Hereditary Hemorrhagic Telangiectasia Management

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After completing this article, the reader should be able to:

- Discuss the incidence and types of hereditary hemorrhagic telangiectasia (HHT).
- Identify the genes and organs affected by HHT.
- Recognize the symptoms of HHT and how the disease is diagnosed.
- Understand the treatment of epistaxis from HHT.
- List the types of arteriovenous malformations (AVMs).
- Describe pulmonary AVM treatment options and follow-up care.

Hereditary hemorrhagic telangiectasia (HHT) is one of the most common inherited autosomal dominant disorders. Incidence of the disease varies, but international incidence is reported to be approximately 1 in 5000 to 1 in 8000. Normally, the junction point of arteries and veins includes capillary beds. Individuals with HHT, however, tend to develop abnormal blood vessels that lack capillary beds. Often, the abnormal connections of vessels instead have a delicate aneurysmal sac that is prone to spontaneous bleeding.

Most often, abnormal connections are noted as red markings called telangiectasias that appear on a patient’s hands, fingertips, face, lips, or inside the mouth and nose and accompany nosebleeds (epistaxis). When the abnormal connections form in larger blood vessels, they are called arteriovenous malformations (AVMs). People who have HHT can have AVMs in the digestive system, as well as in the lungs and brain. There is no cure for the disease; physicians only can treat the sequelae. Treatment varies and is based on the severity of the sequelae. Regardless of severity, however, all patients with HHT should be screened for pulmonary AVMs to help prevent the serious consequences of leaving AVMs untreated.

History and Epidemiology

HHT is rare in North America, appearing in about 1 to 2 people per 100,000 annually. However, its prevalence can vary considerably geographically and among groups of people. For example, the Afro-Caribbean population of the Netherlands Antilles islands exhibits the highest rate of the disease at 1 case per 200 people. Yet the prevalence of HHT on the islands of Curaçao and Bonaire is closer to 1 in 1300. In 2011, an estimated 60,000 U.S. patients had the disease, with the highest frequency in Vermont (1 case per 16,500 people).

About 90% of people with HHT are asymptomatic and, therefore, their...
cases remain undiagnosed. The disease equally affects men and women. HHT has been reported in individuals from all ethnic and racial groups, although the disease appears more often in whites.¹

HHT also is known as Osler-Weber-Rendu syndrome for the physicians who studied the disease in the late 19th and early 20th centuries. At that time, physicians believed patients with HHT had the blood clotting disorder hemophilia. It was not until 1896 that French physician Henri JLM Rendu characterized the HHT symptoms of epistaxis (recurrent nosebleeds) and characteristic red spots as different from hemophilia symptoms. He described the disease as a hereditary disorder that produced abnormal blood vessels. Drs William Osler and Frederick P Weber reported on additional characteristics of HHT in the early 1900s.

However, despite the work of several researchers, modern physicians continue to misdiagnose the physical characteristics of the disease.²-⁵

**Presentation and Evaluation**

The enlarged vessels associated with HHT compress or irritate nearby tissues, frequently causing repeated intense bleeding. An abnormal connection of the small arteries is known as a telangiectasia. Telangiectasias commonly occur on the skin of the hands and face; they also can be found on the thin linings of the nose and mouth (see **Figure 1**). The nasal linings rupture easily, causing epistaxis, the most frequent symptom experienced by individuals with HHT. Telangiectasias also can develop in the gastrointestinal (GI) system, with the stomach and small bowel affected most often. When bleeding occurs at these locations, physicians can use several well-established treatment methods to manage the symptoms.⁴⁻⁶

Normally, arteries do not connect directly to veins. When an artery and vein directly join in larger vessels, the connection is known as an AVM. AVMs can be found in the lungs, liver, brain, or GI tract. Although malformations can develop in several different organs throughout the body, the most serious types occur in the lungs and brain, especially if the AVM is not diagnosed and treated. As a precaution following an HHT diagnosis, patients should be screened for possible AVMs in both the lungs and brain. Prompt treatment can have a significant effect on a patient’s long-term health by decreasing the risk associated with an untreated AVM. Specialized treatment centers have been established for patients with HHT, and the Hereditary Hemorrhagic Telangiectasia Foundation urges individuals with the disease and their family members to have assessment and treatment at one of these centers.⁴

**Genetics**

Autosomal dominant disorders such as HHT lead to affected individuals having an abnormal gene from one parent and one normal gene on a pair of autosomal chromosomes. Autosomal dominant inheritance only requires 1 abnormal gene to make the person susceptible to having the physical traits of the disease. Every pregnancy involving an affected parent increases the
Autosomal dominant disorders differ from autosomal recessive ones. When a disease is autosomal recessive, such as with cystic fibrosis, 2 copies of the abnormal gene are necessary for the individual to express the physical traits of the disease. In most cases, the parents are gene carriers who are not necessarily affected by the disease. With autosomal recessive inheritance, every child born to 2 parents who are carriers of the disease has a 25% chance of inheriting 2 abnormal genes and expressing the physical characteristics of the disease. However, there is a 50% chance the child will inherit only 1 copy of the abnormal gene and will be a carrier without expressing any physical signs of the disease. Finally, there is a 25% chance the child will not inherit any copies of the disease’s genes, and therefore will not express any characteristics of the disease or be a carrier. In this case the child would not be at risk for passing the disease to any future children. Autosomal recessive inheritance also typically affects male and female children equally.

The 5 recognized types of hereditary HHT are types 1, 2, 3, 4, and juvenile polyposis/HHT syndrome (see Table). Of the 5 types, 3 have been linked to a particular gene and the other 2 have been associated with a specific location on the gene’s DNA sequence. All types of HHT can produce characteristic symptoms in any individual; however, some forms of HHT are associated with increased risk of certain malformations. For example, people with HHT1 experience an earlier onset of symptoms and are more prone to develop AVMs in the lungs and brain than are people with other types; individuals with HHT2 and HHT3 have elevated risk of hepatic involvement. Women with HHT1 are more likely than men to develop pulmonary AVMs, and with both HHT1 and HHT2, women are at a higher risk for hepatic involvement. Patients with juvenile polyposis tend to develop malformations in the GI tract, whereas individuals with types 1, 2, and 3 do not.

HHT1 is caused by mutations of the ENG gene. The ENG gene plays a role in the production of the protein endoglin, which is found on the surface of cells that line the blood vessels. Endoglin, growth factors, and other proteins form a complex that helps determine whether a blood vessel becomes a vein or an artery.
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HHT2 is associated with mutations of the ACVRL1 gene. This gene supplies the code for making a protein called activin receptor-like kinase. Activin receptor-like kinase is a receptor protein that is unlocked by a ligand called transforming growth factor beta. These proteins play a part in developing blood vessels, specifically transforming vessels into arteries or veins. More than 600 mutations have been found in the ENG and ACVRL1 families that make up HHT. At a minimum, 80% of patients with the disease have defects on the ENG or ACVRL1 genes.

Only 1% to 2% of HHT cases have mutations of the SMAD4 gene, which also is instrumental in protein formation. The SMAD protein, along with other proteins, forms a complex that allows communication between the cell surface and the nucleus. The protein complex controls cell activity such as growth and division. Mutations on the SMAD4 gene are responsible for juvenile polyposis.

At least 2 more unidentified genes are associated with HHT. HHT3 is caused by a gene on chromosome 5. Chromosome 5 is thought to have at least 900 genes. HHT4 is caused by a gene on chromosome 7, which contains between 900 and 1000 genes. Like ENG and ACVRL1, these genes direct the production of proteins that control the growth and development of arteries and veins. Mutations in these genes result in proteins with limited function. The loss in protein function affects the formation of the blood vessels, resulting in the AVMs associated with HHT.\(^\text{9}\)

Diagnosis

Diagnosis of HHT can be made using consensus diagnostic criteria originally published in 2000, known as the Curaçao criteria. The 4 findings of the Curaçao criteria are\(^\text{5,10-12}\):

- Epistaxis that spontaneously recurs.
- Mucocutaneous telangiectasias that develop at characteristic locations, including the nose, lips, mouth, and fingers, as pink or red pinpoint lesions that are not visible when pressure is applied. Occasionally, the telangiectasias appear as 2-mm to 5-mm marks that are purple or spider-like.
- Presence of hepatic, cerebral, GI, pulmonary, or spinal visceral AVMs.
- Family history of a parent, sibling, or child who has received a diagnosis of HHT using these same criteria.

Using the Curaçao criteria, physicians can make a definitive diagnosis of HHT when 3 to 4 criteria are present. Clinicians can conclude suspicion of the disease from 2 Curaçao findings. HHT is unlikely when a patient shows 0 to 1 Curaçao findings. It is difficult to apply the Curaçao criteria to infants and children because many of the signs and symptoms of HHT appear later in life.

Approximately 50% of people with HHT report having nosebleeds at or before 10 years of age, and 90% at or before age 21 years. Most (95%) individuals diagnosed with HHT eventually report epistaxis. A similar percentage of HHT patients have telangiectasias on their hands and face and in their oral cavity, but these symptoms appear between 5 years and 30 years after the initial onset of epistaxis.\(^\text{5,10-12}\)

Genetic Testing

Genetic testing is available for families who have the signs and symptoms of HHT. The testing involves analyzing the DNA of the affected genes in a laboratory. Genetic testing uses a small sample of blood, or in some cases, a sample of saliva. Three genetic tests are available to diagnose HHT: sequencing, targeted sequencing, and deletion and duplication testing. Sequencing examines a DNA sample and determines the exact order of the nucleotides (adenine, guanine, thymine, and cytosine) within the DNA to determine the existence of abnormalities. Targeted sequencing saves time by looking at a specific area of interest within the DNA. Targeted sequencing is used when another...
family member already has undergone genetic testing in which an abnormal gene was found.

Deletion and duplication testing is a technique used to look for a piece of a gene that is either missing or duplicated. Genetic testing is not required if a definite clinical diagnosis has been made; however, it allows for screening of asymptomatic family members. If a person meets the clinical diagnostic criteria for HHT1 or HHT2, physicians order genetic testing of the ENG and ACVRL1 genes. Typically, the sequencing or deletion and duplication testing yields a nearly 87% success rate in those tested. If the genetic testing of ENG and ACVRL1 genes are negative, then sequencing of the SMAD4 gene will identify a mutation in another 2% of those people. In about 10% to 15% of people diagnosed with HHT, genetic testing cannot find a mutation in any of the known genes associated with HHT.6

Screening

A panel of international experts on HHT has made evidence-based recommendations for HHT screening. Although genetic testing is available, it is limited to known mutations.13 Every mutation has not been differentiated. When HHT is discovered in screening of an individual, the person’s siblings and children should be tested for the same mutation. If relatives have results that are negative for the mutation, no further screening is needed. This is very useful for parents with small children because some of the screening tests involve general anesthesia. Parents with HHT should have their children screened even though the child might not meet the criteria for HHT assessment. Until HHT can be ruled out definitively, children still should be considered at risk.13

Screening for HHT includes a contrast echocardiogram and magnetic resonance (MR) imaging of the brain of individuals who have positive genetic testing results or possible HHT as defined by Curacao criteria. A transthoracic echocardiogram with contrast screens for possible pulmonary AVMs. In young children, measuring O2 saturation on room air can be a useful screening tool until the child can safely undergo a transthoracic echocardiogram with contrast. When a patient has a negative transthoracic echocardiogram with contrast, monitoring every 3 to 5 years with a repeat echocardiogram is recommended to identify possible new pulmonary AVM formations. Any adult who has confirmed HHT or is suspicious for having HHT should get an MR scan with and without contrast. The MR scan uses special sequences that detect blood products. These sequences maximize image sensitivity and screen for cerebral vascular malformation (CVM).

Any child who is suspected of having HHT should be screened for CVM before age 6 months or at the time of HHT diagnosis via an unenhanced MR examination. All patients who have a positive MR result should be referred to a center that specializes in HHT. These facilities have experts in neurovascular abnormalities and can better determine the need for further testing and available treatment options. Because AVMs are believed to be congenital, patients with negative MR results can avoid unnecessary repeated MR examinations. Testing for GI and liver involvement is recommended for patients who experience GI bleeding, anemia, and heart or liver failure.6

Epistaxis Management

Spontaneous and recurrent epistaxes occur in more than 90% of people with HHT by age 40 years. Epistaxis normally is the HHT symptom that triggers people to visit their doctors. The average age of patients at the onset of nosebleeds is 12 years, but this can vary from infancy to adulthood.

Affected individuals might have several nosebleeds a day or several per year. Epistaxis severity also varies from nosebleeds that release only a few drops of blood to more severe bleeding that can lead to chronic anemia and require frequent blood transfusions for management.

Treatment for nosebleeds varies from one individual and instance to another. Physicians should advise patients with epistaxis to avoid use of nasal packing if possible. Packing traumatizes the mucosa and can cause further bleeding when the packing is removed. Using humidifiers and applying nasal lubricants daily can help prevent nosebleeds in those who have HHT.6,10 Some patients find nasal lubricants helpful for reducing dryness and crustizing. However, the act of applying a lubricant is sometimes enough to trigger a bleeding event. A sesame oil/rose geranium oil compound has been reported to improve symptoms significantly in 75% of patients. Other methods, including intranasal tranexamic acid,
caustic soda, snake venom coagulation, and radiation therapy, have shown little evidence of benefit.\textsuperscript{10}

Laser ablation often is recommended to minimize epistaxis occurrence in patients who experience frequent, mild-to-moderate nosebleeds. When bleeding is persistent, the use of an absorbable material such as a gelatin sponge soaked in adrenaline or tranexamic acid can be useful. Packing might be particularly necessary when combined with embolization or arterial ligation. Embolization and arterial ligation can provide immediate results, but no evidence suggests they provide long-term benefit because of blood vessels receiving collateral supply. Silver nitrate nasal cautery should be avoided because it causes full-thickness mucosal damage, which increases the risk of septal perforation. Septal perforation can impede further treatment in patients with epistaxis.\textsuperscript{6,15}

**Medication**

Use of the beta blocker timolol to improve epistaxis has been suggested following successful use of the ophthalmic medication at treating superficial hemangiomas in children. The reasons for the improvement are unknown but could be related to immediate vasoconstriction and later endothelial cell death and decreased vascular endothelial growth factor.\textsuperscript{10}

Antioxidants such as oral N-acetylcysteine reduced frequency and severity of epistaxis in a noncontrolled study. The results were better for patients who had HHT1 than for those who had HHT2.\textsuperscript{13}

Antifibrinolytic agents such as tranexamic acid have been used as systemic or topical medications for managing epistaxis. Geisthoff et al conducted a randomized trial with placebo control and noted a significant reduction in epistaxis over 6 months as measured by patient-reported epistaxis scores.\textsuperscript{15}

Estrogen cream has been shown to flatten prominent nasal telangiectasia and make it more resistant to trauma within 6 months without an increase of serum estriol. The high doses necessary to control epistaxis can lead to adverse effects from the hormones, particularly in men. Medroxyprogesterone has been used with some success and leads to fewer adverse effects from the female hormones. Tamoxifen is a more acceptable hormonal medication for the reduction of epistaxis.

Clinical trials have shown significant reductions in frequency and severity of epistaxis and improvement in hemoglobin levels and short-term quality of life.\textsuperscript{10}

Bevacizumab is a recombinant monoclonal antibody that has been used as treatment for macular degeneration and certain metastatic cancers. Bevacizumab targets vascular endothelial growth factor, which is important in angiogenesis. Several studies and case reports on systemic use of the medication in patients who have HHT have shown improvement in epistaxis and bleeding within the GI tract. However, the medication’s adverse effects have included GI perforation, cytopenia, hypertension, delayed wound healing, septal perforation, weakness, and bleeding. These adverse effects, along with the cost and long-term nature of the treatment, have limited its clinical use for managing symptoms of HHT.\textsuperscript{10}

**Surgery**

Surgical treatment such as endonasal laser coagulation, most often with a potassium titanyl phosphate laser, has been used to manage epistaxis. The laser appears to have the best wavelength and absorption of the color red compared with other available laser treatments. These features lead to coagulation of individual telangiectasias without full-thickness mucosal injury. Laser treatment is a temporary fix only because new telangiectasias inevitably form.\textsuperscript{16}

Septodermoplasty is a procedure designed to replace a patient’s anterior septal mucosa with a skin graft. A physician performs the procedure on one side of the nose and treats the other side 2 to 3 weeks later to reduce the risk of septal perforation. In a trial involving 131 patients treated with septodermoplasty, the investigators reported a 57% reduction in the need for follow-up laser treatment over a 5-year period.\textsuperscript{16}

Nasal closure has been performed as a final resort in patients unresponsive to treatment for severe epistaxis. The procedure is reserved for patients who have a significant reduction in their quality of life because of epistaxis. The physician surgically closes the nasal passages. This prevents airflow and nasal telangiectasias from bleeding. Patients who elect to have this procedure must breathe through their mouths; therefore, oral or lingual lesions will bleed more than previously because
of increased airflow. If patients have the nasal closure reversed, the telangiectasias still are present in the nose and bleeding begins again.10

Interventional Radiology

Endovascular embolization is performed to occlude vessels supplying the nasal mucosa and thus reduce the severity and duration of epistaxis. In emergency cases, embolization can control bleeding until the patient can be stabilized. Although interventional treatment of epistaxis is safe and effective for all patients, people with HHT tend to need more follow-up embolizations and surgical intervention than individuals treated for the idiopathic condition.17

Endovascular treatment normally is performed under conscious sedation or anesthesia. The interventional team first accesses the femoral or radial arteries to place a 5F or 6F sheath and administer 3000 units of intravenous (IV) heparin for thromboembolic prophylaxis. Next, a 5F or 6F guiding catheter is inserted into the common carotid arteries and selective digital subtraction angiography is performed. Although epistaxis embolization takes place in the external carotid artery (ECA), it is important that the team also image the internal carotid artery (ICA) to17:
- Identify dangerous ECA-to-ICA collateral pathways and isolate the predominant blood supply to the ophthalmic artery.
- Assess the anterior and posterior ethmoidal arteries. The anterior and posterior ethmoidal arteries supply blood to the nasal cavity and the nasopharynx. These vessels branch off the ophthalmic artery, so it is important to document any sources of bleeding that cannot be occluded safely. Embolization of the ethmoidal arteries is associated with a significant risk of blindness.17

Following diagnostic arteriography, a microcatheter and guidewire are used to access various branches of the ECA. The interventional team first selects the internal maxillary artery (IMAX) and performs embolization using polyvinyl alcohol particles or an absorbable gelatin sponge. Embolic particles should be 255 μm to 355 μm or larger to prevent tissue necrosis. The physician can place embolism coils, but their use prevents future treatment because the artery cannot be accessed distal to the coil.17

After embolization of the IMAX, the interventional team performs arteriography to identify other bleeding pathways. The ECA supply to the nasal mucosa is rich in collateral vessels; therefore, several branches of the ECA might require treatment, including the facial artery, transverse facial artery, lingual artery, and ascending pharyngeal artery. Because strong side-to-side ECA anastomoses also can supply bleeding mucosa, bilateral embolization might be necessary. In this case, the physician first occludes all ECA vessels supplying the nasal mucosa on the bleeding side, and then treats the contralateral side with less intensity to prevent tissue necrosis. After embolization, the team performs a final arteriogram to assess treatment effectiveness.17

Patients can experience recurrent epistaxis following embolization and require follow-up intervention if appropriate. During follow-up embolization, the physician occludes branches that were not treated during the initial procedure, as well as vessels that might have recanalized since the first embolization.17

The success of endovascular treatment depends on the cause of the epistaxis. In a study comparing treatment of HHT-induced epistaxis and idiopathic epistaxis, embolization had different success rates. Patients with idiopathic epistaxis experienced an 80% success rate with 1 interventional treatment compared with a single-treatment success rate of 25% for patients who have HHT. However, embolization reduced the severity and frequency of nosebleeds in patients with HHT. About 58% of patients who have HHT required another surgery or re-embolization, and 17% continued to have severe epistaxis. This group of patients was managed medically after all other treatment options had been exhausted.17

Medical, surgical, and endovascular treatment of epistaxis in patients who have HHT offers some relief and improvement in quality of life by reducing the severity and frequency of bleeding events, thus limiting trips to the emergency department. Given there is no cure for HHT, these patients often will need a combination of therapies until a cure can be identified.17

GI Bleeding Management

About 25% of people who have HHT will develop bleeding in the GI tract after age 50 years; the
bleeding ranges from mild to severe. Mild GI bleeding requires little or no therapy; persistent bleeding might require multiple, repeated blood transfusions. No links to particular foods or activities contributing to GI bleeding in people with HHT exist, but anticoagulants and nonsteroidal anti-inflammatory drugs (NSAIDs) can worsen the bleeding. In patients with HHT, telangiectasias are found anywhere within the GI tract, including the esophagus, stomach, and small intestine.

Telangiectasias in the GI tract look similar to those found on the skin and do not cause pain or discomfort. The symptoms of bleeding from the GI tract include bloody or black tarry stools and anemia, which can cause shortness of breath, fatigue, lightheadedness, or chest pain. Iron supplements, bismuth, and certain foods also can lead to black stools, as can swallowing of blood from epistaxis. These symptoms can make it difficult for a physician to determine whether the cause of the black stool is HHT. Often, individuals with HHT have minor blood loss from the GI tract. Although the bleeding is not severe enough to change the color of the stool, it can cause anemia.

**Medication**

Various case reports and small uncontrolled studies have noted a decrease in the need for transfusions to treat severe GI bleeding following use of various pharmacologic agents such as oral estrogen–progesterone or tranexamic acid. In addition, some case reports show a dramatic decrease in GI bleeding with IV administration of bevacizumab.

**Surgery**

Surgical or procedural treatment for GI bleeding typically is unnecessary. Some patients require the intervention if aggressive treatment with iron therapy is ineffective at maintaining hemoglobin concentrations in the body. When a patient does not respond to iron therapy treatment, several choices are available to localize the source of the bleeding, including endoscopy or mesenteric and celiac arteriography, and radionuclide studies.

Once the source of bleeding has been identified, endoscopic heater probe coagulation or argon plasma coagulation are treatment options. Once a nuclear medicine study demonstrates the bleeding site, bleeding within the small bowel and large vascular malformations can be repaired surgically.

### AVM Management

#### Hepatic Arteriovenous Malformations

The No. 1 cause of hepatic AVMs in adults is HHT. Although 30% or more of patients with HHT have some form of hepatic involvement, only 5% of these patients are symptomatic. Hepatic AVMs are associated with heart failure, portal hypertension, and biliary disease (see Figure 3). Heart failure occurs when a hepatic AVM diverts blood from the hepatic artery or the portal vein. The blood gets shunted into systemic circulation, producing a hyperdynamic state that causes high-output heart failure.

Portal hypertension is caused by the shunting of hepatic arterial blood into the portal vein. Biliary disease also occurs when blood from the hepatic artery is redirected. This shunting decreases the blood supply to the bile duct, eventually leading to biliary ischemia, biliary necrosis, or the formation of biliary cysts. Other conditions associated with HHT-induced hepatic AVMs include portosystemic encephalopathy, abdominal angina, and nodular regenerative and focal nodular hyperplasia.

International guidelines for diagnosing and managing HHT recommend avoiding hepatic artery embolization in patients with visceral malformations of the liver because of the significant morbidity and mortality associated with this treatment. Embolization should be considered only if the patient’s heart failure cannot be managed medically. Liver transplantation is an option for patients with hepatic AVMs and biliary necrosis, poorly controlled heart failure, or refractory portal hypertension.

#### Cerebral Vascular Malformations

About 23% of patients with HHT have a form of CVM. These vascular malformations include AVMs, along with cavernous malformations, venous angiomas, capillary telangiectasias, vein of Galen malformations, arteriovenous fistulae, and mixed malformations. Individuals with HHT can have any of these types of CVMs, but typically HHT-associated CVMs include cerebral AVMs, arteriovenous fistulae,
embolization, stereotactic radiation therapy, or microsurgery. Expert panels developing international guidelines for diagnosing and managing HHT recommend treating CVMs as the only effective way to eliminate the future risk of bleeding. However, significant risks are associated with treatment. As of this article’s writing, no published studies exist that address the safety and efficacy of treating CVMs in patients who have HHT.

**Pulmonary Arteriovenous Malformation**

Pulmonary AVMs are high-flow shunts with low resistance. These shunts usually have 1 or more arteries that feed the shunt and 1 or more veins that drain blood. Pulmonary AVMs lack a capillary network and instead often are connected via an aneurysmal sac between the artery and the vein. This connection is referred to as a *right-to-left shunt* because of direct communication between the pulmonary artery and vein. The lack of a capillary network increases the risk of complications in patients who have pulmonary AVMs, such as paradoxical emboli, pulmonary hemorrhage, dyspnea, hypoxemia, brain abscess, transient ischemic attacks, stroke, and musculoskeletal or spinal infection. Most (80% to 90%) pulmonary AVMs occur in patients with HHT rather than from other causes. Further, about 30% of patients with HHT have pulmonary AVMs.

Pulmonary AVMs can be classified into 2 categories: simple or complex. Simple malformations have a single segmental artery that is considered the feeding artery (see Figure 4). Complex pulmonary AVMs have 2 or more feeding arteries (see Figure 5). About 80% of pulmonary AVMs are considered simple, and about 20% are complex. Most patients who have pulmonary AVMs remain asymptomatic until they reach middle to older age (40 to 70 years old). The mortality rate among this older age group with pulmonary AVMs is about 15%. Mortality risk also is high among all individuals who have pulmonary AVMs because of increased risk

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**Figure 3.** Early (A) and late (B) digital subtraction arteriogram of celiac artery showing a hepatic arteriovenous malformation (AVM). Notice the early venous filling (arrows). Images courtesy of Scott O Trerotola, MD, FACR.
History of Treatment

In the 1940s, patients who had pulmonary AVMs were treated with pneumonectomy. Over the years, pneumonectomy was replaced with lobectomy and then local excision of the AVM. It was not until 1977 that W. Portsmann performed the first embolization procedure using handmade steel coils. In the early 1990s, thoracic surgeons still advocated for surgical removal of pulmonary AVMs. Today, transcatheter embolization has become the preferred treatment method, eliminating the need for open surgery in most cases.\textsuperscript{21,22}

Interventional Radiology

Once a patient has received an HHT diagnosis, the first objective is to screen the patient for pulmonary AVMs. The first step in pulmonary AVM screening is transthoracic echocardiography with contrast. The agitated saline contrast can help detect right-to-left shunts within the pulmonary system. During transthoracic echocardiography, the contrast is injected into a peripheral vein. The immediate presence of multiple white echoes against a black anechoic background on the left side of the heart indicates an intracardiac right-to-left shunt. A delayed appearance on the contrast-enhanced examination indicates pulmonary right-to-left shunting.\textsuperscript{23}

If the transthoracic echocardiogram results are positive, the next step is a computed tomography (CT) examination of the chest. Debate has continued over whether contrast enhancement is needed for the CT examination, and clinical guidelines vary on CT contrast recommendations. A contrast-enhanced CT scan provides greater detail for planning treatment. In particular, contrast enhancement improves information about the patient’s upper abdomen, and the contrast highlights hepatic AVMs, which would not be seen without the enhancement.

Finally, use of contrast in CT leads to more detailed 3-D analysis of a pulmonary AVM before the patient has an arteriogram and embolization. The contrast-enhanced CT carries increased risk to the patient because of pulmonary AVM anatomy. Another concern is air bubbles could be introduced when injecting contrast for the CT
examination and could enter the pulmonary AVM and become paradoxical emboli. Many treatment centers suggest that with appropriate training and use of a wet-to-wet connection to the injector, the benefits of the contrast-enhanced CT outweigh potential risks.11

Once a CT scan helps confirm a diagnosis of pulmonary AVM, physicians plan treatment to reduce the risks of further pulmonary AVMs. In an initial consultation, the patient meets the interventional radiologist who will treat the AVM. During this consultation, the physician must be as forthright as possible regarding treatment. Patients need to understand the physiology of their lesions and the effects of treatment. It is likely that family members or children of the patient also have HHT. Patients who have a good treatment experience are more likely to comply with follow-up care instructions and help convince other family members to seek evaluation and treatment.

Some treatment centers admit patients with pulmonary AVMs for an overnight stay; others perform the
procedure on an outpatient basis. Centers also vary in how many lesions they treat in a single session, along with how they treat bilateral lesions. Physicians who treat only one lung during initial treatment generally start with the largest lesion first. These physicians cite shorter procedure times, decreased contrast load, less radiation skin dose, and improved patient comfort as the basis for unilateral lung treatment. They also might refer to reports that 20% of pulmonary AVM embolization patients experience pleurisy following the procedure. Conversely, the literature reports on use of improved tools for treating pulmonary AVMs that allow interventional radiologists to more safely treat both lungs and up to 10 lesions in a single session. In bilateral treatment, physicians typically treat the largest lesion first and then address smaller lesions.

In fact, some debate surrounds the size of the arteries feeding pulmonary AVMs and whether some, specifically those less than 3 mm in diameter, are small enough to ignore. Robert White, Jr, MD, from Yale Vascular Malformation Center, Yale University School of Medicine, described in a 2007 article the basis for treating only pulmonary AVMs with a feeding artery of 3 mm in diameter or greater. White states that 3 mm is the threshold for passage of thrombi. In 1992, Rosenblatt et al, from the same institution, reported on 17 patients who had a single dominant pulmonary AVM. The authors wrote that in 4 patients with clinically evident stroke, the feeding artery measured between 2.9 mm and 4.5 mm. According to the organization Cure HHT, if the artery feeding the pulmonary AVM has a diameter larger than 2 to 3 mm, blood clots can move through the pulmonary AVM and to the brain, causing a stroke.

As technology improves, the ability to detect and treat pulmonary AVMs smaller than 3 mm also improves. CT and digital subtraction angiography imaging methods are improving continuously and microcatheter and microwire combinations also enhance the ability to treat lesions as small as 1 mm. Paradoxical emboli can occur in patients who have pulmonary AVMs with feeding arteries smaller than 2 mm in diameter. Although the treatment cutoff at 3 mm was a standard for many years, advances in technology and reports of paradoxical emboli in patients with pulmonary AVMs less than 3 mm have led many HHT treatment centers to begin treating lesions with feeding arteries of less than 3 mm in diameter.

Embolization Procedure

Today, most patients are treated in a single session under conscious sedation. The interventional team begins by accessing the right or left femoral vein and placing a 7F sheath. A diagnostic catheter is inserted through the sheath to measure arterial pressure. Mean pulmonary arterial pressures should be less than 20 mm Hg. Some interventional specialists have stated that treating a patient with high pulmonary arterial pressure will worsen pulmonary hypertension after the AVM is occluded. Therefore, some treatment centers inflate an occlusion balloon at the AVM and then check pulmonary arterial pressures for 20 to 30 minutes before initiating treatment.

After pressures are measured, the interventional team performs pulmonary arteriography. Various injection and film rates can be used. For example, practitioners at the University of Pennsylvania Hospital inject 25 mL of a 50/50 contrast/saline mixture in 1 second, filming at a digital subtraction angiography rate of 7.5 frames/second. With this technique, a complete bilateral diagnostic arteriogram including anteroposterior and oblique projections uses only 50 mL of contrast.

After diagnostic arteriography, the interventional team uses an exchange guidewire to replace the diagnostic catheter with a 7F guiding catheter set. This set is positioned in the feeding artery of the AVM and is used to carry out the embolization procedure (see Figure 6). Various catheter shapes are available to help navigate into the feeding artery. Depending on the size and configuration of the feeding artery, the interventional team will choose either stainless steel or platinum coils (see Figure 7) or occlusive plugs (see Figure 8) to block the vessel. The key to keeping recanalization rates low is to place the device within 1 cm of the aneurysm sac.

Various techniques exist for placing coils and other occlusive devices, including the anchor technique and
Figure 6. A. Postembolization image of simple pulmonary AVM using a vascular plug (arrow). B. Postembolization image of complex pulmonary AVM using 2 vascular plugs (arrows). Images courtesy of the author.

Figure 7. A. Platinum-fibered embolization coil as packaged (Nester Embolization Coil, Cook Medical). B. Platinum-fibered embolization coil stretched out. C. Platinum-fibered coil. Images courtesy of the author.
the scaffold technique. In the anchor technique, the physician places the guiding catheter in the artery feeding the AVM. The inner catheter then is positioned in a side branch as close as possible to the aneurysmal sac. A long embolization coil is placed into the side branch up to the coil’s first 2 cm and the remainder of the coil is deployed just outside the side branch in the feeding artery. Additional coils then are woven into the mass blocking the AVM. This technique is used when coil migration is a concern (see Figure 9).  

The scaffold technique is used to place occlusive devices in high-flow fistulas with large arteries. High-radial-force fibered stainless steel coils are placed first in the artery. The coils must be 2 mm larger than the diameter of the feeding artery and can be secured using the anchor technique if coil migration is a concern. After the initial coil deployment, several smaller high-radial-force coils might be required, followed by softer fibered platinum coils. These coils should be woven into a solid ball until the feeding artery is completely
occluded (see Figure 10). In about 10% of patients the embolization procedure begins by using an inflated occlusion balloon to temporarily block blood flow. As soon as the first coils are placed, the balloon is deflated and exchanged for the coaxial guide catheter combination and embolization is completed.21

Microcatheter Technique

Many published articles address various protocols and products used to treat pulmonary AVMs. Greben et al described a microcatheter technique.21 The authors used a 9F sheath placed in the right femoral vein. From that sheath, they used an 8.3F pulmonary pigtail for pressure measurement and arteriography. After the diagnostic study, physicians exchanged the pigtail for a 6F or 7F guiding catheter using a 260-cm curved exchange wire. Once the catheter was in position to treat the lesion, the team assembled and placed 2 Y adapters on the hub of the guiding catheter. Next, 2 microcatheters were placed through the guiding catheter into the feeding artery. To prevent clot formation and minimize complications such as air embolism, heparinized saline ran continuously through the side port of the sheath, guiding catheter, and microcatheters. The saline also kept hydrophilic guidewires and microcoils wet throughout the procedure.

With 2 microcatheters in position, physicians deposited a framing detachable platinum microcoil via the first microcatheter. To ensure coil stability, the initial coil is left in the venous segment, while the catheter is retracted through the distal aspect of the feeding artery. This coil remains undetached while platinum or hydrogel coated microcoils are placed from the second microcatheter. Treatment is successful when there is no filling of the pulmonary AVM as well as distal occlusion of the feeding artery and outflow vein.21 Despite having a major advantage in coil placement accuracy, the major downside to this microcatheter technique is cost associated with the detachable coils compared to the less expensive standard coils that are pushed into position. Interventional centers can reduce the cost by only using detachable coils to create the initial framework where the other coils will be woven, and using the standard coils to create the dense packing needed to complete the embolization.21

Figure 9. Anchor technique/side branch. This technique is used when coil migration is a concern. The first 2 cm of the embolization coil are deployed in a side branch. The catheter then is pulled back and the remaining coil is pushed into the feeding artery. Image courtesy of Robert I White Jr, MD.

Figure 10. Scaffold technique. High-radial-force coils are used to create a scaffold, allowing softer coils to be packed into the scaffold. This technique is useful in high-flow fistulas with large feeding arteries. Image courtesy of Robert I White Jr, MD.
Procedural Risks

As with any interventional procedure, those designed for treating AVMs are associated with certain risks. Bleeding, infection, and damage to surrounding structures are the most common concerns. The use of sterile technique and ultrasound guidance for access to the femoral vein can minimize these risks. As of this writing, the literature does not report any death directly related to interventional treatment of pulmonary AVMs. Complications are rare and include air embolism, device migration, and paradoxical embolization.

Air embolism has been reported in 4.8% of procedures and is most common when treating small pulmonary AVMs. Air entering the coronary arteries produces angina with associated bradycardia or ST segment of the cardiac rhythm changes on an electrocardiogram. The problem normally resolves within 15 minutes. Air entering the cerebral circulation can cause transient ischemic attack symptoms including perioral and limb paresthesia or expressive aphasia. These symptoms also resolve in 15 minutes in most patients. Careful flushing, observing for back bleeding, and removing wires under water can minimize paresthesia risk. Device migration with paradoxical embolization occurs in about 1% of cases, most often in high-low pulmonary AVMs or AVMs with feeding arteries greater than 8 mm in diameter. This complication requires a longer procedure with use of intravascular retrieval devices. Risk of device migration with paradoxical embolization is reduced with interventional physician experience and by using the anchoring and scaffold techniques.25

Post-treatment Considerations

Patients who have pulmonary AVM embolization require lifelong follow-up and surveillance for AVM growth or recanalization.24 Transthoracic contrast echocardiography is positive in 80% to 90% of patients who undergo embolization of their pulmonary AVMs. This might result from the presence of tiny AVMs that cannot be diagnosed with conventional arteriography or contrast-enhanced CT scans. Rates of recanalization vary from one study to another (4%-19%). This emphasizes the importance of surveillance for pulmonary AVMs after treatment. All patients should have a follow-up CT scan in 6 months to establish a new baseline.

Because of the variation in recanalization and regrowth rate, follow-up scans should continue every 3 years to 5 years for the rest of the patient’s life. By being diligent with care and follow-up, survival rates for patients who have HHT are reported to be slightly lower than for people who do not have HHT.24

Special Considerations

When radiologic technologists conduct imaging examinations on patients who have HHT and pulmonary AVMs, or anytime the patient requires IV injections, technologists need to take special care because of the right-to-left shunt present in these AVMs. During the contrast hookup for a CT scan, staff should take care to make a wet-to-wet connection to avoid injecting air. When placing an IV in a patient who has a pulmonary AVM, staff should place a bubble filter (see Figure 11) on the line closest to the patient to filter out inadvertent bubbles and keep them from entering the patient’s bloodstream. People who have HHT and pulmonary AVMs should be instructed to avoid scuba diving unless they have had negative contrast echocardiogram results within the past 5 years.

Iron deficiency is common in people who have HHT. The deficiency is caused by epistaxis or GI bleeding. If left untreated, iron deficiency can lead to decreased exercise tolerance, chronic fatigue, and poor quality of life. People who have iron deficiency should have aggressive treatment with oral or IV iron supplements. If a patient requires IV iron supplementation, clinical personnel should take care to avoid introducing air into the IV line to avoid right-to-left shunt complications from air in the systemic circulation and risk of transient ischemic attacks. Typically, IV iron infusions flow slowly using a pump with a built-in bubble detector and close staff observation.26

Care also is needed when performing dental work, dental cleaning, and other procedures that can introduce bacteria to the bloodstream of patients with HHT and pulmonary AVMs. Bacteria from dental work that enter the bloodstream can pass through a pulmonary AVM and become lodged in the brain, causing a brain abscess. Patients who have HHT and pulmonary AVMs should have prophylactic treatment with antibiotics before dental work. HHT patients who have had
negative screening results for pulmonary AVMs do not require prophylactic antibiotics.\textsuperscript{27}

Clinical staff also must use caution when caring for pregnant women with HHT. This involves considering the patient’s HHT footprint. For example, a woman who has HHT but has telangiectasia only in the nose without organ involvement typically is not considered at high risk for complications during her pregnancy or delivery. Conversely, pregnancy in a woman who has HHT who has pulmonary AVMs is considered high risk; obstetrics and delivery staff should take precautions to minimize risks.\textsuperscript{28}

**Conclusion**

HHT is an underdiagnosed condition that requires a complex treatment approach. Patients often require care from specialized HHT treatment centers with multidisciplinary teams. Experts on these teams can work together to manage symptoms such as nosebleeds and brain or lung involvement and the overall approach to diagnosis and management of troubling and life-threatening complications.

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**References**


Hereditary Hemorrhagic Telangiectasia Management

To earn continuing education credit:
- Take this Directed Reading quiz online at asrt.org/drquiz.
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Read the preceding Directed Reading and choose the answer that is most correct based on the article.

1. Hereditary hemorrhagic telangiectasia (HHT) also is known as:
   c. Curaçao-Rendu disease.
   d. hemophilia.

2. Which of the following statements is true regarding autosomal dominant disorders?
   a. The disorders occur only when both parents have the abnormal gene.
   b. Parents must have active disease to pass along the abnormal gene.
   c. The disorders affect boys more often than girls.
   d. Every pregnancy involving an affected parent increases the chance of passing on the physical traits of HHT by 50%.

3. Compared with other types of HHT, people who have type 1 experience:
   1. earlier onset of symptoms.
   2. elevated risk of hepatic involvement.
   3. higher risk of developing arteriovenous malformations (AVMs) in the lungs and brain.
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

4. Most individuals diagnosed with HHT eventually report:
   a. telangiectasias on their scalp.
   b. epistaxis.
   c. cerebral vascular malformations.
   d. recurrent, complex pulmonary AVMs.
5. Which of the following statements regarding targeted sequencing is false?
   a. It is a form of genetic testing.
   b. It looks at a specific area of interest within the DNA.
   c. It specifically is used to identify a piece of a gene that is missing or duplicated.
   d. It is used when genetic testing found an abnormal gene in another family member.

6. Parents with HHT should have their children screened even though the child might not meet the criteria for HHT assessment.
   a. true
   b. false

7. ______ often is recommended to help minimize epistaxis occurrence in patients with frequent mild-to-moderate nosebleeds.
   a. Embolization
   b. Arterial ligation
   c. Silver nitrate nasal cautery
   d. Laser ablation

8. When embolizing epistaxis, it is important to image the internal carotid to isolate the:
   a. ethmoidal supply.
   b. ophthalmic artery supply.
   c. facial artery.
   d. internal maxillary artery.

9. According to international guidelines, embolization for hepatic AVMs should be considered:
   a. in all cases because of potential complications.
   b. only when there are signs of biliary disease.
   c. to ease abdominal angina.
   d. only when heart failure cannot be managed medically.

10. A right-to-left shunt associated with a pulmonary AVM:
    a. lacks a capillary network and connects via an aneurysmal sac between the artery and vein.
    b. leads to few complications.
    c. has a strong capillary network.
    d. is a low-flow shunt.

11. When treating pulmonary AVMs, the ______ technique is used to place occlusive devices in high-flow fistulas with large arteries.
    a. scaffold
    b. anchor
    c. microcatheter
    d. bilateral

12. Patients who have HHT and pulmonary AVMs should have ______ before dental work.
    a. embolization
    b. prophylactic treatment with antibiotics
    c. laser ablation
    d. a CT scan of the chest