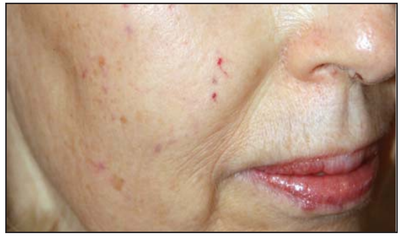
ischemia. Chemical cauterization should always be avoided as it may harm nasal structures. In the presence of anemia, oral iron supplementation or rarely parenteral iron therapy with or without blood transfusion, depending on the level of anemia and clinical symptoms, may be required. An old local remedy using "salt pork" may also be used with some success. Salt pork is cut into plugs the size of the nostril, a loop of thick thread placed through one end, and each plug is wrapped in wax paper and frozen until required. Application of this material provides local hemostasis through vessel constriction due to cold and presence of tissue thromboplastin to enhance local coagulation, while the oily texture allows easy removal without disruption of the clot once formed.

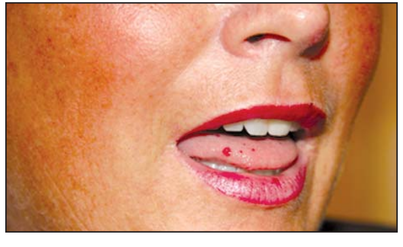
Skin - Multiple telangiectases of the hands, face, and oral cavity occur in similar percentages of patients, but the age at onset is often later than for epistaxis. It is common for patients to report appearance of telangiectases in one or more of these locations in the decade between 30 and 40 years of age (**Figure 2** below). Telangiectases in these locations are not commonly a source of troublesome bleeding and patients may receive treatment for cosmetic reasons. Painful cutaneous telangiectases can be treated with laser therapy.

Figure 2: *Clinical photographs of patients with hereditary hemorrhagic telangiectasia: a) facial telengeictses; b) telangiectases over the lip and tongue.*

a)



b)



Gastrointestinal tract - The prevalence of intestinal telangiectasia varies from 10% to 33% in patients with HHT. They occur anywhere in the gastrointestinal tract, most commonly in the stomach and upper duodenum. Approximately 25% of individuals older than 60 years present with melena or anemia. Bleeding tends to be slow but persistent and may increase in severity with age. Endoscopy and less commonly angiography can demonstrate the presence of large telangiectases, AVMs, or angiodysplasia. Use of photocoagulation with bipolar electrocoagulation or laser techniques is useful for control of bleeding in the short term. In clinical trials, medical treatment with estrogen and progesterone has shown to be beneficial to reduce the incidence of bleeding. Anecdotal reports exist regarding resolution of gastrointestinal HHT lesions after treatment with interferon-α utilized for chronic hepatitis.

Lung - Pulmonary AVMs occur more frequently in patients with HHT1 than HHT2, 75% and 44% respectively. They can occur as discrete lesions versus a diffuse pattern, and are thought to be congenital and may enlarge over time. They are commonly located in the posterior lower lobes. They may be asymptomatic for many years and present insidiously or dramatically with respiratory symptoms such as exercise intolerance, cyanosis or pulmonary hemorrhage, migraine headaches, polycythemia, and clubbing. Approximately 30-40% of individuals with HHT who have pulmonary AVMs will have a CNS presentation with thrombotic and embolic events, such as stroke, brain abscess, or transient ischemic attack, due to right-to-left shunting that can occur even in the presence of near normal pulmonary arterial oxygen tension. It is common for several adverse events to occur before a pulmonary AVM is identified as the source of the CNS event. Pregnant women with untreated pulmonary AVMs are at high risk of pulmonary hemorrhage. Pulmonary disease indistinguishable from PPHN has been reported in multiple patients with HHT with mutations in the ALK1 gene, indicating that close monitoring for the development of PPHN is required.

Pulmonary AVMs with a feeder vessel of more than 3 mm should be treated using transcatheter embolization to reduce the risk of embolic events. Pulmonary AVMs may grow in size over time, so smaller lesions that are detected require ongoing surveillance. **To prevent cerebral abscess, antibiotic prophylaxis is recommended for dental and surgical procedures in any patient with evidence of an intrapulmonary shunt.** Patients with diffuse pulmonary AVMs may require lung transplantation if severely hypoxic. The morbidity and mortality associated with lung transplantation could be the limitation with this therapeutic modality.

Central nervous system - Central nervous system AVMs, including the brain, meninges, and spinal cord, are also thought to be congenital. Cerebral AVMs occur more frequently in individuals with HHT1 than in HHT2, 15-20% versus 1-2% respectively. Although the risk of neurological symptoms increases with multiplicity of pulmonary AVMs, CNS lesions

may present at any age with seizure, headache, or intracranial hemorrhage. Complications, including stroke, transient ischemic attack, and brain abscess, have been reported due to paradoxical embolization of thrombus or bacterial emboli that bypass pulmonary capillaries. CNS lesions may present in the neonatal period, infancy, or childhood in otherwise asymptomatic children. Spinal AVMs are less common, occurring in approximately 1% of individuals with HHT, and may manifest as subarachnoid hemorrhage, progressive myelopathy, radicular pain, or sphincter disturbance. Techniques currently used to treat CNS AVMs include transcatheter embolization, resection, and stereotactic radiosurgery.

Hepatic AVMs - Hepatic vascular lesions include a variety of intrahepatic shunts and disseminated intraparenchymal telangiectases. The prevalence of hepatic involvement in HHT is unknown; in one study hepatic vascular abnormalities were identified by CT in 74% of consecutive HHT patients. In most patients with HHT, liver involvement remains clinically silent, but hepatic vascular lesions (shunts between portal hepatic artery and hepatic vein) can present as high-output heart failure, portal hypertension, biliary disease, and portosystemic encephalopathy.

Hepatic AVMs are not treated in asymptomatic patients as they rarely present with catastrophic emergencies, and unlike pulmonary AVMs, treatment with embolization results in a high mortality rate due to liver infarction. At present, liver transplantation is the treatment of choice for patients with otherwise life-threatening symptoms secondary to hepatic shunts. Recently, a case report of successful treatment of massive hepatic AVM with VEGF antibody (Bevacizumab; dose: 5,mg/kg over 12 weeks period) was published suggesting a potential role of targeted therapies in treatment of HHT.

Indiana Hemophilia & Thrombosis Center
8402 Harcourt Road, Suite 500
Indianapolis, IN 46260

Rare sites of AVMs - AVMs have been described only rarely in other locations, including coronary arteries and the vessels of the eye, spleen, urinary tract, and vagina. These lesions are treated with embolization, ligation, or surgical resection.

Links to Organizations
www. hht.org

Abbreviations
HHT .....Hereditary hemorrhagic telangiectasia
AVM .....Arteriovenous malformation
TGF- .....Transforming growth factor
ALK-1 .....Activin receptor-like kinase 1
BMP .....Bone morphogenesis protein
VEGF.....Vascular endothelial growth factor
CT .....Computerized tomography
CNS .....Central nervous system
Smad4 .....Mothers against decapentaplegic, Drosophila, homolog of, 4
BMPR 2....Bone morphogenetic protein receptor II

For referral of patients with a diagnosis of HHT or for evaluation, please call the IHTC at 1-877-256-8837.

This article was written by:
Anjali Sharathkumar, M.D.

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What is Hereditary Hemorrhagic Telangiectasia?

Hereditary hemorrhagic telangiectasia (HHT; also known as Osler-Weber-Rendu syndrome) is a relatively common and underrecognized disorder. HHT affects all ethnic and racial groups and is seen over a wide geographic distribution with an overall frequency of 1 per 5,000 to 10,000 persons. HHT is inherited as an autosomal-dominant disorder resulting in multisystem vascular dysplasia. Characteristics of HHT include telangiectases and arteriovenous malformations (AVMs) of skin, mucosa, and viscera. HHT was recognized as a distinct disease entity in 1909. The important milestones contributing to improving the understanding of HHT are elaborated in **Table 1**.

Table 1: *Important milestone in understanding HHT or Osler-Weber- Rendu Syndrome*

YEAR	MILESTONES IN HISTORY OF HHT
1864	First description of HHT by Sutton in a man with a vascular malformation and recurrent epistaxis
1896	Rendu recognized combination of hereditary nature of telangiectasia and epistaxis
1901	Osler described familial nature and published as a syndrome in textbook
1907	Weber emphasized the association between hereditary telangiectasia and hemorrhage
1909	Hanes coined the term "Hereditary Hemorrhagic Telangiectasia"

What is a telangiectasis? The individual lesion in HHT is known as telangiectasis (pleural telangiectases) while the process of formation of telangiectasia or telangiectasis is referred as "telangiectasia" (OMIM#187300). The telangiectasis is a small arteriovenous shunt involving both dilated arterioles and venules and appears as 1-2 mm red spot on the skin that blanches with slight pressure.

The morphogenesis of telangiectasis is not fully understood. Based on histopathological findings of skin telangiectases it has been hypothesized that the earliest clinically detectable lesion of HHT is a focal dilatation of postcapillary venules, that continue to enlarge and eventually connect with dilated arterioles through capillaries. In fully developed telangiectases, the venules are markedly dilated and convoluted, extend through the entire dermis, have excessive layers of smooth muscle without elastic fibers, and often connect directly to dilated arterioles.

What is the difference between a telangiectasis and an arteriovenous malformation? Arteriovenous malformations (AVMs), the second most prominent lesion of HHT, lack capillaries and consist of direct connections between arteries and veins and are much larger than telangiectases. Telangiectases, as previously mentioned, are direct connections between arterioles and venules. Both telangiectases and AVMs lead to the common presenting symptoms observed in patients affected with this disorder.

What is the molecular pathogenesis of HHT? HHT is a genetically heterogenous disorder. Mechanisms contributing to the pathogenesis of HHT involve disregulation of the molecular pathways associated with vascular genesis. Studies have demonstrated that mutations in different loci (*ALK1, ENG, BMPRII and MADH 4*) in the transforming growth factor-ß/ Bone Morphogenesis Protein (TGF-ß/BMP) signaling pathway are involved in HHT pathogenesis (Table 2 & Figure 2 on page 2). This pathway regulates a number of biological processes including cell cycle control, embryogenesis, growth, development, and differentiation of cell types including angiogenesis.

Early linkage studies of extended HHT kindreds provided compelling evidence for at least two distinct locations for HHT genes within the human genome: endoglin (*ENG*) for HHT1 (OMIM #187300) and Activin receptor-like kinase 1 (ALK1) for HHT2 (OMIM #600376). Mutations in the *ENG* gene (OMIM#131193) localized on the long arm of chromosome 9 (9q33-q34.1) are responsible for HHT1, whereas HHT2 results from mutations of the *ALK 1* gene (OMIM# 601284) localized on the long arm of chromosome 12 (12q11-q14). Subsequent studies in patients with primary pulmonary hypertension (PPH) and the clinical characteristics of HHT led to the discovery that mutations in bone morphogenetic protein receptor II (*BMPRII*) contribute to the development of the HHT/PPH phenotype. Moreover mutations in *MADH4* or Smad 4 (Mothers Against Decapentaplegic, Drosophila, homolog of, 4; OMIM# 600993) contribute for the development of HHT and juvenile polyposis and HHT phenotypes. In addition, the existence of HHT families without mutations mapping in either ENG or ALK1

continued on page 2

genes led to the identification of the third and fourth loci

genes led to the identification of the third and fourth loci of HHT through linkage analysis.

Approximately 50% of patients at present have identifiable genetic mutations. The percentage of *ENG* and *ALK 1* mutations thus far reported causative of HHT is similar (53% and 47%). Recently an HHT database was established to record all sequence variants identified within these two genes (http://hhtmutation.org/). Information gained from this database suggests that the severity of disease does not correlate with a specific mutation.

Table 2: *Genetic heterogeneity of hereditary hemorrhagic telangiectasia (HHT)*

HHT TYPES	GENE	CHROMOSOMAL LOCUS
HHT 1	Endoglin or ENG	Endoglin (ENG), 9q34.1
HHT 2	Activin receptor like Kinase 1(*ACVRL1/ALK 1*)	12q11-q14
HHT 3	?	5q31.3-q32
HHT 4	?	7p14
HHT + Juvenile Polyposis Coli	MADH4 or SMAD4	18q21.1
HHT 2 + Primary Pulmonary Hypertension (PPH)	BMPRII	2q33

How is HHT diagnosed? The initial diagnosis of HHT in a family relies on ***clinical examination, medical history, and a careful family history***. Curaco established criteria to diagnose HHT **(Table 3)**. Since HHT is an autosomal dominant disorder with almost 100% penetrance one would expect to find clinical symptoms in affected individuals. ***However it is important to recognize that disease penetrance approaches 100% by the age of 40 years and that due to the inheritance pattern and age of disease penetrance, clinical diagnostic criteria have limitations.*** In addition, the inheritance of HHT exhibits the property of "incomplete penetrance," an inability to express the full spectrum of the disease phenotype despite carrying a defective gene, thus making the diagnosis extremely difficult. Furthermore, epistaxis, the most common symptom of HHT, is prevalent in the general unaffected population and is a common manifestation of a large number of clinical entities. These factors all contribute to potentially limiting the diagnosis of HHT.

Table 3: *Diagnostic criteria for hereditary hemorrhagic telangiectasis. Shovlin CL, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome). Am J Med Genet 2000; 91: 66-7.*

HHT is diagnosed in an individual who meets 3 or more of the following diagnostic criteria. The diagnosis is considered possible or suspected when 2 are present, unlikely when fewer than 2 are present:

Criteria

1. Spontaneous, recurrent epistaxis. Nocturnal nosebleeds heighten concern for HHT.
2. Mucocutaneous telangiectases, especially on lips, tongue, oral cavity, fingers and nose.
3. Internal AVM(s) including pulmonary, cerebral, hepatic, gastrointestinal, spinal.
4. First-degree relative with HHT according to these criteria.

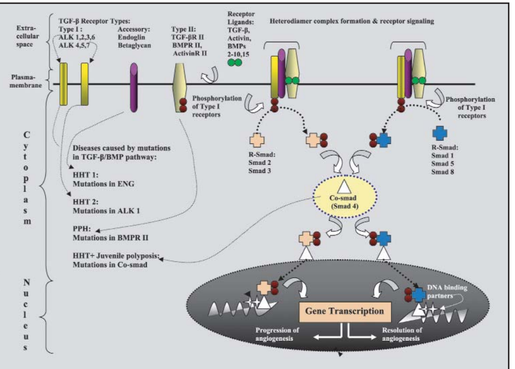

Figure 1: *Signaling Pathway of the Transforming Growth Factor/Bone Morphogenesis Protein (TGF-ß/BMP) Superfamily exploring relationship between hereditary hemorrhagic telangiectasia, primary pulmonary hypertension and juvenile polyposis coli.*

In the extracellular space, ligands to the TGF-/BMP superfamily of receptors bind either to an accessory protein, which presents the ligand to the type II receptor, or directly to the type II receptor on the cell membrane. The accessory receptors betaglycan and endoglin can modulate signaling via the type II and type I receptors. The binding of the ligands to the type II receptor then leads to binding of the type I receptor to form a heteromeric receptor complex at the cell surface. This results in phosphorylation and activation of the kinase domain of the type I receptor, which initiates phosphorylation of cytoplasmic signaling proteins termed receptor Smads (R-Smads). The pathway only splits into two distinct branches downstream of type I receptors: ALK4, ALK5 and ALK7 specifically phosphorylate SMAD2 and SMAD3, whereas ALK1, ALK2, ALK3 and ALK6 specifically phosphorylate SMAD1, SMAD5 and SMAD8. Phosphorylated R-Smad binds to a collaborating Smad (Co-Smad/ Smad 4), and the resulting complex moves from the cytoplasm into the nucleus. The Smad complex associates with a DNA-binding partner in the cell nucleus and interacts with various other transcription factors in a cell-specific manner to regulate gene transcription and to mediate the effects of signaling by the TGF-ß/BMP superfamily of receptors at the cellular level. This pathway controls the balance between progression and resolution of angiogenesis. Defect in this pathway leads to development HHT, PPH (Primary pulmonary hypertension) and juvenile polyposis coli.

What investigations are necessary to evaluate a patient with HHT? Since HHT is a multisystem disease, the initial evaluation once the clinical diagnosis is established should include the following:

1. contrast echocardiography to screen for intrapulmonary shunts and, if identified, chest computed tomography (CT) with 3 mm cuts to characterize pulmonary AVMs;
2. magnetic resonance imaging of the brain to screen for cerebral AVMs; and
3. auscultation for a hepatic bruit and medical history for symptomatic liver shunts.

Table 4 on page 4 illustrates different symptoms of HHT and their related diagnostic evaluation.

How to diagnose HHT in children? The diagnosis of HHT in children may be particularly difficult, especially if not previously established in the family. Bleeding symptoms consistent with HHT are common clinical problems in children and may be overlooked or ascribed to alternative causes; epistaxis may be associated with a variety of common entities, such as allergic disease, sinusitis, and local trauma. Pediatric patients who present with recurrent or persistent clinical bleeding symptoms that are associated with HHT should undergo a detailed physical examination and family history that may help to uncover diagnoses such as HHT; additionally a thorough evaluation for hemostatic disorders including Von Willebrand disease should be completed. Because the clinical stigmata of HHT vary widely and in children can be absent or limited, the diagnosis is not established unless specifically considered.

What is the role of genetic testing in diagnosis of HHT? The fact that mutations that cause HHT have been identified raises the possibility of the use of molecular genetic testing for routine clinical practice. ***Currently genetic testing is not routinely ordered to confirm the diagnosis of HHT because the known HHT mutations are identified in only 50% of patients.*** Besides, the lack of common alleles or highly recurrent mutations, locus heterogeneity, and the presence of mutations in almost all coding exons of the two genes make screening for mutations time-consuming and costly. Hence, genetic testing has a limited role in confirming the diagnosis of HHT. It is important to underscore that, with advances in molecular diagnostic testing, it is likely that genetic testing may play an important role in diagnosis of HHT in near the future.

How is a patient with HHT treated? The overall treatment of HHT is aimed towards (1) control of local and systemic symptoms, (2) surveillance for and of lesions, and (3) measures to prevent complications associated with AVMs.

Since both AVMs and telagiectatic lesions grow with time, life-long periodic surveillance is recommended. Currently, no evidence based guidelines are available regarding the frequency and choice of imaging modality for surveillance of these lesions. Because of the systemic nature of this disease, a multidisciplinary team approach involving an otolaryngologist, pulmonologist, interventional radiologist, neurologist, neuroradiologist, neurosurgeon, geneticist, cardiologist, gastroenterologist, hepatologist, and hematologist should be considered for provision of optimal patient care. Recognizing this need, multidisciplinary specialty clinics for HHT have been established in North America and in other parts of the world. The list of these centers and the various resources for patients and families, and medical professionals are available at the Web site of the HHT Foundation International at **www.hht.org**.

The present role of medical therapy in preventing progression of vascular lesions in HHT is not encouraging. There are anecdotal reports of the efficacy of antiangiogenic medications such as VEGF antibodies (Avastin/Bevacizumab), estrogens, thalidomide and interferon. Clinical studies are underway to clarify the role of these agents in the treatment of HHT (www.ClinicalTrials.gov).

Table 4 on page 4 summarizes the clinical approaches and treatment options in the care of persons with HHT

What are the clinical manifestations and prognosis of HHT according to the organ of involvement? Abnormal vessel formation and subsequent bleeding form the basis of the majority of clinical manifestations of HHT. Although the number and location of lesions vary widely even within the same family, most telangiectases are found in the oral, nasal, and gastrointestinal mucosa and the fingertips, whereas AVMs occur most commonly in the lungs, liver, and CNS. ***In general, smaller telangiectatic lesions usually present with symptoms of recurrent bleeding, whereas symptoms of the larger, internal AVMs do not result in hemorrhage; rather complications of AVMs most often occur as a result of shunting of blood, thrombosis, or embolus.***

Nose - Epistaxis due to telagiectases in the nasal mucosa is the most common and often earliest symptom of HHT. As many as 95% of affected individuals eventually experience recurrent epistaxis, at a mean age of approximately 12 years and a mean frequency of 18 episodes per month. Although severe epistaxis may cause chronic anemia in some patients, others have mild, infrequent nosebleeds that do not require treatment. In general, most patients experience an increase in frequency and severity of epistaxis with advancing age, but some patients report no particular change in their episodes over time, and some even experience improvement.

Beyond use of local measures, including application of local pressure and ice, therapeutic options consisting of high-dose antifibrinolytic agents such as administration of tranexamic acid at 1 to 2 grams 3 times daily either orally or intravenously at the time of epistaxis, or combined estrogen-progesterone preparations have shown some efficacy. If these measures are insufficient and the frequency and duration of episodes impair the patient's quality of life, a photocoagulation laser or a septal mucosal dermoplasty may be recommended. Embolization of the external carotid artery branches has been performed for short-term relief of symptoms, although it is ineffective for long-term management and can lead to complications related to

continued on page 5

Table 4: Clinical manifestations and management of patients with HHT

ORGAN/ SYSTEM	TYPE OF LESION	SITES	CLINICAL SYMPTOMS	EMERGENCIES	SCREENING TOOL	DIAGNOSTIC MODALITY	TREATMENT *
Nose	Telangiectasia	Nasal mucosa	Epistaxis, Iron deficiency anemia	Massive epistaxis	Medical history	Clinical examination	Humidification, packing, Antifibriolytic therapy (EACA and Tranexamic acid), salt pork, topical estrogen/progesterone ointments, local cauterization, septal dermoplasty, laser, embolization of external carotid artery, iron therapy
Skin	Telangiectasia	Lips, tongue, palate, face, conjunctiva, trunk, nail beds, finger pad	Cosmetic disfigurement, bleeding (usually minor)	None	Medical history, clinical examination	Clinical examination	Topical agents, Laser ablation
Lung	AVM	Often multiple; predilection for lower lobes	Asymptomatic, cyanosis, clubbing, migraine, cerebral abscess, embolic stroke, polycythemia, pulmonary hypertension	Massive hemoptysis, hypovolumic shock, hemothorax	Medical history, Auscultation of Bruit over chest, blood gas measurement, orthodeoxia§ pulse oximetry, chest X-ray	High-resolution helical CT scan, Angiography	Transcatheter or streotactic embolization of AVM, Surgical resection of AVM, Ligation of arterial supply of AVM, Iron therapy *Note: Requires infective endocarditis prophylaxis prior to dental and surgical intervention to reduce the risk of brain abscess.*
Central nervous system	AVM	Brain, spinal cord, meninges	Asymptomatic, headache, subarachnoid hemorrhage, asymptomatic bleeding, iron deficiency anemia	TIA/ischaemic stroke, hemorrhagic stroke, brain abscess	Medical history, auscultation of bruit over the skull	MRI/MRV/MRA CT scan	Neurovascular surgery, ligation of the feeding artery, stereotactic surgery, transcatheter embolization of the feeding artery, radiosurgery
Gastro-intestinal tract (except liver)	AVM, telangiectases, angiodysplasias	Stomach, duodenum, small bowel, colon	Asymptomatic bleeding, iron deficiency anemia	Hematemesis, melaena, hematochezia, hypovolumic shock, High output failure	Medical history, Stool guiac examination for occult blood	Endoscopy, Angiography; CT scan	Blood Transfusion, Endoscopic application of photocoagulation, Ethinyl estradiol/ norethindrone, Iron therapy for anemia
Hepatic	AVM, diffuse telangiectases	Liver parenchyma	Asymptomatic, portal hypertension, Biliary disease	Hepatic encephalopathy	Medical history, auscultation of bruit over the liver, ultrasound color doppler studies	CT scan, MRI/MRV/MRA Angiography	No intervention, liver transplantation only for life-threatening lesions

Abbreviation: AVM: Arteriovenous malformation; CT scan: Computed tomography,*: in life-threatening emergencies ABC should be established first; EACA: epsilon amino caproic acid; §: greatest deoxygenation occurs in upright position

Derived from Guttmacher AE, Marchuk DA, White RI Jr. Hereditary hemorrhagic telangiectasia.N Engl J Med. 1995 Oct 5;333(14):918-24.