Safety of Intravenous Iron in Clinical Practice: Implications for Anemia Management Protocols

GEORGE R. ARONOFF
Department of Medicine, University of Louisville Kidney Disease Program, Louisville, Kentucky

Optimizing anemia management is the sole indication for intravenous (IV) iron administration in the patient with chronic kidney disease (CKD): Achieving and maintaining iron sufficiency is crucial to achieving and maintaining target-range hemoglobin (Hgb). Although pica (geophagia) (1) and restless legs syndrome (2,3) may arise in iron-deficient patients, available reports on the efficacy of IV iron therapy for long-term management of nonhematologic manifestations of iron deficiency are inconclusive.

These narrow therapeutic indications constrain tolerance for potential adverse effects of IV iron in CKD patients. To be judged safe, IV iron therapy must show hematologic benefit (increase in Hgb, decrease in erythropoietin (ESP) dose, or both) without risking an increase in mortality or morbidity.

Does IV Iron Therapy Increase Mortality or Morbidity?

The relationship between IV iron use and mortality and morbidity in CKD has been examined only among dialysis-dependent patients. Judicious use of IV iron is not associated with increased mortality or hospitalization. Two teams of investigators, using large-scale databases from national dialysis providers, arrived at this conclusion independently and have either published their results (4) or reported them in abstract form (5). Their results support the safety and continued use of IV iron agents over a wide dosing range in hemodialysis patients, consistent with prevailing clinical practice guidelines.

Why do results differ between prevalent and incident patients? The explanation seems to reside with the timeliness and reliability of comorbidity information. Mortality in dialysis-dependent CKD is highly associated with comorbidity (6–8). Thus, relating iron use to mortality requires adjusting results for patient comorbidity. Comorbidity information obtained before initiating dialysis likely becomes outdated and increasingly unreliable as time on dialysis progresses.

Infection and oxidative stress are two potent contributors to mortality and morbidity in dialysis-dependent CKD patients. Because biologically active iron plays an important role in mediating each process and IV iron agents provide bioactive iron in abundance, the potential for IV iron therapy to increase the incidence of infection and consequences of oxidative stress has come under intense scrutiny. In this regard, it is reassuring to find that IV iron therapy over a wide dose range poses no discernible hazard in incident dialysis patients. Nevertheless, current information on the relationship between IV iron on the one hand and infection and oxidative stress on the other deserves special consideration.

Does IV Iron Therapy Increase Risk of Infection?

Conclusive evidence that IV iron therapy as currently practiced is not associated with an increased risk of infection in hemodialysis patients derives from results of both prospective and retrospective clinical trials. A single prospective, multicenter, cohort-controlled, observational trial (Epidemiology of Bacteremia in Dialysis Patients [EPIBACDIAL]) explored incidence and risk factors for bacteremia in 988 dialysis patients who were followed for 6 mo each in 19 hemodialysis units (9). Results showed that four factors were associated with increased risk of bacteremia: Central venous catheters compared with fistulas (relative risk [RR], 7.6), history of bacteremia (two or more episodes in previous 18 mo compared with none; RR, 7.3), immunosuppressive therapy (RR, 3.0), and anemia (per 1 g/dl Hgb increment; RR, 0.7). Although 5% of patients had serum ferritin levels >1000 ng/ml, risk of bacteremia was related to neither the serum ferritin nor the administration of IV iron therapy (in this case, iron dextran). The most common agent isolated in bacteremic patients was *Staphylococcus aureus*.

The EPIBACDIAL findings are consistent with those obtained in several large-scale prospective clinical trials in which IV iron agents were used but infection was not the primary outcome. In a prospective, multicenter, single-arm clinical trial of IV iron sucrose given in both replacement and maintenance dosing regimens, infection-related hospitalization was not increased among 665 hemodialysis patients who received 8583 doses of IV iron sucrose (10). Similarly, 157 hemodialysis patients in the normal Hgb arm of the Scandinavian Hemoglobin Normalization Trial required high doses of iron sucrose but showed no increase in mortality or hospitalization when compared with patients in the subnormal Hgb arm (11). Specifically, there was no difference in iron sucrose dose between survivors and nonsurvivors in either the normal or the subnormal Hgb group.

Retrospective studies in smaller numbers of peritoneal dialysis patients have yielded results consistent with those of

Correspondence to Dr. George R. Aronoff, University of Louisville, Kidney Disease Program, Division of Nephrology, 615 S. Preston, Louisville, KY 40292. Phone: 502-852-5757; Fax: 502-852-7643; E-mail: gra@louisville.edu

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prospective studies. Peritonitis and catheter infection rates do not increase after initiation of IV iron therapy with iron dextran (12,13) or iron sucrose (12,14).

A single, epoetin-era, retrospective trial in hemodialysis patients reported a possible increase in infection rate associated IV iron therapy (15). However, treatment was not randomized, baseline iron and anemia status differed substantially among treatment cohorts, and cohort size varied widely. Moreover, crucial information on vascular access was lacking, and significant differences in infection rates were found only between two of the three treatment cohorts. These studies yield no reliable conclusions on the relationship between iron dosing and infection. No information is available on the relationship between infection rate and ferric gluconate administration.

Is the Iron-Infection Hypothesis Plausible?

Bacteria require iron to replicate. *In vitro*, addition of IV iron enhances growth of selected bacteria (16). *In vivo*, transfusional iron overload in patients is associated with infection with specific iron-related organisms (17). Spontaneous iron overload in thalassemic mice (18) and experimental iron overload after in septic mice (19) increases lethality of infection. In patients (20) and *in vitro* (21), IV iron is associated with measurable defects in neutrophil function. These observations have prompted the hypothesis that IV iron administration increases infection risk in dialysis-dependent CKD patients.

The iron-infection hypothesis falters under further scrutiny. Macrophages and neutrophils bear specific transporters to ensure uptake of iron (Fe^{+2}) (22) needed to execute key steps in antimicrobial defense, including the oxidative burst and production of nitrogen radicals catalyzed by nitric oxide synthase (23). Experimental iron deficiency induced by chelation impairs neutrophil function and increases susceptibility to salmonellosis in mice (24). Iron deficiency is also associated with defects in cell-mediated immunity (25). Correction of iron deficiency enhances rather than impairs host resistance. In a randomized, double-blind, placebo-controlled trial of 363 children aged 5 to 10, oral iron supplementation for 8 wk was associated with increased iron stores, higher Hgb, reduced infections, and reduced sick days as a result of infection (26).

Most important, evidence linking IV iron to dialysis-related infections is lacking. Organisms that thrive on IV iron *in vitro* or afflict patients with spontaneous iron overload *in vivo* are uncommon among iron-treated dialysis patients. Moreover, the major pathogen among dialysis-dependent CKD patients is a particularly unlikely candidate to be nourished by IV iron. *Staphylococcus aureus* is well equipped to acquire iron from heme (27,28). Heme iron is present in abundance whenever red blood cells, *S. aureus*, and *S. aureus*–produced hemolysins reside in proximity: In CKD patients, this would be along the subcutaneous tracks of hemodialysis needles, central venous catheters, and peritoneal catheters. In short, the iron-infection hypothesis as it applies to IV iron administration and infections in dialysis-dependent CKD patients seems implausible.

Does IV Iron Increase the Risk of Cardiovascular Disease?

The dialytic milieu is characterized by inflammation, infection, oxidant stress, and the propensity for accelerated atherosclerosis (29). Biologically active iron plays a role in each of these processes. IV iron administration provides a rich source for intradialytic bioactive iron (30). All IV iron agents tested, including iron dextran (31), iron polymaltose (32), iron sucrose (16,31,32), and ferric gluconate (31–33), show evidence of bioactive iron release *in vitro* and *in vivo*. Accordingly, evidence for a possible pathogenic link between IV iron administration and cardiovascular disease deserves close examination.

There is little debate that IV iron therapy, tissue iron burden, and oxidative stress are causally related. Acute iron administration, whether IV (34,35) or oral (36,37), clearly generates evidence of oxidative stress. The acute effects of IV iron, however, are modest, transient, and related to the degree of elevation of the transferrin saturation (34). Chronic, repeated IV iron administration produces pro-oxidant effects that are longer lasting and potentially more harmful. The higher the cumulative dose of IV iron administered to dialysis patients, the greater the total body iron burden, the higher the serum ferritin level (38,39), and the greater the evidence of oxidant stress (40,41). Ferritin levels $>$600 ng/ml in dialysis-dependent CKD patients are associated with evidence of a reciprocal elevation of lipid peroxidation and depression of antioxidant defense (40).

The serum ferritin, of course, reflects the burden of both tissue iron and systemic inflammation (42). Inflammation introduces uncertainty to the interpretation of the serum ferritin. It does not, however, diminish the significance of the serum ferritin in the chain of causality linking IV iron therapy to oxidant stress. Prospective studies in hemodialysis patients who undergo maintenance IV iron therapy show that high ferritins are driven principally by the cumulative dose of IV iron. In patients with normal pretreatment ferritin levels, continuous low-dose (31.25 mg/wk) sodium ferric gluconate complex (SFGC) administration produces a predictable rise in serum ferritin, sufficient to exceed 500 ng/ml in 30% of all patients and a majority of patients with a baseline ferritin of 300 ng/ml (43). Moreover, patients with the highest levels of inflammation show the greatest pro-oxidant effects of IV iron administration. The higher the pretreatment ferritin level (40), regardless of its pathogenesis, and the higher the pretreatment levels of inflammatory mediators (44), the greater the observed increase in oxidant stress after IV iron. What is true in inflammation is also true in infection. Among dialysis patients, hepatitis C virus (HCV) infection contributes to oxidant stress. Although the serum ferritin correlates directly with oxidant stress regardless of HCV status, HCV-positive compared with HCV-negative patients show a greater pro-oxidant effect of acute IV iron administration (45). Taken together, these observations are consistent with the known role of iron in mediating inflammation. A high serum ferritin is smoke that signals fire. Whether the fire is due to tissue iron excess or inflammation is not a useful distinction. IV iron is fuel in either case.

Persistent oxidative stress in CKD patients promotes inflammation and, in turn, tissue injury, atherogenesis, and increased cardiovascular morbidity and mortality (46). There is, as we have seen, little evidence that IV iron adversely affects survival in patients with dialysis-dependent CKD. Available evidence relating IV iron administration to atherogenesis is indirect. In dialysis patients younger than 60, common carotid artery intima-media thickness (CCA-IMT), a marker of early atherogenesis, is significantly related to advanced oxidative protein products, cumulative 12-mo iron dose (range, 0 to 3200 mg), gender, CCA diameter, and serum triglycerides. Because the iron dose effect was independent of the advanced oxidative protein products effect and accounted for only 5% of the total variance in CCA-IMT, the significance of these findings is not entirely clear. Nevertheless, the evidence argues for caution, not complacency, in prescribing IV iron.

What Level of Serum Ferritin Is Too High for Further IV Iron Therapy?

IV iron and inflammation each beget a high serum ferritin. IV iron administration begets oxidant stress. IV iron in the presence of either inflammation or high ferritin begets oxidant stress disproportionately. Available information cannot convincingly absolve, individually or collectively, cumulative IV iron dose, high ferritin, or oxidant stress in the pathogenesis of

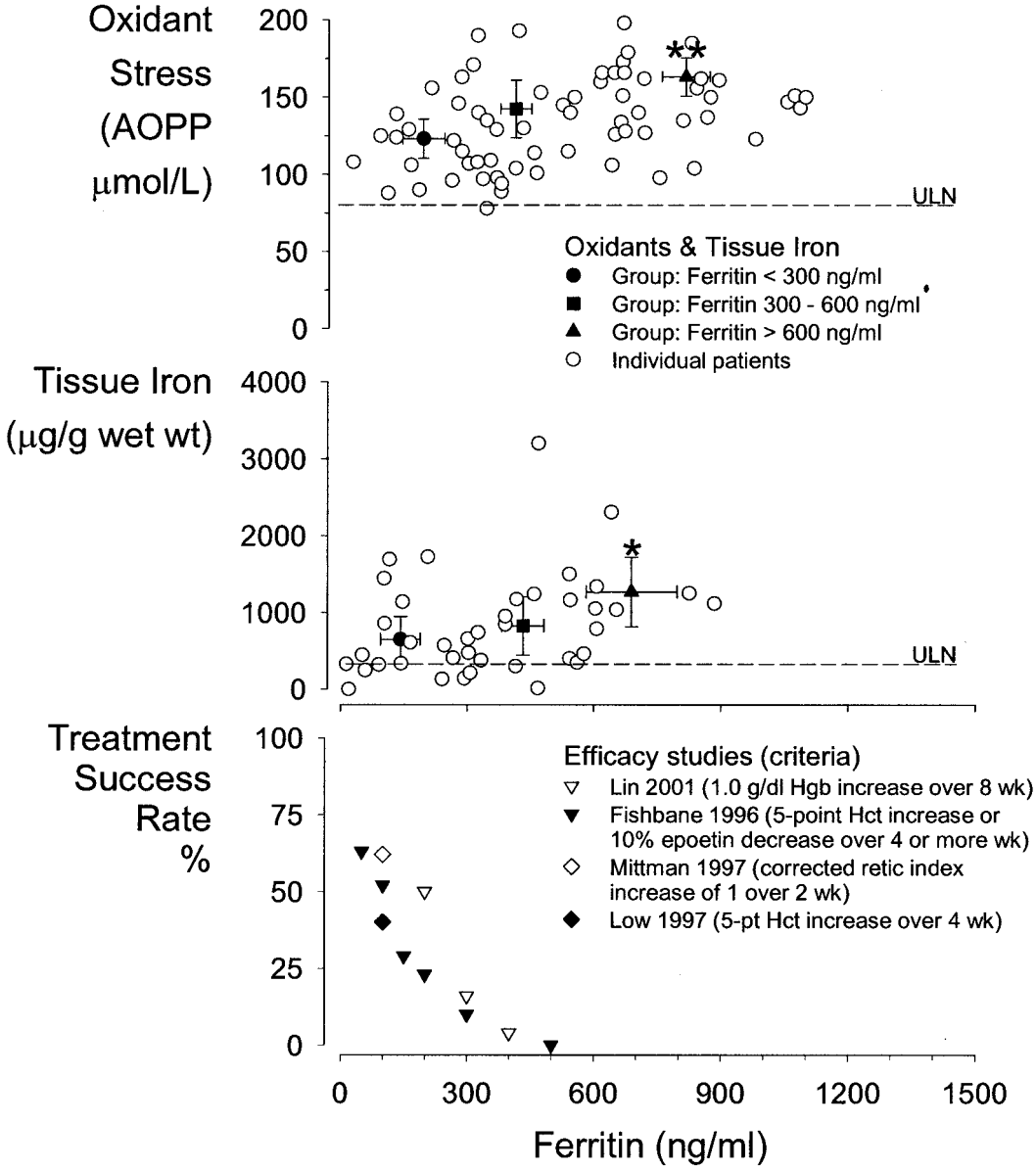

Figure 1. Relationship between serum ferritin and oxidant stress (41), tissue iron (52), and intravenous (IV) iron efficacy (53–56) in dialysis-dependent chronic kidney disease. Cross-hair symbols denote mean ± 95% confidence interval. Ferritin >600 ng/ml *versus* <300 ng/ml: *$P = 0.02$, **$P = 0.0003$. ULN, upper limit of normal. Patients with ferritin levels >600 ng/ml show evidence of increased oxidant stress and excess iron stores. Patients with ferritin levels of 500 ng/ml or greater show ineffective IV iron therapy.

Table 1. Rates of adverse reaction and intolerance to IV iron agents

Iron Agent	Author	Study Design 1	Patients (*n*)	Previous Exposure (Y/N)	Doses (*n*)	Dose Size (mg)	IV Rate (mg/min)	Serious ADE Rate (%)		Nonserious ADE Rate (%)		Intolerance Rate (%)	Notes
								Per Patient	Per Exposure	Per Patient	Per Exposure		
Free iron	Heath *et al.* (57)	P	17			8–80	IM	100					Ferric ammonium citrate (IM)
	Friend *et al.* (58)	P	21			10						10	Ferrous ascorbate
	Goetsch *et al.* (59)	P	14		15	608–1023	2.1–8.6	100					Colloidal ferric hydroxide
Iron dextran	Marchasin and Wallerstein (60)	R	37			100–3000	10–300	0		2.7			Safety information is limited
	Wallerstein (61)	R	2396			500–3000	50–100	1.42					Review
	Hamstra *et al.* (47)	R/P	481		2099	100–2500	50–250	0.6	0.1	10.4	3.1		ADE rate increased at doses >250 mg
	Auerbach *et al.* (62)	P	87		87	1200–2300	2 vs 6	3.5	3.5	46	46	3.5	Infusion rate, premedication showed no effect
	St. Peter *et al.* (63)	P	10		40	100	3.3 vs 50			20	5	0	No difference between rates
	Fishbane *et al.* (64)	R	573					0.7		5.2		3.8	
	Sloand *et al.* (48)	P	20		20	1000	6			10	10		ADE in PD patients weighing <50 kg
	McCarthy *et al.* (65)	R	254	N	3578	300	5–10	0.8	0.06	12.2	0.87	1.65	70% of ADE occurred in incident patients
	Barton *et al.* (66)	R	135		285	500	2.8–4.2	0	0	13		0	All patients were premedicated
	Fletes *et al.* (67)	R	NA		841,252	100			0.02				
	Prakash *et al.* (12)		34		67	500	1.7–2.1	2.9	1.4	14.7	7.4	1	PD patients
	Walters and Van Wyck (68)	R	48,509		1,066,099			0.035	0.035			0.69	Incident
	Sloand *et al.* (48)	P	11	N	11	1000	5.6	0	0	91		0	Randomized, controlled, efficacy trial
Ferric gluconate	Pascual *et al.* (69)	R	63	N		125		4.8				4.8	
	Hallak *et al.* (70)	R	26									1	Intolerance after test dose
	Navarro *et al.* (71)	P	27		162	62.5	2.1	0	0	0	0	0	
	Nissenson *et al.* (72)	P	88	N		62.5–125	2.1	3.4		10.2		3.4	1/88 intolerant to 25-mg test dose
	Kosch *et al.* (73)	P	28		720	62.5	12.5	0	0				Parallel group trial in HD patients
	Panesar and Agarwal (74)	R	58		240	125	0.52–8.33	3.4	1.7				Non-dialysis-dependent CKD
	Michael *et al.* (75)	P	2,534	N	2514	125	12.5	0.6	0.6	3.9	3.9	0.4	Single-dose, placebo-controlled trial
	Jain and Bastani (76)	R	40		79	250	1.0–4.2	5.0	5.1				Hospitalized patients
	Bastani *et al.* (77)	R	13		20	250	1.0–1.4		10				
						500	1.7		30				
	Folkert *et al.* (78)	P	144	Y	571	250	4.2	4.2			0.7	0.69	Rates varied; 4.2 mg/min = "most"
	Michael *et al.* (79)	P	1321	Y	13,151	125–250	<5–125	0.1		3.9	0.6	0.4	Patients from Michael *et al.* (75)) Includes patients from Folkert *et al.* (78))
Iron sucrose	Chandler *et al.* (49)	P	89			200	1.7	0				0	Dose-finding study in HD, PD, and non–dialysis-dependent CKD
			189			300	2.5	0					
			35			400	3.3	6					
			22			500	4.2	36					
	Kosch *et al.* (73)	P	27		720	250	4.2	0	0	0	0	0	Parallel-group trial in HD patients
	Van Wyck *et al.* (80)	P	22	N	223	100	20	0	0	9.0	0.14	0	Previous iron-dextran–intolerant patients
	Charytan *et al.* (81)	P	77	N	757	100	20	0	0	5.0	0.5	0	
	Prakash *et al.* (12)		23	N	46	500	1.7–2.1	4.3	2.2	8.7	4.3	0	
	Charytan *et al.* (82,83)	P	48	N	229	200	50	0	0				HD patients
	Blaustein *et al.* (84)	P	107	N	266	500	3.2			1.8	2.6		Nondialysis CKD patients
	Furuland *et al.* (11)	P	255			100	20	0		0		0	HD, PD, and nondialysis CKD
	Charytan *et al.* (82)	P	130	N		100–200	50–100	0	0	5.7		0	Patients with previous intolerance to iron dextran or SFGC
	Aronoff *et al.* (10)	P	665	N	8583	100	50	0	0	4.4	0.34	0	HD patients
Placebo	Michael *et al.* (75)	P	2514		2514	0	0	0	0			0.1	Placebo arm of SFGC trial, above
	Sloand *et al.* (2)	P	14		14	0	0	0	0	57			Placebo arm of iron dextran trial

[a] IV, intravenous; ADE, adverse drug event; IM, intramuscular; PD, peritoneal dialysis; HD, hemodialysis; CKD, chronic kidney disease; SFGC, sodium ferric gluconate complex.

cardiovascular disease in dialysis-dependent CKD patients. Thus, in determining a threshold ferritin above which no further IV iron should be given, concern for patient safety warrants use of a conservative and accepted standard: *Do no harm*. In short, evidence for efficacy must substantially outweigh evidence for risk.

As the above discussion has made clear, the risks identified in patients with high ferritin values are indirect but troubling. Moreover, because the reported relationship between serum ferritin and oxidant stress is continuous (40,41), no distinct serum ferritin value emerges to serve as the cutoff for an upper limit of safe IV iron therapy (Figure 1).

The relationship between efficacy of IV iron administration and pretreatment serum ferritin levels affords a much clearer definition of the upper limit of ferritin. At least four studies are available to provide evidence on the effect of pretreatment ferritin level on efficacy of IV iron. Whether therapeutic success is defined by a rise in Hgb, a rise in reticulocyte count, or a fall in epoetin α dose and whether the patient is given 500 or 1000 mg of IV iron as a challenge dose, IV iron therapy proves to be only fractionally successful even when the pretreatment serum ferritin is low ($\leq$100 ng/ml). IV iron therapy becomes progressively less successful in patients with higher pretreatment ferritins and is predictably unsuccessful when the pretreatment ferritin exceeds 500 ng/ml (Figure 1).

In short, markers of risk, stores, and efficacy all prompt a single conclusion: IV iron administration is associated with evidence of increased risk and excessive tissue iron stores in the patient with a serum ferritin $>$600 ng/ml and a lack of therapeutic efficacy in the patient with a serum ferritin $>$500 ng/ml. The evidence supports withholding IV iron in patients with pretreatment ferritin values $>$500 ng/ml.

Acute Adverse Events after IV Iron: Allergy or Toxic Reaction?

The nature and frequency of acute adverse reactions after IV iron administration remain subject to considerable controversy. As is readily apparent from a compilation of the available literature (Table 1), it is not the quantity but the quality of information that is deficient. Direct, head-to-head, comparative trials between or among available IV iron agents are altogether lacking. Moreover, key information needed to compare the results of individual, single-agent trials is routinely missing. For example, without information about the number of patients observed and the number of doses administered, it is impossible to calculate adverse drug event (ADE) rates per patient and per exposure. Without information about exposure history, it is impossible to discern ADE rates in incident (previously naive) compared with prevalent (previously exposed) patients. Most important, without information on the size of the iron dose administered or the rate of iron administration, it is impossible to discern whether ADE are due to allergy hypersensitivity or to immediate dose-related drug toxicity.

Consider the available iron dextran ADE literature (Table 1). For the purposes of the information in Table 1, serious reactions are those that are regarded as life-threatening, require hospitalization, or require other therapeutic intervention. Hypersensitivity to dextran is thought to be the cause of serious reactions to iron dextran, yet serious ADE rates clearly show an increase with both the size of the dose and the rate of infusion of iron dextran. Dose dependence and rate dependence suggest toxicity, not allergy. Moreover, both dose-related and rate-related ADE are characteristic of all IV iron agents, including agents that lack dextran, and serious ADE after ferric gluconate are more common among patients with a history of iron dextran sensitivity. However, it would be unwise to dismiss allergy as a cause of any IV iron reaction. Some ADE clearly fit criteria for hypersensitivity reactions: Sudden onset after low dose, with hypotension, bronchospasm, laryngospasm, angioedema, or urticaria or several of these together. In short, circumspection about pathogenesis seems warranted, but both allergy and toxicity, the latter limiting total iron dose and rate of infusion, seem to contribute to acute ADE after IV iron administration.

The distinction between allergy and toxicity is important. If the observed ADE reflects an allergic hypersensitivity to an IV iron agent, then further therapy should be withheld, because exposure to any dose at any infusion rate risks a life-threatening reaction. If, however, the ADE reflects toxicity, then decreasing the dose, the rate of infusion, or both can prove a safe and effective approach to ongoing therapy with the same agent (47–49).

The immunologic basis of allergic hypersensitivity to IV iron agents is not known. Both antibody-mediated and non–antibody-mediated, concentration-dependent mechanisms have been identified in patients after anaphylaxis to iron dextran (50,51). Recent information on the chemistry and biology of labile iron release, however, shed light on the pathogenesis and clinical implications of acute iron toxicity.

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