

Anemia and Heart Failure: Addressing Functional Iron Deficiency

by Amanda Peffer, Pharm.D.

In the U.S., heart failure (HF) is a major cause of hospitalization, morbidity and mortality. A common finding in patients with HF is anemia, defined as Hgb <12g/dL for women or <13g/dL for men.¹ In turn, anemia has been associated with an increased risk of mortality in patients with both pre-existing cardiovascular disease and end-stage renal failure.²⁻⁶ Studies in HF patients with a low baseline Hgb have shown a 12–13% increase in mortality for each 1g/dL decrease in Hgb.^{7,8} In addition, anemia may be an independent risk factor for the development of HF.⁹ In dialysis patients, each 0.5g/dL decrease in Hgb has been associated with a 30% increase in the risk of developing left ventricular hypertrophy (LVH).⁷ Typically, a reduction in Hgb will result in a compensatory increase in cardiac output which, in HF patients, may lead to myocardial remodeling, LVH, and worsening HF.^{3,5,7} Thus, diligent attention to the treatment of anemia is warranted in patients with HF. While determination of the underlying cause of anemia should point to the most rational approach to therapy, the use of iron in combination with exogenous erythropoietin (either epoetin or darbepoetin; [EPO]), appears to be an attractive treatment strategy for many patients. This article will describe the two major causes of anemia associated with HF, summarize the evidence that supports the correction of anemia in this patient population, and illustrate a strategy for the use of iron therapy to maximize treatment with EPO.

The etiology of anemia in HF is multifactorial. Due to many potential contributing factors, including hemodilution and frequent blood draws, an evaluation of the causes of anemia in 143 patients with HF was published by Opasich and colleagues.¹⁰ The investigators found the two main etiologies to be anemia of chronic disease (ACD), present in 59% of patients, and concomitant renal failure, found in 24%. The remaining patients were found to have β -thalassemia (6%), iron deficiency (6%), or folate deficiency (5%). In agreement with the findings of this study, most authors attribute the majority of HF-associated anemias to inflammatory processes as found in ACD and/or concomitant renal failure.^{1,5,6,10,11}

Proinflammatory cytokines are implicated in the pathophysiology of HF, ACD, and renal failure.^{10,12} Such patients tend to have increased levels of tumor necrosis factor (TNF- α), interleukin-6, interleukin-1 β , and interferon- γ .^{4,10} Elevated levels of these cytokines disrupt erythropoiesis by suppressing the production of endogenous erythropoietin, blocking the effects of erythropoietin on the bone marrow, and hindering the release of stored iron from the reticuloendothelial (RE) system.^{4,13} Blockade of endogenous erythropoietin is likely a contributing factor in studies that have correlated an elevated plasma erythropoietin level to worsening of both NYHA functional class and prognosis.^{10,14}

Renal failure is the second most common etiology for anemia in HF patients. Like HF patients with ACD, HF patients with renal failure have elevated levels of inflammatory cytokines that disrupt erythropoiesis.^{6,15} However, unlike patients with ACD who may have elevated plasma erythropoietin levels, endogenous production of erythropoietin by the kidneys is reduced.^{4,10} In patients who are inadequately treated with β -blockers, ACE inhibitors, and an aldosterone antagonist, anemia-induced hypoxia results in vasodilation, hypotension, an increase in neuro-endocrine tone, retention of sodium and water, increased

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The vicious circle of HF, renal failure, and anemia has been labeled “the cardio-renal anemia syndrome.”

Baseline Hgb is one of six laboratory parameters used by the Seattle Heart Failure Model™ (www.seattleheartfailuremodel.org) to predict 1-, 2-, and 5-year survival, mortality, and mean life expectancy.

While anemic HF patients receiving dialysis are typically managed according to NKF-DQI guidelines, caution should be used in extending the protocol to non-dialysis populations.

In practice, FID may be treated like absolute iron deficiency to reach target TSAT and ferritin levels during EPO therapy.

To obtain accurate readings, delay checking iron indices for 7 days after elemental iron for doses ≤125mg, and for 14 days after larger doses.

Differentiation Between Absolute and Functional Iron Deficiency

	Serum Ferritin	TSAT
Absolute Deficiency	Decreased	Decreased
Functional Deficiency	Normal or increased	Decreased

preload, and additional stress on the heart.⁶ This vicious circle of HF, renal failure, and anemia has been labeled the “cardio-renal anemia syndrome.”^{4,6}

Although the etiology of anemia in HF is multifactorial, the two most common etiologies, ACD and renal dysfunction, appear amenable to treatment with exogenous EPO. While the efficacy of EPO is well established in the treatment of chronic renal failure and cancer-related anemias, no specific recommendations have been established for HF patients. To date there have been only four clinical trials assessing the treatment of anemia in HF patients using epoetin with iron supplementation.¹⁶⁻¹⁹ The results of these trials are summarized in Table I. Collectively, they show a positive impact from the correction of anemia in this patient population. In addition, two studies reported by Cleland and colleagues assessed the use of darbepoetin, the hyperglycosylated form of epoetin, in HF patients.²⁰ These results indicate that darbepoetin is a viable alternative to epoetin in the treatment of anemia in HF.

Table I: Summary of Trials in Heart Failure Patients Treated with Epoetin and Iron

Author	Design	Results (from baseline)
Silverberg ¹⁶ (n=26)	Non-controlled study assessing treatment with weekly 2000 units of epoetin and 200mg of iron sucrose in HF patients with renal failure.	Improvements in ejection fraction (28%) and NYHA class (27%), reduced hospitalizations rates (92%), and decreased use of diuretics.
Silverberg ¹⁷ (n=32)	Patients with NYHA class III or IV, ejection fraction <40% and Hgb 10.0 - 11.5g/dL, on maximum tolerated doses of HF medications except furosemide were randomized to either: epoetin + 200mg iron sucrose to increase Hgb to >12.5g/dL, TSAT >40%, or serum ferritin >400µg/L (group A), or no treatment (group B).	Group A vs. Group B Deaths: 0 vs. 4; NYHA class: 42.1% improvement vs. 11.4% decrease; Ejection fraction: 5.5% improvement vs. 5.4% decrease; Serum creatinine: stable vs. 28.6% increase; Use of furosemide: 51.3% decrease in oral vs. 28.5% increase and 91.3% decrease in IV vs. 28.0% increase; Hospitalization: 79% decrease vs. 57.6% increase.
Silverberg ¹⁸ (n=179)	Non-randomized trial of 84 patients with Type II diabetes and 95 non-diabetics with NYHA class III or IV, Hgb of 9.5 -11.5g/dL, and serum creatinines of 2.1-2.4mg/dL. Treatment was epoetin + 200mg iron sucrose every 1-2 weeks to reach a target Hgb of 12.5g/dL and serum ferritin of 500µg/L.	Diabetic vs. Non-diabetic Subjects Hgb increase: From 10.1 (±1.0) to 13.1 (±1.3) vs. 10.5 (±1.0) to 12.9 (±1.2); NYHA class improvement: 34.8% vs. 32.4% Ejection fraction improvement: 7.4% vs. 11.5%; Decreased hospitalization: 96.4% vs. 95.3%. Serum creatinine and GFR: Not significant change.
Mancini ¹⁹ (n=26)	HF patients with NYHA class III or IV, Hct <35%, and serum creatinine <2.5mg/dL randomized to receive placebo or epoetin 3 times weekly + daily 325mg ferrous gluconate and folate 1mg, for 3 months.	Treatment group had a significant increase in Hgb (from 11.0 ± 0.5 to 14.3 ± 1.0g/dL). Iron studies were not done, but 3 patients randomized to epoetin required their dose to be doubled.

It is imperative to recognize that in the management of anemias with exogenous EPO, hyporesponsiveness frequently occurs due to inadequate iron supplementation.²⁰ The use of EPO nearly doubles the daily rate of erythropoiesis, and thereby also doubles the daily requirement for iron, resulting in a 30–40mg/day deficit.²¹ The use of oral iron therapy, such as 325mg of ferrous sulfate providing 65mg of elemental iron, may overcome this deficit in some patients; however, due to problems with absorption and patient adherence, oral iron therapy is frequently inadequate. To avoid this, the National Kidney Foundation “Dialysis Outcomes Quality Initiative” (NKF-DQI) recommends the use of parenteral iron products for the prevention of iron deficiency in patients being treated with EPO.²²

Regardless of the route of iron supplementation, serial monitoring of laboratory iron indices is necessary to optimize the response to exogenous EPO therapy. The main indices that are used to assess iron status and guide the timing of iron replacement are Hgb, serum iron, serum ferritin, and percent transferrin saturation (TSAT).^{23,24} Serum ferritin reflects iron stores in the liver, spleen, and RE system while TSAT, the ratio of serum iron to the total iron binding capacity, is an indicator of the amount of iron that is available for erythropoiesis. To assure an adequate erythropoietic response to exogenous EPO, TSAT should be >20% prior administration.²² Iron indices must be interpreted carefully because

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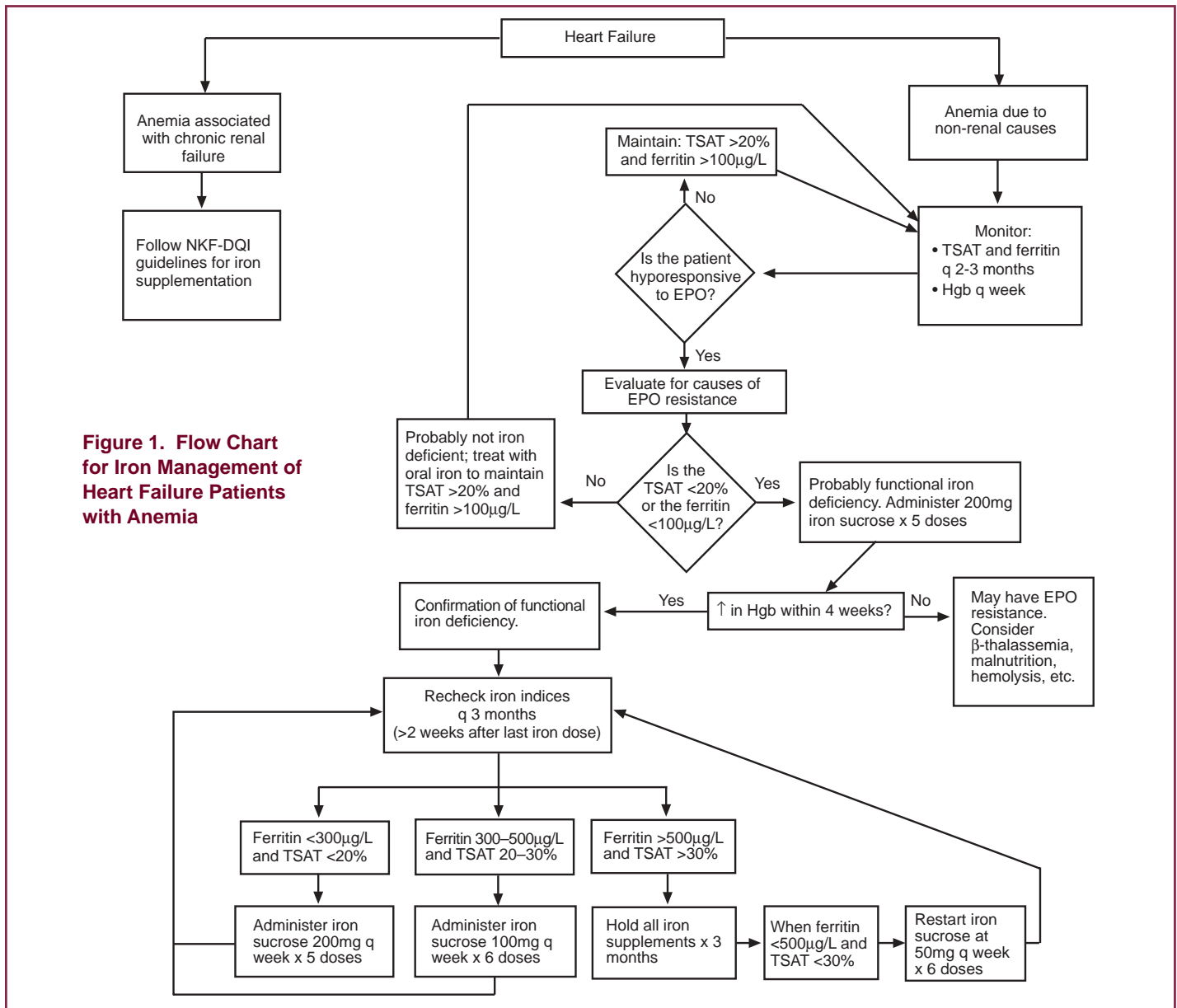


Figure 1. Flow Chart for Iron Management of Heart Failure Patients with Anemia

a number of factors influence their measurement. For example, serum iron exhibits diurnal variation with more elevated concentrations occurring later in the day.^{25,26} Also, anemia complicated by acute inflammation or infection may be associated with transiently high serum ferritin levels.^{25,26} For these reasons, serial, rather than single-point measurements of iron indices should be monitored, especially for patients that appear to have a waning response to exogenous EPO therapy.

A reduction in the response to exogenous EPO over time is commonly due to functional iron deficiency (FID). FID occurs when iron becomes sequestered in RE cells and is unavailable to meet the demands of erythroid cell production.²³ Patients with FID tend to have a low TSAT in conjunction with a normal, or slightly elevated, serum ferritin. When exogenous EPO is given to a patient with FID, the available transferrin is quickly reduced and parenteral iron supplementation is warranted (see Figure 1).^{22,25} An increase in Hgb within 4 weeks after iron administration confirms FID as the cause of EPO hyporesponsiveness.

The recommended parenteral iron dose for renal failure patients undergoing dialysis is 1000mg to supply adequate stores to cover 3 months of EPO therapy.²² This is to replace 400mg of iron lost with dialysis and 600mg to support hemoglobinization of new red blood cells.²² Dosing

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Patients who remain hyporesponsive to EPO after 8 weeks of optimal treatment should be worked up for alternative explanations such as hyperparathyroidism, oxidative stress, or vitamin deficiencies.²⁹

**Elemental Iron Content
of UW Medicine
Formulary Preparations**

- **Ferrous fumarate:** 20mg elemental iron/63mg tablet
- **Ferrous gluconate:** 34mg elemental iron/300mg tablet
- **Ferrous sulfate:**
Tablet: 65mg elemental iron/325mg
Drops: 15mg elemental iron/0.6 mL
Elixir: 44mg elemental iron/5mL
Solution: 60mg elemental iron/5mL
- **Iron sucrose:** 20mg elemental iron/mL
- **Sodium ferric gluconate:** 12.5mg elemental iron/mL

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schedules may vary, but five 200mg doses administered over a 14-day period is recommended by the manufacturer of iron sucrose to correct iron deficiency.²⁷ In HF patients who are being managed with exogenous EPO, but not undergoing dialysis, it follows that 600mg of iron should logically avoid iron overload and be sufficient to cover 3 months of exogenous EPO therapy.

Nevertheless, careful laboratory monitoring of HF patients treated with exogenous EPO and iron is mandatory to guide the safe correction of anemia in this population. However, TSAT and serum ferritin measurements should be delayed for 7 days following elemental iron doses of ≤ 125 mg, and for 14 days following larger doses.²² Hemoglobin levels should be assessed after four weeks of EPO therapy and reassessed at 2–4 week intervals.¹³ Despite adequate iron replacement, hyporesponsiveness to the exogenous EPO administration may still occur. The National Kidney Disease Outcomes Quality Initiative 2000 defines decreased response to epoetin as a failure to achieve a target Hgb with adequate iron stores at a subcutaneous dose of 300units/kg/week within 4–6 months or failure to maintain a target Hgb following subsequent doses.²² Unless FID or iron-deficiency exists, the EPO dose may be cautiously increased by 50% when hyporesponsiveness persists.¹³ Patients who remain hyporesponsive to EPO after 8 weeks of optimal treatment should be worked up for alternative explanations.^{22,28}

In summary, anemia is a prevalent finding in patients with heart failure. It has been shown to impact symptoms of heart failure such as LVH and has been associated with a higher mortality. Although treatable, the anemias found in HF patients are multifactorial and therefore, treatment should be matched to the individual circumstances. Treatment with exogenous EPO is often warranted, but iron stores also need bolstering to meet the increased demands of erythropoiesis. Serial analysis of laboratory iron indices is integral to the process of making ongoing treatment decisions designed to correct the anemias found in these patients.

References available upon request.

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