

The role of intravenous iron in anemia management and transfusion avoidance

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Parenteral iron preparations available in the past were associated with a risk of anaphylaxis and death, which made physicians reluctant to use them. The formulation most frequently responsible for these serious adverse events is high-molecular-weight iron dextran (HMW ID). The availability, first in Europe and more recently in the USA, of three other preparations (low-molecular-weight [LMW] ID, iron sucrose, and ferric gluconate), with a much better safety profile, is changing the pattern of use, thus prompting this review of paradigms of anemia correction by intravenous (IV) iron administration, with an emphasis on transfusion avoidance.

IV iron is important for optimal management of anemia in a number of settings, including cancer chemotherapy, inflammatory bowel disease, patients with malabsorption of iron such as those with celiac disease, obstetrics, surgical blood loss, patients with gastric bypass, and those with intestinal blood losses that exceed the ability of the normal small intestine to absorb ingested iron, as seen in disorders like hemorrhagic telangiectasia (Osler-Weber-Rendu). Recent publications of studies showing the benefit of IV iron in these settings have generated renewed interest of this important therapeutic modality.

ABBREVIATIONS: ESA(s) = erythropoietic-stimulating agent(s); HMW ID = high-molecular-weight iron dextran; IBD = inflammatory bowel disease; LMW ID = low-molecular-weight iron dextran; SC = subcutaneously; TDI(s) = total dose infusion(s).

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TRANSFUSION **,***-**-**.

The advent of erythropoietic-stimulating agents (ESAs) and their use in the anemia of renal failure led to the realization that adequate amounts of readily available iron are needed for their effectiveness. Before the release of recombinant human erythropoietin (EPO) for the treatment of renal failure-associated anemia, a significant number of dialysis patients were treated with red cell (RBC) transfusions.

Soon thereafter the percentage of RBC units transfused to dialysis patients by one transfusion service decreased from 7.34 percent of all RBC units in 1988 to 2.01 percent in 1991.¹ Nonetheless, even with EPO treatment, nearly 40 percent of patients failed to reach target hemoglobin (Hb) levels, defined by the National Kidney Foundation Guidelines to be a Hg level of 11 to 12 g per dL.² As the role of functional iron deficiency in the anemia of chronic disease became more clear, the use of IV iron with EPO to achieve target Hb levels became more common by the mid-1990s.³

Gastrointestinal absorption of iron is limited even in normal individuals as demonstrated in studies of autologous blood donation.⁴ In chronic disease states, increased hepatic production of hepcidin further decreases intestinal iron absorption. Hepcidin also decreases iron availability by increasing sequestration by the reticuloendothelial system. In the perioperative period, these same principles apply.

In this review, we will summarize the literature on the effectiveness of IV iron, with and without EPO, in decreasing the need for transfusion in surgery and other disease states. We will analyze the available randomized clinical trials and several observational studies showing the benefits of EPO, IV iron, or both.

Parenteral iron preparations

At present, there are four commercially available iron preparations in the western world. Characteristics of these compounds are listed in Table 1. The clinical setting for which IV iron is to be used should determine which preparation is chosen. For total dose infusion (TDI), ID is required because the iron salts cause dose-dependent gastrointestinal or vasoactive reactions at doses higher than 200 to 400 mg.⁵ The preferred dextran is the LMW

TABLE 1. Currently available IV iron preparations

Variable	LMW ID	Iron saccharate	Ferric gluconate	HMW ID
Test dose required	Yes	No	No	Yes
Vial volume (mL)	2	5	5	1-2
Milligrams of iron per milliliter	50	20	12.5	50
Black-box warning	Yes	No	No	Yes
TDI	Yes	No	No	Yes
Premedication	TDI only	No	No	TDI only
Preservative	None	None	Benzyl alcohol	None
Molecular weight measured by manufacturer (Da)	165,000 Da	34-60,000 Da	289-440,000 Da	265,000 Da

TABLE 2. Erythropoiesis during blood loss anemia: endogenous plus exogenous EPO

Number of patients	Baseline RBC vol (mL)	Total EPO (U/kg)	RBCs lost (donated)		RBC produced		Iron therapy
			Number of units	Volume (mL)	Volume (mL)	Expansion (%)	
11 female	1796	3600 IV	4.9	809	701	39	PO
12 male	2296	3600 IV	5.9	1097	1102	48	PO
23	2049	3600 IV	5.4	970	911	45	PO
18	2019	3600 IV	5.6	972	856	42	PO
1 male	2241	4200 SC	8	1600	1764	79	Hemochromatosis
75	1535	3600 IV	4.5	684	673	44	PO

PO = oral.

preparation because the HMW preparation is associated with a significantly higher incidence of serious acute events.^{6,7} For patients receiving cyclical therapies such as cancer chemotherapy or dialysis, the iron salts or LMW ID can be used as short 100- to 400-mg infusions.^{5,8,9} In settings such as the preoperative period, pregnancy, menometrorrhagia, gastric bypass, and uncomplicated iron deficiency in those intolerant to oral iron, however, a TDI of LMW ID is more convenient, equally efficacious, and far less expensive. Three studies comparing LMW ID with the two salts show no difference in efficacy or toxicity among the three products, but demonstrate considerable savings and increased convenience with LMW ID.¹⁰⁻¹²

Iron-restricted erythropoiesis

Twenty years ago, Finch¹³ summarized knowledge gained primarily from studies of normal individuals, patients with hereditary hemolytic anemias, and patients with hemochromatosis. Under conditions of basal erythropoiesis in normal subjects, plasma iron turnover (as an index of marrow erythropoietic response) is little affected, whether transferrin saturation ranges from very low to very high levels. In contrast, the erythropoietic response in individuals with congenital hemolytic anemia, in whom erythropoiesis is chronically raised up to six times over basal levels,¹⁴ is affected (and limited) by serum iron levels and by transferrin saturation.¹⁵ Patients with hemochromatosis who underwent serial phlebotomy were observed to mount erythropoietic responses of up to eight times over basal rates, attributed to the maintenance of very high serum iron and transferrin saturation levels¹⁶ (Table 2), whereas normal indi-

viduals were shown to have difficulty providing sufficient iron to support rates of erythropoiesis greater than three times basal rates.¹⁷ These observations led Finch to identify a “relative iron deficiency” state, also known as “functional iron deficiency,” which he defined as circumstances in which increased erythron iron requirements exceed the available supply of iron.¹⁸ In another clinical setting, patients undergoing autologous blood donation represent a model for perisurgical blood loss and the erythropoietic response.

Phlebotomy-induced blood losses with compensatory erythropoiesis mediated via endogenous EPO have been estimated to increase RBC production by up to threefold.^{19,20} No apparent relationship exists between basal iron stores and this magnitude of erythropoiesis, suggesting that under conditions of moderate erythropoiesis, serum iron and transferrin saturation for erythron requirements are adequately maintained by storage iron.^{19,21-23} Little or no benefit to oral iron supplementation was found in two studies,^{21,24} whereas a third study²⁵ found some benefit. IV iron supplementation was not found to be of value in enhancing erythropoiesis under these conditions.^{21,25}

With enhanced erythropoiesis during EPO therapy, iron-restricted erythropoiesis occurs even in patients with measurable storage iron. Despite an eightfold increase in gastrointestinal iron absorption,²⁶ serum ferritin and transferrin saturation levels decline up to 50 percent with EPO therapy.²⁷ Table 2 shows calculated RBC (mL) production and percent expansion (of baseline circulating RBC volume) in published cohorts treated with recombinant human EPO in the setting of autologous blood donation prior to elective orthopedic surgery. The 39 to

48 percent expansion of RBC volume represents a three- to fourfold increase in RBC volume.¹³ This fourfold increase in erythropoietic activity is accompanied by declining reticulocyte counts and the appearance of hypochromic RBCs by the second week of EPO therapy.^{28,29} In a study of escalating (fourfold) increases in EPO dose administered to patients undergoing aggressive phlebotomy, the marrow erythropoietic index increased from 2.9 times (with endogenous EPO stimulation) to 3.6 times over basal rates of erythropoiesis, representing only a 58 percent increase in erythropoiesis.⁴ The superior erythropoietic response in a patient with hemochromatosis further suggests iron-restricted erythropoiesis related to suboptimal transferrin saturation, in patients treated with EPO.²⁸

MANAGEMENT OF IRON-RESTRICTED ERYTHROPOIESIS

The success of EPO therapy in correcting the anemia of chronic renal failure has led to substantial clinical experience in iron therapy and erythropoiesis in this setting.^{30,31}

Hyporesponsiveness to EPO therapy is a common phenomenon^{32,33} due to a variety of comorbid conditions, particularly aluminum toxicity and iron deficiency.

Anemic patients undergoing dialysis may show suboptimal response to oral iron therapy for several reasons. During EPO therapy, absorption of iron increases up to five times.²⁶ External iron losses, however, including hemodialysis and blood testing, exceed gastrointestinal iron absorption.⁸ Poor compliance due to gastrointestinal symptoms is problematic, and significantly reduced iron absorption may occur with some newer iron formulations.³⁴ Iron-restricted erythropoiesis is evident by clinical responses to ascorbate supplementation, thought to facilitate the release of iron from reticuloendothelial stores and increased iron utilization by the erythron,³³ as well as the success of IV iron therapy in reducing EPO dosage.⁸

IV iron administration is used commonly in renal dialysis patients undergoing EPO therapy.³⁵ Patients treated with IV iron (100 mg twice weekly) achieved a 46 percent reduction in EPO dosage required to maintain hematocrit (Hct) levels between 30 and 34 percent, compared to patients

supplemented with oral iron.³⁶ In a study of 38 chronic renal failure (nondialysis) patients, two-thirds of patients who were unresponsive to oral iron responded to weekly IV iron therapy. Improved erythropoiesis occurred despite initial serum ferritin levels as high as 400 μg per L,³⁷ indicating that biochemical markers of storage iron in these patients are not helpful in evaluating iron-restricted erythropoiesis.

IV iron therapy in iron-deficient patients with inflammatory bowel disease also results in improved responses to EPO therapy,³⁸ compared to responses in a similar patient group who received oral iron supplementation.³⁹ The clinical response to IV iron may be attributed to the effect of EPO therapy on iron mobilization from the reticuloendothelial system into RBC precursors.⁴⁰ The risk-benefit profile of IV iron continues to undergo evaluation in renal dialysis patients^{3,41} as well as in patients with anemia of chronic disease.⁴² A recent study on all-cause morbidity and mortality in renal dialysis patients, however, failed to show any negative outcomes with IV iron in patients with ferritin levels up to 1200 ng per mL (Fig. 1). In this study of 58,000 dialysis patients, those

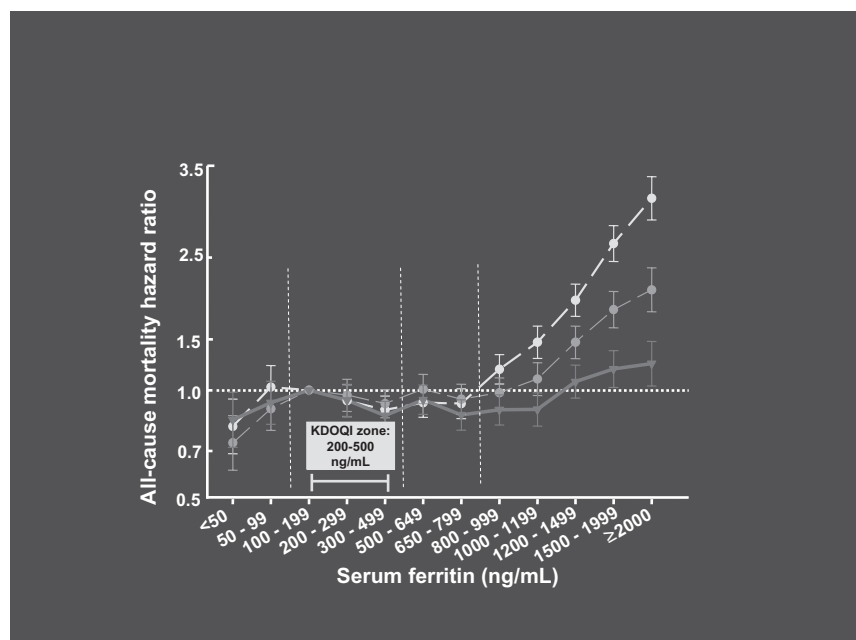


Fig. 1. Risk of all-cause death by serum ferritin level (time-dependent Cox model). KDOQI zone = 200 to 500 ng per mL (current KDOQI guidelines for iron administration to dialysis patients). Hazard ratios of death for time-varying ferritin categories. In unadjusted model, a serum ferritin level of 800 ng per mL during each quarter was associated with increased death rate, whereas in case mix-adjusted model, a tendency toward increased death rate first was observed when the serum ferritin level was greater than 1000 ng per mL. After additional multivariate adjustment for the confounding effect of surrogates of inflammation and malnutrition, there was no increased death rate for ferritin levels as high as 1200 ng per mL. (○) Unadjusted; (●) case mix; (▽) malnutrition-inflammation-cachexia (or complex) syndrome. Reprinted, with permission, from Kalantar-Zadeh et al.⁴³

given IV iron were significantly less likely to die than those not.⁴³

IV iron can allow up to a fivefold erythropoietic response to significant blood loss anemia in normal individuals.^{15,44} A greater rate of Hb production is probably not possible unless red marrow expands into yellow marrow space, as is seen in hereditary anemias.^{14,44} One limitation to IV iron therapy in patients not undergoing EPO therapy may be that much of the administered iron is transported into the reticuloendothelial system as storage iron, where it is less readily available for erythropoiesis.⁴⁵ For iron-deficient patients, 50 percent of IV iron is incorporated into Hb within 3 to 4 weeks,⁴⁶ whereas for patients with anemia of chronic disease or renal failure, IV iron is less rapidly mobilized from the reticuloendothelial system.⁴⁷

Oncology

At present, four studies have been performed with IV iron with ESAs and one without. The results of all these studies are summarized in Table 3. Each of the studies showed a significant benefit in improving Hb and hematopoietic responses (achievement of a Hb of 12 g/dL or a 2-g increment in Hb from baseline). A brief summary of these trials follows.

The first study to show a significant benefit for IV iron in improving responses to ESAs in cancer chemotherapy patients was published in 2004.⁴⁸ A total of 157 patients were enrolled and 155 were treated with EPO 40,000 U subcutaneously (SC) per week and no iron, oral iron as 325 mg of ferrous sulfate twice daily, 100-mg boluses of IV ID weekly until the total calculated deficit was administered, or a single TDI of ID to the same calculated dose. Nineteen patients received transfusions. Although there were significant improvements in Hb levels (Fig. 2, Hb responses with IV Fe) and hematopoietic responses in both IV iron arms, there was no significant difference in transfusions among the four arms. This study was not powered to examine differences in transfusion requirements among the four groups. Only one serious acute event requiring discontinuation of therapy with IV iron occurred. This occurred in a patient receiving ID who received the HMW ID during a brief period when the LMW preparation was unavailable. After recovery this patient received a TDI of LMW ID uneventfully.

Henry and colleagues⁴⁹ published the results of 189 patients randomly assigned to receive EPO given as 40,000 U SC per week plus no iron, oral iron as 325 mg of ferrous sulfate thrice daily, or IV ferrous gluconate as 125-mg weekly boluses. IV iron resulted in improved Hb and hematopoietic responses but there were no differences in the number of patients requiring transfusions. A recently published study by Hedenus and colleagues⁵⁰ randomly assigned 67 patients with lymphoproliferative

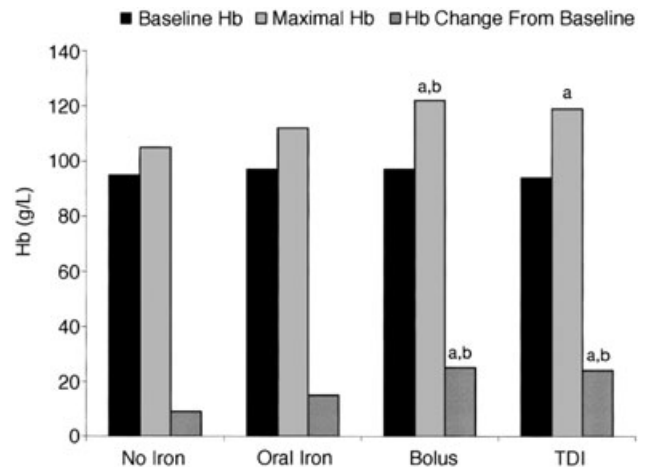


Fig. 2. Hb changes from baseline to endpoint by treatment group for the intent-to-treat population. Difference from baseline to endpoint Hb value, $p < 0.001$ for all treatment groups. ^a $p < 0.05$ versus no-iron group; ^b $p < 0.05$ versus oral-iron group. (■) Baseline Hb; (□) maximal Hb; (▒) Hb change from baseline. Reprinted, with permission, from Auerbach et al.⁴⁸

malignancies not receiving chemotherapy with positive marrow hemosiderin. Again, IV iron resulted in improved Hb and hematopoietic responses but there were no differences in transfusion requirements. This study was not powered to show a difference in transfusion requirements.

At the May 2007 annual meeting of the American Society of Clinical Oncology, Pinter and coworkers⁵¹ presented data on 398 patients with solid tumors and nonmyeloid hematologic malignancies and chemotherapy-induced anemia. Once again, this study showed significant improvement in Hb and hematopoietic responses in the IV iron arm. This study, however, showed a significant reduction in patients receiving transfusions in the IV iron arm (9% vs. 20%; Fig. 3).

Finally, in a population of 75 patients with anemia receiving chemoradiation therapy for carcinoma of the cervix, Kim and coworkers⁵² randomly assigned patients to receive no therapy or IV iron sucrose. None of the patients in either arm received ESAs. Sixty-four percent of the patients in the control arm and 40 percent of the patients in the IV iron arm received transfusions. This study raises the question of the benefit of IV iron alone in decreasing transfusion requirements in patients receiving chemoradiation therapy.

To conclude, there are little data supporting a decreased transfusion requirement from the addition of IV iron in patients with cancer receiving chemotherapy or chemoradiation therapy because the trials were not powered to look for a difference in transfusions. Numerous studies have shown a significant decrease in

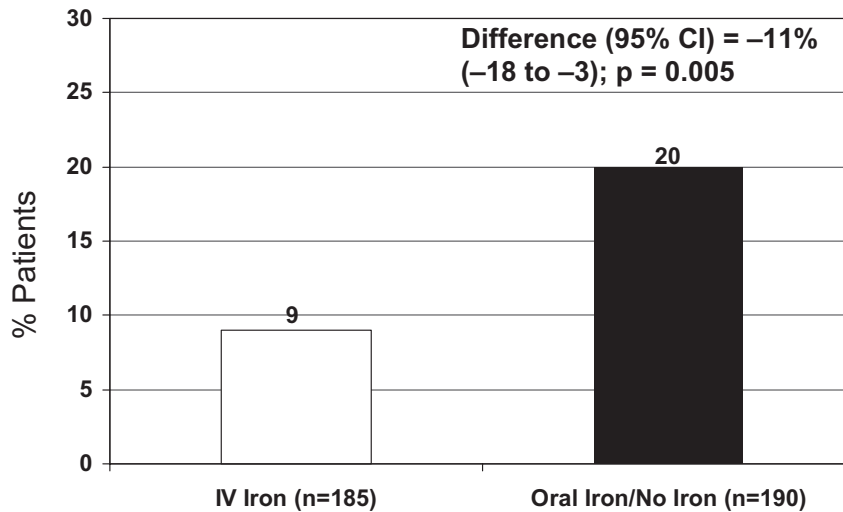


Fig. 3. Percentage of patients who received transfusions, for patients enrolled in the study for at least 29 days. Reprinted, with permission, from Pinter et al.⁵¹

transfusions with ESA therapy in cancer chemotherapy patients. Because every study comparing ESA therapy alone to ESA therapy plus IV iron showed a benefit from the addition of IV iron, a properly powered study to show a difference in transfusion requirements appears indicated.

Inflammatory bowel disease

Iron deficiency has been reported in up to 75 percent of patients with inflammatory bowel disease (IBD). In addition to iron deficiency, concomitant anemia of chronic disease may be present due to the up regulation of hepcidin by inflammatory cytokines released in these conditions.^{53,54} In patients with IBD, oral iron therapy is associated with severe side effects, is poorly absorbed, has limited efficacy, and has actually been associated with worsening of the bowel symptoms.⁵⁵ Published prospective data on the efficacy of IV iron in IBD is limited to iron sucrose.⁵⁶ Gasche and coworkers³⁸ randomly assigned 40 patients with IBD and anemia receiving 200 mg of IV iron sucrose to either EPO or placebo. All patients were either refractory or intolerant to oral iron. All medication was administered weekly, with EPO or placebo starting at Week 9 after iron treatment initiation. Fifteen of 20 patients with iron sucrose alone and 18 of 19 with iron sucrose and EPO responded with at least a 2-g increment in Hb or the achievement of a Hb of 120 g per L. The nonresponders in both groups all had normal iron stores based on pretreatment serum percent transferrin saturation and ferritin levels. Treatment was withheld at a Hb level of 140 g per L or greater. The mean increase in Hb was 3.3 g per dL in the IV iron only group and 4.9 g in the IV iron plus EPO group. Nine of the 40 patients received at least 1 unit of RBCs in the previous year. No treated

patients required transfusion. No significant toxicity was seen with iron sucrose administration. The authors concluded that IV iron sucrose is a viable tool for the treatment of anemia in patients with IBD. The addition of EPO increases the percentage of responders and decreases the time needed to reach target Hb levels.

In the experience of one author (MA), 26 patients with IBD and anemia with evidence of iron deficiency received a TDI of LMW ID. Twenty-three of 26 achieved a Hb level of at least 12 g per mL. The three nonresponders responded to the addition of EPO after developing evidence of anemia of chronic disease based on a low percentage of transferrin saturation, normal serum ferritin, and low endogenous

EPO level. Given the increased convenience, equal efficacy, safety, and reduced cost of this method of IV iron administration, one can conclude that it is the preferred method of iron replacement in this patient population.

A recent systematic review on anemia management in Crohn's disease found the reported prevalence of anemia as ranging from 6.2 to 73.7 percent and iron deficiency the most common underlying condition. The authors point out the lack of diagnostic criteria and treatment guidelines. Oral iron is effective only for short periods, however, as intolerance leads to discontinuation in up to 21 percent of cases. IV iron has been used in more than 250 patients with Crohn's disease and demonstrated to be safe, effective, and well tolerated.⁵⁷

Pregnancy

In 1996, the estimate by the WHO of worldwide cases of anemia of pregnancy was of the order of 20 million. Despite the efforts of programs to correct iron deficiency anemia by the administration of oral iron, the numbers in 2003 were the same, leading to the conclusion that oral iron supplementation programs were not working.

Anemia contributes to maternal mortality due to peripartum blood loss; is associated with neonatal growth retardation, prematurity, and infection; and can contribute to poor postpartum wound healing, depression, and impaired lactation. Even though oral iron is prescribed to most pregnant women, a not insignificant percentage arrives at term with a Hb level of less than 11 g per dL. A Hb level of 11 g per dL in the first and third trimesters, and 10.5 g per dL in the second, is the lowest acceptable level during pregnancy. A Hb level of less than 10.5 g per dL is considered anemia, and treatment is often recommended.

For the diagnosis of iron deficiency anemia in patient populations, a ferritin level of less than 30 µg per L is diagnostic.⁵⁸ Higher levels do not exclude iron deficiency if there is evidence of inflammation with an increase in the C-reactive protein. Oral iron can correct anemia but is often poorly tolerated. In such cases, or if a more rapid response is required, IV iron may be a more rational alternative.

Al-Momen and coworkers⁵⁹ reported the results of a prospective, open-label, parallel-group, controlled study of 52 pregnant women treated with IV iron sucrose and 59 with 300 mg of ferrous sulfate orally thrice daily. Gestational age was less than 32 weeks and Hb level was less than 9.0 g per dL in all women. The Hb level reached 12.85 g per dL in the IV Fe group and 11.14 g per dL in the oral group. The time to maximal response was 7 weeks in the IV Fe group and 14 weeks in the oral group ($p < 0.001$). No adverse effects were noted in the IV Fe group while 6 percent complained of gastrointestinal disturbances and 30 percent had poor compliance, in the oral group.

Bayoumeu and colleagues⁶⁰ randomly assigned 47 women with a Hb level 8 to 10 g per dL and a ferritin level of less than 50 µg per L at 6 months of pregnancy to IV Fe or oral iron. Both groups attained a Hb level of 11.0 g per dL by Day 30, but the IV Fe group had a higher ferritin on Day 30 and at delivery. A higher birth weight was noted in the infants of this group of women. Al and coworkers⁶¹ randomly assigned 90 women with gestational ages between 26 and 34 weeks with Hb levels of 8.0 to 10.5 g per dL and ferritin levels of less than 13 µg per L to IV Fe or oral iron. At 4 weeks, 20 percent in the oral and 60 percent in the IV Fe group reached the target Hb of level 11.0 g per dL ($p < 0.001$). At delivery, 62 percent in the oral and 96 percent in the IV group had a Hb level of 11.0 g per dL ($p < 0.001$).⁶¹

Several recently published studies in obstetric patients used iron sucrose as the iron preparation. Its use has been proven safe with a less than 0.5 percent incidence of minor reactions during pregnancy. It is given in doses of 200 mg over 30 minutes up to three times per week, depending on need.^{62,63} Iron sucrose has also been shown to synergize with EPO.⁶⁴ LMW ID as a source of IV iron can also be given safely as a TDI.⁶⁵ This method is more convenient, equally efficacious and safe, requires only one visit, and is less expensive than multiple injections of either iron sucrose or ferric gluconate. Experience with this method of iron administration has been described as early as 1973.⁶⁶ More than 2000 pregnant women received TDI with nearly 100 percent efficacy and negligible toxicity. No severe reactions were seen. Unfortunately, severe acute reactions reported in up to 1 percent of patients receiving formerly used HMW ID have limited the use of LMW ID in western medicine. With the advent of LMW ID, these acute reactions are rarely seen. In the experience of one author (MA), 28 pregnant

patients with documented iron deficiency were treated with TDIs of LMW ID without toxicity. The correction of Hb levels was complete in all patients. On the other hand, data to show that correction of anemia with IV iron reduces the incidence of allogeneic transfusions are limited.

At the department of obstetrics at the University Hospital of Zurich, more than 2000 patients intolerant or unresponsive to oral iron received IV iron sucrose in doses up to 200 mg and a total dose of 1600 mg. During this period, the percentage of women who received transfusions decreased from 20 percent in 1980 to 0.5 percent in 2005.⁶⁷

Developing countries are beginning to use parenteral iron more commonly in pregnancy. In a Pakistani Hospital where 50 percent of all pregnant women are iron deficient, the transfusion rate was 10 percent at term. Therapy with parenteral iron has resulted in a decrease in transfusions.⁶⁸

A Hb level of less than 10.0 g per dL 48 hours after delivery is considered clinically significant anemia in the postpartum period. Postpartum anemia is a frequent problem and is usually treated with transfusion or iron. The effect of oral iron is limited due to gastrointestinal disturbances and poor compliance. In a recent study by Bhandal and Russell,⁶⁹ 44 women with Hb levels of less than 9 g per dL and ferritin levels of less than 15 µg per L at 24 to 48 hours after delivery were randomly assigned to receive either two doses of 200 mg of IV iron sucrose on Days 2 and 4 or 200 mg of ferrous sulfate daily for 6 weeks. Of the 42 evaluable women, all but 1 had a lower segment cesarean section, with a median blood loss of 750 mL. The Hb level increase on Day 5 was 2.5 g per dL in the IV group and 0.7 g per dL in the oral group. On Day 14 the Hb level was 11.1 g per dL in the IV group and 9.0 g in the oral group. By Day 40, the groups were comparable. Also iron stores were restored only in the IV group. Results from other studies are similar.⁶² Table 4 summarizes existing data in studies with IV iron in pregnancy and the puerperium.

There are no randomized studies showing a beneficial effect of IV iron on transfusion requirements. A study by Broche and coworkers,⁷³ however, is indicative of the beneficial effect. The need for transfusion after delivery was compared in two groups of women, one before and one after IV iron became available. Of 103 women in the first group, 15 received transfusions compared to 5 of 112 in the second group. Twenty-three women in the latter group would have received transfusions, based on their Hb levels, if IV iron were not available.

Based on the safety and efficacy profiles of most parenteral iron preparations, a shift in the treatment paradigm for anemia of pregnancy from oral to IV iron appears indicated. Reasons for this paradigm shift include: 1) maternal anemia is associated with poor neonatal

TABLE 4. Effectiveness of iron sucrose in increasing Hb in pregnancy and the puerperium*

	Al-Momen, 1995 ⁵⁹	Bayoumeu, 2002 ⁶⁰	Polatti, 1983 ⁷⁰	Chamate, 1972 ⁷¹	Gravier, 1999 ⁶³	Breymann, 1991-2004 ⁷²	Bhandal, 2006 ⁶⁹
Period	Pregnancy	Pregnancy	Pregnancy (>24 weeks)	Pregnancy and puerperium	Puerperium	Pregnancy and puerperium	Puerperium
Number of patients	59	25	30	60	60	>1000	44
Dose	200 mg/day	200 mg twice a week	100 mg/day for 14 days	100-200 mg 15-30 days	200 mg 2-3 times	100-200 mg 2-4 times/week	200 mg 2 times
Effectiveness in pregnancy	Better (vs. oral iron)	Hb increase 1.5 g/dL	2.2 g/dL	Hb increase 3.8 g/dL 24 days	Hb increase 3.8 g/dL (vs. oral iron)	Hb increase 1.5 g/dL (25 days) Pregnancy: 1.5 g/dL (25 days)	Hb increase 2.5 g/dL on Day 5 vs. 0.7 g/dL in oral group
In the puerperium							
Tolerance	Good 30% adverse effects with oral Fe	Good	Good	Good	Good	Puerperium: max. 3.2 g/dL (14 days) Side effect rate <0.5%	Good 23% adverse effects with oral Fe

* Modified from Huch and Breymann.⁶⁷

outcomes; 2) oral iron is poorly absorbed in cases where there is a concomitant inflammatory element or bowel disease; 3) compliance with oral iron intake is often poor due to gastrointestinal toxicity; 4) safe preparations for IV iron administration are now available; and 5) women presenting in the third trimester with persistent anemia (Hb < 11.0) will not succeed in correcting the anemia with oral iron before delivery time.

Surgery

Although exact figures are difficult to find, surgery uses approximately 50 percent of the available blood supply in the developed world. Blood conservation efforts, however, with the emphasis on transfusion triggers in some countries have brought this percentage to below 40 percent.⁷⁴ Even so, a significant proportion of the blood collected is used for surgery and further efforts at conservation are warranted in view of the continuously increasing blood shortages. We will review the evidence that a new paradigm optimizing integration of IV iron with ESA therapy may be warranted.

Blood conservation in joint replacement surgery

It has been shown that a third of patients presenting for elective orthopedic surgery have Hb levels of less than 13 g per dL.⁷⁵ The cause of the anemia is often iron deficiency. Recent studies have pointed out the significance of preoperative anemia as a risk factor predisposing to preoperative allogeneic blood transfusion. Rosencher and coworkers⁷⁶ reported on a prospective study carried out in 225 hospitals with 3996 orthopedic procedures, during which 69 percent of patients received transfusions. The authors noted that the probability of allogeneic transfusion decreased with increasing baseline Hb. Querin and Stahl⁷⁷ studied transfusion requirements in 162 consecutive patients undergoing hip or knee replacement for osteoarthritis. Twenty-five percent received transfusions of a mean of 2 units of RBCs per patient (range, 1-4 units). Preoperative Hb for those receiving 1, 2, or 4 units was 13.4, 13.1, and 11.1, respectively, decreasing to 10.5, 10.1, and 6.6 g postoperatively. Multivariate analysis concluded that preoperative Hb was the only variable to independently predict for blood transfusion. Further, in an audit of nearly 8000 patients undergoing elective orthopedic surgery in the United States, one-third were found to be anemic before surgery (Hb < 13 g/dL for men and 12 g/dL for women). The preoperative Hb level was the primary determinant for subsequent allogeneic blood transfusion.⁷⁸

Iron deficiency contributes to a significant degree to the anemia of patients presenting for surgery. Iron deficiency can be corrected with the administration of either oral or IV iron. The major clinical difference seen between the two routes of administration is the speed with which

the Hb increases (7-14 days vs. 30-40 days) and the replenishment of iron stores. In patients scheduled for surgery, rapid correction of the anemia could expedite the procedure and avoid delays, especially in nonelective surgery.⁷⁹ Elderly patients with subcapital hip fracture were given 600 mg of iron sucrose IV plus EPO for 2 days and were operated on the third day after admission. Transfusion rate was 15 percent compared to 36.8 percent in a control group, and the transfusion index was 0.26 units versus 0.77 units per patient.

Garcia-Erce and colleagues,⁸⁰ in Spain, treated 81 hip fracture patients with IV iron sucrose administered as three 200-mg boluses over 48 hours and 40,000 U of EPO SC. The patients were compared to 41 similar patients admitted to a different surgical unit during the same period. Of treated patients, 24 percent required transfusion compared to 70 percent in the controls ($p = 0.001$) and postoperative transfusion was given to 19 percent versus 53 percent in controls. The median number of units transfused was 0 versus 2 ($p = 0.0001$). No adverse events and no differences in 30-day mortality were noted but infections were reduced in the treatment arm ($p = 0.016$).

Garcia-Erce and colleagues⁸¹ also showed a reduction in transfusion requirements in patients with knee replacement surgery. Iron sucrose, administered as two 200-mg boluses over 48 hours, was given to 129 patients. EPO was added in 19 patients with admission Hb levels of less than 13.0 g per dL. Only 7 patients (5%) required transfusion, and at Postoperative Day 30 only 15 percent had anemia.

Munoz and colleagues⁸² compared transfusion requirements in 24 total hip replacement patients receiving 300 mg of IV iron sucrose postoperatively, to 22 total hip replacement patients who did not. The transfusion rate was lower (46% vs. 73%) and the transfusion index was lower (0.96 units/patient vs. 1.68 units/patient) in the treatment arm. No adverse events were noted.

At the institution of one author (DP), surgeons were offered a program to treat patients with anemia with IV Fe and EPO preoperatively. Thirty-five patients were treated 4 weeks before a knee or hip replacement operation with a TDI of 1000 mg of LMW ID and weekly EPO for 2 or 3 weeks. Preoperative Hb levels ranged from 10.0 to 12.5 g per dL. EPO was held for Hb levels of more than 13 g per dL. These 35 patients were matched against 35 similar patients not using EPO and IV Fe. Eighty percent fewer patients and 80 percent fewer RBC units were transfused in the patients receiving EPO and IV Fe.

Large randomized controlled trials are still lacking but the observational studies carried out to date suggest a significant role of IV iron in blood conservation in orthopedic surgery. Both preoperative and postoperative iron administration are likely to reduce the need for perioperative transfusions in this group of patients.

Cardiac surgery

Most studies in cardiac surgery used postoperative IV iron administration and do not show differences in transfusion requirements, although iron stores are significantly increased by IV iron.⁸³ A recently reported review of all published evidence, related to blood conservation during cardiac operations, identified the risk factors associated with postoperative blood transfusion. Preoperative RBC volume was one of the variables predicting for blood transfusion. Based on available evidence, blood conservation techniques were recommended, including pharmacologic interventions such as ESAs and IV iron, that increase preoperative RBC volume. Parenteral iron preparations may be attractive candidates for decreasing RBC transfusions. The combination of EPO with IV iron given preoperatively should be studied in future controlled trials.⁸⁴

Colorectal cancer surgery

There are estimates that 70 percent of colon cancer patients have anemia at diagnosis. The most common cause is iron deficiency secondary to chronic blood loss. Correcting the iron deficit preoperatively has been shown to reduce allogeneic blood transfusion.

Braga and colleagues⁸⁵ studied 151 patients with gastric or colorectal cancer scheduled for potentially curative surgery. The primary endpoint was the ability to donate 1 or 2 autologous units. A Hct level of more than 34 percent was required for donation. A secondary endpoint was number of allogeneic units transfused based on a Hct level of less than 25 percent or clinically significant anemia. Eligibility included a Hct level of less than 34 percent and documented iron deficiency based on serum iron, total iron-binding capacity, percent transferrin saturation, and serum ferritin levels. Patients were divided into two groups: 200 mg of IV iron sucrose daily for 12 days or 300 U per kg recombinant EPO on Day 1 with 200 mg IV iron sucrose. One-hundred units per kg SC EPO was given on Days 4, 8, and 12 along with 200 mg of IV iron sucrose. The control group consisted of 11 similar patients with neither anemia nor iron deficiency. No patients in the iron-alone group could donate blood for autologous transfusion while 8 patients in the EPO-plus-iron group donated at least 1 unit. Further, 4 patients in the iron-only group received at least 1 allogeneic unit contrasted with none in the EPO-plus-iron group. The authors concluded the combination of IV iron sucrose and EPO could potentially reduce perioperative allogeneic blood transfusion.

In another study in 1999, Braga⁸⁶ treated 20 iron-deficient patients with gastrointestinal cancer with either 100 or 50 U per kg SC EPO for 4 days. Patients in both groups received IV ferric gluconate daily for 15 days. Hb increase was higher in the 100 U per kg arm (22.3 g/L vs. 14.1 g/L). Although autologous donation was greater in

the 100 U per kg arm no difference in allogeneic transfusion was noted. No conclusion could be made about the benefit of IV ferric gluconate.

Finally, Kosmadakis and associates⁸⁷ treated 75 patients with nonmetastatic gastrointestinal malignancies preoperatively. Patients received either 300 U per kg EPO daily for 14 days or placebo for the same period. All patients received 100 mg of IV iron sucrose daily. Patients in the treatment arm had significantly fewer allogeneic transfusions (29% vs. 59.3%) and significantly fewer post-operative complications (12.9% vs. 40.6%).

Conflicting data exist with the combination of oral iron and EPO. Rau and coworkers⁸⁸ treated 57 patients with 200 U per kg EPO or placebo for 11 days. All patients received oral ferrous sulfate daily. Eighty-three autologous units were donated in the treatment arm versus 59 in the placebo arm. No difference in allogeneic transfusions between the two groups was noted, however. In contrast Kettelhack and coworkers⁸⁹ treated 102 patients with 20,000 U EPO SC or placebo plus oral ferrous sulfate for at least 10 days and showed no difference in either autologous donation or allogeneic transfusion between the groups.

These data were reviewed by Munoz and colleagues⁹⁰ who concluded that IV iron but not oral iron synergizes with EPO in increasing autologous blood donation and reducing allogeneic transfusion in the perioperative period. They further concluded IV iron can be used safely in colorectal cancer patients to correct preoperative iron deficiency anemia.

CONCLUSIONS

In an effort to reduce allogeneic RBC usage, transfusion alternatives have been explored in recent years.⁷¹ Emerging evidence in developed countries suggests that ESAs and IV iron result in decreased transfusion rates. There are now numerous publications supporting an essential role for IV iron in the management of anemia, particularly as an adjunct to ESA therapy. Furthermore, the use of IV iron as an adjunct to ESA therapy in nephrology has resulted in decreased numbers of transfusions and decreased ESA exposure in dialysis patients.

We believe that the information supplied in this review supports the need for larger controlled trials with IV iron to further decrease the need for RBC transfusions in settings where transfusions are likely.

REFERENCES

1. Goodnough LT, Strasburg D, Riddell J, Verbrugge D, Wish J. Has recombinant human erythropoietin therapy minimized red-cell transfusions in hemodialysis patients? *Clin Nephrol* 1994;41:303-7.
2. Eschbach JW. Current concepts of anemia management in chronic renal failure: impact of NKF-DOQI. *Semin Nephrol* 2000;20:320-9.
3. Eschbach JW, Adamson JW. Iron overload in renal failure patients: changes since the introduction of erythropoietin therapy. *Kidney Int Suppl* 1999;69:S35-S43.
4. Goodnough LT, Skikne B, Brugnara C. Erythropoietin, iron, and erythropoiesis. *Blood* 2000;96:823-33.
5. Chandler G, Harchowal J, Macdougall IC. Intravenous iron sucrose: establishing a safe dose. *Am J Kidney Dis* 2001;38:988-91.
6. Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmen J. Update on adverse drug events associated with parenteral iron. *Nephrol Dial Transplant* 2006;21:378-82.
7. Mamula P, Piccoli DA, Peck SN, Markowitz JE, Baldassano RN. Total dose intravenous infusion of iron dextran for iron-deficiency anemia in children with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2002;34:286-90.
8. Fishbane S, Frei GL, Maesaka J. Reduction in recombinant human erythropoietin doses by the use of chronic intravenous iron supplementation. *Am J Kidney Dis* 1995;26:41-6.
9. Macdougall IC, Roche A. Administration of intravenous iron sucrose as a 2-minute push to CKD patients: a prospective evaluation of 2,297 injections. *Am J Kidney Dis* 2005;46:283-9.
10. Critchley J, Dundar Y. Adverse events associated with intravenous iron infusion (low-molecular-weight iron dextran and iron sucrose): a systematic review. *Transfus Altern Transfus Med* 2007;9:8-36.
11. Moniem KA, Bhandari SU. Tolerability and efficacy of parenteral iron therapy in hemodialysis patients, a comparison of preparations. *Transfus Altern Transfus Med* 2007;9:37-42.
12. Sav T, Tokgoz B, Sipahioglu MH, Deveci M, Sari I, Oymak O, Utas C. Is there a difference between the allergic potencies of the iron sucrose and low molecular weight iron dextran? *Ren Fail* 2007;29:423-6.
13. Finch CA. Erythropoiesis, erythropoietin, and iron. *Blood* 1982;60:1241-6.
14. Crosby WH. The metabolism of hemoglobin and bile pigment in hemolytic disease. *Am J Med* 1955;18:112-22.
15. Hillman RS, Henderson PA. Control of marrow production by the level of iron supply. *J Clin Invest* 1969;48:454-60.
16. Crosby WH. Treatment of haemochromatosis by energetic phlebotomy; one patient's response to the letting of 55 litres of blood in 11 months. *Br J Haematol* 1958;4:82-8.
17. Coleman DH, Stevens AR Jr, Dodge HT, Finch CA. Rate of blood regeneration after blood loss. *AMA Arch Intern Med* 1953;92:341-9.
18. Finch CA, Huebers H. Perspectives in iron metabolism. *N Engl J Med* 1982;306:1520-8.
19. Goodnough LT, Price TH, Friedman KD, Johnston M, Ciavarella D, Khan N, Sacher R, Vogler WR, Wissel M, Abels RI. A phase III trial of recombinant human erythropoietin therapy in nonanemic orthopedic patients subjected to

- aggressive removal of blood for autologous use: dose, response, toxicity, and efficacy. *Transfusion* 1994;34:66-71.
20. Goodnough LT, Marcus RE. Erythropoiesis in patients stimulated with erythropoietin: the relevance of storage iron. *Vox Sang* 1998;75:128-33.
 21. Weisbach V, Skoda P, Rippel R, Lauer G, Glaser A, Zingsem J, Zimmermann R, Eckstein R. Oral or intravenous iron as an adjuvant to autologous blood donation in elective surgery: a randomized, controlled study. *Transfusion* 1999;39:465-72.
 22. Goodnough LT, Rudnick S, Price TH, Ballas SK, Collins ML, Crowley JP, Kosmin M, Kruskall MS, Lenes BA, Menitove JE, Silberstein LE, Smith KJ, Wallas CH, Abels R, von Tress M. Increased preoperative collection of autologous blood with recombinant human erythropoietin therapy. *N Engl J Med* 1989;321:1163-8.
 23. Goodnough LT, Price TH, Rudnick S, Soegiarso RW. Preoperative red cell production in patients undergoing aggressive autologous blood phlebotomy with and without erythropoietin therapy. *Transfusion* 1992;32:441-5.
 24. Biesma DH, Kraaijenhagen RJ, Poortman J, Marx JJ, van de WA. The effect of oral iron supplementation on erythropoiesis in autologous blood donors. *Transfusion* 1992;32:162-5.
 25. Kasper SM, Lazansky H, Stark C, Klimek M, Laubinger R, Borner U. Efficacy of oral iron supplementation is not enhanced by additional intravenous iron during autologous blood donation. *Transfusion* 1998;38:764-70.
 26. Skikne BS, Cook JD. Effect of enhanced erythropoiesis on iron absorption. *J Lab Clin Med* 1992;120:746-51.
 27. Heiss MM, Tarabichi A, Delanoff C, Allgayer H, Jauch KW, Hernandez-Richter T, Mempel W, Beck KG, Schildberg FW, Messmer K. Perisurgical erythropoietin application in anemic patients with colorectal cancer: a double-blind randomized study. *Surgery* 1996;119:523-7.
 28. Brugnara C, Chambers LA, Malynn E, Goldberg MA, Kruskall MS. Red blood cell regeneration induced by subcutaneous recombinant erythropoietin: iron-deficient erythropoiesis in iron-replete subjects. *Blood* 1993;81:956-64.
 29. Biesma DH, Beguin Y, Kraaijenhagen RJ, Marx JJ. Erythropoietic activity and iron metabolism in autologous blood donors during recombinant human erythropoietin therapy. *Eur J Clin Invest* 1994;24:426-32.
 30. Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. *N Engl J Med* 1987;316:73-8.
 31. Sadjadi SA. Reduction in recombinant human erythropoietin doses by the use of chronic intravenous iron supplementation. *Am J Kidney Dis* 1995;26:1000-1.
 32. Means RT Jr. Commentary: an anemia of chronic disease, after all? *J Invest Med* 1999;47:203.
 33. Tarnag DC, Huang TP, Chen TW, Yang WC. Erythropoietin hyporesponsiveness: from iron deficiency to iron overload. *Kidney Int Suppl* 1999;69:S107-S118.
 34. Wingard RL, Parker RA, Ismail N, Hakim RM. Efficacy of oral iron therapy in patients receiving recombinant human erythropoietin. *Am J Kidney Dis* 1995;25:433-9.
 35. Adamson JW, Eschbach JW. Erythropoietin for end-stage renal disease. *N Engl J Med* 1998;339:625-7.
 36. Silverberg DS, Iaina A, Peer G, Kaplan E, Levi BA, Frank N, Steinbruch S, Blum M. Intravenous iron supplementation for the treatment of the anemia of moderate to severe chronic renal failure patients not receiving dialysis. *Am J Kidney Dis* 1996;27:234-8.
 37. Taylor JE, Peat N, Porter C, Morgan AG. Regular low-dose intravenous iron therapy improves response to erythropoietin in haemodialysis patients. *Nephrol Dial Transplant* 1996;11:1079-83.
 38. Gasche C, Dejaco C, Waldhoer T, Tillinger W, Reinisch W, Fueger GF, Gangl A, Lochs H. Intravenous iron and erythropoietin for anemia associated with Crohn disease. A randomized, controlled trial. *Ann Intern Med* 1997;126:782-7.
 39. Schreiber S, Howaldt S, Schnoor M, Nikolaus S, Bauditz J, Gasche C, Lochs H, Raedler A. Recombinant erythropoietin for the treatment of anemia in inflammatory bowel disease. *N Engl J Med* 1996;334:619-23.
 40. Weiss G, Houston T, Kastner S, Johrer K, Grunewald K, Brock JH. Regulation of cellular iron metabolism by erythropoietin: activation of iron-regulatory protein and upregulation of transferrin receptor expression in erythroid cells. *Blood* 1997;89:680-7.
 41. KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. *Am J Kidney Dis* 2006;47(5 Suppl 3):S11-45.
 42. Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med* 2005;352:1011-23.
 43. Kalantar-Zadeh K, Regidor DL, Mcallister CJ, Michael B, Warnock DG. Time-dependent associations between iron and mortality in hemodialysis patients. *J Am Soc Nephrol* 2005;16:3070-80.
 44. Hamstra RD, Block MH. Erythropoiesis in response to blood loss in man. *J Appl Physiol* 1969;27:503-7.
 45. Beutler E. The utilization of saccharated Fe⁵⁹ oxide in red cell formation. *J Lab Clin Med* 1958;51:415-9.
 46. Wood JK, Milner PF, Pathak UN. The metabolism of iron-dextran given as a total-dose infusion to iron deficient Jamaican subjects. *Br J Haematol* 1968;14:119-29.
 47. Beamish MR, Davies AG, Eakins JD, Jacobs A, Trevett D. The measurement of reticuloendothelial iron release using iron-dextran. *Br J Haematol* 1971;21:617-22.
 48. Auerbach M, Ballard H, Trout JR, McIlwain M, Ackerman A, Bahrain H, Balan S, Barker L, Rana J. Intravenous iron optimizes the response to recombinant human erythropoietin in cancer patients with chemotherapy-related anemia: a multicenter, open-label, randomized trial. *J Clin Oncol* 2004;22:1301-7.

49. Henry DH, Dahl NV, Auerbach M, Tchekmedyian S, Laufman LR. Intravenous ferric gluconate significantly improves response to epoetin alfa versus oral iron or no iron in anemic patients with cancer receiving chemotherapy. *Oncologist* 2007;12:231-42.
50. Hedenus M, Birgegard G, Nasman P, Ahlberg L, Karlsson T, Lauri B, Lundin J, Larfars G, Osterborg A. Addition of intravenous iron to epoetin beta increases hemoglobin response and decreases epoetin dose requirement in anemic patients with lymphoproliferative malignancies: a randomized multicenter study. *Leukemia* 2007;21:627-32.
51. Pinter T, Mossman T, Suto J, Vansteenkiste J. Effects of intravenous (IV) iron supplementation on responses to every-3-week (Q3W) darbepoetin alfa (DA) by baseline hemoglobin in patients (pts) with chemotherapy-induced anemia (CIA) [abstract]. *J Clin Oncol* 2007 ASCO Annual Meeting Proceedings 25[18S], 9106. 2007.
52. Kim YT, Kim SW, Yoon BS, Cho HJ, Nahm EJ, Kim SH, Kim JH, Kim JW. Effect of intravenously administered iron sucrose on the prevention of anemia in the cervical cancer patients treated with concurrent chemoradiotherapy. *Gynecol Oncol* 2007;105:199-204.
53. Macdonald TT, Hutchings P, Choy MY, Murch S, Cooke A. Tumour necrosis factor-alpha and interferon-gamma production measured at the single cell level in normal and inflamed human intestine. *Clin Exp Immunol* 1990;81:301-5.
54. Mahida YR, Wu K, Jewell DP. Enhanced production of interleukin 1-beta by mononuclear cells isolated from mucosa with active ulcerative colitis of Crohn's disease. *Gut* 1989;30:835-8.
55. de Silva AD, Tsironi E, Feakins RM, Rampton DS. Efficacy and tolerability of oral iron therapy in inflammatory bowel disease: a prospective, comparative trial. *Aliment Pharmacol Ther* 2005;22:1097-105.
56. Gasche C, Kulnigg S. Intravenous iron in inflammatory bowel disease. *Semin Hematol* 2006;43(4 Suppl 6):S18-22.
57. Kulnigg S, Gasche C. Systematic review: managing anaemia in Crohn's disease. *Aliment Pharmacol Ther* 2006;24:1507-23.
58. Mast AE, Blinder MA, Gronowski AM, Chumley C, Scott MG. Clinical utility of the soluble transferrin receptor and comparison with serum ferritin in several populations. *Clin Chem* 1998;44:45-51.
59. al-Momen AK, al-Meshari A, al-Nuaim L, Saddique A, Abotalib Z, Khashoggi T, Abbas M. Intravenous iron sucrose complex in the treatment of iron deficiency anemia during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 1996;69:121-4.
60. Bayoumeu F, Subiran-Buisset C, Baka NE, Legagneur H, Monnier-Barbarino P, Laxenaire MC. Iron therapy in iron deficiency anemia in pregnancy: intravenous route versus oral route. *Am J Obstet Gynecol* 2002;186:518-22.
61. Al RA, Unlubilgin E, Kandemir O, Yalvac S, Cakir L, Haberal A. Intravenous versus oral iron for treatment of anemia in pregnancy: a randomized trial. *Obstet Gynecol* 2005;106:1335-40.
62. Dede A, Uygur D, Yilmaz B, Mungan T, Ugur M. Intravenous iron sucrose complex vs. oral ferrous sulfate for postpartum iron deficiency anemia. *Int J Gynaecol Obstet* 2005;90:238-9.
63. Gravier A, Descargues G, Marpeau L. [How to avoid transfusion in the post-partum period: importance of an intravenous iron supplement]. *J Gynecol Obstet Biol Reprod (Paris)* 1999;28:77-8.
64. Zimmermann R, Breyman C, Huch R, Huch A. rHuEPO in the treatment of postpartum anemia: subcutaneous versus intravenous administration. *Clin Invest* 1994;72(6 Suppl):S25-S30.
65. Auerbach M, Ballard H, Glaspy J. Clinical update: intravenous iron for anaemia. *Lancet* 2007;369:1502-4.
66. Kanakaraddi VP, Hoskatti CG, Nadig VS, Patil CK, Maiya M. Comparative therapeutic study of T.D.I. and I.M. injections of iron dextran complex in anaemia. *J Assoc Physicians India* 1973;21:849-53.
67. Huch R, Breyman C. Anaemia in pregnancy and the puerperium. 2nd ed. Bremen: UNI-MED Science Verlag; 2006.
68. Wali A, Mushtaq A, Nilofer. Comparative study—efficacy, safety and compliance of intravenous iron sucrose and intramuscular iron sorbitol in iron deficiency anemia of pregnancy. *J Pak Med Assoc* 2002;52:392-5.
69. Bhandal N, Russell R. Intravenous versus oral iron therapy for postpartum anaemia. *BJOG* 2006;113:1248-52.
70. Polatti F, Mandelli B. Treatment with intravenous iron of hypochromic anemia in pregnancy [translation]. *Bollettino della Societa Medico-Chirurgica di Pavia* 1983;97:13-6.
71. Chamate E. Treatment of iron deficiency anemia in pregnancy and the immediate puerperium and other ferro-penic conditions with saccharate iron administered intravenously in fractionated doses. XIVth International Congress of Hematology; 1972; Sao Paulo, Brazil.
72. Breyman C. Iron supplementation during pregnancy. *Fetal and Maternal Medicine Reviews* 2002;13(1):1-29.
73. Broche DE, Gay C, Armand-Branger S, Grangeasse L, Terzibachian JJ. [Acute postpartum anaemia. Clinical practice and interest of intravenous iron]. *Gynecol Obstet Fertil* 2004;32:613-9.
74. Cobain TJ, Vamvakas EC, Wells A, Titlestad K. A survey of the demographics of blood use. *Transfus Med* 2007;17:1-15.
75. Bernstein LH, Coles M, Granata A. The Bridgeport Hospital experience with autologous transfusion in orthopedic surgery. *Orthopedics* 1997;20:677-80.
76. Rosencher N, Kerckamp HE, Macheras G, Munuera LM, Menichella G, Barton DM, Cremers S, Abraham IL. Orthopedic Surgery Transfusion Hemoglobin European Overview (OSTHEO) study: blood management in elective knee and hip arthroplasty in Europe. *Transfusion* 2003;43:459-69.

77. Querin JJ, Stahl LD. 12 simple sensible steps for successful blood transfusions. *Nursing* 1990;20:68-81.
78. Bierbaum BE, Callaghan JJ, Galante JO, Rubash HE, Tooms RE, Welch RB. An analysis of blood management in patients having a total hip or knee arthroplasty. *J Bone Joint Surg Am* 1999;81:2-10.
79. Cuenca J, Garcia-Erce JA, Martinez AA, Solano VM, Molina J, Munoz M. Role of parenteral iron in the management of anaemia in the elderly patient undergoing displaced sub-capital hip fracture repair: preliminary data. *Arch Orthop Trauma Surg* 2005;125:342-7.
80. Garcia-Erce JA, Cuenca J, Munoz M, Izuel M, Martinez AA, Herrera A, Solano VM, Martinez F. Perioperative stimulation of erythropoiesis with intravenous iron and erythropoietin reduces transfusion requirements in patients with hip fracture. A prospective observational study. *Vox Sang* 2005;88:235-43.
81. Garcia-Erce JA, Cuenca J, Martinez F, Cardona R, Perez-Serrano L, Munoz M. Perioperative intravenous iron preserves iron stores and may hasten the recovery from post-operative anaemia after knee replacement surgery. *Transfus Med* 2006;16:335-41.
82. Munoz M, Naveira E, Seara J, Palmer JH, Cuenca J, Garcia-Erce JA. Role of parenteral iron in transfusion requirements after total hip replacement. A pilot study. *Transfus Med* 2006;16:137-42.
83. Madi-Jebara SN, Sleilaty GS, Achouh PE, Yazigi AG, Haddad FA, Hayek GM, Antakly MC, Jebara VA. Postoperative intravenous iron used alone or in combination with low-dose erythropoietin is not effective for correction of anemia after cardiac surgery. *J Cardiothorac Vasc Anesth* 2004;18:59-63.
84. Ferraris VA, Ferraris SP, Saha SP, Hessel EA, Haan CK, Royston BD, Bridges CR, Higgins RS, Despotis G, Brown JR, Spiess BD, Shore-Lesserson L, Stafford-Smith M, Mazer CD, Bennett-Guerrero E, Hill SE, Body S. Perioperative blood transfusion and blood conservation in cardiac surgery: the Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists clinical practice guideline. *Ann Thorac Surg* 2007;83(5 Suppl):S27-S86.
85. Braga M, Gianotti L, Vignali A, Gentilini O, Servida P, Di Bordignon CC, V. Evaluation of recombinant human erythropoietin to facilitate autologous blood donation before surgery in anaemic patients with cancer of the gastrointestinal tract. *Br J Surg* 1995;82:1637-40.
86. Braga M. Randomized multicentre trial of the influence of recombinant human erythropoietin on intraoperative and postoperative transfusion need in anaemic patients undergoing right hemicolectomy for carcinoma. *Br J Surg* 1998;85:1306-7.
87. Kosmadakis N, Messaris E, Maris A, Katsaragakis S, Leandros E, Konstadoulakis MM, Androulakis G. Perioperative erythropoietin administration in patients with gastrointestinal tract cancer: prospective randomized double-blind study. *Ann Surg* 2003;237:417-21.
88. Rau B, Schlag PM, Willeke F, Herfarth C, Stephan P, Franke W. Increased autologous blood donation in rectal cancer by recombinant human erythropoietin (rhEPO). *Eur J Cancer* 1998;34:992-8.
89. Kettelhack C, Hones C, Messinger D, Schlag PM. Randomized multicentre trial of the influence of recombinant human erythropoietin on intraoperative and postoperative transfusion need in anaemic patients undergoing right hemicolectomy for carcinoma. *Br J Surg* 1998;85:63-7.
90. Munoz M, Campos A, Garcia-Erce JA. Intravenous iron in colorectal surgery. *Semin Hematol* 2006;43(4 Suppl 6):S36-8. 