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REVIEW ARTICLE

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Pulmonary vascular manifestations of hereditary haemorrhagic telangiectasia

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Abstract

Hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant, multisystem disorder that manifests with a spectrum of disease including cardiopulmonary complications. HHT is characterised by aberrant signalling via the transforming growth factor β (TGFβ) pathway, with loss of vascular integrity, angiogenesis and vascular dysplasia. The disease has an estimated prevalence of 1 in 5000 persons and the penetrance increases with increasing age. HHT commonly presents with epistaxis and telangiectasia, while visceral arteriovenous malformations are not uncommon. Mutations in the ENG, ACVRL1 and MADH4 genes account for 97% of all HHT cases, and it is recommended that genetic tests are used in combination with the clinical Curaçao criteria to confirm the diagnosis. HHT can be complicated by significant pulmonary vascular disease including pulmonary arteriovenous malformations, pulmonary arterial hypertension and high output cardiac failure. These are associated with substantial morbidity and mortality and therefore timely diagnosis is important to mitigate complications and optimise preventative strategies. This article outlines important advances in our understanding of the pathobiology of HHT and current recommendations regarding the diagnosis and screening of HHT with a specific focus on adult patients with pulmonary vascular disease. Important therapeutic advances, novel therapies on the horizon and unmet needs are also explored.

KEYWORDS

bevacizumab, hereditary haemorrhagic telangiectasia, pulmonary arterial hypertension, pulmonary vascular disease

INTRODUCTION

Hereditary haemorrhagic telangiectasia (HHT) is an inherited, multisystem disorder that is characterised by vascular dysplasia. It is an autosomal dominant disorder, with age-related penetrance, and frequently presents with epistaxis, telangiectasia and visceral arteriovenous malformations (AVMs).[1] The first published cases of HHT appeared in the 1860s describing patients with severe epistaxis.[2,3] The eponyms Osler-Weber-Rendu

syndrome and Rendu-Osler-Weber syndrome were frequently employed to describe the disease, recognising the three physicians who independently described the condition in the early twentieth century.[4] The name HHT was subsequently coined by Haynes in 1909 and is now the preferred term. The Curaçao criteria were published nearly a century later in 2000 to facilitate clinical diagnosis.[5] These criteria outline the clinical characteristics that are necessary to confirm HHT and the diagnosis is considered definite if three or more of the following features are present: spontaneous and recurrent epistaxis, telangiectasia, visceral AVMs or gastrointestinal telangiectasia, and the presence of a first degree relative with HHT.[5] A number of causative genes have been identified and genetic testing is increasingly employed to assist in making the diagnosis. These include mutations in endoglin (ENG), activin receptor-like kinase 1 (ACVRL1) and Mothers against decapentaplegic homolog 4 (MADH4) genes, which encodes for SMAD4.[1,6,7] Mutations in these genes result in aberrant transforming growth factor β (TGFβ) signalling, loss of vascular integrity and angiogenesis.

HHT is a multisystem disorder and can manifest with a spectrum of disease, including cardiopulmonary complications. Screening for complications at the time of presentation is an integral part of HHT care to prevent complications and improve outcomes. The treatment and prognosis are specific to individual patient characteristics and manifestations of the disease. This article focuses on the pulmonary vascular complications of adult patients with HHT including the pathobiology, presentation and management of pulmonary AVMs (pAVMs), pulmonary arterial hypertension (PAH) and high output cardiac failure (HOCF).

Epidemiology and pathobiology of HHT

HHT has an estimated prevalence of 1 in 5000 persons.[1] There is considerable geographic variability and the highest point prevalence is reported in Curaçao and Bonaire at 1 in 1,331 inhabitants.[8] The European Reference Network For Rare Vascular Diseases (VASCERN) estimates that HHT affects ~85,000 European citizens.[1,9–12] The prevalence of HHT is equal in men and women, however there is some evidence to suggest that specific disease manifestations such as liver vascular malformations (VMs) or PAVMs may be higher in women.[1,13] Disease penetrance is age-related and most patients display symptoms and signs by the age of 50 years.[10–12]

Approximately 80% of HHT cases are caused by mutations in the ENG (HHT Type-1) and ACVRL1 (HHT Type-2) genes.[1] Additionally, mutations in MADH4 have been associated with a syndrome of combined HHT and juvenile polyposis syndrome (JP-HHT).[6] These three genes account for approximately 97% of all HHT cases. Missense mutations of the growth differentiation factor 2 (GDF2) gene which encodes bone morphogenetic protein-9 (BMP9) have also been associated with HHT (HHT Type-5).[14]

At least two other HHT loci have been described in the literature which were assigned HHT Type-3 (HHT3) and HHT Type-4 (HHT4), though the causal genes remain elusive nearly two decades later.[15,16] Recently Shovlin et al., employed whole genome sequencing on 'gene negative' individuals with HHT, including the original HHT3 family who had a clinical diagnosis of HHT using the Curaçao criteria. This revealed that there is now no evidence for an independent 'HHT3' locus.[17,18]

Aberrant TGFβ signalling is common to ENG, ACVRL1, SMAD4 and GDF2 gene mutations as illustrated in Figure 1. ENG and ACVRL1 are cell surface receptors for TGFβ ligands, SMAD4 mediates gene expression in response to TGFβ stimulation and BMP9 is a cytokine of the TGFβ superfamily.[1,6,14,19] TGFβ is important for diverse biological processes including cell growth and differentiation, vascular remodelling and angiogenesis.[20] Interestingly, mutations in BMP receptor 2 (BMPR2) have been identified in patients with PAH with characteristics of HHT including PAVMs.[21–23] This association is thought-provoking as BMPR2 is a member of the TGFβ superfamily and an important cause of hereditary PAH (HPAH).

Vascular endothelial growth factor (VEGF) has also been implicated in the pathobiology of HHT. VEGF encompass a family of proteins including VEGF-A. VEGF-A is an endothelial cell mitogen and angiogenic factor, which binds to VEGF receptor 1 (VEGFR1) and VEGF receptor 2 (VEGFR2). These receptors have different properties, as signalling via VEGFR1 down regulates proangiogenic signals, while VEGFR2 mediates proangiogenic effects.[20] Interestingly, an imbalance in these receptors has been demonstrated in subjects with HHT2, with reduced VEGFR1 expression and increased VEGFR2 signalling, resulting in angiogenesis and vascular dysplasia.[24] Anti-VEGF therapies are increasingly used in HHT and demonstrate promising results in specific cohorts.

HHT type -1

In 1994 mutations in the ENG gene on chromosome 9 were identified as a causative gene for HHT.[18,25] The ENG gene encodes a membrane glycoprotein called

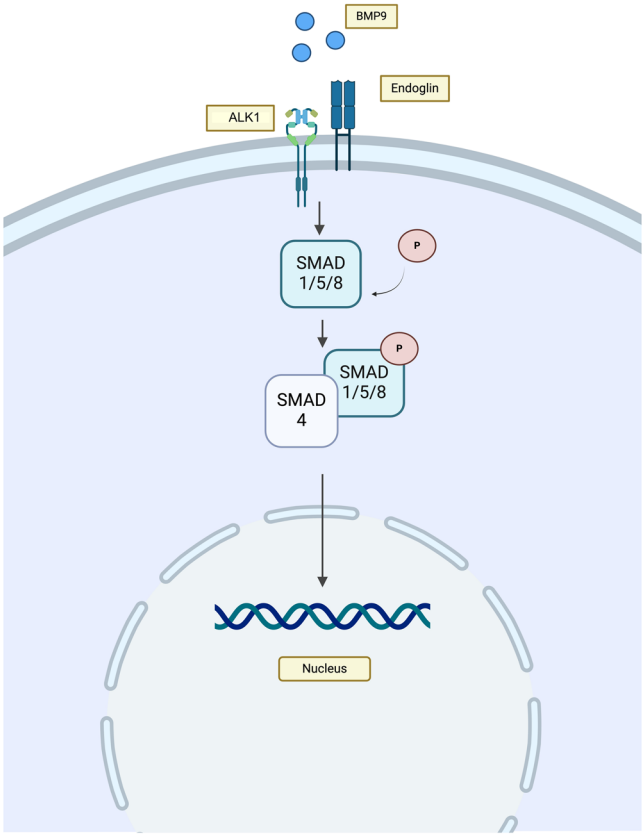

FIGURE 1 Molecular pathways in HHT. Figure 1 outlines important ligands, receptors and intracellular signalling molecules which are implicated in the pathobiology of HHT. BMP9 ligands, which are encoded by GDF2, bind to cell surface receptors such as endoglin. Endoglin acts as an auxiliary receptor and promotes signalling via ALK1. This promotes phosphorylation of SMAD 1/5/8, *which forms a complex with SMAD 4 (encoded by MADH4) and translocates to the nucleus to modify gene expression. Abbreviations: BMP9: bone morphogenetic protein-9, ALK1: activin receptor-like kinase-1, SMAD: suppressors of mothers against decapentaplegic 4, GDF2: Growth differentiation factor 2. Created with Biorender. com.*

endoglin which is highly expressed in vascular endothelial cells. This acts as a coreceptor for ligands of the TGFβ superfamily and regulates downstream signalling including vascular remodelling and angiogenesis. ENG mutations are associated with an increased risk of pulmonary and cerebral AVMs.

HHT type -2

The ACVRL1 gene is located on chromosome 12 and codes for the protein activin receptor-like kinase 1 (ALK1). This protein also binds ligands from the TGFβ superfamily and mutations in this gene result in HHT type-2. These patients have an increased risk of developing hepatic AVMs and pulmonary arterial hypertension (PAH).[26,27]

HHT and juvenile polyposis syndrome

A combined syndrome of juvenile polyposis and HHT was associated with mutations in Mothers against decapentaplegic homolog 4 (MADH4) in 2004.[6] The MADH4 gene encodes suppressors of mothers against decapentaplegic 4 (SMAD4), which is involved in intracellular TGFβ mediated signal transduction to the nucleus. MADH4 is expressed in diverse cell types and is important for numerous biological processes.[6]

HHT associated with growth differentiation factor 2 mutations

GDF2 encodes BMP9, which is a cytokine of the TGFβ superfamily.[14] BMP9 binds to endothelial cell surface receptors such as endoglin and ALK-1 and results in phosphorylation of SMAD 1/5/8. These subsequently form a complex with SMAD4, which translocates to the nucleus. Mutations in BMP9 result in clinical characteristics which overlap with HHT Type-1 and 2.[14,28]

Pathophysiology and presentation

Vascular dysplasia is the hallmark of HHT and frequently presents with telangiectasia on mucocutaneous surfaces and AVMs in internal organs.[29,30] Telangiectasia are comprised of dilated postcapillary venules, with a perivascular mononuclear infiltrate and additional layers of smooth muscle cells without elastic fibres.[29] AVMs on the other hand, are much larger than telangiectasia and represent direct connections between arteries and veins, without intermediary capillaries.[30] The precise reasons why AVMs develop in specific organs and locations remains unclear, but additional stimuli including sheer stress and angiogenic stimuli are proposed to play a role in their formation. The histopathology of AVMs demonstrate irregular deposition of collagen, elastin and smooth muscle cells.[30,31] The following section focuses on pulmonary vascular complications of HHT including PAVMs, PAH and HOCF (Figure 2).

Pulmonary AVMs

PAVMs are the most common internal organ complication of HHT and occur in 15–50% of patients.[1] PAVMs typically occur at the lung bases, are often multiple and are more common in individuals with ENG mutations.[27,32] PAVMs are direct communication between

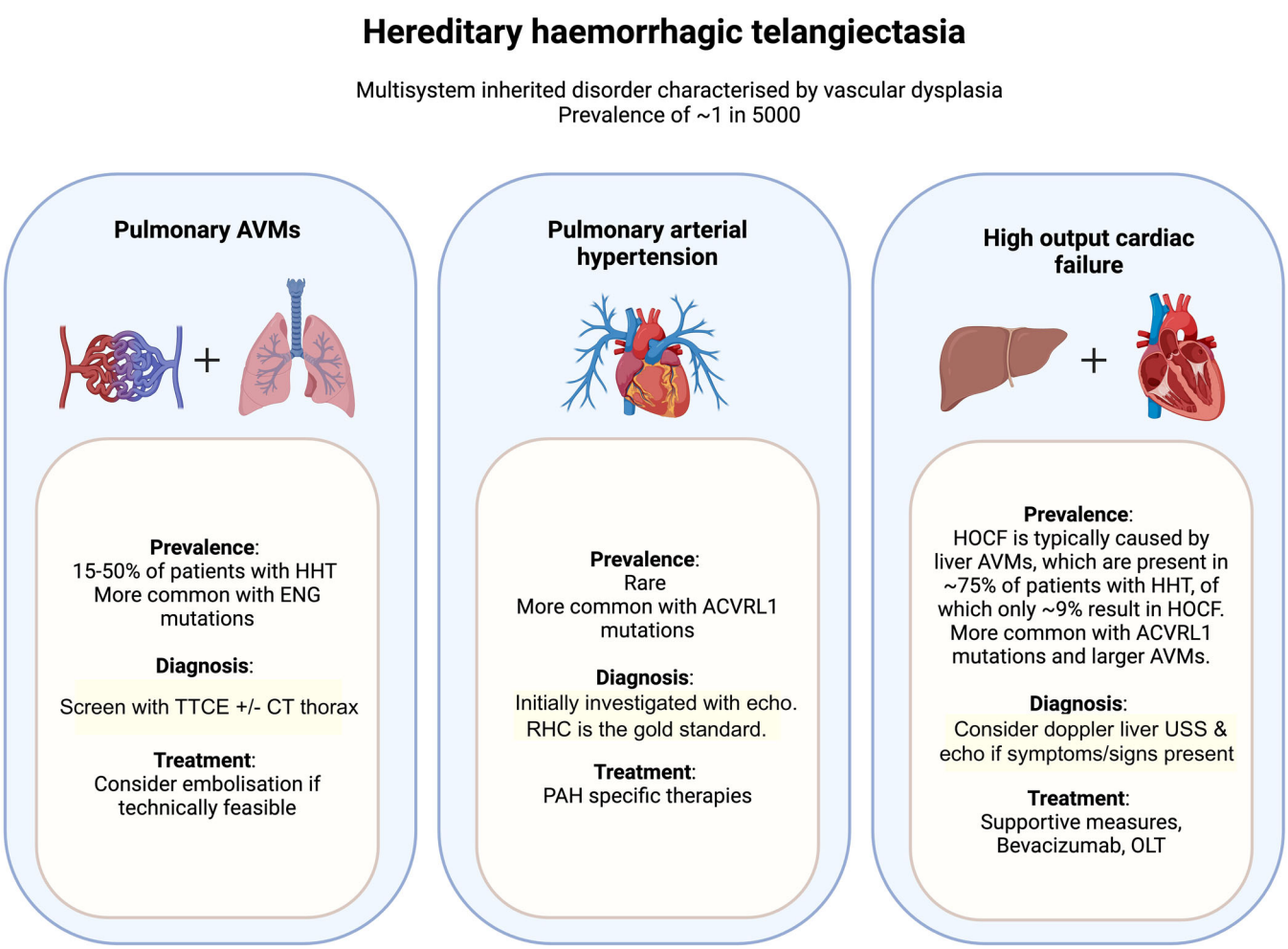

FIGURE 2 Pulmonary vascular complications. Figure 2 outlines important pulmonary vascular complications in HHT, which are described in greater detail in the manuscript. Abbreviations: TTCE: Transthoracic contrast echocardiogram, Echo: echocardiogram, RHC: right heart catheterisation, PAH: pulmonary arterial hypertension, HOCF: high output cardiac failure, AVMs: arteriovenous malformation, Liver VMs: liver vascular malformations, OLT: orthotopic liver transplantations. Created with Biorender. com.

pulmonary arteries, containing deoxygenated blood, and pulmonary veins. This right to left shunt can result in hypoxia and cyanosis, which characteristically does not correct with the administration of 100% oxygen.

Importantly, PAVMs are frequently asymptomatic and therefore routine screening is advised, which is outlined later in this article.[1] When symptoms and signs are present, these can include dyspnoea, haemoptysis, digital clubbing, orthodeoxia and cyanosis. Important complications of PAVMs include cerebral embolization resulting in transient ischaemic attacks, cerebrovascular accidents and cerebral abscess and spontaneous haemothorax. Interestingly, migraines have an increased prevalence in patients with PAVMs and have been reported to improve upon treatment of same.[27] This may relate to embolization of serotonin or microemboli that would otherwise have been trapped or metabolised in the pulmonary capillary bed.

Pulmonary arterial hypertension

Pulmonary hypertension (PH) is characterised by elevated pressures within the pulmonary circulation and patients with HHT are susceptible to specific forms. These include HPAH and portopulmonary PH which are allocated within Group 1 PAH. Patients with HHT can develop PAH which is clinically and histologically comparable to other PAH subgroups including idiopathic PAH (IPAH). Most cases of PAH associated with HHT (PAH-HHT) are the result of mutations in the ACVRL1 gene, with a smaller proportion attributed to ENG mutations.[33–35] PAH-HHT demonstrates a female preponderance, potentially implicating female sex hormones in the pathobiology.[36] The incidence of PAH-HHT is rare and estimated to account for less than 5% of PH cases.[37]

Pulmonary vascular specimens in PAH-HHT demonstrate intimal fibrosis, medial hypertrophy and plexiform

lesions, which are similar to those of IPAH.[27] This pulmonary vascular remodelling results in luminal narrowing, increased sheer stress and elevated intravascular pressures. This increases right ventricular afterload and can ultimately lead to right heart failure. A diagnosis of PAH requires a RHC and the careful measurement of specific parameters which are outlined later in this article. In brief, in a patient with PAH-HHT one would expect to observe a precapillary pattern of PH at RHC, which includes a mean pulmonary artery pressure (mPAP) > 20 mmHg, a pulmonary vascular resistance (PVR) > 2WU and a pulmonary artery wedge pressure (PAWP) < 15 mmHg (Table 1).[38]

A study by Girerd et al suggested that individuals with PAH-HHT and ACVRL1 mutations present with PAH at a younger age and have a worse prognosis when compared to other patients with PAH.[34] While cases of PAH-HHT may be identified in asymptomatic individuals if they are screened for the condition, typically patients present with symptomatic disease, which includes progressive dyspnoea, palpitations, and syncope. Examination may reveal a pansystolic murmur of tricuspid regurgitation at the left sternal edge, a loud pulmonary component of the second heart sound, a third and fourth heart sound and signs of right heart failure.

Individuals with HHT are also at risk of developing portopulmonary hypertension due to portal hypertension and hepatic complications of liver vascular malformations (VMs). However, it is more common for patients with large liver VMs to develop HOCF and Group 2 PH associated with left heart disease.[35]

High output cardiac failure

Shunting of significant volumes of blood through large or multiple AVMs can lead to a hyperdynamic state. This is more common in subjects with HHT and liver VMs, which may be present in between 41% and 78% of patients with HHT. Liver VMs demonstrate a female predominance and are associated with ACVRL1 mutations.[1,27] Liver VMs in HHT are typically multiple, small hepatic lesions associated with regenerative activity such as focal nodular hyperplasia, rather than large discrete lesions.[1]

HOCF is an important complication of liver VMs. In right to left shunts, blood passes directly from arterial to venous circulations bypassing the capillary bed and leading to a fall in systemic vascular resistance and arterial blood pressure. This is compensated by an increase in cardiac output and baroreceptor mediated neurohormonal activation, resulting in salt and water retention and plasma volume expansion.[39] Increased left ventricular (LV) filling pressures can result in pulmonary venous congestion and post-capillary PH. A high cardiac output is commonly described as a cardiac output (CO) > 8 L/min and a cardiac index > 4 L/min/m^2.[39,40] PH associated with a high CO typically has a mPAP >20 mmHg, an elevated PAWP > 15 mmHg and a normal PVR of <2WU (Table 1).[38,41] However, chronic high flow and sheer stress can result in irreversible pulmonary vascular remodelling and an increase in the PVR to ≥ 2 WU. This combined pre- and post-capillary PH can be more complex and difficult to manage.[38]

Depending on the communication between hepatic arteries, hepatic veins and/or portal veins, patients can present with a variety of complications including HOCF, portal hypertension, encephalopathy and even biliary ischaemia. HOCF typically occurs in the context of hepatic artery to hepatic vein shunts.[42] However, cases of biliary ischaemia have been identified in patients with shunting between arteriovenous and arterioportal liver VMs and is a rare but important potential complication.[42]

TABLE 1 Haemodynamic profiles.

Diagnosis	mPAP mmHg	PVR WU	PAWP mmHg	CO L/min
Pre-capillary PH				
HPAH, PoPH	>20	>2	<15	−/↓
Post-capillary PH				
Isolated post-capillary PH	>20	≤2	>15	−/↓
Combined pre- and post- capillary PH	>20	>2	>15	−/↓
Unclassified PH or post-capillary PH				
High output cardiac failure	↑	<2	−/↑	↑

Table 1 outlines the haemodynamic profiles at right heart catheterisation that are observed in patients with pre-capillary PH, post-capillary PH and high output cardiac failure (HOCF). Of note, subjects with HOCF typically demonstrate an increased mPAP, reduced PVR, normal or increased PAWP and an increased cardiac output (CO). A cardiac output of >8 L/min is considered high, while a CO < 5 L/min is typically considered reduced.

Abbreviations: PH, Pulmonary hypertension; HPAH, Hereditary pulmonary arterial hypertension; PoPH, Portopulmonary hypertension; mPAP, Mean pulmonary artery pressure; PVP, Pulmonary vascular resistance; PAWP, Pulmonary artery wedge pressure; CO, Cardiac output.

Furthermore, liver VMs may also cause a left to right shunt, which may result in a step-up in oxygen saturations from the mid inferior vena cava to the right atrium which can be detected at RHC.[43]

HOCF may present with dyspnoea, fatigue, palpitations and signs of right heart failure such as peripheral oedema and ascites.[27] Tachycardia, a wide pulse pressure and warm extremities are described. PH due to HOCF in HHT has not been allocated to a specific PH diagnostic group and it would be reasonable to define it as unclassified PH as per recent guidelines.[38]

Additional pulmonary vascular considerations

In addition to the above mentioned complications, patients with HHT can encounter a spectrum of additional pulmonary vascular complications and PH due to a variety of reasons. In a study of 23 patients with HHT and a mPAP >20 mmHg at RHC, it was noted that concomitant airways disease and left heart disease were common. Furthermore, cases of comorbid chronic thromboembolic disease and portal hypertension were also noted, emphasising the multifactorial nature of PH in this population and the importance of a comprehensive assessment.[36]

While HHT is typically considered a disorder associated with an increased risk of bleeding, it is also associated with an elevated risk of thrombosis.[44] In a study of 394 adults with HHT, the incidence of VTE was 4.6%, which is considerably higher than that of unaffected individuals of a similar age.[45] Elevated factor VIII levels, iron deficiency and hospitalisations are associated with an increased thrombotic risk in HHT.[44–46] When antiplatelet therapies and anticoagulation are indicated in individuals with HHT, their prescription should be made with careful consideration of risks and benefits and individual patient characteristics.

The physiological changes of pregnancy, including an increased circulating blood volume and increased cardiac output, can have deleterious effects on both AVMs and PH in women with HHT. Pregnant women with HHT should be managed by a multidisciplinary team, as outlined by the International Guidelines for the Diagnosis and Management of HHT.[1] Where possible, pre-pregnancy consultation is recommended to discuss the 50% risk of transmission to offspring and to provide an opportunity for AVM screening and management.[1] Pregnancy-related deaths have been reported, and the presence of PAVMs are associated with an elevated risk.[1,17] Despite advances in therapies for PAH, the maternal mortality associated with pregnancy in patients with PAH remains high, reportedly ranging from 11% to 25%.[38] Therefore current guidelines advise against pregnancy in women with PAH irrespective of the underlying aetiology.[38]

DIAGNOSIS

The accurate and timely diagnosis of HHT is important to facilitate appropriate screening, to prevent complications and to inform family members.[5] This is enabled by the clinical Curaçao criteria and recent advances in genetic testing.[1]

Diagnosis and assessment

The Curaçao criteria are consensus diagnostic criteria that were published in 2000 and assess for the presence or absence of four clinical criteria.[5] These include spontaneous or recurrent epistaxis, telangiectasia at characteristic sites, AVMs or gastrointestinal telangiectasia, and a first degree relative with HHT.[5] The diagnosis is considered definite if ≥3 of 4 criteria are present, possible if 2 criteria are met and unlikely in adults if 1 or 0 criteria are present. Genetic tests are now available and recent guidelines advise genetic testing to identify the mutations in an HHT family and to facilitate screening in relatives. Mutations in ENG and ACVRL are responsible for the majority of HHT cases and therefore these should be assessed first, with subsequent consideration of SMAD4 mutations if these are negative.[1]

The manifestations of HHT vary between individuals and increase with age. Patients may be entirely asymptomatic and diagnosed through genetic screening if there is an affected relative, or present with specific symptoms and signs related to complications. Epistaxis is often the initial manifestation of the disease and may present in childhood.[1] It is typically followed by the development of telangiectasia at mucocutaneous sites such as the face, mouth and hands. Pulmonary vascular complications of HHT may be identified on routine screening tests or present with cardiorespiratory symptoms. PAVMs are the most common serious complication of HHT and occur in up to 50% of patients.[1] Shunting of deoxygenated blood from pulmonary arteries to pulmonary veins bypasses the capillary bed and can result in dyspnoea, hypoxia, cyanosis, orthodeoxia and clubbing. Bruits may be heard on auscultation of the chest. Paradoxical embolism resulting in stroke or brain abscesses are potential complications. AVM rupture and haemorrhage are uncommon but have been reported especially during pregnancy.[27,47] The

presentation of PAH-HHT is frequently characterised by the insidious onset of progressive dyspnoea, which may initially be attributed to other causes. Additionally, patients may report palpitations, presyncope, syncope and symptoms of right heart failure. Examination may reveal a loud pulmonary component of the second heart sound (P2), a third or fourth heart sound (S3, S4) and signs of right heart failure such as an elevated JVP and limb oedema. Lung bruits may be noted with large PAVMs. Digital clubbing is not a feature of PAH-HHT and if present, should prompt assessment for alternative causes such as PAVMs or liver disease. When present, liver VMs are often multiple and are the primary cause of HOCF in this population. HOCF can present with dyspnoea, paroxysmal nocturnal dyspnoea and palpitations. There may be a wide pulse pressure, warm extremities, tachycardia, and features of heart failure such as an elevated JVP and limb oedema. Rare complications of liver VMs include portal hypertension (hepatoportal AVMs) and biliary ischaemia (portovenous AVMs).[27]

Screening for complications

Screening for potential complications is a core principle in the management of HHT. At every assessment, patients should receive a full clinical examination, with evaluation of peripheral oxygen saturations, heart rate, blood pressure and respiratory rate. Iron deficiency anaemia is common and therefore a full blood count, ferritin +/- iron studies should be assessed at every visit, at least annually. All patients should be screened for PAVMs and cerebral AVMs at baseline as per international guidelines, and patients with SMAD4 mutations and juvenile polyposis syndrome should be linked in with colorectal screening services.[1]

Recommendations for the optimum initial screening test for PAVMs vary between centres and typically include either a transthoracic contrast echocardiogram (TTCE) with agitated saline, followed by a CT thorax if the TTCE is abnormal (Figure 3).[1,27,47] TTCE is a highly sensitive test

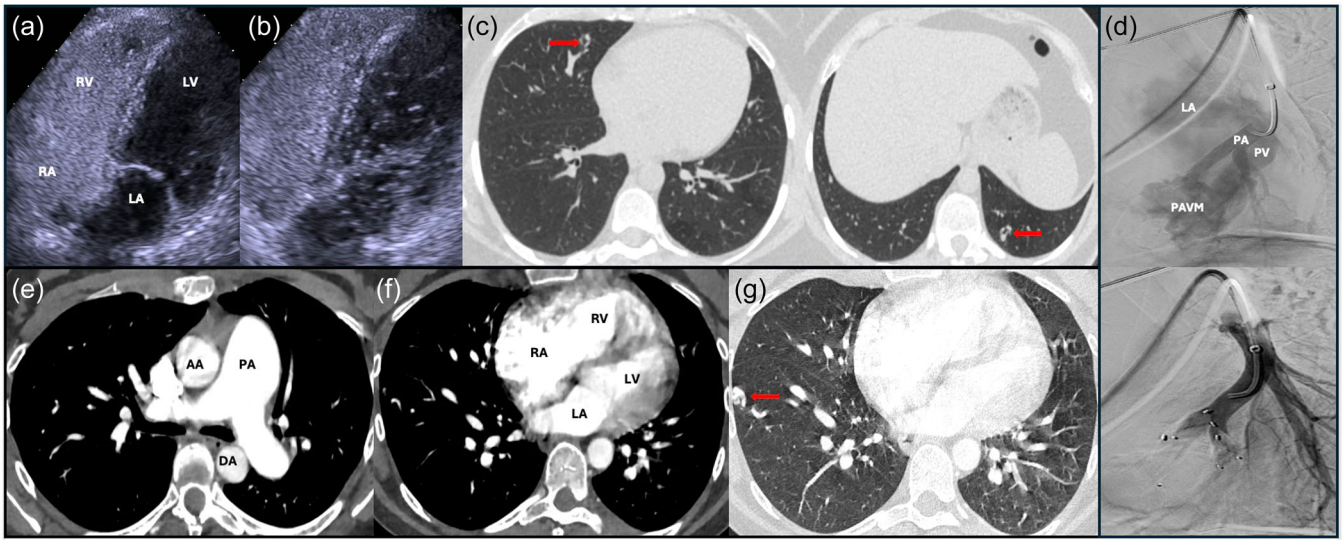

FIGURE 3 Illustrates echocardiographic, CT and pulmonary angiogram features of PAVMs in subjects with HHT. Figure 3A: Apical 4-chamber view from patient with newly-diagnosed HHT with an endoglin mutation, following agitated saline injection, demonstrating opacification of right-sided chambers. Figure 3B: Moderate number of bubbles seen in the left heart after 4 cardiac cycles, consistent with an intrapulmonary shunt. Figure 3C: High Resolution CT from the same patient demonstrating small right middle and left lower lobe PAVMs (arrows). The patient was referred for consideration of PAVM embolization. Figure 3D: Pulmonary angiogram of large left lower lobe PAVM in an 18-year-old with known HHT and endoglin mutation, pre- and post-embolization with multiple microvascular plugs. Figures E-G: CT pulmonary angiogram images of a 34-year-old with known HHT with ACRVL1 mutation who developed exertional dyspnoea over the period of 1 year. Figure 3E: Dilated main pulmonary artery. Figure 3F: Dilated right heart chambers with a non-dilated left atrium. Figure 3G. Right lower lobe PAVM (arrow). Subsequent right heart catheterisation demonstrated pre-capillary pulmonary hypertension with mean right atrial pressure 9 mmHg, mean pulmonary arterial pressure 60 mmHg, pulmonary arterial wedge pressure 10 mmHg, cardiac output 4.9 L/min, cardiac index 2.7 L/min/m^2 and pulmonary vascular resistance of 10.2 WU. The patient responded to dual oral combination therapy with the subsequent addition of an IP prostacyclin receptor agonist. The PAVM was subsequently closed with no evidence of cardiovascular deterioration. *Abbreviations: RV, right ventricle; RA, right atrium; LV, left ventricle; LA, left atrium; AA, ascending aorta; PA, pulmonary artery; DA, descending aorta; PV, pulmonary vein; PAVM, pulmonary arteriovenous malformation.*

for PAVMs and is associated with a relatively low risk of complications. During this test an agitated saline solution is injected into a peripheral vein and concurrent transthoracic echo (TTE) views are obtained. The test is negative if no microbubbles are visible in the left heart. This indicates that the microbubbles have diffused into the alveoli when passing through the pulmonary capillaries. If bubbles are visible in the left heart on TTE then the test is positive and warrants further assessment for PAVMs with CT thorax. However, a positive test is not specific for PAVMs and may indicate alternative conditions including intracardiac shunting via a patent forman ovale or atrial septal defect (in which cases bubbles are seen within the left heart earlier, often within 3 cardiac cycles).[27] In centres with specific expertise, graded TTCE can be employed to categorise the amount of contrast visible in the left ventricle into one of four grades, ranging from minimal to extensive opacification.[48,49] This is valuable to quantify the degree of shunting, minimise radiation exposure and detect treatable PAVMs in patients following embolization.[50]

If there is no evidence of PAVMs or if they are too small for intervention, then regular clinical and radiological follow-up is advised (Table 2). Some HHT centres have moved away from scheduling regular interval CTs to monitor for PAVM development or growth to avoid cumulative radiation exposure.[1,27,47] However, many centres would advocate a follow-up CT after 5 years or 3 years during puberty or pregnancy.

If PAVMs are identified at screening then they should be reviewed by a multidisciplinary team including an interventional radiologist to ascertain if they are amenable to embolization. Following embolization, patients should have both clinical and radiological evaluation of PAVMs approximately 6 months following the procedure. Pregnant women with PAVMs should be managed as a high-risk pregnancy by a multidisciplinary team and screening for PAVMs should be repeated following pregnancy, as it is associated with PAVM growth and new PAVM formation.[47]

Echocardiography is also a valuable tool to assess for HOCF in patients with liver VMs and to screen for complications such as PH. Current HHT guidelines do not recommend routine screening for PH in asymptomatic patients with HHT. However, most patients with HHT will have an echocardiogram at presentation to screen for PAVMs or to check for HOCF if liver VMs are present and this is an opportunity to also screen for PH. When PH is present, this can manifest with structural and functional right heart changes that are visible on TTE. Peak tricuspid regurgitation velocity (TRV) is an important parameter that stratifies the probability of PH into low (<2.8 m/s), intermediate

TABLE 2 HHT screening considerations.

HHT considerations	Baseline assessment	Interval surveillance
Iron deficiency anaemia	CBC, ferritin +/- iron studies	Assess at every visit, at least annually.
Pulmonary AVMS*	TTCE and/or CT thorax	PAVMs absent: Clinical assessment. PAVMs present & untreated: Clinical evaluation +/- CT as indicated. PAVMs present & treated: Clinical assessment and CXR/CT at 6/12 Following pregnancy: Repeat PAVM screening irrespective of prior screening results
Liver AVMs	Doppler ultrasound Liver + TTE in patients with symptoms or signs indicative of liver involvement.	The scheduling of surveillance scans in patients with liver VMs is guided by clinical factors and prognostic assessment.
Cerebral AVMs	MRI brain with and without contrast.	Guided by neurovascular expertise with individualised management
Education checklist	Written epistaxis advice to all patients Antibiotics prophylaxis before dental/surgical procedure for patients with PAVMs. Information regarding the risk of air embolism for patients with PAVMs Pregnancy and PAVM advice for women of childbearing age with PAVMs	

Table 2 outlines important screening and education recommendations for patients with HHT, with a specific focus on pulmonary vascular complications and baseline screening for AVMs at the time of diagnosis. Subsequent imaging if often guided by individual patient characteristics and expert opinion.

Abbreviations: CBC, Complete blood count; TTCE, Transthoracic contrast echocardiogram; CT, Computed tomography; CXR, chest radiograph; PAVMs, pulmonary arteriovenous malformations; Liver VMs, liver vascular malformation.[9,47] *Note: Where available, graded TTCE can also be used at baseline and interval surveillance assessments for PAVMs. If the initial test is negative then graded TTCE may be repeated at 5 year intervals. When the initial graded TTCE is positive, a bespoke surveillance is requested depending on the grade of shunting.

(2.8-3.4 m/s) or high risk (>3.4 m/s). If there is inadequate tricuspid regurgitation, then TRV can be difficult to quantify and additional TTE features should be assessed. This include careful characterisation of the right atrium, right ventricle, pulmonary artery and the inferior vena cava as outlined in the 2022 ESC/ERS Guidelines for the diagnosis and treatment of PH.[38] If there are findings suggestive of PH on TTE or if there is still clinical concern for same then a formal RHC should be performed. This will facilitate confirmation of the diagnosis and description of the haemodynamic pattern (Table 1).

In patients with HOCF there is increased blood flow through the pulmonary circulation, which can result in pulmonary venous congestion, PH and an elevated PAWP. Typically, in the early stages of the disease the PVR is normal as there is no intrinsic pulmonary vascular disease (Table 1). Oxygen saturations should be incrementally assessed during every RHC, as a significant step-up in saturations between the mid inferior vena cava and the right atrium would indicate a hepatic artery to vein shunt.[43]

All patients with HHT and signs or symptoms suggestive of liver VMs should undergo investigations including liver imaging and echocardiogram. Doppler ultrasonography is a safe and reliable investigation and is often used as a first line test for liver VMs.[51,52] Multiphase contrast CT and MRI liver are also suitable alternatives to screen for liver VMs.[1] Buscarini et al devised criteria to grade the severity of liver VMs in HHT using doppler ultrasonography, which ranges from 0+ to stage IV liver VMs. Stage IV liver VMs are defined by decompensation of AVM shunt, with dilatation of hepatic and/or portal veins and evidence of flow abnormalities.[53] Current guidelines recommend that interval liver VMs imaging should be guided by clinical factors and prognostic assessment.[1] Currently there are only a few studies that explore which parameters might be helpful to estimate prognosis of liver VMs and therefore make decisions regarding surveillance imaging.[54–56] Older age, female gender, haemoglobin <8 g/dL, alkaline phosphatase >300 IU/L and stage 4 liver VMs at the time of presentation are associated with clinically significant liver disease and worse outcomes, and therefore indicate that short interval imaging is required.[54–56] Additionally, echocardiogram is a valuable test to assess for HOCF when liver VMs are present. Unlike the management of PAVMS, the treatment of liver VMs is reserved for symptomatic patients and those with complications.

While the screening of cerebral AVMs and gastrointestinal complications are outside the scope of this article, they are equally important and are described in detail in recent international HHT guidelines.[1]

Treatment of the pulmonary vascular complications of HHT

The HHT working group of the European Reference Network for Rare Vascular Diseases (VASCERN) constructed specific outcome measures to ensure high standards of HHT care, emphasizing the importance of patient education and holistic care. This includes the provision of written advice to patients regarding nosebleeds, pregnancy and PAVMs, and antibiotic prophylaxis before dental or surgical procedures.[9] These standards encourage physicians to optimise preventative strategies, mitigate complications of HHT and empower patients through education.[9] Similarly patients should be advised regarding regular exercise and a healthy lifestyle.

The medical management of patients with heart failure from PAH or HOCF should include optimisation of fluid balance, salt and water intake and diuretic therapy. Iron deficiency anaemia is common in HHT due to epistaxis and gastrointestinal blood losses and should also be addressed with oral iron or intravenous (IV) iron if necessary. Of note, patients with chronic hypoxaemia related to large or multiple PAVMs should mount a secondary erythrocytosis and its absence should alert the clinician to the possibility of iron deficiency resulting in an inability to increase haemoglobin levels appropriately. Patients with documented PAVMs should be advised regarding the risk of paradoxical embolization leading to complications such as cerebral infarcts and hence the importance of antibiotic prophylaxis before procedures that may be associated with transient bacteraemia such as dental procedures and endoscopy. Extra care should be taken when obtaining IV access in patients with PAVMs to avoid air embolism while scuba diving is also not advised due to the risk of paradoxical gas embolism.[1]

The management of pulmonary AVMs

PAVMs bypass the pulmonary capillary bed and are associated with an increased risk of paradoxical embolism. Routine screening for PAVMs is recommended as patients may be asymptomatic. There is no definite size threshold for the treatment of PAVMs, and generally intervention should be considered once it is technically feasible, to prevent complications. Interventional radiologists typically decide to intervene based on the size of the feeding artery entering the pAVM (2-3 mm) as smaller feeding arteries preclude the safe deployment of embolization materials. When performed by an experienced interventional radiologist, embolization is effective and safe, and can reduce polycythaemia, hypoxia, migraines, and nosebleeds.[27] Potential risks include lung

infarction, haemoptysis, air embolism and migration of embolization material.[27] Long-term follow up is recommended to detect new PAVMs or reperfusion of previously treated PAVMs (Table 2).[1] Surgical resection is rarely performed now for PAVMs and only a limited number of lung transplantations have been reported in the literature for this indication.[57–65] Occasionally, patients may have diffuse PAVMs that result in profound hypoxemia and can be difficult to manage. These patients are often still referred for consideration for lung transplantation given limited treatment options.

The optimum management of PAVMs in patients with concomitant PH is not as clearly defined and there is a paucity of evidence based guidelines. Theoretically the embolization of PAVMs in patients with significant PH could lead to an increase in right ventricular afterload due to an abrupt cessation of right to left shunting via PAVMs and this could acutely worsen PH. In a study of 143 patients with HHT and mild to moderate PH (mPAP range 6-45 mmHg, mean of 13.5 mmHg), embolization of PAVMs was not associated with any consistent rise in the mPAP following the procedure.[66] However, patients with severe PH were excluded from this study and there are documented cases of fatal increases in pulmonary pressures post PAVM embolization.[66,67] In light of this, the risks of PAVM embolization in patients with severe PH generally outweigh the benefits and should only be performed after careful consideration of the individual patient.[66]

Pulmonary arterial hypertension specific therapies

Recommendations regarding the management of PAH are outlined in the 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension and recently revised at the 7th World Symposium on PH.[38,68] This section focuses on PAH specific therapies for patients with PAH, including those with HPAH and portopulmonary hypertension which can affect patients with HHT.

There are now four primary treatment pathways for patients with PAH, including the nitric-oxide-soluble guanylate cyclase (NO-sGC) pathway, endothelin receptor antagonists (ERA), prostacyclin and the activin signalling pathway (Table 3). The aim of therapy is to augment signalling via the NO-sGC and the prostacyclin pathways, to attenuate signalling via the endothelin pathway and to reduce activin signalling. This facilitates pulmonary vascular vasodilatation and potentially mitigates remodelling. Typical dosing and common side effects are outlined in Table 3. Generally, patients with PAH who do not have significant comorbidities will start with double combination therapy with a drug from the NO-sGC pathway and the endothelin pathway. A third agent from the prostacyclin pathway will be considered if they fail to reach low-risk status at 3 months.

Recently, sotatercept has been approved as a 4th pathway for the treatment of PAH.[38] Sotatercept is a novel fusion protein that acts as a ligand trap for members of the TGFβ superfamily including activins and growth differentiation factors. It aims to rebalance signalling via the antiproliferative BMP receptor 2 (BMPR2)-SMAD1/5/8 pathway and the proproliferative activin receptor type IIA (ActRIIA)-SMAD 2/3 pathways.[71,72] Sotatercept is administered subcutaneously at doses of 0.3-0.7 mg/kg every 3 weeks, and common adverse events include telangiectasia, epistaxis, polycythaemia, thrombocytopenia and headaches.[69] Phase three trials of sotatercept in PAH demonstrated an improvement in 6 min walk distance (6MWD) when compared to placebo. However, patients with portopulmonary hypertension were excluded from these studies and sotatercept has not been specifically studied in patients with HHT. Therefore the role of sotatercept in patients with HHT is unclear and the associated side effects of telangiectasia and epistaxis could limit its use in a population of patients who already experience these complications.[71,72] It remains to be determined whether this propensity to develop telangiectasia will ultimately mean that sotatercept will be contraindicated in HHT-PAH. Furthermore, sotatercept is associated with thrombocytopaenia, which may be problematic in patients with PoPH.

Anaemia is common in HHT and may also be a side effect of certain PAH therapies. A fall in haemoglobin is frequently observed in patients prescribed ERAs and they should therefore be avoided in individuals with a haemoglobin less than <8 g/gL. Anaemia occurred in 13% of patients with PAH prescribed macitentan in the SERAPHIN study and appears to be dose dependent.[73] The precise mechanism of this remains unclear, but it is not thought to be caused by bleeding or haemolysis, and might be related to plasma volume expansion.[74] Furthermore, prostacyclin analogs such as epoprostenol can inhibit platelet aggregation and have been associated with thrombocytopaenia and bleeding, which is particularly relevant for patients with HHT who may experience bleeding from telangiectasia.[70]

The management of high output cardiac failure

The treatment of HOCF due to liver VMs should be confined to symptomatic patients.[52] The management of

TABLE 3 Pulmonary arterial hypertension specific therapies.

PAH specific therapies	Route of administration	Doses	Common & important side effects
Nitric oxide-sGC pathway			
Sildenafil	PO IV (less common)	20-80 mg TDS	Headache Flushing Hypotension Nasal congestion Diarrhoea and dyspepsia Ocular hyperaemia and visual events
Tadalafil	PO	20-40 mg OD	Headache Flushing Hypotension Nasal congestion Dyspepsia Ocular hyperaemia and visual events
Riociguat	PO	1-2.5 mg TDS	Headache Flushing Dizziness Dyspepsia Haemoptysis Teratogenic
Endothelin receptor antagonists			
Macitentan	PO	10 mg OD	Nasopharyngitis, bronchitis Headache Anaemia Oedema and fluid retention LFT derangement Teratogenic
Ambrisentan	PO	5-10 mg OD	Nasopharyngitis Headache Flushing, hypotension AnaemiaOedema and fluid retentionLFT derangement Teratogenic
Bosentan	PO	62.5-125 mg BD	Headache Flushing, hypotension LFT derangement Anaemia Teratogenic
Prostacyclin analogues			
Epoprostenol	IV	Start: 2 ng/kg/min 20-40 ng/kg/min*	Hypotension, tachycardia, flushing Headache, Jaw pain Nausea, Vomiting, Diarrhoea Thrombocytopaenia Infusion line complications e.g. infection.
Treprostinil	IV, SC, PO, inhal	SC/IV: Start 1.25 ng/kg/min 40-60 ng/kg/min* PO: 0.125-5 mg BD/ TDS (max 120 mg daily)	Hypotension, tachycardia, flushing Headache, Jaw pain Nausea, Vomiting, Diarrhoea Infusion line complications: E.g. infection. SC: Site pain and infections

(Continues)

TABLE 3 (Continued)

PAH specific therapies	Route of administration	Doses	Common & important side effects
		Inhal: 18-54 mcg four times a day	Inhal: Cough, throat irritation
Iloprost	Inhal	2.5-5 mcg 6-9 times per day	Flushing Headache, Jaw pain Nausea, Vomiting, Diarrhoea Chest discomfort, cough, haemoptysis
Prostacyclin receptor antagonist			
Selexipag	PO	200-1600 mg BD	Headache Diarrhoea, vomiting, nausea Jaw pain, myalgia Anaemia and hypothyroidism

Table 3 Provides an overview of the drugs commonly prescribed to treat pulmonary arterial hypertension. *Epoprostenol and Treprostinil doses vary between patients. Titrations are guided by patients symptoms and individual patient doses are heterogeneous[69,70]

HOCF should address general supportive measures and include consideration of additional therapies such as the antiangiogenic therapy bevacizumab and liver transplantation. Supportive measures for patients with HOCF include optimisation of fluid balance, diuretics and the treatment of comorbidities. The pros and cons of treatment with bevacizumab and of liver transplantation are described below. Of note, hepatic artery ligation, banding and embolization are no longer recommended, as these interventions are associated with considerable morbidity and mortality and are not curative in nature.[1]

Bevacizumab

Bevacizumab is a humanised monoclonal antibody that binds and neutralises VEGF-A, inhibiting angiogenesis.[75] It was first approved by the FDA for the treatment of metastatic colorectal cancer in 2004 and it has since been investigated in a number of conditions including HHT.[75] The International Guidelines for the Diagnosis and Management of HHT suggest to consider bevacizumab for patients with HHT and symptomatic HOCF associated with liver VMs.[1] Furthermore, there is increasing evidence that intravenous (IV) bevacizumab reduces epistaxis, improves anaemia and enhances QOL in HHT patients.[1] The elimination half-life is approximately 17-21 days and there is no current evidence to suggest an antibody response.

The induction dose of IV bevacizumab is 5 mg/kg every 2 weeks for 6 doses. Maintenance doses vary, and suggested regimens include the administration of 5 mg/kg every 1-3 months for the first 12 months, with subsequent prolongation of treatment intervals guided by clinical response.[1,76] It should be noted that there are no prospective randomised controlled trial data regarding maintenance therapy with bevacizumab for HHT and therefore decisions regarding dosing intervals and treatment duration are often made on a case by case basis.

Reported side effects that should be monitored at each visit include hypertension, fatigue, proteinuria, thromboembolic events and wound healing complications.[76] In an international study of 238 HHT patients receiving bevacizumab, systemic hypertension was reported in 18%, proteinuria in 9% and venous thromboembolism in 2% over the course of 343.9 patient years of treatment.[77] Bevacizumab is contraindicated in pregnancy as it inhibits foetal angiogenesis and therefore appropriate contraception is advised. Furthermore, it is recommended that bevacizumab is stopped 6–8 weeks before any surgery and that it should not be restarted until at least 4 weeks postoperatively, once wounds are fully healed.[78]

There is currently no evidence regarding the safety or efficacy of bevacizumab for the treatment of PAH associated with HHT. Conversely, there are several case reports suggesting a potential link between bevacizumab and the development of drug associated PAH.[79,80] However, it is interesting to note that endothelial cells in plexiform lesions overexpress VEGFR2, which is associated with a proangiogenic phenotype, and therefore further research is needed to clarify the potential role of bevacizumab in PAH-HHT.[81,82]

In the following sections we describe two clinic cases which demonstrate the practical utility of bevacizumab in patients with HHT and pulmonary vascular complications.

CASE 1

A 57-year old female with HHT2 (ACVRL1 mutation) reported progressive dyspnoea and limb oedema. She was iron deficient, with a haemoglobin <80 g/L and required frequent iron and blood transfusions. She reported only moderate epistaxis (epistaxis severity score of 3.4) and therefore additional investigations were requested to investigate her anaemia and progressive symptoms, which are outlined in Figure 4. A capsule endoscopy revealed multiple small bowel angioectasia and a CT showed numerous liver VMs. An echocardiogram revealed bi-atrial and right ventricular dilatation, hyperdynamic biventricular function and a peak tricuspid regurgitant velocity of 3.8 m/s, indicating a high probability of PH. A RHC was performed and showed a mPAP of 40 mmHg, a PAWP of 18 mmHg, a cardiac output of 13.6 L/min, a cardiac index of 8.4 L/min/m^2, a PVR 1.4 WU and saturations of 64% in the superior vena cava, 89% in the inferior vena cava, 94% in the hepatic artery and 84% in the pulmonary artery. This showed a picture of HOCF with a post-capillary element due to liver VMs and she was listed for liver transplantation. Diuretic therapy was initiated and argon plasma coagulation (APC) via double-balloon push-enteroscopy was performed for the gastrointestinal angioectasia. However, she remained transfusion dependent and debilitated by symptoms and was therefore commenced on intravenous bevacizumab at a dose of 5 mg/kg every 2 weeks for 6 doses, followed by 3-monthly intervals. The initiation of

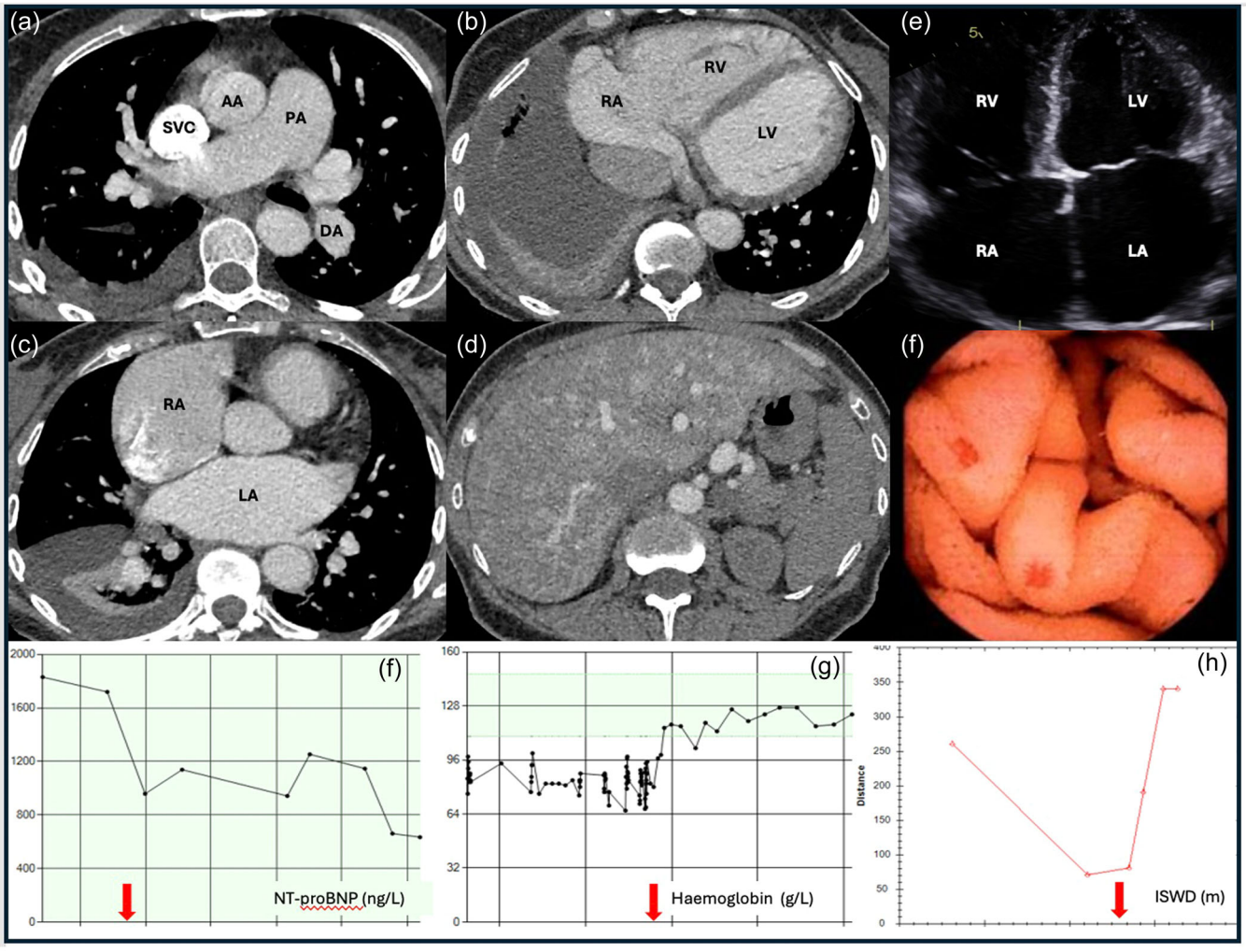

FIGURE 4 Describes a case of HOCF associated with liver VMs and severe anaemia. Figure 4A: CT demonstrating a dilated main pulmonary artery. Figure 4B: CT image shows mild dilatation of the right ventricle. Figure 4C: CT demonstrates bi-atrial enlargement and shows a right effusion (transudate). Figure 4D: CT demonstrates evidence of multiple hepatic vascular malformations. Figure 4E: Echocardiogram apical 4-chamber view shows bi-atrial and right ventricular dilatation. Figure 4F: Images from capsule endoscopy demonstrate multiple small bowel angioectasia. Figure 4F-H: illustrate significant improvements in NT-proBNP, haemaglobin and incremental shuttle walking distance following initiation of bevacizumab (red arrow). *Abbreviations: RV, right ventricle; RA, right atrium; LV, left ventricle; LA, left atrium; SVC, superior vena cava; AA, ascending aorta; PA, pulmonary artery; DA, descending aorta; ISWD, incremental shuttle walking distance.*

bevacizumab was accompanied by a substantial improvement in clinical parameters including NT-proBNP, haemoglobin and incremental shuttle walking distance (Figure 4) and she did not require any further iron or blood transfusions. This case outlines the potential role of bevacizumab in cases of HOCF associated with liver VMs and refractory anaemia.

CASE 2

A 20-year old woman with PAH-HHT (ACVRL1 mutation) was referred to the national lung transplant unit for assessment regarding suitability for lung transplantation. She was diagnosed with PAH-HHT at the age of six and was prescribed maximal medical therapy with ambrisentan, tadalafil and intravenous epoprostenolol. Her background was also significant for a reverse Potts shunt (Figure 5) and recurrent gastrointestinal bleeds for which she was transfusion dependent. She reported FC II dyspnoea, had a 6 min walk distance of 320 m and a repeat RHC demonstrated a severe pre-capillary pattern, with a mPAP of 70 mmHg, PAWP of 11 mmHg, PVR 12 WU, CO 4.9 L/min and pulmonary artery saturations of 67.7%.

She had recurrent admissions with haematemesis and lower gastrointestinal (GI) bleeds necessitating transfusion for haemoglobin counts <80 g/L. She was diagnosed with GI angioectasia and managed medically in each instance. Concern was expressed that her PAH therapies might exacerbate these bleeding episodes, however given the severity of her disease it was decided that these medications would be continued irrespective, with careful monitoring. In light of recurrent GI bleeds and multiorgan disease she was deemed high-risk and unsuitable for lung transplantation.

She subsequently initiated bevacizumab in March 2024 and had a dramatic rise in her haemoglobin from 73 to 180 g/L in 2 months (Figure 5c). Although there were concerns regarding the possibility of bevacizumab worsening PAH, there was no evidence of any persistent worsening of her pulmonary vascular status. Since the initiation of bevacizumab she has had a dramatic improvement in her quality of life as she does not need to attend hospital for regular transfusions or iron infusions. This case outlines the barriers to lung transplantation in patients with multiorgan involvement with HHT and the role of bevacizumab to mitigate GI bleeding and improve tolerance for PAH therapies.

TRANSPLANTATION

A limited number of lung transplantations have been performed for PAVMs and PAH-HHT.[57–65] A study by Shovlin et al explored the long-term outcomes of hypoxic patients with HHT and PAVMs who were referred for lung transplantation but did not undergo the procedure.[83] This study revealed that the survival in these 'transplant-considered' patients exceeded typical lung transplant survival figures, indicating the importance of careful consideration of quality of life and survival estimates before lung transplant referral.[83] Lung transplantation is typically still considered for patients with diffuse PAVMs that are not amenable to embolization, and many of these cases are children. These decision should be made a case-by-case basis and it is our experience that these referrals are often rejected if there is any evidence of extrapulmonary manifestations of HHT.

Conversely, current guidelines advise consideration of orthotopic liver transplantation (OLT) in symptomatic patients with complications of liver VMs such as HOCF, portal hypertension and biliary ischaemia that is not responsive to

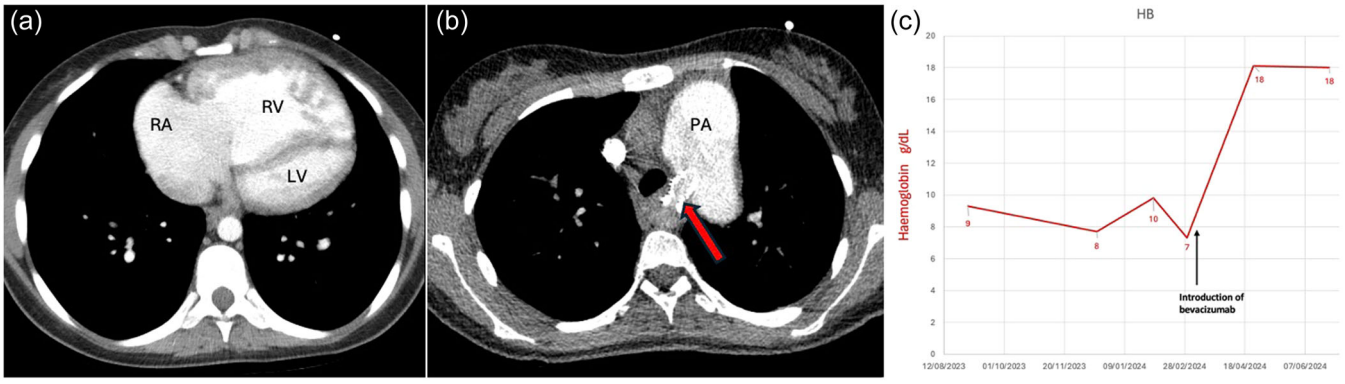

FIGURE 5 A case of PAH-HHT and recurrent gastrointestinal bleeds which responded to bevacizumab. Figure 5A: CT thorax demonstrating a dilated right heart with compression of the intraventricular septum and left ventricular cavity in a patient with PAH-HHT. Figure 5B highlights the reverse Potts shunt (red arrow) and dilated pulmonary artery. Figure C illustrates a rise in haemoglobin following the initiation of bevacizumab, with subsequent stabilisation. *Abbreviations: RV, right ventricle; RA, right atrium; LV, left ventricle; PA, pulmonary artery.*

other interventions.[1] OLT can result in partial or complete reversal of HOCF and PH, and AVM recurrence is rare.[1,27] The reported long-term survival is good at 82- 92%.[27] Patients should be screened for PH pre OLT as it is associated with increased postoperative morbidity and mortality. OLT can be considered if the mPAP is <35 mmHg, or if the mPAP is 35-45 mmHg and the PVR is <3WU. A mPAP is >45 mmHg despite treatment with PAH specific therapies is considered an absolute contraindication to OLT.[84]

Additional agents

Thalidomide has immunosuppressive and antiangiogenic effects and has been studied in patients with HHT, particularly for the management of epistaxis.[85–87] Thalidomide and its analogues such as pomalidomide downregulate VEGF and improve vascular integrity.[1] While it appears to be effective at reducing epistaxis in this cohort, its long-term use is limited by side effects including neuropathy and teratogenicity.[86] It is not currently recommended in the International Guidelines for the Diagnosis and Management of HHT.

Additional drugs under investigation for complications of HHT include pazopanib, an oral tyrosine kinase inhibitor.[88] This inhibits VEGF receptors 1, 2 and 3, platelet derived growth factor (PDGFR) -α and -β, and c-kit and has demonstrated efficacy in 13 subjects with transfusion-dependent HHT.[89,90] It is generally well tolerated with reported adverse effects of hypertension, lymphocytopenia, and fatigue, though additional studies are required to clarify its efficacy, safety and specific role in HHT.[89] A Phase II/III randomized controlled trial is currently in progress to evaluate the effect of pazopanib on HHT related epistaxis and anaemia (NCT03850964).

Prognosis

Increasing age is associated with increased disease penetrance, hospitalisations, complications and worse outcomes in HHT.[91] Unscreened patients have a reduced life expectancy, emphasizing the importance of comprehensive screening in HHT.[1] Patients appropriately screened and treated for PAVMS have an excellent prognosis, similar to the general population.[92] Certain liver VMs characteristics at initial screening such as stage IV liver VMs and symptomatic liver VMs are associated with worse outcomes, which should prompt the treating physician to urgently optimise management.[54–56] It is reported that 14% of patients with symptomatic liver VMs do not respond to first line therapies and develop progressive disease.[1]

PH in patients with HHT is associated with worse outcomes, irrespective of the underlying aetiology.[93] While there are limited studies in this population, a study of 32 subjects with PAH associated with ACVRL1 gene mutations demonstrated worse outcomes when compared to other PAH subgroups.[34] Similarly, 9 patients with PAH-HHT had a 1- and 3- year survival of 78% and 53%, which was significantly lower than those with IPAH.[94] This underscores the importance of aggressive management of PAH in subjects with HHT and the unmet need for additional therapies.

CONCLUSION

Pulmonary vascular disease is an important complication of HHT which is associated with considerable morbidity and mortality if left untreated. Routine screening for specific complications at the time of HHT diagnosis provides an opportunity to identify problems early and address them in a timely fashion. It is common practice to screen for PAVMs in patients with HHT and to embolise them if it is technically feasible. Conversely, screening for liver VMs is often only performed when indicative clinical signs and symptoms are present, as intervention is only advised for those who are symptomatic or who have evidence of complications such as HOCF. Prognostic assessment of liver VMs using doppler ultrasound and echocardiography can help identify those who require close surveillance. Finally, PAH-HHT is a devastating diagnosis and can be difficult to treat as treatment can be associated with notable side effects such as bleeding and anaemia. Furthermore, lung transplantation may not be an option for many patients with PAH-HHT who have evidence of extrapulmonary disease. Considering this, and the poor outcomes in this population, there is an urgent unmet need for additional research and new therapies.

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