

## THE APPROACH TO THE IRON DEFICIENT PATIENT

In this attempt to forge a useful algorithm for the management of iron deficiency, it is prudent to have a discussion of the difference between overt iron deficiency, where the body iron stores are depleted, and functional iron deficiency, also known as iron restricted erythropoiesis, where ample iron is present, but unavailable. Prior to the discovery of hepcidin, the hepatic synthesized iron regulatory protein, functional iron deficiency was referred to as anemia of chronic disease. We now know that hepcidin, blocks iron absorption by inactivating the only known iron exporter, ferroportin in intestinal enterocytes. Hepcidin also blocks iron release from circulating macrophages by inactivating ferroportin in these cells as well. Since hepcidin is upregulated in a huge variety of disease states, anemia of chronic disease occurs due to iron lack.

True, or overt iron deficiency, is due to iron loss from bleeding. In the western world there is no other cause. Even if one wishes to postulate that severe nutritional iron lack could theoretically lead to iron deficiency, since flour is fortified with iron, it is likely that starvation would ensue prior to clinically significant iron deficiency based on poor intake. Therefore, although not the topic of this discussion, it is absolutely imperative that the healthcare provider treating the iron deficiency meticulously search for sources of blood loss to avoid missing potentially treatable life threatening illnesses.

### DIAGNOSIS OF IRON DEFICIENCY

Both overt and functional iron deficiency are associated with decreased red cell production which is manifested by reticulocytopenia. In the approach to the anemic patient, the measurement of the reticulocyte count is therefore always indicated. For practical purposes, an absolute reticulocyte count of  $<75,000$  in the presence of a decreased hemoglobin represents hypoproliferation (or decreased red cell production). Once increased destruction is excluded, confirmatory tests for iron deficiency should be done. In the well patient (without concomitant co-morbidities), a serum iron, total iron binding capacity (TIBC), percent transferrin saturation (Fe/TIBC) and serum ferritin should suffice. The MCV can be helpful as well; however, since the hemoglobin falls prior to the MCV, iron deficiency anemia is often normochromic. Further, at least 30% of anemias of chronic disease have microcytosis. Therefore, the MCV is only inferential and not confirmatory.

It should be noted that these tests should be done fasting. There is a diurnal variation of iron levels and recent food intake can markedly affect the serum iron level which in turn affects the transferrin saturation. If either the percent saturation is low when the TIBC is high or the ferritin is low, then absolute iron deficiency is diagnosed. However, if the percent transferrin saturation is low and the TIBC is low, unless the ferritin is truly low, absolute iron deficiency cannot be diagnosed and functional iron deficiency is present. There are other tests of iron lack such as the reticulocyte hemoglobin content, soluble transferrin receptor, percent hypochromic reticulocytes, and zinc protoporphyrin. All of these tests are useful, but all of them are difficult to obtain timely, and none of them predict a response to iron (DRIVE II, Coyne et al). Therefore, it is our recommendation they not be used.

If long standing iron deficiency is suspected, a simple question about ice craving (pagophagia) can be diagnostic. Lastly, classical physical findings include a glasslike tongue and ridged fingernails (Mees' lines).

### MANAGEMENT OF ABSOLUTE IRON DEFICIENCY

Although the main thrust of this article is to instruct on the safety, efficacy and administration of intravenous iron, oral iron remains the standard of care for the initial treatment of uncomplicated iron deficiency.

The most common causes include women with menorrhagia or pregnancy, those with acute blood loss from benign conditions such as peptic or gastric ulcers and those with uncomplicated surgical blood loss. A discussion of absolute iron deficiency associated with chronic illnesses will follow.

Ferrous sulfate is the most effective oral iron. Many other oral iron preparations are available, but none has been shown to be more effective and less toxic than ferrous sulfate. There are preparations such as timed-release iron and iron surrounded by dioctylsodiumsulfosuccinate (FerroSequels). While these preparations are less toxic, they are also ineffective and are specifically proscribed by brand in *Williams Textbook of Hematology*.

We all learn that oral iron is “well tolerated” during out training. Although it certainly is well tolerated in some patients, the overwhelming majority of patients complain of mild to significant toxicities. These include stomach cramping, constipation or diarrhea, a constant metallic taste, nausea, sticky stool that is green and malodorous and abdominal bloating. Compared to intravenous iron, oral iron is far less efficacious, takes considerably longer to work, is ineffective in the presence of chronic diseases such as collagen vascular disease, chronic renal failure, malignancies and a whole host of disorders associated with chronic blood loss, where the oral iron simply cannot keep up with the blood loss. These latter disorders include AV malformations of the intestine, angiodysplasia which is common in disease with small vessel pathology like diabetes, patients who have undergone bariatric surgery, and those individuals with hereditary hemorrhagic telangiectasias (Osler-Weber-Rendu). Oral iron is contraindicated in inflammatory bowel disease where it is directly toxic to the intestinal endothelium exacerbating the inflammation, yet it remains widely used (Gaseche).

For any patient with any disorder where oral iron is unable or unlikely to work, IV iron is administered. There are five IV iron preparations on the US pharmacopoeia (Table 1). These include high and low molecular weight iron dextrans (HMW and LMW ID); two iron salts; ferric gluconate (FG) and iron sucrose (IS); and a recently approved modified iron dextran, ferumoxytol. A discussion of each of these preparations follows.

The first of these compounds to be available in the US was LMW ID (INFeD, Watson, Morristown, NJ) which replaced a HMW ID (Imferon, Fisons, Homes Chapel England) which was removed from the market in 1992, shortly after LMW ID’s approval by the FDA. LMW ID became the standard of care in dialysis, and was used virtually seamlessly (Auerbach, KI, 2008) until 1996, when another HMW ID (Dexferrum, American Regent Labs, Shirley, NY) was approved as an alternative. While LMW ID remained the major product used, pharmacies often purchased the lower priced HMW ID, especially for use in hospitals. Although only approved for 100 mg bolus injections, after a test dose, both of these compounds can be given as a total dose intravenous infusion in a single setting. The test is required due to the potential risk of anaphylaxis, ostensibly with both LMW and HMW ID. The important safety differences between these two drugs will be discussed later in this article.

In 2001, FG (Ferrlecit, Watson) was introduced to the U.S. market for use in dialysis associated anemia. Shortly thereafter, IS (Venofer, American Regent) was also approved. In 2002 and 2003, two well done retrospective studies (Michel, KI and Coyne, KI) showed that serious acute events with the iron salts were far less likely to occur than with iron dextran and were safe in those previously sensitive to iron dextran. As a result of these two papers, FG and IS rapidly replaced iron dextran in dialysis patients. Unlike ID where the total dose can be given in a single setting, the salts can only be given in small doses not to exceed 200 mg of FG and 300 mg for IS (Chandler et al, AJKD 2000). This requires multiple visits and multiple infusions. However, for dialysis patients coming three times a week for their treatments, the need for frequent IV iron administration is not clinically or logistically relevant.

In 1997, LMW ID was unavailable for a short period of time. During this time there was an 1100% increase in SAE's due to IV iron administration reported to the FDA (Freedom of Information Act). However, it was not until 2004, that Chertow et al (NDT, 2004) showed in a retrospective study of nearly 50 million doses of IV iron, that virtually all SAE's associated with IV iron were due to HMW ID. The authors also pointed out that when HMW ID is avoided, the other irons are safe with an incidence of SAE's of <1:200,000. Subsequently, over 15 papers have warned against the use of HMW ID, it has been specifically proscribed by brand by the NCCN in their 2008 anemia guidelines (JNCCN 2008), the VA medical systems have removed it from their formularies in all of the hospitals in the U.S. and its protectorates and it has been removed from the market in western Europe. Given the lower cost and greater ease of administration of LMW ID than with the iron salts, these data call in question the decision to abandon LMW ID in dialysis patients (Auerbach KI, 2008).

In June of 2009, a new compound, ferumoxytol (Feraheme, AMAG), was approved for administration to iron deficient patients with chronic renal failure. This drug is supplied in a 510 mg vial, five to eight times the dose of the other compounds, increasing convenience by decreasing pharmacists' time for preparation. The drug can be injected as a bolus push in less than 30 seconds. From the registrational trials it appears to be extremely safe and reasonably effective. There is no data at the present time with the administration of higher doses. Therefore, complete replacement for iron deficient patients requires at least two visits. This drug is three times the price of LMW ID and nearly 50% more expensive than the iron salts. Those of us working in the IV iron arena, eagerly await data on full replacement dosing with this exciting new compound.

#### **OPTIONS FOR IV IRON ADMINISTRATION**

Absent nephrology patients, only ID is approved for administration for iron deficient patients with overt or functional iron deficiency. It is extremely important to note, that premedication prior to the administration of IV iron should NOT be administered. Barton et al (AJM, 2000) showed that the majority of perceived SAE's with IV iron were due to premedication, especially diphenhydramine, which can cause hypotension, supraventricular tachycardia, and mimic symptoms of anaphylaxis which will likely be attributed to the IV iron.

Although three new irons, including ferumoxytol, show promise to make the correction of iron deficiency even more felicitous, the easiest, least expensive, most efficacious and probably least toxic means of correcting iron deficiency is with a total dose infusion (TDI) of LMW iron dextran. We have now given approximately 400 patients 1000 mg of LMW ID in one hour. The drug is diluted in 250 ml of normal saline. The test dose can be administered as a separate IV push or as a slow infusion of the diluted material. If after 5-10 minutes no adverse reaction is seen, none will occur. The remaining dose can be administered at 250 ml per hour such that the infusion can be completed in 60 minutes. For patients with a history of multiple drug allergies, a prior sensitivity to iron dextran or asthma, 125 mg methylprednisolone should be administered prior to the test dose. Otherwise, premedication should be avoided.

Although anaphylaxis has been reported with LMW ID, we have administered >70,000 doses in our practice (one dose=100 mg) without a single SAE. However, two adverse events uncommonly occur, but may be seen. The first of these was described by Fishbane (Auerbach, Lancet 2007) which is the acute onset of chest and back pain or tightness WITHOUT hypotension, tachypnea, tachycardia, wheezing, stridor, or periorbital edema. This harmless reaction, which never leaves residua, abates in minutes and does not recur with rechallenge. Should this reaction occur, NO TREATMENT should be administered, the patient should be reassured, observed for a few minutes, and treatment proceeded with cautiously after abatement of all symptoms. The second adverse event which occurs in approximately 10% of patients consists of arthralgias and myalgias, usually occurring about 24 hours after the

infusion. These reactions also never leave residua, abate without therapy, but more quickly when non-steroidal anti-inflammatories are administered. LMW ID costs about \$240 per gram.

Based on the preponderance of published literature it seems prudent to use HMW ID with caution. If your pharmacist is not aware of its danger and inadvertently purchases it, you should inform him/her immediately. Unfortunately, the U.S. is the only remaining country where this drug is still available. Further, the J-code for HMW ID is the same as for LMW ID and many pharmacists are unaware of the differences (Auerbach J Am Pharm Asso 2008; Rodgers et al, JASN 2008)

FG and IS may be used with equal safety and efficacy. FG may be given as a short 187.5 mg (three vials) infusion over 10-15 minutes and IS similarly in doses up to 300 mg. Higher doses of either of these drugs are associated with unpleasant vasoactive and gastrointestinal symptoms. The "Fishbane reaction" (see above) may occur with either of these drugs, but is less common than with ID. Both of these drugs are about twice the price of ID. The undiluted drugs may be pushed slowly or infused in a small volume of normal saline. The cost of both of these drugs is approximately \$450 per gram.

Ferumoxytol may be given as a 510 mg IV push over approximately 20-30 seconds. The drug always causes an asymptomatic 10-12 mm drop in systolic pressure that abates without treatment or symptoms. Other adverse events are uncommon. Anaphylaxis has been reported with this drug as well as with all of the other iron compounds. Currently the approval for this drug is restricted to patients with chronic renal failure. The cost of this drug is \$792 per gram.

#### **IV IRON AS AN ADJUNCT TO ESAs (USE IN IRON RESTRICTED ERYTHROPOIESIS (FUNCTIONAL IRON DEFICIENCY))**

Implicit in this discussion is the absence of absolute iron deficiency. Under the current parlance regulating usage of ESA if iron deficiency is present, ESAs are contraindicated until iron repletion has been accomplished. The conundrum is that there is no ICD9 code for either functional iron deficiency or iron restricted erythropoiesis, which for all intents and purposes are the same thing. Further the current guidance from the Committees for Medicare and Medicaid Services (CMS) restrict payment if ESA and IV iron is given on the same day. Although inexplicable at first, as this regulation clearly increases the number of office visits outside of dialysis centers, where the regulation does not apply, given the requirement for iron repletion prior to ESA usage, if iron deficiency (280.9) is placed on a billing form the ESA will not be paid for. On the other hand, if 280.9 is not placed on the billing form, the IV iron will not be reimbursed.

Clearly, the lack of codes for functional iron deficiency creates a problem in hematology and oncology practices where these drugs are widely used. For patients with chemotherapy induced anemia (CIA) and anemia of chronic renal failure not requiring dialysis, functional iron deficiency is virtually ubiquitous. Functional iron deficiency is characterized by a low percent saturation of transferrin in the presence of a low total iron binding capacity and a normal or elevated serum ferritin. If the serum ferritin is below the lower limit of normal, concomitant absolute iron deficiency is present and iron must be given prior to ESAs. There is no standard of care outside of dialysis for this situation.

Nine studies in CIA have shown a clear benefit from the addition of IV, and not oral, iron to ESA therapy with only one, albeit well done, clinical trial showing no benefit (Steensma, ASH 2009). In the nine studies showing benefit, the common denominators were improved hemoglobin response, shortened time to target hemoglobin, and decreased ESA usage for the same benefit. Safety data for the use of IV iron exists up to ferritins of 1000 ng/ml and TSAT's up to 40%. We therefore recommend that IV iron be added to the treatment paradigm for CIA in all patients hyporesponsive to ESAs at four weeks with ferritins <1000 ng/ml and TSATs <40%.

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Iron dextran is currently the only compendia listed agent in CIA however some payers will reimburse for FG and IS. Feraheme is not approved in this setting.

1. Iron dextran (LMW) can be given as intermittent bolus therapy in doses up to 400 mg until the desired dose is reached or as a single TDI (1000 mg in one hour). (Katodritou E, Verrou E, Zervas K. Intravenous iron: a useful therapeutic tool but not a panacea. Am J Hematol. 2008 Jul;83(7):521-3. Erratum in: Am J Hematol.2008 Aug;83(8):690. PubMed PMID: 18506701; Blood. 2009;114(Suppl): 1555; Fishbane et al, Kidney International Vol. 52 (1997), pp. 217—222; Auerbach et al, AJH 2010;85:655-63).
2. Ferric gluconate can only be given as intermittent bolus therapy in doses that should not exceed 250 mg (Fulkert, Am Journal of Kidney Disease, 2003) until the desired total dose is achieved.
3. Iron sucrose can only be given as intermittent bolus therapy in doses that should not exceed 300 mg (three vials) until the desired dose is achieved. (Chandler G, et al Intravenous iron sucrose: establishing a safe dose. Am J Kidney Dis. 2001 Nov;38(5):988-91. PubMed PMID: 11684551).

These guidelines apply to all situations where functional iron deficiency is present and ESAs are used. The one exception is for patients with non-dialysis chronic renal failure where in addition to the above three options, ferumoxytol can be given as 510 mg boluses in 20-30 seconds.

The Iron Corner was developed to debunk the folklore about efficacy and toxicity associated with this extremely valuable and underutilized therapy. Recent evidence suggests that IV iron has a salutary role in the treatment of congestive heart failure (Anker, NEJM, 2009) and restless leg syndrome (Ondo, Sleep Medicine, 2010). Studies are underway to evaluate the benefit of IV iron without ESAs in CIA where ESAs are proscribed (Hb>10 G/dl, curable malignancies, head and neck cancer and adjuvant therapy). We hope these tools assist providers to use IV iron appropriately.

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