Review
Iron supplementation in the intensive care unit: when, how much, and by what route?
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Abstract

Derangements of iron metabolism may be present in critically ill patients who develop anemia during a stay in the intensive care unit. Iron supplementation may be appropriate, especially if an underlying nutritional disorder is present. It may be even more critical to replace iron when erythropoietin therapy is used because of the consumption of iron stores that occurs during heme synthesis. Iron therapy is not without risks, and controversy persists regarding the potential for iron overload and infections. Clinical trials that define the optimal dose, route, and timing of iron administration in critically ill patients are lacking. However, studies of iron supplementation in chronic kidney disease, pregnancy, and anemia of prematurity may provide some guidance about approaches to treatment. Clinical evidence and limitations that can assist clinicians in managing iron therapy in the intensive care unit are presented.

Keywords anemia, critical illness, erythropoietin, intensive care, iron supplementation

The development of anemia during critical illness is hematologically similar to the anemia of chronic disease/inflammation (ACD), except that the onset is generally acute. Blunting of endogenous erythropoietin production, mediated through the action of inflammatory cytokines, is thought to be the most important cause of this common syndrome [1]. Because low serum iron and elevated serum ferritin levels are also clinical features of ACD, investigators once believed that altered iron metabolism was responsible for this condition. This early hypothesis has merit because iron utilization plays a key role in anemia and can affect the response to endogenous or exogenously administered erythropoietin [2]. Nutritional deficiencies (folic acid, vitamin B_{12}, and iron) can possibly contribute to the etiology of early anemia in the intensive care unit (ICU). In a study conducted by Rodriguez and colleagues [3], 13% of critically ill patients were identified as having potentially correctable nutritional abnormalities, with 9% having laboratory values consistent with iron deficiency (i.e. iron/total iron binding capacity <15%, with a ferritin level <100 ng/ml).

The relevant iron parameters that characterize anemia in chronic disease or critical illness, as compared with those in iron deficiency anemia and normal individuals, are summarized in Table 1. In ACD-type disorders, absorption of iron is actually stimulated and there are adequate stores of iron in the bone marrow. Stored iron may not be effectively utilized, however. Release of iron from macrophages in the reticuloendothelial system is defective, ferritin concentrations are increased, and serum transferrin levels are normal, rather than elevated [4]. This 'functional iron deficiency', when diagnosed by cytometry, is present in 35% of patients on admission to the ICU [5]. Disturbed iron metabolism from enhanced immune activation has also been documented in surgical ICU patients [6] and in patients with multiple organ dysfunction syndrome [7].

Regardless of whether iron supply is limited as a result of nutritional or functional factors, when the iron available to developing erythroblasts is insufficient to meet the demands of heme synthesis, maturing red cells may contain suboptimal hemoglobin [8]. To prevent the synthesis of hypochromic red cells, administration of iron in conjunction with erythropoietin therapy should be considered in the critically ill patient, but when, how much, and by what route should iron be given?

ACD = anemia of chronic disease/inflammation; CKD = chronic kidney disease; ICU = intensive care unit; TPN = total parenteral nutrition.

Table 1

Iron parameters characteristic of anemia in chronic disease or critical illness

Parameter (units)	ACD	Iron deficiency	Normal
Serum ferritin (μg/l)	>50	<50	15–300
Serum iron (μg/dl)	<30	<30	50–150
TIBC (μmol/l)	Normal	Elevated	47–70
% Saturation	>20%	<15%	16–40%
RBC zinc protoporphyrin (μg/dl)	<1.24	>1.24	<70
Erythropoietin level (mU/ml)	Normal (inappropriately low)	Elevated	4–28
STfR (mg/l)	Normal	Elevated	2.8–8.5
TfR-F index	Low (<1)	High (>4)	1–4

ACD, anemia of chronic disease/inflammation; % saturation = (iron/total iron binding capacity) × 100; STfR, serum transferrin receptor; TfR-F index, sTfR/ferritin. Values derived from Rodriguez and coworkers [3], Hudson and Comstock [22], Miller and coworkers [49], and Punnonen and coworkers [50].

In a recent review of best practice and research in clinical hematology [8], it was noted that iron uptake into developing erythroblasts begins at an early stage and is completed before late erythroblastosis. Precisely when to administer iron with erythropoietin therapy has not been systematically investigated. In a study examining health-related quality of life in rheumatoid arthritis patients receiving treatment with erythropoietin, all 28 patients who completed the study responded to treatment with erythropoietin [9]. However, 82% developed functional iron deficiency and were well supported with a mean absolute dose of 710 ± 560 mg intravenous iron sucrose. In that 12-week study, iron support was not initiated until the deficiency was noted (after a mean of 4.5 weeks of treatment). In other small studies conducted in elderly or critically ill patients, iron support was initiated concurrently with erythropoietin therapy [10]. Of note, daily intravenous iron therapy alone or in combination with folic acid did not result in a significant increase in reticulocyte count among critically ill patients. The timing of iron administration with erythropoietin clearly warrants further study in larger populations.

Administration of iron in critically ill patients is regarded by some as undesirable because free iron may promote bacterial growth and have detrimental effects in patients who are immunosuppressed or susceptible to infection and sepsis [11,12]. Iron overload is most commonly associated with chronic transfusions in patients with refractory anemia [4] because there is no physiological mechanism to excrete iron; chelation therapy is generally required to remove it. This constitutes an important reason for careful consideration of iron dosing and route of administration in the critically ill patient. When given by the parenteral route, iron has been implicated in increased susceptibility to bacterial infection [11–14]. This effect is believed to be related to the influence of iron on the immune system [15]. The cytokine-mediated defect in iron release from macrophages in humans is said to have evolved as a primitive mechanism of defense against microbial pathogens to limit their access to iron [12]. Studies on the effects of iron on host defense suggest that increased iron availability, seen with increased transferrin saturation, leads to less efficient bacterial killing of various pathogens by plasma [16]. Elevated serum ferritin level is a risk factor for bacterial infection in hemodialysis patients [17]. This finding was corroborated by Hoen and colleagues at serum ferritin levels greater than 500 ng/ml [18], but this was later refuted when they found no association between serum ferritin and infection in a large prospective trial [19]. In these studies it is not clear whether high ferritin levels are associated with iron overload or an acute phase reaction, or both. In light of this rather limited evidence, some advocate that these observations should not limit iron utilization in patients with chronic kidney disease (CKD) [20]. Additional studies in critically ill patients are needed to determine whether there is a clinically relevant link between infection, septicemia, and iron availability.

Studies of iron supplementation are plentiful in the CKD literature, in pregnancy, and in the pediatric setting. However, even in the well studied CKD population, the dosing, route, and frequency of iron administration are controversial [21–23]. Concomitant use of intravenous iron was deemed superior to oral iron in patients with chronic renal failure treated with erythropoietin [24]. Total dose infusion therapy versus low dose intravenous iron replacement were equally effective in hemodialysis patients receiving erythropoietin therapy [25]. In pregnancy, the intravenous route of iron administration was similar to the oral route in terms of measured hemoglobin increases and toxicity, but intravenous iron increased ferritin concentrations significantly more than did oral iron [26].

Studies in premature infants have attempted to address the dosage and timing of iron supplementation. In neonates with anemia of prematurity, high dose iron (16 mg/kg per day) was no more effective than low dose (8 mg/kg per day) during erythropoietin therapy [27]. Early iron supplementation in infants

Table 2

Parenteral iron formulations

Preparation	Tradename(s)	Dose	Comments
Iron dextran	InFed® Dexferrum®	250–500 mg [51] Replacement iron = 0.3 × weight (lb) × (100 – [Hb × 100/14.8]) [35]	Requires test dose (25 mg) 1 hour before starting therapy Large single doses (100–500 mg) are appropriate Available in small single doses (50 or 100 mg in 1 or 2 ml) May cause anaphylaxis
Sodium ferric gluconate	Ferrlecit®	High dose used in patients with severe chronic renal insufficiency: 250 mg intravenously over 14 hours [52] Low dose in hemodialysis patients: 62.5 mg/week [53]	No test dose required Available in single dose (62.5 mg in 5 ml) May cause flu-like symptoms
Iron sucrose (also known as iron saccharate)	Venofer®	100–300 mg [54] High dose: 250 mg/month in hemodialysis patients [53]	No test dose required Available in single dose (100 mg in 5 ml) May cause hypotension and cramps

Hb, hemoglobin.

was safe and prevented red blood cell transfusions as compared with late iron supplementation [28]; no erythropoietin was given in that study. Because there is substantial need for iron in erythropoietin-stimulated erythroid progenitors, Tarng and colleagues [29] recommended maintenance of serum ferritin and transferrin saturation levels over 300 ng/ml and 30%, respectively. They also asserted that, in uremic patients, oral iron is unlikely to keep pace with iron demand, rendering the response to erythropoietin suboptimal. Thus, intravenous iron therapy is believed to be the most appropriate choice, leading to reductions in erythropoietin dosage and costs [29].

Although oral supplements are usually the first line of treatment because of cost and convenience, oral iron may be poorly absorbed, associated with increased gastrointestinal distress, and may not maintain iron stores in critically ill patients receiving erythropoietic therapy. Studies designed to examine the optimal dose and route of iron supplementation in critically ill patients are lacking. In otherwise healthy adults treated with erythropoietin before elective surgery [30], intravenous iron (200 mg iron sucrose twice weekly) was superior to daily oral iron (160 mg iron sulfate). Parenteral iron formulations are summarized in Table 2. Pain and discoloration at the injection site, as well as reports of sarcoma at the site of injection of iron dextran, have discouraged administration of iron by the intramuscular route. Thus, parenteral iron is now only given by intravenous infusion. Iron dextran has also been associated with important incidents of anaphylactic reaction; however, the newest formulations are considered safer [22,31]. According to Zager and colleagues [32], parenteral iron formulations are highly potent pro-oxidants that can induce tubular and endothelial cell death. In *in vitro* animal studies, each formulation demonstrated a markedly different toxicity profile, with iron sucrose being the most toxic, followed by iron gluconate, then iron dextran. Correct timing of infusion and dose are important to avoiding oversaturation of

physiologic transport mechanisms [33]. Iron administered via total parenteral nutrition (TPN) solutions has been advocated in some publications [34]. However, product literature states that iron formulations should not be mixed with other medications or in TPN. The administration of iron through TPN should not be regarded as a first-line option in critically ill patients until safety, physical compatibility, and efficacy data become available in the literature [35].

How effective is iron alone in the treatment of anemia or ACD type disorders? With regard to reducing the need for transfusions, iron has not proven very effective in improving the capacity for autologous blood donation or in reducing transfusion requirements [10,13,36,37]. Iron was helpful in reducing erythropoietin requirements for the maintenance of hemoglobin in end-stage renal disease patients on hemodialysis, but a similar study has not been done in ICU patients [38]. After 1 month of treatment, intravenous iron alone was sufficient to increase hematocrit in patients with CKD, but the response was less than that noted in the group administered erythropoietin plus iron [39]. In orthopedic surgery patients, those treated with iron alone did not experience a significant increase in erythropoietic variables over baseline values, and the effects of erythropoietin were seen irrespective of the route (oral or intravenous) of iron administration [40]. Two studies of erythropoietin in the critically ill were conducted [36,37] in which patients were treated with iron therapy, but neither of these two studies addressed the preferred route of iron administration. Oral iron (at least 150 mg/day elemental iron) or parenteral iron (if unable to take oral formulation or inadequate response to iron therapy defined by transferrin saturation <20% and serum ferritin <100 ng/ml) were administered to all patients starting on study day 1 for 2–4 weeks.

The question has been raised as to whether iron therapy is really needed as an adjuvant to erythropoietin therapy. Iron supplementation was found unnecessary in one small, limited

observational study of critically ill surgical patients undergoing erythropoietin treatment [41], because iron store deficiency was not noted during the course of their ICU stay. However, the majority of clinical evidence shows that, if properly balanced, iron therapy can help to optimize erythropoietin treatment. Furthermore, iron deficiency is also the most common cause of resistance to erythropoietin treatment in CKD [42]. Finally, adjuvant therapy, such as ascorbic acid, to increase oral iron absorption and physiologic utilization has been used in many clinical CKD settings and must be tested in critically ill patients [43].

Another clinical concern related to iron supplementation in the ICU is its risk to affect the physiological redox potential. Iron is a mineral that is essential to cellular homeostasis, but an excess of iron can affect physiology and lead to cell injury [44]. During biologic stress, free radicals are formed. These radicals can have detrimental effects at different cellular levels (such as nucleic acid modification) and are involved in many biologic processes that can damage lipid and protein membranes [45]. The role of oxidative stress secondary to iron-derived free radicals and depressed antioxidant reserves has also been associated with pathologic damage in humans [46]. Free hydroxyl radical formation is catalyzed by iron via the Fenton reaction, which involves ferrous iron and peroxide. Although the clinical significance of this biologic reaction and the formation of reactive oxygen species is still debated, stress oxidation is certainly a viable reason to avoid iron overload and to monitor iron parameters during iron supplementation and critical illness [47]. Biologic tissues exposed to higher concentrations of free iron may be prone to oxidative damage [48].

In summary, clinicians must first understand that the majority of the clinical data available are derived from the CKD population. The final decision to administer supplemental iron will depend ultimately on the etiology of anemia in the critically ill patient. Because iron deficiency is noted in a small subset of critically ill patients, iron supplementation following identification of such patients is appropriate. If anemia is multifactorial, as is usually the case in a critically ill patient, then iron alone may not be sufficient to stimulate erythropoiesis but may be useful as an adjunct with erythropoietin. Although not specifically evaluated in the critically ill, studies in pregnant females, neonates, and patients with renal disease suggest that higher iron doses are not more effective than lower ones. Iron overload should be avoided because of its association with adverse effects. Therefore, until proven otherwise, clinicians should probably monitor iron parameters on a regular basis if they elect to administer iron and erythropoietin therapies concomitantly. Based on the CKD population, these parameters may help in optimizing therapy while preventing iron overload. Specific populations of ICU patients (i.e. those with severe infection or sepsis) may not benefit from iron therapy because of possibly increased risk for iron-mediated infection, although this association is still very controversial and is not

based on robust clinical evidence. The optimal dose, route, and timing of iron administration in critically ill patients, especially when given concurrently with erythropoietin therapy, remains an open issue that requires further study.

Competing interests

The author is a member of both the Speakers Bureau and Advisory Board for Ortho Biotech Products, L.P.

References

1. Krantz SB: **Pathogenesis and treatment of the anemia of chronic disease.** *Am J Med Sci* 1994, **307:**353-359.
2. Cavill I: **Iron and erythropoietin in renal disease.** *Nephrol Dial Transplant* 2002, **17:**19-23.
3. Rodriguez RM, Corwin HL, Gettinger A, Corwin MJ, Gubler D, Pearl RG: **Nutritional deficiencies and blunted erythropoietin response as causes of the anemia of critical illness.** *J Crit Care* 2001, **16:**36-41.
4. Andrews NC: **Disorders of iron metabolism.** *N Engl J Med* 1999, **341:**1986-1995.
5. Patteril MV, Davey-Quinn AP, Gedney JA, Murdoch SD, Bellamy MC: **Functional iron deficiency, infection and systemic inflammatory response syndrome in critical illness.** *Anaesth Intensive Care* 2001, **29:**473-478.
6. Viljoen M, Coetzee IH, Roux LJ, Pretorius JP: **Anemia in surgical intensive care patients.** *Haematologica* 1994, **79:**19-24.
7. Gabriel A, Kozek S, Chiari A, Fitzgerald R, Grabner C, Geissler K, Zimpfer M, Stockenhuber F, Bircher NG: **High-dose recombinant human erythropoietin stimulates reticulocyte production in patients with multiple organ dysfunction syndrome.** *J Trauma* 1998, **44:**361-367.
8. Cavill I: **Erythropoiesis and iron.** *Best Pract Res Clin Haematol* 2002, **15:**399-409.
9. Kaltwasser JP, Kessler U, Gottschalk R, Stucki G, Moller B: **Effect of recombinant human erythropoietin and intravenous iron on anemia and disease activity in rheumatoid arthritis.** *J Rheumatol* 2001, **28:**2430-2436.
10. van Iperen CE, Gaillard CAM, Kraaijenhagen RJ, Braam BG, Marx JJM, van de Wiel A: **Response of erythropoiesis and iron metabolism to recombinant human erythropoietin in intensive care unit patients.** *Crit Care Med* 2000, **28:**2773-2778.
11. Hoen B: **Iron and infection: clinical experience.** *Am J Kidney Dis* 1999, **Suppl 2:**S30-S34.
12. Jurado RL: **Iron, infections, and anemia of inflammation.** *Clin Infect Dis* 1997, **25:**888-895.
13. Besarab A, Frinak S, Yee J: **An indistinct balance: the safety and efficacy of parenteral iron therapy.** *J Am Soc Nephrol* 1999, **10:**2029-2043.
14. Collins A, J Ebben, J Ma: **Frequent IV iron dosing is associated with higher infectious deaths [abstract].** *J Am Soc Nephrol* 1997, **8:**190A.
15. Cunningham-Rundles S, Giardina PJ, Grady RW, Califano C, McKenzie P, de Sousa M: **Effect of transfusional iron overload on immune response.** *J Infect Dis* 2000, **Suppl 1:**S115-S121.
16. Hunter RL, Bennett B, Towns M, Vogler WR: **Transferrin in disease II: defects in the regulation of transferrin saturation with iron contribute to susceptibility to infection.** *Am J Clin Pathol* 1984, **81:**748-753.
17. Kessler M, Hoen B, Mayeux D, Hestin D, Fontenaille C: **Bacteremia in patients on chronic hemodialysis. A multicenter prospective survey.** *Nephron* 1993, **64:**95-100.
18. Hoen B, Kessler M, Hestin D, Mayeux D: **Risk factors for bacterial infections in chronic haemodialysis adult patients: a multicentre prospective survey.** *Nephrol Dial Transplant* 1995, **10:** 377-381.
19. Hoen B, Paul-Dauphin A, Hestin D, Kessler M: **EPIBACDIAL: a multicenter prospective study of risk factors for bacteremia in chronic hemodialysis patients.** *J Am Soc Nephrol* 1998, **9:**869-876.
20. Fishbane S: **Review of issues relating to iron and infection.** *Am J Kidney Dis* 1999, **Suppl 2:**S47-S52.
21. Besarab A, Kaiser JW, Frinak S: **A study of parenteral iron regimens in hemodialysis patients.** *Am J Kidney Dis* 1999, **34:**21-28.

22. Hudson JQ, Comstock TJ: **Considerations for optimal iron use for anemia due to chronic kidney disease.** *Clin Ther* 2001, **23:** 1637-1671.
23. Rutherford CJ, Schneider TJ, Dempsey H, Kirn DH, Brugnara C, Goldberg MA: **Efficacy of different dosing regimens for recombinant human erythropoietin in a simulated perisurgical setting: the importance of iron availability in optimizing response.** *Am J Med* 1994, **96:**139-145.
24. Aggarwal HK, Nand N, Singh S, Singh M, Hemant, Kaushik G: **Comparison of oral versus intravenous iron therapy in predialysis patients of chronic renal failure receiving recombinant human erythropoietin.** *J Assoc Physicians India* 2003, **51:**170-174.
25. Saltissi D, Sauvage D, Westhuyzen J: **Comparative response to single or divided doses of parenteral iron for functional iron deficiency in hemodialysis patients receiving erythropoietin (EPO).** *Clin Nephrol* 1998, **49:**45-48.
26. 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:**518-522.
27. Bader D, Kugelman A, Maor-Rogin N, Weinger-Abend M, Hershkowitz S, Tamir A, Lanir A, Attias D, Barak M: **The role of high-dose oral iron supplementation during erythropoietin therapy for anemia of prematurity.** *J Perinatol* 2001, **21:**215-220.
28. Franz AR, Mihatsch WA, Sander S, Kron M, Pohlandt F: **Prospective randomized trial of early versus late enteral iron supplementation in infants with a birth weight of less than 1301 grams.** *Pediatrics* 2000, **106:**700-706.
29. Tarng D-C, Huang T-P, Tzen W, Yang W-C: **Erythropoietin hyporesponsiveness: from iron deficiency to iron overload.** *Kidney Int Suppl* 1999, **69:**S107-S118.
30. Rohling RG, Zimmermann AP, Breymann C: **Intravenous versus oral iron supplementation for preoperative stimulation of hemoglobin synthesis using recombinant human erythropoietin.** *J Hematother Stem Cell Res* 2000, **9:**497-500.
31. Fishbane S: **Safety in iron management.** *Am J Kidney Dis* 2003, **41(5 suppl):**18-26.
32. Zager RA, Johnson AC, Hanson SY, Wasse H: **Parenteral iron formulations: a comparative toxicologic analysis and mechanisms of cell injury.** *Am J Kidney Dis* 2002, **40:**90-103.
33. Beris P: **The use of iron to increase red cell mass.** *Can J Anaesth* 2003, **Suppl:**S3-S9.
34. Burns DL, Mascioli EA, Bistrian BR: **Effect of iron-supplemented total parenteral nutrition in patients with iron deficiency anemia.** *Nutrition* 1996, **12:**411-415.
35. Kumpf VJ: **Parenteral iron supplementation.** *Nutr Clin Pract* 1996, **11:**139-146.
36. Corwin HL, Gettinger A, Rodriguez RM, Pearl RG, Gubler KD, Enny C, Colton T, Corwin MJ: **Efficacy of recombinant human erythropoietin in the critically ill patient: a randomized, double-blind, placebo-controlled trial.** *Crit Care Med* 1999, **27:** 2346-2350.
37. Corwin HL, Gettinger A, Pearl RG, Fink MP, Levy MM, Shapiro MJ, Corwin MJ, Colton T: **Efficacy of recombinant human erythropoietin in critically ill patients: a randomized controlled trial.** *JAMA* 2002, **288:**2827-2835.
38. Besarab A, Amin N, Ahsan M, Vogel SE, Zazuwa G, Frinak S, Zazra JJ, Anandan JV, Gupta A: **Optimization of epoetin therapy with intravenous iron therapy in hemodialysis patients.** *J Am Soc Nephrol* 2000, **11:**530-538.
39. Silverberg DS, Blum M, Agbaria Z, Deutsch V, Irony M, Schwartz D, Baruch R, Yachnin T, Steinbruch S, Iaina A: **The effect of i.v. iron alone or in combination with low-dose erythropoietin in the rapid correction of anemia of chronic renal failure in the predialysis period.** *Clin Nephrol* 2001, **55:**212-219.
40. Olijhoek G, Megens JG, Musto P, Nogarin L, Gassmann-Mayer C, Vercammen E, Hayes-Licitra SA: **Role of oral versus IV iron supplementation in the erythropoietic response to rHuEPO: a randomized, placebo-controlled trial.** *Transfusion* 2001, **41:** 957-963.
41. Gwardschaladse C: **Exogenous iron supplementation is not necessary in critically ill patients receiving recombinant epoietin alpha [abstract].** *Crit Care Med* 2002, **30:**A63.
42. Horl WH: **Non-erythropoietin-based anaemia management in chronic kidney disease.** *Nephrol Dial Transplant* 2002, **Suppl 11:**35-38.
43. Tarng DC, Wei YH, Huang TP, Kuo BI, Yang WC: **Intravenous ascorbic acid as an adjuvant therapy for recombinant erythropoietin in hemodialysis patients with hyperferritinemia.** *Kidney Int* 1999, **55:**2477-2486.
44. Britton RS, Leicester KL, Bacon BR. **Iron toxicity and chelation therapy.** *Int J Hematol* 2002, **76:**219-228.
45. Meneghini R. **Iron homeostasis, oxidative stress, and DNA damage.** *Free Rad Biol Med* 1997, **23:**783-792.
46. Loebstein R, Lehotay DC, Luo X, Bartfay W, Tyler B, Sher GD. **Diabetic nephropathy in hypertransfused patients with thalassemia.** *Diabetic Care* 1998, **21:**1306-1309.
47. Saran M, Michel C, Stettmaier K, Bors W. **Arguments against the significance of the Fenton reaction contributing to signal pathways under in vivo conditions.** *Free Rad Res* 2000, **33:**567-579.
48. Urbanski NK, Beresewicz A. **Generation of OH initiated by interaction of Fe and Cu with dioxygen; comparison with the Fenton chemistry.** *Acta Biochim Pol* 2000, **47:**951-962.
49. Miller CB, Jones RJ, Piantadosi S, Abeloff MD, Spivak JL: **Decreased erythropoietin response in patients with the anemia of cancer.** *N Engl J Med* 1990, **322:**1689-1692.
50. Punnonen K, Irjala K, Rajamaki A: **Serum transferrin receptor and its ratio to serum ferritin in the diagnosis of iron deficiency.** *Blood* 1997, **89:**1052-1057.
51. Hamstra RD, Block MH, Schocket AL: **Intravenous iron dextran in clinical medicine.** *JAMA* 1980, **243:**1726-1731.
52. Jain AK, Bastani B: **Safety profile of a high dose ferric gluconate in patients with severe chronic renal insufficiency.** *J Nephrol* 2002, **15:**681-683.
53. Kosch M, Bahner U, Bettger H, Matzkies F, Teschner M, Schaefer RM: **A randomized, controlled parallel-group trial on efficacy and safety of iron sucrose (Venofer) vs iron gluconate (Ferrlecit) in haemodialysis patients treated with rHuEpo.** *Nephrol Dial Transplant* 2001, **16:**1239-1244.
54. Yee J, Besarab A: **Iron sucrose: the oldest iron therapy becomes new.** *Am J Kidney Dis* 2002, **40:**1111-1121.