Hereditary Haemorrhagic Telangiectasia
A clinical and scientific review

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Running Title: HHT 2009

Key words: Nosebleeds, anaemia, AVMs, stroke, endothelial, TGF-β

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Word counts:
Abstract 79
Text 4211
References 63
ABSTRACT
The autosomal dominant trait hereditary haemorrhagic telangiectasia (HHT) affects 1 in 5-8,000. Genes mutated in HHT (most commonly for endoglin or ALK-1) encode proteins that modulate TGF-β superfamily signalling in vascular endothelial cells; mutations lead to the development of fragile telangiectatic vessels and arteriovenous malformations. In this article we review the underlying molecular, cellular and circulatory pathobiology; explore HHT clinical and genetic diagnostic strategies; present detailed considerations regarding screening for asymptomatic visceral involvement; and provide overviews of management strategies.

IN BRIEF
- Autosomal dominant;
- Commonly results from mutations in endoglin (HHT1) or ACVRL1 (HHT2);
- Rarely due to mutations in Smad4, or other genes ;
- Known disease genes involved in TGF-β superfamily signalling;
- Marked intrafamilial variation;
- Often only associated with nosebleeds, telangiectasia and a normal life-span;
- Up to a third of patients have chronic or severe anaemia, with gastrointestinal bleeding increasing with age.
- Asymptomatic arteriovenous malformations occur in pulmonary (~50%), hepatic (≥30%), cerebral (~10%) and spinal (~1%) circulations;
- Common AVM complications include stroke (ischaemic and haemorrhagic) and brain abscess;
Rarer HHT complications include deep venous thromboses; symptomatic liver disease requiring liver transplantation; severe pulmonary hypertension; pregnancy-related death, and spinovascular accidents;

INTRODUCTION

The vascular disorder hereditary haemorrhagic telangiectasia (HHT) affects 1 in 5-8,000 \textsuperscript{1,2}, and is inherited as an autosomal dominant trait. HHT disease-causing genes encode proteins that modulate TGF-beta superfamily signalling in vascular endothelial cells. Genetic testing for endoglin (HHT type 1), ALK-1 (HHT type 2) and Smad4 (HHT in association with juvenile polyposis (JPHT) is available; further genes are predicted at loci identified by linkage analyses on chromosomes 5 (HHT3) and 7 (HHT4) (Table 1). While HHT predominantly manifests as a heterozygous condition, several studies investigating children with two affected parents support \textit{in utero} or infantile homozygous lethality in HHT \textsuperscript{3-5}.

HHT gene mutations lead to the development of abnormal vascular structures which range from dilated microvessels to large arteriovenous malformations (AVMs) measuring several centimeters in diameter (Figure 1). These occur at specific sites in systemic and pulmonary circulations (Figure 2). Fragile walls and turbulent blood flow render these vessels more prone to haemorrhage than normal vessels. However, for pulmonary and hepatic AVMs, it is the consequences of arteriovenous shunting that lead to most clinical features (Table 2). Complications commonly occur from previously silent AVMs, and complications can be prevented if AVMs are recognised
and treated. Asymptomatic screening and treatment programmes form major components of HHT management. Useful recent reviews include 6 7 8 9.

**CLINICAL OVERVIEW**

HHT was first described as a familial disease characterised by anaemia, severe recurrent nose bleeds, and gastrointestinal blood loss 15 16. There was early recognition of HHT-affected individuals developing abnormal vascular structures at other sites, particularly arteriovenous malformations (AVMs) of the pulmonary 17 hepatic 18 and cerebral 19 circulations. The majority of HHT patients will be affected by AVMs in at least one of these sites, with AVMs usually remaining silent 20. More recently, the HHT disease spectrum has expanded further to encompass pulmonary hypertension (two forms predominate in HHT); juvenile polyposis; a prothrombotic state; and potential immune dysfunction (see Table 2 for references).

HHT presentation patterns are highly variable even within families. Spontaneous recurrent nose bleeds are the most common and usually earliest clinical manifestation of HHT, often commencing pre school age. Telangiectases of the skin and buccal mucosa typically present from about the third decade of life, and increase with age. Recurrent haemorrhage from the gastrointestinal tract is a feature of later years in 15-20% of individuals 21. Major complications of HHT include severe anaemia from chronic nasal and gastrointestinal haemorrhage; stroke (ischaemic and brain abscess from pulmonary AVMs; haemorrhagic from cerebral AVMs); deep venous thromboses, and in rarer cases symptomatic liver disease requiring liver transplantation; severe pulmonary hypertension; pregnancy-related death, and spinovascular accidents (see Table 2). Most HHT-affected individuals however will not have life-limiting consequences from their HHT 22. Presymptomatic AVM
screening programmes highlight that prior to screening, the majority of affected individuals are unaware of their HHT diagnosis 23.

The goal of HHT management is to optimise the overall outcome of affected individuals, without raising excessive alarm about vascular lesions which may be of little consequence. Symptomatic patients with active medical problems due to their HHT deserve review by informed specialised services. For people with HHT who are well, the focus is on education (including recently published recommendations regarding dental care and pregnancy management) and presymptomatic screening programmes. Exact clinical management regimes differ between countries, predominantly due to differing healthcare practices^.

MOLECULAR AND GENETIC BASIS OF THE DISEASE

**Mutated genes and new loci**

Three HHT disease-causing genes have been identified to date (Table 2). HHT type 1 results from mutations in *ENG* encoding endoglin24(Figure 3A); HHT type 2 from mutations in *ACVRL1* encoding activin receptor like kinase (ALK1) 25(Figure 3B), and HHT in association with juvenile polyposis (JPHT) from mutations in *MADH4* 26. There are at least two further unidentified genes that can cause classical HHT, *HHT3* mapped to chromosome 5q between *D5S2011* and *D5S2490* (Figure 3C) and *HHT4* on chromosome 7p between *D7S2252* and *D7S510* (Figure 3D) 27,28.

**Distribution and frequency of gene mutations**

The majority of HHT patients (>80%) will have mutations in either *ENG* or *ACVRL*, *ENG* mutations being more common (61%) than *ACVRL1* mutations (37%) or
MADH4 (2%) \textsuperscript{29}. There is a geographical variation, with both North American and European series demonstrating either ACVRL1 predominance (US \textsuperscript{30}, European \textsuperscript{31,32}) or an ENG bias (US \textsuperscript{33}; European \textsuperscript{34 35}). It is therefore not clear whether this reflects the referral practice of HHT centres, or genuine geographical variation.

More than 600 different mutations have been found in ENG or ACVR in HHT families (see www.hhtmutation.org). Neither gene displays a common mutation; and the majority of mutations have been reported only once. All types of mutations are found in ENG and ACVRL1, including deletions, insertions, missense, nonsense and splice site (Figure 3). The JPHT mutations found to date are in the last four exons of Smad4 (exons 8-11): mutations types include missense, nonsense and frameshift, with a high incidence of de novo mutations \textsuperscript{26,29}.

Genotype phenotype relationships

Recent large series support early observations, finding pulmonary and cerebral AVMs more common in HHT1 (ENG mutations), and hepatic AVMs more common in HHT2 (ACVRL1 mutations) \textsuperscript{35 34 30,33 31,32}. Although there was an initial suggestion that overall severity of disease is greater in HHT1 than HHT2 \textsuperscript{36}, this study predated the recognition of pulmonary hypertension, and there was no difference in 90 month mortality in a later series \textsuperscript{35}.

Pulmonary hypertension \textsuperscript{37} (Figure 1B) and juvenile polyposis \textsuperscript{26} are recognised as part of the spectrum of HHT for particular families. As illustrated in Figure 2B, pulmonary hypertension is not a single disease entity, and can result from multiple secondary causes in HHT. The pure pulmonary arterial hypertension (PAH) phenotype seen in patients with HHT is indistinguishable from PAH in the general population due to mutations in the related BMPRII (Figure 4). Juvenile polyposis (JP) seen in HHT patients with Smad4 mutations is indistinguishable from JP in the
general population most commonly due to mutations in \textit{BMPR1A} which encodes a related protein. In HHT, pulmonary artery hypertension and JP were initially considered attributable solely to \textit{ACVRL1} and \textit{Smad4} mutations respectively. There are rare reports of both pulmonary artery hypertension and JP associated with \textit{ENG} missense mutations. Further evaluation is needed to determine whether these sequence variations are disease-causing or benign variants.

These genotype-phenotype correlation studies suggest that while normal function of the gene products of \textit{ENG}, \textit{ACVRL1} and \textit{MADH4} are all required to prevent development of an HHT-like phenotype, there are likely to be differences in the normal requirements for the three proteins in different vascular beds and cell types.

\textit{Biology of the disease}

Phenotypic considerations, expression analysis of mutant endoglin and ALK1 proteins, and HHT-like phenotypes in heterozygous mice implicate haploinsufficiency of the respective protein as the cause of \textit{HHT1} and \textit{HHT2} \textsuperscript{6,34}. Dominant negative mutations in endoglin can be generated but may cause different phenotypes: for example, truncated soluble endoglin is associated with the non HHT phenotype of pre-eclampsia \textsuperscript{38}

The genes mutated in HHT encode proteins involved in transforming growth factor (TGF)-\(\beta\) superfamily signalling; perturbation of this signalling pathways is therefore implicated in the pathogenesis of HHT. Superfamily ligands such as TGF-\(\beta\)s, BMPs, activins, nodals, GDFs and inhibins normally regulate diverse cellular functions such as cellular survival, proliferation and differentiation by binding to a heteromeric complex of type I and type II transmembrane serine/threonine kinase receptors (Figure 4). Signalling can be propogated via Smad-dependent and Smad-independent
pathways \textsuperscript{39}. In Smad-dependent pathways in which all 3 known HHT gene products function, ligand binding activates a TGF-β type II receptor which in turn phosphorylates and activates a type I receptor. The type I receptor subsequently phosphorylates and activates receptor associated (R)-Smads (Smads 1, 2, 3, 5, and/or 8) which bind to Smad4 and translocate to the nucleus where they influence transcriptional activation with co-activators and co-repressors. Inhibitory Smads (Smad6/7) target R-Smads for degradation and provide a negative feedback loop for this pathway. In most cell types TβRII signalling transmits through ALK5 (TβRI) via the Smad2/3 pathway. In endothelial cells however, TβRII signalling can also be propagated through ALK1 via the Smad1/5/8 pathway \textsuperscript{40}. The ALK1 ligand has been unknown for a long time but recently it was demonstrated that BMP9 and BMP10 are specific ALK1 ligands that, can also bind endoglin (Figure 4) \textsuperscript{41,42}.

Several series of HHT animal models are now described. Null mice for Eng and Acvrl1 die between E10.5-11.5 due to gross vascular and cardiac defects comparable to multiple other null mice, potentially reflecting aberrant placental vascular development. Heterozygous mice develop variable but more HHT-specific features including nosebleeds, telangiectasia, dilated vessels and AVMs \textsuperscript{6,40}. Conditional LoxP knockout alleles have been generated for all three HHT genes, for ALK1 resulting in a model in which HHT-like vascular malformations occurred in a consistent and predictable manner \textsuperscript{43}. These and other models are under active study.

\textbf{Current HHT models}

What causes the pathogenesis of HHT? This has been a controversial topic for many years and remains unresolved, in part due to the non-uniformity of the disease process in affected vascular beds. The precise sequence of events remains to be determined.
but most likely involves aberrant endothelial cell responses to TGF-β/BMP signalling in specific settings.

A favored model has been generated from data focussing on the two TβRII-associated type I receptors (ALK5 and ALK1), suggesting that the endothelial state depends on the predominant type I receptor utilised, and that abnormal vasculature in HHT resulted from a perturbation of this balance. This balance model has been both challenged, and supported by recent data, and remains a helpful tool in clarifying signalling pathway inter-relationships.

For example, endoglin and ALK1 are involved in angiogenesis, the process in which new blood vessels are formed from pre-existing ones. During angiogenesis, mural cells (smooth muscle cells; pericytes) detach, and brief periods of endothelial cell activation, proliferation and migration are co-ordinated with controlled proteolytic remodelling of the basement membrane and extracellular matrix, expression of endothelial cell survival factors, and recruitment of mural cells to stabilise the nascent blood vessels. There are complex context-dependent biological activities of the HHT gene products in these processes such that over-expression of constitutively active ALK1, or under-expression of endoglin can each either promote or inhibit specific endothelial cell responses according to the experimental conditions. However, evidence suggests that endoglin and ALK-1 responses promote opposing endothelial cell responses (such as proliferation; migration) to ALK5, and that the ratio of ALK5 and ALK1 activation by TGF-β superfamily ligands can influence whether pro or anti-angiogenic genes are predominantly expressed.

MANAGEMENT
DIAGNOSTIC APPROACHES

Clinical diagnosis of HHT

The Curacao criteria, published in 2000 [49], remain the mainstay of HHT clinical diagnosis. A definite diagnosis of HHT is made in the presence of at least three separate manifestations:

- spontaneous recurrent nosebleeds;
- mucocutaneous telangiectasia (multiple at characteristic sites: fingertip pulps, lips, oral mucosa, tongue);
- visceral involvement (gastrointestinal, pulmonary, hepatic, cerebral or spinal AVM)
- family history: a first degree relative affected according to these criteria

Family history plus one criterion: When reviewing individuals from HHT families, clinicians are often faced with individuals with only one additional diagnostic criterion. In clinical practice, if the non familial criterion is a visceral AVM which would be very rare in the general population, the diagnosis of HHT is essentially confirmed. This is not the case for nosebleeds which are common in the general population, or non-florid telangiectasia which can be readily confused with non HHT pathologies. For research and epidemiological studies, the labels of possible or suspected HHT should be used for all individuals with only two diagnostic criteria [49].

Family history only: While HHT is likely to present with nosebleeds during childhood, the condition cannot be excluded on clinical grounds even at the age of 30-40 years. For an apparently unaffected child of an HHT-affected parent, clinical data on age-related penetrance in European HHT populations allow estimations of the
probability of HHT-affected status ranging from 0.5 at 0 years; 0.22 at 16 years; 0.05 at 40 years and 0.01 at 60 years. ‘Possible HHT’ can be added to the medical records of such individuals.

**Molecular diagnosis**

Genetic testing for endoglin, ACVRL1/ALK-1, and Smad4 is available and can confirm the diagnosis for the family, and confirm or refute the diagnosis in family members. Strategies to use genetic tests vary between units.

For patients with definite clinical HHT, molecular testing is not required to confirm their diagnosis, but may assist management of other family members. Mutations are not found in about 20% of HHT families, hence failure to detect a causative HHT mutation in a family does not exclude HHT. Not all HHT gene sequence variations in HHT families are disease-causing (www.hhtmutation.org): where it is difficult to distinguish from incidental polymorphisms, assessment of co-segregation in a distant affected relative may be helpful.

Genetic testing is most helpful in the settings of

- a patient with suggestive but not confirmatory clinical features of HHT in which a positive test would be diagnostic;
- a potentially unaffected family member in whom the diagnosis of HHT cannot be excluded clinically.

*Other genetic counselling issues*
The hallmark of clinical HHT is the variability between different affected members of the same HHT family. Nevertheless there are genotype-phenotype correlations related to the causative HHT gene mutation, and as yet unidentified genetic modifiers.

Prenatal diagnosis is technically feasible and chosen by some families. Generally however, there has been little interest in, or use of, prenatal molecular diagnosis for HHT in view of the longevity and pauci-symptomatic state of most HHT patients (see Acknowledgements section).

A positive molecular diagnosis at present, does not modify recommended screening or management, except in the setting of HHT-affected individuals with a family history of gastrointestinal polyps/malignancy: identification of a Smad4 mutation would lead to institution of gastrointestinal screening programmes.

**CLINICAL WORK UP**

The basic work up approach for suspected HHT patients is illustrated in Figure 5. Following a clinical evaluation including a detailed family history, emphasis is placed upon

- ensuring that patients with a particular problem are reviewed by an organ-specific specialist aware of HHT issues (details of management are beyond the scope of this text, but outlined within Table 2);
- screening for asymptomatic AVMs according to local or regional practice (see below);
- formalising the diagnosis of HHT which may require molecular testing;
• providing information and opportunity for follow up and family screens.

**Screening**

The medical justification for screening regimes in asymptomatic individuals from the HHT population centres on the degree of danger posed by silent AVMs (as opposed to symptomatic AVMs), the safety/tolerability of the diagnostic tool, the advantages offered by the correct diagnosis in term of patient management and follow up, and the safety of effective treatments. Risk-benefit evaluations are then performed to determine whether the detection and treatment of the asymptomatic AVM is likely to carry overall positive health benefits for the patient.

Where risk benefit considerations are less clear cut, different interpretations are observed, and generally reflect the overall healthcare practices of particular countries and cultures. In order to reflect these differing practices, and the evolving nature of recommendations as new data regarding natural history and treatment safety/efficacy become available, Figure 5 presents only limited data regarding specific particular screening and management regimes. Detailed considerations are presented below.

**Pulmonary AVMs**

Pulmonary AVMs are usually silent at the time of PAVM-induced strokes and brain abscess, can be diagnosed at low risk; and have an effective and safe treatment with embolisation shown to reduce or abolish neurological risks. Hence detection and treatment of asymptomatic pulmonary AVMs is recommended worldwide for adults.

For highly sensitive screening tests, the choice lies between thoracic CT scans and contrast echocardiography (CE). Use of either test means that very few pulmonary PAVMs will be missed in an HHT population whereas chest x-rays, blood oxygen levels and right to left shunt measurements are insufficiently sensitive to exclude
pulmonary AVMs. Both tests also allow for the detection of severe pulmonary hypertension which is a relative contraindication to embolisation.

Many specialised units utilise a multistep screening programme using contrast echocardiography as a first line screen: Following intravenous injection of contrast or microbubbles which should be removed by the normal pulmonary capillary bed, right to left shunting through pulmonary AVMs results in the appearance of microbubbles in the left side of the circulation. Arrival is delayed compared to intracardiac shunts, with bubbles arriving after 3-10 cardiac cycles associated with pulmonary AVMs. Shunt severity may be graded by the number of microbubbles appearing on a single frame. Higher grade shunts (>20-30 microbubbles per frame) have higher positive predictive values. Following a positive study, patients proceed to thoracic CT scans to determine anatomical features and suitability for embolisation treatment.

Other institutions, including our own, do not utilise CE routinely as the majority of studies are positive, and there are substantial time and resource implications. The new generations of CT scanners mean that a diagnosis of pulmonary AVMs can be made efficiently and quickly using a single thoracic CT scan which carries a radiation burden, but has the benefit of identifying additional pathology and embolisation contraindications, such as severe pulmonary hypertension.

Discussion continues regarding the degree to which a negative screen (by CT or CE) can be used to rule out small PAVMs which may nevertheless carry risks of dental bacteraemias and decompression illness during scuba diving. Current practice at our institution is to provide recommendations regarding dental hygiene to all HHT patients, and to refer divers for specialist advice and evaluation.
**Cerebral AVMs:**

Screening of asymptomatic patients for cerebral AVMs is recommended in many countries but remains controversial in others: Cerebral haemorrhages in HHT patients are usually life-changing and may be fatal. Conversely most HHT-related cerebral arteriovenous malformations will never bleed, and investigation and treatments carry risks. Both sets of considerations differ with the precise anatomy and location of the AVM. Other important considerations are that cerebral AVM are more common in HHT1 families³⁵ ³⁴ ³⁰,³³ {Sabba, 2007 #39; Lesca, 2007 #38, and that the lifelong risk of haemorrhage is greater for younger patients due to their longer predicted lifespan.

In the UK, we have followed the interpretation articulated by the late Pierre Lasjaunias, that risk-benefit considerations for asymptomatic cerebral AVMs are usually not interpreted in favour of treatment because the risks of intervention are too high for the low risk of haemorrhage {Lasjaunias, 2007 #55}. Thus up to 10% of screened individuals would be faced with the identification of cerebral AVMs for which no treatment or management options would be recommended at the current time. At our institution, we discuss these considerations openly with the patient and generally, cerebral MRI is not performed. However, for any individual with a family member who has had a cerebral haemorrhage, or where there is any concern regarding cerebral symptoms, a cerebral MRI is recommended in order to rule out chance inheritance of familial aneurysms (which carry a higher risk of haemorrhage ⁵⁶), or presence of an unstable, symptomatic cerebral AVM.

**Hepatic AVMs**
Screening considerations for hepatic AVMs in asymptomatic individuals differ from those for cerebral and pulmonary AVMs since hepatic AVM management is directed towards symptomatic patients who receive intensive medical treatment, with liver transplantation (which is effective in HHT) reserved for non responders. However, since there is a totally non invasive and effective screening tool (Doppler US), and because a correct diagnosis can help to clarify the diagnosis of HHT and improve subsequent patient management, screening of asymptomatic individuals for hepatic AVMs has been recommended.

Special considerations in pregnancy
The overwhelming majority of pregnancies in women with HHT proceed normally, but there are small risks of life-threatening maternal complications: in a recent series of 484 pregnancies, 1.02% (95% confidence intervals 0.13, 1.92%) resulted in a major PAVM bleed; 1.24% (0.25, 2.23%) in stroke (not all were HHT-related); and 1.00% (0.13, 1.92%) in maternal death. In British obstetric terminology, this renders HHT pregnancies high risk, for greater obstetric medical review than recommended for low risk pregnancies.

The data for and against screening asymptomatic women during pregnancy for pulmonary, cerebral or spinal AVMs were discussed in detail in the paper. The Anglo-French authors’ recommendations for their obstetric healthcare systems were in the absence of symptoms, to defer pulmonary AVM screens, only perform cerebral imaging if warranted by family history, and to consider spinal MRI where the possibility of spinal AVMs would lead obstetric anaesthetists to withhold epidural analgesia. There are strong opinions in other countries that asymptomatic women should be screened and treated for pulmonary AVMs during pregnancy. As a result, there are different practices between countries.
Children
Occasional children from HHT families have major complications from HHT, but the majority most have healthy childhoods, with or without nosebleeds, and usually without anaemia. AVMs may be present (cerebral AVMs usually develop perinatally and can bleed in childhood; pulmonary AVMs may develop in the pre pubertal period but complications in asymptomatic children must be extremely rare\(^\text{23}\)). There are few data regarding dedicated risk-benefit considerations for the paediatric population, particularly concerning their increased susceptibility to diagnostic radiation-induced morbidity from CT scans\(^{58-60}\) and angiography\(^{61}\). The ethics of screening an asymptomatic child, who is too young to give consent and will likely not understand the implications of testing, need also to be carefully be considered before proceeding. Institutions therefore differ in their screening regimes. Practice ranges from screening for all manifestations of HHT, to deferring screening in most asymptomatic children until post puberty unless dictated otherwise by family history.

TREATMENT AND CARE
Brief details of medical management are given in Table 2 for clinicians. Additional information is warranted for several points for clinicians and patients alike. Our practice is to provide this general advice for the whole family, with a particular focus for individual patients according to aspects of HHT known to affect them. This is particularly important when the presence of HHT would modify general clinical protocols for management of common conditions such as stroke, and prophylaxis against deep venous thrombosis (see below)
**Anaemia:** It is unusual to be able to abolish nasal and gastrointestinal bleeding. Prevention and management of anaemia becomes paramount in at least a third of HHT patients. Dietary advice for iron containing foods, and identification of oral iron preparations that suit the individual are important steps to reduce the need or frequency of transfusions or iron infusions required for severely affected individuals.

**Pulmonary AVMs:** Irrespective of size or symptoms, these carry risks of paradoxical embolic stroke and brain abscess which can be reduced or abolished by embolisation. Due to brain abscesses links with dental microorganisms, scrupulous dental hygiene, and antibiotic prophylaxis at the time of dental procedures has been recommended, and this advice has been recently confirmed by senior British dentists, recognising the differences between HHT/PAVM patients, and individuals at risk of infective endocarditis for whom prophylaxis was withdrawn.

**Stroke advice:** HHT-affected families should be aware in the event of stroke-like features, their doctors may need to be alerted to their three potential stroke types (haemorrhagic; ischaemic and brain abscess), leading to modification of local stroke management protocols.

**Liver evaluations:** Hepatic AVMs commonly lead to asymptomatic abnormalities in biochemical markers of cholestasis, and the benign condition of focal nodular hyperplasia. These are of little clinical importance but potentially could result in unnecessary diagnostic tests. HHT patients should be advised to exclude liver biopsy unless imaging has excluded hepatic AVMs.
Deep venous thrombosis prophylaxis: Prophylaxis against deep venous thromboses is often modified or withheld for patients with haemorrhagic conditions such as HHT. Recent data highlight that HHT-affected individuals are at risk for thrombotic events, and should be considered for full prophylaxis at appropriate times, particularly in periods following a pulmonary AVM-induced brain abscess 12.

Pregnancy: Irrespective of prior screening and treatment, obstetricians should be alerted to the presence of HHT for all women with HHT. Any haemoptysis or sudden severe dyspnoea should be considered a potential emergency prompting immediate hospital admission 56.

CONCLUSION
The diagnosis of HHT has been facilitated with the identification of several disease causing genes, but management of both symptomatic and asymptomatic individuals remains highly challenging for experienced specialists. Discussion of risks and complex risk-benefit analyses need to be handled sensitively and appropriately for age, family, cultural and national background. Major clinical and research hurdles remain if we are to be able to more closely predict and prevent likely pathology in a condition in which the majority of individuals will not have major complications.

SELF-HELP WEBSITES FOR HHT FAMILIES
Country and language-specific information for HHT patients and families is available via a number of websites. The EuroHHT Consortium plans an umbrella entry European website for 2009 (www.EuroHHT.com)

Denmark www.osler.dk
France www.amro-france.org
Acknowledgments

The authors thank Jamie McDonald (US), Elisabetta Buscarini (Italy), Kees Westermann (Netherlands) and Roberto Zarrabeitia (Spain) for reviewing and commenting on the manuscript; medical members of the EuroHHT consortium for helpful discussions including approval of the highlighted ^ statements by Gregor Bachmann-Harildstad (Norway), Elisabetta Buscarini (Italy), Sophie Dupuis-Girod (France), Anette Kjeldsen (Denmark), Pascal Lacombe (France), Henri Plauchu (France), Carlo Sabba (Italy), Kees Westermann (Netherlands), and Roberto Zarrabeitia (Spain); for specific pulmonary and neurovascular discussions, James Jackson (UK) and Pierre Lasjaunias (France); and for approval of paediatric statements Nicky Coote (UK) and Andrew Bush (UK). FSG is supported by a British Heart Foundation PhD studentship. CLS is grateful for support from the NIHR Biomedical Research Centre Funding Scheme, and thanks the British HHT families whose donations have supported HHT clinical research at Hammersmith Hospital.
LEGENDS TO FIGURES

**Figure 1: HHT images:** A) Fingertip and B) gastrointestinal telangiectasia (largest examples arrowed). C): 40X magnification of oral telangiectasis in individual with HHT compared to control (inset). Note thin wall denoted by arrow. D). Pulmonary AVMs (arrowed) pre (i) and post(ii) embolisation: Angiograms courtesy of Dr James Jackson.

**Figure 2. Circulatory explanation of HHT phenotypes.**
A) Schematic of systemic and pulmonary circulations demonstrating capillary beds in which HHT telangiectasia and AVMs occur. Note the pulmonary post capillary veins in direct communication with the left atrium, and portal vein (arrow) draining from gastrointestinal tract to liver acinus.

B) Illustration of two separate pathologies resulting in severe pulmonary hypertension in two women with HHT (reported in \(^{63}\)). Note Case 1 has markedly elevated intrinsic pulmonary vascular resistance, whereas this is near-normal in Case 2 who has hepatic AVM-associated high output cardiac failure characterised by elevated cardiac output, cardiac index (not shown) and left atrial pressure.

**Figure 3: Schematic representations of HHT1-4.**

A: **HHT1:** Summary of 311 ENG mutations reported to www.hhtmut.org. Note high proportion of out-of-frame mutations.

B) **HHT2:** Summary of 250 ACVRL1 mutations reported to www.hhtmut.org. Note higher frequency in exons 3, 7 and 8, and lower proportion of out-of-frame mutations.

C) **HHT3:** 6 Mb HHT3 interval defined by key recombinants (black bars) between D5S2011 and D5S2490. Uninformative regions are shown in dashed bars \(^{27}\). Ensembl predicts 29 genes in this interval.
D) **HHT4:** 7 Mb *HHT4* interval between *D7S2252* and *D7S510* \(^{28}\), Ensembl predicts 57 genes in this interval. Mb = mega base.

**Figure 4:** TGF-β signalling pathway. Endoglin can interact with both type I and type II receptors. The genes mutated in HHT are highlighted in bold.

**Figure 5:** Schematic of management approaches. Similar principles operate throughout most HHT specialised services. Further details are provided in the text.
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### Table 1: HHT genes.

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<td>SMAD4</td>
<td>Smad 4</td>
<td>NM 005359</td>
<td>MADH4</td>
<td>DPC4</td>
</tr>
<tr>
<td>HHT3</td>
<td>%601101</td>
<td>Type 3</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HHT4</td>
<td>%610655</td>
<td>Type 4</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2: HHT Clinical features and management overview

<table>
<thead>
<tr>
<th>Feature</th>
<th>%</th>
<th>Haem.</th>
<th>Other complications</th>
<th>Management if symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Curacao Criteria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Iron deficiency anaemia</td>
<td></td>
</tr>
<tr>
<td>Mucocutaneous</td>
<td>80</td>
<td>++</td>
<td></td>
<td>Laser or other ablation therapies</td>
</tr>
<tr>
<td>telangiectasia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>20</td>
<td>+++</td>
<td>(chronic)</td>
<td>Iron +/- transfusions for anaemia. Gastroenterology: Repeated laser therapy; surgery or embolisation for emergency control</td>
</tr>
<tr>
<td>telangiectasia</td>
<td></td>
<td></td>
<td>Iron deficiency anaemia</td>
<td></td>
</tr>
<tr>
<td>Pulmonary AVMs</td>
<td>50</td>
<td>+</td>
<td></td>
<td>Embolisation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Right-to-left shunt:</strong> dyspnoea, stroke/ TIA; brain abscess; migraine; decompression illness</td>
<td>Dental hygiene and prophylactic antibiotics Caution against scuba diving</td>
</tr>
<tr>
<td>Cerebral AVMs</td>
<td>10</td>
<td>++</td>
<td><strong>Space occupying lesion +/- vascular steal:</strong> headache, fit</td>
<td>Cerebral MRI. Refer to neurology for multidisciplinary evaluation of risk-benefits of treatment in an experienced centre</td>
</tr>
<tr>
<td>Hepatic AVMs</td>
<td>≥30</td>
<td></td>
<td><strong>Left to right shunt:</strong> high output cardiac heart failure; pulmonary hypertension. <strong>Hepato-portal shunt:</strong> portal hypertension. <strong>Porto-hepatic shunt:</strong> biliary ischaemia, encephalopathy</td>
<td>Refer to specialised hepatology services for intensive medical management: liver transplantation is the treatment of choice if symptoms fail to respond to medical treatment</td>
</tr>
<tr>
<td>Spinal AVMs</td>
<td>&lt;1</td>
<td>++</td>
<td>Pain, asymmetric growth</td>
<td>Spinal MRI. Refer to neurology for multidisciplinary evaluation of risk-benefits of treatment in an experienced centre</td>
</tr>
</tbody>
</table>
### Non criterion manifestations

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Prevalence</th>
<th>Symptoms</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juvenile polyposis (Smad4)</td>
<td>&lt;1</td>
<td>Haemorrhage, malignancy</td>
<td>Refer to Gastroenterology, and follow national surveillance guidelines such as 11</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>&lt;2</td>
<td>Dyspnoea, right heart failure</td>
<td>Refer to Cardiorespiratory; Exclude hepatic AVMs; if present, consider liver transplant</td>
</tr>
<tr>
<td>Prothrombotic state 12</td>
<td></td>
<td>Deep venous thrombosis, pulmonary emboli</td>
<td>As per national guidelines eg 13</td>
</tr>
<tr>
<td>Immune dysfunction 14</td>
<td></td>
<td>Uncertain</td>
<td></td>
</tr>
</tbody>
</table>

**Legend**: %: Estimated prevalence across all age groups. Haem: haemorrhage frequency scale 0 to ++++. ± Ensure not prothrombotic first. 12. Further agents are undergoing clinical evaluation, particularly in the setting of severe gastrointestinal and nasal haemorrhage. Shunt anatomy: right-to-left: pulmonary artery to pulmonary vein, left-to-right: hepatic artery to hepatic vein, Hepato-portal: hepatic artery to portal vein; Porto-hepatic: portal vein to hepatic vein. * Recommended in Europe in certain circumstances (see text).
Figure 1
Figure 2

A

B

<table>
<thead>
<tr>
<th></th>
<th>Pulmonary artery pressure (systolic PAP) mm/Hg</th>
<th>Pulmonary wedge (left atrial) pressure (mm/Hg)</th>
<th>Cardiac output (left and right ventricles) litres/minute</th>
<th>Intrinsic pulmonary vascular resistance (dyn sec/ cm5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal</strong></td>
<td>&lt;26</td>
<td>&lt;13</td>
<td>4-5</td>
<td>&lt; 99</td>
</tr>
<tr>
<td><strong>Case 1:</strong> Pulmonary arterial hypertension</td>
<td>80</td>
<td>2</td>
<td>3.3</td>
<td>1160</td>
</tr>
<tr>
<td><strong>Case 2:</strong> Post capillary PH secondary to hepatic AVM-related high output cardiac failure</td>
<td>74</td>
<td>17</td>
<td>7.0</td>
<td>272</td>
</tr>
</tbody>
</table>
Figure 3

Ai

Endoglin protein

extracellular domain

cytoplasmic domain

Number of different mutations

ENG exons

Aiii

DSS2011

DSS402

DSS436

DSS2490

Mb

135 141 142 143 144 145 146 147 152 153 160

II.1

II.3

III.7

HHT3

Gene legend

Ensembl Novel Pseudogene

Ensembl Novel Protein Coding

Known Novel Protein Coding

RNA pseudogene (Novel)

RNA pseudogene (Novel)

Aii

ALK-1 protein

cytoplasmic domain

Number of different mutations

ACVRL1 exons

Aiv

D7S2252

D7SS10

Mb

32 33 34 35 36 37 38 39

HHT4
Figure 4

Smad-dependent

Ligand
Activins
Inhibins
Nodals
GDFs
ActRII/IIB
ALK4,7
ALK5 (TβRII)
ALK1
ALK2, ALK3, ALK6
Smad2
Smad3
Smad6
Smad7
Smad1
Smad5
Smad8
Smad4

Co-activators
Co-repressors

Smad-independent

Ligands
Erk, JNK, MAPK kinase, Rho GTPase pathways
Figure 5

Clinical assessment and detailed family history

Identify **symptoms** needing specialist management

Arrange **screening** for asymptomatic manifestations according to **local** practice

Clinical HHT diagnosis

Information to patient

Consider molecular tests

Opportunity for follow up

Family screen

Refer to organ-specific specialist(s)

Optimise management of HHT features present