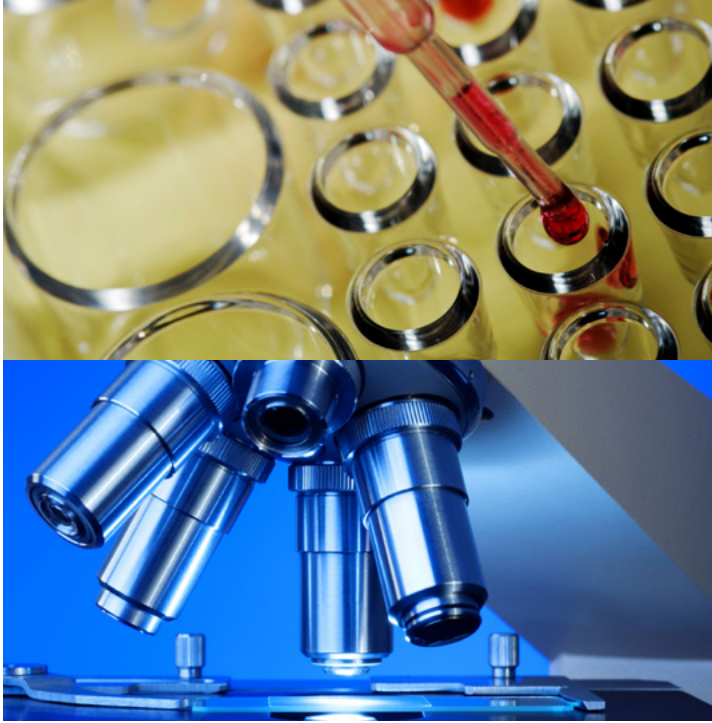


# IRON DEFICIENCY IN HHT

Raj Kasthuri, MD

Director, UNC at Chapel Hill HHT Center of Excellence

Iron deficiency is common among people with HHT and is primarily a consequence of bleeding from telangiectasias in the lining of the nose and intestinal tract. Iron deficiency tends to be both under-diagnosed and under-treated in HHT patients and can lead to decreased exercise tolerance, chronic fatigue, and poor quality of life. The purpose of this article is to highlight the common manifestations of iron deficiency and discuss its treatment.



## Why do we need iron?

Iron is required for the production of hemoglobin in red blood cells and the protein myoglobin in muscle cells. Iron is also a component of many proteins and enzymes in the body and plays important roles in energy metabolism and immunity. The total amount of iron in an adult is about 3-4 grams. The majority of this (about 2.5 grams) is present in hemoglobin within circulating and developing red blood cells. About a gram of iron is present as 'stored iron' mostly in the bone marrow, liver and spleen. Of note, women of child-bearing age usually have lesser amounts of stored iron, as they use more iron to make up for menstrual blood loss and iron requirements during pregnancy, childbirth and nursing.

## How much iron do we need?

The amount of iron in the body is tightly regulated. As the body cannot make iron, the amount of iron absorbed from the diet needs to equal the amount of iron lost on a daily basis. This is about 1mg of iron per day. The daily requirement is slightly higher in adult women (2mg/day) secondary to menstrual loss. The iron requirements are higher during adolescent years due to growth and development. Iron requirements also increase during pregnancy and the total amount of iron utilized during pregnancy, childbirth and nursing is about 1 gram. Foods that are rich in iron include red meats, liver, egg yolk, salmon, tuna and oysters (iron in these foods are in the form of hemoglobin and myoglobin, referred to as heme-iron). Iron is also present in vegetables, fruits and grains, but this iron (referred to as non-heme iron) is harder for the body to absorb.

## Causes of iron deficiency

The overwhelming cause of iron deficiency in developed countries is blood loss. Less likely causes include decreased intestinal absorption (e.g. Celiac disease, following gastric bypass surgery), and decreased iron intake (in extreme diets). Unless an individual experiences sudden and massive blood loss, iron deficiency tends to develop slowly over time. At first, the body progressively uses up its iron stores due to an imbalance between the supply and demand for iron in the body. In this early stage people do not yet have anemia, as there is sufficient iron available for hemoglobin synthesis. However, if the imbalance persists (such as with continued bleeding as can happen in HHT), over time the iron stores become exhausted resulting in iron deficiency anemia. It is important to realize that iron deficiency can occur in the absence of anemia, affected individuals can develop clinical symptoms from iron deficiency even without anemia. This state can be diagnosed using routine laboratory tests.

## Clinical features of iron deficiency

The clinical features of iron deficiency are mainly related to anemia and include fatigue, weakness, headaches, irritability, and decreased exercise tolerance. Rarely, affected individuals can develop dry mouth, hair loss, and brittle fingernails. In children and adolescents, iron deficiency (with or without anemia) can also cause poor cognitive function (difficulty with concentration and learning, memory, school performance, etc) and poor physical performance (running, endurance). Further, studies have shown improvement in performance with correction of the iron deficiency. A classic but uncommon finding in individuals with iron deficiency anemia is a craving for ice or substances like clay (referred to as 'pica'). Iron deficiency has also been associated with Restless Leg Syndrome, a condition causing an urge to repeatedly move the legs or arms because of an uncomfortable feeling in the affected body part.

## How do we diagnose iron deficiency?

Iron deficiency should be suspected in any person with HHT who develops one or more of the above mentioned clinical features. Further evaluation should consist of doing the following blood work: a complete blood count (CBC), reticulocyte count, and an iron panel (serum iron, iron saturation, total iron binding capacity, ferritin). These together provide information on a person's iron stores and whether or not an individual is iron deficient/anemic.

## How do we treat iron deficiency?

Once a person has been diagnosed with iron deficiency, this should be corrected by replacing the iron stores. The goal is to correct the iron deficiency as well as replenish the body iron stores. This can be achieved by taking iron by mouth in the form of iron supplements (tablets, liquid, suspension or elixir) or by replacing iron directly into the vein (intravenous or IV). Generally, the initial approach is to pursue oral iron replacement. A number of oral iron preparations are available and some of the common preparations, their trade names and the amount of elemental iron they contain are summarized in Table 1. It is important to note that oral iron supplements can be associated with gastrointestinal side effects such as nausea, bloating, and constipation that frequently limit their use. The side effects appear to be related to the amount of elemental iron and, therefore, preparations that contain less elemental iron tend to be better tolerated. Once the hemoglobin becomes normal, there is still a deficiency in the total amount of iron in the body, and it is recommended that iron treatment be

continued for an additional 6 months to replace the missing iron stores in the body.

In individuals with severe iron deficiency anemia or frequent/severe bleeding, oral iron may be inadequate to treat the iron deficiency. In such cases, and in individuals who do not tolerate oral iron, treatment with intravenous iron should be considered. A number of intravenous iron preparations are currently available. The number of doses of intravenous iron necessary to correct a person's iron deficiency will vary depending on the preparation being used. The currently available drugs and the amount of iron they contain are summarized in Table 2. Of note, preparations that contain less iron (Ferrlecit, Venofer, etc) have the advantage of quicker infusions. On the other hand, the iron dextran preparations (INFeD, Dexferrum) take a few hours to administer but offer the option of replacing the entire iron deficit in a single infusion. Regardless of the preparation used, intravenous iron can be associated with allergic reactions. Some preparations require the use of a small test dose and pre-treatment with antihistamines (e.g. Benadryl) for this reason.

**TABLE 1: ORAL IRON PREPARATIONS**

Generic names [available formulations]	Product names	Amount of iron (varies depending on the preparation between tablets, liquids, elixirs, etc.) Generic names [available formulations]		Generic names [available formulations]
		Total dose	Elemental iron	
Ferrous gluconate [available as tablets]	Fergon	240-325mg	27-38mg	Non-heme iron products. These products contain higher amounts of elemental iron compared to heme- iron containing products. These are also associated with greater GI toxicity compared to heme- iron products.
Ferrous sulfate [available as liquid, elixir, suspension, tablets, timed- release tablets and enteric coated tablets]	Feosol Slow FE Fer-iron Fer-In-Sol Mykidz Iron	75-325mg	15-65mg	
Ferrous fumarate [available as regular and timed release tablets]	Femiron Ferretts Ferro-Sequels Hemocyte Iron	63-325mg	20-106mg	
Polysaccharide-iron complex [available as capsule and elixir]	Niferex Nu-Iron Ferrex-150 ProFe Poly-Iron 150		60-180mg	
Iron polypeptide as dietary supplements	Proferrin ES	formulations]	12mg	Heme-iron product
Combined heme and non-heme dietary iron supplement	Bifera		6mg as iron- polypeptide 22mg as polysaccharide-iron complex	

Following iron replacement, one can begin to see a rise in the hemoglobin in 2-4 weeks. It is important to realize that treatment with iron, either oral or

intravenous, will not immediately correct the anemia. Therefore, individuals with symptomatic anemia may need to receive an initial blood transfusion to improve their symptoms. While transfused red blood cells contain iron (about 250mg/unit of blood), this alone is inadequate to correct the iron deficiency.

It is essential in individuals with HHT who have frequent nose bleeds or intestinal bleeding to continue to aggressively treat/prevent iron deficiency. Once treatment with iron is started, it is important to repeat a CBC and iron panel in 2-3 months to assess response to treatment. Individuals with chronic nose or GI bleeding who tolerate oral iron should continue to take this long term. Individuals that require treatment with intravenous iron may require repeated treatments based on the severity of bleeding.

## Key points

- Iron deficiency is an important and under-appreciated cause of symptoms and poor quality of life among individuals with HHT.
- People with HHT who suffer from bleeding should be routinely screened for iron deficiency. The appropriate blood tests for the physician to order are: CBC, reticulocyte count, and iron panel.
- If iron deficiency is found, this should be treated aggressively.
- If oral iron preparations are poorly tolerated or the iron deficiency is very pronounced, iron can be given intravenously in easy to give preparations.

**TABLE 2: INTRAVENOUS IRON PREPARATIONS\***

Generic names	Product names	Duration of dose administration [approximate]	
Ferric gluconate	Ferrlecit	125mg	2 hours
Iron sucrose	Venofer	200mg	75 minutes
Ferumoxitol	Feraheme	510mg	Rapid infusion
Iron dextran#	INFeD [low molecular weight dextran]  Dexferrum [high molecular weight dextran]	50mg/mL – dose calculated based on weight and hemoglobin to replace total iron stores in a single infusion	3-4 hours
Ferric carboxymaltose@	Ferinject	1gram	15 minutes

\* All intravenous iron products can be associated with potentially life threatening allergic reactions

# High molecular weight carries the highest risk of life threatening allergic reaction, which occur in about 11 per million doses administered. This is less with the low molecular weight dextran (3 per million doses).

@ Not available in the USA

