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Intravenous Iron Therapy [Medicare]

Clinical Policy Bulletins | Medical Clinical Policy Bulletins

Number: 0575m

Commercial CPB (0575.html) | Medicare CPB

Medicare Part B Step Therapy Criteria

Feraheme, **Injectafer**, and **Monoferric**, for the indications listed below:

- Treatment of iron deficiency anemia after intolerance to oral iron or unsatisfactory response to oral iron; *or*
- Treatment of iron deficiency anemia in members with chronic kidney disease (CKD)

  Are not covered for new starts, unless the member meets ANY of the following:

  1. Inadequate response to a trial of Ferrlecit (sodium ferric gluconate), INFeD, or Venofer
  2. Intolerable adverse event to Ferrlecit (sodium ferric gluconate), INFeD, or Venofer
  3. Ferrlecit (sodium ferric gluconate), INFeD, or Venofer is contraindicated for the member.

Policy

Policy History

Effective: 01/01/2022

Next Review: 06/23/2022

Definitions

Additional Information

Clinical Policy Bulletin Notes

Note: Requires Precertification:

Precertification of ferric carboxymaltose injection (Injectafer) and ferumoxytol injection (Feraheme) are required of all Aetna participating providers and members in applicable plan designs. For precertification of ferric carboxymaltose injection (Injectafer) or ferumoxytol injection (Feraheme), call (866) 752-7021 (Commercial), (866) 503-0857 (Medicare), or fax (866) 267-3277.

Note: For the purposes of this policy, iron deficiency anemia (IDA) is defined as the following (unless otherwise specified in the policy):

- IDA without chronic kidney disease (CKD): serum ferritin less than 30 ng/dL or a transferrin saturation (TSAT) less than 20 percent confirms IDA.
- IDA with non-dialysis CKD: serum ferritin less than 100 ng/mL or TSAT less than 20 percent. If serum ferritin is 100-300 ng/mL, TSAT less than 20 percent is required to confirm IDA.
- IDA with hemodialysis-dependent CKD:
    - serum ferritin less than or equal to 200 ng/mL and TSAT less than or equal to 20 percent; or
    - serum ferritin less than 500 ng/mL and TSAT less than or equal to 30 percent and member has a hemoglobin less than 10 g/dL or is being treated with an erythropoiesis-stimulating agent (ESA).
- IDA with peritoneal dialysis-dependent CKD:
    - serum ferritin less than or equal to 100 ng/mL and TSAT less than or equal to 20 percent; or
    - serum ferritin is less than or equal to 500 ng/mL and TSAT less than or equal to 30 percent and member has a hemoglobin less than 10 g/dL.
- IDA with acute or chronic inflammatory conditions: serum ferritin less than 100 ng/mL or TSAT less than 20 percent. If serum ferritin is 100-300 ng/mL, TSAT less than 20 percent is required to confirm iron deficiency.

- Cancer-associated or chemotherapy-associated anemia:

  - absolute iron deficiency: serum ferritin less than 30 ng/mL and TSAT less than 20 percent; or
  - functional iron deficiency in members receiving ESAs is defined as a serum ferritin 30-500 ng/mL and TSAT less than 50 percent.

Ferric Carboxymaltose (Injectafer)

I. *Criteria for Initial Approval*

Aetna considers ferric carboxymaltose (Injectafer) intravenous iron therapy medically necessary for the following indications:

A. Member has documented iron deficiency anemia with an unsatisfactory response, intolerance or contraindication to oral iron administration, including:

1. Members needing iron supplementation who are unable to tolerate compounds given orally; *or*
2. Members who are losing iron (blood) at a rate too rapid for oral intake to compensate for the loss. This includes iron deficiency anemia due to heavy uterine bleeding, and members who are donating large amounts of blood for autologous programs; *or*
3. 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*
4. Members who repeatedly fail to heed instructions for oral iron supplementation or are incapable of accepting or following them; *or*
5. Members with iron deficiency following gastric bypass surgery and/or subtotal gastric resection and who exhibited decreased absorption of oral iron;

B. Member has documented iron deficiency and a diagnosis of *either* of the following:

1. Non-dialysis dependent (NDD) chronic kidney disease (CKD) and iron deficiency anemia; *or*
2. New York Heart Association (NYHA) functional class II or III heart failure with reduced ejection fraction (HRrEF) and iron deficiency (with or without anemia) (ferritin less than 100 ng/mL or 100-300 ng/mL if TSAT is less than 20 percent);

C. For management of cancer-associated or chemotherapy-associated anemia with or without combination use with an erythropoiesis-stimulating agent (ESA) (e.g., epoetin alpha, darbepoetin alfa);
D. For management of perioperative iron deficiency anemia when *all* the following criteria are met:

1. Member is scheduled for major abdominal surgery (e.g., gastric bypass, gastrectomy, colorectal resection, hysterectomy); *and*
2. Expected blood loss is greater than 500 mL; *and*
3. Member has documented iron deficiency anemia (defined as serum ferritin less than 30 ng/ml, or less than 100 ng/ml with TSAT less than 20%);

E. For treatment of moderate to severe restless leg syndrome (RLS) when member has low iron stores and member has an unsatisfactroy response, intolerance or contraindication to oral iron administration.

Aetna considers all other indications as experimental and investigational (for additional information, see Experimental and Investigational and Background sections).

II. *Continuation of Therapy*

Aetna considers continuation of ferric carboxymaltose (Injectafer) intravenous iron therapy medically necessary for members who meet criteria for an indication listed in Section I.

Ferric Derisomaltose (Monoferric)

I. *Criteria for Initial Approval*

Aetna considers ferric derisomaltose (Monoferric) intravenous iron therapy medically necessary for the following indications:

A. Member has documented iron deficiency anemia with an unsatisfactory response, intolerance or contraindication to oral iron administration, including:

1. Members needing iron supplementation who are unable to tolerate compounds given orally; *or*
2. Members who are losing iron (blood) at a rate too rapid for oral intake to compensate for the loss. This includes iron deficiency anemia due to heavy uterine bleeding, and members who are donating large amounts of blood for autologous programs; *or*
3. 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*
4. Members who repeatedly fail to heed instructions for oral iron supplementation or are incapable of accepting or following them; *or*
5. Members with iron deficiency following gastric bypass surgery and/or subtotal gastric resection and who exhibited decreased absorption of oral iron;

B. Member has documented iron deficiency anemia and a diagnosis of non-dialysis dependent (NDD) chronic kidney disease (CKD);

C. For management of cancer-associated or chemotherapy-associated anemia with or without combination use with an erythropoiesis-stimulating agent (ESA) (e.g., epoetin alpha, darbepoetin alfa).

Aetna considers all other indications as experimental and investigational (for additional information, see Experimental and Investigational and Background sections).

II. *Continuation of Therapy*

Aetna considers continuation of ferric derisomaltose (Monoferric) intravenous iron therapy medically necessary for members who meet criteria for an indication listed in Section I.

Ferumoxytol (Feraheme)

I. *Criteria for Initial Approval*

Aetna considers ferric ferumoxytol (Feraheme) intravenous iron therapy medically necessary for the following indications:

A. Member has documented iron deficiency anemia with an unsatisfactory response, intolerance or contraindication to oral iron administration, including:

1. Members needing iron supplementation who are unable to tolerate compounds given orally; *or*
2. Members who are losing iron (blood) at a rate too rapid for oral intake to compensate for the loss - this includes iron deficiency anemia due to heavy uterine bleeding, and members who are donating large amounts of blood for autologous programs; *or*
3. 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*
4. Members who repeatedly fail to heed instructions for oral iron supplementation or are incapable of accepting or following them; *or*
5. Members with iron deficiency following gastric bypass surgery and/or subtotal gastric resection and who exhibited decreased absorption of oral iron;

B. Member has documented iron deficiency anemia and a diagnosis of chronic kidney disease (CKD);
C. For management of cancer-associated or chemotherapy-associated anemia with or without combination use with an

erythropoiesis-stimulating agent (ESA) (e.g., epoetin alpha, darbepoetin alfa).

Aetna considers all other indications as experimental and investigational (for additional information, see Experimental and Investigational and Background sections).

II. *Continuation of Therapy*

Aetna considers continuation of ferric ferumoxytol (Feraheme) intravenous iron therapy medically necessary for members who meet criteria for an indication listed in Section I.

Iron Dextran (INFeD)

I. *Criteria for Initial Approval*

Aetna considers iron dextran (INFeD) intravenous iron therapy medically necessary for the following indications:

A. Member has documented iron deficiency with an unsatisfactory response, intolerance or contraindication to oral iron administration, including:

1. Members needing iron supplementation who are unable to tolerate compounds given orally; *or*
2. Members who are losing iron (blood) at a rate too rapid for oral intake to compensate for the loss - this includes iron deficiency anemia due to heavy uterine bleeding, and members who are donating large amounts of blood for autologous programs; *or*
3. 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*
4. Members who repeatedly fail to heed instructions for oral iron supplementation or are incapable of accepting or following them; *or*

5. Members with iron deficiency following gastric bypass surgery and/or subtotal gastric resection and who exhibited decreased absorption of oral iron;

B. For management of cancer-associated or chemotherapy-associated anemia with or without combination use with an erythropoiesis-stimulating agent (ESA) (e.g., epoetin alpha, darbepoetin alfa).

Aetna considers all other indications as experimental and investigational (for additional information, see Experimental and Investigational and Background sections).

II. *Continuation of Therapy*

Aetna considers continuation of iron dextran (INFeD) intravenous iron therapy medically necessary for members who meet criteria for an indication listed in Section I.

Iron Sucrose (Venofer)

I. *Criteria for Initial Approval*

Aetna considers iron sucrose (Venofer) intravenous iron therapy medically necessary for the following indications:

A. Member has documented iron deficiency anemia with an unsatisfactory response, intolerance or contraindication to oral iron administration, including:

1. Members needing iron supplementation who are unable to tolerate compounds given orally; *or*
2. Members who are losing iron (blood) at a rate too rapid for oral intake to compensate for the loss - this includes iron deficiency anemia due to heavy uterine bleeding, and members who are donating large amounts of blood for autologous programs; *or*
3. 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*

4. Members who repeatedly fail to heed instructions for oral iron supplementation or are incapable of accepting or following them; *or*
5. Members with iron deficiency following gastric bypass surgery and/or subtotal gastric resection and who exhibited decreased absorption of oral iron;

B. Member has documented iron deficiency anemia and a diagnosis of chronic kidney disease (CKD);
C. For management of cancer-associated or chemotherapy-associated anemia with or without combination use with an erythropoiesis-stimulating agent (ESA) (e.g., epoetin alpha, darbepoetin alfa).

Aetna considers all other indications as experimental and investigational (for additional information, see Experimental and Investigational and Background sections).

II. *Continuation of Therapy*

Aetna considers continuation of iron sucrose (Venofer) intravenous iron therapy medically necessary for members who meet criteria for an indication listed in Section I.

Sodium Ferric Gluconate Complex (Ferrlecit)

I. *Criteria for Initial Approval*

Aetna considers sodium ferric gluconate complex (Ferrlecit) intravenous iron therapy medically necessary for the following indications:

A. For treatment of iron deficiency anemia in members with chronic kidney disease (CKD) receiving hemodialysis and who are receiving supplemental epoetin therapy (e.g., epoetin alpha, darbepoetin alfa);

B. For management of cancer-associated or chemotherapy-associated anemia with or without combination use with an erythropoiesis-stimulating agent (ESA) (e.g., epoetin alpha, darbepoetin alfa).

Aetna considers all other indications as experimental and investigational (for additional information, see Experimental and Investigational and Background sections).

II. *Continuation of Therapy*

Aetna considers continuation of sodium ferric gluconate complex (Ferrlecit) intravenous iron therapy medically necessary for members who meet criteria for an indication listed in Section I.

Sodium Ferric Gluconate Complex with Ferric Pyrophosphate Citrate (Triferic)

I. *Criteria for Initial Approval*

Aetna considers sodium ferric gluconate complex with ferric pyrophosphate citrate (Triferic) intravenous iron therapy medically necessary for the replacement of iron to maintain hemoglobin (above 9 g/dL) in members with hemodialysis-dependent chronic kidney disease (HDD-CKD). Note: Triferic is not intended for use in members receiving peritoneal dialysis, and has not been studied in persons receiving home hemodialysis.

Aetna considers all other indications as experimental and investigational (for additional information, see Experimental and Investigational and Background sections).

II. *Continuation of Therapy*

Aetna considers continuation of sodium ferric gluconate complex with ferric pyrophosphate citrate (Triferic) intravenous iron therapy medically necessary for members who meet criteria for an indication listed in Section I.

See also CPB 0195 - Erythropoiesis Stimulating Agents (../100_199/0195.html) or CPB 0195m - Erythropoiesis Stimulating Agents [Medicare] (../100_199/0195m.html).

Dosage and Administration

The following dosing information is based on FDA-approved indications and recommendations per the prescribing information.

Feraheme (ferumoxytol)

Available as 510 mg iron per 17 mL (30 mg per mL) in single-dose vials.

Iron deficiency anemia in adults who have intolerance to oral iron or have had unsatisfactory response to oral iron, or who have chronic kidney disease (CKD):

- The recommended dose of Feraheme is an initial 510 mg dose followed by a second 510 mg dose 3 to 8 days later. Administer as intravenous infusion in 50-200 mL 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP over at least 15 minutes.

Source: AMAG Pharmaceuticals, 2020

Ferrlecit (sodium ferric gluconate complex)

Available as 62.5 mg/5 mL (12.5 mg/mL) in single-dose vials.

Iron deficiency anemia in adults and pediatrics age 6 years and older with chronic kidney disease (CKD) receiving hemodialysis who are receiving supplemental epoetin therapy:

- Recommended dose for adults: 10 mL (125 mg of elemental iron) diluted in 100 mL of 0.9% sodium chloride administered by intravenous infusion over 1 hour per dialysis session or undiluted as a slow intravenous injection (at a rate of up to 12.5 mg/min) per dialysis session;

- Recommended dose for pediatrics: 0.12 mL/kg (1.5 mg/kg of elemental iron) diluted in 25 mL 0.9% sodium chloride and administered by intravenous infusion over 1 hour per dialysis session;
- Ferrlecit treatment may be repeated if iron deficiency reoccurs.

Source: sanofi-aventis U.S., 2020

INFeD (iron dextran)

Available 50 mg/mL. Each mL contains the equivalent of 50 mg of elemental iron (as an iron dextran complex), approximately 0.9% sodium chloride, in water for injection.

Indicated for treatment of persons with documented iron deficiency in whom oral administration is unsatisfactory or impossible. Dosing is formula based. Please refer to the full prescribing information for more information.

Source: Allergan USA, 2020

Injectafer (ferric carboxymaltose)

Available as 750 mg iron per 15 mL single-dose vial.

Iron deficiency anemia in adults who have intolerance to oral iron or have had unsatisfactory response to oral iron, or who have non-dialysis dependent chronic kidney disease:

- Weight 50 kg (110 lb) or more: Give in two doses separated by at least 7 days. Give each dose as 750 mg for a total cumulative dose of 1500 mg of iron per course;
- Weight less than 50 kg (110 lb): Give in two doses separated by at least 7 days and give each dose as 15 mg/kg body weight;
- Injectafer treatment may be repeated if iron deficiency anemia reoccurs.

Source: American Regent, 2020

Monoferric (ferric derisomaltose)

Available in single-dose vials as 1,000 mg iron /10 mL (100 mg/mL), 500 mg iron/5 mL (100 mg/mL), and 100 mg iron/mL.

Iron deficiency anemia in adults who have intolerance to oral iron or have had unsatisfactory response to oral iron, or who have non-hemodialysis dependent chronic kidney disease:

- Weight 50 kg or more: Administer 1,000 mg as an intravenous infusion;
- Weight less than 50 kg: Administer as 20 mg/kg actual body weight as an intravenous infusion;
- Repeat treatment if iron deficiency anemia reoccurs.

Source: Pharmacosmos Therapeutics, 2020

Triferic (sodium ferric gluconate complex with ferric pyrophosphate citrate)

Available as 27.2 mg of iron (III) per 5 mL ampule (5.44 mg of iron (III) per mL), 272 mg of iron (III) per 50 mL ampule (5.44 mg of iron (III) per mL), and 272 mg iron (III) per powder packet.

Replacement of iron to maintain hemoglobin in adults with hemodialysis-dependent chronic kidney disease (HDD-CKD):

- Triferic solution or powder is to be added to the bicarbonate concentrate used for generation of hemodialysate. The final concentration of Triferic iron (III) in the final hemodialysate is 2 micromolar (110 mcg/L). The dosage of Triferic solution is expressed as mg of iron (III). Each mL of Triferic solution contains 5.44 mg of iron as iron (III).

    - Add one 5 mL Triferic ampule to 2.5 gallons of bicarbonate concentrate to achieve a final concentration of Triferic iron (III) in the final hemodialysate of 2 µM (110 mcg/L).
    - Add one 50 mL ampule of Triferic to each 25 gallons of bicarbonate concentrate to achieve a final concentration of

Triferic iron (III) in the final hemodialysate of 2 µM (110 mcg/L).

- Add one packet of Triferic powder to each 25 gallons of bicarbonate concentrate to achieve a final concentration of Triferic iron (III) in the final hemodialysate of 2 µM (110 mcg/L).

Administer Triferic at each dialysis procedure for as long as persons are receiving maintenance hemodialysis therapy for CKD. Hemodialysis bicarbonate solutions should be used within 24 hours of the preparation of the bicarbonate concentrate mixture.

Triferic is not intended for use in persons receiving peritoneal dialysis. Triferic has not been studied in persons receiving home hemodialysis.

Source: Rockwell Medical, 2018

Venofer (iron sucrose)

Available as 50 mg/2.5 mL, 100 mg/5 mL, or 200 mg/10 mL (20 mg/mL) in single-dose vials.

Indicated for the treatment of iron deficiency anemia (IDA) in persons with chronic kidney disease (CKD):

- Adult Hemodialysis Dependent Chronic Kidney Disease (HDD-CKD): 100 mg slow intravenous injection or infusion.
- Adult Non-Dialysis Dependent Chronic Kidney Disease (NDD-CKD): 200 mg slow intravenous injection or infusion.
- Adult Peritoneal Dialysis Dependent-Chronic Kidney Disease (PDD-CKD): 300 mg or 400 mg intravenous infusion.
- Pediatric HDD-CKD, PDD-CKD or NDD-CKD: 0.5 mg/kg slow intravenous injection or infusion.

Source: American Regent, 2020

Experimental and Investigational

I. Aetna considers intravenous iron therapy contraindicated and considered experimental and investigational for members with genetic hemochromatosis or hemochromatosis secondary to iron overload.

II. Aetna considers intravenous iron therapy experimental and investigational for all other indications including the following (not an all-inclusive list) because its clinical value for these indications has not been established.

A. Acute mountain sickness
B. Anemia of inflammation (excludes inflammatory bowel disease)
C. Anemia of pregnancy that does not meet medical necessity criteria above
D. Post-partum anemia that does not meet medical necessity criteria above
E. Prophylactic use to improve function in non-anemic persons undergoing orthopedic surgery (e.g., hip fracture)
F. Treatment of post-operative anemia following cardiothoracic surgery and neurosurgery that does not meet medical necessity criteria above.

III. Aetna considers pre-operative intravenous iron therapy experimental and investigational for reduction in need for transfusions from major surgery (excludes abdominal surgery per above) because the effectiveness of this approach has not been established.

IV. Aetna considers the Intrinsic Hepcidin IDxTest experimental and investigational for the management of iron-restricted disorders and iron overload disorders because its clinical value has not been established.

Background

Intravenous iron products provide supplemental iron, thereby increasing iron and ferritin levels while decreasing the total iron binding capacity. Intravenous (IV) iron products are used for the treatment of iron deficiency with or without anemia. Treatment is focused on addressing the underlying cause of the deficiency and replenishing adequate iron stores, regardless of the presence of symptoms. The rationale is that treatment will prevent the progression of anemia and risk for organ damage and/or ischemia. An exception is when iron depletion is used therapeutically (eg, porphyria cutanea tarda, polycythemia vera) (Auerbach, 2021b).

Short (2013) states that "ferritin reflects iron stores and is the most accurate test to diagnose iron deficiency anemia. Although levels below 15 ng per mL (33.70 pmol per L) are consistent with a diagnosis of iron deficiency anemia, using a cutoff of 30 ng per mL (67.41 pmol per L) improves sensitivity from 25 to 92 percent, and specificity remains high at 98 percent. Ferritin is also an acute phase reactant and can be elevated in patients with chronic inflammation or infection. In patients with chronic inflammation, iron deficiency anemia is likely when the ferritin level is less than 50 ng per mL (112.35 pmol per L). Ferritin values greater than or equal to 100 ng per mL (224.70 pmol per L) generally exclude iron deficiency anemia".

"A ferritin level below 30 ng/mL is considered diagnostic of iron deficiency regardless of the patient's underlying condition or hemoglobin concentration. A [transferrin saturation] TSAT <19 percent can also be used, mostly used in patients for whom the ferritin is thought to be unreliable due to an inflammatory state. The optimal threshold for TSAT has not been established. Confidence in the diagnosis of iron deficiency is very high if TSAT is <10% (<19% if concomitant inflammation); some experts use a threshold of <16%". More complex patients may require additional testing including TSAT, soluble transferrin receptor (sTfR) or sTfR-ferritin index, reticulocyte hemoglobin content (CHr), or bone marrow iron stain (Auerbach, 2021a).

Camaschella (2019) states that low serum ferritin levels are the hallmark of absolute iron deficiency, reflecting exhausted stores. Levels less than 30 mg/L are the accepted threshold that identifies mild cases; in the presence of anemia, ferritin levels are usually lower (less than 10-12

mg/L). In the absence of inflammations/infections, serum ferritin shows the best correlation with bone marrow stainable iron, once the gold standard in assessing depletion of iron stores. The author states that measuring transferrin saturation (less than 16%) is unnecessary for diagnosis, although it has diagnostic value in functional deficiency when serum ferritin is unreliable.

When treatment is indicated, the usual approach is repletion of iron. Blood transfusion is not routinely recommended as a treatment for iron deficiency unless the individual has severe anemia with hemodynamic instability (Auebach, 2021b).

Feraheme (ferumoxytol)

U.S. Food and Drug Administration (FDA)-Approved Indications for Feraheme (ferumoxytol)

- Feraheme is an iron replacement product indicated for the treatment of iron deficiency anemia (IDA) in adult patients:
  - who have intolerance to oral iron or have had unsatisfactory response to oral iron; or
  - who have chronic kidney disease (CKD).

Compendial Use for Feraheme (ferumoxytol)

- For management of cancer-associated or chemotherapy-associated anemia with or without combination use with an erythropoiesis-stimulating agent (ESA).

Fermumoxytol is available as Feraheme (AMAG Pharmaceuticals, Inc). Feraheme received FDA approval for intravenous use in 2009.

Feraheme carries a black box warning for risk for serious hypersensitivity and anaphylaxis reactions. The prescribing information states to only administer Feraheme as an intravenous infusion over at least 15 minutes and only when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions. Healthcare providers are to observe for signs or symptoms of hypersensitivity

reactions during and for at least 30 minutes following Feraheme infusion including monitoring of blood pressure and pulse during and after Feraheme administration. Hypersensitivity reactions have occurred in patients in whom a previous Feraheme dose was tolerated.

Feraheme includes the following warnings and precautions:

- Greater risk of anaphylaxis in patients with multiple drug allergies;
- Feraheme may cause hypotension;
- Iron Overload: Regularly monitor hematologic responses during Feraheme therapy. Do not administer Feraheme to patients with iron overload;
- Magnetic Resonance Imaging Test Interference: Feraheme can alter magnetic resonance imaging (MRI) studies.

The most common adverse reactions (2% or more) inlcude diarrhea, headache, nausea, dizziness, hypotension, constipation, and peripheral edema.

Ferrlecit (sodium ferric gluconate complex)

U.S. Food and Drug Administration (FDA)-Approved Indications for Ferrlecit (sodium ferric gluconate complex)

- Ferrlecit is an iron replacement product for treatment of iron deficiency anemia in adult patients and in pediatric patients age 6 years and older with chronic kidney disease receiving hemodialysis who are receiving supplemental epoetin therapy.

Compendial Use for Ferrlecit (sodium ferric gluconate complex)

- For management of cancer-associated or chemotherapy-associated anemia with or without combination use with an erythropoiesis-stimulating agent (ESA).

Sodium ferric gluconate complex is available as Ferrlecit (sanofi-aventis U.S.). Ferrlecit was approved for use by the FDA in 1999. Ferrlecit is used to replete the body content of iron. Iron is critical for normal

hemoglobin synthesis to maintain oxygen transport. Additionally, iron is necessary for metabolism and various enzymatic processes.

Ferrlecit carries the following warnings and precautions:

- Hypersensitivity Reactions: Monitor patients for signs and symptoms of hypersensitivity during and after Ferrlecit administration for at least 30 minutes and until clinically stable following completion of the infusion. Only administer Ferrlecit when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions.
- Ferrlecit may cause hypotension.
- Iron Overload: Regularly monitor hematologic responses during Ferrlecit therapy. Do not administer Ferrlecit to patients with iron overload.
- Benzyl Alcohol Toxicity: Premature and low-birth-weight infants may be more likely to develop toxicity.

The most commonly reported adverse reactions (10% or more) in adult patients were nausea, vomiting and/or diarrhea, injection site reaction, hypotension, cramps, hypertension, dizziness, dyspnea, chest pain, leg cramps, and pain. In patients 6 to 15 years of age the most common adverse reactions (10% or more) were hypotension, headache, hypertension, tachycardia and vomiting.

INFeD (iron dextran)

U.S. Food and Drug Administration (FDA)-Approved Indications for INFeD (iron dextran)

- INFeD is indicated for treatment of patients with documented iron deficiency in whom oral administration is unsatisfactory or impossible.

Compendial Uses for INFeD (iron dextran)

- For management of cancer-associated or chemotherapy-associated anemia with or without combination use with an erythropoiesis-stimulating agent (ESA).

Iron dextran is available as INFeD (Allergan USA). INFed was approved by the FDA for the treatment of iron deficiency anemia in whom oral administration is unsatisfactory or impossible. INFeD has been used clinically in the U.S since 1992. INFeD had been out of stock due to changes in the final product manufacturing site and issues with raw material supply, but re-entered the market in 2009 by Watson Pharmaceuticals, Inc.

INFeD carries a black box warning for risk for anaphylactic-type reactions, including fatalities, have followed the parenteral administration of iron dextran injection. The factors that affect the risk for anaphylactic-type reactions to iron dextran products are not fully known but limited clinical data suggest the risk may be increased among patients with a history of drug allergy or multiple drug allergies.

INFeD should be used with extreme care in patients with serious impairment of liver function. It should not be used during the acute phase of infectious kidney disease. Adverse reactions experienced following administration of INFeD may exacerbate cardiovascular complications in patients with pre-existing cardiovascular disease. A risk of carcinogenesis may attend the intramuscular injection of iron-carbohydrate complexes. Such complexes have been found under experimental conditionsto produce sarcoma when large doses or small doses injected repeatedly at the same site were given to rats, mice, and rabbits, and possibly in hamsters. The long latent period between the injection of a potential carcinogen and the appearance of a tumor makes it impossible to measure accurately the risk in man. There have, however, been several reports in the literature describing tumors at the injection site in humans who had previously received intramuscular injections of iron-carbohydrate complexes. Unwarranted therapy with parenteral iron will cause excess storage of iron with the consequent possibility of exogenous hemosiderosis. Such iron overload is particularly apt to occur in patients with hemoglobinopathies and other refractory anemias that might be erroneously diagnosed as iron deficiency anemias (Allergan, 2020).

Patients with rheumatoid arthritis may have an acute exacerbation of joint pain and swelling following the administration of INFeD. Reports in the literature from countries outside the United States (in particular, New

Zealand) have suggested that the use of intramuscular iron dextran in neonates has been associated with an increased incidence of gram-negative sepsis, primarily due to E. Coli (Allergan, 2020).

Injectafer (ferric carboxymaltose)

U.S. Food and Drug Administration (FDA)-Approved Indications for Injectafer (ferric carboxymaltose)

- Injectafer is an iron replacement product indicated for the treatment of iron deficiency anemia (IDA) in adult patients:
  - who have intolerance to oral iron or have had unsatisfactory response to oral iron; or
  - who have non-dialysis dependent (NDD) chronic kidney disease (CKD).

Compendial Uses for Injectafer (ferric carboxymaltose)

- For perioperative anemia management in abdominal surgery
- For treatment of iron-deficiency anemia in inflammatory bowel disease (IBD)
- For treatment of iron deficiency in heart failure with reduced ejection fraction (HRrEF)
- For treatment of moderate to severe restless leg syndrome (RLS) when patient has low iron stores.
- For management of cancer-associated or chemotherapy-associated anemia with or without combination use with an erythropoiesis-stimulating agent (ESA).

Ferric carboxymaltose is available as Injectafer (American Regent, Inc). Ferric carboxymaltose is a colloidal iron (III) hydroxide in complex with carboxymaltose, a carbohydrate polymer that releases iron. Injectafer was approved for use by the FDA in 2013.

Injectafer carries warnings and precautions for hypersensitivity reactions, symptomatic hypophosphatemia and hypertension. Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in

patients receiving Injectafer. In clinical trials, serious anaphylactic/anaphylactoid reactions were reported in 0.1% (2/1775) of subjects receiving Injectafer. Other serious or severe adverse reactions potentially associated with hypersensitivity which included, but not limited to, pruritus, rash, urticaria, wheezing, or hypotension were reported in 1.5% (26/1775) of these subjects (American Regent, 2020).

Symptomatic hypophosphatemia requiring clinical intervention has been reported in patients at risk of low serum phosphate in the postmarketing setting. These cases have occurred mostly after repeated exposure to Injectafer in patients with no reported history of renal impairment. Possible risk factors for hypophosphatemia include a history of gastrointestinal disorders associated with malabsorption of fatsoluble vitamins or phosphate, concurrent or prior use of medications that affect proximal renal tubular function, hyperparathyroidism, vitamin D deficiency and malnutrition. In most cases, hypophosphatemia resolved within three months (American Regent, 2020).

In clinical studies, hypertension was reported in 3.8% (67/1,775) of subjects in clinical trials 1 and 2. Transient elevations in systolic blood pressure, sometimes occurring with facial flushing, dizziness, or nausea were observed in 6% (106/1,775) of subjects in these two clinical trials. These elevations generally occurred immediately after dosing and resolved within 30 minutes.

The most common adverse reactions (2% or more) include nausea, hypertension, flushing, hypophosphatemia, and dizziness.

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.

Koo and colleagues (2020) stated that patient blood management aims to maintain Hb level, minimize blood loss, and avoid unnecessary blood transfusion. Ferric carboxymaltose, an i.v. iron agent, was included as a part of surgical patient blood management strategy. However, it is still controversial that ferric carboxymaltose can reduce transfusion requirements. In a systematic review and meta-analysis, these investigators examined the benefits of peri-operative ferric carboxymaltose on the post-operative hematological parameters and transfusion requirements; RCTs evaluating the effects of ferric carboxymaltose were searched through databases: Medline, Embase, CENTRAL, CINAHL, Scopus, Web of Science, and KoreaMed. Meta-analysis was performed using random effect models. A total of 8 studies (n = 471) were included in the final analysis. Post-operative Hb was higher in the ferric carboxymaltose group than in the control group (MD, 0.58 g/dL; 95 % CI: 0.36 to 0.80; p < 0.00001). Post-operative serum ferritin and transferrin saturation were also higher in the ferric carboxymaltose group (MD, 373.85 μg/L; 95 % CI: 298.13 to 449.56; p < 0.00001; MD, 10.35 %; 95 % CI: 4.59 to 16.10; p < 0.00001, respectively). However, there were no significant differences in the number of transfused patients, LOS, and AEs between groups. Subgroup analysis revealed that AEs were lower in the ferric carboxymaltose group than the oral iron group. The authors concluded that the findings of this study supported that ferric carboxymaltose may increase the post-operative Hb level in surgical patients. However, transfusion

requirements could not be reduced by ferric carboxymaltose. Moreover, these researchers stated that optimal dose and time should be further analyzed.

Monoferric (ferric derisomaltose)

U.S. Food and Drug Administration (FDA)-Approved Indications for Monoferric (ferric derisomaltose)

- Monoferric is an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients:
  - who have intolerance to oral iron or have had unsatisfactory response to oral iron
  - who have non-hemodialysis dependent (NDD) chronic kidney disease (CKD).

Compendial Use for Monoferric (ferric derisomaltose)

- For management of cancer-associated or chemotherapy-associated anemia with or without combination use with an erythropoiesis-stimulating agent (ESA).

Ferric derisomaltose is available as Monoferric (Pharmacosmos Therapeutics, Inc.). Ferric derisomaltose is a complex of iron (III) hydroxide and derisomaltose, an iron carbohydrate oligosaccharide that releases iron. Iron binds to transferrin for transport to erythroid precursor cells to be incorporated into hemoglobin (Pharmacosmos Therapeutics, 2020).

On January 16, 2020, the Food and Drug Administration (FDA) granted approval to ferric derisomaltose (Monoferric) 100 mg/mL for the treatment of iron deficiency anemia (IDA) in adult patients who have an intolerance or had unsatisfactory response to oral iron or patients who have non-hemodialysis dependent chronic kidney disease (NDD-CKD). The safety and efficacy of ferric derisomaltose for treatment of iron deficiency anemia (IDA) were evaluated in two 8-week, randomized, open-label, actively-controlled clinical trials performed in a total of 3050 patients with IDA of different etiology who were randomized to treatment with ferric

derisomaltose or iron sucrose. Trial 1 included patients with IDA who had intolerance to oral iron or who had had unsatisfactory response to oral iron or for whom there was a clinical need for rapid repletion of iron stores (Auerbach 2019; NCT02940886). Trial 2 included patients with IDA who had non-dialysis dependent chronic kidney disease (NDDCKD) (Bhandari 2019; NCT02940860). Both trials demonstrated the noninferiority of ferric derisomaltose (Monoferric) for change in hemoglobin from baseline to compared to iron sucrose.

Trial 1 included 1512 adult patients with IDA caused by different etiologies, who had documented intolerance or lack of response to oral iron or screening hemoglobin (Hb) measurement sufficiently low to require repletion of iron stores were randomized in a 2:1 ratio to treatment with ferric derisomaltose (n=1009) or iron sucrose (n=503). Adult patients aged ≥18 years with baseline Hb ≤11 g/dL, TSAT <20%, and s-ferritin <100 ng/mL were eligible for enrollment. The median age of patients was 44 years (range 18-91) and 89% were women. The primary efficacy endpoint was the change in Hb from baseline to week 8. Noninferiority was demonstrated for change in Hb from baseline to Week 8 with ferric derisomaltose compared with iron sucrose (2.49 vs. 2.49; 95% CI: -0.13, 0.13) (Auerbach 2019).

Trial 2 was a randomized, open-label, comparative, multi-center trial in 1538 patients with NDD-CKD. Patients were randomized 2:1 to either ferric derisomaltose administered at baseline as a single dose of 1000mg infused over 20 min or iron sucrose administered as 200 mg IV injections according to label and repeated up to 5 times. Adult patients aged ≥18 years with Hb ≤11 g/dL, s-ferritin ≤100 ng/mL (or ≤300 ng/mL if TSAT ≤30%), chronic renal impairment with eGFR between 15-59 mL/min, and either no ESAs or ESAs at a stable dose (+/-20 %) for 4 weeks before randomization were eligible for enrollment. The median age of patients was 69 years (range 25-97), 63% were female. All patients achieved the full dose in 1 visit with ferric derisomaltose whereas the majority of patients (79%) received 5 doses of iron sucrose. The co-primary endpoints were (1) change in hemoglobin from baseline to week 8 and (2) serious or severe hypersensitivity reactions (if the upper boundary of the 95% CI was <3%, the safety objective was met). Additional key safety endpoints included the risk of composite cardiovascular adverse events (AEs) and hypophosphatemia. Hypersensitivity reactions and

cardiovascular AEs were adjudicated and confirmed by an independent and blinded adjudication committee (Bhandari 2019). Non-inferiority in Hb change from baseline to week 8 was demonstrated for ferric derisomaltose (1.22 g/dL) versus iron sucrose (1.14 g/dL); 95% CI: -0.06, 0.23. Ferric derisomaltose led to a significantly more rapid and increased Hb response in the first 4 weeks. This was reflected in both Hb change from baseline (least square means) and proportion of responders with a Hb increase ≥1g/dL. The frequency of patients with serious or severe hypersensitivity reactions was 0.3% in the ferric derisomaltose group with an upper 95% CI of 0.86%. Thus, the primary safety objective was met. No reaction was observed with iron sucrose with an upper 95% CI of 0.73%, and there was no statistically significant difference between the groups. The incidence of patients with composite cardiovascular AEs was statistically significantly lower in the ferric derisomaltose group compared to the iron sucrose group (4.1 vs 6.9%, p=0.026). The frequency of hypophosphatemia (s-phosphate <2mg/dL) was low in both treatment groups, and no patient had a s-phosphate <1mg/dL (Bhandari 2019).

Ferric derisomaltose injection is contraindicated in patients with a history of serious hypersensitivity to ferric derisomaltose or any of its components. The most commonly reported adverse reactions (i.e., an incidence of 1% or greater) with ferric derisomaltose injections were rash (1.0%) and nausea(1.2%) (Monoferric Prescribing Information 2020). The prescribing information notes the dosage is expressed in mg of elemental iron and each mL of ferric derisomaltose contains 100 mg of elemental iron. The recommended dose of ferric derisomaltose recommends is 1000 mg by intravenous infusion over at least 20 minutes as a single dose for patients weighing 50 kg or more, with clinicians repeating dose if iron deficiency anemia reoccurs. In patients weighing under 50 kg, the recommended dose is 20 mg/kg actual body weight by intravenous infusion over at least 20 minutes as a single dose, with clinicians repeat dose if iron deficiency anemia reoccurs (Monoferric Prescribing Information 2020).

Triferic (sodium ferric gluconate complex with ferric pyrophosphate citrate)

U.S. Food and Drug Administration (FDA)-Approved Indications for Triferic (sodium ferric gluconate complex with ferric pyrophosphate citrate)

- Triferic is an iron replacement product indicated for the replacement of iron to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD).

  Limitations of Use:

  - Triferic is not intended for use in patients receiving peritoneal dialysis.
  - Triferic has not been studied in patients receiving home hemodialysis.

Sodium ferric gluconate complex with ferric pyrophosphate citrate is available as Triferic (Rockwell Medical, Inc.). Triferic was approved in 2015 by the FDA as the only FDA-approved therapy indicated to replace iron and maintain hemoglobin in hemodialysis -dependent chronic kidney disease patients via dialysate during each dialysis treatment, Triferic contains ferric pyrophosphate citrate, an iron solution for addition to bicarbonate dialysate for the replacement of iron to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease. Triferic binds iron immediately and completely to transferrin (carrier of iron in the body) upon entry into the blood and is then transported directly to the bone marrow to be incorporated into hemoglobin, with no increase in ferritin and no anaphylaxis. Triferic is available as 27.2 mg/mL solution for hemodialysis, and as 272 mg powder for solution for hemodialysis in hemodialysis -dependent chronic kidney disease patients. The Centers for Medicare & Medicaid Services (CMS) has established a new Level II Healthcare Common Procedure Coding System (HCPCS) code, or J-code (J1444), for Triferic powder packet, by Rockwell Medical, Inc. This unique J-code for the powder packet is separate and distinct from the existing J-code (J1443) that describes Triferic solution. The new J1444 code has the following descriptor "Injection, ferric pyrophosphate citrate powder, 0.1 mg of iron".

Triferic includes warnings and precautions for risk of hypersensitivity reactions. The most common adverse reactions in (greater than 3%) include procedural hypotension, muscle spasms, headache, peripheral edema, pain in extremity, dyspnea, pyrexia, urinary tract infection, back pain, asthenia, fatigue, AV fistula thrombosis, and AV fistula site hemorrhage.

Fishbane et al (2015; CRUISE 1 and CRUISE 2) stated administration of ferric pyrophosphate citrate (FPC, Triferic™) via hemodialysate may allow replacement of ongoing uremic and hemodialysis-related iron losses. FPC donates iron directly to transferrin, bypassing the reticuloendothelial system and avoiding iron sequestration. Two identical Phase 3, randomized, placebo-controlled trials (CRUISE 1 and 2) were conducted in 599 iron-replete chronic hemodialysis patients. Patients were dialyzed with dialysate containing 2 μM FPC-iron or standard dialysate (placebo) for up to 48 weeks. Oral or intravenous iron supplementation was prohibited, and doses of erythropoiesis-stimulating agents were held constant. The primary efficacy end point was the change in hemoglobin (Hgb) concentration from baseline to end of treatment (EoT). Secondary end points included reticulocyte hemoglobin content (CHr) and serum ferritin. In both trials, Hgb concentration was maintained from baseline to EoT in the FPC group but decreased by 0.4 g/dL in the placebo group ($P < 0.001$, combined results; 95% confidence interval [CI] 0.2-0.6). Placebo treatment resulted in significantly larger mean decreases from baseline in CHr (-0.9 pg versus -0.4 pg, $P < 0.001$) and serum ferritin (-133.1 μg/L versus -69.7 μg/L, $P < 0.001$) than FPC treatment. The proportions of patients with adverse and serious adverse events were similar in both treatment groups. The authors concluded that FPC delivered via dialysate during hemodialysis replaces iron losses, maintains Hgb concentrations, does not increase iron stores and exhibits a safety profile similar to placebo. FPC administered by hemodialysis via dialysate represents a paradigm shift in delivering maintenance iron therapy to hemodialysis patients.

Gupta et al (2015) stated ferric pyrophosphate citrate (FPC) is a water-soluble iron salt administered via dialysate to supply iron directly to transferrin. The PRIME study tested whether treatment with FPC could reduce prescribed erythropoiesis-stimulating agent (ESA) use and maintain hemoglobin in hemodialysis patients. This 9-month, randomized, placebo-controlled, double-blind, multicenter clinical study included 103 patients undergoing hemodialysis 3-4 times weekly. The FPC group received dialysate containing 2 μmol/l of iron. The placebo group received standard dialysate. A blinded central anemia management group facilitated ESA dose adjustments. Intravenous iron was administered according to the approved indication when ferritin levels fell below 200 μg/l. The primary end point was the percentage change from baseline in

prescribed ESA dose at end of treatment. Secondary end points included intravenous iron use and safety. At the end of treatment, there was a significant 35% reduction in prescribed ESA dose in FPC-treated patients compared with placebo. The FPC patients used 51% less intravenous iron than placebo. Adverse and serious adverse events were similar in both groups. Thus, FPC delivered via dialysate significantly reduces the prescribed ESA dose and the amount of intravenous iron needed to maintain hemoglobin in chronic hemodialysis patients.

Gupta et al (1999) stated soluble iron salts are toxic for parenteral administration because free iron catalyzes free radical generation. Pyrophosphate strongly complexes iron and enhances iron transport between transferrin, ferritin, and tissues. Hemodialysis patients need iron to replenish ongoing losses. We evaluated the short-term safety and efficacy of infusing soluble ferric pyrophosphate by dialysate. Maintenance hemodialysis patients receiving erythropoietin were stabilized on regular doses of intravenous (i.v.) iron dextran after oral iron supplements were discontinued. During the treatment phase, 10 patients received ferric pyrophosphate via hemodialysis as monthly dialysate iron concentrations were progressively increased from 2, 4, 8, to 12 micrograms/dl and were then sustained for two additional months at 12 micrograms/dl (dialysate iron group); 11 control patients were continued on i.v. iron dextran (i.v. iron group). Hemoglobin, serum iron parameters, and the erythropoietin dose did not change significantly from month 0 to month 6, both within and between the two groups. The weekly dose of i.v. iron (mean +/- SD) needed to maintain iron balance during month 6 was 56 +/- 37 mg in the i.v. iron group compared with 10 +/- 23 mg in the dialysate iron group (P = 0.001). Intravenous iron was required by all 11 patients in the i.v. iron group compared with only 2 of the 10 patients receiving 12 micrograms/dl dialysate iron. The incidence of adverse effects was similar in both groups. The authors concluded that slow infusion of soluble iron pyrophosphate by hemodialysis may be a safe and effective alternative to the i.v. administration of colloidal iron dextran in maintenance hemodialysis patients.

Pratt et al (2018) state tgere are several options available for intravenous application of iron supplements, but they all have a similar structure:-an iron core surrounded by a carbohydrate coating. These nanoparticles require processing by the reticuloendothelial system to release iron,

which is subsequently picked up by the iron-binding protein transferrin and distributed throughout the body, with most of the iron supplied to the bone marrow. This process risks exposing cells and tissues to free iron, which is potentially toxic due to its high redox activity. A new parenteral iron formation, ferric pyrophosphate citrate (FPC), has a novel structure that differs from conventional intravenous iron formulations, consisting of an iron atom complexed to one pyrophosphate and two citrate anions. In this study, we show that FPC can directly transfer iron to apo-transferrin. Kinetic analyses reveal that FPC donates iron to apo-transferrin with fast binding kinetics. In addition, the crystal structure of transferrin bound to FPC shows that FPC can donate iron to both iron-binding sites found within the transferrin structure. Examination of the iron-binding sites demonstrates that the iron atoms in both sites are fully encapsulated, forming bonds with amino acid side chains in the protein as well as pyrophosphate and carbonate anions. Taken together, these data demonstrate that, unlike intravenous iron formulations, FPC can directly and rapidly donate iron to transferrin in a manner that does not expose cells and tissues to the damaging effects of free, redox-active iron.

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.

Absolute iron deficiency is defined as a serum ferritin < 30 ng/mL *or* transferrin saturation (TSAT) < 15% (obtained within the last 30 days). A functional iron deficiency is defined as a serum ferritin < 100 ng/mL *and* TSAT < 20% (obtained within the last 30 days).

Venofer (iron sucrose)

U.S. Food and Drug Administration (FDA)-Approved Indications for Venofer (iron sucrose)

- Venofer is an iron replacement product indicated for the treatment of iron deficiency anemia (IDA) in patients with chronic kidney disease (CKD).

Compendial Uses for Venofer (iron sucrose)

- Iron deficiency anemia, (in patients without chronic kidney disease who are unresponsive to or poorly tolerant of oral iron therapy).
- For treatment of iron-deficiency anemia in inflammatory bowel disease (IBD).
- For management of cancer-associated or chemotherapy-associated anemia with or without combination use with an erythropoiesis-stimulating agent (ESA).
- For patients who have had bariatric surgery and are intolerant or refractory to oral iron or have refractory deficiency due to severe iron malabsorption.

Iron sucrose is available as Venofer (American Regent, Inc.). Venofer is an aqueous complex of poly-nuclear iron (III)-hydroxide in sucrose. Following intravenous administration, Venofer is dissociated into iron and sucrose and the iron is transported as a complex with transferrin to target cells including erythroid precursor cells. The iron in the precursor cells is incorporated into hemoglobin as the cells mature into red blood cells (American Regent, 2020).

Venofer was FDA approved in the U.S. in 2000. Venofer carries warnings and precautions for risk of hypersensitivity reactions, hypotension and iron overload. In adult patients, the most common adverse reactions (2% or more) include diarrhea, nausea, vomiting, headache, dizziness, hypotension, pruritus, pain in extremity, arthralgia, back pain, muscle cramp, injection site reactions, chest pain, and peripheral edema. In pediactic patients, the most most common adverse reactions (2% or more) include headache, respiratory tract viral infection, peritonitis, vomiting, pyrexia, dizziness, cough, nausea, arteriovenous fistula thrombosis, hypotension, and hypertension.

Abdominal Surgery and Iron Deficiency

DeFilipp et al (2013) noted that iron deficiency is a major post-operative complication of Roux-en-Y gastric bypass surgery. Oral replacement can fail to correct the deficiency. Thus, recourse to parenteral iron administration might be necessary. These researchers evaluated the safety and effectiveness of a standardized 2-g intravenous iron dextran

infusion in the treatment of iron deficiency after Roux-en-Y gastric bypass surgery. The setting was a university-affiliated community hospital in the United States. These investigators reviewed the medical records of 23 patients at their institution who had received 2 g of iron dextran intravenously for recalcitrant iron deficiency after Roux-en-Y gastric bypass surgery. They obtained the demographic data and the complete blood count and serum iron studies obtained before treatment and at outpatient visits after infusion. Before treatment, all 23 patients were iron deficient (average ferritin 6 ng/ml) and anemic (average hemoglobin 9.4 g/dL). By 3 months, the average ferritin and hemoglobin had increased to 269 ng/ml and 12.3 g/dL, respectively. The hemoglobin levels remained stable throughout the follow-up period. The iron stores were adequately replaced in most patients. Four patients required a repeat infusion by 1 year, because the ferritin levels had decreased to less than 15 ng/ml. The probability of remaining in an iron replete state was 84.6 % (95 % confidence interval: 78 to 91.2 %). One patient required warm compresses for superficial phlebitis. No other significant adverse events were reported. The authors concluded that intravenous administration of 2 g of iron dextran corrected the anemia and repleted the iron stores for greater than or equal to 1 year in most patients. This therapy is safe, tolerable, efficient, and effective.

Malone et al (2013) evaluated their management of Roux-en-Y gastric bypass surgery (RYGB) patients with iron deficiency (ID) and anemia. Clinic visit records of RYGB patients with ID or anemia from January 1, 2008, to February 1, 2010 were evaluated. Demographic characteristics, post-surgery iron and anemia indices, and prescribed treatments were recorded. Three separate definitions for ID and anemia were used (standard textbook, ASBMS, and recent literature). An intravenous iron protocol was later implemented, and follow-up laboratory values were obtained. A total of 125 with ID or anemia (89 % female, 86 % Caucasian), mean (SD) age of 44.7 (8.6) years, and body mass index (BMI) of 47.3 (10.8) kg/m(2) at time of RYGB, were included. Proportion of values meeting criteria for ID or anemia at first follow-up: standard textbook, hemoglobin (Hb, 35 %), transferrin saturation (Tsat, 48 %), ferritin (28 %); ASBMS, ferritin (43 %); recent literature, ferritin (58 %), serum iron (21 %). At mean follow-up of 45.7 (43) months, oral iron (n = 49) or intravenous iron (n = 4) had been prescribed for 53 (42.4 %) patients, and 32 (25.6 %) patients received multiple blood transfusions.

Nine patients received intravenous iron using the new protocol (400 to 1,400 mg), resulting in increases in Hb (1.8 g/dL; $p < 0.05$) and ferritin (31.8 ng/ml; $p < 0.002$). The authors concluded that iron management was inadequate. Hematologic values often were deficient for sustained periods. Initially, few patients received intravenous iron after oral iron failure, many received no iron supplementation, and there was high use of blood transfusions. Subsequently, administration of intravenous iron was beneficial.

Obinwanne et al (2014) stated that laparoscopic Roux-en-Y gastric bypass (LRYGB) can lead to iron malabsorption through exclusion of the duodenum and proximal jejunum, decreased gastric acidity, and modified diet. Intravenous (IV) iron is a treatment for severe iron deficiency, but the incidence of iron deficiency and the frequency of treatment with IV iron after LRYGB are largely unknown. These researchers determined the incidence of iron deficiency and the frequency of IV iron administration after LRYGB. After obtaining IRB approval, the medical records of patients who underwent LRYGB from September 2001 to December 2011 were retrospectively reviewed. Inclusion criteria consisted of determination of at least 1 ferritin value after surgery. Patients were grouped by level of iron deficiency. Patients with at least 1 ferritin less than 50 ng/ml were considered iron deficient. Statistical analysis included ANOVA. There were 959 patients included; 84.9 % were female. Mean age was 43.8 years, and pre-operative body mass index was 47.4 kg/m(2); 492 (51.3 %) patients were iron deficient. Of these, 40.9 % were severely iron deficient, with a ferritin less than 30 ng/ml. Intravenous iron was required by 6.7 % (64 patients). After IV iron therapy, 53 % (34 patients) had improvement in hemoglobin and ferritin values, and 39 % (25 patients) had improvement in ferritin values only. The authors concluded that given the incidence of iron deficiency after LRYGB observed in this series, patients should have iron status monitored carefully by all providers and be appropriately referred for treatment. Female patients should be counseled that there is a 50 % chance they will become iron deficient after LRYGB.

The American Association of Clinical Endocrinologists, the Obesity Society, and the American Society for Metabolic & Bariatric Surgery's clinical practice guidelines on "The perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient -- 2013 update"

(Mechanick et al, 2013) stated that “Intravenous iron infusion (preferably with ferric gluconate or sucrose) may be needed for patients with severe intolerance to oral iron or refractory deficiency due to severe iron malabsorption”.

The University of Rochester Medical Center (2014) states that iron deficiency and anemia are common after a gastric bypass or other weight-loss surgery, especially in women. In fact, iron deficiency can occur in more than 50 % of women who are pre-menopausal who have this surgery. For some people, usually women with heavy menstrual periods, supplements aren’t enough. They may need iron through an IV, blood transfusions, or even surgical revision of the bypass to raise the amount of iron absorbed.

Furthermore, the American Society of Hematology (2014) notes that people who have undergone bariatric procedures, especially gastric bypass operations, are among individuals who are at highest risk for iron-deficiency anemia. In some cases, one’s doctor may recommend intravenous (IV) iron; IV iron may be necessary to treat iron deficiency in patients who do not absorb iron well in the gastro-intestinal tract, patients with severe iron deficiency or chronic blood loss, patients who are receiving supplemental erythropoietin, a hormone that stimulates blood production, or patients who cannot tolerate oral iron.

An UpToDate review on “Treatment of the adult with iron deficiency anemia” (Schrier and Auerbach, 2015) states that “For those who have undergone gastric bypass surgery and/or subtotal gastric resection, the limited ability of the remaining stomach to provide acid to protect ferric iron from being converted to an insoluble form, and for facilitating intestinal absorption of ferric as well as ferrous iron, makes intravenous iron an especially good choice. Some patients, especially those having undergone minimally invasive procedures, such as gastric banding, may tolerate oral iron. This is less likely in Roux-en-Y or bilio-pancreatic diversion procedures. However, it is important to remember that all gastric bypass patients have a host of other nutritional perturbations post-operatively, and intravenous iron may simplify care”.

Montano-Pedroso and associates (2016) stated that anemia and iron deficiency are common complications following post-bariatric abdominoplasty. Given the low oral absorbability of iron resulting from bariatric surgery, it has been hypothesized that post-operative intravenously administered iron supplementation could be used to treat anemia and to prevent the development of iron deficiency in these patients. In this multi-center, open-label, randomized clinical trial, 56 adult women undergoing post-bariatric anchor-line abdominoplasty will be allocated at a ratio of 1:1 for post-operative supplementation with 2 intravenously administered applications of 200-mg of iron saccharate or post-operative supplementation with 100-mg of iron polymaltose complex administered orally, twice-daily for 8 weeks. The primary outcome is the difference in mean Hb levels between the 2 groups at 8 post-operative weeks. Secondary outcomes evaluated at 1, 4 and 8 post-operative weeks include iron profile, reticulocyte count, overall quality of life measured using the Short-Form 36 Health Survey (SF-36) questionnaire, fatigue measured using the Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F), adverse effects and post-operative complications. The authors stated that this randomized clinical trial aims to evaluate the hematopoietic effectiveness of intravenously administered iron supplementation in patients undergoing post-bariatric abdominoplasty. A more effective recovery of Hb levels could help improve the patients' quality of life and could provide an improved hematological status in preparation for the subsequent and frequent plastic surgeries these patients undergo.

Munoz et al. (2017) developed a series of best-practice and evidence-based statements to advise on patient care with respect to anemia and iron deficiency in the peri-operative period. Recommendations include: The presence of anemia should be investigated in all surgical procedures with expected moderate-to-high blood loss (> 500 ml). Serum ferritin level < 30 μg.l−1 is the most sensitive and specific test used for the identification of absolute iron deficiency. However, in the presence of inflammation (C-reactive protein > 5 mg.l−1) and/or transferrin saturation < 20%, a serum ferritin level < 100 μg.l−1 is indicative of iron deficiency. Major, non-urgent surgery should be postponed to allow the diagnosis and treatment of anemia and iron deficiency. When treating anemia pre-operatively, the target hemoglobin concentration should be ≥ 130 g.l−1 in both sexes, to minimize the risk of transfusion-associated unfavorable

outcomes. Serum ferritin and transferrin saturation (TSAT) are commonly used for an initial evaluation of iron status. Serum ferritin level is the most widely-used test for evaluating iron stores, while TSAT reflects iron availability for erythropoiesis (TSAT < 20% indicates insufficient iron supply to support normal erythropoiesis).

Laso-Morales and associates (2018) stated that evidence on the role of IVI supplementation after colorectal cancer (CRC) surgery is rather scant. In a retrospective, single-center, observational study, these investigators examined the benefit of post-operative IVI administration after elective CRC surgery. Anemia was defined as a Hb of less than 13 g/dL, regardless of gender. Anemic patients received 200 mg IVI up to 3 times a week to cover iron deficiency (IVI group). Those who did not receive IVI were placed on standard care (NIVI group). The primary outcome was the proportion of anemic patients on post-operative day (POD)1 and POD30; secondary outcomes included Hb changes from POD1 to POD30, transfusion requirements and complication rates. Of the 159 patients studied, 139 (87 %) presented with anemia: 47 (34 %) of these received post-operative IVI and 92 (66 %) did not. Patients in the IVI group had lower POD1 Hb levels compared to those in the NIVI group ($p = 0.001$). On POD30, only 103 had their Hb measured (34 IVI, 69 NIVI). Anemia was more prevalent and more severe among the patients in the IVI group ($p = 0.027$), despite their greater increment in Hb (2.0 ± 1.5 g/dL versus 1.1 ± 1.2 g/dL; $p = 0.001$); 11 patients needed post-operative transfusions (7 IVI, 4 NIVI; $p = 0.044$). There were no differences in post-operative complication rates between the groups. No IVI-related AEs were recorded. The authors concluded that compared with standard care, post-operative IVI administration to anemic patients improved the recovery of Hb levels at POD30, without increasing post-operative complications. Moreover, they stated that a prospective, randomized study to provide convincing evidence of the benefits of post-operative IVI therapy and to determine the potential for adverse effects in subjects undergoing CRC surgery is ongoing.

Wilson and co-workers (2018) stated that in patients with CRC, iron therapy, and especially IVI therapy, is increasingly used to treat anemia and reduce the use of blood transfusions. However, iron has also been shown to be an essential nutrient for rapidly proliferating tissues and cells. In this respect, anemia of inflammation, characterized by limited

duodenal iron uptake and sequestration of iron into the reticulo-endothelial system, might be regarded as a potentially effective defense strategy of the human body against tumor growth. These investigators hypothesized that iron therapy, by supporting colorectal tumor growth and increasing the metastatic potential, may worsen tumor prognosis in CRC patients. This hypothesis is particularly supported for CRC by laboratory, epidemiological and animal studies, demonstrating the role of iron in all aspects of tumor development growth. Compared to non-malignant colon cells, tumor cells differ in the levels and activity of many iron import and export proteins, resulting in an increase in intracellular iron level and enhanced proliferation. In addition, it has been demonstrated that iron is able to amplify Wnt signaling in tumors with Apc mutation, a critical mutation in the development of CRC. The authors concluded that if their hypothesis is to be confirmed, current practice of iron administration, as treatment for anemia and as replacement of blood transfusions, can be hazardous and should be completely reconsidered.

Warner et al. (2020) state that anemia is common in the perioperative period and is associated with poor patient outcomes. This article provides practical information regarding the implementation of anemia management strategies in surgical patients throughout the perioperative period. This includes evidence-based recommendations for the prevention, diagnosis, and treatment of anemia, including the utility of iron supplementation and erythropoiesis-stimulating agents (ESAs). It must be recognized that currently used definitions of anemia (ie, hemoglobin <12 g/dL in adult nonpregnant women, <13 g/dL in adult men according to World Health Organization [WHO] criteria) are primarily derived from observed distributions of hemoglobin concentrations in epidemiologic studies and not by the physiologic significance of those values. Notably, women presenting for surgery with hemoglobin of 12 g/dL are twice as likely to be transfused as men presenting with hemoglobin of 13 g/dL, suggesting that preoperative hemoglobin values of 13 g/dL may be warranted irrespective of sex. Screening may be done using a point-of-care hemoglobin test, but should be confirmed with standard laboratory analysis before treatment. Assessment of iron status, storage, and synthetic capacity should be performed using commonly available tests such as serum iron level, ferritin level, transferrin saturation, total iron-binding capacity (TIBC), and reticulocyte hemoglobin content (CHr), to help differentiate between anemia states. Iron supplementation is the

treatment of choice for IDA. The choice between oral iron and intravenous (IV) iron should be one of shared patient decision-making considering patient preferences, the degree of anemia, and the timing of surgery. Oral iron therapy may be considered preoperatively when iron deficiency is mild and there is ample time before elective surgery. Oral therapy has several limitations despite its low cost, ease of access, and relative safety. The major limitation is gastrointestinal side effects, which drive adherence rates to <50%. These include nausea, abdominal pain, diarrhea, constipation, and black or tarry stools. In addition, oral iron may negatively impact the colonic microbiome, promote intestinal inflammation, and exacerbate colitis in those with inflammatory bowel disease. Beyond gastrointestinal side effects, oral supplementation is unlikely to correct IDA in the setting of ongoing bleeding, because the amount of iron absorbed from the gastrointestinal tract is limited to a few milligrams per day. Iron absorption is further diminished with meals, antacids, proton pump inhibitors, and inflammation. IV iron is preferred for patients who defer oral therapy, are intolerant or unresponsive to oral therapy, have severe anemia with hemoglobin <10 g/dL, and whose planned surgery is within 6 weeks. Formulations with very low labile iron content (low molecular weight iron dextran, ferumoxytol, ferric carboxymaltose, and iron isomaltoside) allow for rapid administration of large single doses, or total dose infusion (TDI).

Acute Mountain Sickness

In a randomized, double-blinded, placebo-controlled study, Ren et al (2015) examined the role of intravenous iron supplementation in the prevention of acute mountain sickness (AMS). A total of 41healthy Chinese low-altitude inhabitants living in Beijing, China (altitude of about 50 meters) were randomly assigned into intravenous iron supplementation (ISS group; n = 21) and placebo (CON group; n = 20) groups. Participants in the ISS group received iron sucrose supplement (200 mg) before flying to Lhasa, China (altitude of 4,300 meters). Acute mountain sickness (AMS) severity was assessed with the Lake Louise scoring (LLS) system within 5 days after landing on the plateau (at high altitude). Routine check-ups, clinical biochemistry, and blood tests were performed before departure and 24 hours after arrival. A total of 38 participants completed the study (ISS group: n = 19; CON group: n = 19). The rate of subjects with AMS (LLS greater than 3) was lower in the ISS

group compared with the CON group, but no significant differences were obtained ($p > 0.05$). There were no differences in patients' baseline characteristics. The physiological indices were similar in both groups except for serum iron concentrations (19.44 ± 10.02 versus 85.10 ± 26.78 μmol/L) and transferrin saturation rates (28.20 ± 12.14 versus 68.34 ± 33.12 %), which were significantly higher in the ISS group ($p < 0.05$). Finally, heart rate was identified as a contributing factor of LLS. The authors concluded that these preliminary findings suggested that intravenous iron supplementation has no significant protective effect on AMS in healthy Chinese low-altitude inhabitants.

Cancer-Associated and Chemotherapy-Induced Iron Deficiency Anemia

The National Comprehensive Cancer Network Drugs and Biologics Compendium (NCCN, 2021) recomend consideration for the use of IV iron supplementation for management of cancer- and chemotherapy-induced anemia. NCCN defines absolute iron deficiency as a serum ferritin less than 30 ng/mL and transferrin saturation (TSAT) less than 20%. A functional iron deficiency in members receiving ESAs is defined as a serum ferritin 30-500 ng/mL and TSAT less than 50%. Possible functional iron deficiency is defined as serum ferritin greater than 500-800 ng/mL and TSAT less than 50%.

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 % 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 = 0.0099 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 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.

Mhaskar and colleagues (2016) stated that ESAs are commonly used to treat chemotherapy-induced anemia (CIA). However, approximately 50 % of patients do not benefit. These investigators evaluated the benefits and harms related to the use of iron as a supplement to ESA and iron alone compared with ESA alone in the management of CIA. They searched for relevant trials from the Cochrane Central Register of Controlled Trials (CENTRAL) (issue January 1, 2016), Medline (1950 to February 2016), and www.clinicaltrials.gov without using any language limits. All RCTs comparing “iron plus ESA” or “iron alone” versus “ESA alone” in people with CIA were eligible for inclusion. They used standard methodological procedures expected by Cochrane. These researchers included 8 RCTs (12 comparisons) comparing ESA plus iron versus ESA alone enrolling 2,087 participants. They did not find any trial comparing iron alone versus ESAs alone in people with CIA. None of the included RCTs reported overall survival (OS). There was a beneficial effect of iron supplementation to ESAs compared with ESAs alone on hematopoietic response (RR 1.17, 95 % CI: 1.09 to 1.26; $p < 0.0001$; 1,712 participants; 11 comparisons; high-quality evidence). Assuming a baseline risk of 35 % to 80 % for hematopoietic response without iron supplementation, between 7 and 16 patients should be treated to achieve hematopoietic response in 1 patient. In subgroup analyses, RCTs that used IV iron favored ESAs and iron (RR 1.20 (95 % CI: 1.10 to 1.31); $p < 0.00001$; 1,321 participants; 8 comparisons), whereas the authors found no evidence for a difference in hematopoietic response in RCTs using oral iron (RR 1.04 (95 % CI: 0.87 to 1.24); $p = 0.68$; 391 participants; 3

comparisons). There was no evidence for a difference between the subgroups of IV and oral iron (p = 0.16). There was no evidence for a difference between the subgroups of types of iron (p = 0.31) and types of ESAs (p = 0.16) for hematopoietic response. The iron supplementation to ESAs might be beneficial as fewer participants treated with iron supplementation required RBC transfusions compared to the number of participants treated with ESAs alone (RR 0.74 (95 % CI: 0.60 to 0.92); p = 0.007; 1,719 participants; 11 comparisons; moderate-quality evidence). Assuming a baseline risk of 7 % to 40 % for RBC transfusion without iron supplementation, between 10 and 57 patients should be treated to avoid RBC transfusion in 1 patient. These researchers found no evidence for a difference in the median time to hematopoietic response with addition of iron to ESAs (HR 0.93 (95 % CI: 0.67 to 1.28); p = 0.65; 1,042 participants; 7 comparisons; low-quality evidence). In subgroup analyses, RCTs in which dextran (HR 0.95 (95 % CI: 0.36 to 2.52); p = 0.92; 340 participants; 3 comparisons), sucrose iron (HR 1.15 (95 % CI: 0.60 to 2.21); p = 0.67; 102 participants; 1 comparison) and sulfate iron (HR 1.24 (95 % CI: 0.99 to 1.56); p = 0.06; 55 participants; 1 comparison) were used showed no evidence for difference between iron supplementation versus ESAs alone compared with RCTs in which gluconate (HR 0.78 (95 % CI 0.65 to 0.94); p = 0.01; 464 participants; 2 comparisons) was used for median time to hematopoietic response (p = 0.02). There was no evidence for a difference between the subgroups of route of iron administration (p = 0.13) and types of ESAs (p = 0.46) for median time to hematopoietic response. These findings indicated that there could be improvement in the Hb levels with addition of iron to ESAs (MD 0.48 (95 % CI: 0.10 to 0.86); p = 0.01; 827 participants; 7 comparisons; low-quality evidence). In RCTs in which IV iron was used there was evidence for a difference (MD 0.84 (95 % CI: 0.21 to 1.46); p = 0.009; 436 participants; 4 comparisons) compared with oral iron (MD 0.07 (95 % CI: -0.19 to 0.34); p = 0.59; 391 participants; 3 comparisons) for mean change in Hb level (p = 0.03); RCTs in which dextran (MD 1.55 (95 % CI: 0.62 to 2.47); p = 0.001; 102 participants; 2 comparisons) was used showed evidence for a difference with iron supplementation versus ESAs alone compared with RCTs in which gluconate (MD 0.54 (95 % CI: -0.15 to 1.22); p = 0.12; 334 participants; 2 comparisons) and sulfate iron (MD 0.07 (95 % CI: -0.19 to 0.34); p = 0.59; 391 participants; 3 comparisons) were used for mean change in Hb level (p = 0.007); RCTs in which epoetin was used showed evidence for a difference with iron supplementation versus ESAs alone

(MD 0.77 (95 % CI: 0.25 to 1.29); p = 0.004; 337 participants; 5 comparisons) compared with darbepoetin use (MD 0.10 (95 % CI: -0.13 to 0.33); p = 0.38; 490 participants; 2 comparisons) for mean change in Hb level (p = 0.02). These researchers found no evidence for a difference in quality of life (QOL) with addition of iron to ESAs (SMD 0.01 (95 % CI: -0.10 to 0.12); p = 0.88; 1,124 participants; 3 RCTs; high-quality evidence). These investigators found no evidence for a difference in risk of grade III to IV thromboembolic events (RR 0.95 (95 % CI: 0.54 to 1.65); p = 0.85; 783 participants; 3 RCTs; moderate-quality evidence). The incidence of treatment-related mortality (TRM) was 0 % (997 participants; 4 comparisons; high-quality evidence). Other common AEs included vomiting, asthenia, and leukopenia, and were similar in both arms. Overall, the risk of bias across outcomes was high to low. Since the included RCTs had shorter follow-up duration (up to 20 weeks), the long-term effects of iron supplementation are unknown. The authors concluded that the findings of this systematic review showed that addition of iron to ESAs offers superior hematopoietic response, reduced the risk of RBC transfusions, and improved Hb levels, and appeared to be well-tolerated; none of the included RCTs reported OS. The authors found no evidence for a difference in QOL with iron supplementation.

Roger and colleagues (2017) noted that higher dosages of ESAs have been associated with adverse events (AEs). Intravenous iron is used to optimize ESA response and reduce ESA doses in hemodialysis (HD) patients; this meta-analysis evaluated the magnitude of this effect. These researchers performed a literature search using Medline, Embase and the Cochrane Collaboration Central Register of Clinical Trials from inception until December 2014, to identify of intravenous iron and ESA, in patients undergoing HD for end-stage kidney disease (ESKD). Dosing of IV iron in concordance with the Kidney Disease Improving Global Outcomes guidelines was considered optimal iron therapy. Of the 28 RCTs identified, 7 met the criteria for inclusion in the meta-analysis. Results of random-effects meta-analysis showed a statistically significant weighted mean (95 % CI) difference of -1,733 [-3073 to -392] units/week in ESA dose for optimal iron versus suboptimal iron. The weighted average change in ESA dose was a reduction of 23 % (range of -7 % to -55 %) attributable to appropriate dosing of IV iron. A comparison of IV iron versus oral iron/no iron (5 trials) showed a greater reduction in ESA dose, although this did not reach statistical significance (weighted mean

difference, 95 % CI: -2,433 [-5183 to 318] units/week). The weighted average change in ESA dose across the 5 trials was a reduction of 31 % (range of -8 % to -55 %). The authors concluded that significant reductions in ESA dosing may be achieved with optimal IV iron usage in the HD population, and suboptimal iron use may require higher ESA dosing to manage anemia.

Chronic Kidney Disease and Iron Deficiency

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 can not maintain adequate iron stores, particularly in the hemodialysis patient treated with erythropoiesis-stimulating agents (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.

Kidney Disease Improving Global Outcomes practice guidelines for anemia in chronic kidney disease (KDIGO; 2012) includes the following recommendations:

- Use of iron to treat anemia in CKD. When prescribing iron therapy, balance the potential benefits of avoiding or minimizing blood transfusions, erythropoiesis-stimulating agent (ESA) therapy, and anemia-related symptoms against the risks of harm in individual patients (e.g., anaphylactoid and other acute reactions, unknown long-term risks);
- For all pediatric CKD patients with anemia not on iron or ESA therapy, oral iron (or IV iron in CKD HD patients) administration is recommended when TSAT is less than or equal to 20% and ferritin is less than or equal to 100 ng/ml;
- For all pediatric CKD patients on ESA therapy who are not receiving iron supplementation, oral iron (or IV iron in CKD HD patients) administration is recommended to maintain TSAT greater than 20% and ferritin greater than 100 ng/ml;
- For adult CKD patients with anemia not on iron or ESA therapy, a trial of IV iron (or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy) is suggested if an increase in Hb concentration without starting ESA treatment is desired and TSAT is less than or equal to 30% and ferritin is less than or equal to 500 ng/ml;
- For adult CKD patients on ESA therapy who are not receiving iron supplementation, a trial of IV iron (or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy) is suggested if an increase in Hb concentration or a decrease in ESA dose is desired and TSAT is less than or equal to 30% and ferritin is less than or equal to 500 ng/ml;
- It is common practice to provide an initial course of IV iron amounting to approximately 1000 mg; this may be repeated if an initial dose fails to increase Hb level and/or allow a decrease in ESA dose and if the TSAT remains less than or equal to 30% and serum ferritin remains less than or equal to 500 ng/ml (less than or equal to 500 mg/l);
- There is no evidence that a higher ferritin target of 200 ng/ml (200 mg/l) is the appropriate or inappropriate cutoff in pediatric CKD HD patients. Consequently no change has been made to the 2006 KDOQI guideline in CKD in children with anemia, which recommended a ferritin target greater than 100 ng/ml (100 mg/l) for CKD 5HD, as well as for CKD 5PD and CKD ND who are on ESA therapy.

Macdougall et al. (2016) state that "the diagnosis of absolute iron deficiency is usually based on low serum ferritin concentrations (<20–30 µg/l) that reflect low body iron stores. In CKD patients, because of the presence of inflammation, threshold values indicating iron deficiency are generally considered to be higher than in those without kidney disease. Serum ferritin levels of 100 or 200 µg/l are frequently cited as a cutoff value in non-dialysis CKD and dialysis patients, respectively. Although the evidence is rather limited, it is generally felt that a transferrin saturation <20% is indicative of absolute iron deficiency, although transferrin saturations above this do not exclude this condition".

Camaschella (2019) states that intravenous iron is more effective than oral iron in CKD patients treated with erythropoiesis-stimulating agents (ESAs) and avoids oxidative damage to the intestinal mucosa in active inflammatory bowel diseases.

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 a Cochrane review, Gurusamy and colleagues (2014) evaluated the safety and effectiveness of iron therapies for the treatment of adults with anemia who are not pregnant or lactating and do not have CKD. These investigators ran the search on July 11, 2013. They searched the

Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, EMBASE (Ovid SP), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) Plus (EBSCO Host), the Institute for Scientific Information Web of Science (ISI WOS) Scientific Citation Index (SCI)-EXPANDED (1970) and Conference Proceedings Citation Index (CPCI)-Science (1990) and Clinicaltrials.gov; we also screened reference lists. An updated search was run on November 24, 2014 but the results have not yet been incorporated into the review. Two review authors independently selected references for further assessment by going through all titles and abstracts. Further selection was based on review of full-text articles for selected references. Two review authors independently extracted study data. These investigators calculated the RR with 95 % CI for binary outcomes and the mean difference (MD) or the standardized mean difference (SMD) with 95 % CI for continuous outcomes. They performed meta-analysis when possible, when I(2) was less than or equal to 80 % using a fixed-effect or random-effects model, using Review Manager software. The range of point estimates for individual studies is presented when I(2) is greater than 80 %. These researchers included in this systematic review 4,745 participants who were randomly assigned in 21 trials. Trials were conducted in a wide variety of clinical settings. Most trials included participants with mild-to-moderate anemia and excluded participants who were allergic to iron therapy. All trials were at high risk of bias for one or more domains. They compared both oral iron and parenteral iron versus inactive controls and compared different iron preparations. The comparison between oral iron and inactive control revealed no evidence of clinical benefit in terms of mortality (RR 1.05, 95 % CI: 0.68 to 1.61; 4 studies, n = 659; very low-quality evidence). The point estimate of the mean difference in Hb levels in individual studies ranged from 0.3 to 3.1 g/dL higher in the oral iron group than in the inactive control group. The proportion of participants who required blood transfusion was lower with oral iron than with inactive control (RR 0.74, 95 % CI: 0.55 to 0.99; 3 studies, n = 546; very low-quality evidence). Evidence was inadequate for determination of the effect of parenteral iron on mortality versus oral iron (RR 1.49, 95 % CI: 0.56 to 3.94; 10 studies, n = 2,141; very low-quality evidence) or inactive control (RR 1.04, 95 % CI: 0.63 to 1.69; 6 studies, n = 1,009; very low-quality evidence). Hemoglobin levels were higher with parenteral iron than with oral iron (MD -0.50 g/dL, 95 % CI: -0.73 to -0.27; 6 studies, n = 769; very low-quality evidence). The point estimate of the mean

difference in Hb levels in individual studies ranged between 0.3 and 3.0 g/dL higher in the parenteral iron group than in the inactive control group. Differences in the proportion of participants requiring blood transfusion between parenteral iron and oral iron groups (RR 0.61, 95 % CI: 0.24 to 1.58; 2 studies, n = 371; very low-quality evidence) or between parenteral iron groups and inactive controls (RR 0.84, 95 % CI: 0.66 to 1.06; 8 studies, n = 1,315; very low-quality evidence) were imprecise. Average blood volume transfused was less in the parenteral iron group than in the oral iron group (MD -0.54 units, 95 % CI: -0.96 to -0.12; very low-quality evidence) based on 1 study involving 44 people. Differences between therapies in quality of life or in the proportion of participants with serious adverse events were imprecise (very low-quality evidence). No trials reported severe allergic reactions due to parenteral iron, suggesting that these are rare. Adverse effects related to oral iron treatment included nausea, diarrhea and constipation; most were mild. Comparisons of one iron preparation over another for mortality, Hb or serious adverse events were imprecise. No information was available on quality of life. Thus, little evidence was found to support the use of one preparation or regimen over another. Subgroup analyses did not reveal consistent results; therefore these researchers were unable to determine whether iron is useful in specific clinical situations, or whether iron therapy might be useful for people who are receiving erythropoietin. The authors concluded that (i) very low-quality evidence suggested that oral iron might decrease the proportion of people who require blood transfusion, and no evidence indicated that it decreases mortality; (ii) oral iron might be useful in adults who can tolerate the adverse events, which are usually mild; (iii) very low-quality evidence suggested that intravenous iron resulted in a modest increase in Hb levels compared with oral iron or inactive control without clinical benefit; and (iv) no evidence can be found to show any advantage of one iron preparation or regimen over another. They stated that additional randomized controlled trials (RCTs) with low risk of bias and powered to measure clinically useful outcomes such as mortality, quality of life and blood transfusion requirements are needed.

Berns (2020a) states that among hemodialysis patients, "neither the TSAT nor serum ferritin accurately predicts which patients will have an improved response to ESAs after iron supplementation. Many

hemodialysis patients with TSAT 20 to 30 percent and serum ferritin 200 to 500 ng/mL will respond to supplemental iron administration with an increase in Hb level and/or reduction in ESA dose. As a result, such patients are commonly treated with iron prior to treatment with an ESA".

For treatment of iron deficiency in peritoneal dialysis patients, Berns (2020c) recommends IV iron for moderate or severe anemia (defined as Hb <10 g/dL, TSAT ≤30 percent, and ferritin ≤500 ng/mL). Although most peritoneal dialysis patients with TSAT of 20 to 30 percent and ferritin 200 to 500 ng/mL will have normal iron stores on bone marrow biopsy, many will respond to IV iron with an increase in Hb or decrease in erythropoiesis-stimulating agent (ESA) dose.

Heart Failure and Iron Deficiency

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 % confidence interval [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.

The 2016 European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic heart failure includes a Class IIa, A recommendation for IV ferric carboxymaltose in symptomatic patients with heart failure with reduced ejection fraction (HFrEF) and iron

deficiency (serum ferritin less than 100 0 µg/L, or ferritin between 100–299 µg/L and transferrin saturation <20%) in order to alleviate HF symptoms, and improve exercise capacity and quality of life.

According to the 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline in the managment of heart failure, anemia is independently associated with HF disease severity, and iron deficiency appears to be uniquely associated with reduced exercise capacity. When iron deficiency is diagnosed and after full evaluation for cause, intravenous repletion of iron, especially in the setting of concomitant hepcidin deficiency in HF, may improve exercise capacity and QoL. In patients with NYHA class II and III heart failure (HF) and iron deficiency (ferritin less than 100 ng/mL or 100 to 300 ng/mL if transferrin saturation is less than 20 percent), intravenous iron replacement might be reasonable to improve functional status and quality of life (LOE IIb, B-R).

Inflammation and Iron Deficiency Anemia

Dignass et al. (2018) state that patients with inflammatory conditions may have "restricted availability of iron for erythropoiesis and other cell functions due to increased hepcidin expression, despite normal or high levels of serum ferritin. The standard threshold for iron deficiency (<30 µg/L) therefore does not apply and transferrin saturation (TSAT), a marker of iron availability, should also be assessed. A serum ferritin threshold of <100 µg/L or TSAT < 20% can be considered diagnostic for iron deficiency in CHF, CKD, and IBD. If serum ferritin is 100–300 µg/L, TSAT < 20% is required to confirm iron deficiency".

Lofruthe and colleagues (2016) stated that intravenous iron supplementation is an effective therapy in IDA, but controversial in anemia of inflammation (AI). Unbound iron can be used by bacteria and viruses for their replication and enhance the inflammatory response. Nowadays available high molecular weight iron complexes for intravenous iron substitution, such as ferric carboxymaltose, might be useful in AI, as these pharmaceuticals deliver low doses of free iron over a prolonged period of time. These researchers tested the effects of intravenous iron carboxymaltose in murine AI: Wild-type mice were exposed to the heat-killed Brucella abortus (BA) model and treated with or without high molecular weight intravenous iron; 4 hours after BA

injection followed by 2 hours after intravenous iron treatment, inflammatory cytokines were up-regulated by BA, but not enhanced by iron treatment. In long-term experiments, mice were fed a regular or an iron-deficient diet and then treated with intravenous iron or saline 14 days after BA injection. Iron treatment in mice with BA-induced AI was effective 24 hours after iron administration. In contrast, mice with IDA (on iron deficiency diet) prior to BA-IA required 7 days to recover from AI. In these experiments, inflammatory markers were not further induced in iron-treated compared to vehicle-treated BA-injected mice. These results demonstrated that intravenous iron supplementation effectively treated the murine BA-induced AI without further enhancement of the inflammatory response. The authors concluded that further studies of intravenous iron treatment with high molecular weight complexes in other murine models (e.g., with viable and replicable pathogens) of AI, as well as in patients with acute or chronic inflammatory conditions, will have to be performed.

Inflammatory Bowel Disease and Iron Deficiency Anemia

Mamula et al (2002) noted that iron-deficiency anemia (IDA) is a frequent complication in children with inflammatory bowel disease (IBD). Parenteral iron therapy is rarely prescribed because of concern about potential side effects. These researchers retrospectively evaluated the safety and effectiveness of total dose intravenous (TDI) iron therapy. Charts of all the pediatric patients with IBD who received TDI iron therapy between February of 1994 and February of 2000 were reviewed. A total of 70 patients (20 with ulcerative colitis [UC] and 50 with Crohn disease [CD]) received a total of 119 TDI iron dextran infusions; 34 patients qualified for the efficacy analysis. The average increase in Hb concentration was 2.9 g/dL, ($p < 0.0001$); 11 immediate hypersensitivity reactions developed in 10 patients (9 % of the total number of infusions). None of the reactions was life-threatening and none required hospitalization. The authors concluded that total dose intravenous infusion of iron dextran, when appropriately used, is a safe and potentially effective treatment for children with IBD and IDA who are unresponsive to or non-compliant with oral iron therapy.

Plantz et al (2016) stated that IDA is a common complication of pediatric IBD. The effectiveness of oral iron supplementation in the treatment of IDA is limited by its slow onset of action, daily dosing, gastro-intestinal side effects, and potential for exacerbation of intestinal inflammation. Intravenous iron sucrose (IS) is a safe and effective alternative treatment for IDA in adults with IBD, but its role in the treatment of IDA in pediatric IBD is unclear. The primary aim of this study was to evaluate the use of IS in pediatric IBD patients with IDA and determine the clinical response measured by improvement in Hb. Secondary aim was to describe adverse events associated with IS use in this population. A retrospective chart review of all pediatric IBD patients receiving IS infusions for IDA at the Children's Hospital of Philadelphia between January 2011 and August 2015 was performed. The diagnosis of IDA was based on low Hb for age and sex, although serum concentrations of iron, ferritin, mean corpuscular volume, total iron-binding capacity, and red blood cell distribution width were also referenced to confirm the diagnosis. Patients who had a transfusion of blood products within 2 months of an IS infusion or who had no follow-up laboratory evaluation within 2 months of the last IS infusion were excluded from the efficacy analysis. Adverse events were reported descriptively. Repeated measures ANOVA was used to evaluate paired continuous variables with post-hoc testing performed using Tukey's test. A total of 75 patients (57 with Crohn disease, 10 with ulcerative colitis, and 8 with indeterminate colitis) received a total of 280 IS infusions with 4 patients receiving multiple treatment courses. Patients were administered 200 mg per dose, 2 mg/kg per dose, or dosing calculated based on total iron deficit. The mean treatment course (± SD) was 3.5 ± 1.6 doses; 52 patients qualified for analysis. The mean age (± SD) was 14.6 ± 3.1 years. There was a statistically significant increase in Hb over the treatment course, with mean Hb increasing from 9.6 ± 1.2 g/dL at baseline to 12.0 ± 1.3 g/dL after IS treatment ($p < 0.0001$). Post-hoc analysis revealed that change in Hb was greatest after 4 infusions with subsequent dosing having no increased benefit. There were no statistically significant differences in change in Hb between the 3 different IS doses. Twenty-two adverse events were reported in 15 patients (7.9 % of the total number of infusions), including blood pressure (8/22) and pulse fluctuations (6/22), pain at IV site (6/22), chills (1/22), and IV infiltration (1/22). No anaphylaxis reactions occurred. The patient with IV infiltration required IS infusion discontinuation. Otherwise, none of the adverse events resulted in IS discontinuation and none was life-

threatening, required treatment, or hospitalization. The authors concluded that this was one of the first reported studies on IS therapy in a cohort of children with IBD and suggested that IS is a safe and potentially effective treatment for IDA in pediatric IBD.

The American Gastroenterological Association (AGA) clinical practice guidelines on the gastrointestinal evaluation of iron deficiency anemia (Ko et al., 2020) state that serum ferritin is the most commonly used test for diagnosing iron deficiency, with proposed cutoff values ranging from 15 to 100 ng/mL. In patients with anemia, the AGA recommends using a cutoff of 45 ng/mL over 15 ng/mL when using ferritin to diagnose iron deficiency [Strong recommendation, high-quality evidence]. In patients with inflammatory conditions or chronic kidney disease, other laboratory tests such as C-reactive protein, transferrin saturation, or soluble transferrin saturation, may be needed in conjunction with ferritin to diagnose iron deficiency anemia. In some patients, such as those with chronic inflammatory conditions or chronic kidney disease, ferritin levels may not accurately reflect body iron stores. In these situations, other clinical tests, such as the serum iron, transferrin saturation, soluble transferrin receptor, or C-reactive protein, may be useful adjunctive tests to assist in the diagnosis of iron deficiency.

Intrinsic Hepcidin IDx Test

The Intrinsic Hepcidin IDx Test is a monoclonal antibody-based quantitative competitive enzyme-linked immunosorbent assay (ELISA) that aids in management of iron-restricted disorders, such as iron deficiency anemia, anemia of inflammation, and iron-refractory iron deficiency anemia (IRIDA). Hepcidin also aids in the management of iron overload disorders, such as hereditary hemochromatosis, and iron-loading anemias.

Liu and colleagues (2016) noted that iron is needed for most forms of organisms, and it is the most essential element for the functions of many iron-containing proteins involved in oxygen transport, cellular respiration, DNA replication, and so on. Disorders of iron metabolism are associated with diverse diseases, including anemias (e.g., iron-deficiency anemia and anemia of chronic diseases) and iron overload diseases, such as hereditary hemochromatosis and β-thalassemia. Hepcidin (encoded by

Hamp gene) is a peptide hormone synthesized by hepatocytes, and it plays an important role in regulating the systematic iron homeostasis. As the systemic iron regulator, hepcidin, not only controls dietary iron absorption and iron egress out of iron storage cells, but also induces iron re-distribution in various organs. Deregulated hepcidin is often observed in various iron-related diseases including anemias and iron overload disorders. In the case of iron overload disorders (e.g., hereditary hemochromatosis and β-thalassemia), hepatic hepcidin concentration is significantly reduced. Since hepcidin deregulation is responsible for iron disorder-associated diseases, these researchers examined the recent findings on therapeutics targeting hepcidin. Continuous efforts have been made to search for hepcidin mimics and chemical compounds that could be used to increase hepcidin level. These investigators carried out a literature search in PubMed, and research papers relevant to hepcidin regulation or hepcidin-centered therapeutic work were reviewed. On the basis of literature search, these researchers recapitulated recent findings on therapeutic studies targeting hepcidin, including agonists and antagonists to modulate hepcidin expression or its down-stream signaling. They also discussed the molecular mechanisms by which hepcidin level and iron metabolism are modulated. Elevating hepcidin concentration is an optimal strategy to ameliorate iron overload diseases, and also to relieve β-thalassemia phenotypes by improving ineffective erythropoiesis. These researchers stated that compared with conventional therapies (namely phlebotomy and blood transfusion), strategies targeting the hepcidin-ferroportin (FPN) axis may open a new avenue for hepcidin regulation through an endogenous physiological way by avoiding secondary iron overload and other implications.

Camaschella and co-workers (2020) stated that iron is biologically essential, but also potentially toxic; as such it is tightly controlled at cell and systemic levels to prevent both deficiency and overload. Iron regulatory proteins post-transcriptionally control genes encoding proteins that modulate iron uptake, recycling and storage and are themselves regulated by iron. The master regulator of systemic iron homeostasis is the liver peptide hepcidin, which controls serum iron through degradation of FPN in iron-absorptive enterocytes and iron-recycling macrophages. These investigators examined the most recent findings in iron biology, deregulation of the hepcidin-FPN axis in iron disorders and how research results have an impact on clinical disorders. Insufficient hepcidin

production is central to iron overload while hepcidin excess leads to iron restriction. Mutations of hemochromatosis genes result in iron excess by down-regulating the liver bone morphogenetic protein (BMP)-mothers against decapentaplegic homolog (SMAD) signaling pathway or by causing hepcidin-resistance. In iron-loading anemias, such as β-thalassemia, enhanced albeit ineffective erythropoiesis releases erythroferrone, which sequesters BMP receptor ligands, thereby inhibiting hepcidin. In iron-refractory, iron-deficiency anemia mutations of the hepcidin inhibitor TMPRSS6 up-regulate the BMP-SMAD pathway. Interleukin-6 (IL-6) in acute and chronic inflammation increases hepcidin levels, causing iron-restricted erythropoiesis and anemia of inflammation in the presence of iron-replete macrophages. The improved understanding of iron homeostasis and its regulation is having an impact on the established schedules of oral iron treatment and the choice of oral versus intravenous iron in the management of iron deficiency. Moreover, it is leading to the development of targeted therapies for iron overload and inflammation, mainly centered on the manipulation of the hepcidin-FPN axis.

The authors stated that ELISA kits can measure serum hepcidin levels; however, this does not provide any information additional to serum ferritin, since the 2 variables are tightly related. Some researchers proposed determining hepcidin levels in order to choose the better therapeutic route of administration of iron supplementation (oral versus intravenous), as well as its correct timing and schedule. However, besides being subject to circadian oscillations, hepcidin levels change rapidly in response to activating and inhibitory signals, making their measurement useful in only a limited number of conditions. A kit to measure human serum ERFE concentration is available for research purposes.

Kowdley and associates (2021) stated that hepcidin is the central regulator of systemic iron homeostasis via its interaction with FPN, the major cellular iron export protein . Hepcidin binding to FPN results in reduced iron export from macrophages and intestinal absorptive cells, leading to decreased serum iron levels. Hepcidin expression is influenced by several factors that include serum and liver iron stores, erythropoiesis, hypoxia, inflammation, and infection. Erythropoietic drive and hypoxia suppress hepcidin expression and promote red cell production. In contrast, inflammation and infection are associated with

increased hepcidin production to sequester iron intracellularly as a means of depriving microorganisms of iron. Chronic inflammation may up-regulate hepcidin expression through the IL-6-Janus kinase 2 (JAK2)-signal transducer and activator of transcription 3 (STAT3) pathway. The bone morphogenetic protein BMP- SMAD pathway is a major positive driver of hepcidin expression in response to either increased circulating iron in the form of transferrin or iron loading in organs. Hereditary hemochromatosis (HH) consists of several inherited disorders that cause inappropriately reduced hepcidin expression in response to body iron stores, leading to increased iron absorption from a normal diet. The most common form of HH is due to a mutation in the HFE gene, which causes a failure in the hepatocyte iron-sensing mechanism, leading to reduced hepcidin expression; the clinical manifestations of HFE-HH include increased serum transferrin-iron saturation and progressive iron loading in the liver and other tissues over time among patients who express the disease phenotype. The authors reviewed the physiologic mechanisms and cellular pathways by which hepcidin expression is regulated, and the different forms of HH resulting from various mutations that cause hepcidin deficiency. They also reviewed other drivers of hepcidin expression and the associated pathophysiologic consequences. Moreover, these researchers stated that hepcidin levels are also influenced by infection, inflammation, erythropoiesis, and hypoxia. Infection and inflammation increase hepcidin levels, whereas erythropoiesis and hypoxia reduce hepcidin levels. “Anemia of chronic disease” is likely a phenomenon of unopposed hepcidin production due to ongoing chronic inflammation. The understanding of the molecular biology and cell biology of hepcidin will allow for rational therapies using agonists or antagonists to hepcidin activity, and such compounds are already being studied in clinical trials.

Afsar et al (2021) stated that iron is an essential trace element involved in oxidation-reduction reactions, oxygen transport and storage, and energy metabolism. Iron in excess can be toxic for cells since iron produces reactive oxygen species and is important for survival of pathogenic microbes. There is a fine-tuning in the regulation of serum iron levels, determined by intestinal absorption, macrophage iron recycling, and mobilization of hepatocyte stores versus iron utilization, primarily by erythroid cells in the bone marrow. Hepcidin is the major regulatory hormone of systemic iron homeostasis and is up-regulated during inflammation. Hepcidin metabolism is altered in chronic kidney disease.

Ferroportin is an iron export protein and mediates iron release into the circulation from duodenal enterocytes, splenic reticuloendothelial macrophages, and hepatocytes. Systemic iron homeostasis is controlled by the hepcidin-FPN axis at the sites of iron entry into the circulation. Hepcidin binds to FPN, induces its internalization and intracellular degradation; thus, inhibiting iron absorption from enterocytes, and iron release from macrophages and hepatocytes. Recent data suggested that hepcidin, by slowing or preventing the mobilization of iron from macrophages, may promote atherosclerosis and may be associated with increased cardiovascular disease risk. These researchers examined the available evidence regarding the molecular and cellular pathways of systemic and autocrine hepcidin production and ascertains the answer to the question whether changes in hepcidin translate into clinical outcomes of all-cause and cardiovascular mortality, and cardiovascular and renal end-points.

Fisher and Babitt (2021) stated that iron homeostasis is tightly regulated to balance the iron requirement for erythropoiesis and other vital cellular functions, while preventing cellular injury from iron excess. The liver hormone hepcidin is the master regulator of systemic iron balance by controlling the degradation and function of the sole known mammalian iron exporter FPN. Liver hepcidin expression is coordinately regulated by several signals that indicate the need for more or less iron, including plasma and tissue iron levels, inflammation, and erythropoietic drive. Most of these signals regulate hepcidin expression by modulating the activity of the BMP-SMAD pathway, which controls hepcidin transcription. Genetic disorders of iron overload and iron deficiency have identified several hepatocyte membrane proteins that play a critical role in mediating the BMP-SMAD and hepcidin regulatory response to iron. However, the precise molecular mechanisms by which serum and tissue iron levels are sensed to regulate BMP ligand production and promote the physical and/or functional interaction of these proteins to modulate SMAD signaling and hepcidin expression remain uncertain. The authors focused on the current understanding and key unanswered questions regarding how the liver senses iron levels to regulate BMP-SMAD signaling and thereby hepcidin expression to control systemic iron homeostasis.

Furthermore, an UpToDate review on “Regulation of iron balance” (Camaschella, 2021) states that “Because of the lack of a standardized assay, hepcidin testing is not ready for regular clinical use, although a number of test platforms are under active investigation. Serum hepcidin levels may have diagnostic value in certain iron disorders”.

Orthopedic Surgery (e.g., Hip Fracture)

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 morbid-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.

Bielza Galindo and colleagues (2018) noted that there are no previous studies evaluating the effect of intravenous iron therapy on functional and cognitive status of patients with hip fracture (HF). A single-center randomized, placebo-controlled, double-blind and parallel treatment, clinical trial has been designed to evaluate the effectiveness of intravenous iron therapy during the peri-operative period in elderly patients suffering from a HF. Blinding will be ensured by the packaging of the drug infusion system. On days 1, 3, and 5 from admission, the intervention group will receive 200 mg Venofer (iron sucrose) diluted in 100 ml saline, and the control group 10 0ml saline, also on days 1, 3 and 5. Patients will received conventional treatment in ortho-geriatric unit of the Hospital Infanta Sofia. Functional variables (activities of daily living and walking), cognitive (cognitive status and delirium), surgical, demographic and clinical characteristics will be collected during admission in order to assess the impact of treatment. A safety analysis of the treatment will also performed. Patients will be followed-up at 3, 6, and 12 months. The study will attempt to provide evidence on the impact of the intravenous iron administration on functional recovery. It will be determined whether iron therapy negatively affects the incidence of post-operative delirium. Finally, report will be presented on the safety data of intravenous iron in elderly HF patients, as well as the impact on allogenic blood transfusion savings. The authors stated that the inclusion of elderly HF patients admitted to an ortho-geriatric unit, in a clinical trial, will help to improve the knowledge of the treatment impact on a usual scenario, and provide useful data for use in other units.

Shin and colleagues (2019) noted that peri-operative anemia frequently occurs in patients undergoing orthopedic surgery. In a systematic review and meta-analysis, these researchers examined the efficacy of peri-operative intravenous iron therapy (IVIT) on transfusion and recovery profiles during orthopedic surgery. They searched PubMed, Embase,

Cochrane, and Google Scholar for eligible clinical trials (RCTs; case-control studies [CCSs]) in comparing IVIT and no iron therapy, up to September 2018. Primary outcomes were the effects of IVIT on the proportion of patients transfused and units of RBCs transfused peri-operatively. Secondary outcomes were the effects of IVIT on recovery profiles, such as LOS, post-operative infection, and mortality. Subgroup analysis was performed based on iron dose (low: less than or equal to 300 mg, high: greater than 400 mg), IVIT period (pre-operative, post-operative, peri-operative), and study design. These investigators identified 12 clinical trials (4 RCTs with 616 patients and 8 CCSs with 1,253 patients); IVIT significantly reduced the proportion of patients transfused by 31 % (RR, 0.69; p = 0.0002), and units of RBCs transfused by 0.34 units/person (MD, -0.34; p = 0.0007). For subgroup analysis by iron dose, low- or high-dose IVIT significantly reduced the proportion of patients transfused (RR, 0.73, p = 0.005; RR, 0.68, p = 0.008), and RBC units transfused (MD, -0.47, p < 0.0001; MD, -0.28, p = 0.04). For subgroup analysis by period, IVIT administered post-operatively significantly reduced the proportion of patients transfused (post-operative: RR, 0.60, p = 0.002; pre-operative: RR, 0.74, p = 0.06) and RBC units transfused (post-operative: MD, -0.44, p < 0.00001; pre-operative: MD, -0.29, p = 0.06). For subgroup analysis by study design, IVIT decreased the proportion of patients transfused and RBC units transfused in the group of CCSs, but IVIT in the group of RCTs did not. IVIT significantly shortened LOS by 1.6 days (p = 0.0006) and reduced post-operative infections by 33 % (p = 0.01). IVIT did not change mortality. The authors concluded that peri-operative IVIT during orthopedic surgery, especially post-operatively, appeared to reduce the proportion of patients transfused and units of RBCs transfused, with shorter LOS and decreased infection rate, but no change in mortality rate. However, these were only found in CCSs and not in RCTs due to the relatively small number of RCTs with low-to-high risk of bias. These researchers recommended that there be large, prospective, well-designed RCTs to confirm the efficacy of peri-operative IVIT in patients with functional iron deficiency anemia during major surgery.

The authors stated that this study had several sources of potential bias and a moderate-to-high level of heterogeneity in the outcomes. First, the publication bias existed in the parameters of LOS and post-operative infection. Second, for 12 clinical trials comprising 4 RCTs and 8 CCSs, 2

RCTs were considered to have a high level of bias in the blinding of participants or outcome assessments, and 4 CCSs used retrospective data in the control group. All CCSs assessed the outcomes using unblinded or unknown methods. Third, 3 CCSs did not clearly identify the selection of a control group. Fourth, 4 included clinical trials had overlapping research groups, which may add further bias to the meta-analysis. Finally, the methods and results of the included trials comprised varying types and doses of IV iron preparations, and transfusion periods.

Post-Operative Anemia Following Cardiothoracic Surgery and Neurosurgery

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.

Peters and colleagues (2018) noted that post-operative anemia is associated with increased morbidity and mortality. Positive effects of post-operative intravenous iron (IVI) after elective orthopedic, abdominal and genito-urinary surgery have been reported. The current observational trial examined the prevalence of post-operative anemia, the effect of IVI on Hb levels, the use of blood transfusions and diagnoses related to infections. A total of 1,265 patients on five ICUs of Munster University Hospital were screened for post-operative anemia. In 1 ICU, patients were screened for iron deficiency and, if indicated, supplemented with 500 mg of ferric carboxymaltose. Primary outcome measures were Hb levels, C-reactive protein (CRP), white blood cell (WBC) count, transfusion requirements, documented infection and antibiotic treatment. Anemia was prevalent in 86.2 % of patients upon ICU admission; 429 patients were screened for iron deficiency anemia; 95 patients were eligible, 35 were treated with IVI. An increase of +0.4 g/dL in Hb levels 7 days after IVI compared to -0.1 g/dL in non-treated anemic patients was observed. The number of RBC transfusions, ICD codes related to infections and infectious parameters were similar between groups. The authors concluded that IVI treatment was safe and resulted in higher median Hb levels; further RCTs are needed to clarify if cardiothoracic patients respond well to IV iron.

Post-Operative Anemia in Elective Surgeries

Perelman and colleagues (2018) stated that post-operative anemia is a common occurrence in surgical patients and leads to an increased risk for allogeneic blood transfusions. The efficacy of iron therapy in treating post-operative anemia has not been firmly established. In a systematic review, these investigators evaluated the efficacy of post-operative oral iron and IVI therapy in increasing Hb levels and improving patient outcomes following elective surgery. The databases Medline, Embase, CENTRAL, the Transfusion Evidence Library, and ClinicalTrials.gov were searched. Eligible studies were RCTs or prospective cohorts having a control group, where post-operative oral iron or IVI was administered to elective surgery patients. Primary outcomes were Hb levels and patient-centered outcomes of QOL and functioning; secondary outcomes were the safety of post-operative iron and blood transfusion requirement. Meta-analysis using a random-effects model was performed. A total of 17 relevant studies were identified, of which 7 investigated IVI, 7 investigated oral iron, and 3 compared IVI with oral iron. Post-operative oral iron and IVI therapies were ineffective in improving QOL and functioning (the Grading of Recommendations Assessment, Development and Evaluation [GRADE]: moderate-low quality). Compared with control, IVI increased mean Hb levels by 3.40 g/L (95 % CI: 1.18 to 5.62) (GRADE: moderate quality); however, this increase was likely not clinically meaningful. Overall, oral iron was ineffective in increasing Hb concentrations compared with control (MD = 0.77, 95 % CI: -1.48 to 3.01) (GRADE: moderate quality). Post-operative iron therapy did not significantly reduce the risk of blood transfusion (RR = 0.75; 95 % CI: 0.53 to 1.07) (GRADE: low quality); IVI was not associated with a significantly increased risk of AEs (RR = 4.50, 95 % CI: 0.64 to 31.56). There was insufficient information to determine the risk of AEs for post-operative oral iron. The authors concluded that this systematic review found no evidence to support the routine use of post-operative iron therapy in all elective surgery patient populations; however, results were based largely on studies with non-iron-deficient patients pre-operatively. They stated that further research on the role of post-operative IVI is needed for certain high-risk groups, including patients with iron deficiency or anemia prior to surgery.

Post-Partum Anemia

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 randomized, double-blind, parallel-group, placebo-controlled, single-center clinical trial, Perello et al (2014) evaluated the effectiveness of intravenous iron versus placebo added to standard oral iron therapy in the treatment of severe post-partum anemia. A cohort of 72 women with severe post-partum anemia (6.0 to 8.0 g/dL) treated with oral ferrous sulphate (2 tablets of 525 mg) were included in this study. Women were randomized to receive either intravenous ferrous sucrose (200 mg/24 hours for 2 consecutive days) or intravenous placebo, in addition to standard iron therapy. Clinical and laboratory data were obtained at 1, 2, and 6 weeks. Main outcome measures were Hb and hematocrit at 1, 2, and 6 weeks. Other hematological and clinical parameters, psychological status, and adverse side effects were also evaluated. Hemoglobin and hematocrit values were comparable in women receiving intravenous iron or placebo in addition to oral iron therapy at any of the time-points. At 6 weeks, Hb level (mean ± SD) was 12.2 ± 1.0 versus 12.2 ± 0.9 g/dL, with a mean difference of -0.03 (95 % CI: -0.6 to 0.6), in the placebo and in the intravenous iron groups, respectively. No differences were found between clinical symptoms of anemia, psychological status, and adverse side effects between groups. The authors concluded that intravenous iron added to oral iron therapy did not show significant benefits over placebo, neither in Hb rise nor in symptoms or adverse side effects.

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).

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 can not 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 Cochrane review, Markova et al (2015) evaluated the effectiveness and harms of the available treatment modalities for women with post-partum iron deficiency anemia. The Cochrane Pregnancy and Childbirth Group's Trials Register (April 9, 2015); the WHO International Clinical Trials Registry Portal (ICTRP), and the Latin-American and Caribbean Health Sciences Literature database (LILACS) (April 8, 2015) and reference lists of retrieved studies were searched. These investigators included published, unpublished and ongoing RCTs that compared a treatment for post-partum iron deficiency anemia with placebo, no treatment, or another treatment for post-partum iron deficiency anemia, including trials described in abstracts only. Cluster-randomized trials were eligible for inclusion. These researchers included both open-label trials and blinded trials, regardless of who was blinded. The participants were women with a post-partum hemoglobin of 120 g/L or less, for which treatment was initiated within 6 weeks after childbirth. Non-randomized trials, quasi-randomized trials and trials using a cross-over design were excluded. Two review authors independently assessed studies for inclusion, quality, and extracted data. They contacted study authors and pharmaceutical companies for additional information. The authors included 22 RCTs (2,858 women), most of which had high risk of bias in several domains. They performed 13 comparisons; many comparisons were based on a small number of studies with small sample sizes. No analysis of the primary outcomes contained more than 2 studies. Intravenous iron was compared to oral iron in 10 studies (1,553 women). Fatigue was reported in 2 studies and improved significantly favoring the intravenously treated group in one of the studies. Other anemia symptoms were not reported. One woman died from cardiomyopathy (RR 2.95; 95 % CI: 0.12 to 71.96; 2 studies; 1 event; 374 women; low quality evidence). One woman developed arrhythmia. Both cardiac complications occurred in the intravenously treated group. Allergic reactions occurred in 3 women treated with intravenous iron, not statistically significant (average RR 2.78; 95 % CI: 0.31 to 24.92; 8 studies; 1,454 women; I^2 = 0 %; low quality evidence). Gastro-intestinal

events were less frequent in the intravenously treated group (average RR 0.31; 95 % CI: 0.20 to 0.47; 8 studies; 169 events; 1,307 women; I^2 = 0 %; very low quality evidence). One study evaluated red blood cell transfusion versus non-intervention. General fatigue improved significantly more in the transfusion group at 3 days (MD -0.80; 95 % CI: -1.53 to -0.07; women 388; low quality evidence), but no difference between groups was seen at 6 weeks. Maternal mortality was not reported. The remaining comparisons evaluated oral iron (with or without other food substances) versus placebo (3 studies), intravenous iron with oral iron versus oral iron (2 studies) and erythropoietin (alone or combined with iron) versus placebo or iron (7 studies). These studies did not investigate fatigue; maternal mortality was rarely reported. The authors concluded that the body of evidence did not allow a clear conclusion regarding the effectiveness of the interventions on post-partum iron deficiency anemia to be reached. The quality of evidence was low. Clinical outcomes were rarely reported. Laboratory values may not be reliable indicators for effectiveness, as they did not always correlate with clinical treatment effects. They stated that it remained unclear which treatment modality is most effective in alleviating symptoms of post-partum anemia. Intravenous iron was superior regarding gastro-intestinal harms, however anaphylaxis and cardiac events occurred and more data are needed to establish whether this was caused by intravenous iron. The clinical significance of some temporarily improved fatigue scores in women treated with blood transfusion is uncertain and this modest effect should be balanced against known risks, e.g., maternal mortality (not reported) and maternal immunological sensitization, which can potentially harm future pregnancies. When comparing oral iron to placebo it remained unknown whether effectiveness (relief of anemia symptoms) outweighs the documented gastro-intestinal harms. The authors could not draw conclusions regarding erythropoietin treatment due to lack of evidence. They stated that further research should evaluate treatment effect through clinical outcomes, i.e., presence and severity of anemia symptoms balanced against harms, i.e., survival and severe morbidity.

Pre-Operative Intravenous Iron Therapy

Hallet et al (2014) noted that peri-operative anemia is common, yet detrimental, in surgical patients. However, red blood cell transfusions (RBCTs) used to treat anemia are associated with significant post-operative risks and worse oncologic outcomes. Peri-operative iron has been suggested to mitigate peri-operative anemia. This meta-analysis examined the impact of peri-operative iron compared to no intervention on the need for RBCT in gastro-intestinal (GI) surgery. These investigators systematically searched Medline, Embase, Web of Science, Cochrane Central, and Scopus to identify relevant randomized controlled trials (RCTs) and non-randomized studies (NRSs). They excluded studies investigating autologous RBCT or erythropoietin. Two independent reviewers selected the studies, extracted data, and assessed the risk of bias using the Cochrane tool and Newcastle-Ottawa scale. Primary outcomes were proportion of patients getting allogeneic RBCT and number of transfused patient. Secondary outcomes were Hb change, 30-day post-operative morbidity and mortality, length of stay, and oncologic outcomes. A meta-analysis using random effects models was performed. From 883 citations, these researchers included 2 RCTs and 2 NRSs (n = 325 patients), all pertaining to colorectal cancer surgery. Randomized controlled trials were at high risk for bias and under-powered. One RCT and 1 NRS using pre-operative oral iron reported a decreased proportion of patients needing RBCT. One RCT on pre-operative intravenous iron and 1 NRS on post-operative PO iron did not observe a difference. Only 1 study revealed a difference in number of transfused patients. One RCT reported significantly increased post-intervention Hb. Among 3 studies reporting length of stay, none observed a difference. Other secondary outcomes were not reported. Meta-analysis revealed a trend toward fewer patients requiring RBCT with iron supplementation (RR, 0.66 [0.42, 1.02]), but no benefit on the number of RBCT per patient (weighted mean difference, -0.91 [-1.61, -0.18]). The authors concluded that although preliminary evidence suggested that it may be a promising strategy, there is insufficient evidence to support the routine use of peri-operative iron to decrease the need for RBCT in colorectal cancer surgery. They stated that well-designed RCTs focusing on the need for RBCT and including long-term outcomes are needed.

Elhenawy et al (2015) stated that pre-operative anemia is a common and potentially serious hematological problem in elective surgery and increases the risk for peri-operative RBC transfusion. Transfusion is

associated with post-operative morbidity and mortality. Pre-operative IV iron therapy has been proposed as an intervention to reduce peri-operative transfusion; however, studies are generally small, limited, and inconclusive. These investigators proposed performing a systematic review and meta-analysis. They will search MEDLINE, EMBASE, EBM Reviews, Cochrane-controlled trial registry, Scopus, registries of health technology assessment and clinical trials, Web of Science, ProQuest Dissertations and Theses, and conference proceedings in transfusion, hematology, and surgery. They will contact the study drug manufacturer for unpublished trials. Titles and abstracts will be identified and assessed by 2 reviewers for potential relevance. Eligible studies are: randomized or quasi-randomized clinical trials comparing pre-operative administration of IV iron with placebo or standard of care to reduce peri-operative blood transfusion in anemic patients undergoing major surgery. Screening, data extraction, and quality appraisal will be conducted independently by 2 authors. Data will be presented in evidence tables and in meta-analytic forest plots. Primary efficacy outcomes are change in Hb concentration and proportion of patients requiring RBC transfusion. Secondary outcomes include number of units of blood or blood products transfused peri-operatively, transfusion-related acute lung injury, neurologic complications, adverse events, post-operative infections, cardiopulmonary complications, intensive care unit (ICU) admission/re-admission, length of stay, acute kidney injury, and mortality. Dichotomous outcomes will be reported as pooled relative risks and 95 % CIs. Continuous outcomes will be reported using calculated weighted mean differences. Meta-regression will be performed to evaluate the impact of potential confounding variables on study effect estimates. The authors concluded that reducing unnecessary RBC transfusions in peri-operative medicine is a clinical priority. This involves the identification of patients at risk of receiving transfusions along with blood conservation strategies. Of potential pharmacological blood conservation strategies, IV iron is a compelling intervention to treat preoperative anemia; however, existing data are uncertain. These researchers proposed performing a systematic review and meta-analysis evaluating the safety and effectiveness of IV iron administration to anemic patients undergoing major surgery to reduce transfusion and peri-operative morbidity and mortality.

Hogan et al (2015) stated that anemia is common in patients with cardiac disease and also in those undergoing cardiac surgery. There is increasing evidence that pre-operative anemia is associated with increased patient morbidity and mortality following surgery. These researchers performed a systematic literature review to assess the impact of anemia and IV iron supplementation on outcomes in cardiac surgery. A total of 16 studies examined pre-operative anemia in detail. One study examined the role of pre-operative IV iron administration and a further 3, the effect of post-operative iron supplementation on Hb levels and the need for transfusion. Pre-operative anemia was associated with higher mortality, more post-operative blood transfusions, longer ICU and total hospital stay and also a greater incidence of post-operative cardiovascular events. In the single study that examined pre-operative IV iron in combination with erythropoietin treatment, there was decreased blood transfusion, shorter hospital stay and an increase in patient survival. However, this was a small retrospective cohort study, with the observation and treatment groups analyzed over different time periods. Post-operative administration of IV iron therapy, either alone or in combination with erythropoietin, was not effective in raising Hb levels or reducing red cell concentrate transfusion. The authors concluded that on the basis of currently available evidence, the effect of peri-operative administration of IV iron to cardiac surgery patients, alone or in combination with erythropoietin, remains unproven. They stated that well-designed and appropriately powered prospective RCTs are needed to evaluate peri-operative iron supplementation in the context of cardiac surgery.

In a Cochrane review, Ng and colleagues (2015) evaluated the effects of pre-operative iron therapy (enteral or parenteral) in reducing the need for allogeneic blood transfusions in anemic patients undergoing surgery. These researchers ran the search on March 25, 2015. They searched the Cochrane Injuries Group's Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library), Ovid Medline(R), Ovid Medline(R) In-Process & Other Non-Indexed Citations, Ovid Medline(R) Daily and Ovid OldMedlineR), Embase Classic and Embase (Ovid), CINAHL Plus (EBSCO), PubMed, clinical trials registries, conference abstracts, and these investigators screened reference lists. They included all RCTs that compared pre-operative iron monotherapy to placebo, no treatment, standard of care or another form of iron therapy for

anemic adults undergoing surgery. Anemia was defined by hemoglobin values less than 13 g/dL for males and 12 g/dL for non-pregnant females. Data were collected by 2 authors on the proportion of patients who receive a blood transfusion, amount of blood transfused per patient (units) and hemoglobin measured as continuous variables at pre-determined time-points: pre-treatment, pre-operatively but post-treatment, and post-operatively. Statistical analysis was performed using the Cochrane statistical software, Review Manager 2014. Outcome data were summarized in tables and a forest plot. A total of 3 prospective RCTs evaluated pre-operative iron therapy to correct anemia (2 in colorectal and 1 in gynecological surgery) and included 114 patients in total. One compared oral iron versus standard care (Lidder 2007); 1 intravenous iron versus control (Edwards 2009); and 1 study compared oral versus intravenous iron (Kim 2009). Both colorectal trials reported the primary outcome (proportion of patients who received allogeneic blood transfusions) and meta-analysis showed a reduction in blood transfusions with the administration of iron therapy, but the reduction was not statistically significant (RR 0.56, 95 % CI: 0.27 to 1.18). All studies reported hemoglobin change but data for the anemic patients were only available for 2 studies (Edwards 2009 and Kim 2009). Edwards 2009 showed no difference in hemoglobin at the end of treatment pre-operatively. The intravenous versus oral iron study showed an increase in hemoglobin with intravenous iron at the end of treatment pre-operatively (MD 1.90 g/dL, 95 % CI: 1.16 to 2.64; participants = 56), but the results were at high risk of bias because participants with less than 80 % compliance with therapy were excluded from the analysis and compliance was lower in the oral iron group due to the side-effects of treatment (Kim 2009). None of the studies reported quality of life, short- or long-term mortality or post-operative morbidity. The authors concluded that the use of iron therapy for pre-operative anemia did not show a statistically significant reduction in the proportion of patients who received an allogeneic blood transfusion compared to no iron therapy. However, the 38 patients in the analysis fell far short of the 819 patients the information size calculation recommended to detect a 30 % reduction in blood transfusions. These investigators noted that intravenous iron may be more effective than oral iron at increasing hemoglobin. However, all these conclusions were drawn from only 3 small RCT. They stated that further well-designed, adequately powered RCTs are needed to determine the true effectiveness of iron therapy for pre-operative anemia.

Richards et al (2015) noted that PREVENTT is a phase III double-blind RCT that will compare the use of intravenous ferric carboxymaltose (dose 1,000 mg) with placebo 10 to 42 days before major open abdominal surgery in 500 patients with anemia (Hb less than 120 g/L). The primary outcome measure will be the need for blood transfusion and secondary end-points will include post-operative recovery, length of hospital stay, health care utilization and cost analysis.

Froessler et al. (2016) state that preoperative iron deficiency anemia (IDA) occurs frequently; however, if left untreated, there is increased risk for need of allogeneic blood transfusion (ABT). Furthermore, there is limited evidence to support IDA treatment with preoperative intravenous (IV) iron. Thus, the authors conducted a randomized controlled trial to evaluate the role for IV iron in perioperative patient blood management in major abdominal surgery to determine if preoperative IV iron improves outcomes and reduces the need for ABT. Between August 2011 and November 2014, 72 patients with IDA were assigned to receive either IV iron or usual care. Patients eligible for inclusion (>18 yrs with IDA, ferritin <300 mcg/L, transferrin saturation <25%, Hb <12.0 g/dL for women, Hb <13.0 g/dL for men). The primary endpoint was incidence of ABT. Secondary endpoints were various hemoglobin (Hb) levels, change in Hb between time points, length of stay, iron status, morbidity, mortality, and quality of life 4 weeks postsurgery. A 60% reduction in ABT was observed in the IV iron group compared with the usual care group (31.25% vs 12.5%). Hb values, although similar at randomization, improved by 0.8 g/dL with IV iron compared with 0.1 g/dL with usual care (p = 0.01) by the day of admission. The IV iron group had higher Hb 4 weeks after discharge compared with the usual care group (1.9 vs 0.9 g/dL, p= 0.01), and a shorter length of stay (7.0 vs 9.7 d, p = 0.026). There was no difference in discharge Hb levels, morbidity, mortality, or quality of life. The authors concluded that administration of perioperative IV iron reduces the need for blood transfusion, and is associated with a shorter hospital stay, enhanced restoration of iron stores, and a higher mean Hb concentration 4 weeks after surgery.

Keeler and colleagues (2017) compared the efficacy of pre-operative intravenous and oral iron in reducing blood transfusion use in anemic patients undergoing elective colorectal cancer surgery. Anemic patients with non-metastatic colorectal adenocarcinoma were recruited at least 2

weeks before surgery and randomized to receive oral (ferrous sulphate) or intravenous (ferric carboxymaltose) iron. Peri-operative changes in Hb, ferritin, transferrin saturation and blood transfusion use were recorded until post-operative out-patient review. A total of 116 patients were included in the study. There was no difference in blood transfusion use from recruitment to trial completion in terms of either volume of blood administered ($p = 0.841$) or number of patients transfused ($p = 0.470$). Despite this, increases in Hb after treatment were higher with intravenous iron (median of 1.55 (inter-quartile range [IQR] 0.93 to 2.58) versus 0.50 (-0.13 to 1.33) g/dL; $p < 0.001$), which was associated with fewer anemic patients at the time of surgery (75 versus 90 %; $p = 0.048$). Hemoglobin levels were thus higher at surgery after treatment with intravenous than with oral iron (mean of 11.9 (95 % CI: 11.5 to 12.3) versus 11.0 (10.6 to 11.4) g/dL, respectively; $p = 0.002$), as were ferritin ($p < 0.001$) and transferrin saturation ($p < 0.001$) levels. The authors concluded that intravenous iron did not reduce the blood transfusion requirement but was more effective than oral iron at treating pre-operative anemia and iron deficiency in patients undergoing colorectal cancer surgery.

According to Munting (2019), pre-optimization of anemia in surgical patients leads to higher pre-operative hemoglobin concentrations and less need for transfusion. Patients undergoing major surgery (defined as blood loss > 500 ml expected or possible) should be optimized if their hemoglobin concentration is less than 130 g.l−1 on screening. Detection of anemia should follow listing for surgery as soon as possible to allow enough time for optimization. The most common cause of pre-operative anemia is iron deficiency, which can be treated with iron therapy. Iron deficiency anemia is the most common type of anemia both worldwide and in the surgical population.

Spahn (2020) states that surgical bleeding contributes to anemia, increases transfusions, and independently increases mortality. In addition, transfusion of allogeneic blood products is associated with increased morbidity and mortality and increased costs, and allogeneic blood products are a limited resource. Therefore, as a pragmatic solution, the concept of Patient Blood Management was developed and published in its preliminary form, first in the anesthesia literature as an editorial in Anesthesiology in 2008. The authors hypothesized that “Patient Blood Management will decrease the use of allogeneic erythrocyte transfusion

and its cost and adverse sequelae significantly." The author state that preoperative anemia is common in patients scheduled for major surgery, ranging from 8% in patients undergoing radical prostatectomy to 64% in gynecologic surgery. As expected, the prevalence of iron deficiency (ferritin less than 30 ng/ml or ferritin less than 100 ng/ml with transferrin saturation less than 20% or C-reactive protein greater than 5 mg/l) is high in anemic patients (absolute iron deficiency, 62%). Interestingly, iron deficiency was also highly prevalent (33% overall) in nonanemic patients with 60% in gynecologic surgery and 44% in colorectal cancer surgery. Also in cardiac surgery, iron deficiency is frequent with approximately 50% of anemic patients and 20% of nonanemic patients having absolute iron deficiency. Ferritin less than 100 ng/ml has recently been shown to be associated with a more than threefold increase in 90-day mortality irrespective of the presence or absence of anemia. While several definitions of iron deficiency have been used, the most accepted one is a ferritin less than 100 ng/ml or transferrin saturation less than 20%. Interestingly, there are no studies describing anemia or iron deficiency treatment specifically before gynecologic surgery. However, the authors expect that also on gynecologic surgery preoperative treatment of anemia and iron deficiency is beneficial.

Restless Legs Syndrome

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 restless leg syndrome (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 (risk ratio [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.

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 an open-label, pilot study, Schneider and colleagues (2015) examined the safety and effectiveness of intravenous ferric carboxymaltose (FCM) in pregnant women with RLS and iron deficiency or anemia. A total of 19 women in the 3rd trimester of pregnancy with moderate-to-severe RLS and serum ferritin levels less than 35 µg/L or Hb less than 11.0 g/dL were included in the study; RLS was graded according to the International Restless Legs Syndrome (IRLS) Study Group rating scale. All participants had a score of greater than or equal to 20 or had RLS greater than or equal to 3 times/week. Based on the Hb levels, 500 or 700 mg of FCM was administered over 20 mins. The primary end-point was a greater than or equal to 50 % reduction in the mean IRLS score 1 week after FCM infusion. The secondary end-points included periodic limb movements (PLMs; assessed using nocturnal foot actigraphy), sleep quality (assessed using the Pittsburgh Sleep Quality Index), and safety. The IRLS score decreased from 23 ± 7 (baseline) to 13 ± 7 ($p < 0.01$), whereas the PLM index decreased from 35 ± 26 (baseline) to 25 ± 20 ($p < 0.001$). Significant improvement in sleep quality was also reported ($p < 0.029$), and treatment was well-tolerated; 3 serious adverse events (AEs) were reported, but they were considered unrelated to treatment. The authors conclude that these findings provided promising evidence on the safety and effectiveness of FCM for moderate-to-severe RLS in pregnant women with iron deficiency or anemia. Therefore, a future placebo-controlled study is needed.

The American Academy of Neurology (AAN)'s practice guideline on "Treatment of restless legs syndrome" (Winkelman et al, 2016) stated that "There is insufficient evidence to support or refute an effect of IV ferric carboxymaltose on subject sleep measures … Studies investigating iron sucrose use in RLS had insufficient precision to support or refute a treatment effect (2 Class II studies did not reach statistical significance but had CIs including clinically important effects". It should also be noted that neither ferric carboxymaltose nor iron sucrose is FDA-approved for RLS.

Allen et al. (2018) discussed the evidence-based and consensus clinical practice guidelines for the iron treatment of restless legs syndrome (RLS), also known as Willis-Ekbom disease, in adults and and children. The authors state that brain iron deficiency has been implicated in the pathophysiology of RLS, and current RLS treatment guidelines recommend iron treatment when peripheral iron levels are low. In order to assess the evidence on the oral and intravenous (IV) iron treatment of RLS and periodic limb movement disorder (PLMD) in adults and children, the International Restless Legs Syndrome Study Group (IRLSSG) formed a task force to review these studies and provide evidence-based and consensus guidelines for the iron treatment of RLS in adults, and RLS and PLMD in children. The authors conducted a literature search to identify papers appearing in MEDLINE from its inception to July 2016. The following inclusion criteria were used: human research on the treatment of RLS or periodic limb movements (PLM) with iron, sample size of at least five, and published in English. Two task force members independently evaluated each paper and classified the quality of evidence provided. A total of 299 papers were identified, of these 31 papers met the inclusion criteria. Four studies in adults were given a Class I rating (one for IV iron sucrose, and three for IV ferric carboxymaltose); only Class IV studies have evaluated iron treatment in children. Ferric carboxymaltose (1000 mg) is effective for treating moderate to severe RLS in those with serum ferritin less than 300 µg/l and could be used as first-line treatment for RLS in adults. Oral iron (65 mg elemental iron) is possibly effective for treating RLS in those with serum ferritin less than or equal to 75 µg/l. However, there is insufficient evidence to make conclusions on the efficacy of oral iron or IV iron in children. The consensus recommendations include the following: iron treatments should be considered for all RLS patients; morning, fasting serum iron,

ferritin, TIBC and %TSAT should be obtained; no iron treatment should be used if %TSAT is greater than 45; oral iron treatment if tolerated and safe should be considered for ferritin less than or equal to 75 µg/L; and IV iron should be considered when oral iron is not appropriate provided ferritn is less than or equal to 100 µg/L.

An UpToDate review on "Treatment of restless legs syndrome and periodic limb movement disorder in adults" (Silber, 2021) state that "iron replacement is suggested in patients with restless legs syndrome (RLS) whose fasting serum ferritin level is ≤75 mcg/L. As serum ferritin is an acute phase reactant, percentage transferrin saturation less than 20 percent may be a more accurate measure of low iron stores in patients with acute or chronic inflammatory disorders. Iron therapy should not be prescribed empirically because it may result in iron overload, especially in patients with previously unsuspected hemochromatosis". The author recommends a trial of oral iron therapy for patients with iron deficiency or low-normal ferritin levels (i.e., serum ferritin level less than 75 mcg/L) (Grade 2C). "IV iron therapy is generally reserved for patients with a serum ferritin ≤100 mcg/L, transferrin saturation <45 percent, and either a malabsorption state, complete intolerance to oral iron preparations, moderate to severe symptoms despite a trial of oral iron, or the need for a more rapid response due to severity of symptoms".

Appendix

Table: FDA-approved Indications of Intravenous Iron Preparations

Brand Name	Generic Name	FDA-Approved Indications
Feraheme	ferumoxytol	Treatment of iron deficiency anemia in adult patients with chronic kidney disease or with intolerance or unsatisfactory response to oral iron.
Ferrlecit	sodium ferric gluconate complex in sucrose	Treatment of iron deficiency anemia in adult patients and in pediatric patients age 6 years and older with chronic kidney disease receiving hemodialysis who are receiving supplemental erythropoietin therapy.

INFeD	iron dextran	Treatment of patients with documented iron deficiency in whom oral administration is unsatisfactory or impossible.
Injectafer	ferric carboxymaltose	Treatment of iron deficiency anemia in adult patients who have non-dialysis dependent chronic kidney disease or who have intolerance or unsatisfactory response to oral iron.
Monoferric	ferric derisomaltose	Treatment of iron deficiency anemia in adult patients who have non-hemodialysis dependent chronic kidney disease or who have intolerance or unsatisfactory response to oral iron.
Triferic	sodium ferric gluconate complex containing ferric pyrophosphate citrate	Replacement of iron to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease. Not intended for use in patients receiving peritoneal dialysis. Not been studied in patients receiving home hemodialysis.
Venofer	iron sucrose	Treatment of iron deficiency anemia in patients with chronic kidney disease.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

Code	Code Description
CPT codes not covered for indications listed in the CPB:	
0251U	Hepcidin-25, enzyme-linked immunosorbent assay (ELISA), serum or plasma
Other CPT codes related to the CPB:	
33016 - 33999	Surgery - Cardiovascular System, Heart and Pericardium
44005 - 44799	Surgery - Digestive System, Intestines
61000 - 64999	Surgery - Nervous System
96365 - 96368	Intravenous infusion administration

Code	Code Description
96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
96374 - 96379	Intravenous push administration
HCPCS codes covered if selection criteria are met:	
J1437	Injection, ferric derisomaltose, 10 mg
J1439	Injection, ferric carboxymaltose, 1 mg
J1443	Injection, ferric pyrophosphate citrate solution, 0.1 mg of iron
J1750	Injection, iron dextran, 50 mg
J1756	Injection, iron sucrose, 1 mg
J2916	Injection, sodium ferric gluconate complex in sucrose injection, 12.5 mg
Q0138	Injection, Ferumoxytol, for treatment of iron deficiency anemia, 1mg (non-ESRD use) [Feraheme] [for iron deficiency anemia with chronic kidney disease]
Q0139	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
J0887	Injection, epoetin beta, 1 microgram, (for ESRD on dialysis)
J0888	Injection, epoetin beta, 1 microgram, (for non-ESRD use)
Q4081	Injection, epoetin alfa, 100 units (for ESRD on dialysis)
ICD-10 codes covered if selection criteria are met (not all-inclusive):	
D50.0 - D50.9	Iron deficiency anemias
D63.1	Anemia in chronic kidney disease
D64.0 - D64.3	Sideroblastic anemia
D64.81	Anemia due to antineoplastic chemotherapy
E83.10, E83.118 - E83.119	Disorders of iron metabolism
G25.81	Restless legs syndrome

Code	Code Description
I42.0, I42.2 I42.5, I42.8	Other cardiomyopathies (e.g., congestive, constrictive, familial, hypertrophic, idiopathic, non-obstructive, obstructive, restrictive)
I50.1 - I50.9	Heart failure
K50.00 - K50.919	Crohn's disease [regional enteritis]
K51.00 - K51.919	Ulcerative colitis
N18.1 - N18.9	Chronic kidney disease (CKD)
N92.0 - N92.1	Excessive and frequent menstruation
N92.2	Excessive menstruation at puberty
N92.4	Excessive bleeding in the premenopausal period
N95.0	Postmenopausal bleeding
T45.1x5+	Adverse effect of antineoplastic and immunosuppressive drugs [chemotherapy-induced anemia]
Z52.000 - Z52.098	Blood donor
Z91.11 - Z91.19	Patient's noncompliance with medical treatment and regimen
Z99.2	Dependence on renal dialysis
ICD-10 codes not covered for indications listed in the CPB:	
D56.1	Beta thalassemia
D62	Acute posthemorrhagic anemia [not covered for post-operative anemia following major surgery (e.g., cardiothoracic surgery, colorectal cancer surgery, and neurosurgery)]
D63.8	Anemia in other chronic diseases classified elsewhere [anemia of inflammation]
E66.0 - E66.9	Overweight and obesity
O99.011 - O99.019	Anemia complicating pregnancy
S72.001A - S72.26xS	Fracture of head and neck of femur
T70.29	Other effects of high altitude [acute mountain sickness]

Code	Code Description
Z98.84	Bariatric surgery status
ICD-10 codes contraindicated for indications listed in the CPB:	
E83.110 - E83.111	Hemochromatosis

The above policy is based on the following references:

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