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REVIEW

Hereditary haemorrhagic telangiectasia: an overview from an ear, nose and throat perspective

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Abstract

Patients with hereditary haemorrhagic telangiectasia can present with a multitude of symptoms caused by telangiectasia and arteriovenous malformations in the nose, brain, gastrointestinal tract, liver and spinal cord. Clinicians should be aware of the potential diagnosis of hereditary haemorrhagic telangiectasia and how to manage these patients both in the acute and chronic setting. Identifying these patients and optimising their management can help reverse the reduced life expectancy back to that of the normal population.

The management of these patients is complex and often requires a multidisciplinary approach, with difficult discussions to be had around screening for arteriovenous malformations and genetic testing. The stepwise management ladder can be used in both the medical and surgical strategies; there are multiple pharmacological and surgical options available, all with their own side effects and risks.

Patient education is key to help informed decision making. This article outlines the clinical characteristics of the disease and management options available.

Key words: Arteriovenous malformations; Epistaxis; Genetic testing; Hereditary haemorrhagic; Lasers; Solid state; Telangectasia

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Introduction

Hereditary haemorrhagic telangiectasia is a genetic condition that typically presents to ear, nose and throat surgeons as a result of the propensity of frequent epistaxis. However, the vascular anomalies are not always restricted to the nose, but may affect the brain, lungs, intestines, liver and spinal cord. Therefore, it requires truly multidisciplinary management. Recurrent epistaxis may be one of the most predominant symptoms, but knowledge of how hereditary haemorrhagic telangiectasia affects other organ systems is important for all specialists who may come across patients with this condition.

This article raises awareness among clinicians and provides a comprehensive overview of how to manage these patients in the acute and chronic setting. By identifying hereditary haemorrhagic telangiectasia and optimising management, the reduced life expectancy can often be extended back to normal (Donaldson et al, 2015).

Epidemiology and pathogenesis

Hereditary haemorrhagic telangiectasia is an autosomal dominant genetic disorder affecting 1 in 5000 people. Significantly fewer cases than this are seen clinically, with many patients going undiagnosed for years before referral (Dakeishi et al, 2002). Hereditary haemorrhagic telangiectasia is characterised by telangiectasia and arteriovenous malformations. Small telangiectasia can lead to large arteriovenous malformations as a result of vascular remodelling (Shovlin, 2010). The generation of telangiectasia and arteriovenous malformations is thought to be caused by activation of quiescent endothelial cells by an angiogenesis stimulant or cell injury. This leads to excessive proliferation of endothelial cells associated with impaired recruitment of vascular mural cells to vessel walls (Shovlin, 2010).

It affects both children and adults, and men and women are affected equally. There is substantial variation in disease expression, even between members of the same family.

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At present five different types of hereditary haemorrhagic telangiectasia gene mutations are recognised: the two most common mutations are ENG (Endoglin), found in patients with hereditary haemorrhagic telangiectasia type 1 and ACVRL1/ALK1, found in patients with hereditary haemorrhagic telangiectasia type 2 (Johnson et al, 1996). Patients with ENG have more frequent pulmonary and cerebral arteriovenous malformations whereas those with ALK1 will have more frequent hepatic arteriovenous malformations (Letteboer et al, 2005).

The disorder was originally known as Osler–Weber–Rendu syndrome, and it was thought to be limited to just the nasal cavity and respiratory systems. This is now known not to be true as patients can present with a multitude of symptoms caused by vascular lesions in the brain, gastrointestinal tract, liver and spinal cord. Many patients still experience delay in recognition and diagnosis.

Clinical characteristics

The Curacao classification provides clinicians with a diagnostic tool for identifying patients with possible hereditary haemorrhagic telangiectasia who can then be referred for genetic testing to establish the diagnosis (Shovlin et al, 2000). Criteria include epistaxis, telangiectases, visceral lesions and a first degree family relative (Table 1).

The presence of three or more criteria is considered a 'definite' diagnosis; two criteria equate to a 'possible or suspected' diagnosis; one or no criterion makes a diagnosis of hereditary haemorrhagic telangiectasia unlikely (Shovlin et al, 2000). An overview of the diagnosis and management of hereditary haemorrhagic telangiectasia is covered in the latest international guidelines (Faughnan et al, 2020).

Epistaxis

The most common symptom described by patients is epistaxis and up to 90% experience repeated episodes (Guttmacher et al, 1995). Telangiectasias develop (Figure 1) and get worse with age

Table 1. The Curacao classification

Criteria	Description
Epistaxis	Spontaneous and recurrent
Telangiectases or telangiectasias	Multiple, at characteristic sites: lips, oral cavity, fingers, nose
Visceral lesions	Gastrointestinal telangiectasias, pulmonary, hepatic, cerebral or spinal arteriovenous malformations
Family history	A first degree relative with hereditary haemorrhagic telangiectasia according to these criteria

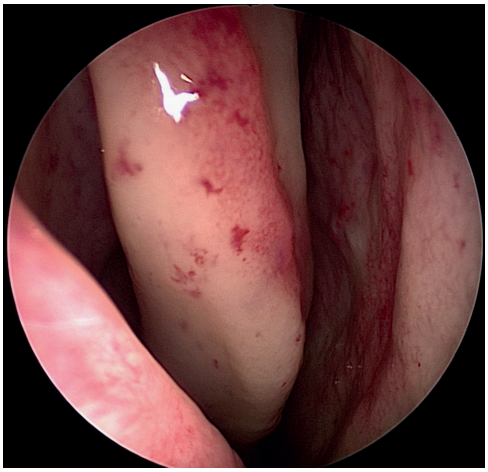

Figure 1. Endoscopic image of telangiectasia in the nasal cavity.

and, combined with delayed diagnosis, patients with hereditary haemorrhagic telangiectasia often present later in life (Pasculli et al, 2004). Nosebleeds vary from light to profuse bleeds that necessitate hospital admission, interventional treatment and sometimes blood transfusion.

A useful clinical tool to assess and monitor the severity of bleeding is the calculated Epistaxis Severity Score, this can be accessed at https://curehht.org/understanding-hht/diagnosis-treatment/nosebleed-severity-score/ (Hoag et al, 2010).

Lung

Pulmonary arteriovenous malformations are found in up to half of patients with hereditary haemorrhagic telangiectasia (Cottin et al, 2004). There is a reduction in alveolar gas exchange and an increased risk of embolic and infective cerebral events with a pulmonary arteriovenous malformation. Hereditary haemorrhagic telangiectasia patients with pulmonary arteriovenous malformations are several hundred-fold more likely to develop a brain abscess compared to the general population (Kjeldsen et al, 2014). In a study of patients referred for pulmonary arteriovenous malformation embolotherapy, 40% reported a prior transient ischaemic attack and 18% had experienced a clinical stroke (White et al, 1988).

Most patients are asymptomatic but pulmonary arteriovenous malformations in patients with hereditary haemorrhagic telangiectasia may cause dyspnoea, but occasionally spontaneous rupture leads to massive haemoptysis or haemothorax (1–8%) (Ference et al, 1994).

Patients with haemoptysis should seek urgent medical assistance, especially during pregnancy, to exclude the possibility of pulmonary arteriovenous malformation rupture before the onset of massive haemorrhage.

Pulmonary hypertension is relatively common in hereditary haemorrhagic telangiectasia (8–23%), and may progress to right-sided heart failure and lead to a poor prognosis (Trembath et al, 2001).

Brain

Cerebrovascular malformations affect around 10% of patients with hereditary haemorrhagic telangiectasia and include multiple subtypes including cerebral arteriovenous malformations, arteriovenous fistulas, capillary telangiectasias and cavernous malformations (Shovlin et al, 2018). The main concern is intracranial haemorrhage and the risk differs markedly according to the individual vascular lesion. Symptoms of cerebral arteriovenous malformations relate to their location and size, with 50% of arteriovenous malformations being symptomatic (Eker et al, 2020). Symptoms of headache, focal neurological deficit or seizures may be present as well as symptoms of a haemorrhagic stroke if a rupture occurs.

Gastrointestinal

Gastrointestinal involvement is present in the majority of patients (46–91%) and is predominantly seen in the stomach and proximal bowel (Canzonieri et al, 2014). Gastroenterologists need to be aware of one of the rarer mutations, SMAD4, that is responsible for juvenile polyposis syndrome. Juvenile polyposis in hereditary haemorrhagic telangiectasia with SMAD4 mutations is indistinguishable from juvenile polyposis in the general population and carries the same increased risk of colorectal cancer (Schwenter et al, 2012). Patients with SMAD4 mutations need to be enrolled into a bowl screening programme. The recommendation is screening every 3 years if no polyps are found and yearly if polyps are found (Faughnan et al, 2020).

Gastrointestinal haemorrhage is a common presentation of hereditary haemorrhagic telangiectasia and is seen in about 13–30% of patients, usually presenting in the fourth to fifth decade (Meier et al, 2018).

Liver

Hepatic arteriovenous malformations (found in 15% of cases) are more common than cerebral ones but are only symptomatic in 8% of patients (Memeo et al, 2005). Hepatic manifestations of hereditary haemorrhagic telangiectasia include arteriovenous malformations and focal nodular hyperplasia, and studies have shown that routine screening increases the incidence of liver involvement (Barral et al, 2012). Once patients become symptomatic, they tend to present in one of three ways, in isolation or combined with other features:

- High-output cardiac failure
- Portal hypertension, resulting in massive ascites
- Ischaemia of the peribiliary plexus leading to biliary necrosis.

Anaemia

One dominant clinical feature is iron deficiency anaemia as a result of recurrent bleeds from either nasal or gastrointestinal telangiectasias. Hereditary haemorrhagic telangiectasia patients who have anaemia may present with lethargy but low serum iron levels have been linked to an increased risk of stroke. Management should be according to local guidance on iron deficiency anaemia; haemoglobin and iron should be monitored as per European VASCERN guidance (Shovlin et al, 2018).

Management

Epistaxis

Emergency management

Standard first aid principles should be applied. The general principles of management for persistent nose bleeding are to avoid packing if possible, or use a low pressure pack to limit mucosal trauma that will worsen bleeding. Medical adjuncts such as tranexamic acid and haemostatic agents should be considered. A pilot study compared the haemostatic agent Floseal with nasal packs in the acute setting and showed encouraging results (Lee et al, 2019). Medical disorders such as hypertension should be controlled.

Should resuscitation be required following profuse haemorrhage, conventional nasal packing may provide valuable time to stabilise the patient. Targeted arterial embolisation tends to be reserved for haemodynamically compromised patients who continue to bleed even after failed packing and surgical management, and is effective in these circumstances (Trojanowski et al, 2011).

Chronic management

Medical: All patients should be given advice on the management of epistaxis as per the European guidance (Shovlin et al, 2018). This includes avoiding trauma to the nose as much as possible and regular emollients with either antibiotic ointments or Vaseline is the first line for most patients. Oestrogen creams have been tried with little evidence to support long-term outcomes.

Tamoxifen is a selective oestrogen receptor modulator and has anti-angiogenic properties that reduce the number of episodes and severity of epistaxis (Yaniv et al, 2009). The main contraindications are pregnancy, previous thromboembolic event and uterine cancer.

Tranexamic acid is an anti-fibrinolytic agent. Studies have demonstrated a reduction in the duration and frequency of bleeding in patients with hereditary haemorrhagic telangiectasia (Kamhieh and Fox, 2016). Care needs to be taken in women who are on the combined oral contraceptive pill, and a recent thromboembolic event is a contraindication.

Propranolol reduces the expression of vascular endothelial growth factor and Contis et al (2017) demonstrated a significant decrease in the severity and number of bleeds. Care must be taken in patients with a previous history of cardiac disease or asthma.

Thalidomide was originally designed as a sedative but is a potent immunosuppressive and antiangiogenic drug. It is currently used as part of a treatment regimen where vascular endothelial growth factor plays an important role in tumour growth. Thalidomide has been used to treat hereditary haemorrhagic telangiectasia patients with severe epistaxis or gastrointestinal bleeding refractory to other treatments, especially where significant blood transfusions are necessary (Pérez-Encinas et al, 2002; Invernizzi et al, 2015).

Thalidomide and bevacizumab both show encouraging results in the management of patients with severe bleeds, but both have the potential to cause adverse events (Buscarini et al, 2019). The most serious risk is teratogenicity; both are absolutely contraindicated in women who are, or could become, pregnant (Buscarini et al, 2019).

Bevacizumab is a recombinant, humanised monoclonal antibody that binds to and inhibits vascular endothelial growth factor. A randomised control trial on submucosal nasal

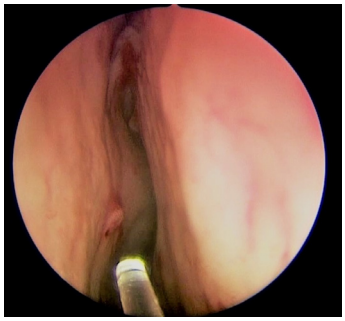

Figure 2. Potassium titanyl phosphate (KTP) laser targeting a telangiectasia on the inferior turbinate.

bevacizumab has demonstrated encouraging results, but topical applications have been ineffective (Riss et al, 2015). The International HHT Intravenous Bevacizumab Investigative Team study of Bleeding (InHIBITBleed) has published results from 12 hereditary haemorrhagic telangiectasia centres of excellence using systemic bevacizumab (Al-Samkari et al, 2021). Of 257 patients treated for epistaxis or gastrointestinal bleeding, there was an increase in mean haemoglobin level of 3.2 g/dl ($P<0.0001$) with a decrease in the Epistaxis Severity Score of 3.37 points ($P<0.0001$). The need for iron and blood transfusions was significantly reduced, venous thromboembolism was seen in 2% and there were no fatal adverse events (Al-Samkari et al, 2021).

Surgical: As in the medical approach to treatment, a stepwise surgical approach should be considered.

Thermal energy treatments: Treatments such as laser coagulation (Figure 2) or coblation are the preferred first-line surgical management options (Jørgensen et al, 2011). Targeted bipolar and unipolar diathermy is also effective if a dedicated specific coagulating laser is unavailable.

Septodermoplasty: This procedure involves removal of the affected anterior septal mucosa and replacing it with a full or split-thickness skin graft. It reduces the need for multiple laser procedures by up to 57% (Harvey et al, 2008). However, new telangiectatic vessels arise in the surrounding mucosa and lateral nasal wall, and bleeding eventually recurs.

Nasal closure: This is a radical procedure, described by Young (1967), in which the nasal passages are surgically completely closed. This is a useful last resort when all other medical and surgical options have been exhausted and the patient needs regular transfusions. Complete cessation of epistaxis in has been achieved in 94% of patients, as long as closure is complete (Lund et al, 2017).

Management of pulmonary arteriovenous malformations

The strategic aim of treating pulmonary arteriovenous malformations is to improve oxygenation, and reduce the risk of emboli and septic complications such as brain abscesses (Meier et al, 2018). Therapeutic embolisation has been the gold standard in management of arteriovenous malformations since the 1980s (White et al, 1996). The size of the pulmonary arteriovenous malformation is the limiting factor with regard to the technical feasibility and safety of embolisation (Faughnan et al, 2000).

If a pulmonary arteriovenous malformation has been identified or until patients have completed the appropriate screening, prophylactic antibiotics are recommended for any contaminated or 'dirty' procedures that may produce a bacteraemia. This is to reduce the risk of cerebral infections (Shovlin et al, 2008). The risk of air embolism during intravenous infusions is reduced by using in-line filters. SCUBA diving should also be avoided.

Management of cerebral arteriovenous malformations

The screening process for cerebral arteriovenous malformations is controversial and practice varies around the world. Current management options are endovascular embolisation, surgical resection or radiosurgery, which all have significant associated risks. The ARUBA trial was halted early as a result of a threefold increased risk of adverse outcomes in the intervention

group compared to the medical management group (Mohr et al, 2014). A publication by VASCERN concluded that 'hereditary haemorrhagic telangiectasia patients should have the opportunity to discuss brain screening issues with their healthcare provider'(Eker et al, 2020). Discussions regarding management should be on an individual patient-to-patient basis because of the differing types of vascular malformation and the variable risks of bleeding.

Management of gastrointestinal haemorrhage

Acute gastrointestinal haemorrhage should be managed per hospital protocol. Potential colorectal malignancies should always be considered in the older patient with hereditary haemorrhagic telangiectasia who presents with occult blood in the stool (Jackson et al, 2017). Upper gastrointestinal endoscopy is indicated if chronic bleeding is suspected or blood work showing blood loss in the absence of epistaxis would explain this. If the endoscopy is normal then consider a capsule endoscopy (Faughnan et al, 2020).

The management of chronic gastrointestinal bleeding is similar to that of epistaxis. Initially try conservative measures, tranexamic acid being an option. Endoscopy and argon plasma coagulation can be used to treat symptomatic chronic bleeding. As with patients who have epistaxis, there is growing evidence that thalidomide and bevacizumab can help control symptoms when bleeding is severe (Pérez-Encinas et al, 2002; Invernizzi et al, 2015). Bevacizumab is now recommended in patients when first-line treatments have failed (Faughnan et al, 2020).

The management of complicated or symptomatic liver arteriovenous malformations should ideally take place in a unit with cardiology and pulmonary hypertension input. Intensive first-line management in patients with high output cardiac failure should include management of anaemia, salt restriction and diuretics as needed. Portal hypertension treatment is the same as those without hereditary haemorrhagic telangiectasia.

Partial liver resection may be offered to patients with significant hepatic arteriovenous malformation involvement. Liver transplantation is indicated for ischaemic biliary necrosis, intractable heart failure or portal hypertension (Jackson et al, 2017). Bevacizumab can be used to treat high output cardiac failure and can, in some cases, reverse the need for liver transplantation (Mitchell et al, 2008; Dupuis-Girod et al, 2012).

Conclusions

Hereditary haemorrhagic telangiectasia is a multisystem disorder that can present with diverse symptoms, although most patients present with epistaxis. An accurate family history can be particularly helpful.

The management is based on screening for and treating arteriovenous malformations, with optimisation of additional symptoms. There is growing evidence demonstrating the effectiveness of thalidomide and bevacizumab in severe disease with complications such as severe epistaxis, gastrointestinal haemorrhage and cardiac failure secondary to hepatic arteriovenous malformations.

Key points

- Hereditary haemorrhagic telangiectasia is a complex disease which can present to healthcare professionals in multiple ways.
- Early diagnosis and screening can help to prevent some of the complications of arteriovenous malformations.
- Initial screening and management should be offered in a multidisciplinary setting.
- Pulmonary screening is advised in all patients with cerebral and hepatic screening offered on a case-by-case basis, depending on symptoms and discussions with the patient.
- Developments in medical management show promising results for patients with moderate to severe disease.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

References

Al-Samkari H, Kasthuri RS, Parambil JG et al. An international, multicenter study of intravenous bevacizumab for bleeding in hereditary hemorrhagic telangiectasia: the InHIBIT-Bleed study. Haematologica. 2021;106(8):2161–2169. https://doi.org/10.3324/haematol.2020.261859

Barral M, Sirol M, Placé V et al. Hepatic and pancreatic involvement in hereditary hemorrhagic telangiectasia: quantitative and qualitative evaluation with 64-section CT in asymptomatic adult patients. Eur Radiol. 2012;22(1):161–170. https://doi.org/10.1007/s00330-011-2243-y

Buscarini E, Botella LM, Geisthoff U et al. Safety of thalidomide and bevacizumab in patients with hereditary hemorrhagic telangiectasia. Orphanet J Rare Dis. 2019;14(1):28. https://doi.org/10.1186/s13023-018-0982-4

Canzonieri C, Centenara L, Ornati F et al. Endoscopic evaluation of gastrointestinal tract in patients with hereditary hemorrhagic telangiectasia and correlation with their genotypes. Genet Med. 2014;16(1):3–10. https://doi.org/10.1038/gim.2013.62

Contis A, Gensous N, Viallard JF et al. Efficacy and safety of propranolol for epistaxis in hereditary haemorrhagic telangiectasia: retrospective, then prospective study, in a total of 21 patients. Clin Otolaryngol. 2017; 42(4):911–917. https://doi.org/10.1111/coa.12821

Cottin V, Plauchu H, Bayle JY et al. Pulmonary arteriovenous malformations in patients with hereditary hemorrhagic telangiectasia. Am J Respir Crit Care Med. 2004;169(9):994–1000. https://doi.org/10.1164/rccm.200310-1441OC

Dakeishi M, Shioya T, Wada Y et al. Genetic epidemiology of hereditary hemorrhagic telangiectasia in a local community in the northern part of Japan. Hum Mutat. 2002;19(2):140–148. https://doi.org/10.1002/humu.10026

Donaldson JW, McKeever TM, Hall IP et al. Complications and mortality in hereditary hemorrhagic telangiectasia: a population-based study. Neurology. 2015; 84(18):1886–1893. https://doi.org/10.1212/WNL.0000000000001538

Dupuis-Girod S, Ginon I, Saurin J-C et al. Bevacizumab in patients with hereditary hemorrhagic telangiectasia and severe hepatic vascular malformations and high cardiac output. JAMA. 2012;307(9):948–955. https://doi.org/10.1001/jama.2012.250

Eker OF, Boccardi E, Sure U et al. European Reference Network for Rare Vascular Diseases (VASCERN) position statement on cerebral screening in adults and children with hereditary haemorrhagic telangiectasia (HHT). Orphanet J Rare Dis. 2020; 15(1):1–0. https://doi.org/10.1186/s13023-020-01386-9

Faughnan ME, Lui YW, Wirth JA et al. Diffuse pulmonary arteriovenous malformations: characteristics and prognosis. Chest. 2000;117(1):31–38. https://doi.org/10.1378/chest.117.1.31

Faughnan ME, Mager JJ, Hetts SW et al. Second international guidelines for the diagnosis and management of hereditary hemorrhagic telangiectasia. Ann Intern Med. 2020;173(12):989–1001. https://doi.org/10.7326/M20-1443

Ference BA, Shannon TM, White RI Jr et al. Life-threatening pulmonary hemorrhage with pulmonary arteriovenous malformations and hereditary hemorrhagic telangiectasia. Chest. 1994;106(5):1387–1390. https://doi.org/10.1378/chest.106.5.1387

Guttmacher AE, Marchuk DA, White RI Jr. Hereditary hemorrhagic telangiectasia. N Engl J Med. 1995;333(14):918–924. https://doi.org/10.1056/NEJM199510053331407

Harvey RJ, Kanagalingam J, Lund VJ. The impact of septodermoplasty and potassium-titanyl-phosphate (KTP) laser therapy in the treatment of hereditary hemorrhagic telangiectasia-related epistaxis. Am J Rhinol. 2008; 22(2):182–187. https://doi.org/10.2500/ajr.2008.22.3145

Hoag JB, Terry P, Mitchell S et al. An epistaxis severity score for hereditary hemorrhagic telangiectasia. The Laryngoscope. 2010;120(4):838–843. https://doi.org/10.1002/lary.20818

Invernizzi R, Quaglia F, Klersy C et al. Efficacy and safety of thalidomide for the treatment of severe recurrent epistaxis in hereditary haemorrhagic telangiectasia: results of a non-randomised, single center, phase 2 study. Lancet Haematol. 2015;2(11):e465–73. https://doi.org/10.1016/S2352-3026(15)00195-7

Jackson SB, Villano NP, Benhammou JN et al. Gastrointestinal manifestations of hereditary hemorrhagic telangiectasia (HHT): a systematic review of the literature. Dig Dis Sci. 2017; 62(10):2623–2630. https://doi.org/10.1007/s10620-017-4719-3

Jørgensen G, Lange B, Wanscher JH et al. Efficiency of laser treatment in patients with hereditary hemorrhagic telangiectasia. Eur Arch Otorhinolaryngol. 2011;268(12):1765–1770. https://doi.org/10.1007/s00405-011-1677-9

Johnson DW, Berg JN, Baldwin MA et al. Mutations in the activin receptor-like kinase 1 gene in hereditary haemorrhagic telangiectasia type 2. Nat Genet. 1996;13(2):189–195. https://doi.org/10.1038/ng0696-189

Kamhieh Y, Fox H. Tranexamic acid in epistaxis: a systematic review. Clin Otolaryngol. 2016;41(6):771–776. https://doi.org/10.1111/coa.12645

Kjeldsen AD, Torring PM, Nissen H et al. Cerebral abscesses among Danish patients with hereditary haemorrhagic telangiectasia. Acta Neurol Scand. 2014;129(3):192–197. https://doi.org/10.1111/ane.12167

Lee JM, Wu V, Faughnan ME et al. Prospective pilot study of Floseal® for the treatment of anterior epistaxis in patients with hereditary hemorrhagic telangiectasia (HHT). J Otolaryngol Head Neck Surg. 2019;48(1):48. https://doi.org/10.1186/s40463-019-0379-y

Letteboer TGW, Mager JJ, Snijder RJ et al. Genotype–phenotype relationship in hereditary haemorrhagic telangiectasia. J Med Genet. 2005;43(4):371–377. https://doi.org/10.1136/jmg.2005.035451

Lund VJ, Darby Y, Rimmer J et al. Nasal closure for severe hereditary haemorrhagic telangiectasia in 100 patients. The Lund modification of the Young's procedure: a 22-year experience. Rhinology. 2017;55(2):135–141. https://doi.org/10.4193/Rhin16.315

Meier NM, Foster ML, Battaile JT. Hereditary hemorrhagic telangiectasia and pulmonary arteriovenous malformations: clinical aspects. Cardiovasc Diagn Ther. 2018;8(3):316–324. https://doi.org/10.21037/cdt.2017.12.07

Memeo M, Stabile Ianora AA, Scardapane A et al. Hereditary haemorrhagic telangiectasia: study of hepatic vascular alterations with multi-detector row helical CT and reconstruction programs. Radiol Med. 2005;109(1-2):125–138

Mitchell A, Adams LA, MacQuillan G et al. Bevacizumab reverses need for liver transplantation in hereditary hemorrhagic telangiectasia. Liver Transpl. 2008;14(2):210–213. https://doi.org/10.1002/lt.21417

Mohr JP, Parides MK, Stapf C et al. Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, nonblinded, randomised trial. Lancet. 2014;383(9917):614–621. https://doi.org/10.1016/S0140-6736(13)62302-8

Pasculli G, Resta F, Guastamacchia E et al. Health related quality of life in a rare disease: hereditary hemorrhagic telangiectasia (HHT) or Rendu–Osler–Weber disease. Qual Life Res. 2004;13(10):1715–1723. https://doi.org/10.1007/s11136-004-7865-y

Pérez-Encinas M, Rabunal Martinez MJ, Bello Lopez JL. Is thalidomide effective for the treatment of gastrointestinal bleeding in hereditary hemorrhagic telangiectasia. Haematologica. 2002;87(8):ELT 34

Riss D, Burian M, Wolf A et al. Intranasal submucosal bevacizumab for epistaxis in hereditary hemorrhagic telangiectasia: a doublebind, randomized, placebo-controlled trial. Head Neck. 2015;37(6):783–787. https://doi.org/10.1002/hed.23655

Schwenter F, Faughnan ME, Gradinger AB et al. Juvenile polyposis, hereditary hemorrhagic telangiectasia, and early onset colorectal cancer in patients with SMAD4 mutation. J Gastroenterol. 2012;47(7):795–804. https://doi.org/10.1007/s00535-012-0545-8

Shovlin CL. Hereditary haemorrhagic telangiectasia: pathophysiology, diagnosis and treatment. Blood Reviews. 2010;24(6):203–219. https://doi.org/10.1016/j.blre.2010.07.001

Shovlin CL, Guttmacher AE, Buscarini E et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Am J Med Genet. 2000;91(1):66–67. https://doi.org/10.1002/(SICI)1096-8628(20000306)91:1<66::AID-AJMG12>3.0.CO;2-P

Shovlin C, Bamford K, Wray D. Post-NICE 2008: antibiotic prophylaxis prior to dental procedures for patients with pulmonary arteriovenous malformations (PAVMs) and hereditary haemorrhagic telangiectasia. Br Dent J. 2008;205(10):531–533. https://doi.org/10.1038/sj.bdj.2008.978

Shovlin CL, Buscarini E, Kjeldsen AD et al. European reference network for rare vascular diseases (VASCERN) outcome measures for hereditary Haemorrhagic telangiectasia (HHT). Orphanet J Rare Dis. 2018; 13(1):1–5. https://doi.org/10.1186/s13023-018-0850-2

Trembath RC, Thomson JR, Machado RD et al. Clinical and molecular genetic features of pulmonary hypertension in patients with hereditary hemorrhagic telangiectasia. N Engl J Med. 2001;345(5):325–334. https://doi.org/10.1056/NEJM200108023450503

Trojanowski P, Jargiełło T, Trojanowska A et al. Epistaxis in patients with hereditary hemorrhagic telangiectasia treated with selective arterial embolization. Acta Radiol. 2011;52(8):846–849. https://doi.org/10.1258/ar.2011.110132

White RI, Jr, Lynch-Nyhan A, Terry P et al. Pulmonary arteriovenous malformations: techniques and long-term outcome of embolotherapy. Radiology. 1988;169(3):663–669. https://doi.org/10.1148/radiology.169.3.3186989

White RI, Jr, Pollak JS, Wirth JA. Pulmonary arteriovenous malformations: diagnosis and transcatheter embolotherapy. J Vasc Interv Radiol. 1996;7(6):787–804. https://doi.org/10.1016/S1051-0443(96)70851-5

Yaniv E, Preis M, Hadar T, Shvero J, Haddad M. Antiestrogen therapy for hereditary hemorrhagic telangiectasia: a double-blind placebo-controlled clinical trial. The Laryngoscope. 2009;119(2):284–288. https://doi.org/10.1002/lary.20065

Young A. Closure of the nostrils in atrophic rhinitis. J Laryngol Otol. 1967;81(5):515–524. https://doi.org/10.1017/S0022215100067426