
بسم الله الرحمن الرحيم

# Iron treatment

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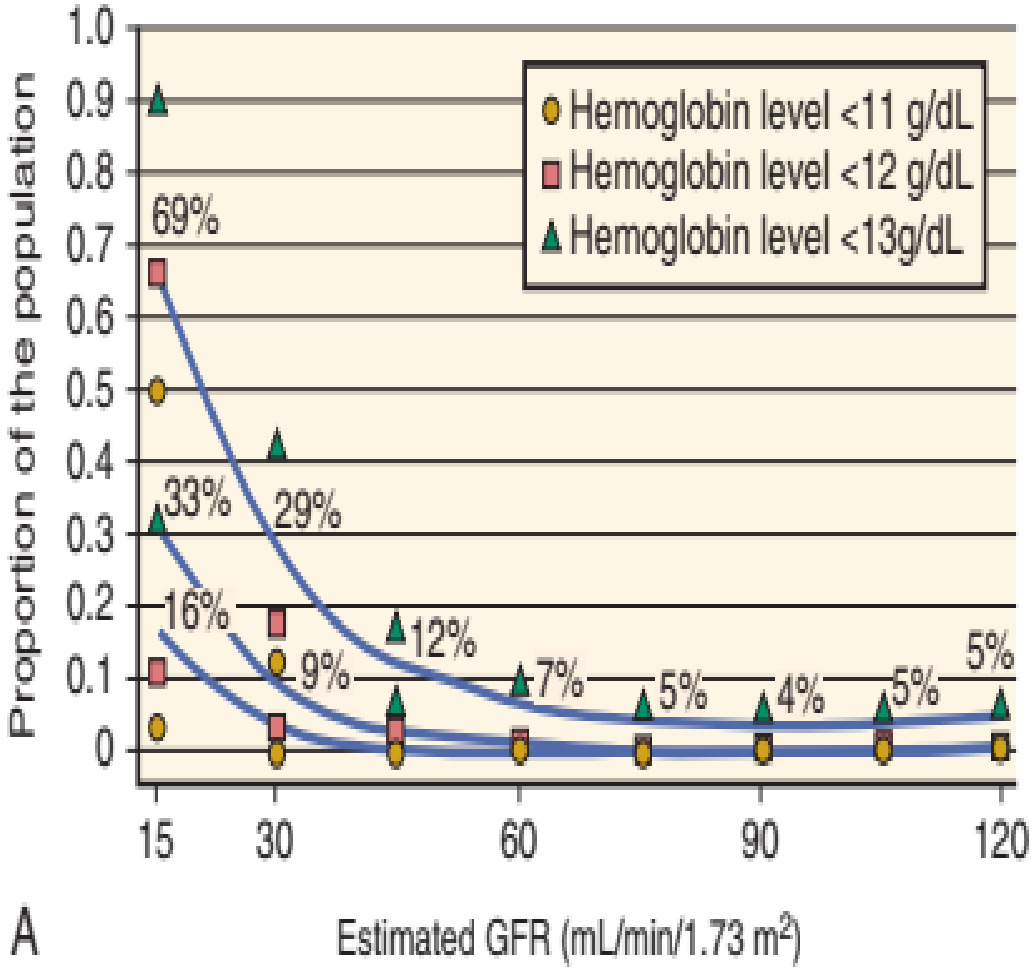
**Anemia is a frequent comorbidity of chronic kidney disease (CKD) and is associated with a decreased patient health-related quality of life.**

**The prevalence begins to increase significantly with an eGFR below 60 mL/min/1.73 m2, but anemia is generally not a frequent or severe complication of CKD until the GFR is below 30 , becoming almost universal in ESRD.**






Iron treatment

# Hematologic Aspects of Kidney Disease

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Carlo Brugnara | Kai-Uwe Eckardt

CHAPTER OUTLINE

ANEMIA OF KIDNEY DISEASE, 1861
DISORDERS OF HEMOSTASIS IN CHRONIC KIDNEY DISEASE, 1892
WHITE CELL FUNCTION IN CHRONIC KIDNEY DISEASE, 1897

**At all stages of CKD, serum EPO values were found to be higher than in nonanemic normal subjects, but EPO concentrations are inappropriately low for the degree of anemia**

**Among patients with mild to moderate CKD, the correlation was inverse, with lower Hgb concentrations being associated with higher serum EPO concentrations.**

**However, among patients with creatinine clearances below 40 mL/min, mean serum EPO concentrations were severely depressed and uncorrelated with the degree of anemia.**

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**Anemia is defined by WHO as a hemoglobin (Hb) concentration <13 g/dL for adult males and postmenopausal females and an Hb concentration <12 g/dL for premenopausal females.**

**However, the WHO definition of anemia does not define goals of treatment among hemodialysis patients.**

**In hemodialysis ,We check Hb monthly unless there is a clinical indication for more frequent testing (such as recent blood loss or major surgical procedures).**

**TSAT and ferritin should be checked at least every three months unless there is a clinical indication for more frequent testing**

# Causes of Iron Deficiency in Hemodialysis Patients

- **Depletion of iron stores**
- **Chronic blood loss**

1. **Blood retention by the dialysis lines and filter**
2. **Blood sampling for laboratory testing**
3. **Accidents related to the vascular access**
4. **Surgical blood loss**
5. **Occult gastrointestinal bleeding**

- **Decreased dietary iron absorption**

1. **Phosphate binders inhibit iron absorption**
2. **Histamine-2 blockers, proton-pump blockers, and functional achlorhydria impair iron absorption**
3. **Uremic gut does not absorb iron optimally**

- **Increased iron demand**

1. **Due to increased rate of erythropoiesis induced by erythropoiesis stimulating agents**
2. **Impaired release of iron from storage tissues (reticuloendothelial blockade)**



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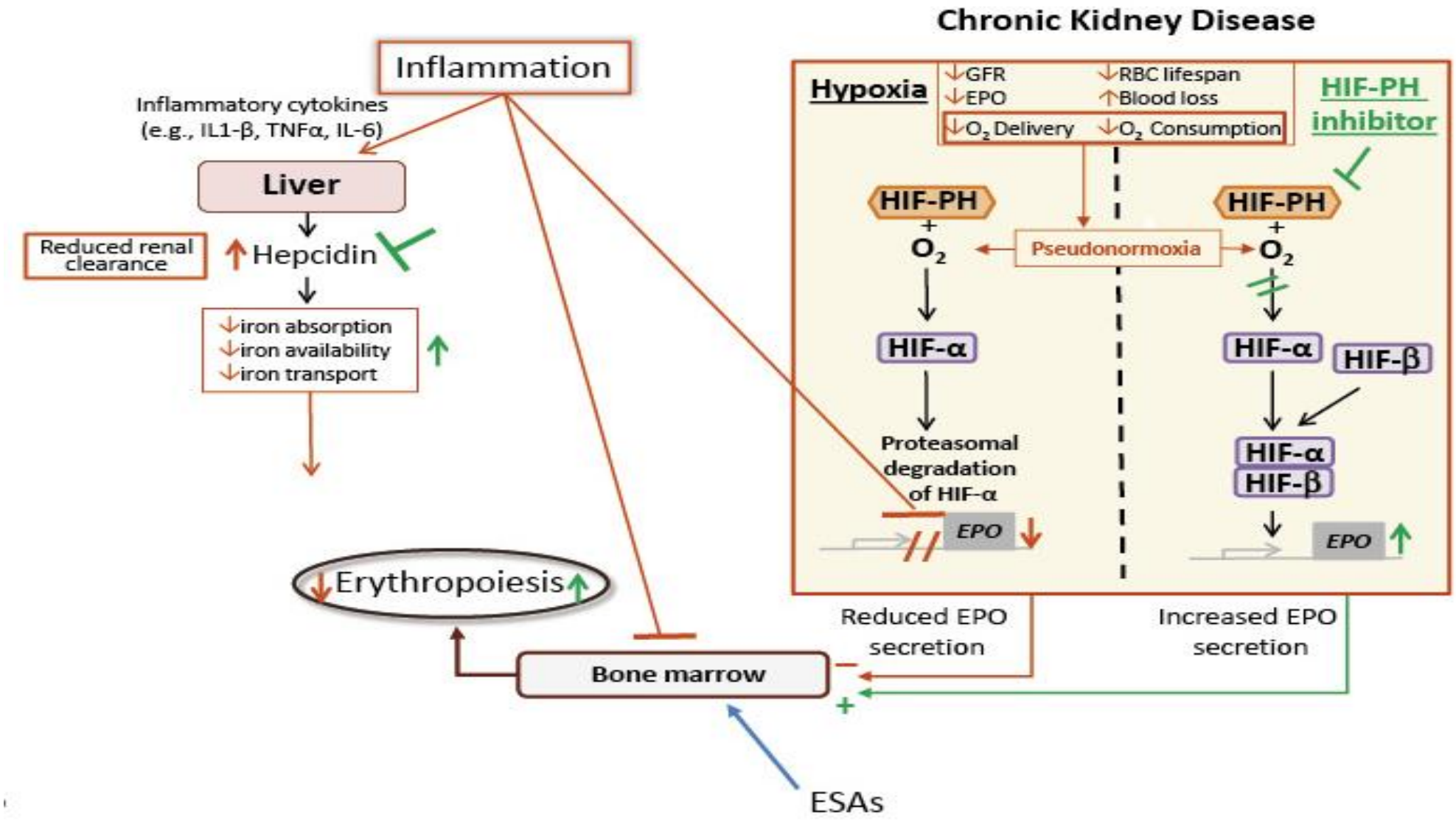
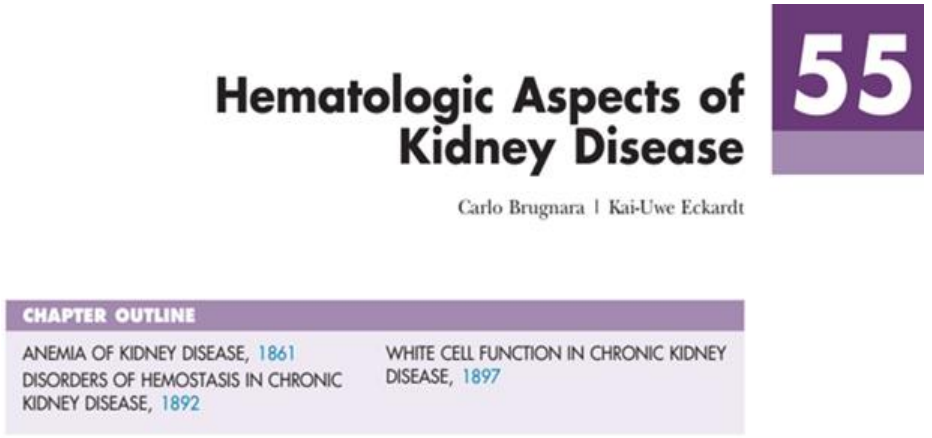



**Iron treatment**

**The yearly estimated iron loss in hemodialysis patients is typically 1 to 2 g (approximately 100 to 200 mg monthly) and can be as high as 4 to 5 g in some patients**




# Clinical Relevance

**When using ESAs, always consider the possibility of functional iron deficiency, especially in women and men with normal or borderline normal iron stores. Serum ferritin values are not indicative of iron stores in the presence of inflammation and in most patients with CKD or ESKD.**

**Functional iron deficiency can manifest as a low TSAT with normal or elevated ferritin levels.**

# Hb <10 g/dL and TSAT ≤30 percent

loading dose of intravenous (IV) iron with repeated courses, as needed, until the TSAT is >30 (upper limit of ferritin is between 500 and 1300 ng/mL)

Patients who do not respond to the loading dose of iron with an increase in Hb and iron indices should be evaluated for potential sources of bleeding, particularly gastrointestinal blood loss.

If Hb remains less than 10 g/dL after iron stores are replete, then most patients are started on an ESA.

Patients who have an elevated ferritin (>500 ng/mL) with a low TSAT may also benefit from an evaluation for occult sources of inflammation (high ferritin) or malnutrition (low TSAT).

## Hb <10 g/dL and TSAT >30 percent

**Such patients are usually started on an ESA**

**TSAT >30 percent and a ferritin >500 ng/mL since no studies have proven a benefit of iron among such patients.**

# Hb ≥10 g/dL and TSAT ≤20 percent and ferritin ≤200 ng/mL

**Such patients are likely iron deficient. However, the treatment of the iron deficiency with a loading dose of iron among such patients is controversial.**

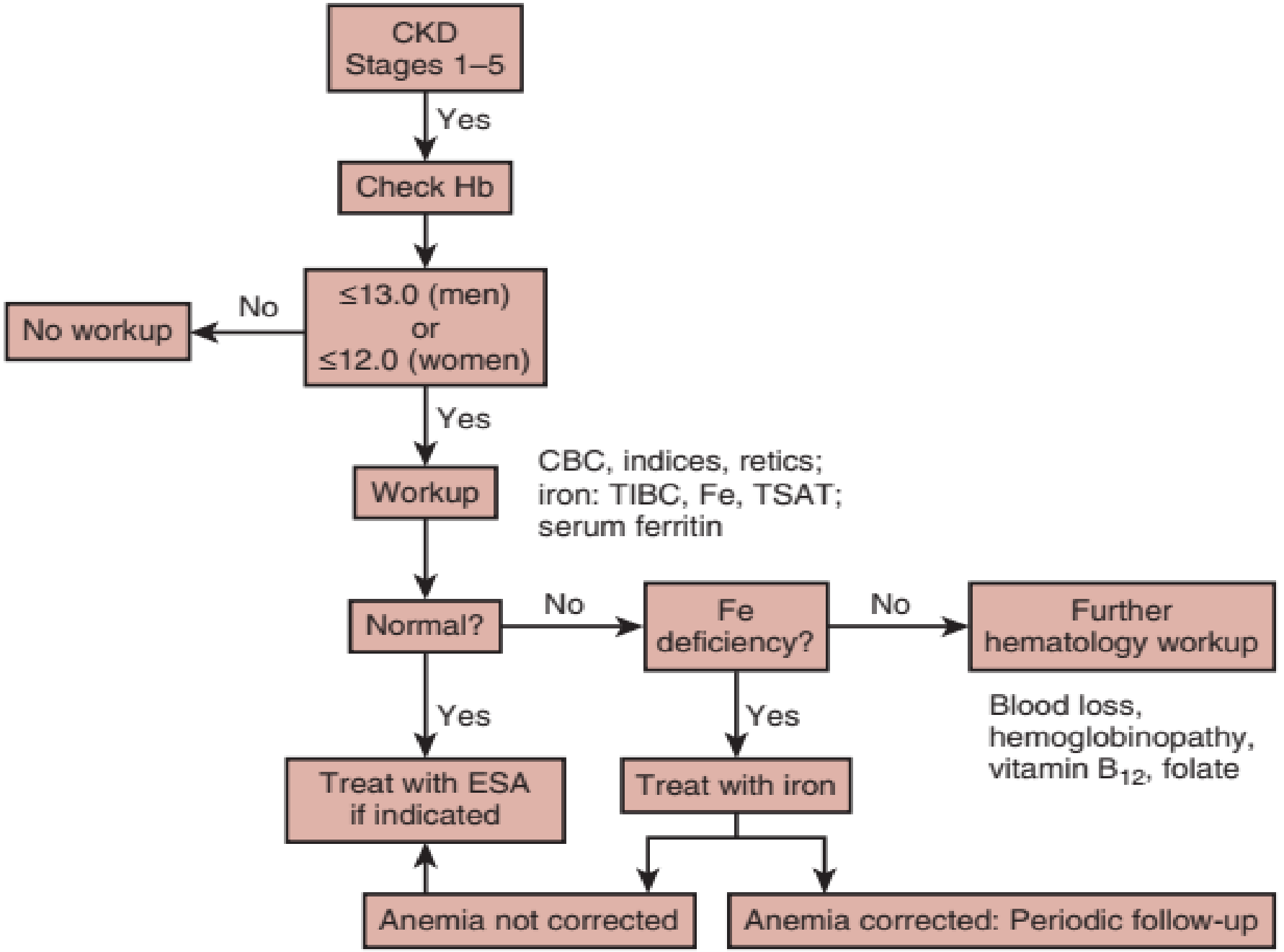
**We treat such patients, with a loading dose of IV iron until the TSAT is 20 to 30 percent because blood loss with hemodialysis will eventually lead to anemia with Hb <10 g/dL.**



Iron treatment

## Hb ≥10 g/dL and TSAT >20 percent and ferritin >200 ng/mL

**Such patients are not treated with a loading dose of iron or an ESA. However, they can be treated with a maintenance dose of iron until the TSAT is >40 percent or the ferritin is >700 ng/mL.**






Iron treatment

# Iron treatment

***a.*** **General principles. Iron therapy is an integral component of anemia treatment in ESKD. Intravenous iron may be administered on an episodic basis as needed when iron deficiency develops, or by the repeated administration of small doses to maintain iron balance.**

***b.*** **Oral iron. Oral iron preparations are safe and relatively inexpensive. However, these supplements are associated with poor efficacy and troublesome side effects, such as constipation, dyspepsia, bloating, or diarrhea. Three randomized trials have compared oral iron with either placebo or no iron treatment in hemodialysis patients; none of the three was able to demonstrate any efficacy for oral iron. Therefore, oral iron should not be used for most hemodialysis patients. For patients on peritoneal dialysis, oral iron is much more convenient than intravenous iron. Since these patients experience less chronic blood loss, oral iron may be sufficient to maintain iron stores. Intravenous iron therapy should be used in peritoneal dialysis patients when resistance to ESA is present and the serum ferritin is <100 ng/mL and the TSAT is <20%.**

**Dosage and administration.** Oral iron usually is given as ferrous sulfate, fumarate, or gluconate, in a dosage of 200 mg of elemental iron per day. The timing of the iron dose is important; ideally, iron should be taken on an empty stomach to optimize efficacy. The primary sites of iron absorption are the duodenum and proximal jejunum, and gastrointestinal symptoms are proportional to the amount of elemental iron presented to the duodenum at a single time; reduction of symptomatology may require changing the oral preparation, using pediatric dosages at more frequent intervals, or even taking the iron dosage with food. Others have suggested giving the medication during dialysis sessions (e.g., at the beginning and the end of the session) to help ensure patient compliance. Yet another strategy is to give oral iron only at bedtime. A common problem with oral iron is constipation, which can be partially managed, if necessary, with stool softeners or laxatives. Some iron preparations contain small doses of ascorbic acid to enhance iron absorption, but the advantage of the added vitamin is not established. **Phosphorus binders, antacids, histamine-2 antagonists, and proton-pump inhibitors may all inhibit the absorption of oral iron supplements**. On the other hand, some novel phosphorus binders such as ferric citrate contain iron, and their use serves not only to reduce serum phosphorus in dialysis patients, but also to supply measurable amounts of iron via the gastrointestinal tract with lower requirements for IV iron and ESA

**Intravenous iron.** Four preparations are available in the United States: Iron dextran, ferric gluconate, ferumoxytol, and iron sucrose. Intravenous iron therapy has superior availability and efficacy when compared with oral iron therapy. In hemodialysis patients, the target hemoglobin level is difficult to achieve without intravenous iron treatment. As a result, most hemodialysis patients will require intravenous iron on a regular basis. In contrast, intravenous therapy costs more, and its safety profile is less clear than that of oral iron. There are two commonly used intravenous iron dosing strategies. One is to treat established iron deficiency with a repletive 1,000-mg dose administered over 8–10 consecutive hemodialysis treatments. Alternatively, since iron deficiency occurs so frequently in hemodialysis patients, a weekly maintenance dose of 25–100 mg may be used. A recent observational study found the repletion method to have greater efficacy compared with maintenance dosing (Kshirsagar, 2013a), while not obviously increasing the risk for cardiovascular events (Kshirsagar, 2013b). However, a repletion strategy may have a greater infection risk compared with bolus therapy (Brookhart, 2013). When intravenous iron is required for peritoneal dialysis patients, infusions of 250 mg of iron may be administered over 1–2 hours.

# Complications:

## Anaphylaxis:

**The best understood complication of intravenous iron treatment is the rare occurrence of anaphylactoid-type reactions. These are characterized by the abrupt occurrence of hypotension, dyspnea, flushing, and back pain. With iron dextran, the rate has been estimated as 0.7% of patients treated. Such reactions are less frequently observed, and tend to be of milder intensity with the nondextran forms of iron.**

# Infection:

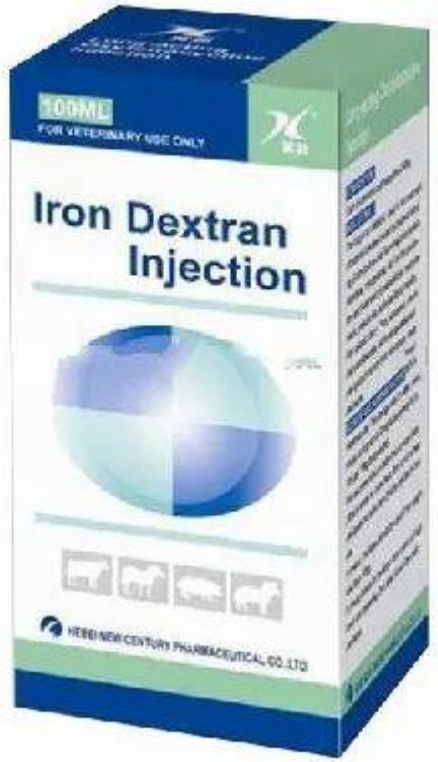
**Iron is a vital growth factor for microorganisms, and intravenous iron treatment has the potential to make iron more readily available to these pathogens. In addition, in vitro studies suggest that iron treatment may interfere with phagocytic function of white blood cells. Early retrospective studies found higher serum ferritin levels in hemodialysis patients to be associated with increased risk of infection. In contrast, a large, prospective, multicenter study (Hoen, 2002) found no relation between serum ferritin or treatment with intravenous iron and risk of bacteremia. The current literature on this subject remains inconclusive (Brookhart, 2013), but a prudent approach would be to avoid intravenous iron treatment during acute infectious episodes.**

# Oxidation:

Iron is a highly oxidative substance, and treatment with intravenous iron has the potential to overburden the body's native antioxidant systems. Oxidative damage to tissue and molecules has been clearly demonstrated experimentally, although the clinical significance of such findings is not clear (Fishbane, 2014). A potential harmful effect of vascular oxidation would be an acceleration of atherosclerotic processes.

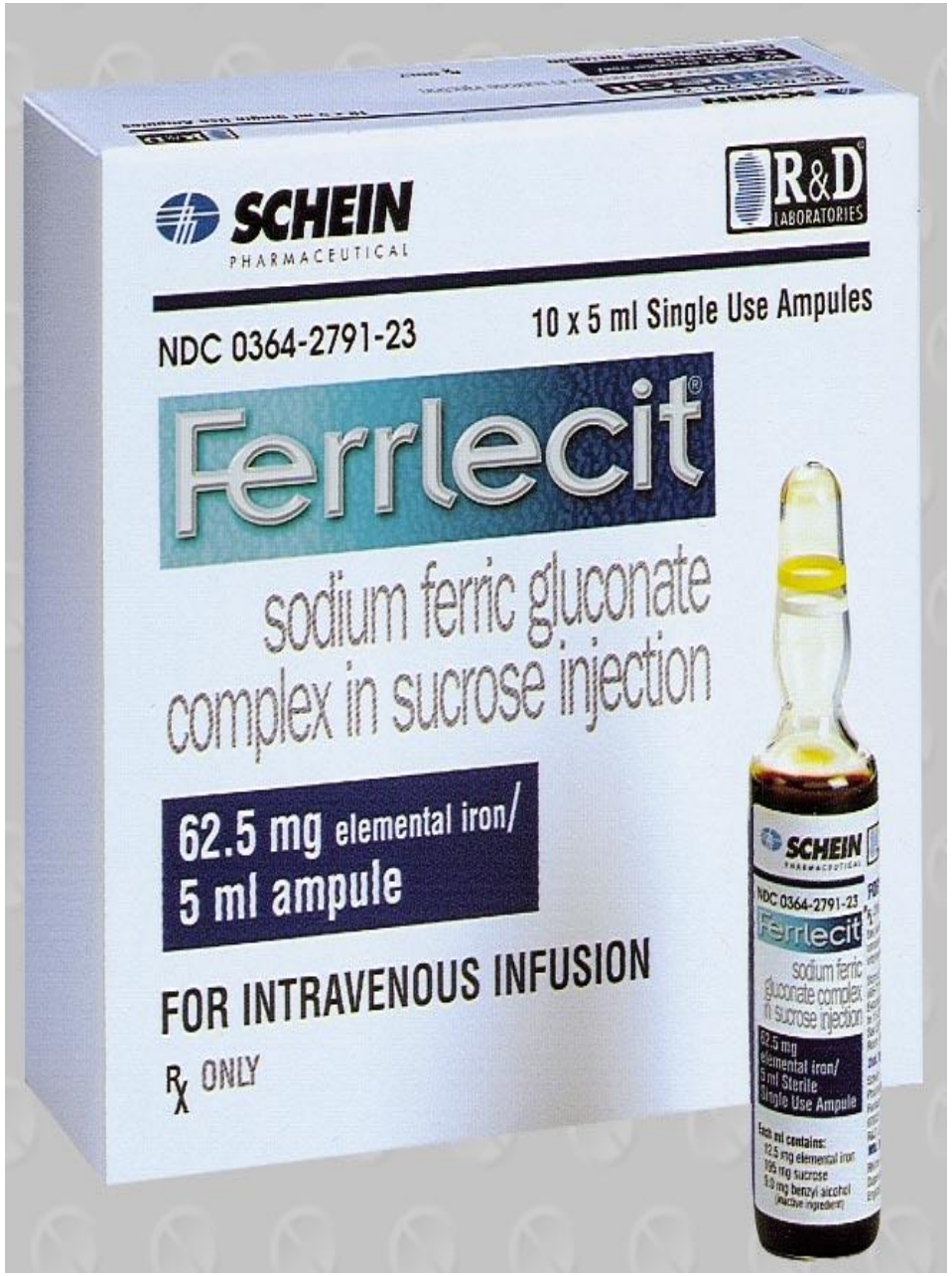
## Intravenous iron dextran

**Because of the higher expected risk of anaphylaxis, iron dextran use should generally be reserved for patients who have a long history of prior safe use of the drug. This is probably true for all current forms of iron dextran, but particularly the high molecular weight variety (Chertow, 2006). In nonuremic patients, immediate allergic reactions to intravenous iron dextran have been reported. These usually occur within 5 minutes of injection but may be delayed by 45 minutes or more. For this reason, epinephrine and other means to treat anaphylaxis must be at hand when intravenous iron dextran is administered. Importantly, Walters and Van Wyck (2005) reported that almost all severe reactions occur with the test dose or first therapeutic dose. Milder immediate hypersensitivity reactions to iron dextran infusion include itching and urticaria. Delayed reactions can manifest as lymphadenopathy, myalgia, arthralgia, fever, and headache.**



## Sodium ferric gluconate

Intravenous sodium ferric gluconate is a nondextran form of iron used in the United States since 1999 and in Europe for several decades. As discussed above, adverse reactions are probably less frequent and less severe than those seen with iron dextran. With single-dose exposure the rate of severe reactions was 0.04%, and no severe reactions were observed with repeated administration of 13,151 doses to 1,321 patients (Michael, 2002; Michael, 2004). Intravenous sodium ferric gluconate may be administered to hemodialysis patients in the amount of 1,000 mg given in divided doses over eight consecutive treatments (i.e., 125 mg/dose).



# Ferumoxytol

**This is marketed by AMAG Pharmaceuticals (Lexington, MA) as Feraheme. It is an iron oxide nanoparticle with a polyglucose sorbitol carboxymethylether coating designed to minimize immunologic sensitivity and release of free iron, allowing a rapid injection of a large dose (510 mg)**


**Ferumoxytol is the only IV iron preparation possessing super magnetic properties, similar to MRI contrast agents, which may alter MRI imaging for up to 3 months owing to its uptake into the reticuloendothelial system.**

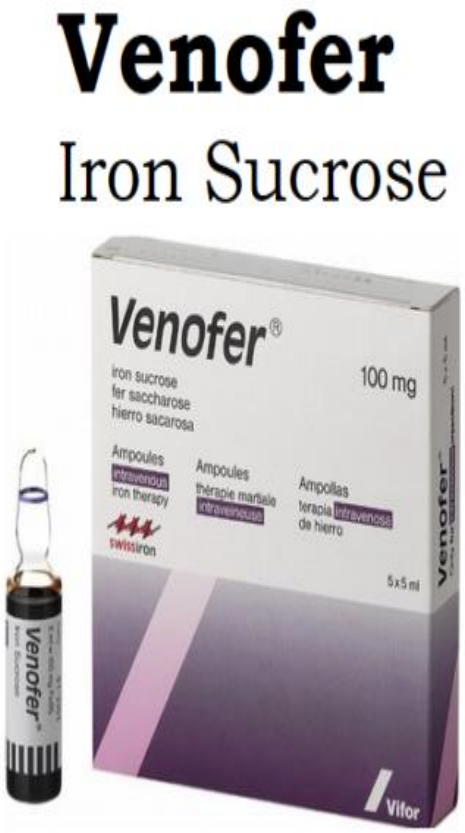
# Ferric Carboxymaltose

**This is marketed as either Ferinject .A significant advantage of this preparation is the possibility of infusing up to 750 mg of iron in a short time (15 minutes), Transient hypophosphatemia has been reported in patients without CKD and in those with ND-CKD treated,. FGF23 plays an important role.**

**In non–dialysis-dependent CKD cases, with serum ferritin values between 400 and 600 ng/mL (FIND-CKD trial), ferric carboxymaltose was better than oral iron in delaying and/or reducing ESA requirements.**

## Iron sucrose

**Intravenous iron sucrose was approved for use in the United States in 2000 and has been in use in Europe for many years. Like sodium ferric gluconate, the other widely used nondextran form of iron, reports generally indicate a good safety and efficacy profile. No serious adverse reactions occurred in 665 hemodialysis patients receiving 8,583 doses of the drug (Aronoff, 2004). The drug may be administered as iron replacement therapy, 100 mg for 10 consecutive doses, or as a weekly dose of 25–100 mg.**



## Relative vitamin B12 deficiency

Vitamin B12 and folic acid levels should be checked when unexplained ESA resistance is present; a case can be made for more routine evaluation of this parameter. Many dialysis patients are taking proton-pump inhibitors, known to be associated with subnormal B12 levels, and intensive, high-flux hemodialysis and hemodiafiltration treatments have been shown to lower vitamin B12 levels. In one study from Australia (Killen, 2014), 91/142 hemodialysis patients had serum vitamin B12 levels of less than 300 pmol/L, a level suggesting deficiency. Only five patients had levels of less than 150 pmol/L, which represents clear-cut deficiency. A short course of three treatments of hydroxycobalamin 1,000 mcg per week was given. Treatment was repeated if B12 levels remained below 300 pmol/L. Hydroxycobalamin treatment resulted in a more than 50% reduction in median EPO requirement, from 11 to 5 thousand units per week. IV iron requirements were also reduced by half. The authors also suggest that cyanocobalamin (a form of B12 commonly used in oral supplements) should not be given to ESKD patients because of cyanide accumulation, but that hydroxycobalamin be used. In this study, B12 was given intramuscularly. It is not clear whether subcutaneous administration would lead to similar results.

## Ascorbic acid

Although the literature is mixed, several studies have found that intravenous ascorbic acid may improve epoetin responsiveness for patients on hemodialysis. A typical regimen is intravenous vitamin C given three times weekly with the hemodialysis treatment. Deved (2009) conducted a meta-analysis. While concerned about small sample sizes and deficits in study quality, the authors found ascorbic acid to generally result in increased Hgb and decreased ESA dose. Since vitamin C may lead to increases in oxalate production, appropriate caution must be used in patient selection and duration of therapy.