg tablets	>20 tablets	3730 (668)	>6 hr
12 mo	Ferrous sulfate 325 mg tablets	35–40 tablets	4023 (720)	4 hr
14 mo	Ferrous sulfate 325 mg tablets	Unknown	2088 (374)	3–4 hr
18 mo	Ferrous sulfate 325 mg tablets	40 tablets	1651 (296)	9 hr
2 yr	Ferrous sulfate	90 tablets	14,000 (2507)	Unknown
2 yr	Ferrous sulfate	35 tablets	6350 (1137)	4 hr
3 yr	Ferrous sulfate 325 mg tablets	30 tablets	>10,000 (>1790)	4 hr
3 yr	Ferrous sulfate	Unknown	377 (68)	3 hr
15 mo	Iron tablets	Unknown	>400 (>72)	>24 hr
17 mo	Prenatal vitamins with iron (65 mg Fe/tab)	''Whole bottle''	18,150 (3250)	Unknown
18 mo	Prenatal vitamins with iron (65 mg Fe/tab)	''4–5 tablets'' (likely an underestimation)	>1000 (>179)	4.5 hr
12 mo	Iron tablets	Unknown	1555 (278)	30 min
19 mo	Iron tablets (65 mg Fe/tab)	35 tablets	6000 (1074)	1 hr
15 mo	Prenatal vitamins with iron (325 mg ferrous sulfate/tab)	50 tablets	4500 (806)	6 hr
16 mo	Prenatal vitamins with iron	Unknown	1200 (215)	Unknown
16 mo	Prenatal vitamins with iron (325 mg ferrous sulfate/tab)	50 tablets	1440 (258)	Unknown
21 mo	Prenatal vitamins with iron (65 mg Fe/tab)	90 tablets	1858 (333)	10 hr
20 mo	Ferrous sulfate 325 mg tablets	Unknown	1080 (193)	Unknown
11 mo	Iron tablets	50–70 tablets	8800 (1576)	2 hr
23 mo	Prenatal vitamins with iron	Unknown	251 (45)	36 hr
18 mo	Ferrous sulfate 325 mg tablets	Unknown	Not done	
22 mo	Ferrous sulfate 325 mg tablets	96 tablets	2583 (463)	6.5 hr
1 yr	Prenatal vitamins with iron	Unknown	5900 (1057)	12–14 hr
16 mo	Prenatal vitamins with iron	Unknown	397 (71)	>3 days
17 mo	Prenatal vitamins with iron	>25 tablets	1055 (189)	6 hr
16 mo	Ferrous sulfate	Unknown	12,000 (2149)	>4 hr
14 mo	Iron tablets	Unknown	18,750 (3358)	3 hr
36 yr	Unknown iron preparation	Unknown	345 (62)	Unknown
14 yr	Iron tablets	140 mg/kg	476 (85)	Unknown
34 yr	Prenatal vitamins with iron	Unknown	92 (17)	Unknown

ingested only four or five tablets. This was likely not an accurate estimate of the number that had been ingested. In the adult cases, the amount ingested was unknown in two cases and in one case was reported as 140 mg/kg of elemental iron (2). A summary of these cases is provided in Table 3.

EVALUATION OF EVIDENCE REGARDING GASTROINTESTINAL DECONTAMINATION PROCEDURES

Syrup of Ipecac

No level 1–3 studies were found concerning the effectiveness of ipecac syrup-induced emesis in the management of iron poisoning. There were five case reports (level 4) dealing with this topic. In three of the case reports, the patients required gastrotomies to remove concretions of iron tablets. In all three cases, the authors stated that the patients had previously received ipecac-induced emesis without effective removal of the concretions (125–127). The other article reported two cases (128). Case 1 was a 17-month-old child with a ferrous sulfate ingestion. An initial abdominal radiograph showed nine tablets in his stomach and one in his small intestine. He was given ipecac syrup, which resulted in three episodes of vomiting. A subsequent radiograph showed the same 10 tablets but in different positions. Case 2 was a 16-year-old girl who ingested 100 ferrous sulfate tablets. She was given ipecac syrup resulting in four episodes of vomiting, expelling 15 tablets over 1 hour. A radiograph after emesis showed more than 50 tablets remaining in the stomach.

Activated Charcoal

It has been generally felt that activated charcoal is ineffective in adsorption of iron because of the small molecular weight and ionic nature of iron (16,129). This was recently confirmed by an animal study and questioned by a human volunteer study. The animal study showed no effect of activated charcoal on the extent of iron absorption in rats when the 240-g animals were given 100 mg of elemental iron followed by activated charcoal in charcoal-to-iron ratios of 1:1, 2:1, and 4:1 (130). The human volunteer study (level 1b) demonstrated that oral administration of a premixed combination of one part deferoxamine and three parts activated charcoal given following a dose of liquid ferrous sulfate produced a reduction in serum iron concentration compared to the untreated control or activated charcoal arms of the study. The study used a small dose of liquid iron, and it is highly unlikely that deferoxamine would be available in an out-of-hospital situation. Therefore, this approach has no application in the out-of-hospital management of the typical iron poisoning (113).

Other Oral Binding or Complexing Agents

During the 1970s and 80s, oral administration of sodium bicarbonate was frequently advocated with the intention of decreasing oral absorption of iron. The in-vitro and in-vivo experimental evidence does not support this procedure. Czajka et al. (131) demonstrated in vitro that bicarbonate solutions complexed more iron than phosphate solutions. However, 83% of the iron remained in solution. In a rat model, Dean et al. (132) found no effect of sodium bicarbonate or sodium dihydrogen phosphate lavage solutions on the absorption of iron. Corby et al. (133) found decreased iron absorption in dogs following administration of magnesium hydroxide. However, increased serum concentrations of magnesium were noted. A human volunteer study (level 1b) demonstrated a 50% reduction in iron absorption with the administration of magnesium hydroxide (94). However, the volunteers were given 4.5 g of magnesium hydroxide for each gram of iron, a ratio unlikely to be tolerated by many patients with toxic iron ingestions. For example, a 10-kg child ingesting 60 mg/kg of elemental iron would require approximately 36 mL of milk of magnesia while a 70-kg adult ingesting 60 mg/kg would need 250 mL of milk of magnesia to achieve these ratios. In addition to these doses being large volumes that might be difficult to consume and tolerate, they could cause significant diarrhea. Another study (level 1b) did not find a significant difference in iron absorption following the administration of magnesium hydroxide to human volunteers given 10 mg/kg of ferrous sulfate (93). In clinical use, bicarbonate and phosphate solutions used for gastric lavage or as oral complexing agents have resulted in significant adverse events, morbidity, and mortality (28,134).

New oral iron chelating agents, such as deferiprone (135) and sodium HBED ligand (136), have been shown to improve survival and enhance iron excretion in iron-poisoned animals. In addition, modifications of deferoxamine, such as conjugation with dextran or hydroxyethyl starch, have shown the potential for enhanced efficacy and improved patient tolerability (137). Additional research must be conducted to determine the role for these agents.

Cathartics

No evidence was found supporting the use of cathartics in iron poisoning. As whole bowel irrigation is not an out-of-hospital procedure, it is not discussed in this guideline.

CONCLUSIONS

Key Decision Points for Triage

The expert consensus panel chose to emphasize the importance of information that would be needed in order to make a triage decision for a patient who has ingested an iron product. These variables include the patient's intent, the dose and formulation of the specific product ingested and other coingestants, the time of the ingestion, and the patient's symptoms or underlying medical conditions. The panel agreed that in each case the judgment of the specialist in

poison information, with the assistance of their medical consultant or preapproved policies, might override any specific recommendation.

Patient Intent

The expert consensus panel concluded that all patients with a suicidal intent or in whom a malicious intent is suspected (e.g., child abuse or neglect) should be expeditiously transported to an emergency department. Patients without these characteristics are candidates for consideration of out-of-hospital management of their ingestion.

Dose and Formulation

The expert consensus panel concluded that the published evidence and the death reports did not provide solid evidence upon which to base a referral threshold dose for adult formulations of ferrous salts. The clinical judgment of the panel members supported the indications from the literature that a healthcare facility referral threshold of 40 mg/kg of elemental iron is safe for both adults and children. The available evidence does not support a different threshold value for pregnant women. As most iron ingestions in pregnant women are likely to be intentional in nature, most pregnant patients will be referred regardless of the amount ingested. However, the panel concluded that if a mg/kg calculation is to be performed for a pregnant woman, the calculation should be based upon the prepregnancy weight of the patient. The panel also acknowledged that there are isolated case reports of adverse events such as bowel perforations occurring following the ingestion of amounts of iron unlikely to cause systemic poisoning.

The panel noted that there are no published case reports of symptomatic systemic iron poisoning following ingestions of children's chewable vitamins with iron. In addition, a review of TESS data involving a large number of exposures to these products found no evidence of serious poisoning or death. The panel concluded that referral to a healthcare facility for ingestions of children's chewable vitamins plus iron is usually unnecessary. Referral might be needed for the treatment of dehydration if vomiting and diarrhea occur and are severe or prolonged.

The panel concluded that the limited evidence indicates that carbonyl iron and polysaccharide-iron complex formulations are less toxic than ferrous salt formulations. There are no reported deaths, no reports of serious toxicity, and animal and human evidence indicates that large doses (up to 140 mg/kg in adult volunteers) can be taken without toxicity. The panel concluded that referral to a healthcare facility for ingestions of these products is not necessary. However, the panel felt that until additional evidence is reported in the literature, these patients should receive follow-up calls from the poison center.

Time to Onset of Effects

The panel concluded that the case report evidence indicates that the onset of symptoms following ingestions of all types of ferrous salt formulations, in all age groups, is typically within 4 hours of ingestion and is unlikely to extend beyond 6 hours. The two cases where the onset of symptoms appears to have been delayed were considered to be the result of unusual circumstances.

Potential Out-of-Hospital Management

Gastrointestinal Decontamination

Although emesis, either spontaneous or induced, may remove some ingested iron, the expert consensus panel concluded that the published literature does not provide evidence that the out-of-hospital use of ipecac syrup in iron ingestions positively affects patient outcome. The panel also concluded that the evidence does not support the out-of-hospital use of activated charcoal in iron ingestions. It should be considered in cases where other agents have been coingested. There is no evidence supporting the use of cathartics.

Oral Alkalinizing or Complexing Agents

The expert consensus panel concluded that the evidence does not support the out-of-hospital use of oral alkalinizing or complexing agents such as bicarbonate or phosphate solutions. The use of these agents has resulted in substantial morbidity and mortality.

RECOMMENDATIONS

1. Patients with stated or suspected self-harm or who are victims of malicious administration of an iron product should be referred to an acute care medical facility immediately. This activity should be guided by local poison center procedures. In general, this should occur regardless of the amount ingested (Grade D).
2. Pediatric or adult patients with a known ingestion of 40 mg/kg or greater of elemental iron in the form of adult ferrous salt formulations or who have severe or persistent symptoms related to iron ingestion should be referred to a healthcare facility for medical evaluation. Patients who have ingested less than 40 mg/kg of elemental iron and who are having mild symptoms can be observed at home. Mild symptoms, such as vomiting and diarrhea, occur frequently. These mild symptoms should not necessarily prompt referral to a healthcare facility. Patients with more serious symptoms, such as persistent vomiting and diarrhea, alterations in level of consciousness, hematemesis, and bloody diarrhea, require referral. The same dose threshold should be used for pregnant women; however, when calculating the mg/kg dose ingested,

the prepregnancy weight of the woman should be used (Grade C).
3. Patients with ingestions of children's chewable vitamins plus iron should be observed at home with appropriate follow-up. The presence of diarrhea should not be the sole indicator for referral as these products are often sweetened with sorbitol. Children may need referral for the management of dehydration if vomiting or diarrhea is severe or prolonged (Grade C).
4. Patients with unintentional ingestions of carbonyl iron or polysaccharide-iron complex formulations should be observed at home with appropriate follow-up (Grade C).
5. Ipecac syrup, activated charcoal, cathartics, or oral complexing agents, such as bicarbonate or phosphate solutions, should not be used in the out-of-hospital management of iron ingestions (Grade C).
6. Asymptomatic patients are unlikely to develop symptoms if the interval between ingestion and the call to the poison center is greater than 6 hours. These patients should not need referral or prolonged observation. Depending on the specific circumstances, follow-up calls might be indicated (Grade C).

These recommendations are summarized in Appendix 4.

IMPLICATIONS FOR RESEARCH

The expert consensus panel identified the following topics where additional research is needed or analysis of existing databases might be useful.

1. The use of oral chelating agents should be examined. Human studies to verify efficacy are required as well as studies examining the potential out-of-hospital use for these agents.
2. Although the published information suggests that carbonyl and polysaccharide-iron complex appear to have less toxicity than ferrous salts, the panel felt that this requires additional confirmatory studies.
3. Additional research should be conducted to determine if the threshold value for referral to a healthcare facility of 40 mg/kg of elemental iron in the form of adult iron formulations can be safely increased.
4. Additional research should be conducted to determine the risk of toxicity following ingestion of liquid iron products and to determine if a different referral threshold value should be established for these formulations.

DISCLOSURES

There are no potential conflicts of interest reported by the expert consensus panel or project staff regarding this guideline.

APPENDIX 1

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APPENDIX 2

Grades of Recommendation and Levels of Evidence

Grade of recommendation	Level of evidence	Description of study design
A	1a	Systematic review (with homogeneity) of randomized clinical trials
	1b	Individual randomized clinical trials (with narrow confidence interval)
	1c	All or none (all patients died before the drug became available, but some now survive on it; or when some patients died before the drug became available, but none now die on it.)
B	2a	Systematic review (with homogeneity) of cohort studies
	2b	Individual cohort study (including low quality randomized clinical trial)
	2c	''Outcomes'' research
	3a	Systemic review (with homogeneity) of case-control studies
	3b	Individual case-control study
C	4	Case series, single case reports (and poor quality cohort and case control studies)
D	5	Expert opinion without explicit critical appraisal or based on physiology or bench research
Z	6	Abstracts

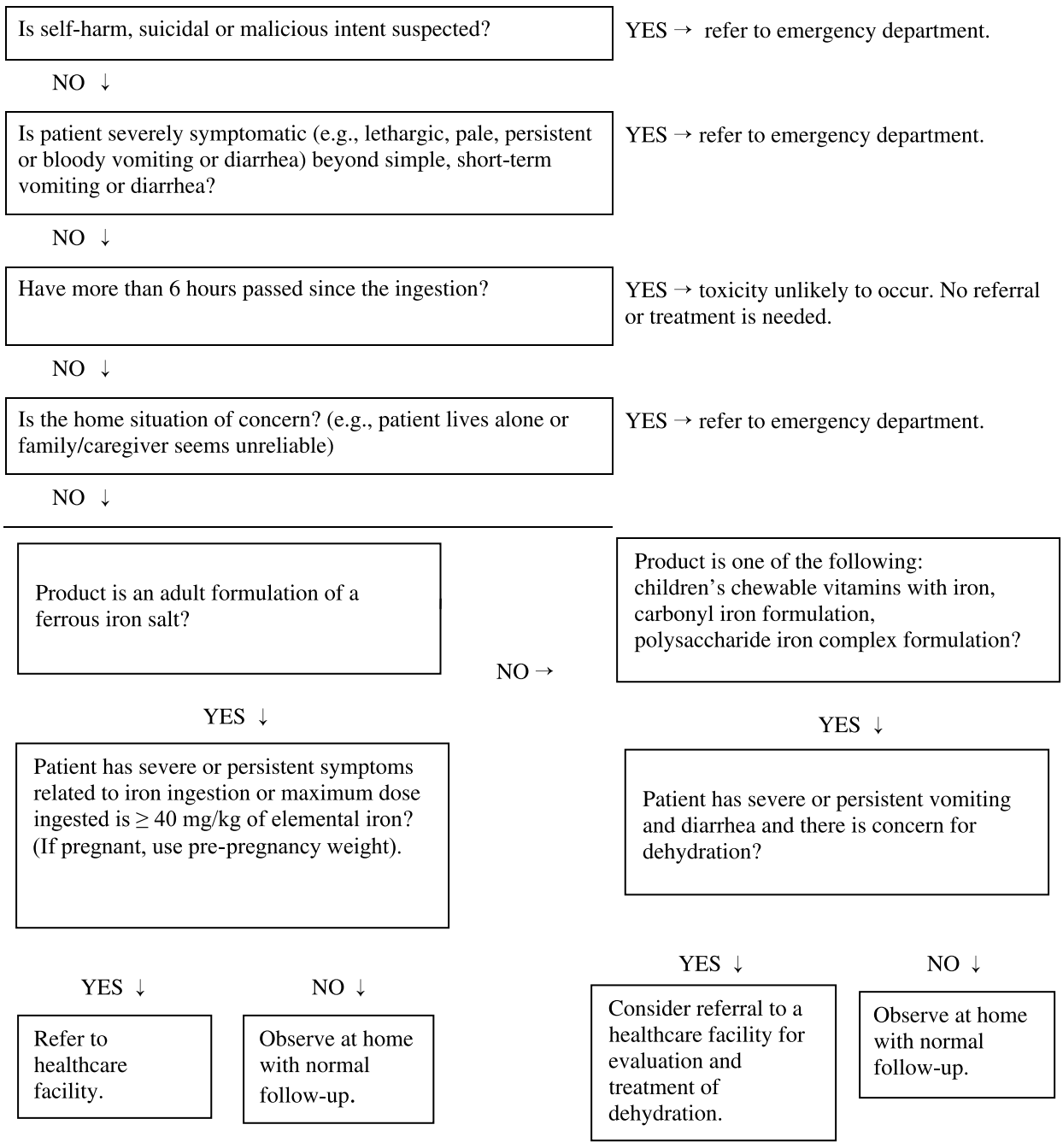
APPENDIX 3

Secondary Review Panel Organizations

Ambulatory Pediatric Association
American Academy of Breastfeeding Medicine
American Academy of Emergency Medicine
American Academy of Pediatrics
American Association for Health Education
American College of Clinical Pharmacy
American College of Emergency Physicians
American College of Occupational and Environmental Medicine
American Public Health Association
American Society of Health System Pharmacists
Association of Maternal and Child Health Programs
Association of Occupational and Environmental Clinics
Association of State and Territorial Health Officials
Canadian Association of Poison Control Centres
Centers for Disease Control and Prevention—National Center for Injury Prevention and Control
Consumer Federation of America
Consumer Product Safety Commission
Department of Transportation
Emergency Medical Services for Children
Emergency Nurses Association
Environmental Protection Agency
European Association of Poisons Control Centers and Clinical Toxicologists
Food and Drug Administration
National Association of Children's Hospitals and Related Institutions
National Association of Emergency Medical Services Physicians
National Association of Emergency Medical Technicians
National Association of School Nurses
National Association of State Emergency Medical Services Directors
National Safe Kids Campaign
Teratology Society
World Health Organization International Programme on Chemical Safety

APPENDIX 4

Algorithm for Triage of Iron Ingestions



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