Clinical Policy Bulletin: Intravenous Iron Therapy

Number: 0575

Policy

I. Aetna considers intravenous iron therapy medically necessary for any of the following indications:

A. For members needing iron supplementation who are unable to tolerate compounds given orally; or
B. For members who are losing iron (blood) at a rate too rapid for oral intake to compensate for the loss; or
C. For members with a disorder of the gastrointestinal tract, such as inflammatory bowel disease (ulcerative colitis and Crohn's disease), in which symptoms may be aggravated by oral iron therapy; or
D. For members 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 (IDA) in members undergoing chronic hemodialysis who are receiving supplemental erythropoietin/epoetin therapy; or
E. For members with IDA associated with peritoneal dialysis and non-dialysis- dependent (NDD) chronic kidney disease (Note: Venofer [iron sucrose] and Feraheme [ferumoxytol]is are indicated for such use, not Ferrlecit [sodium ferric gluconate]); or
F. For members who are donating large amounts of blood for autologous programs; or
G. For members who repeatedly fail to heed instructions for oral iron supplementation or are incapable of accepting or following them; or
H. For members with chemotherapy-induced anemia; or
I. For members with heart failure and iron deficiency, with or without anemia; or
J. For members with IDA due to heavy uterine bleeding.

II. Aetna considers intravenous iron therapy experimental and investigational for all other indications (e.g., anemia of pregnancy who do not meet criteria
above, treatment of restless legs syndrome) because its clinical value for these indications has not been established.

See also CPB 0195 - Erythropoiesis Stimulating Agents

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 must 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 (Hb) formation, as is erythropoietin (EPO). Several important issues related to iron deficiency and its management in the patients with chronic kidney disease (CKD), particularly in patients receiving epoetin therapy should be considered:

1. Iron (blood) losses are high, particularly in the hemodialysis patient.
2. Oral iron usually cannot maintain adequate iron stores, particularly in the hemodialysis patient treated with ESAs.
3. ESAs, by stimulating erythropoiesis to greater than normal levels, often leads to functional iron deficiency.
4. 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.
5. 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.
6. 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, although not FDA-approved for doses greater than 100 mg, 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.

7. Since the amount of iron sucrose per vial differs from that of iron dextran, the Work Group recommends that the substitution of iron sucrose for iron dextran would be 5 doses of 200 mg of iron sucrose (over 4 weeks per quarter), or 5 doses of 200 mg of iron sucrose over 4 weeks instead of 10 doses of 100 mg of iron dextran over 10 weeks.

8. Venofer, (iron sucrose, USP) can be given in doses of 100 mg undiluted as a slow intravenous injection over 2 to 5 mins, or as an infusion of 100 mg diluted in 100 ml of 0.9 % NaCl or as a 200 mg undiluted as a slow intravenous injection over 2 to 5 mins on 5 different occasions for CKD patients. There is limited experience with administration of 500 mg of Venofer diluted in a maximum of 250 ml of 0.9 % NaCl over a period of 3.4 to 4 hours on day 1 and 14. In peritoneal dialysis, administer Venofer in 3 divided doses, given by slow intravenous infusion over a 28-day period: 2 infusions each of 300 mg over 1.5 hours; 14 days apart followed by one 400 mg infusion over 2.5 hours 14 days later. Dilute Venofer in a maximum of 250 ml of 0.9 % NaCl.

Routine supplementation with IV iron usually results in higher hemoglobin and hematocrit values or a decrease in epoetin requirements in patients with anemia and chronic kidney disease. 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 IV iron supplementation alone or in combination with a single dose of recombinant-human EPO (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 EPO. Additionally, these authors stated that further high-quality trials assessing the treatment of post-partum anemia with iron supplementation (e.g., IV administration of iron) and blood transfusions are needed.

In a prospective study, Cuenca and associates (2005) examined the effect of pre-operative IV 200 to 300 mg (n = 20) iron sucrose on allogeneic blood transfusion (ABT) requirements and post-operative morbid-mortality in patients undergoing surgery for displaced subcapital hip fracture (DSHF) repair. A previous series of 57 DSHF 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 DSHF 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 IV 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, among 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 IV 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 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 IV 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 author noted that further investigation is needed to support evidence-based guidelines for the treatment of iron deficiency in the non-dialysis CKD population because this population differs from hemodialysis patients in the decreased extent of blood loss.
In an open-label, 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 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 to 2.7) for FG (p = 0.0092 versus oral iron; p = 0.0044 versus no iron), 1.6 g/dL (95 % CI: 1.1 to 2.1) for oral iron (p = 0.7695 versus no iron), and 1.5 g/dL (95 % CI: 1.1 to 1.9) for no iron. Hemoglobin response (increase greater than or equal to 2 g/dL) was 73 % for FG (p = 0.0029 versus no iron; 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) 1,000 mg or less intravenously over 15
mins or less, repeated weekly to a calculated replacement dose (maximum 2,500 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) stated 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 % 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 and Russell (2006) comparing oral versus IV iron sucrose for post-partum anemia, finding that women treated with IV 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 Hb levels of the two groups. The ACOG guidelines concluded that, in most circumstances, oral iron preparations are appropriate and sufficient.

Beucher and colleagues (2011) evaluated the effectiveness and the safety of prevention and treatment of iron deficiency anemia during pregnancy. French and English publications were searched using PubMed and Cochrane library. Early screening of iron deficiency by systematic examination and blood analysis seemed
essential. Maternal and perinatal complications were correlated to the severity and to the mode of appearance of anemia. Systematic intakes of iron supplements seemed not to be recommended. In case of anemia during pregnancy, iron supplementation was not associated with a significant reduction in substantive maternal and neonatal outcomes. Oral iron supplementation increased blood parameters but exposed to digestive side effects. Women who received parenteral supplementation were more likely to have better hematological response but also severe potential side effects during pregnancy and in post-partum. The maternal tolerance of anemia motivated the choice between parenteral supplementation and blood transfusion. The authors concluded that large and methodologically strong trials are needed to evaluate the effects of iron supplementation on maternal health and pregnancy outcomes.

In a randomized, controlled, observer-blinded trial, Okonko et al (2008) tested the hypothesis that IV iron improves exercise tolerance in anemic and non-anemic patients with symptomatic chronic heart failure (CHF) and iron deficiency. These investigators randomized 35 patients with CHF (age 64 +/- 13 years, peak oxygen consumption [pVO2] 14.0 +/- 2.7 ml/kg/min) to 16 weeks of IV iron (200 mg weekly until ferritin greater than 500 ng/ml, 200 mg monthly thereafter) or no treatment in a 2:1 ratio. Ferritin was required to be less than 100 ng/ml or ferritin 100 to 300 ng/ml with transferrin saturation less than 20 %. Patients were stratified according to Hb levels (less than 12.5 g/dl [anemic group] versus 12.5 to 14.5 g/dl [non-anemic group]). The observer-blinded primary end point was the change in absolute pVO2. The difference (95 % CI) in the mean changes from baseline to end of study between the iron and control groups was 273 (151 to 396) ng/ml for ferritin (p < 0.0001), 0.1 (-0.8 to 0.9) g/dl for hemoglobin (p = 0.9), 96 (-12 to 205) ml/min for absolute pVO2 (p = 0.08), 2.2 (0.5 to 4.0) ml/kg/min for pVO2/kg (p = 0.01), 60 (-6 to 126) seconds for treadmill exercise duration (p = 0.08), -0.6 (-0.9 to -0.2) for New York Heart Association (NYHA) functional class (p = 0.007), and 1.7 (0.7 to 2.6) for patient global assessment (p = 0.002). In anemic patients (n = 18), the difference (95 % CI) was 204 (31 to 378) ml/min for absolute pVO2 (p = 0.02), and 3.9 (1.1 to 6.8) ml/kg/min for pVO2/kg (p = 0.01). In non-anemic patients, NYHA functional class improved (p = 0.06). Adverse events were similar. The authors concluded that IV iron loading improved exercise capacity and symptoms in patients with CHF and evidence of abnormal iron metabolism. Benefits were more evident in anemic patients.

Anker et al (2009) examined if treatment with IV iron (ferric carboxymaltose) would improve symptoms in patients who had heart failure, reduced left ventricular ejection fraction (LVEF), and iron deficiency, either with or without anemia. These researchers enrolled 459 patients with CHF of NYHA functional class II or III, a LVEF of 40 % or less (for patients with NYHA class II) or 45 % or less (for NYHA class III), iron deficiency (ferritin level less than 100 microg/L or between 100 and 299 microg/L, if the transferrin saturation was less than 20 %), and a Hb level of 95 to 135 g/L. Patients were randomly assigned, in a 2:1 ratio, to receive 200 mg of IV iron (ferric carboxymaltose) or saline (placebo). The primary end points were the self-reported Patient Global Assessment and NYHA functional class, both at week 24. Secondary end points included the distance walked in 6 minutes and the health-related quality of life. Among the patients receiving ferric carboxymaltose, 50 % reported being much or moderately improved, as compared with 28 % of patients receiving placebo, according to the Patient Global Assessment (odds ratio
for improvement, 2.51; 95 % CI: 1.75 to 3.61). Among the patients assigned to ferric carboxymaltose, 47 % had an NYHA functional class I or II at week 24, as compared with 30 % of patients assigned to placebo (odds ratio for improvement by one class, 2.40; 95 % CI: 1.55 to 3.71). Results were similar in patients with anemia and those without anemia. Significant improvements were seen with ferric carboxymaltose in the distance on the 6-minute walk test and quality-of-life assessments. The rates of death, adverse events, and serious adverse events were similar in the two study groups. The authors concluded that treatment with IV ferric carboxymaltose in patients with CHF and iron deficiency, with or without anemia, improves symptoms, functional capacity, and quality of life; the side-effect profile was acceptable.

In a randomized, controlled trial, Van Wyck and colleagues (2009) assessed the safety and effectiveness of rapid, large-dose IV administration of ferric carboxymaltose compared to oral iron in correcting iron deficiency anemia due to heavy uterine bleeding. A total of 477 women with anemia, iron deficiency, and heavy uterine bleeding were assigned to receive either IV ferric carboxymaltose (less than or equal to 1,000 mg over 15 mins, repeated weekly to achieve a total calculated replacement dose) or 325 mg of ferrous sulfate (65 mg elemental iron) prescribed orally thrice-daily for 6 weeks. Compared to those assigned to ferrous sulfate, more patients assigned to ferric carboxymaltose responded with a Hb increase of 2.0 g/dL or more (82 % versus 62 %, 95 % CI for treatment difference: 12.2 to 28.3, p < 0.001), more achieved a 3.0 g/dL or more increase (53 % versus 36 %, p < 0.001), and more achieved correction (Hb greater than or equal to 12 g/dL) of anemia (73 % versus 50 %, p < 0.001). Patients treated with ferric carboxymaltose compared to those prescribed ferrous sulfate reported greater gains in vitality and physical function and experienced greater improvement in symptoms of fatigue (p < 0.05). There were no serious adverse drug events. The authors concluded that in patients with iron deficiency anemia due to heavy uterine bleeding, rapid IV administration of large doses of a new iron agent, ferric carboxymaltose, is more effective than oral iron therapy in correcting anemia, replenishing iron stores, and improving quality of life.

In a randomized, double-blind, placebo-controlled, multi-center study, Grote et al (2009) examined the effect of IV iron sucrose or placebo on symptoms in patients with restless legs syndrome (RLS) and mild-to-moderate iron deficit. A total of 60 patients with primary RLS (7 males, age of 46 +/-9 years, S-ferritin less than or equal to 45 microg/L) were recruited from a cohort of 231 patients and were randomly assigned in a 12-months double-blind, multi-center study of iron sucrose 1,000 mg (n = 29) or saline (n = 31). The primary efficacy variable was the RLS severity scale (IRLS) score at week 11. Median IRLS score decreased from 24 to 7 (week 11) after iron sucrose and from 26 to 17 after placebo (p = 0.123, non-significant for between treatment comparison). The corresponding scores at week 7 were 12 and 20 in the two groups (p = 0.017). Drop-out rate because of lack of efficacy at 12 months was 19/31 after placebo and 5/29 patients after iron sucrose (Kaplan-Meier estimate, log-rank test p = 0.0006) suggesting an iron induced superior long-term RLS symptom control. Iron sucrose was well-tolerated. This study showed a lack of superiority of iron sucrose at 11 weeks but found evidence that iron sucrose reduced RLS symptoms both in the acute phase (7 weeks) and during long-term follow-up in patients with variable degree of iron deficiency. The authors concluded that further studies on target patient groups, dosing and dosing
intervals are needed before iron sucrose could be considered for treatment of iron deficient patients with RLS.

In a randomized, double-blind, placebo-controlled trial, Earley et al (2009) examined if high-dose (1,000 mg) IV iron sucrose could improve symptoms and change brain iron concentrations in idiopathic RLS. Primary measures of the clinical status were global rating scale (GRS) and periodic leg movements of sleep (PLMS). Primary measures of brain iron status were cerebrospinal fluid (CSF) ferritin and magnetic resonance imaging (MRI)-determined iron in the substantia nigra. At the time of the interim analysis, there were 7 placebo and 11 iron-treated subjects. At 2 weeks post-treatment, iron treatment resulted in a small but significant increase in CSF ferritin and a decrease in RLS severity (GRS); but did not change PLMS or MRI iron index. None of the secondary outcomes changed with treatment. There was no single case of clear treatment benefit in any of the patients. This interim analysis revealed an effect size that was too small to allow for adequate power to find significant differences with the planned 36-subject enrollment for either the primary objective outcome of PLMS or any of the secondary outcomes. The study was stopped at this planned break-point given the lack of both adequate power and any indication for clinically significant benefit. The authors concluded that high-dose IV iron failed to demonstrate the robust changes reported in 3 prior open-label studies. Differences in iron formulation, dosing regiment, and peripheral iron status may explain some of the discrepancies between this and previous IV iron treatment studies.

Zilberman et al (2010) evaluated the prevalence of RLS in anemic patients with CHF and chronic renal failure (CRF) and evaluated the effect of anemia treatment on RLS. A total of 38 anemic CHF-CRF patients were treated with subcutaneous EPO and IV iron over 1 year. They were questioned initially and at 3 months post-treatment about symptoms of RLS according to standard criteria. They were also contacted by telephone about RLS symptoms 12 months after onset of anemia treatment. Restless legs syndrome was found in 15 (39.5 %) of the 38 patients. In 10 (66.7 %) patients it was present at least 6 days a week. The prevalence of the RLS initially was not related to Hb, to serum iron or % transferrin saturation. Diabetes and lower serum ferritin were more common in the RLS group (p < 0.05). After 3 months of treatment, Hb increased from 10.4 +/- 0.8 to 12.3 +/- 1.2 g/dL, but RLS symptoms did not change. By 12 months, the prevalence and frequency of RLS complaints was similar to what it had been initially. The authors concluded that RLS is common and often undiagnosed and untreated in anemic CHF-CRF patients. Unfortunately, successful treatment of anemia with EPO and IV iron did not improve this condition.

In a Cochrane review, Trotti et al (2012) evaluated the effects of iron supplementation (oral or intravenous) for patients with RLS. These investigators searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (January 1995 to April 2011); EMBASE (January 1995 to April 2011); PsycINFO (January 1995 to April 2011); and CINAHL (January 1995 to April 2011). Corresponding authors of included trials and additional members of the International Restless Legs Syndrome Study Group were contacted to locate additional published or unpublished trials. Controlled trials comparing any formulation of iron with placebo, other medications, or no treatment in adults diagnosed with RLS according to expert clinical interview or explicit diagnostic
criteria. Two review authors extracted data and at least 2 authors assessed trial quality. They contacted trial authors for missing data. A total of 6 studies (192 total subjects) were identified and included in this analysis. The quality of trials was variable. The primary outcome was restlessness or uncomfortable leg sensations, which was quantified using the IRLS severity scale in 4 trials and another RLS symptom scale in a 5th trial. Combining data from the 4 trials using the IRLS severity scale, there was no clear benefit from iron therapy (mean difference in IRLS severity scores of -3.79, 95% CI: -7.68 to 0.10, p = 0.06).

However, the 5th trial did find iron therapy to be beneficial (median decrease of 3 points in the iron group and no change in the placebo group on a 10-point scale of RLS symptoms, p = 0.01). Quality of life was improved in the iron group relative to placebo in some studies but not others. Changes in periodic limb movements were not different between groups (measured in 2 studies). Objective sleep quality, subjective sleep quality and daytime functioning were not different between treatment groups in the studies that assessed them. The single study of subjects with end stage renal disease did show a benefit of therapy. Most trials did not require subjects to have co-morbid iron deficiency and several excluded patients with severe anemia. The single study that was limited to iron deficient subjects did not show clear benefit of iron supplementation on RLS symptoms. There was no clear superiority of oral or intravenous delivery of iron. Iron therapy did not result in significantly more side effects than placebo (RR 1.39, 95% CI: 0.85 to 2.27). The authors concluded that there is insufficient evidence to determine whether iron therapy is beneficial for the treatment of RLS. They stated that further research to determine whether some or all types of RLS patients may benefit from iron therapy, as well as the best route of iron administration, is needed.

CPT Codes / HCPCS Codes / ICD-9 Codes

Other CPT codes related to the CPB:

- 96365 - Intravenous infusion administration
- 96368
- 96372 - Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
- 96374 - Intravenous push administration
- 96379

HCPCS codes covered if selection criteria are met:

- J1750 - Injection, iron dextran, 50 mg
- J1756 - Injection, iron sucrose, 1 mg
- J2916 - Injection, sodium ferric gluconate complex in sucrose injection, 12.5 mg
Intravenous Iron Therapy

Q1038 Injection, Ferumoxytol, for treatment of iron deficiency anemia, 1mg (non-ESRD use) [Feraheme] [for iron deficiency anemia with chronic kidney disease]

Q1039 Injection, Ferumoxytol, for treatment of iron deficiency anemia, 1mg (for ESRD on dialysis) [Feraheme] [for iron deficiency anemia in chronic kidney disease]

Other HCPCS codes related to the CPB:

J0885 Injection, epoetin alfa, (for non-ESRD use), 1,000 units
J0886 Injection, epoetin alfa, 1000 units (for ESRD on dialysis)
Q4081 Injection, epoetin alfa, 100 units (for ESRD on dialysis)

ICD-9 codes covered if selection criteria are met (not all-inclusive):

275.0 Disorders of iron metabolism
280.0 - 280.9 Iron deficiency anemias
285.0 Sideroblastic anemia
285.8 Other specified anemias [chemotherapy-induced anemia]
425.4 Other primary cardiomyopathies (e.g., congestive, constrictive, familial, hypertrophic, idiopathic, non-obstructive, obstructive, restrictive)
428.0 - 428.9 Heart failure
555.0 - 555.9 Regional enteritis [Crohn's disease]
556.0 - 556.9 Ulcerative colitis
585.1 - 585.9 Chronic kidney disease (CKD)
626.2 Excessive or frequent menstruation
626.3 Pubertal menorrhagia
627.0 Premenopausal menorrhagia
627.1 Postmenopausal bleeding
E933.1 Antineoplastic and immunosuppressive drugs causing adverse effects in therapeutic use [chemotherapy-induced anemia]
V15.81 Noncompliance with medical treatment
V45.11 - Renal dialysis status
V45.12
V59.01 Donors, blood, whole blood
ICD-9 codes not covered for indications listed in the CPB:

333.94 Restless legs syndrome

The above policy is based on the following references:

13. Madi-Jebara SN, Steilaty GS, Achoh PE, et al. Postoperative intravenous iron used alone or in combination with low-dose erythropoietin is not


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