Hereditary haemorrhagic telangiectasia (HHT, Osler-Weber-Rendu syndrome): a view from the 21st century

M E Begbie, G M F Wallace, C L Shovlin

Hereditary haemorrhagic telangiectasia (HHT) affects one in 5–8000, and no longer can be viewed as solely causing anaemia (due to nasal and gastrointestinal bleeding) and characteristic mucocutaneous telangiectasia. Arteriovenous malformations commonly occur, and in the pulmonary and cerebral circulations demand knowledge of risks and benefits of asymptomatic screening and treatment. HHT is inherited as an autosomal dominant trait and there is no age cut off when apparently unaffected offspring of an individual with HHT can be told they are unaffected. This review focuses on the evolving evidence base for HHT management, issues regarding pregnancy and prothrombotic treatments, and discusses the molecular and cellular changes that underlie this disease.

Hereditary haemorrhagic telangiectasia (HHT, Osler-Weber-Rendu syndrome) has been subject to under-reporting for many years. Recent careful epidemiological studies in France, Denmark, and Japan, however, reveal an incidence of one in 5–8000. Individuals with HHT present to a wide range of specialties spanning medical, surgical, and general practice disciplines. Advances in medical practice mean that an expectant approach to management is no longer appropriate, and patients are increasingly aware of this through patient self help websites (see end of article). However, many specialists lack appreciation of the full range of consequences of diagnosis for patients and their families, and still view HHT as a “rare” disease, compounded by the generally poor recognition of cases.

In this article we highlight the modern view of HHT. We also cover the scientific background of a disease which features prominently in postgraduate medical examinations due to the ready availability of outpatient with classical stigmata (a recent survey indicated that HHT occurred in approximately one in 20 short case examinations for MRCP).1

OVERVIEW OF HHT: THE DIFFERENCES BETWEEN 19TH CENTURY AND MODERN VIEWS OF HHT

Historical view
HHT was first recognised in the 19th century as a familial disorder causing nose bleeds, gastrointestinal bleeding, and abnormal vascular structures. Later descriptions by Osler, Weber, and Hanes brought the disorder to the attention of the general medical community. These resulted in the eponym Osler-Weber-Rendu syndrome, although Hanes’ suggestion of hereditary haemorrhagic telangiectasia is often preferred. The combination of nose bleeds, gastrointestinal bleeding, and iron deficiency anaemia associated with characteristic telangiectasia on the lips, oral mucosa, and fingertips (fig 1) has become firmly established as a medical entity. Yet this constitutes only “19th century HHT” (fig 2), and may not be evident in HHT patients who still have life threatening manifestations of disease.

Modern view of HHT
By the 1940s, additional abnormal vessels were being described in HHT, particularly arteriovenous malformations (AVMs) of the pulmonary, hepatic, and cerebral circulations. Initially it was suspected that such involvement was rare, but this was based on the frequency of asymptomatic presentation to an astute practitioner. With the onset of asymptomatic screening programmes for clinical or research purposes, a much higher frequency of involvement was seen. We now estimate that at least 30% of HHT patients have pulmonary involvement, 30% hepatic involvement, and 10%–20% cerebral involvement. Faced with such high figures, there is a reasoned debate regarding the extent to which these studies have overestimated risk based on screening of preselected “severe” HHT populations (that is, relatives of patients with a pulmonary AVM) or screening tests with high false positive rates. However, the figures in fig 2 provide a fair reflection of data currently available.

It is recognised that the manifestations of HHT are not present generally at birth, but develop with increasing age such that nasal bleeds are usually the earliest sign of disease, often occurring in childhood, pulmonary AVMs becoming apparent from puberty, with mucocutaneous and gastrointestinal telangiectasia developing progressively with age (fig 3). Data suggest that by the age of 16 years, 71% of individuals will have developed some sign of HHT, rising to over 90% by

Abbreviations: AVM, arteriovenous malformation; HHT, hereditary haemorrhagic telangiectasia; MRI, magnetic resonance imaging; TGF-β, transforming growth factor-β
the age of 40 years. However these data mean that during their childbearing years, an apparently unaffected child of an HHT patient still has a 5%–20% chance of actually carrying the HHT disease gene.

DIAGNOSIS OF HHT

Not every individual with recurrent nose bleeds, even familial nose bleeds, will have HHT yet as indicated below, it is important that the diagnosis of HHT is considered in such cases. To permit a high level of clinical suspicion without leading to overdiagnosis, recent international consensus diagnostic criteria were developed based on the four criteria of spontaneous recurrent nosebleeds, mucocutaneous telangiectasia, visceral involvement, and an affected first degree relative. These define “definite HHT” where three criteria are present, “possible” or “suspected” if two criteria are present, or “unlikely” if fewer than two criteria are present.

Criteria

1. Epistaxis: spontaneous, recurrent nose bleeds.
2. Telangiectases multiple, at characteristic sites:
   - Lips.
   - Oral cavity.
   - Fingers.
   - Nose.
3. Vascular lesions such as:
   - Gastrointestinal telangiectasia (with or without bleeding).
   - Pulmonary AVM.
   - Hepatic AVM.
   - Cerebral AVM.
   - Spinal AVM.
4. Family history a first degree relative with HHT according to these criteria.

All offspring of an individual with HHT are at risk of having the disease since HHT may not manifest until late in life. If there is any concern regarding the presence of physical signs, an experienced physician should be consulted. Coagulation disorders should be excluded. The presence of visceral abnormalities in children should prompt a particularly careful check of other family members. These criteria are likely to be further refined as molecular diagnostic tests become available in the next few years.

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CLINICAL FEATURES OF HHT

Nose bleeds

Spontaneous recurrent nose bleeds from telangiectasia of the nasal mucosa are the most common clinical manifestation of HHT. While some patients will have only occasional nose bleeds, others will experience significant bleeds on a daily basis. Many patients require no treatment other than iron supplementation by diet and oral supplements, whereas others may require transfusions and emergency nasal packing. A number of topical, systemic, and surgical treatments are available (table 1), and in expert hands there are uncontrolled data that each appears to reduce bleeding, though responses are variable. Cauterisation is best avoided due to damage of nasal mucosa prompting vascular regrowth. The adage “to do as little as possible for as long as possible” is taking hold in HHT circles, and treatments are generally directed to patients either experiencing massive haemorrhages, or experiencing daily nose bleeds. Systemic treatments have also been introduced, and are discussed with gastrointestinal haemorrhage below.

Figure 1 Classical HHT. (A) sparse telangiectasia on lips and (B) more extensive on conjunctiva.

Figure 2 The changing face of HHT. The familial basis of HHT was recognised in both settings.

Figure 3 Age of onset of HHT features. Symptomatic HHT data points (circled) derived from references 20–22. PAVM (pulmonary AVM) and CAVM (cerebral AVM) figures highly approximated.
Gastrointestinal haemorrhage

This probably contributes less frequently to iron deficiency than under-recognised nose bleeds; in many patients, improvement in nasal haemorrhage is able to significantly reduce iron and transfusion requirements. However, recurrent gastrointestinal tract haemorrhage occurs in a substantial group of patients. The onset is usually from the fifth or sixth decade. Telangiectasia occur throughout the gastrointestinal tract, and are more common in the stomach or duodenum, than in the colon. They are visualised by endoscopy and are similar in size and appearance to mucocutaneous telangiectases but may be surrounded by an anaemic halo. Less commonly AVMs and aneurysms may occur, depicted by gastrointestinal angiography.

Most patients are satisfactorily managed conservatively with oral iron therapy and, if necessary, blood transfusions. Repeated laser therapy may also be used to control bleeding in the short term, though results are not as good as in the non-HHT population. Surgery has limited success due to recurrent disease, but may be useful for emergency control of haemorrhage from discrete lesions, as may embolisation. Antihaeorrhagic medical treatments have been sought. The only therapy supported by evidence from randomised controlled trials is the use of female hormones (50 µg ethinylestradiol and 1 µg norethisterone) in heavily transfusion-dependent patients. Additional manoeuvres are discussed below in the “Current debates” section.

Mucocutaneous telangiectasia

Telangiectases of the skin and buccal mucosa occur in about 75% of individuals, typically presenting later in life than epistaxis from about the third decade of life, and increasing in size and number with age. They mostly occur on the face, lips, tongue and buccal mucosa, and fingertips, but can occur elsewhere. They may bleed but this is rarely clinically important and the main concern is cosmetic, when short term benefits of laser or other ablation therapies may be obtained.

Pulmonary AVMs

Pulmonary AVMs are thin walled abnormal vessels that replace normal capillaries between the pulmonary arterial and venous circulations, often resulting in bulbous sac-like structures (fig 4A). They provide a direct capillary-free communication between the pulmonary and systemic circulations with three main clinical consequences:

• Pulmonary arterial blood passing through these right-to-left shunts cannot be oxygenated, leading to hypoxaemia.

• The absence of a filtering capillary bed allows particulate matter to reach the systemic circulation where it impacts in other capillary beds, causing clinical sequelae particularly in the cerebral circulation.

• The fragile vessels may haemorrhage into a bronchus or the pleural cavity.

Patients with clinically silent pulmonary AVMs are still at risk of haemorrhage, and more commonly neurological sequelae due to paradoxical embolism. Catastrophic embolic cerebral events (cerebral abscess and embolic stroke), and transient ischaemic attacks occur in patients regardless of the degree of respiratory symptoms and still carry significant morbidity and mortality. Indeed, in published series of approximately 400 patients the majority of pulmonary AVM patients had no respiratory symptoms, and, only a third of affected individuals exhibited physical signs indicating a massive right-to-left shunt (cyanosis, clubbing, and polycythaemia; see table 2), implying that pulmonary AVM complications can be limited if the condition is recognised and treated, with transcatheter embolotherapy offering the safest methods of treatment. In experienced centres, there are proved long term physiological benefits of embolisation, with excellent safety profiles, and this has supported the trend towards earlier treatment of the asymptomatic patient, accompanied by clinical screening of high risk groups. In addition, prophylactic antibiotics are recommended at the time of dental and surgical procedures to reduce the risk of brain abscess (fig 4B).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Treatment options for epistaxis</th>
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<tr>
<th>Modality</th>
<th>Data from RCTs</th>
<th>Data from case reports/uncontrolled series</th>
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<tbody>
<tr>
<td>Laser: argon, Nd:YAG</td>
<td>None</td>
<td>Short term success in expert hands</td>
</tr>
<tr>
<td>Cauterisation</td>
<td>Not recommended due to local tissue damage</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septal dermatoplasty</td>
<td>None</td>
<td>May be beneficial</td>
</tr>
<tr>
<td>Septal closure</td>
<td>None</td>
<td>Beneficial if tolerated</td>
</tr>
<tr>
<td>Arterial ligation</td>
<td>None</td>
<td>Case reports only, long term effects unknown</td>
</tr>
<tr>
<td>Embolisation</td>
<td>None</td>
<td>Anecdotal only: short term benefits (7–1 year)</td>
</tr>
<tr>
<td>Systemic therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oestrogen-progesterone</td>
<td>Beneficial in heavily transfusion-dependent patients</td>
<td></td>
</tr>
<tr>
<td>Tranexamic acid and antifibrinolytics</td>
<td>None</td>
<td>Short term benefit and risks unknown (see debate)</td>
</tr>
<tr>
<td>Topical therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal sprays and creams</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

RCTs, randomised controlled trials.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Complications of untreated pulmonary AVMs</th>
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<tr>
<th>Feature</th>
<th>Mean (%)</th>
<th>Range (%)</th>
<th>No of cases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>49</td>
<td>25–58</td>
<td>260</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>49</td>
<td>27–71</td>
<td>483</td>
</tr>
<tr>
<td>Chest pain</td>
<td>14</td>
<td>6–18</td>
<td>198</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>11</td>
<td>4–18</td>
<td>479</td>
</tr>
<tr>
<td>Haemotherax</td>
<td>&lt;1</td>
<td>0–2</td>
<td>192</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>30</td>
<td>9–73</td>
<td>275</td>
</tr>
<tr>
<td>Clubbing</td>
<td>32</td>
<td>6–68</td>
<td>267</td>
</tr>
<tr>
<td>Bruit</td>
<td>49</td>
<td>25–58</td>
<td>263</td>
</tr>
<tr>
<td>Cerebral abscess</td>
<td>9</td>
<td>0–25</td>
<td>368</td>
</tr>
<tr>
<td>CVA or TIA</td>
<td>27</td>
<td>11–55</td>
<td>401</td>
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*Number of published cases in which frequency of feature assessed. CVA, cerebrovascular accident; TIA, transient ischaemic attack.

www.postgradmedj.com
Significant clinical concerns remain however. First, many patients with pulmonary AVMs remain under regular follow up in respiratory units without consideration of intervention. Second, published and anecdotal data suggests higher rates of complications in inexperienced hands. These include periprocedural events and long term development of systemic arterial feeders to the sac resulting in catastrophic haemorrhage, but this is not widely recognised. Finally, modern detection methods reveal more disease than is treatable with today’s technologies and much of current management lies in the long term prevention of cerebral embolic events in patients with residual disease following maximal embolotherapy.

**Cerebral AVMs**

HHT patients may have cerebral involvement with telangiectases, cerebral AVMs, aneurysms, or cavernous angiomas. Most complications arise from cerebral AVMs that are thought to affect more than 10% of HHT patients. They can lead to headache, seizures, ischaemia of the surrounding tissue due to a steal effect, or haemorrhage. Haemorrhage usually has devastating effects (significant long term morbidity after cerebral AVM rupture in the non-HHT population is quoted as 53%–81%), and patients with symptoms suggestive of cerebral AVMs deserve further assessment as in the non-HHT population, including non-invasive imaging and ultimately assessment by experienced neurointerventional centres. Cerebral magnetic resonance imaging (MRI) is currently the most sensitive non-invasive test, though will fail to detect a significant proportion of AVMs, and generally should not be performed in patients with pulmonary AVMs embolised with non-MRI compatible coils (the majority until the late 1990s). The question of whether asymptomatic HHT patients should be screened for cerebral AVM remains hotly debated and is discussed below.

**Hepatic involvement**

Silent hepatic involvement occurs in up to 30% of patients, though symptomatic involvement is much less frequent, with fewer than 100 patients reported in worldwide series. When patients do present it is usually with high output heart failure, portal hypertension, or biliary disease, reflecting different patterns of vascular involvement. Hyperdynamic circulations, and less commonly high output cardiac failure and steal syndromes causing aniga result from large AVMs between the hepatic artery and vein, causing a substantial left to right shunt. Portal hypertension and hepatic encephalopathy particularly after gastrointestinal tract bleeding may result from shunts between the hepatic vein and portal vein, and more commonly appear to result from increased sinusoidal blood flow (that may in turn lead to increased deposition of fibrous tissue and pseudocirrhosis of the liver). Hepatic AVMs, suspected by hepatomegaly, a liver bruist, or abnormal liver function tests can be diagnosed by angiography, computed tomography, MRI, or Doppler sonography.

The treatment of hepatic AVMs has changed in the last two to three years. Embolisation of feeding vessels used to be performed-but after several cases of fatal hepatic necrosis, HHT physicians in the United States have placed a moratorium on this treatment unless supported by a liver transplantation programme. In the rare cases when acute hepatic failure develops, liver transplantation may be life saving.

**HOW TO MANAGE THE HHT PATIENT**

The majority of patients with HHT will still effectively have “19th century” HHT, experiencing only nose bleeds, mucocutaneous telangiectasia, and a tendency to iron deficiency anaemia. For HHT patients who do not present spontaneously to medical practitioners before the age of 60 years, there is no excess mortality. However, there is significant morbidity and mortality in younger patients, predominantly attributed to the consequences of visceral involvement, particularly pulmonary and cerebral involvement leading to early onset strokes and brain abscess.

General principles of HHT management are illustrated in box 2 overleaf.

**Special circumstances and debated topics in HHT**

**The pregnant HHT patient**

Pregnancy poses a risk to a small proportion of women with HHT, and individual patients may need to be cautioned against pregnancy on a case-by-case basis. However, for the majority of patients, pregnancy is uneventful. The patient should be aware that any offspring will have a 50% risk of inheriting HHT, that there may be complications due to enlargement of pulmonary AVMs, and that as spinal AVMs affect perhaps as many as 1%–2% of HHT patients, many anaesthetists will not perform epidural analgesia for HHT mothers unless MRI scans have excluded this possibility. Otherwise, anecdotal data suggests nose bleeds may get worse, and skin telangiectasia become more prominent, with no firm data regarding effects on hepatic and cerebral AVMs.

Medical practitioners should be aware that any pulmonary AVMs will enlarge during pregnancy, and fatal haemorrhage from maternal pulmonary AVMs has been described. Women with HHT should be screened for pulmonary AVMs and treated maximally before pregnancy, though treatment may...
be safely undertaken in late pregnancy if required.  Any haemoptysis should be seen as a medical emergency and prompt immediate admission.

Should asymptomatic patients be screened for cerebral AVMs?

The question of whether asymptomatic HHT patients should be screened for cerebral AVMs remains hotly debated since diagnostic and interventional modalities carry significant risks, and many believe cerebral AVMs identified in an asymptomatic HHT population by screening to have a lower rate of haemorrhage than those in other populations.  The North American and European management approaches to individuals with HHT differ markedly.  Many centres in North America advocate and practice screening of HHT neonates, whereas screening is not performed in the majority of European centres.  This is a difficult issue in patient management as many patients will access US based websites.  However, all patients should be aware that the risk-benefit of asymptomatic screening is by no means clear cut and remains the subject of intense scrutiny on both sides of the Atlantic.

How safe is it to use hormones and antifibrinolytics to modify the haemorrhagic phenotype?

In a double blind randomised controlled trial, 50 μg ethinylestradiol and 1 mg norethisterone resulted in a significant reduction in transfusion requirements in 10 patients with a mean transfusion requirement of 19.4 packed cells units per year.  These data have been extrapolated in clinical practice to patients with lesser degrees of haemorrhage not necessarily associated with regular transfusion requirements.  The use of higher dose conjugated oestrogens in the “hormone replacement” range of over 625 μg ethinylestradiol equivalent, or prothrombotic agents such as tranexamic acid and aminocaproic acid are also widespread in management of HHT-related bleeding, though not supported by data from randomised controlled trials.  However, it should be remembered that HHT patients are at risk of thromboembolic disease, and in our experience there is concern that these practices may increase the risk of thrombotic events in HHT patients.

How safe is it to ascribe unusual presentations to rare complications of HHT?

As potential complications of HHT become better appreciated, there is the genuine concern that HHT patients may not undergo the full range of diagnostic investigations for particular clinical presentations.  It is crucial that assessments are based on an appreciation of the likely frequency of HHT complications and possible rare complications and possible complications associated with current management.  Even for lower gastrointestinal bleeding, at least one colonoscopy to exclude a malignant aetiology is usually warranted.

MOLECULAR AND CELLULAR BASIS OF HHT

HHT is inherited as an autosomal dominant trait with varying penetrance and expressivity.  Mutations in two genes, endoglin and ALK-1, have been shown to be responsible for HHT, with the disease subtypes designated HHT1 and HHT2, respectively.  The search for a third disease locus in families shown to map to neither of these loci is ongoing.  The search for a third disease locus in families shown to map to neither of these loci is ongoing.  The search for a third disease locus in families shown to map to neither of these loci is ongoing.

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ongoing.  Confirmation that endoglin mutations are causative is available from experiments in transgenic mice.  Some mice carrying one normal and one mutated copy of the endoglin gene (that is, endoglin−/− heterozygotes) display features of HHT.  Endoglin and ALK-1 encode proteins expressed on vascular endothelial cells.  Most gene products resulting from HHT causing mutations in these genes are unstable at the level of mRNA or protein, and it has been shown that endothelial cells derived from HHT1 or HHT2 patients express approximately one half of the normal endoglin or ALK-1 levels, respectively. Therefore it is believed that in most if not all cases, HHT results from endoglin or ALK-1 haploinsufficiency—that is, lack of sufficient protein for normal function.  As endothelial cells derived directly from arteriovenous malformations also express half the normal levels of endoglin, these malformations do not appear to be due to an additional local loss of endoglin expression due to a “second hit”.

How do mutations in endoglin and ALK-1 result in HHT?

These genes encode proteins that are involved with signalling by the transforming growth factor-beta (TGF-β) superfamily. This group of peptide growth factors includes TGF-βs, activins, and the bone morphogenetic proteins, which affect cellular growth and differentiation through signal transduction cascades from transmembrane receptor complexes (for review, see Heldin et al44). Generally, type II TGF-β receptors bind the ligand directly, recruit and activate type I receptors that activate downstream cytoplasmic signalling molecules including SMADs. SMADs then bind into complexes and translocate to the nucleus, where they modulate the expression of target genes through direct binding to DNA.

As ALK-1 is a TGF-β superfamily type I receptor, and endoglin associates with different signalling receptors and can modify TGF-β1 signalling, it is expected that the abnormal vessels in HHT develop because of aberrant TGF-β signalling at some stage during vascular development and homeostasis. Endoglin and ALK-1 work together to play specific parts in governing cellular responses such as proliferation and adhesion induced by members of the TGF-β superfamily. As other HHT disease genes are identified, these will also likely play a part in this signalling pathway possibly either as ligands, receptors, or downstream transducers of TGF-β family member signals.
However, understanding whether patients have endoglin or ALK-1 mutations does not allow a strong prediction of the likely course of HHT since all features of HHT can be seen in both HHT1 and HHT2. The different pattern of disease in different members of the same families in man (and in the mouse models) suggest that other genetic and environmental influences modify the HHT phenotype. Understanding these modifications will be critical to furthering our understanding of the development of the vascular lesions in HHT, and may help our understanding of the pathways by which normal vascular integrity is maintained.

ACKNOWLEDGEMENTS
We thank Dr James Jackson FRCC, MRCP for performing the pulmonary angiogram illustrated in fig 4A, and Mr William Grant FRCS, for helpful comments on the manuscript.

MULTIPLE CHOICE QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AT END OF REFERENCES)
Q1. Hereditary haemorrhagic telangiectasia (HHT), Osler-Weber-Rendu syndrome:
(A) Affects approximately one in 100 000 individuals
(B) Can be safely ignored in the patient who just has nose bleeds
(C) Is only life threatening with a patient with nose bleeds and facial telangiectasia
(D) Does not influence mortality in epidemiological studies of the over 60s
(E) Frequently causes early onset strokes

Q2. A child of an individual with HHT:
(A) Can be told they do not have HHT if they show no manifestation of the disease by the age of 30
(B) Has a one in two chance of developing HHT
(C) If develops HHT, is likely to have the same type of HHT as their parent
(D) Has definite HHT if they develop nose bleeds
(E) Does not require medical review if they do not have nose bleeds

Q3. An individual with HHT complains of feeling generally unwell. Possible diagnoses to consider are:
(A) Anaemia
(B) Hypoxaemia
(C) Recent onset stroke
(D) Liver disease
(E) Transient ischaemic attacks

Q4. Patients who are fit and well with HHT should be screened for:
(A) Gastrointestinal telangiectasia
(B) Pulmonary AVMs
(C) Cerebral AVMs
(D) Hepatic AVMs
(E) Spinal AVMs

Q5. The science of HHT:
(A) HHT develops in the presence of only a single abnormal mutated gene
(B) The genes mutated in HHT are implicated in signalling by fibroblast growth factor
(C) The genes mutated in HHT allow prediction of the pattern of HHT in the individual
(D) No environmental modifiers of HHT have been found to date
(E) The disease genes in HHT are likely to be the only genetic factors influencing the HHT phenotype

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REFERENCES

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ANSWERS

Q1. (A) F (one in 8000), (B) F (needs pulmonary AVM screening), (C) F, (D) T, (E) T. Q2. (A) F, (B) T, (C) F, (D) F (only suspected HHT), (E) F. Q3. (A) T, (B) T, (C) T, (D) T, (E) T. Q4. (A) F, (B) T, (C) do not know; subject remains topic for debate, (D) F, (E) F, though there may be special circumstances, such as epidural analgesia when this might be considered. Q5. (A) T, (B) F, (C) F, (D) F (pregnancy precipitates pulmonary AVM development), (E) F.
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