Medical Policy

**MP 5.01.605**

Intravenous Iron Therapy

**DISCLAIMER**

Our medical policies are designed for informational purposes only and are not an authorization, explanation of benefits or a contract. Receipt of benefits is subject to satisfaction of all terms and conditions of the coverage. Medical technology is constantly changing, and we reserve the right to review and update our policies periodically.

**POLICY**

Intravenous iron therapy is considered **medically necessary** for patients with documented anemia and any of the following indications:

- For patients needing iron supplementation who are unable to tolerate compounds given orally, and have had adequate work up for cause of anemia; or
- For patients who are losing iron (blood) at a rate too rapid for oral intake to compensate for the loss; or
- For patients with a disorder of the gastrointestinal tract, such as ulcerative colitis, in which symptoms may be aggravated by oral iron therapy; or
- For patients who are unable to maintain iron balance on treatment with hemodialysis (Note: Venofer, an iron sucrose injection, and Ferrlecit, a sodium ferric gluconate complex in sucrose injection, are indicated for the treatment of iron deficiency anemia in members undergoing chronic hemodialysis who are receiving supplemental erythropoietin/epoetin therapy and Triferic, a ferric pyrophosphate citrate, is indicated for the replacement of iron to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD)\(^2\); or
- For patients who are donating large amounts of blood for autotransfusion programs; or
- For patients with chemotherapy-induced anemia.

Intravenous iron therapy is considered **investigational** for all other indications including fatigue or other symptoms without anemia because its clinical value for these indications has not been established.

**POLICY GUIDELINES**

When IV iron therapy is deemed medically necessary, dose requests will be evaluated according to iron deficit as calculated by the Ganzoni equation \([\text{Total Iron Deficit} = \text{Weight (kg)} \times (\text{Target Hb} – \text{Actual Hb}) \{g/l\} \times 2.4 + \text{Iron stores } \{\text{mg}\}]\)

**BACKGROUND**

The established indications for intravenous iron therapy were adapted from Wintrobe's Clinical Hematology (1999). Parenteral iron therapy is as effective but somewhat more dangerous and
considerably more expensive than oral therapy. Nevertheless, failure of oral therapy is to be expected in certain clinical situations. According to Wintrobe's Clinical Hematology, a history of failure to respond to oral iron, however, is not by itself an indication for parenteral therapy. The reasons for failure should be analyzed.

The most common use for intravenous iron is in hemodialysis patients. According to guidelines from the National Kidney Foundation (NKF), a trial of oral iron is acceptable in the hemodialysis patient, but is unlikely to maintain adequate iron balance. The NKF guidelines state that, to achieve and maintain an hemoglobin level of 11 to 12 g/dL (hematocrit of 33% to 36%), most hemodialysis patients will require intravenous iron on a regular basis. The NKF guideline summary states:

Iron is essential for hemoglobin formation, as is erythropoietin. Several important issues related to iron deficiency and its management in the patients with chronic kidney disease; particularly in patients receiving Epoetin therapy should be considered:

- Iron (blood) losses are high, particularly in the hemodialysis patient.
- Oral iron usually cannot maintain adequate iron stores, particularly in the hemodialysis patient treated with Epoetin.
- Epoetin, by stimulating erythropoiesis to greater than normal levels, often leads to functional iron deficiency.
- Prevention of functional (and absolute) iron deficiency by regular use of intravenous iron (i.e., small doses, weekly, to replace predicted blood losses) improves erythropoiesis.
- The serum iron, total iron binding capacity, and serum ferritin are the best indicators of iron available for erythropoiesis and iron stores, but they do not provide absolute criteria for either iron deficiency or iron overload.

These guidelines suggest that the regular use of small doses of intravenous (IV) iron, particularly in the hemodialysis patient, will prevent iron deficiency and promote better erythropoiesis than can oral iron therapy.

- Prior to July 1999, the only IV iron preparation available in the United States was iron dextran. The doses recommended for iron dextran are detailed in these Guidelines. Since July 1999, iron gluconate and iron sucrose have become available for IV use in the United States. Since the amount of iron gluconate per vial differs from that of iron dextran, the Work Group recommends that the substitution of iron gluconate for iron dextran would be 8 doses of 125 mg of iron gluconate (over 8 weeks per quarter), or 8 doses of 62.5 mg of iron gluconate over 8 weeks instead of 10 doses of 50 mg of iron dextran over 10 weeks. Doses of iron gluconate larger than 125 mg given at one time are not recommended by the manufacturer, whereas iron dextran can be given at one time at doses of 250, 500, and/or 1,000 mg doses, if indicated. Iron sucrose can be given in doses of 100 mg or less.

Routine supplementation with intravenous iron usually results in higher hemoglobin and hematocrit values or a decrease in epoetin requirements in patients with anemia and chronic renal failure. Morbidity and mortality decrease in epoetin-treated patients with chronic renal failure as the anemia improves.

In a randomized controlled study (n = 120), Madi-Jabera et al (2004) reported that post-operative intravenous iron supplementation alone or in combination with a single dose of recombinant-human erythropoietin (300 U/kg) is not effective in correcting anemia after cardiac surgery. A Cochrane review (Dodd et al, 2004) concluded that there is some limited evidence of favorable outcomes for treatment of post-partum anemia with erythropoietin. Additionally, these authors stated that further high-quality
trials assessing the treatment of post-partum anemia with iron supplementation (e.g., intravenous administration of iron) and blood transfusions are needed.

In a prospective study, Cuenca and associates (2005) examined the effect of pre-operative intravenous 200-300 mg (n= 20) iron sucrose on allogeneic blood transfusion (ABT) requirements and post-operative morbidity-mortality in patients undergoing surgery for displaced subcapital hip fracture (DSHF) repair. A previous series of 57 DSF patients served as the control group. All patients were older than 65 years, were operated on the 3rd day after admission to the hospital, by the same medical team, and using the same implant. Age, gender, American Society of Anesthesiologists classification, surgical procedure, peri-operative hemoglobin, requirements for ABT, post-operative infection, length of hospital stay (LOS) and 30-day mortality rate were examined. No adverse reactions to the iron administration were observed. The iron group had a lower transfusion rate (15% versus 36.8%), lower transfusion index (0.26 versus 0.77 units per patient), lower 30-day mortality rate (0 versus 19.3%), shorter LOS (11.9 versus 14.1 days), as well as a trend to a lower post-operative infection rate (15% versus 33%). These researchers concluded that pre-operative parenteral iron administration could be a safe and effective way to reduce the ABT requirements in DSF patients. This reduction in the ABT requirements is accompanied by a reduction in the morbidity-mortality rate and LOS. Moreover, the authors noted that a large, randomized, controlled trial to confirm these results is warranted.

In a pilot study, Munoz, et al. (2006) examined the effect of post-operative administration of 300 mg of intravenous iron sucrose on ABT requirements in patients undergoing total hip replacement (THR) (n = 24). A previous series of 22 THR patients served as the control group. All patients were operated on by the same surgeon, using the same implant, and a set of clinical data was gathered. No adverse reactions to iron administration were observed. The group given iron showed a trend to a lower transfusion rate (46% versus 73%; p = 0.067), and lower transfusion index (0.96 versus 1.68 units/patient; p = 0.038). Moreover, amongst the non-transfused patients, admission hemoglobin levels were lower in those coming from the iron group than those from the control group (12.7 +/- 0.9 versus 14.0 +/- 1.2 g dL(-1), respectively; p = 0.017). The authors noted that post-operative parenteral iron administration could be a safe and effective way to reduce ABT requirements in the THR patients. However, a large, randomized, controlled trial is needed to confirm these results.

A Cochrane review on treatments for iron-deficiency anemia during pregnancy stated that despite the high incidence and burden of disease associated with this condition, there is a paucity of good quality studies evaluating clinical maternal and neonatal effects of iron administration in pregnant women with anemia. Daily oral iron therapy improves hematological indices but is associated with gastrointestinal adverse effects. Intramuscular and intravenous iron therapy enhances hematological response, compared with oral iron, but there are concerns regarding possible important adverse effects. The authors noted that large, good quality studies that evaluate clinical outcomes including adverse effects are needed (Reveiz et al, 2007).

Fishbane (2007) stated that iron deficiency has been studied extensively in patients with chronic kidney disease (CKD) on hemodialysis. However, few studies examined iron treatment in the non-dialysis CKD population. Limited data suggest that iron deficiency is common in patients with CKD with anemia, which can impair the effectiveness of erythropoiesis. The diagnosis of iron deficiency should entail clinical judgment, with an emphasis on the patient's clinical characteristics because of limited evidence examining the interpretation of iron testing results. When iron deficiency is diagnosed in non-dialysis patients with CKD, any sources of blood loss must be investigated. After addressing any blood loss, the preferred route of iron therapy must be ascertained. To date, no clear advantage has been shown with intravenous versus oral administration in non-dialysis patients, as shown in the hemodialysis setting. Thus, oral iron therapy may be a more reasonable option unless oral therapy previously failed. The
In a randomized, multi-center study, Henry and colleagues (2007) evaluated the safety and effectiveness of IV sodium ferric gluconate complex (FG), oral ferrous sulfate, or no iron to increase hemoglobin (Hb) in anemic cancer patients receiving chemotherapy and epoetin alfa. A total of 187 patients with chemotherapy-induced anemia/CIA (Hb less than 11 g/dL; serum ferritin greater than or equal to 100 ng/ml or transferrin saturation greater than or equal to 15 %) scheduled to receive chemotherapy and epoetin alfa (40,000 U subcutaneously weekly) were randomized to 8 weeks of 125 mg of IV FG weekly, 325 mg of oral ferrous sulfate 3 times daily, or no iron. The primary outcome was a change in Hb from baseline to endpoint, first whole-blood or red blood cell (RBC) transfusion, or study withdrawal. A total of 129 patients were evaluable for effectiveness (FG, n = 41; oral iron, n = 44; no iron, n = 44). Mean increase in Hb was 2.4 g/dL (95 % confidence interval [CI], 2.1 - 2.7) for FG (p = 0.0092 versus oral iron; p = 0.0044 versus no iron), 1.6 g/dL (95 % CI, 1.1 - 2.1) for oral iron (p = 0.7695 versus no iron), and 1.5 g/dL (95 % CI, 1.1 - 1.9) for no iron. Hemoglobin response (increase greater than or equal to 2 g/dL) was 73 % for FG (p = 0.0099 versus oral iron; p = 0.0029 versus no iron), 46 % for oral iron (p = 0.6687 versus no iron), and 41 % for no iron. Intravenous sodium ferric gluconate complex was well-tolerated. The authors concluded that for cancer patients with CIA receiving epoetin alfa, FG produces a significantly greater increase in Hb and Hb response compared with oral iron or no iron, supporting more aggressive treatment with IV iron supplementation for these patients.

In a randomized, multi-center study, Hedenus and co-workers (2007) assessed if IV iron improves Hb response and permits decreased epoetin dose in anemic (Hb 9 - 11 g/dL), transfusion-independent patients with stainable iron in the bone marrow and lympho-proliferative malignancies not receiving chemotherapy. Patients (n = 67) were randomized to subcutaneous epoetin beta 30 000 IU once-weekly for 16 weeks with or without concomitant IV iron supplementation. There was a significantly (p < 0.05) greater increase in mean Hb from week 8 onwards in the iron group and the percentage of patients with Hb increase greater than or equal to 2 g/dL was significantly higher in the iron group (93 %) than in the no-iron group (53 %) (per-protocol population; p = 0.001). Higher serum ferritin and transferrin saturation in the iron group indicated that iron availability accounted for the Hb response difference. The mean weekly patient epoetin dose was significantly lower after 13 weeks of therapy (p = 0.029) and after 15 weeks approximately 10 000 IU (greater than 25 %) lower in the iron group, as was the total epoetin dose (p = 0.051). The authors concluded that the Hb increase and response rate were significantly greater with the addition of IV iron to epoetin treatment in iron-replete patients and a lower dose of epoetin was required.

Bastit and colleagues (2008) stated that concomitant use of IV iron as a supplement to erythropoiesis-stimulating agents (ESAs) in patients with CIA is controversial. In a randomized, multi-center study, these investigators assessed safety and effectiveness of darbepoetin alpha given with IV iron versus with local standard practice (oral iron or no iron). A total of 396 patients with non-myeloid malignancies and Hb less than 11 g/dL received darbepoetin alpha 500 microg with (n = 200) or without (n = 196) IV iron once every 3 weeks (Q3W) for 16 weeks. The hematopoietic response rate (proportion of patients achieving Hb greater than or equal to 12 g/dL or Hb increase of greater than or equal to 2 g/dL from baseline) was significantly higher in the IV iron group: 86 % versus 73 % in the standard practice group (difference of 13 % [95 % CI, 3 % to 23 %]; p = 0.011). Fewer RBC transfusions (week 5 to the end of the treatment period) occurred in the IV iron group: 9 % versus 20 % in the standard practice group (difference of -11 % [95 % CI, -18 % to -3 %]; p = 0.005). Both treatments were well-tolerated with no notable differences in adverse events. Serious adverse events related to iron occurred in 3 % of patients in the IV iron group and were mostly gastrointestinal in nature. The authors concluded that addition of
IV iron to darbepoetin alpha Q3W in patients with CIA is an important advance in anemia management, allowing more patients to experience the benefit of anemia treatment, with a shorter lag time to response and fewer transfusions.

Pedrazzoli et al (2008) noted that unresponsiveness to ESAs occurring in 30% to 50% of patients, is a major limitation to the treatment of CIA. These researchers prospectively evaluated if IV iron can increase the proportion of patients with CIA who respond to darbepoetin. A total of 149 patients with lung, gynecological, breast, and colorectal cancers and greater than or equal to 12 weeks of planned chemotherapy were enrolled from 33 institutions. Patients were required to have Hb less than or equal to 11 g/L and no absolute or functional iron deficiency. All patients received darbepoetin 150 microg subcutaneously once-weekly for 12 weeks and were randomly assigned to IV FG 125 mg weekly for the first 6 weeks (n = 73) or no iron (n = 76). Primary end point of the study was the percentage of patients achieving hematopoietic response (Hb greater than or equal to 12 g/dL or greater than or equal to 2 g/dL increase). Hematopoietic response by intention-to-treat analysis was 76.7% (95% CI, 65.4% to 85.8%) in the darbepoetin/iron group and 61.8% (95% CI, 50.0% to 72.7%) in the darbepoetin group (p = 0.0495). Among patients fulfilling eligibility criteria and having received at least 4 darbepoetin administrations, hematopoietic responses in the darbepoetin/iron group (n = 53) and in the darbepoetin-only group (n = 50) were 92.5% (95% CI, 81.8% to 97.9%) and 70% (95% CI, 55.4% to 82.1%), respectively (p = 0.0033). Increase of Hb during treatment period showed a time profile favoring darbepoetin/iron with statistically significant effect from week 5 on. The safety profile was comparable in the two arms. The authors concluded that in patients with CIA and no iron deficiency, IV iron supplementation significantly reduces treatment failures to darbepoetin without additional toxicity. They stated that based on their findings and those by Henry et al (2007) as well as Hedenus et al (2007), IV iron supplementation should become an integral and routine component of ESA therapy, and should be incorporated into clinical guidelines.

In an editorial that accompanied the studies by Bastit et al as well as Pedrazzoli et al, Auer Bach (2008) stated that IV iron supplementation should be considered a component of the management of anemia of cancer and cancer chemotherapy. This is in agreement with the observation of Shord et al (2008) who noted that parenteral iron should be administered to patients receiving ESA therapy to improve hematopoietic response.

In a randomized, controlled clinical trial, Seid and colleagues (2008) assessed the safety, effectiveness, and tolerability of IV ferric carboxymaltose and compared with oral ferrous sulfate in women with post-partum anemia. A total of 291 women less than 10 days after delivery with Hb 10 g/dL or less were randomized to receive ferric carboxymaltose (n = 143) 1000 mg or less intravenously over 15 minutes or less, repeated weekly to a calculated replacement dose (maximum 2500 mg) or ferrous sulfate (n = 148) 325 mg orally thrice-daily for 6 weeks. Ferric carboxymaltose-treated subjects were significantly more likely to: (i) achieve a Hb greater than 12 g/dL in a shorter time period with a sustained Hb greater than 12 g/dL at day 42, (ii) achieve Hb rise 3 g/dL or greater more quickly, and (iii) attain higher serum transferrin saturation and ferritin levels. Drug-related adverse events occurred less frequently with ferric carboxymaltose. The authors concluded that IV ferric carboxymaltose was safe and well-tolerated with an efficacy superior to oral ferrous sulfate in the treatment of post-partum iron deficiency anemia.

In an open, randomized controlled trial, Westad et al (2008) analyzed the effect of IV ferrous sucrose compared with oral ferrous sulphate on hematological parameters and quality of life in women with post-partum anemia. A total of 128 post-partum women with hemorrhagic anemia (Hb between 6.5 g/100 ml and 8.5 g/100 ml) were included in this study. The intervention group (n = 59) received 600 mg iron sucrose intravenously followed by 200 mg iron sulphate daily from week 5. The control group (n = 70) were given 200 mg iron sulphate daily. Randomization and start of treatment occurred within 48
hours of the delivery. Participants were followed-up at 4, 8 and 12 weeks. Main outcome measures included Hb, ferritin and quality of life assessed with the Medical Outcomes Study Short Form 36 (SF-36) and the Fatigue Scale. After 4 weeks, the mean Hb values in both groups were similar (11.9 g/100 ml versus 12.3 g/100 ml, p = 0.89). The mean serum ferritin value after 4 weeks was significantly higher in the intervention group with 13.7 microg/L versus 4.2 microg/L in the control group (p < 0.001). At 8 and 12 weeks, the hematological parameters were similar. The total fatigue score was significantly improved in the intervention group at week 4, 8 and 12, whereas SF-36 scores did not differ. The authors concluded that women who received 600 mg IV iron sucrose followed by standard oral iron after 4 weeks, replenished their iron stores more rapidly and had a more favorable development of the fatigue score indicating improved quality of life.

Guidelines from the American College of Obstetricians and Gynecologists on anemia of pregnancy (ACOG, 2008) state that parenteral iron is useful in the rare patient who cannot tolerate or will not take modest doses or oral iron. Patients with malabsorption syndrome and severe iron deficiency anemia may benefit from parenteral therapy. The guidelines note that anaphylactic reactions have been reported in 1 percent of patients receiving parenteral iron dextran. In comparison with patients who take iron dextran, patients who take ferrous sucrose have fewer allergic reactions (8.7 versus 3.3 allergic events per 1 million doses) and a significantly lower fatality rate (31 versus 0, p < 0.001). The guidelines cited a randomized controlled clinical study by Bhandal & Russell (2006) comparing oral versus intravenous iron sucrose for postpartum anemia, finding that women treated with intravenous iron had higher hemoglobin levels in the short term (on days 5 and 14) but that by day 40, there was no significant difference in the hemoglobin levels of the two groups. The ACOG guidelines concluded that, in most circumstances, oral iron preparations are appropriate and sufficient.

REFERENCES


**CODES**

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**POLICY HISTORY**

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