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CLINICAL GUIDELINE

Second International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

Marie E. Faughnan, MD, MSc; Johannes J. Mager, MD, PhD; Steven W. Hetts, MD; Valerie A. Palda, MD, MSc; Kelly Lang-Robertson; Elisabetta Buscarini, MD; Erik Deslandres, MD; Raj S. Kasthuri, MD; Andrea Lausman, MD; David Poetker, MD, MA; Felix Ratjen, MD; Mark S. Chesnutt, MD; Marianne Clancy, RDH, MPA; Kevin J. Whitehead, MD; Hanny Al-Samkari, MD; Murali Chakinala, MD; Miles Conrad, MD; Daniel Cortes, BscPhm; Claudia Crocione; Jama Darling, MD; Els de Gussem, MD; Carol Derksen; Sophie Dupuis-Girod, MD, PhD; Patrick Foy, MD; Urban Geisthoff, MD; James R. Gossage, MD; Adrienne Hammill, MD; Ketil Heimdal, MD; Katharine Henderson, MS, CGC; Vivek N. Iyer, MD, MPH; Anette D. Kjeldsen, MD; Masaki Komiyama, MD; Kevin Korenblatt, MD; Jamie McDonald, MS, CGC; Jack McMahon; Justin McWilliams, MD; Mary E. Meek, MD; Meir Mei-Zahav, MD; Scott Olitsky, MD, MBA; Sara Palmer, PhD; Rose Pantalone, RN; Jay F. Piccirillo, MD; Beth Plahn, RN, MHA; Mary E.M. Porteous, MD; Marco C. Post, MD, PhD; Ivan Radovanovic, MD; Paul J. Rochon, MD; Josanna Rodriguez-Lopez, MD; Carlo Sabba, MD; Marcelo Serra, MD; Claire Shovlin, PhD, MA; Dennis Sprecher, MD; Andrew J. White, MD; Ingrid Winship, MBChB, MD; and Roberto Zarrabeitia, MD

Description: Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disease with an estimated prevalence of 1 in 5000 that is characterized by the presence of vascular malformations (VMs). These result in chronic bleeding, acute hemorrhage, and complications from shunting through VMs. The goal of the Second International HHT Guidelines process was to develop evidence-based consensus guidelines for the management and prevention of HHT-related symptoms and complications.

Methods: The guidelines were developed using the AGREE II (Appraisal of Guidelines for Research and Evaluation II) framework and GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology. The guidelines expert panel included expert physicians (clinical and genetic) in HHT from 15 countries, guidelines methodologists, health care workers, health care administrators, patient advocacy representatives, and persons with HHT. During the preconference process, the expert panel generated clinically relevant questions in 6 priority topic areas. A systematic literature search was done in June 2019, and articles meeting a priori criteria were included to generate evidence tables, which were used as the basis for recommendation development. The expert panel subsequently convened during a guidelines conference to conduct a structured consensus process, during which recommendations reaching at least 80% consensus were discussed and approved.

Recommendations: The expert panel generated and approved 6 new recommendations for each of the following 6 priority topic areas: epistaxis, gastrointestinal bleeding, anemia and iron deficiency, liver VMs, pediatric care, and pregnancy and delivery (36 total). The recommendations highlight new evidence in existing topics from the first International HHT Guidelines and provide guidance in 3 new areas: anemia, pediatrics, and pregnancy and delivery. These recommendations should facilitate implementation of key components of HHT care into clinical practice.

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For author, article, and disclosure information, see end of text.
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Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disease with an estimated prevalence of approximately 1 in 5000 (1). It is characterized by clinically significant vascular malformations (VMs) of skin and mucous membranes of the nose and gastrointestinal (GI) tract as well as the brain, lung, and liver. It is underdiagnosed, and a long diagnostic delay is common (2). A diagnosis of HHT allows appropriate screening and preventive treatment to be undertaken in a patient and their affected family members. The most common symptom of HHT, epistaxis, has an age-related expression, as does the appearance of the typical telangiectasia (3). Consensus clinical diagnostic criteria known as the Curaçao criteria were published in 2000 (4) (**Table 1** of **Supplement 1**, available at Annals.org) and upheld in the first International HHT Guidelines (5). The first guidelines also recommended genetic testing for HHT diagnosis, primarily for asymptomatic persons from a family with known HHT, as detailed in the **Table**. In 97% of patients with a definite clinical diagnosis of HHT, a causative mutation is identified in one of these genes: endoglin (*ENG*, HHT type 1), activin receptor-like kinase-1 (*ACVRL1*, HHT type 2), and Mothers against decapentaplegic homolog 4 (*SMAD4*, juvenile polyposis–HHT overlap) (6).

The goal of this Second International HHT Guidelines process was to develop evidence-informed consensus guidelines regarding the diagnosis of HHT, prevention of HHT-related complications, and treatment of symptomatic disease in areas not previously addressed by guidelines and those where significant new literature had been published. Several other recommendations from the first International HHT Guidelines were not reassessed during this process and remain currently recommended (**Table**).

Methods

The Second International HHT Guidelines were developed using the AGREE II (Appraisal of Guidelines for

See also:

Web-Only
Supplements

Table. Clinical Recommendations From the Second International HHT Guidelines and Currently Recommended Clinical Recommendations From the First International HHT Guidelines*

Listed here are the clinical recommendations with ≥80% consensus at the Second International HHT Guidelines conference. These are followed by the clinical recommendations from the first International Guidelines that had ≥80% consensus and were not reassessed by the 2019 International Guidelines Working Group. The expert panel is aware of new evidence and insights regarding some of these existing guidelines, and they have been prioritized for updating in the next guidelines process (Part 4 of **Supplement 2**, available at Annals.org).

Epistaxis management

*A1: The expert panel recommends that patients with HHT-related epistaxis use moisturizing topical therapies that humidify the nasal mucosa to reduce epistaxis.**
Quality of evidence: moderate (agreement, 98%)
Strength of recommendation: strong (agreement, 100%)

*A2: The expert panel recommends that clinicians consider the use of oral tranexamic acid for the management of epistaxis that does not respond to moisturizing topical therapies.**
Quality of evidence: high (agreement, 92%)
Strength of recommendation: strong (agreement, 94%)

*A3: The expert panel recommends that clinicians should consider ablative therapies for nasal telangiectasias, including laser treatment, radiofrequency ablation, electrosurgery, and sclerotherapy, in patients that have failed to respond to moisturizing topical therapies.**
Quality of evidence: moderate (agreement, 83%)
Strength of recommendation: weak (agreement, 94%)

*A4: The expert panel recommends that clinicians consider the use of systemic antiangiogenic agents for the management of epistaxis that has failed to respond to moisturizing topical therapies, ablative therapies, and/or tranexamic acid.**
Quality of evidence: moderate (agreement, 92%)
Strength of recommendation: strong (agreement, 82%)

*A5: The expert panel recommends that clinicians consider a septodermoplasty for patients whose epistaxis has failed to respond sufficiently to moisturizing topical therapies, ablative therapies, and/or tranexamic acid.**
Quality of evidence: low (agreement, 92%)
Strength of recommendation: weak (agreement, 88%)

*A6: The expert panel recommends that clinicians consider a nasal closure for patients whose epistaxis has failed to respond sufficiently to moisturizing topical therapies, ablative therapies, and/or tranexamic acid.**
Quality of evidence: moderate (agreement, 86%)
Strength of recommendation: strong (agreement, 82%)

A7: The expert panel recommends that physicians advise patients with HHT-related epistaxis to use agents that humidify the nasal mucosa to prevent epistaxis. (Agreement, 94%)†
Level of evidence: III
Strength of recommendation: weak

A8: The expert panel recommends that clinicians refer HHT patients with epistaxis and who desire treatment to otorhinolaryngologists with HHT expertise for evaluation and treatment. (Agreement, 87%)†
Level of evidence: III
Strength of recommendation: weak

A9: The expert panel recommends that when considering nasal surgery for reasons other than epistaxis, the patient and clinician obtain consultation from an otorhinolaryngologist with expertise in HHT-related epistaxis. (Agreement, 100%)†
Level of evidence: III
Strength of recommendation: weak

A10: The expert panel recommends that the treatment for acute epistaxis requiring intervention include packing with material or products that have a low likelihood of causing rebleeding with removal (e.g., lubricated low-pressure pneumatic packing). (Agreement, 93%)†
Level of evidence: III
Strength of recommendation: weak

***Table*–Continued**

GI bleeding management*

B1: The expert panel recommends esophagogastroduodenoscopy as the first-line diagnostic test for suspected HHT-related bleeding. Patients who meet colorectal cancer screening criteria and patients with SMAD4-HHT (genetically proven or suspected) should also undergo colonoscopy.
Quality of evidence: low (agreement, 82%)
Strength of recommendation: strong (agreement, 94%)

B2: The expert panel recommends considering capsule endoscopy for suspected HHT-related bleeding when esophagogastroduodenoscopy does not reveal significant HHT-related telangiectasia.
Quality of evidence: low (agreement, 92%)
Strength of recommendation: strong (agreement, 88%)

B3: The expert panel recommends that clinicians grade the severity of HHT-related GI bleeding and proposes the following framework:
- *Mild HHT-related GI bleeding: patient who meets their hemoglobin goals‡ with oral iron replacement*
- *Moderate HHT-related GI bleeding: patient who meets their hemoglobin goals‡ with intravenous iron treatment*
- *Severe HHT-related GI bleeding: patient who does not meet their hemoglobin goals‡ despite adequate iron replacement or requires blood transfusions*

Quality of evidence: low (expert consensus) (agreement, 96%)
Strength of recommendation: strong (agreement, 96%)

B4: The expert panel recommends that endoscopic argon plasma coagulation be only used sparingly during endoscopy.
Quality of evidence: low (expert consensus) (agreement, 88%)
Strength of recommendation: weak (agreement, 81%)

B5: The expert panel recommends that clinicians consider treatment of mild HHT-related GI bleeding with oral antifibrinolytics.
Quality of evidence: low (agreement, 94%)
Strength of recommendation: weak (agreement, 90%)

B6: The expert panel recommends that clinicians consider treatment of moderate to severe HHT-related GI bleeding with intravenous bevacizumab or other systemic antiangiogenic therapy.
Quality of evidence: moderate (agreement, 94%)
Strength of recommendation: strong (agreement, 98%)

Anemia and anticoagulation*

C1: The expert panel recommends that the following HHT patients be tested for iron deficiency and anemia:
- *All adults, regardless of symptoms*
- *All children with recurrent bleeding and/or symptoms of anemia*

Quality of evidence: high (agreement, 98%)
Strength of recommendation: strong (agreement, 96%)

C2: The expert panel recommends iron replacement for treatment of iron deficiency and anemia as follows:
- *Initial therapy with oral iron*
- *Intravenous iron replacement for patients in whom oral is not effective, not absorbed, or not tolerated, or who are presenting with severe anemia*

Quality of evidence: moderate (agreement, 88%)
Strength of recommendation: strong (agreement, 100%)

C3: The expert panel recommends red blood cell transfusions in the following settings:
- *Hemodynamic instability/shock*
- *Comorbidities that require a higher hemoglobin target*
- *Need to increase the hemoglobin acutely, such as prior to surgery or during pregnancy*
- *Inability to maintain an adequate hemoglobin despite frequent iron infusions*

Quality of evidence: low (agreement, 92%)
Strength of recommendation: strong (agreement, 96%)

C4: The expert panel recommends considering evaluation for additional causes of anemia in the setting of an inadequate response to iron replacement.
Quality of evidence: low (agreement, 100%)
Strength of recommendation: strong (agreement, 100%)

C5: The expert panel recommends that HHT patients receive anticoagulation (prophylactic or therapeutic) or antiplatelet therapy when there is an indication, with consideration of their individualized bleeding risks; bleeding in HHT is not an absolute contraindication for these therapies.

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Table–Continued

Quality of evidence: low (agreement, 98%)
Strength of recommendation: strong (agreement, 98%)

C6: The panel recommends avoiding the use of dual antiplatelet therapy and/or combination of antiplatelet therapy and anticoagulation, where possible, in patients with HHT.
Quality of evidence: low (expert consensus) (agreement, 83%)
Strength of recommendation: weak (agreement, 92%)

Liver VMs in HHT

*D1: The expert panel recommends that screening for liver VMs be offered to adults with definite or suspected HHT.**
Quality of evidence: low (agreement, 84%)
Strength of recommendation: weak (agreement, 93%)

*D2: The expert panel recommends diagnostic testing for liver VMs in HHT patients with symptoms and/or signs suggestive of complicated liver VMs (including heart failure, pulmonary hypertension, abnormal cardiac biomarkers, abnormal liver function tests, abdominal pain, portal hypertension, or encephalopathy), using Doppler ultrasound, multiphase contrast CT scan, or contrast abdominal MRI for diagnostic assessment of liver VMs.**
Quality of evidence: high (agreement, 98%)
Strength of recommendation: strong (agreement, 100%)

D3: The expert panel recommends an intensive first-line management only for patients with complicated and/or symptomatic liver VMs, tailored to the type of liver VM complication(s).

*The expert panel recommends that HHT patients with high-output cardiac failure and pulmonary hypertension be comanaged by the HHT Center of Excellence and an HHT cardiologist or a pulmonary hypertension specialty clinic.**
Quality of evidence: moderate (agreement, 88%)
Strength of recommendation: strong (agreement, 88%)

*D4: The expert panel recommends that clinicians estimate prognosis of liver VMs using available predictors, to identify patients in need of closer monitoring.**
Quality of evidence: moderate (agreement, 89%)
Strength of recommendation: strong (agreement, 82%)

*D5: The expert panel recommends considering intravenous bevacizumab for patients with symptomatic high-output cardiac failure due to liver VMs who have failed to respond sufficiently to first-line management.**
Quality of evidence: moderate (agreement, 98%)
Strength of recommendation: strong (agreement, 98%)

*D6: The expert panel recommends referral for consideration of liver transplantation for patients with symptomatic complications of liver VMs, specifically refractory high-output cardiac failure, biliary ischemia, or complicated portal hypertension.**
Quality of evidence: moderate (agreement, 83%)
Strength of recommendation: strong (agreement, 92%)

D7: The expert panel recommends that liver biopsy be avoided in any patient with proven or suspected HHT. (Agreement, 97%)†
Level of evidence: III
Strength of recommendation: strong

D8: The expert panel recommends that hepatic artery embolization be avoided in patients with liver VMs as it is only a temporizing procedure associated with significant morbidity and mortality. (Agreement, 94%)†
Level of evidence: III
Strength of recommendation: strong

Pediatric care*

E1: The expert panel advises that diagnostic genetic testing be offered for asymptomatic children of a parent with HHT.
Quality of evidence: high (agreement, 96%)
Strength of recommendation: strong (agreement, 94%)

E2: The expert panel recommends screening for pulmonary AVMs in asymptomatic children with HHT or at risk for HHT at the time of presentation/diagnosis.
Quality of evidence: moderate (agreement, 94%)
Strength of recommendation: strong (agreement, 94%)

E3: The expert panel recommends that large pulmonary AVMs and pulmonary AVMs associated with reduced oxygen saturation be treated in children to avoid serious complications.
Quality of evidence: moderate (agreement, 98%)
Strength of recommendation: strong (agreement, 98%)

Table–Continued

E4: The expert panel recommends repeating pulmonary AVM screening in asymptomatic children with HHT or at risk for HHT, typically at 5-year intervals.
Quality of evidence: low (agreement, 92%)
Strength of recommendation: strong (agreement, 86%)

E5: The expert panel recommends screening for brain VM in asymptomatic children with HHT or at risk for HHT, at the time of presentation/diagnosis.
Quality of evidence: low (agreement, 86%)
Strength of recommendation: strong (agreement, 86%)

E6: The expert panel recommends that brain VMs with high-risk features be treated.
Quality of evidence: low (agreement, 100%)
Strength of recommendation: strong (agreement, 98%)

Pregnancy and delivery*

F1: The expert panel recommends that clinicians discuss preconception and prenatal diagnostic options, including preimplantation genetic diagnosis, with HHT-affected individuals.
Quality of evidence: very low (agreement, 86%)
Strength of recommendation: strong (agreement, 83%)

F2: The expert panel recommends testing with unenhanced MRI in pregnant women with symptoms suggestive of brain VMs.
Quality of evidence: very low (agreement, 98%)
Strength of recommendation: strong (agreement, 92%)

F3: The expert panel recommends that pregnant women with HHT who have not been recently screened and/or treated for pulmonary AVM should be approached as follows:
- *In asymptomatic patients, initial pulmonary AVM screening should be performed using either agitated saline transthoracic contrast echocardiography (TTCE) or low-dose noncontrast chest CT, depending on local expertise. Chest CT, when performed, should be done early in the second trimester.*
- *In patients with symptoms suggestive of pulmonary AVM, diagnostic testing should be performed using low-dose noncontrast chest CT. This testing can be performed at any gestational age, as clinically indicated.*
- *Pulmonary AVMs should be treated starting in the second trimester unless otherwise clinically indicated.*

Quality of evidence: moderate (agreement, 88%)
Strength of recommendation: strong (agreement, 83%)

F4: The expert panel recommends that pregnant women with HHT be managed at a tertiary care center by a multidisciplinary team if they have untreated pulmonary AVMs and/or brain VMs or have not been recently screened for pulmonary AVMs.
Quality of evidence: very low (agreement, 94%)
Strength of recommendation: strong (agreement, 85%)

F5: The expert panel recommends not withholding an epidural because of a diagnosis of HHT, and that screening for spinal vascular malformations is not required.
Quality of evidence: low (agreement, 98%)
Strength of the recommendation: strong (agreement, 92%)

F6: The expert panel recommends that women with known, non–high-risk brain VMs can labor and proceed with vaginal delivery. Patients may require an assisted second stage on a case-by-case basis.
Quality of evidence: moderate (agreement, 94%)
Strength of the recommendation: strong (agreement, 94%)

Diagnosis of HHT†

G1: The expert panel recommends that clinicians diagnose HHT using the Curaçao criteria or by identification of a causative mutation. (Agreement, 82%)
Level of evidence: III
Strength of recommendation: weak

G2: The expert panel recommends that clinicians consider the diagnosis of HHT in patients with one or more Curaçao criteria. (Agreement, 91%)
Level of evidence: III
Strength of recommendation: weak

G3: The expert panel recommends that asymptomatic children of a parent with HHT be considered to have possible HHT, unless excluded by genetic testing. (Agreement, 87%)
Level of evidence: III
Strength of recommendation: weak

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***Table*–Continued**

G4: The expert panel recommends that clinicians refer patients for diagnostic genetic testing for HHT (Agreement, 80%)
1. *to identify the causative mutation in a family with clinically confirmed HHT;*
2. *to establish a diagnosis in relatives of a person with a known causative mutation, including*
   a. *individuals who are asymptomatic or minimally symptomatic and*
   b. *individuals who desire prenatal testing; and*
3. *to assist in establishing a diagnosis of HHT in individuals who do not meet clinical diagnostic criteria.*

Level of evidence: III
Strength of recommendation: weak

G5: The expert panel recommends that for individuals who test negative for ENG *and* ACVRL1 *coding sequence mutations,* SMAD4 *testing should be considered to identify the causative mutation.* (Agreement, 93%)
Level of evidence: III
Strength of recommendation: weak

Brain VMs†

H1: The expert panel recommends the use of MRI for brain VM screening in adults with possible or definite HHT using a protocol with and without contrast administration and using sequences that detect blood products, to maximize sensitivity. (Agreement, 100%)
Level of evidence: III
Strength of recommendation: weak

H2: The expert panel recommends that adults presenting with an acute hemorrhage secondary to a brain VM be considered for definitive treatment in a center with neurovascular expertise. (Agreement, 94%)
Level of evidence: III
Strength of recommendation: strong

H3: The expert panel recommends that all other adults with brain VMs be referred to a center with neurovascular expertise to be considered for invasive testing and individualized management. (Agreement, 84%)
Level of evidence: III
Strength of recommendation: strong

H4: The expert panel recommends that pregnant women with suspected or confirmed HHT harboring an asymptomatic brain VM during pregnancy have definitive treatment of their brain VM deferred until after delivery of their fetus. The expert panel recommends that the delivery of the fetus follow obstetrical principles. (Agreement, 80%)
Level of evidence: III
Strength of recommendation: weak

Pulmonary AVMs†

I1: The expert panel recommends that clinicians screen all patients with possible or confirmed HHT for pulmonary AVMs. (Agreement, 96%)
Level of evidence: III
Strength of recommendation: strong

I2: The expert panel recommends that clinicians use transthoracic contrast echocardiography as the initial screening test for pulmonary AVM. (Agreement, 96%)
Level of evidence: II
Strength of recommendation: weak

I3: The expert panel recommends that clinicians treat pulmonary AVMs with transcatheter embolotherapy. (Agreement, 96%)
Level of evidence: II
Strength of recommendation: strong

I4: The expert panel recommends that clinicians provide the following long-term advice to patients with documented pulmonary AVMs (treated or untreated):
1. *Antibiotic prophylaxis for procedures with risk of bacteremia*
2. *When IV access is in place, take extra care to avoid IV air*
3. *Avoidance of SCUBA diving* (Agreement, 87%)

Level of evidence: III
Strength of recommendation: weak

I5: The expert panel recommends that clinicians provide long-term follow-up for patients who have pulmonary AVMs, in order to detect growth of untreated pulmonary AVMs and also reperfusion of treated AVMs. (Agreement, 100%)
Level of evidence: II
Strength of recommendation: strong

AVM = arteriovenous malformation; CT = computed tomography; EGD = esophagogastroduodenoscopy; GI = gastrointestinal; HHT = hereditary hemorrhagic telangiectasia; IV = intravenous; MRI = magnetic resonance imaging; VM = vascular malformation.
* Second HHT Guidelines.
† First HHT Guidelines.
‡ Hemoglobin goals should reflect age, gender, symptoms, and comorbidities.

Research and Evaluation II) framework and GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology. The international HHT community provided priority topics to be updated on the basis of new evidence or added because not previously addressed. The **Table** details recommendations that were not revisited but are still currently recommended. Topic groups were appointed for each of the 6 areas selected for update or new review. They identified key questions to guide the systematic search strategy of the literature. A medical librarian (K.L.R.) developed and executed 6 sets of search strategies between May and June 2019 in Ovid MEDLINE with input from the chair of the Guidelines Working Group (GWG). Through a series of predetermined steps illustrated in Part 1 of **Supplement 2** (available at Annals.org), including double review of both abstracts and full-text articles, 221 articles were summarized into evidence tables. The quality of included randomized controlled trials (RCTs) was assessed (Part 2 of **Supplement 2**) using the structured framework of the Cochrane Risk of Bias Tool (7). In the months preceding the conference, the 6 topic groups generated draft recommendations that were based on key questions and the evidence tables and were consistent with GRADE (8) formatting for levels of evidence and strength of recommendation. Draft recommendations were distributed to all panel members 2 weeks before the consensus meeting.

The GWG convened at the guidelines conference in November 2019 in Toronto, Canada, to partake in a structured consensus process. The GWG included clinical and genetic experts in all aspects of HHT from 15 countries, guidelines methodologists, health care workers, health care administrators, HHT clinic staff, medical trainees, patient advocacy representatives, and patients with HHT. The GWG completed individual conflict-of-interest disclosures, and the chair reviewed potential conflicts. The GWG was presented draft recommendations with supporting quality of evidence, voted anonymously on the wording and quality of evidence, was presented the draft strength of recommendation with justification by GRADE methodology, and then voted on the strength of recommendation. Consensus of 80% was required for the recommendation to be included in the guidelines. A structured process was used to identify sources of disagreement for votes with less than 80% agreement (**Supplement 1**). The recommendations were sent for external review to HHT experts and organizations; their comments were collated and ad-

dressed (Part 3 of **Supplement 2**). The funding sources had no role in the design, conduct, or reporting of the guidelines or in the decision to submit for publication. Although the funding sources were not directly involved in the generation of the recommendations, some participants in the guidelines process were also board members, officers, or committee members of Cure HHT.

RECOMMENDATIONS

A summary of all the recomendations is available in the **Table**.

Epistaxis Management

Recommendation A1: The expert panel recommends that patients with HHT-related epistaxis use moisturizing topical therapies that humidify the nasal mucosa to reduce epistaxis. (Quality of evidence: moderate [agreement, 98%])

Topical saline has been shown to reduce epistaxis severity score compared with baseline in an RCT of topical therapies (9) (**Table 2** of **Supplement 1**). (Strength of recommendation: strong [agreement, 100%])

Clinical considerations: Topical saline (spray or gel) is typically used twice daily.

Recommendation A2: The expert panel recommends that clinicians consider the use of oral tranexamic acid for the management of epistaxis that does not respond to moisturizing topical therapies. (Quality of evidence: high [agreement, 92%])

Two RCTs of oral tranexamic acid showed a significant decrease in epistaxis severity (10, 11) with minimal adverse events (**Table 2** of **Supplement 1**). (Strength of recommendation: strong [agreement, 94%])

Clinical considerations: **Table 4** of **Supplement 1** gives prescribing and safety monitoring guidance for oral tranexamic acid.

Recommendation A3: The expert panel recommends that clinicians should consider ablative therapies for nasal telangiectasias, including laser treatment, radiofrequency ablation, electrosurgery, and sclerotherapy, in patients that have failed to respond to moisturizing topical therapies. (Quality of evidence: moderate [agreement, 83%])

One RCT showed reduced epistaxis severity score with sclerotherapy (12). Multiple uncontrolled series demonstrated that various ablative therapies temporarily reduced epistaxis (13–15) (**Tables 2** and **3** of **Supplement 1**). (Strength of recommendation: weak [agreement, 94%])

Clinical considerations: Clinicians and patients should choose a specific ablative therapy on the basis of local expertise, understanding that ablative therapy is a temporizing treatment of epistaxis and that perforation of the nasal septum is a known complication of all techniques.

Recommendation A4: The expert panel recommends that clinicians consider the use of systemic antiangiogenic agents for the management of epistaxis that has failed to respond to moisturizing topical therapies, ablative therapies, and/or tranexamic acid. (Quality of evidence: moderate [agreement, 92%])

Multiple uncontrolled series demonstrated that intravenous (IV) bevacizumab reduced epistaxis, improved anemia, reduced transfusion requirements, or improved quality of life (QOL) (16–23) (**Table 3** of **Supplement 1**). (Strength of recommendation: strong [agreement, 82%])

Clinical considerations: **Table 4** of **Supplement 1** gives prescribing and safety monitoring guidance for IV bevacizumab.

Recommendation A5: The expert panel recommends that clinicians consider a septodermoplasty for patients whose epistaxis has failed to respond sufficiently to moisturizing topical therapies, ablative therapies, and/or tranexamic acid. (Quality of evidence: low [agreement, 92%])

Multiple uncontrolled series demonstrated that septodermoplasty reduced epistaxis, improved anemia, reduced surgical reintervention, or improved QOL (24–29) (**Table 3** of **Supplement 1**). (Strength of recommendation: weak [agreement, 88%])

Clinical considerations: Clinicians and patients should consider septodermoplasty when epistaxis affects QOL or is life-threatening; they should consider the risks and benefits, as well as alternatives, such as nasal closure and antiangiogenic medications.

Recommendation A6: The expert panel recommends that clinicians consider a nasal closure for patients whose epistaxis has failed to respond sufficiently to moisturizing topical therapies, ablative therapies, and/or tranexamic acid. (Quality of evidence: moderate [agreement, 86%])

Multiple uncontrolled series demonstrated that nasal closure reduced epistaxis (26, 28) (**Table 3** of **Supplement 1**). (Strength of recommendation: strong [agreement, 82%])

Clinical considerations: Clinicians and patients should consider nasal closure when epistaxis affects QOL or is life-threatening; they should consider the risks and benefits, as well as alternatives, such as septodermoplasty and antiangiogenic medications.

GI Bleeding Management

Recommendation B1: The expert panel recommends esophagogastroduodenoscopy as the first-line diagnostic test for suspected HHT-related bleeding. Patients who meet colorectal cancer screening criteria and patients with SMAD4*-HHT (genetically proven or suspected) should also undergo colonoscopy.* (Quality of evidence: low [agreement, 82%])

Several cross-sectional studies of diagnostic yield demonstrated a high yield from esophagogastroduodenoscopy (EGD) for upper GI telangiectases in patients with HHT and suspected GI bleeding (30–32) (**Table 5** of **Supplement 1**). (Strength of recommendation: strong [agreement, 94%])

Clinical considerations: Clinicians should consider performing EGD in an experienced center given potential unusual complications during the procedure (such as massive epistaxis) and should also be aware of the

precautions required for patients with HHT and pulmonary arteriovenous malformations (AVMs) (**Table**).

In suspected or proven *SMAD4*-HHT, screening colonoscopy is recommended starting at age 15 years and repeated every 3 years if no polyps are found or every year along with EGD if colonic polyps are found. Other patients with HHT (non-*SMAD4*) should be screened for colon cancer following general population guidelines.

Recommendation B2: The expert panel recommends considering capsule endoscopy for suspected HHT-related bleeding when esophagogastroduodenoscopy does not reveal significant HHT-related telangiectasia. (Quality of evidence: low [agreement, 92%])

Several cross-sectional studies of diagnostic yield demonstrated a high yield from capsule endoscopy, with an excellent safety profile, for small-bowel GI telangiectases in patients with HHT and suspected GI bleeding (30–34) (**Table 5** of **Supplement 1**). (Strength of recommendation: strong [agreement, 88%])

Clinical considerations: Capsule endoscopy remains complementary to EGD when anemia is unexplained by the severity of epistaxis and gastric involvement or when the EGD findings are negative.

Recommendation B3: The expert panel recommends that clinicians grade the severity of HHT-related GI bleeding and proposes the following framework:

- *Mild HHT-related GI bleeding: patient who meets their hemoglobin goals* with oral iron replacement*
- *Moderate HHT-related GI bleeding: patient who meets their hemoglobin goals* with intravenous iron treatment*
- *Severe HHT-related GI bleeding: patient who does not meet their hemoglobin goals* despite adequate iron replacement or requires blood transfusions*

** Hemoglobin goals should reflect age, gender, symptoms, and comorbidities.* (Quality of evidence: low [expert consensus] [agreement, 96%])

Case series describe a severity range for HHT-related GI bleeding, with secondary anemia, reduced QOL, blood transfusion requirements, hospitalization, morbidity, and mortality (32, 35–41). (Strength of recommendation: strong [agreement, 96%])

Clinical considerations: Hemoglobin goals (not levels) are specified to reflect the patient's individual physiologic needs. This classification applies to patients who have had at least 3 months of iron therapy.

Recommendation B4: The expert panel recommends that endoscopic argon plasma coagulation be only used sparingly during endoscopy. (Quality of evidence: low [expert consensus] [agreement, 88%])

Expert consensus in HHT and case series in patients without HHT show some benefit from endoscopic argon plasma coagulation (42, 43). (Strength of recommendation: weak [agreement, 81%])

Clinical considerations: Argon plasma coagulation is best administered concurrent with the initial endoscopic evaluation for bleeding lesions and significant (1- to 3-mm) nonbleeding lesions. Repeated sessions are discouraged to avoid repeated iatrogenic injury to the intestinal mucosa.

Recommendation B5: The expert panel recommends that clinicians consider treatment of mild HHT-related GI bleeding with oral antifibrinolytics. (Quality of evidence: low [agreement, 94%])

One case series reported reduced need for endoscopic management in patients treated with oral tranexamic acid (44) (**Table 6** of **Supplement 1**) with a good safety profile. (Strength of recommendation: weak [agreement, 90%])

Clinical considerations: **Table 4** of **Supplement 1** gives prescribing and safety monitoring guidance for oral tranexamic acid.

Recommendation B6: The expert panel recommends that clinicians consider treatment of moderate to severe HHT-related GI bleeding with intravenous bevacizumab or other systemic antiangiogenic therapy. (Quality of evidence: moderate [agreement, 94%])

Small uncontrolled series showed that systemic antiangiogenic therapies alleviated anemia, reduced transfusion requirements, or improved QOL (19, 21, 45) (**Table 6** of **Supplement 1**). (Strength of recommendation: strong [agreement, 98%])

Clinical considerations: **Table 4** of **Supplement 1** gives prescribing and safety monitoring guidance for IV bevacizumab.

Anemia and Anticoagulation

Recommendation C1: The expert panel recommends that the following HHT patients be tested for iron deficiency and anemia:

- *All adults, regardless of symptoms*
- *All children with recurrent bleeding and/or symptoms of anemia* (Quality of evidence: high [agreement, 98%])

Three case series reported iron deficiency anemia as a common complication of HHT, typically in adults (36, 46, 47). (Strength of recommendation: strong [agreement, 96%])

Clinical considerations: Testing typically includes complete blood count and ferritin measurement. If a patient is anemic but ferritin is not reduced, serum iron, total iron-binding capacity, and transferrin saturation should be measured and a hematology consultation should be considered.

Recommendation C2: The expert panel recommends iron replacement for treatment of iron deficiency and anemia as follows:

- *Initial therapy with oral iron*
- *Intravenous iron replacement for patients in whom oral is not effective, not absorbed, or not tolerated, or who are presenting with severe anemia* (Quality of evidence: moderate [agreement, 88%])

Evidence for iron replacement and initial dosing are based on case series in HHT and non-HHT iron deficiency anemia (48–53). (Strength of recommendation: strong [agreement, 100%])

Clinical considerations: Iron replacement typically starts with once-daily oral dosing of 35 to 65 mg of elemental iron, 2 hours before or 1 hour after meals. An increase in hemoglobin of less than 10 g/L is considered inadequate in anemic patients, and every-other-day dosing or an alternate preparation of oral iron should be attempted. In refractory anemia or severe chronic bleeding, regularly scheduled iron infusions may be required. Initial IV iron dosing can be calculated (54), or a total initial dose of 1 g of IV iron can be provided, as a single infusion or divided doses. **Supplement 1** details additional safety and prescribing information.

Recommendation C3: The expert panel recommends red blood cell transfusions in the following settings:

- *Hemodynamic instability/shock*
- *Comorbidities that require a higher hemoglobin target*
- *Need to increase the hemoglobin acutely, such as prior to surgery or during pregnancy*
- *Inability to maintain an adequate hemoglobin despite frequent iron infusions* (Quality of evidence: low [agreement, 92%])

Expert consensus in HHT. (Strength of recommendation: strong [agreement, 96%])

Clinical considerations: Hemoglobin targets and thresholds for red blood cell transfusion should be individualized in HHT, depending on patient symptoms, severity of ongoing HHT-related bleeding, response to other therapies and iron supplementation, presence of comorbid conditions, and acuity.

Recommendation C4: The expert panel recommends considering evaluation for additional causes of anemia in the setting of an inadequate response to iron replacement. (Quality of evidence: low [agreement, 100%])

One case series reported folate deficiency and hemolysis as additional causes of anemia in patients with HHT (55). (Strength of recommendation: strong [agreement, 100%])

Clinical considerations: Evaluation should include measurement of folate, vitamin B_{12}, mean corpuscular volume, and thyroid-stimulating hormone; smear; reticulocyte counts; and work-up for hemolysis, with referral to hematology in unresolved cases.

Recommendation C5: The expert panel recommends that HHT patients receive anticoagulation (prophylactic or therapeutic) or antiplatelet therapy when there is an indication, with consideration of their individualized bleeding risks; bleeding in HHT is not an absolute contraindication for these therapies. (Quality of evidence: low [agreement, 98%])

Expert consensus in HHT and 2 case series demonstrated that anticoagulation or antiplatelet therapy is well tolerated by most patients with HHT (56, 57). (Strength of recommendation: strong [agreement, 98%])

Clinical considerations: When anticoagulation is pursued, unfractionated heparin, low-molecular-weight heparin, and vitamin K antagonists are preferred over direct-acting oral anticoagulants, which are less well tolerated in HHT (58). In cases of atrial fibrillation, if anticoagulation is not tolerated, alternate approaches can be considered, such as left atrial appendage closure (59).

Recommendation C6: The panel recommends avoiding the use of dual antiplatelet therapy and/or combination of antiplatelet therapy and anticoagulation, where possible, in patients with HHT. (Quality of evidence: low (expert consensus) [agreement, 83%])

Expert consensus in HHT. (Strength of recommendation: weak [agreement, 92%])

Clinical considerations: If dual or combination therapies are required, duration of therapy should be minimized and patients should be monitored closely.

Liver VMs in HHT

Recommendation D1: The expert panel recommends that screening for liver VMs be offered to adults with definite or suspected HHT. (Quality of evidence: low [agreement, 84%])

Several cross-sectional diagnostic studies demonstrated high yield and accuracy of Doppler ultrasonography, multiphase contrast computed tomography (CT), and magnetic resonance imaging (MRI) for detection of liver VMs (5, 60–68) (**Table 7** of **Supplement 1**); Doppler ultrasonography severity grading was predictive of outcomes (69). Anicteric cholestasis, reported in one third of patients with liver VMs, correlated with severity of liver VMs and complications (69–71). (Strength of recommendation: weak [agreement, 93%])

Clinical considerations: The rationale for screening is that awareness of liver VMs could improve subsequent patient management or help confirm the diagnosis of HHT. The imaging test of choice is Doppler ultrasonography because of its accuracy, safety, tolerability, low costs, and operating characteristics. However, depending on local availability of and expertise in Doppler ultrasonography, as well as patient preference, patients may be screened clinically (history, physical examination, and blood work) or alternative imaging may be considered, including multiphase contrast CT or MRI.

Recommendation D2: The expert panel recommends diagnostic testing for liver VMs in HHT patients with symptoms and/or signs suggestive of complicated liver VMs (including heart failure, pulmonary hypertension, abnormal cardiac biomarkers, abnormal liver function tests, abdominal pain, portal hypertension, or encephalopathy), using Doppler ultrasound, multiphase contrast CT scan, or contrast abdominal MRI for diagnostic assessment of liver VMs. (Quality of evidence: high [agreement, 98%])

Several cross-sectional diagnostic studies demonstrated high yield and accuracy of Doppler ultrasonography, multiphase contrast CT, and MRI for diagnosis of liver VMs (5, 60–68) (**Table 7** of **Supplement 1**). (Strength of recommendation: strong [agreement, 100%])

Clinical considerations: The choice of imaging method should be informed by the risk–benefit balance, local expertise, and availability or cost. Contrast studies (CT and MRI) should be avoided if kidney dys-

function is present. Echocardiography provides additional information about the hemodynamic effect of liver VMs. These tests will be most informative when done in the context of a clinical assessment at an HHT center of excellence.

Recommendation D3: The expert panel recommends an intensive first-line management only for patients with complicated and/or symptomatic liver VMs, tailored to the type of liver VM complication(s).

The expert panel recommends that HHT patients with high-output cardiac failure and pulmonary hypertension be comanaged by the HHT Center of Excellence and an HHT cardiologist or a pulmonary hypertension specialty clinic. (Quality of evidence: moderate [agreement, 88%])

One large series showed moderate response to first-line therapy tailored to liver VM complication (69). Expert consensus supported the recommendation for specialized center management. (Strength of recommendation: strong [agreement, 88%])

Clinical considerations: **Supplement 1** describes first-line therapies, by specific liver VM complication. Typically, patients with symptomatic liver VMs are managed by an expert team at an HHT center of excellence, with at least annual follow-up.

Recommendation D4: The expert panel recommends that clinicians estimate prognosis of liver VMs using available predictors, to identify patients in need of closer monitoring. (Quality of evidence: moderate [agreement, 89%])

Three observational studies identified clinical predictors of complications from liver VMs (69, 70, 72). (Strength of recommendation: strong [agreement, 82%])

Clinical considerations: Clinicians should plan monitoring for patients with liver VMs on the basis of estimated prognosis.

Recommendation D5: The expert panel recommends considering intravenous bevacizumab for patients with symptomatic high-output cardiac failure due to liver VMs who have failed to respond sufficiently to first-line management. (Quality of evidence: moderate [agreement, 98%])

Small uncontrolled series showed that IV bevacizumab improved cardiac output or clinical symptoms in 80% of patients with severe liver VMs, primarily in those with high-output cardiac failure (16) (**Table 8** of **Supplement 1**). The adverse event rate was reported at 50 per 100 person-years, including 1 fatal event probably related to bevacizumab (73). (Strength of recommendation: strong [agreement, 98%])

Table 4 of **Supplement 1** gives prescribing and safety monitoring guidance for IV bevacizumab.

Recommendation D6: The expert panel recommends referral for consideration of liver transplantation for patients with symptomatic complications of liver VMs, specifically refractory high-output cardiac failure, biliary ischemia, or complicated portal hypertension. (Quality of evidence: moderate [agreement, 83%])

Small uncontrolled series of orthotopic liver transplantation for liver VMs in HHT demonstrated excellent 5- to 10-year survival (82% to 92%) (74, 75) with asymptomatic rare and late recurrence of liver VMs after liver transplantation (76). (Strength of recommendation: strong [agreement, 92%])

Clinical considerations: Timing for listing a symptomatic patient for orthotopic liver transplantation should be based on prognostic predictors and the severity of liver VM complications, including pulmonary hypertension. Liver transplantation can be undertaken in the presence of pulmonary hypertension if pulmonary vascular resistance, estimated by right heart catheterization, is less than 3 Woods units.

Pediatric Care

Recommendation E1: The expert panel advises that diagnostic genetic testing be offered for asymptomatic children of a parent with HHT. (Quality of evidence: high [agreement, 96%])

Two cross-sectional diagnostic studies demonstrated that genetic testing can identify subclinical or presymptomatic disease in children of HHT families with known mutation (77–79). (Strength of recommendation: strong [agreement, 94%])

Clinical considerations: An affected family member should be tested first to determine the causative mutation before testing an asymptomatic child who does not meet the clinical diagnostic criteria for HHT (Curaçao criteria) (4). The benefits of testing, alternatives, pros, and cons should be discussed with children or—as appropriate—their parents.

Recommendation E2: The expert panel recommends screening for pulmonary AVMs in asymptomatic children with HHT or at risk for HHT at the time of presentation/diagnosis. (Quality of evidence: moderate [agreement, 94%])

Several pediatric case series demonstrated a prevalence of pulmonary AVMs similar to that in adults and a risk for life-threatening complications with good outcomes from embolization (80–85). Several series have reported 2 sensitive screening protocols in children (86–90) (**Table 9** of **Supplement 1**). (Strength of recommendation: strong [agreement, 94%])

Clinical considerations: Screening may be performed with either chest radiography and pulse oximetry or transthoracic contrast echocardiography. Screening with CT is not recommended, although chest CT remains the confirmatory diagnostic test when screening tests have positive findings.

Recommendation E3: The expert panel recommends that large pulmonary AVMs and pulmonary AVMs associated with reduced oxygen saturation be treated in children to avoid serious complications. (Quality of evidence: moderate [agreement, 98%])

Case series demonstrated that children are at risk for serious complications from large pulmonary AVMs (or AVMs causing hypoxemia) (82, 83, 85) and that embolization is safe and effective (85) (**Table 10** of **Supplement 1**). (Strength of recommendation: strong [agreement, 98%])

Clinical considerations: Pulmonary AVMs with feeding arteries at least 3 mm in diameter are suitable for embolotherapy. Follow-up is indicated to detect recanalization and reperfusion of treated AVMs and growth

of small untreated AVMs. Specific protocols vary among centers (CT, oximetry, or transthoracic contrast echocardiography), as do intervals.

Recommendation E4: The expert panel recommends repeating pulmonary AVM screening in asymptomatic children with HHT or at risk for HHT, typically at 5-year intervals. (Quality of evidence: low [agreement, 92%])

One case series showed growth of pulmonary AVMs during childhood (91). (Strength of recommendation: strong [agreement, 86%])

Clinical considerations: Screening is typically repeated every 5 years after negative findings. In children with indeterminate or borderline screening results based on either imaging or oximetry, screening should be repeated sooner.

Recommendation E5: The expert panel recommends screening for brain VM in asymptomatic children with HHT or at risk for HHT, at the time of presentation/diagnosis. (Quality of evidence: low [agreement, 86%])

Case series demonstrated risk for intracranial hemorrhage from brain VMs (92–95) in children; MRI as a sensitive screening test (96–98); and benefits of surgical and endovascular management (99, 100), also with significant risk. (Strength of recommendation: strong [agreement, 86%])

Clinical considerations: First-line screening is MRI (contrast-enhanced is more sensitive) to identify brain VMs and determine subtype and risk factors for hemorrhage. This typically requires sedation or anesthesia in young children. The decision to treat versus observe is based on risk of treatment versus risk for hemorrhage. As such, the decision to screen the child should be shared among clinicians, caregivers, and the child (where possible). Clinical practice differs across countries, from screening asymptomatic children with MRI in infancy to no routine screening of asymptomatic children for brain VMs. Patient representatives felt strongly that children should be screened for brain VMs and cited anecdotal evidence of disastrous outcomes in unscreened patients.

Recommendation E6: The expert panel recommends that brain VMs with high-risk features be treated. (Quality of evidence: low [agreement, 100%])

Case series demonstrated risk for intracranial hemorrhage from brain VMs (92–95); identified high-risk features (95, 101, 102); and showed the benefits of surgical and endovascular management (99, 100), also with significant risk. (Strength of recommendation: strong [agreement, 98%])

Clinical considerations: Given the need to balance natural history risk with treatment risk, children with HHT who have brain VMs should be referred to a center with multidisciplinary expertise in neurovascular disease management. Treated brain VMs require close follow-up; the follow-up for small (untreated) brain VMs is not well defined.

Pregnancy and Delivery

Recommendation F1: The expert panel recommends that clinicians discuss preconception and prenatal diagnostic options, including preimplantation genetic diagnosis, with HHT-affected individuals. (Quality of evidence: very low [agreement, 86%])

Expert consensus in HHT. (Strength of recommendation: strong [agreement, 83%])

Clinical considerations: Once the causative familial mutation is identified in an affected parent, it can be screened for in future offspring. Available options, including preimplantation, postconception, and postdelivery testing (**Supplement 1**), vary internationally. The discussion will be influenced by local legislation pertaining to preimplantation diagnosis and termination of pregnancy.

Recommendation F2: The expert panel recommends testing with unenhanced MRI in pregnant women with symptoms suggestive of brain VMs. (Quality of evidence: very low [agreement, 98%])

Expert consensus in HHT. (Strength of recommendation: strong [agreement, 92%])

Clinical considerations: For symptomatic patients, including those with previous cerebral hemorrhage, MRI without gadolinium should be planned in the second trimester. Asymptomatic patients do not require routine screening during pregnancy.

Recommendation F3: The expert panel recommends that pregnant women with HHT who have not been recently screened and/or treated for pulmonary AVM should be approached as follows:

- *In asymptomatic patients, initial pulmonary AVM screening should be performed using either agitated saline transthoracic contrast echocardiography (TTCE) or low-dose noncontrast chest CT, depending on local expertise. Chest CT, when performed, should be done early in the second trimester.*
- *In patients with symptoms suggestive of pulmonary AVM, diagnostic testing should be performed using low-dose noncontrast chest CT. This testing can be performed at any gestational age, as clinically indicated.*
- *Pulmonary AVMs should be treated starting in the second trimester unless otherwise clinically indicated.* (Quality of evidence: moderate [agreement, 88%])

Case series demonstrated elevated risk for complications from pulmonary AVMs during pregnancy (103–105) and low risk of imaging and embolization in the second trimester (106). (Strength of recommendation: strong [agreement, 83%])

Clinical considerations: Technique for embolization in pregnant patients should include measures to reduce fetal radiation exposure, including avoidance of fluoroscopy over the abdomen and pelvis, use of pulsed or low-dose fluoroscopy, minimization of angiography runs, and use of tight collimation. For both CT and angiography, abdominal shielding is not helpful and may in fact increase scattered radiation to the fetus.

Recommendation F4: The expert panel recommends that pregnant women with HHT be managed at a

tertiary care center by a multidisciplinary team if they have untreated pulmonary AVMs and/or brain VMs or have not been recently screened for pulmonary AVMs. (Quality of evidence: very low [agreement, 94%])

Expert consensus in HHT. (Strength of recommendation: strong [agreement, 85%])

Clinical considerations: Pregnant women with untreated pulmonary AVMs or brain VMs, as well as those who have not been screened, should be considered high-risk for hemorrhagic and neurologic complications and be managed accordingly by a high-risk team with HHT expertise.

Recommendation F5: The expert panel recommends not withholding an epidural because of a diagnosis of HHT, and that screening for spinal vascular malformations is not required. (Quality of evidence: low [agreement, 98%])

Two case series showed no evidence of hemorrhagic complications from epidural or spinal anesthesia (103, 107). (Strength of recommendation: strong [agreement, 92%])

Clinical considerations: Patients should meet with an anesthetist during the early third trimester to discuss anesthesia options. The risks for complications from spinal VMs during epidural anesthesia are unsubstantiated and only theoretical.

Recommendation F6: The expert panel recommends that women with known, non–high-risk brain VMs can labor and proceed with vaginal delivery. Patients may require an assisted second stage on a case-by-case basis. (Quality of evidence: moderate [agreement, 94%])

Two case series showed no intracranial hemorrhage during delivery from brain VMs in patients with HHT (103, 107). (Strength of recommendation: strong [agreement, 94%])

Clinical considerations: If a brain VM has not previously ruptured, patients may proceed with method of delivery based on obstetric indications and discussion with their obstetric care provider. Vaginal delivery is not contraindicated. Patients with "high-risk" brain VMs should be considered for cesarean section or epidural to allow passive descent of the presenting part, with consideration of an assisted second stage. Diligent management of blood pressure is imperative in these higher-risk cases, and obtaining the opinion a multidisciplinary neurovascular team is prudent.

From St. Michael's Hospital, Li Ka Shing Knowledge Institute, and University of Toronto, Toronto, Ontario, Canada (M.E.F.); St. Antonius Hospital, Nieuwegein, the Netherlands (J.J.M.); University of California, San Francisco, San Francisco, California (S.W.H., M.C.); University of Toronto, Toronto, Ontario, Canada (V.A.P.); Centre for Effective Practice, Toronto, Ontario, Canada (K.L.); HHT Reference Center ERN, Ospedale Maggiore, ASST Crema, Crema, Italy (E.B.); Centre Hospitalier de l'Université de Montréal, Hôtel-Dieu, Montreal, Quebec, Canada (E.D.); University of North Carolina at Chapel Hill, Chapel Hill, North Carolina (R.S.K., J.D.); St. Michael's Hospital and University of Toronto, Toronto, Ontario, Canada (A.L., R.P.); Froedtert and Medical College of Wisconsin, Milwaukee, Wisconsin (D.P., P.F.); The Hospital for Sick Children and University of Toronto, Toronto, Ontario, Canada (F.R.); VA Portland Health Care System and Oregon Health & Science University, Portland, Oregon (M.S.C.); Cure HHT, Monkton, Maryland (M.C., S.O.); University of Utah Medical Center, Salt Lake City, Utah (K.J.W., J.M.); Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts (H.A.); Washington University School of Medicine, St. Louis, Missouri (M.C., K.K., J.F.P., A.J.W.); St. Michael's Hospital and Unity Health Toronto, Toronto, Canada (D.C.); HHT Europe, Rome, Italy (C.C.); Grace Hospital, Winnipeg, Manitoba, Canada (E.D.); HHT Canada, Spruce Grove, Alberta, Canada (C.D.); Hospices Civils de Lyon, Femme-Mère-Enfant, Lyon, France (S.D.); University Hospital of Marburg and Phillips University Marburg, Marburg, Germany (U.G.); Augusta University, Augusta, Georgia (J.R.G.); Cincinnati Children's Hospital and University of Cincinnati, Cincinnati, Ohio (A.H.); Oslo University Hospital, Rikshospitalet, Oslo, Norway (K.H.); Yale University School of Medicine, New Haven, Connecticut (K.H.); Mayo Clinic, Rochester, Minnesota (V.N.I.); Odense University Hospital, Odense, Denmark (A.D.K.); Osaka City General Hospital, Osaka, Japan (M.K.); Chester, New Jersey (J.M.); University of California, Los Angeles, Los Angeles, California (J.M.); University of Arkansas for Medical Sciences, Little Rock, Arkansas (M.E.M.); Schneider Children's Medical Center of Israel and Sackler School of Medicine of Tel Aviv University, Tel Aviv, Israel (M.M.); Baltimore, Maryland (S.P.); Sioux Falls, South Dakota (B.P.); University of Edinburgh, Edinburgh, Scotland (M.E.P.); St. Antonius Hospital, Nieuwegein, and University Medical Center Utrecht, Utrecht, the Netherlands (M.C.P.); Toronto Western Hospital and University of Toronto, Toronto, Ontario, Canada (I.R.); University of Colorado Hospital, Aurora, Colorado (P.J.R.); Massachusetts General Hospital, Boston, Massachusetts (J.R.); University of Bari, Bari, Italy (C.S.); Hospital Italiano de Buenos Aires, Buenos Aires, Argentina (M.S.); Hammersmith Hospital, London, England (C.S.); Blue Bell, Pennsylvania (D.S.); Royal Melbourne Hospital and University of Melbourne, Melbourne, Victoria, Australia (I.W.); and Hospital Sierrallana (Servicio Cántabro de Salud), Torrelavega, Spain (R.Z.).

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Corresponding Author: Marie E. Faughnan, MD, MSc, St. Michael's Hospital, University of Toronto, 30 Bond Street, Toronto, ON M5B 1W8, Canada; e-mail, marie.faughnan@unityhealth.to.

Current author addresses and author contributions are available at Annals.org.

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Current Author Addresses: Drs. Faughnan, Palda, and Lausman; Mr. Cortes; and Ms. Pantalone: St. Michael's Hospital, University of Toronto, 30 Bond Street, Toronto, ON M5B 1W8, Canada.
Drs. Mager and Post: St. Antonius Hospital, Koekoekslaan 1, Nieuwegein 3435 CM, the Netherlands.
Dr. Hetts: Department of Neurointerventional Radiology, University of California, San Francisco, 505 Parnassus Avenue, L-351, San Francisco, CA 94143.
Ms. Lang-Robertson: Centre for Effective Practice, 400 University Avenue, Suite 2100, Toronto, ON M5G 1S5, Canada.
Dr. Buscarini: UOC Gastroenterologia ed Endoscopia Digestiva, Ospedale Maggiore, ASST Crema, Largo Dossena 2, Crema, 26013 Italy.
Dr. Deslandres: Department of Gastroenterology, CHUM, Hotel Dieu, 1051 Rue Sanguinet, C.02.7013, Montreal, QC H2X 0C1, Canada.
Dr. Kasthuri: Division of Hematology/Oncology, University of North Carolina, Chapel Hill, 116 Manning Drive, CB7035, 8206B Mary Ellen Jones, Chapel Hill, NC 27599.
Dr. Poetker: Department of Otolaryngology, Froedtert and Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226.
Dr. Ratjen: Department of Pediatrics, The Hospital for Sick Children, 555 University Avenue, Toronto, ON M5G 1X8, Canada.
Dr. Chesnutt: VA Portland Health Care System, HHT Center of Excellence, 3710 SW US Veterans Hospital Road, P2IES, Portland, OR 97221.
Ms. Clancy and Dr. Olitsky: Cure HHT, PO Box 329, Monkton, MD 21111.
Dr. Whitehead: Department of Cardiovascular Medicine and Pediatric Cardiology, University of Utah Medical Center, 30 North 1900 South, Room 4A100, Salt Lake City, UT 84132.
Dr. Al-Samkari: Division of Hematology, Massachusetts General Hospital, Harvard Medical School, Zero Emerson Place Suite 118, Office 112, Boston, MA 02114.
Dr. Chakinala: Department of Pulmonology and Critical Care, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8052, St. Louis, MO 63110.
Dr. Conrad: Zuckerberg San Francisco General Hospital, 1001 Potrero Avenue, San Francisco, CA 94114.
Ms. Crocione: HHT Europe, Via Europa 63, Rome, 05022 Italy.
Dr. Darling: Department of Hepatology, University of North Carolina, Chapel Hill, 8014 Burnett Womack Building, CB 7584, Chapel Hill, NC 27599.
Dr. de Gussem: Department of Medicine, Section of Respirology, Grace Hospital, 300 Booth Drive, Winnipeg, MB R3J 3M7, Canada.
Dr. Dupuis-Girod: Hospices Civils de Lyon, Femme-Mère-Enfant, 59 Boulevard Pinel, 69677 Bron, France.
Dr. Foy: Department of Hematology, Froedtert and Medical College of Wisconsin, 9200 West Wisconsin Avenue, Milwaukee, WI 53226.
Dr. Geisthoff: Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital of Marburg, Phillips University Marburg, Baldingerstraße, 35043 Marburg, Germany.
Dr. Gossage: Augusta University, 1120 Fifteenth Street, BBR-5513, Augusta, GA 30912.
Dr. Hammill: Division of Hematology, Cancer and Blood Diseases Institute, Cincinnati Children's Hospital, and Department of Pediatrics, University of Cincinnati, 3333 Burnet Avenue, MLC 7015, Cincinnati, OH 45229.
Dr. Heimdal: Department of Genetics, Oslo University Hospital, Rikshospitalet, PO Box 4950 Nydalen, 4950 Oslo, Norway.
Ms. Henderson: Yale University School of Medicine, PO Box 208042, New Haven, CT 06520.
Dr. Iyer: Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN 55905.
Dr. Kjeldsen: Department of Otorhinolaryngology Head and Neck Surgery, HHT-center OUH, J.B.Winsløws Vej 4, 5000 Odense, Denmark.
Dr. Komiyama: Department of Neurointervention, Osaka City General Hospital, 2-13-22, Miyakojima-Hondori, Miyakojima, Osaka 534-0021, Japan.
Dr. Korenblatt: Department of Hepatology, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8124, St. Louis, MO 63110,
Ms. McDonald: Department of Pathology and Radiology, University of Utah Medical Center, 50 North Medical Drive 4A100, Salt Lake City, UT 84132.
Dr. McWilliams: Department of Interventional Radiology, University of California, Los Angeles, 757 Westwood Plaza, Suite 2125C, Los Angeles, CA 90095.
Dr. Meek: Department of Interventional Radiology, University of Arkansas for Medical Sciences, 4301 West Markham Street, Slot 556, Little Rock, AR 72205.
Dr. Mei-Zahav: Pulmonary Institute, Schneider CMCI, 14 Kaplan Street, Petach Tikva, 49202, Israel.
Dr. Piccirillo: Department of Otolaryngology-Head & Neck Surgery, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8115, St. Louis, MO 63110.
Dr. Porteous: Department of Genetics University of Edinburgh, Center of Molecular Medicine, Crewe Road, Edinburgh EH4 2XU, Scotland.
Dr. Radovanovic: Department of Neurosurgery, University Health Network, Toronto Western Hospital, 399 Bathurst Street, Toronto, ON M5T 2S8, Canada.
Dr. Rochon: University of Colorado Hospital, 12631 East 17th Avenue, Mailstop 8200, Aurora, CO 80048.
Dr. Rodriguez-Lopez: Department of Pulmonology, Massachusetts General Hospital, 55 Fruit Street, Bulfinch 148, Boston, MA 02114.
Dr. Sabba: Department of Internal Medicine, University of Bari, Policlinico, Piazza Giulio Cesare, Bari, 70124 Italy.
Dr. Serra: Department of Internal Medicine, Hospital Italiano de Buenos Aires, Araoz 2067, Buenos Aires 1425, Argentina.
Dr. Shovlin: Department of Pulmonology, Hammersmith Hospital, Du Cane Road, London W12 0NN, England.
Dr. White: Division of Pediatric Immunology and Rheumatology, Washington University School of Medicine, One Children's Place, St. Louis, MO 63110.
Dr. Winship: Genomic Medicine, Royal Melbourne Hospital and University of Melbourne, Grattan Street, Melbourne, VIC 3002, Australia.
Dr. Zarrabeitia: Hospital Sierrallana, Barrio Ganzo s/n, 39300 Torrelavega, Cantabria, Spain.

Author Contributions: Conception and design: M.E. Faughnan, J.J. Mager, S.W. Hetts, V.A. Palda, E. Buscarini, E. Deslandres, R.S. Kasthuri, F. Ratjen, M.S. Chesnutt, E. de Gussem, A. Hammill, A.D. Kjeldsen, J. McDonald, M. Mei-Zahav, S. Olitsky, B. Plahn, M.C. Post, C. Shovlin, A.J. White, I. Winship.
Analysis and interpretation of the data: M.E. Faughnan, J.J. Mager, S.W. Hetts, V.A. Palda, E. Buscarini, E. Deslandres, R.S. Kasthuri, D. Poetker, F. Ratjen, M.S. Chesnutt, M. Clancy, K.J.

Whitehead, H. Al-Samkari, M. Conrad, C. Crocione, J. Darling, E. de Gussem, P. Foy, U. Geisthoff, J.R. Gossage, K. Heimdal, K. Henderson, V.N. Iyer, A.D. Kjeldsen, M. Komiyama, J. McDonald, J. McMahon, J. McWilliams, M.E. Meek, M. Mei-Zahav, S. Olitsky, S. Palmer, R. Pantalone, J.F. Piccirillo, M.E.M. Porteous, I. Radovanovic, P.J. Rochon, C. Sabba, M. Serra, C. Shovlin, D. Sprecher, A.J. White, I. Winship, R. Zarrabeitia.

Drafting of the article: M.E. Faughnan, J.J. Mager, S.W. Hetts, V.A. Palda, K. Lang-Robertson, E. Buscarini, E. Deslandres, R.S. Kasthuri, A. Lausman, D. Poetker, F. Ratjen, M.S. Chesnutt, M. Clancy, K.J. Whitehead, M. Chakinala, E. de Gussem, J.R. Gossage, K. Henderson, V.N. Iyer, M. Mei-Zahav, R. Pantalone, B. Plahn, M.C. Post, P.J. Rochon, M. Serra, R. Zarrabeitia.

Critical revision of the article for important intellectual content: M.E. Faughnan, J.J. Mager, S.W. Hetts, V.A. Palda, E. Buscarini, E. Deslandres, R.S. Kasthuri, A. Lausman, D. Poetker, F. Ratjen, M.S. Chesnutt, K.J. Whitehead, H. Al-Samkari, M. Chakinala, M. Conrad, J. Darling, E. de Gussem, S. Dupuis-Girod, P. Foy, U. Geisthoff, J.R. Gossage, A. Hammill, K. Heimdal, K. Henderson, V.N. Iyer, A.D. Kjeldsen, K. Korenblatt, J. McWilliams, M. Mei-Zahav, R. Pantalone, J.F. Piccirillo, M.E.M. Porteous, M.C. Post, I. Radovanovic, P.J. Rochon, J. Rodriguez-Lopez, C. Sabba, M. Serra, C. Shovlin, D. Sprecher, A.J. White, I. Winship, R. Zarrabeitia.

Final approval of the article: M.E. Faughnan, J.J. Mager, S.W. Hetts, V.A. Palda, K. Lang-Robertson, E. Buscarini, E. Deslandres, R.S. Kasthuri, A. Lausman, D. Poetker, F. Ratjen, M.S. Chesnutt, M. Clancy, K.J. Whitehead, H. Al-Samkari, M. Chakinala, M. Conrad, D. Cortes, C. Crocione, J. Darling, E. de Gussem, C. Derksen, S. Dupuis-Girod, P. Foy, U. Geisthoff, J.R. Gossage, A. Hammill, K. Heimdal, K. Henderson, V.N. Iyer, A.D. Kjeldsen, M. Komiyama, K. Korenblatt, J. McDonald, J. McMahon, J. McWilliams, M.E. Meek, M. Mei-Zahav, S. Olitsky, S. Palmer, R. Pantalone, J.F. Piccirillo, B. Plahn, M.E.M. Porteous, M.C. Post, I. Radovanovic, P.J. Rochon, J. Rodriguez-Lopez, C. Sabba, M. Serra, C. Shovlin, D. Sprecher, A.J. White, I. Winship, R. Zarrabeitia.

Provision of study materials or patients: F. Ratjen, E. de Gussem, J. McDonald.

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Collection and assembly of data: M.E. Faughnan, J.J. Mager, S.W. Hetts, K. Lang-Robertson, E. Buscarini, E. Deslandres, R.S. Kasthuri, A. Lausman, D. Poetker, F. Ratjen, H. Al-Samkari, M. Chakinala, D. Cortes, E. de Gussem, J.R. Gossage, A. Hammill, K. Henderson, V.N. Iyer, A.D. Kjeldsen, M. Komiyama, J. McDonald, J. McWilliams, M. Mei-Zahav, M.C. Post, I. Radovanovic, P.J. Rochon, J. Rodriguez-Lopez, M. Serra, C. Shovlin, A.J. White, I. Winship, R. Zarrabeitia.