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Gastrointestinal Manifestations of Hereditary Hemorrhagic Telangiectasia (HHT): A Systematic Review of the Literature

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Abstract Hereditary hemorrhagic telangiectasia (HHT), also called Osler–Weber–Rendu syndrome, is an autosomal dominant genetic disease that affects the vasculature of numerous organs. The prevalence of HHT is estimated to be between 1.5 and 2 persons per 10,000. While there is still much to learn about this condition, there is an increasing understanding its underlying pathophysiology, genetic basis, presentations, and management. Recognizing that the clinical manifestations of HHT can involve a number of organ systems will provide clinicians with a higher index of suspicion for the disease. This early diagnosis and genotyping can greatly reduce mortality for a patient with HHT through appropriate screening for complications. This review will focus on the gastrointestinal manifestations of HHT and how these can dictate treatment and prognosis.

Keywords Hereditary hemorrhagic telangiectasia (HHT) · Osler–Weber–Rendu syndrome · Arteriovenous malformation · Juvenile polyposis syndrome

Abbreviations

HHT	Hereditary hemorrhagic telangiectasia
AVM	Arteriovenous malformation
JPHT	Juvenile polyposis/hereditary hemorrhagic telangiectasia
GI	Gastrointestinal
VCE	Video capsule endoscopy
EGD	Esophagogastroduodenoscopy

Introduction

Hereditary hemorrhagic telangiectasia (HHT), also called Osler–Weber–Rendu syndrome, is an inherited autosomal dominant vascular disease with varying clinical manifestations. Patients typically present with epistaxis, gastrointestinal bleeding, and iron deficiency anemia due to mucocutaneous telangiectasias. However, patients with HHT are also at risk of developing arteriovenous malformations in the cerebral, pulmonary, and hepatic circulations, which can lead to end-organ damage. Initial screening for HHT often utilizes the Curaçao criteria, consisting of epistaxis, telangiectasia, visceral vascular malformations, and a first-degree relative with HHT [1]. Treatment is largely based on management of symptoms and complications and early screening for AVMs. In this article, we will further review the pathophysiology, presentation, and defining characteristics of HHT, with a particular focus on gastrointestinal, dermatological, and pulmonary manifestations.

Epidemiology

The prevalence of HHT is estimated to be between 1.5 and 2 persons per 10,000 [2], although some sources estimate

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that the disease is underreported due to variable penetrance and many patients having only minor symptoms until later ages [3]. As a result, established diagnoses of the disease are significantly lower than the estimated global prevalence. The disease has a higher prevalence in certain populations, including in Afro-Caribbean residents of Curaçao and Bonaire [4].

Genetics of HHT

HHT is an autosomal dominant disease that can result from a wide variety of mutations that ultimately cause a disruption in transforming growth factor β (TGF- β)-mediated pathways in vascular endothelial cells. A given disruption in this pathway results in aberrant blood vessel development, leading to extreme fragility and arteriovenous malformations [4]. There are over 600 such mutations that have been discovered and three HHT disease-causing genes that have been identified to date [5]. HHT type 1 results from mutations in *ENG*, which encodes endoglin, while HHT type 2 results from mutations in *ACVRL1* which encodes ALK1. Both of the resulting proteins are components of the cell surface receptor for the TGF- β family of ligands. HHT caused by a mutation in *MADH4* is associated with juvenile polyposis (JPHT); *MADH4* encodes the Smad4 co-transcriptional factor downstream of the TGF- β pathway [6–8]. There are at least two further unidentified mutations that can cause classical HHT: *HHT3* and *HHT4*.

The two most common mutations, *ENG* and *ACVRL1*, comprise about 61% and 37% of cases, respectively. *MADH4* mutations are less common and account for nearly 2% of cases. Pulmonary AVMs are more commonly seen in HHT1, while hepatic AVMs are more common in HHT2 [9]. There has been some debate about whether HHT1 or HHT2 represents a more severe manifestation of the disease, but a more recent study showed no significant difference in mortality over a 90-month period [9].

Clinical Presentation

Patients with HHT will most commonly report a history of epistaxis and/or gastrointestinal bleeding. Epistaxis is extremely common; half of patients will become symptomatic before age 20s, and the lifetime prevalence of epistaxis is 78–96% [10]. The classic vascular malformations of HHT present throughout the body and are known to widely affect the gastrointestinal (GI) system. These malformations include telangiectasias (small dilated blood vessels), arteriovenous malformations (AVMs, tangles of abnormal arteries and veins), aneurysms, venous varicosities, and arteriovenous fistulas (abnormal direct connections between arteries and veins). More severe complications develop when these malformations are

present in the lung, brain, and liver. Pulmonary hypertension, defined as a sustained elevation of mean pulmonary artery pressure above 25 mmHg at rest (or 30 mmHg during exercise), is commonly seen in HHT [11]. Olivieri et al. found ultrasound evidence of elevated right ventricular systolic pressure on 9 of 44 HHT patients (20.5%), while Sopena et al. noted similar findings in 9 of 29 (31%) of patients hospitalized for HHT [12, 13]. This is a chronic, progressive disease which manifests shortness of breath and dyspnea on exertion and which may progress to right-sided heart failure. It is commonly divided into pre-capillary and post-capillary variants, though either may be seen in HHT. Most commonly, hepatic AVMs lead to high-output cardiac failure, causing increased venous return and compensatory pulmonary arterial dilation, left arterial congestion, and finally post-capillary pulmonary hypertension (these AVMs were found in 67% of patients with evidence of pulmonary hypertension in Sopena et al.) [11, 13]. However, HHT may also lead to a pre-capillary condition from remodeling of small pulmonary arteries and which is clinically and histologically identical to primary pulmonary hypertension that is seen in individuals with *BMPRII* mutations [11, 14]. It has been hypothesized that this is due to both conditions originating from mutations in the TGF- β receptor superfamily, though pulmonary hypertension seems more common in patients with *ACVRL1* mutations. Among patients with pulmonary hypertension and equivalent treatment, presence of this mutation leads to shorter survival times and no evidence exists for those with *ENG* mutations [15]. Treatment recommendations are currently identical to other pulmonary hypertension patients and include endothelin receptor antagonists, phosphodiesterase inhibitors, prostacyclins, and symptomatic treatment with diuretics, oxygen, and digoxin [14].

Physical Examination Findings

The classic physical examination finding of HHT is the presence of telangiectasias, which appear in approximately 74% of patients [16]. These vascular malformations are dilated blood vessels that appear as thin spider-web-like red and dark purple lesions that blanch with pressure. They are found on the skin, especially mucocutaneous surfaces including the lips, oral and nasal cavity, and buccal mucosa. They can also appear on the chest, face, and hands [17]. Telangiectasias in the fingertips can be more easily found by transillumination with a penlight [18]. In the nasal cavity, these telangiectasias can promote epistaxis, which is the most common physical sign of HHT [16]. Telangiectasias develop abruptly, typically before the age of 30. Other physical examination findings are particular to complications that may be present, including signs of GI

hemorrhage, liver dysfunction, and pulmonary hypertension. Patients may demonstrate pallor from their anemia, signs of high-output heart failure from numerous AVMs, or a hepatic bruit from prominent hepatic AVMs [17] (Fig. 1).

Imaging Findings

Imaging findings can vary depending on the presentation of the disease. In general, the presence of unexplained pulmonary, cerebral, or hepatic AVMs should raise suspicion for HHT. Pulmonary AVMs are detectable by CT or X-ray and have been shown to be visible in patients as early as adolescence, although the study demonstrating this had a relatively small pediatric sample size [19]. Cerebral AVMs are present in about 10% of patients with HHT and are best visualized by MRI [20]. Several types of hepatic AVMs can be seen (dilated arteries, heterogeneous enhancement, arteriovenous or arterioportal shunting, telangiectasias) and are discussed in further detail below. These are best seen on CT, while focal nodular hyperplasia may be visualized with CT (Fig. 2), MRI, or ultrasound [21]. Classic endoscopy reveals scattered telangiectasias throughout the upper GI tract (Fig. 3), and colonoscopy may show lower GI manifestations such as telangiectasias and intramural hematomas.

Upper Gastrointestinal Tract Involvement

GI telangiectasias are thought to affect the majority patients with HHT and are found predominantly in the stomach and proximal small bowel. Gastric telangiectasias can be found throughout the stomach, though there is often predominance in the fundus. Various studies have used esophagogastroduodenoscopy (EGD) and video capsule endoscopy (VCE) to estimate the incidence of these findings and compare to that of the general population.

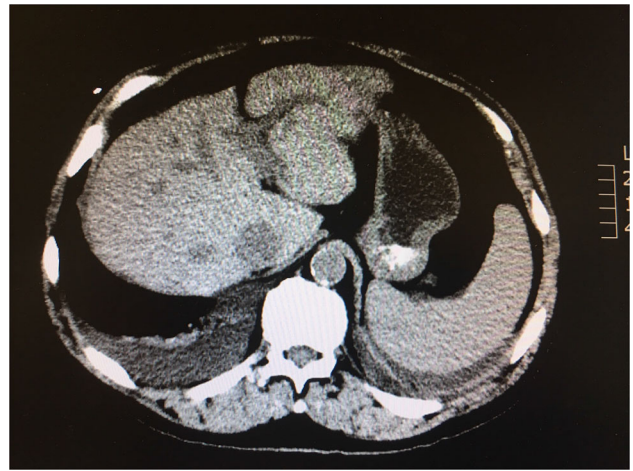


Fig. 2 CT image of the abdomen demonstrating focal nodular hyperplasia of the left lobe of the liver and early cirrhosis in a patient with genetically confirmed HHT

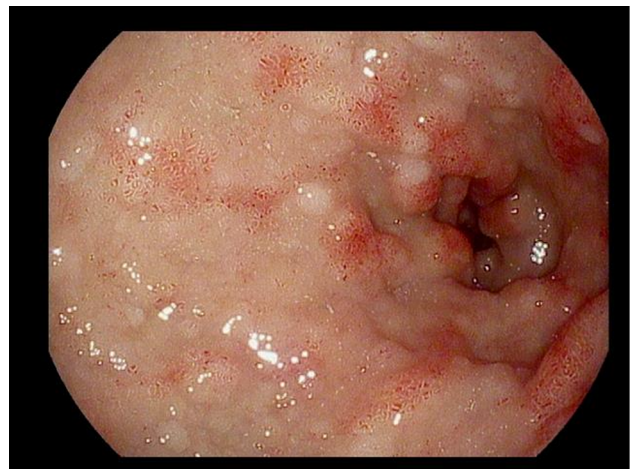


Fig. 3 Endoscopic images of the gastric body and antrum in a patient with genetically confirmed HHT demonstrating multiple telangiectasias predominantly in the distal body and antrum

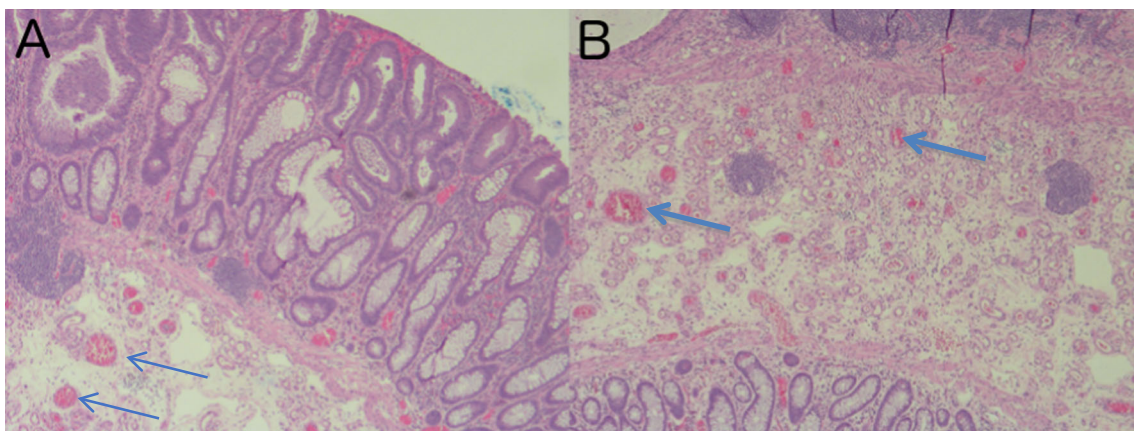


Fig. 1 Transverse colon polyp biopsy with H&E stain (magnification $\times 50$) showing abnormal vascular formations throughout the mucosa (a) and submucosa (b) consistent with HHT. Arrows point to the areas of vascular dilation

Canzonieri et al. [22] measured the extent of GI involvement in 22 men with HHT using EGD, VCE, and colonoscopy and found gastric and small bowel telangiectasias in 64 and 91% of HHT patients, respectively. Grève [23] reported similar findings in 46.7 and 86.7% of HHT patients, though this study was primarily composed of HHT2 patients. Chamberlain et al. [24] used VCE to compare 32 patients with HHT to 48 members of the general population and found gastric telangiectasias in 29% and small bowel telangiectasias in 81% of the HHT group, compared to 0 and 21%, respectively, of the control group. Interestingly, this same study reported a higher incidence of small bowel polyps and masses (6.2 and 2.1%) in patients with HHT. Ingrosso et al. [25] found 75 and 56% of HHT patients to have gastric and small bowel telangiectasias and that those who were found to have small bowel lesions on VCE were older (62 vs. 45yo) than those that did not. Patients are typically classified as having few (≤ 10) or multiple (>10) vascular lesions based on endoscopic findings, though estimates of the average number in a given patient show great variation between sources [24, 25]. Though Letteboer et al. reported similar incidence of GI telangiectasias in HHT1 and HHT2 patients [26], Van Tuyl et al.'s findings found such lesions in 100% and 63% of HHT1 and HHT2 patients, respectively [27].

More uncommon upper GI vascular lesions have also been reported. Esophageal telangiectasias have been reported in 26% of patients, though typically these are quite scarce (6 or less) and their role in pathology is unclear [28]. Jejunal telangiectasias are also common, and Longacre reported their presence in 56% of patients studied with enteroscopy [29]. One case report describes a 60-year-old previously undiagnosed woman presenting with 7–8 years of epistaxis and found to have a pulsatile abdominal mass on examination. A CT with contrast revealed severe narrowing of the proximal celiac artery with post-stenosis dilation of the celiac artery coupled with the more commonly seen tortuous proper/common hepatic artery and hepatic artery to hepatic vein anastomoses. She was diagnosed with HHT and confirmed to have an ACVRL1 mutation on genetic analysis [30]. In another report, a 23-year-old Japanese male with a 2-year history of iron deficiency anemia and protein-losing enteropathy presented with bipedal edema and fatigue. The result of his stool was positive for occult blood though upper and lower endoscopies were inconclusive. The patient had significant upper GI bleeding while hospitalized but was stabilized. He returned 2 years later with profuse melena and celiac angiography showed lack of capillary phase vessels in the small bowel and opacification of the hepatic veins. This patient developed DIC and died from complications of massive GI hemorrhage and bowel infarction. On autopsy,

telangiectasias were seen throughout the GI tract and many lymphangiectasias were seen on small bowel biopsy. A postmortem diagnosis of HHT was made from these findings [31].

Lower Gastrointestinal Tract Involvement

Large bowel telangiectasias are less common, and data on their prevalence are scarce and conflicting. Grève et al., using VCE, reported these lesions primarily in the cecum and in 10–13% of patients, which is comparable to those of the general population. However, others have employed colonoscopy and noted large bowel vascular malformations in 31–32% of HHT patients [28, 29]. In one such study [28], all of these patients had HHT1 and no such lesions were found in corresponding HHT2 patients. These lesions can be mistaken for angiodysplasia on endoscopy but are easily distinguished on histological examination as demonstrated in Fig. 1 [32]. Colonic vascular malformations, while more uncommon than their counterparts in the small bowel, can be quite clinically significant. Sivarani et al. published a report of a postpartum intraperitoneal hemorrhage in a 35-year-old woman localized via mesenteric arteriography to ruptured AVMs in the large bowel [33]. Polyps and adenomas, which are found at a rate of roughly 13 and 7%, respectively, do not seem to be more common than in those without HHT. Patients with mutations of *SMAD4*, one of the genes responsible for the development of juvenile polyposis syndrome (JP), present almost universally with HHT concurrent with the polyposis. Juvenile polyposis seen in HHT patients with *SMAD4* mutations is indistinguishable from JP in the general population resulting from *BMPRI1A* mutations [5] and carries the same increased risk of colorectal cancer [34]. Although rare, intramural hematomas have been reported in those with confirmed HHT. One case report of a patient with left lower quadrant pain and a palpable mass found a sigmoid colon hematoma which resolved without intervention. These can pose a diagnostic challenge as they may not be revealed on VCE [35].

GI hemorrhage is a common presentation of HHT and is seen in about 13–30% of patients (compared to about ~3% in the general population) and usually presents in the 4th–5th decade. Presentations in younger patients are rare, seen in only 1.5% of patients, with case reports in children being even rarer. However, it is believed that these numbers are likely an underestimation as many cases of GI bleeding are misattributed to epistaxis or go completely undetected by the patient [36]. About 50% of patients with such a bleed will eventually require a transfusion. In addition, patients with JP and HHT are at increased risk of anemia compared to HHT patients with other mutations (69% compared to 3–7%) due to the dual sources of GI hemorrhage.

Hepatic Involvement

Hepatic manifestations of HHT include AVMs and focal nodular hyperplasia. While estimates of hepatic involvement in HHT were once thought to be between 8 and 31%, this is increasingly felt to be an underestimation as HHT does not commonly present with hepatic symptoms and is often underreported. Hepatic involvement has been shown to be more common in HHT type 2 than in type 1 [37, 38]. Letteboer et al. [26] reported hepatic AVMs to be present in roughly 40.6% of HHT2 patients compared to 7.6% of HHT1 patients, though hepatic pathology had only been sought out once symptoms developed or abnormal LFTs resulted. Patients were not routinely screened as is done for pulmonary or cerebral AVMs. Such a screening approach was undertaken by Barral in a control study using 64-section helical CT to look at 19 patients with HHT and with no personal history or reported symptoms of hepatic or pancreatic disease, including normal hepatic function panels and pancreatic enzymes [39]. The HHT patients showed a high rate of dilated and tortuous hepatic arteries (95% compared to 0% in controls), which provided a 95% sensitivity and 100% specificity for the diagnosis of HHT. Also seen were heterogeneous hepatic enhancement (74% compared with 0% of controls), intrahepatic and intra-pancreatic telangiectasias (58 and 42%, respectively, compared with 0% of controls), as well as arteriportal and arteriovenous shunting (63 and 53%, respectively, compared with 0% of controls). Focal nodular hyperplasia, appearing as “pseudocirrhosis” on CT imaging, is seen in about 1.9% of patients, with a female/male ratio of 4:1 [20]. Ravard et al. [40] using helical CT estimated that liver involvement is present in 79% of patients with HHT and asymptomatic in 74% of these cases. To our knowledge, there are no reported cases of liver involvement in pediatric patients.

When patients do become symptomatic, hepatic sequelae of the disease can carry significant morbidity and mortality. Garcia-Tsao et al. [41] looked at a cohort of HHT patients with symptomatic or laboratory evidence of liver involvement and found three distinct presentations. High-output cardiac failure due to arteriovenous shunting is the most common presentation of hepatic vascular malformations and can be quite refractory to medical management. Portal hypertension can be caused by simple arteriportal shunting or by focal nodular hyperplasia compressing venous outflow and leading to sinusoidal hypertension. This can lead to massive ascites and is one of the poorest prognostic indicators in HHT. The third presentation is ischemia of the peribiliary plexus (a branch of the hepatic artery) due to arteriportal or arteriovenous shunts. This can lead to biliary necrosis and subsequent cholangitis, bile duct stricture, cyst formation, and

extravasation of bile. These patients are at high risk of sepsis and liver failure. These three entities can present alone, in unison, or in succession. Also cholestasis and common bile duct dilatation from stenotic lesions have been reported [42, 43]. Less common hepatic presentations of HHT may also be seen. Portosystemic encephalopathy from diverting of portal blood to the hepatic vein can present identical to that seen in cirrhosis. Described rarely in the literature is mesenteric ischemia from divergence of blood to large hepatic arteriovenous AVMs. A patient with HHT undergoing examination for hemobilia was found via cholangioscopy to have AVMs within the common bile duct requiring embolization [44].

Diagnosis

Curaçao Criteria

The diagnosis of HHT is deemed probable if patients present with two criteria and definitive if three or four criteria are met (Table 1) [10]. It is recommended that genetic testing to establish a diagnosis of HHT be performed in symptomatic patients who do not meet clinical diagnostic criteria or in a relative of a patient with a known causative mutation who is minimally symptomatic, asymptomatic, or desires prenatal testing. Genetic testing should also be pursued in families with a multiple cases of confirmed HHT to identify a causative mutation. If a disease-causing mutation is identified in a patient, testing can subsequently be offered to family members. Generally, ENG and ACVRL1 genes are tested for coding sequence mutations first, with SMAD4 being tested if no mutation is identified. Patients with mutations identified in SMAD4 gene should undergo gastrointestinal screening for polyposis and gastrointestinal malignancies. This consists of colonoscopies at 15–18 years old or 5 years younger than that at which the youngest family member developed colon cancer and each 2 years after, as well as upper GI surveillance with esophagogastroduodenoscopy/enteroscopy/small bowel series or video capsule endoscopy at 25 years old and every 2 years after. Whole-exome sequencing and genetic counseling are becoming more routinely available in clinical practice and could be considered to screen family members [17].

Screening Recommendations

Currently, experts recommend all asymptomatic adult patients over the age of 18 years old with possible or definite HHT be screened for cerebral vascular malformations (CVMs) with a one-time MRI with and without contrast. Children are recommended to undergo a non-contrast MRI before the age of 6 months, as a risk of

Table 1 Curaçao's diagnostic criteria for hereditary hemorrhagic telangiectasia [1]

Diagnosis of HHT	
1. Definite:	3 criteria below
2. Possible:	2 criteria below
3. Unlikely:	less than 2 criteria below
Symptoms:	
(a)	Epistaxis-spontaneous and recurrent
(b)	Telangiectasias; multiple and characteristic sites (lips, mouth, fingers, nose)
(c)	Visceral/gastrointestinal telangiectasias, pulmonary AVMs, hepatic AVMs, cerebral AVMs and spinal AVMs
(d)	Family history: one first-degree relative

developing a major cerebrovascular event is high during this period. All patients with possible or confirmed HHT should be screened for pulmonary arteriovascular malformations (PAVMs). In adults, the screening method of choice is transthoracic contrast echocardiography (TTCE). Positive results from TTCE should then be confirmed by high-resolution thoracic CT. The choice of screening in children may include physical examination, supine and upright pulse oximetry, chest radiograph, and/or TTCE. Regarding hepatic vascular malformations (HVMs), screening via Doppler ultrasound or triphasic helical CT is recommended in all patients with HHT and abnormal liver enzyme tests or clinical evidence of complications from HVMs, including high-output heart failure, portal hypertension, and cholestasis. Screening for HVMs can also be used for evidence for the diagnosis of HHT in patients with an inconclusive clinical picture and in whom genetic testing is unavailable or inconclusive [10].

Treatment

The management of HHT is largely tailored to which complications are present in the patient. The chronic iron deficiency anemia characteristic of the disease is managed with simple iron replacement therapy, typically oral therapy unless larger quantities are required, in which case intravenous iron replacement is indicated. It is recommended that acute epistaxis be managed with low-pressure less-traumatic packing techniques. Studies have shown mild benefit with humidifiers to prevent chronic epistaxis, while there have been no controlled trials comparing more definitive surgical techniques such as nasal artery embolization or coagulation techniques. Acute gastrointestinal hemorrhage should be managed per hospital protocol. In addition, potential colorectal malignancies should always be considered in the elderly HHT patient presenting with occult blood in the stool, just as they would be for the general population [24].

Management of cerebral AVMs is highly controversial. One study investigating this is the ARUBA trial, a multi-center randomized clinical trial that compared medical management with interventional therapy (neurosurgery, embolization, and/or stereotactic radiotherapy), with medical management alone. It was halted early as those that had undergone intervention for detected cerebral AVMs were found to have a threefold higher risk of stroke [45]. If CVMs are found, patients should be referred to a center with neurovascular expertise for definitive management. In patients where PAVMs are identified, it is recommended that transcatheter embolotherapy be performed and subsequent long-term follow-up be provided. Gastrointestinal vascular malformations can be managed with endoscopic cauterization; hormonal or antifibrinolytic therapy may be used as adjunct therapy to prevent ongoing bleeding [10]. Pulmonary arteriovenous malformations are of greatest concern and should be managed with transcatheter embolization therapy in adults and symptomatic children. In those with confirmed HVMs, embolization is not recommended given the risk post-embolization necrosis and death. Only if HVMs become symptomatic or complications develop should they be considered for surgical intervention. Partial liver resection has also been shown to be a safe therapy for those with significant hepatic AVM involvement [46]. However, in cases of ischemic biliary necrosis or intractable heart failure or portal hypertension, liver transplantation is indicated.

Prognosis

Most individuals with HHT who have regular access to health care will have normal life expectancies. Acute complications from AVMs are the main cause of increased mortality, though inadequate healthcare maintenance plays a role as well [47]. There is a bimodal distribution of mortality, with peaks at age 50 and then from 60 to 79 [48]. The most life-threatening AVM sites are in the brain, the GI tract, and the lungs, which can lead to life-threatening cerebral hemorrhage, gastrointestinal bleeds, or severe hemoptysis [49]. Less common but clinically significant bleeding sites include the spleen, kidney, bladder, liver, and meninges.

Summary

- HHT is an autosomal dominant condition resulting from mutations in the TGF β signaling pathway in vascular endothelial cells.
- The prevalence of HHT is approximately 1–2 per 10,000 persons and is underreported because of variable penetrance.

- HHT may present with dermatologic, gastrointestinal, and pulmonary vascular malformations.
- Recognition of HHT is important because it can result in significant bleeding
- Availability of whole-exome sequencing and genetic counseling should be considered in patients who present with clinical evidence of vascular malformations.
- Treatment is tailored to reducing the bleeding by physical means; however, a greater understanding of the signaling pathways may result in directed medical therapies in the future.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics statement The authors certify that this manuscript is an original work and is not published or submitted for publication elsewhere. We have no related material submitted elsewhere and will not submit this manuscript or part of this manuscript to other publishers. We certify that each author has participated substantially in the work to create and revise this manuscript. We have no financial disclosures or conflicts of interest to declare.

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