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POLICY STATEMENT

IRON REPLACEMENT THERAPY IN HHT

Iron deficiency anemia is common in people with HHT with an estimated prevalence of 50%. Further, a number of people with HHT develop symptomatic iron deficiency without anemia. Iron deficiency is an under recognized and sub-optimally managed complication in people with HHT.

We recommend the following guidance for the management of iron deficiency in people with HHT. This guideline is meant to highlight the issues facing HHT patients and to serve as general guidance. The ultimate decision about when to give iron and in what form it should be given may involve other clinical factors not mentioned in this statement:

- All patients with HHT should be maintained in a fully iron-replete state.
- All adults with HHT should have routine monitoring of CBC, transferrin saturation (iron and total iron binding capacity) and ferritin. **The specific interval of this monitoring will be patient-specific and may change as bleeding worsens or improves with hemostatic therapies.**
- A serum ferritin of <50 ng/mL **usually** indicates the need to start iron replacement therapy.
- Oral iron therapy is frequently inadequate and parenteral iron replacement is required to replete iron stores. **Unlike many other etiologies of iron deficiency in which a single IV repletion is adequate, HHT patients requiring IV iron often require regular, ongoing infusions to maintain a ferritin >50 ng/mL and a transferrin saturation >20%.**

- Large amounts of iron may be required to achieve and maintain normal iron levels given ongoing recurrent mucocutaneous bleeding. Although there are a number of iron replacement products, some deliver more iron than others and infusion times vary which may make some products more convenient for patients than others. When possible, treatment plans that allow larger doses of iron to be given are preferable given the frequency and time commitments needed to maintain adequate levels in many HHT patients. Ferric carboxymaltose (FCM) (Injectafer, Ferinject) should be avoided given its risk of hypophosphatemia. The mechanism by which hypophosphatemia occurs (loss of phosphate in the urine due to the impact of the drug on the kidneys, occurring in 50-75% of patients after a single FCM treatment course and often lasting for weeks to months) is such that oral and intravenous phosphate supplementation is ineffective. This is particularly important given the fact that people with HHT often need regular iron infusions and repeat iron infusions over time can have a significant negative impact on bone health. The FDA recently updated its warning regarding hypophosphatemia due to FCM to include HHT as a risk factor. It should be noted that HHT itself is not a risk factor for FCM-induced hypophosphatemia, but the fact that most HHT patients receive continuing, and sometimes frequent, infusions places them at risk. While FCM should be avoided, we do recognize that for some patients and in some countries there may not be an alternative. Only in the unavoidable situation in which no other intravenous iron formulation is available in a given country should a patient with HHT receive FCM, and in this circumstance phosphate levels should be monitored at weeks 1 and 2 following an FCM infusion, and if the patient is found to be hypophosphatemic, weekly monitoring should continue until phosphate levels normalize. Pathologic fractures have been reported in HHT patients receiving this form of iron.

Approved by Cure HHT's North American Science and Medical Council – March 2025