

WHAT YOU NEED TO KNOW ABOUT HHT



FOR THE HEMATOLOGIST

Recurrent, often severe mucosal bleeding (epistaxis, GI bleeding, heavy menstrual bleeding) and recurrent iron deficiency anemia are the most common and most pervasive manifestations of hereditary hemorrhagic telangiectasia (HHT). Systemic antiangiogenic and coagulation-modifying therapies are now the standard of care in the management of HHT-associated bleeding, replacing the old paradigm of repeat procedural therapies. Additionally, solid organ AVMs result in numerous morbid bleeding and non-bleeding manifestations, including the recent recognition that HHT has the highest incidence of intracranial hemorrhage, venous thromboembolism, and arterial thromboembolism of any of the common inherited bleeding disorders (von Willebrand disease, HHT, hemophilia). Because of this paradigm shift in treatment and expanded modern understanding of the clinical spectrum of HHT, hematologists are now the **medical home and serve as the primary providers for patients with HHT**, much like they are in patients with hemophilia. Both of these multidisciplinary inherited bleeding disorders rely on multiple specialists to deliver proper care to patients, but the role of quarterback is most appropriately played by the hematologist.

This fact sheet provides a brief synopsis of HHT and the role hematologists play in its diagnosis and treatment. Key areas include the genetics of HHT, identifying patients who may have HHT, screening for systemic complications and managing the bleeding that occurs in most patients.



GENETICS OF HHT

HHT is an autosomal dominant genetic disorder caused by mutations in specific genes, therefore a patient with HHT has a 50% chance of passing the mutated gene to each child.

Patients with suspected HHT should undergo genetic testing to identify the gene mutation and all at risk family members should then be tested to see if they also have the gene mutation. Testing can be done at birth.



DIAGNOSING HHT

HHT can be diagnosed clinically in most adults by using the Curacao criteria in a couple of minutes in the office with a simple history and brief skin and oral exam. Diagnosis should be confirmed with genetic testing, particularly in ambiguous cases and in children. The Curacao criteria is less specific in children and genetic testing can provide a diagnosis earlier in life which allows for screening to be performed before symptoms may start. Most intracranial hemorrhages in HHT occur prior to age 25, so early diagnosis is crucial.



MULTISYSTEM INVOLVEMENT

HHT involves multiple organs, including the nose, gastrointestinal tract, brain, lungs, and liver.

Although the most common symptom of HHT is nosebleeds, not every patient with HHT gets nosebleeds and the presence of nosebleeds or their severity does not correlate with other organ involvement. Therefore, the absence of nosebleeds cannot be used to rule out HHT or indicate screening is not necessary.

All patients with HHT should have screening for systemic AVM formation and this screening can be started shortly after birth. In addition to mucosal bleeding, most patients with HHT develop AVMs in at least one solid organ.



BLEEDING MANAGEMENT

Chronic blood loss is common and the majority of HHT patients are anemic and/or iron deficient.

Most patients require recurrent iron replacement, which may be frequent.

Oral iron is rarely effective in HHT patients with chronic bleeding and IV iron is needed in the majority of patients needing iron supplementation.

The goal of iron replacement should be to maintain normal hemoglobin levels, an iron saturation above 20% and a ferritin level above 50.

Ferric carboxymaltose carries a high risk of hypophosphatemia in HHT patients who require frequent iron replacement and can result in severe osteomalacia and fractures, therefore it should be avoided.

If hemoglobin, iron and ferritin levels cannot be maintained with appropriate iron replacement or the frequency of treatments is too frequent, antifibrinolytics and antiangiogenics should be considered.

There are several therapeutics which have been shown to effectively limit bleeding in HHT patients (bevacizumab, pazopanib, pomalidomide, etc.) and several more are undergoing clinical studies.

The therapeutic landscape is rapidly expanding in HHT, all with classes of drugs impacting coagulation and angiogenesis that are squarely within the domain of the hematologist / oncologist. Drugs being developed specifically for HHT include multiple oral AKT inhibitors, a plasminogen knockdown RNAi agent, a bispecific antibody agonizing the lesioned ALK1 signaling pathway, and an antibody antagonizing a G-protein-coupled receptor critical in angiogenesis. All of these are in development primarily to treat bleeding in HHT.

**ADDITIONAL
RESOURCES**

