MY HHT CARE CHECKLIST

USING THE HHT GUIDELINES

HHT=hereditary hemorrhagic telangiectasia

Date: _____

Name: _____

Please check all that apply

☐ I HAVE HHT OR I SUSPECT THAT I MIGHT HAVE IT.

- ☐ Review the HHT Diagnosis Care Checklist with my doctor, to confirm or rule out my HHT diagnosis and to determine if I need genetic testing.

☐ I AM AN ADULT WITH HHT OR POSSIBLE HHT.

- ☐ Review the HHT Epistaxis Care Checklist with my doctor, because I have nosebleeds.
- ☐ Review the HHT Brain VM Care Checklist with my doctor, even if I am not sure if I have brain VMs.
- ☐ Review the HHT Pulmonary AVM Care Checklist with my doctor, even if I am not sure if I have lung AVMs.
- ☐ Review the HHT Liver VM Care Checklist with my doctor, even if I am not sure if I have liver VMs.
- ☐ Review the HHT GI Bleeding Care Checklist with my doctor, even if I am not sure if I have bleeding from the stomach or bowels.
- ☐ Review the HHT Anemia and Iron Deficiency Care Checklist with my doctor, even if I am not aware of any bleeding symptoms.

☐ I AM PREGNANT OR PLANNING A PREGNANCY, AND I MIGHT HAVE HHT.

- ☐ Review the HHT Pregnancy and Delivery Care Checklist.

☐ I AM A TEEN AND I MIGHT HAVE HHT.

- ☐ Review the HHT Teen Years Pediatric Care Checklist.

☐ I HAVE CHILDREN AND THEY MIGHT HAVE HHT.

- ☐ Review the HHT Pediatric Care Checklist.

INTERNATIONAL HHT GUIDELINES

WHAT ARE THE HHT GUIDELINES AND WHY ARE THEY IMPORTANT?

- The HHT Guidelines are recommendations for care based on evidence and expertise from HHT experts from around the world.
- The HHT Guidelines help ensure that people living with HHT get the best care possible.

WHAT IS MY ROLE AS SOMEONE LIVING WITH HHT?

- Be aware of the Guidelines. Share them with your care team. Ideally you should be seen at an HHT Center of Excellence or your care team may want to consult with one.
- Read up on your condition and know what care is available for HHT.
- **Prepare ahead of time for your appointments**: Bring your HHT Care Checklists and a family member or friend. They can help you communicate your questions and priorities, as well as act as a second set of ears. Share your experiences, worries and priorities to help your care team better understand your needs and provide individualized care.

MY HHT DIAGNOSIS CARE CHECKLIST

USING THE HHT GUIDELINES

The HHT Diagnosis Guidelines are detailed on the next pages

Date: _____

Name: _____

Please check all that apply

☐ I THINK I MIGHT HAVE HHT, BUT I HAVE NOT BEEN FORMALLY DIAGNOSED.

- ☐ I assume I have HHT until the diagnosis is ruled out.
- ☐ Check with my doctor to confirm if I meet the criteria for a definite clinical diagnosis of HHT (using the Curaçao Criteria).
- ☐ Ask my relatives if they have been diagnosed with HHT or have typical symptoms.
- ☐ Check with family to find out if an HHT mutation has been identified in our family.
- ☐ I am still unsure if I have HHT and my family's mutation is known: Ask my doctor to refer me for genetic testing to determine if I carry the family mutation.
- ☐ I am still unsure if I have HHT but my family's mutation is not known: Ask my doctor to refer me for genetic testing, to determine if I have a typical HHT mutation.

☐ I HAVE A DEFINITE CLINICAL DIAGNOSIS OF HHT. DO I ALSO NEED GENETIC TESTING?

- ☐ I don't require genetic testing for my own personal HHT care.
- ☐ If no one else in the family has had genetic testing or if results are unclear, I can ask for HHT genetic testing, so that my results can help sort out my relatives' diagnoses.

☐ I HAVE NO SYMPTOMS OF HHT, BUT MY RELATIVES HAVE IT.

- ☐ I assume I have HHT until the diagnosis is ruled out.
- ☐ Check with my doctor to confirm if I meet the criteria for a definite clinical diagnosis of HHT (using the Curaçao Criteria).
- ☐ Check with family to find out if an HHT mutation has been identified in our family.
- ☐ If the family's genetic mutation is known: Ask my doctor to refer me for genetic testing to determine if I carry the family mutation.
- ☐ If my family's mutation is not known or available: Ask my doctor to refer me for genetic testing, to determine if I have a typical HHT mutation.

INTERNATIONAL HHT GUIDELINES

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WHAT IS MY ROLE AS SOMEONE LIVING WITH HHT?

- Be aware of the Guidelines. Share them with your care team. Ideally you should be seen at an HHT Center of Excellence or your care team may want to consult with one.
- Read up on your condition and know what care is available for HHT.
- **Prepare ahead of time for your appointments**: Bring your HHT Care Checklists and a family member or friend. They can help you communicate your questions and priorities, as well as act as a second set of ears. Share your experiences, worries and priorities to help your care team better understand your needs and provide individualized care.

DIAGNOSIS OF HHT

Making the diagnosis of HHT in a patient allows for the appropriate screening and preventative treatment to be undertaken in the patient and their affected family members. The cornerstone of HHT diagnosis is the clinical diagnosis, but HHT can now also be diagnosed using genetic testing. The clinical diagnostic criteria are called the "Curaçao Criteria" (Table) and are based on the typical symptoms, signs and organ involvement in HHT, as well as the family history. The goal of genetic testing for HHT is to clarify the specific HHT mutation in an HHT family, allowing diagnosis among those relatives (often children and young adults) who do not meet clinical diagnostic criteria.

HHT GUIDELINES RECOMMENDATIONS

DIAGNOSIS OF HHT

Making the diagnosis of HHT in a patient allows for the appropriate screening and preventative treatment to be undertaken in the patient and their affected family members. The cornerstone of HHT diagnosis is the clinical diagnosis, but HHT can now also be diagnosed using genetic testing. The clinical diagnostic criteria are called the "Curaçao Criteria" (Table) and are based on the typical symptoms, signs and organ involvement in HHT, as well as the family history. The goal of genetic testing for HHT is to clarify the specific HHT mutation in an HHT family, allowing diagnosis among those relatives (often children and young adults) who do not meet clinical diagnostic criteria.

The expert panel recommends that:
(all recommendations are from the First HHT Guidelines)

G1 CLINICIANS DIAGNOSE HHT USING THE CURAÇAO CRITERIA (TABLE) OR BY IDENTIFICATION OF A CAUSATIVE MUTATION.

Clinical Considerations: Applying the Curaçao Criteria for clinical diagnosis of HHT requires a targeted, multigeneration family history for HHT, given that most individuals with HHT will have an affected parent, grandparent and other close relatives. When applying the Curaçao Criteria, the clinician should consider the patient's age, given the frequently delayed appearance of the signs and symptoms of HHT. At least 90% of patients with HHT meet the clinical criteria by age 40, but few do in the first decade of life. If a patient has clinical features suggestive of HHT, but no family history, it is possible that patient has a new mutation and therefore the diagnosis of HHT remains possible.

G2 CLINICIANS CONSIDER THE DIAGNOSIS OF HHT IN PATIENTS WITH ONE OR MORE CURAÇAO CRITERIA (TABLE).

Clinical Considerations: When applying the Curaçao Criteria for clinical diagnosis, identifying 2 or less of the criteria after clinical examination and history should not be considered sufficient evidence to rule out the diagnosis, particularly in the first few decades of life.

G3 ASYMPTOMATIC CHILDREN OF A PARENT WITH HHT BE CONSIDERED TO HAVE POSSIBLE HHT, UNLESS EXCLUDED BY GENETIC TESTING.

Clinical Considerations: Given the expected poor sensitivity of the Curaçao Criteria for clinical diagnosis in children, the clinician can clarify the diagnosis using genetic testing, if a familial mutation has been identified. If genetic testing is not possible, the clinician should proceed as if the child has HHT and consider appropriate screening for visceral AVMs.

G4

CLINICIANS REFER PATIENTS FOR DIAGNOSTIC GENETIC TESTING FOR HHT:

- To identify the causative mutation in a family with clinically confirmed HHT
- To establish a diagnosis in relatives of a person with a known causative mutation, including:
  a. Individuals who are asymptomatic or minimally symptomatic
  b. Individuals who desire prenatal testing
- To assist in establishing a diagnosis of HHT in individuals who do not meet clinical diagnostic criteria

Clinical Considerations: Genetic testing for HHT is a multistep process. In an experienced lab, the index case is generally tested by sequence and deletions/duplications analysis of both the ENG and ACVRL1 genes. It is reasonable to perform the deletion/duplication analysis either simultaneously with the sequence analysis or only in cases in which the sequence analysis is negative or equivocal. If an HHT causing mutation is identified in the index case (test is positive), diagnostic genetic testing for HHT can be offered to all at risk relatives. These relatives would have "family specific" mutation testing by targeted sequencing. If no mutation is identified (test is negative) in the index case, diagnostic genetic testing can not be offered to other family members. Such families should be advised that, in the future, currently undetectable HHT mutations will become detectable as new genes and testing methods are discovered. In the meantime, diagnosis and medical management of at risk family members will rely on clinical findings and knowledge of the natural history of HHT. If a genetic variant of uncertain significance is identified (test is equivocal) in the index case, additional confirmatory testing may be available, or additional interpretive information may become available in the future, to clarify whether the genetic variant in question is in fact a benign variant or a disease causing mutation.

G5

FOR INDIVIDUALS WHO TEST NEGATIVE FOR ENG AND ACVRL1 CODING SEQUENCE MUTATIONS, SMAD4 TESTING SHOULD BE CONSIDERED TO IDENTIFY THE CAUSATIVE MUTATION.

Table: Curaçao Criteria for Clinical Diagnosis of HHT: Using these criteria, a diagnosis of HHT is considered 'definite' if three or more Curaçao criteria are present, 'possible or suspected' if two criteria are present, and 'unlikely' if 0 or 1 criterion is present.

Criteria	Description
Epistaxis	Spontaneous and recurrent
Telangiectases	Multiple, at characteristic sites: lips, oral cavity, fingers, nose
Visceral lesions	Such as gastrointestinal telangiectasia, pulmonary, hepatic, cerebral or spinal AVMs
Family history	A first degree relative with HHT according to these criteria

(Shovlin C. et al. AJMG 2000)

MY CHILD'S HHT CARE CHECKLIST

USING THE HHT GUIDELINES

The HHT Pediatric Care Guidelines are detailed on the next pages

Date: _____

Child's Name: _____

Please check all that apply

☐ MY CHILD HAS A PARENT WITH HHT AND WE DON'T KNOW IF MY CHILD IS AFFECTED.

- ☐ Talk to my child's doctor about genetic testing for my child.

☐ MY CHILD HAS HHT OR MAY HAVE HHT (THE HHT DIAGNOSIS HAS NOT BEEN RULED OUT).

- ☐ Ask the doctor for screening for lung arteriovenous malformations (AVMs).
- ☐ Ask the doctor for screening (usually MRI) for brain vascular malformations (VMs).

☐ MY CHILD HAS LUNG (PULMONARY) AVMs.

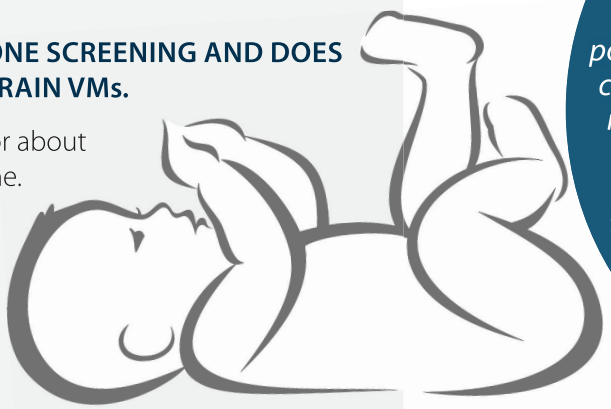
- ☐ Consider preventative treatment (embolization) for large AVMs or if my child has low oxygen levels.
- ☐ Talk to my child's dentist and other health care professionals about the need for lung AVM precautions, lifelong.
- ☐ Plan regular follow-up for the lung AVMs, whether or not they are treated.

☐ MY CHILD HAS BRAIN VMs.

- ☐ Ask for a referral to an expert multi-disciplinary neurovascular team for assessment of my child's risk of bleeding from the VM(s) and for consideration for treatment.

☐ MY CHILD HAS UNDERGONE SCREENING AND DOES NOT HAVE LUNG AVMs OR BRAIN VMs.

- ☐ Talk to my child's doctor about re-screening in 5 years' time.



INTERNATIONAL HHT GUIDELINES

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WHAT IS MY ROLE AS SOMEONE LIVING WITH HHT?

- Be aware of the Guidelines. Share them with your care team. Ideally you should be seen at an HHT Center of Excellence or your care team may want to consult with one.
- Read up on your condition and know what care is available for HHT.
- **Prepare ahead of time for your appointments**: Bring your HHT Care Checklists and a family member or friend. They can help you communicate your questions and priorities, as well as act as a second set of ears. Share your experiences, worries and priorities to help your care team better understand your needs and provide individualized care.

PEDIATRIC CARE

While some manifestations of HHT, such as telangiectasia and epistaxis, are age dependent and may be absent in young children with HHT, potentially serious and even life-threatening complications of pulmonary arteriovenous malformations (AVMs) and brain vascular malformations (VMs) can occur at any age. The pediatric HHT guidelines focus therefore on screening and management of pulmonary AVMs and brain VMs in children.

HHT GUIDELINES RECOMMENDATIONS

PEDIATRIC CARE

While some manifestations of HHT, such as telangiectasia and epistaxis, are age dependent and may be absent in young children with HHT, potentially serious and even life-threatening complications of pulmonary arteriovenous malformations (AVMs) and brain vascular malformations (VMs) can occur at any age. The pediatric HHT guidelines focus therefore on screening and management of pulmonary AVMs and brain VMs in children.

The expert panel recommends:

E1 THAT DIAGNOSTIC GENETIC TESTING BE OFFERED FOR ASYMPTOMATIC CHILDREN OF A PARENT WITH HHT.

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

E2 SCREENING FOR PULMONARY AVMs IN ASYMPTOMATIC CHILDREN WITH HHT OR AT RISK FOR HHT AT THE TIME OF PRESENTATION / DIAGNOSIS.

Clinical Considerations: Screening may be performed with either chest X-ray and pulse oximetry OR transthoracic contrast echocardiography (TTCE). Screening with CT is not recommended, though CT chest remains the confirmatory diagnostic test when screening tests are positive.

E3 THAT LARGE PULMONARY AVMs AND PULMONARY AVMs ASSOCIATED WITH REDUCED OXYGEN SATURATION BE TREATED IN CHILDREN TO AVOID SERIOUS COMPLICATIONS.

Clinical Considerations: Pulmonary AVMs with feeding arteries ≥3 mm 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 TTCE), as do intervals.

E4 REPEATING PULMONARY AVM SCREENING IN ASYMPTOMATIC CHILDREN WITH HHT OR AT RISK FOR HHT; TYPICALLY AT 5 YEAR INTERVALS.

Clinical Considerations: Typically, negative screening is repeated every 5 years. In children with indeterminate or borderline screening results, either based on imaging or oximetry, screening should be repeated sooner.

E5 SCREENING FOR BRAIN VM IN ASYMPTOMATIC CHILDREN WITH HHT, OR AT RISK FOR HHT, AT THE TIME OF PRESENTATION / DIAGNOSIS.

Clinical Considerations: First-line screening is MRI (contrast enhanced more sensitive) to identify brain VM 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 of hemorrhage. As such, the decision to screen the child should be a shared decision among clinicians, caregivers and the child (where possible). There are important differences in clinical practice across countries: from screening asymptomatic children with MRI in infancy, to no routine screening of asymptomatic children for brain VM. Patient representatives felt strongly that children should be screened for brain VMs citing anecdotal evidence of disastrous outcomes in unscreened patients.

E6 THAT BRAIN VMS WITH HIGH RISK FEATURES BE TREATED.

Clinical Considerations: Given the need to balance natural history risk with treatment risk, children with HHT who have brain VM 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.

MY ANEMIA CARE CHECKLIST

USING THE HHT GUIDELINES

The HHT Anemia Guidelines are detailed on the next pages

Date: _____

Name: _____

Please check all that apply

☐ I AM AN ADULT WITH HHT AND SO I AM AT RISK OF ANEMIA AND IRON DEFICIENCY, EVEN IF I HAVE NOT NOTICED ANY BLEEDING.

- ☐ Talk to my doctor about testing for anemia (hemoglobin) and iron deficiency (ferritin).

OR

☐ I AM A CHILD/TEEN WITH HHT WITH SOME BLEEDING SYMPTOMS, AND SO I AM AT RISK OF ANEMIA AND IRON DEFICIENCY.

- ☐ Talk to my doctor about testing for anemia (hemoglobin) and iron deficiency (ferritin).

☐ I HAVE IRON DEFICIENCY OR IRON DEFICIENCY ANEMIA.

- ☐ See my doctor about treatment with oral iron supplements.

☐ I HAVE IRON DEFICIENCY OR IRON DEFICIENCY ANEMIA WHICH HAS NOT IMPROVED ON ORAL IRON SUPPLEMENTS.

- ☐ Talk to my doctor about intravenous iron supplements (also consider this option if I can't tolerate oral iron).
- ☐ Talk to my doctor about additional testing I might need for other causes of anemia.
- ☐ See my doctor about getting blood transfusions if I have severe anemia and I am symptomatic of it, despite intravenous iron, or if I have other serious illness that makes the anemia more dangerous for my health.

☐ I HAVE A MEDICAL INDICATION FOR A BLOOD THINNER (SUCH AS BLOOD CLOT IN A LEG VEIN) OR ANTI-PLATELET THERAPY (SUCH AS HEART DISEASE).

- ☐ Taking one of these medications is not absolutely out of the question; Discuss with an HHT expert as many people with HHT can tolerate.
- ☐ Taking two anti-platelets simultaneously is not absolutely out of the question but is often not tolerated in HHT; discuss with an HHT expert.

INTERNATIONAL HHT GUIDELINES

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- The HHT Guidelines help ensure that people living with HHT get the best care possible.

WHAT IS MY ROLE AS SOMEONE LIVING WITH HHT?

- Be aware of the Guidelines. Share them with your care team. Ideally you should be seen at an HHT Center of Excellence or your care team may want to consult with one.
- Read up on your condition and know what care is available for HHT.
- **Prepare ahead of time for your appointments**: Bring your HHT Care Checklists and a family member or friend. They can help you communicate your questions and priorities, as well as act as a second set of ears. Share your experiences, worries and priorities to help your care team better understand your needs and provide individualized care.

ANEMIA & ANTICOAGULATION IN HHT

Anemia is a common complication in people with HHT, occurring in approximately 50%, typically diagnosed in adulthood and only rarely in children with HHT. The primary etiology of anemia is iron deficiency secondary to chronic mucocutaneous bleeding (epistaxis and/or GI bleeding from telangiectases). Patients with HHT should be screened for iron deficiency and anemia, and then supported with iron replacement and red blood cell transfusion, as detailed below. Anticoagulation is not absolutely contraindicated in HHT patients. When there is an indication for anticoagulant or antiplatelet therapy, individualized patient bleeding risks should be considered.

HHT GUIDELINES RECOMMENDATIONS

ANEMIA AND ANTICOAGULATION IN HHT

Anemia is a common complication in people with HHT, occurring in approximately 50%, typically diagnosed in adulthood and only rarely in children with HHT. The primary etiology of anemia is iron deficiency secondary to chronic mucocutaneous bleeding (epistaxis and/or GI bleeding from telangiectases). Patients with HHT should be screened for iron deficiency and anemia, and then supported with iron replacement and red blood cell transfusion, as detailed below. Anticoagulation is not absolutely contraindicated in HHT patients. When there is an indication for anticoagulant or antiplatelet therapy, individualized patient bleeding risks should be considered.

The expert panel recommends:

C1

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

Clinical Considerations: Testing typically includes complete blood count (CBC) and ferritin. If anemic but ferritin is not reduced, serum iron, total iron binding capacity, and transferrin saturation should be performed, and a hematology consultation should be considered.

C2

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

Clinical Considerations: Iron replacement typically starts with once daily oral dosing of 35-65 mg of elemental iron, 2 hours before or 1 hour after meals. An increase in hemoglobin of less than 1.0 gram/dL is considered inadequate in anemic patients, and every-other-day dosing or an alternate oral iron preparation should be attempted. In refractory anemia and/or severe chronic bleeding, regularly scheduled iron infusions may be required. Initial IV iron dosing can be calculated or total initial dose of 1 gram of IV iron can be provided, as single infusion or divided doses. Additional safety and prescribing information are detailed in the online supplement (see link to "Second International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia.")

C3

RED BLOOD CELL (RBC) 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

Clinical Considerations: Hemoglobin targets and thresholds for RBC transfusion should be individualized in HHT, depending on patient symptoms, severity of ongoing HHT-related bleeding, response to other therapies and iron supplementation, the presence of comorbidities and acuity.

C4 **CONSIDERING EVALUATION FOR ADDITIONAL CAUSES OF ANEMIA IN THE SETTING OF AN INADEQUATE RESPONSE TO IRON REPLACEMENT.**

Clinical Considerations: Evaluation should include measurement of folate, Vitamin B12, MCV, smear, reticulocyte counts, TSH and work-up for hemolysis, with referral to hematology in unresolved cases.

C5 **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.**

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. In cases of atrial fibrillation, if anticoagulation is not tolerated, alternate approaches can be considered, such as left atrial appendage closure.

C6 **AVOIDING THE USE OF DUAL ANTIPLATELET THERAPY AND/OR COMBINATION OF ANTIPLATELET THERAPY AND ANTICOAGULATION, WHERE POSSIBLE, IN PATIENTS WITH HHT.**

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

MY BRAIN VM CARE CHECKLIST

USING THE HHT GUIDELINES

Brain VMs= brain vascular malformations AKA cerebral VMs. The HHT Brain VM Guidelines are detailed on the next pages.

Date: _____

Name: _____

Please check all that apply

☐ I HAVE HHT OR MIGHT HAVE HHT (THE HHT DIAGNOSIS HAS NOT BEEN RULED OUT).

- ☐ Talk to my doctor about whether brain VM screening is appropriate for me.
- ☐ If I choose to have brain VM screening, ask my doctor for an MRI of the brain, with and without contrast, and also special sequences to detect blood products.
- ☐ Consider having my screening done at an HHT Center of Excellence.

☐ I HAVE BRAIN VMs AND I HAVE HAD A BLEED IN MY BRAIN.

- ☐ Ask my doctor to refer me to a center with neurovascular disease, so that I can be considered for definitive treatment of my brain VMs.

☐ I HAVE BRAIN VMs, BUT THEY HAVE NEVER BLED.

- ☐ Ask my doctor to refer me to a center with neurovascular disease, so that I can be considered for further testing to confirm the brain VMs.
- ☐ Ask my doctor to refer me to a center with neurovascular disease, so that I can get an expert opinion about whether my brain VMs should be treated.

☐ I HAVE BRAIN VMs AND I AM PREGNANT.

- ☐ Review the Pregnancy and Delivery HHT Care Checklist.

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- Read up on your condition and know what care is available for HHT.
- **Prepare ahead of time for your appointments**: Bring your HHT Care Checklists and a family member or friend. They can help you communicate your questions and priorities, as well as act as a second set of ears. Share your experiences, worries and priorities to help your care team better understand your needs and provide individualized care.

BRAIN VMs IN HHT

Vascular malformations (VMs), are abnormal vessels with direct artery to vein connections. At least 10% of people with HHT have VMs in the brain (cerebral) blood vessels. People are often unaware that they have brain VMs until they develop a life-threatening complication, such as stroke or seizure. With the right screening and treatment, these life-threatening complications can be prevented, however, there is no single 'standard treatment' that can be recommended for all brain VMs in HHT at the current time.

HHT GUIDELINES RECOMMENDATIONS

BRAIN VMs IN HHT

Vascular malformations (VMs), are abnormal vessels with direct artery to vein connections. At least 10% of people with HHT have VMs in the brain (cerebral) blood vessels. People are often unaware that they have brain VMs until they develop a life-threatening complication, such as stroke or seizure. With the right screening and treatment, these life-threatening complications can be prevented, however, there is no single 'standard treatment' that can be recommended for all brain VMs in HHT at the current time.

The expert panel recommends:
(all recommendations are from the First HHT Guidelines)

H1 **THE USE OF MRI FOR CEREBRAL 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.**

Clinical Considerations: If patients have received previous embolization, coil compatibility with MRI must be confirmed prior to MR examination. The expert panel acknowledges that the optimum age for adult screening remains unknown but felt that age 18 was appropriate as patients enter adulthood. In the presence of a negative MRI in adulthood no further screening tests are suggested. There may be additional benefits to performing an MRI at initial assessment, in the detection of infarcts and other central nervous system complications of HHT.

H2 **THAT ADULTS PRESENTING WITH AN ACUTE HEMORRHAGE SECONDARY TO A CEREBRAL VM BE CONSIDERED FOR DEFINITIVE TREATMENT IN A CENTER WITH NEUROVASCULAR EXPERTISE.**

H3 **THAT ALL OTHER ADULTS WITH CEREBRAL VMs BE REFERRED TO A CENTER WITH NEUROVASCULAR EXPERTISE TO BE CONSIDERED FOR INVASIVE TESTING AND INDIVIDUALIZED MANAGEMENT.**

Clinical Considerations: The expert panel recognizes that asymptomatic cerebral VMs discovered during screening of HHT patients may carry a more favorable natural history. These patients should be managed on an individualized basis. Since some cerebral VMs may carry a favorable natural history, referral to a center with neurovascular expertise prior to performing invasive imaging (catheter angiography) may minimize unnecessary testing.

H4 **THAT PREGNANT WOMEN WITH SUSPECTED OR CONFIRMED HHT HARBORING AN ASYMPTOMATIC CEREBRAL VM DURING PREGNANCY HAVE DEFINITIVE TREATMENT OF THEIR CEREBRAL VM DEFERRED UNTIL AFTER DELIVERY OF THEIR FETUS. THE EXPERT PANEL RECOMMENDS THAT THE DELIVERY OF THE FETUS FOLLOW OBSTETRICAL PRINCIPLES.**

MY GI BLEEDING CARE CHECKLIST

USING THE HHT GUIDELINES

GI Bleeding in HHT is usually chronic bleeding from stomach and/or small bowel. The HHT GI Bleeding Guidelines are detailed on the next pages.

Date: _____

Name: _____

Please check all that apply

☐ I AM CONCERNED THAT I MIGHT HAVE CHRONIC LOW-GRADE BLEEDING FROM TELANGIECTASIA IN MY STOMACH AND/OR BOWELS (GI BLEEDING), BECAUSE I HAVE IRON DEFICIENCY OR ANEMIA.

- ☐ Talk to my doctor about getting a scope of the stomach and small bowel (Upper GI scope AKA Esophagoduodenoscopy or EGD) for diagnosis.
- ☐ Talk to my doctor about getting a capsule endoscopy (camera pill) if my EGD didn't show any significant telangiectasia.
- ☐ Talk to my doctor about whether I am due for a colonoscopy for colon cancer screening.

☐ MY HHT GI BLEEDING IS CAUSING ONGOING IRON DEFICIENCY, DESPITE ORAL IRON SUPPLEMENTS.

- ☐ See my doctor about treatment with tranexamic acid tablets.
- ☐ Avoid routine repetitive endoscopic therapy with Argon Plasma Coagulation, though an initial treatment might be helpful.

☐ MY HHT GI BLEEDING IS CAUSING ONGOING ANEMIA, REQUIRING INTRAVENOUS IRON AND/OR BLOOD TRANSFUSIONS.

- ☐ See an HHT expert about systemic antiangiogenic therapy, such as bevacizumab.

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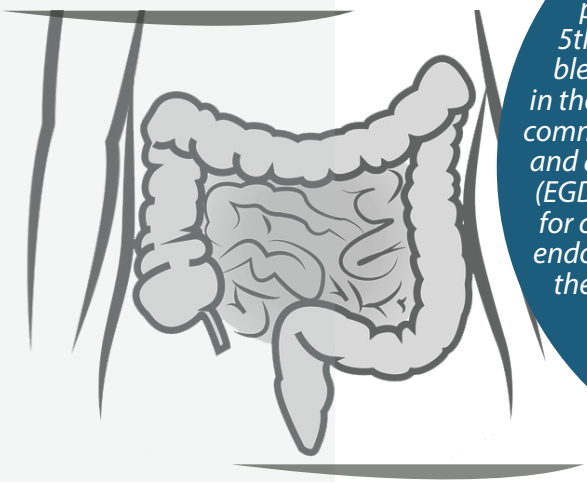
WHAT IS MY ROLE AS SOMEONE LIVING WITH HHT?

- Be aware of the Guidelines. Share them with your care team. Ideally you should be seen at an HHT Center of Excellence or your care team may want to consult with one.
- Read up on your condition and know what care is available for HHT.
- **Prepare ahead of time for your appointments**: Bring your HHT Care Checklists and a family member or friend. They can help you communicate your questions and priorities, as well as act as a second set of ears. Share your experiences, worries and priorities to help your care team better understand your needs and provide individualized care.

GI BLEEDING IN HHT



HHT-related GI bleeding develops in approximately 30% of HHT patients, typically manifesting in the 5th and 6th decades. Chronic low-grade bleeding, typically from GI telangiectases in the stomach and the small bowel, and less commonly in the colon, lead to iron deficiency and anemia. Esophagogastroduodenoscopy (EGD) remains the diagnostic gold standard for confirming HHT-related GI bleeding, but endoscopic management is limited. Medical therapies are often considered, including oral antifibrinolytics and systemic antiangiogenic therapy, with the approach as recommended below.

HHT GUIDELINES RECOMMENDATIONS

GI BLEEDING IN HHT

HHT-related GI bleeding develops in approximately 30% of HHT patients, typically manifesting in the 5th and 6th decades. Chronic low-grade bleeding, typically from GI telangiectases in the stomach and the small bowel, and less commonly in the colon, lead to iron deficiency and anemia. Esophagogastroduodenoscopy (EGD) remains the diagnostic gold standard for confirming HHT-related GI bleeding, but endoscopic management is limited. Medical therapies are often considered, including oral antifibrinolytics and systemic antiangiogenic therapy, with the approach as recommended below.

The expert panel recommends:

B1

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.

Clinical Considerations: Clinicians should consider performing esophagogastroduodenoscopy (EGD) in experienced center, given potential unusual complications during EGD (such as massive epistaxis), and also be aware of precautions required for HHT patients with pulmonary AVMs (Table). In suspected or proven SMAD4-HHT, screening colonoscopy is recommended, starting at age 15 years, repeated every three years if no polyps are found OR every year along with EGD if colonic polyp(s) are found. Other HHT patients (non-SMAD4) should be screened for colon cancer as per general population guidelines.

B2

CONSIDERING CAPSULE ENDOSCOPY FOR SUSPECTED HHT-RELATED BLEEDING, WHEN ESOPHAGOGASTRODUODENOSCOPY DOES NOT REVEAL SIGNIFICANT HHT-RELATED TELANGIECTASIA.

Clinical Considerations: Capsule endoscopy (CE) remains complementary to EGD when anemia is unexplained by the severity of epistaxis and gastric involvement, or when the EGD is negative.

B3

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 IV 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.*

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

B4

THAT ENDOSCOPIC ARGON PLASMA COAGULATION BE ONLY USED SPARINGLY DURING ENDOSCOPY.

Clinical Considerations: Argon Plasma Coagulation (APC) is best administered concurrent with the initial endoscopic evaluation, for bleeding lesions and significant (1-3 mm) non-bleeding lesions. Repeated APC sessions are discouraged to avoid repeated iatrogenic injury to the intestinal mucosa.

B5 **THAT CLINICIANS CONSIDER TREATMENT OF MILD HHT-RELATED GI BLEEDING WITH ORAL ANTIFIBRINOLYTICS.**

Clinical Considerations: Prescribing and safety monitoring guidance for IV bevacizumab is detailed in Supplement Table 4 (see www.HHTGuidelines.org).

B6 **THAT CLINICIANS CONSIDER TREATMENT OF MODERATE TO SEVERE HHT-RELATED GI BLEEDING WITH INTRAVENOUS BEVACIZUMAB OR OTHER SYSTEMIC ANTI-ANGIOGENIC THERAPY.**

Clinical Considerations: Prescribing and safety monitoring guidance for IV bevacizumab is detailed in Supplement Table 4 (see www.HHTGuidelines.org).

MY LIVER VM CARE CHECKLIST

USING THE HHT GUIDELINES

Liver VMs= liver vascular malformations. The HHT Liver VM Guidelines are detailed on the next pages.

Date: _____

Name: _____

Please check all that apply

☐ I AM CONCERNED THAT I MIGHT HAVE LIVER VMs EVEN THOUGH I HAVE NOT HAD ANY SYMPTOMS OR COMPLICATIONS OF LIVER VMs.

- ☐ Talk to my doctor about being screened for liver VMs, and the full range of options available, from "routine physical and bloodwork" to specialized imaging.

☐ I AM CONCERNED THAT I MIGHT HAVE SYMPTOMS OR COMPLICATIONS OF LIVER VMs, SUCH AS HEART FAILURE, PULMONARY HYPERTENSION, CHRONIC LIVER PAIN, BILE DUCT INFECTIONS, ETC.

- ☐ Talk to my doctor about getting diagnostic imaging for liver VMs, using specialized Doppler ultrasound, CT or MRI with special contrast (dye) protocols.
- ☐ Ask my doctor about getting an expert opinion at an HHT Center of Excellence.
- ☐ Ask my doctor about getting a cardiac echo to look for cardiac effects of liver VMs.

☐ I HAVE SYMPTOMS OR COMPLICATIONS FROM LIVER VMs, SUCH AS HEART FAILURE, PULMONARY HYPERTENSION, CHRONIC LIVER PAIN, BILE DUCT INFECTIONS, PORTAL HYPERTENSION, OR OTHER.

- ☐ Ask my doctor about getting an expert opinion at an HHT Center of Excellence.
- ☐ Talk to my doctor about getting first-line treatment of my specific liver VM complications, as detailed in the full HHT Guidelines online supplement.
- ☐ Ask my doctor about involving a cardiologist or pulmonary hypertension doctor with HHT experience if my liver VMs are causing heart problems.
- ☐ Avoid biopsy of the liver.
- ☐ Avoid embolization of liver VMs, in most cases.

☐ I HAVE ONGOING HEART FAILURE SYMPTOMS DESPITE FIRST-LINE MANAGEMENT.

- ☐ See my doctor about treatment with intravenous bevacizumab.
- ☐ See my doctor about consideration for liver transplant.

☐ I HAVE ONGOING BILE DUCT PROBLEMS OR LIVER DYSFUNCTION DESPITE FIRST-LINE MANAGEMENT.

- ☐ See my doctor about consideration for liver transplant.

INTERNATIONAL HHT GUIDELINES

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WHAT IS MY ROLE AS SOMEONE LIVING WITH HHT?

- Be aware of the Guidelines. Share them with your care team. Ideally you should be seen at an HHT Center of Excellence or your care team may want to consult with one.
- Read up on your condition and know what care is available for HHT.
- **Prepare ahead of time for your appointments**: Bring your HHT Care Checklists and a family member or friend. They can help you communicate your questions and priorities, as well as act as a second set of ears. Share your experiences, worries and priorities to help your care team better understand your needs and provide individualized care.

LIVER VMs IN HHT

Liver VMs occur in approximately 75% of HHT patients, more commonly in women and often presenting in the 5th decade. The clinical presentation is typically more severe in patients with ACVRL1 mutation (HHT2). Liver VMs in HHT typically present as diffuse small lesions (telangiectases) throughout the liver, and rarely as discrete large AVMs. Clinicians should offer screening for liver VMs and be aware of possible symptoms or complications and prognostic factors. First-line management depends on symptoms.

HHT GUIDELINES RECOMMENDATIONS

LIVER VMs IN HHT

Liver VMs occur in approximately 75% of HHT patients, more commonly in women and often presenting in the 5th decade. The clinical presentation is typically more severe in patients with ACVRL1 mutation (HHT2). Liver VMs in HHT typically present as diffuse small lesions (telangiectases) throughout the liver, and rarely as discrete large AVMs. Clinicians should offer screening for liver VMs and be aware of possible symptoms or complications and prognostic factors. First-line management depends on symptoms.

The expert panel recommends:

D1 **THAT SCREENING FOR LIVER VMs BE OFFERED TO ADULTS WITH DEFINITE OR SUSPECTED HHT.**

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 ultrasound due to its accuracy, safety, tolerability, low costs and operating characteristics. However, depending on local Doppler ultrasound availability and expertise, as well as patient preference, patients may be screened clinically (history, physical and blood work) or alternative imaging may be considered, including multiphase contrast CT or MRI.

D2 **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.**

Clinical Considerations: The choice of imaging modality should be informed by the risk/benefit balance, local expertise and availability/cost. Contrast studies (CT and MRI) should be avoided if kidney dysfunction. Echocardiography provides additional information about the hemodynamic impact of liver VMs. These tests will be most informative when performed in a center with HHT expertise, in the context of a clinical assessment at an HHT Center of Excellence.

D3 **AN INTENSIVE FIRST-LINE MANAGEMENT ONLY FOR PATIENTS WITH COMPLICATED AND/OR SYMPTOMATIC LIVER VMs, TAILORED TO THE TYPE OF LIVER VM COMPLICATION(S).**

THAT HHT PATIENTS WITH HIGH-OUTPUT CARDIAC FAILURE AND PULMONARY HYPERTENSION BE CO-MANAGED BY THE HHT CENTER OF EXCELLENCE AND AN HHT CARDIOLOGIST OR A PULMONARY HYPERTENSION SPECIALTY CLINIC.

Clinical Considerations: First-line therapies, by specific liver VM complications, are described in the online supplement (see www.HHTGuidelines.org). Typically, patients with symptomatic liver VMs are managed by an expert team at an HHT Center of Excellence, with at least annual follow-up.

D4 **THAT CLINICIANS ESTIMATE PROGNOSIS OF LIVER VMs USING AVAILABLE PREDICTORS, TO IDENTIFY PATIENTS IN NEED OF CLOSER MONITORING.**

Clinical Considerations: Clinicians should plan monitoring for patients with liver VMs patients based on estimated prognosis.

D5 **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.**

Clinical Considerations: Prescribing and safety monitoring guidance for IV bevacizumab is detailed in Supplement Table 4 (see www.HHTGuidelines.org).

D6 **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.**

Clinical Considerations: Timing for listing a symptomatic patient for orthotopic liver transplantation (OLT) should be based on prognostic predictors and the severity of liver VMs complications, including pulmonary hypertension. Liver transplant can be undertaken in the presence of pulmonary hypertension if pulmonary vascular resistance, estimated by right heart catheterization, is < 3 Woods Units.

From the First HHT Guidelines:

D7 **THAT LIVER BIOPSY BE AVOIDED IN ANY PATIENT WITH PROVEN OR SUSPECTED HHT.**

Clinical Considerations: The rationale for recommending against liver biopsy for diagnosis of liver VMs is that the diagnosis is established with imaging studies whereas biopsy exposes the patient to an unnecessary risk of hemorrhage.

D8 **THAT HEPATIC ARTERY EMBOLIZATION BE AVOIDED IN PATIENTS WITH LIVER VMS AS IT IS ONLY A TEMPORIZING PROCEDURE ASSOCIATED WITH SIGNIFICANT MORBIDITY AND MORTALITY.**

Clinical Considerations: Given the elevated risk of post-embolization necrosis, and death this procedure should not be considered as a first-line therapeutic option. It may be reasonable for the clinician to consider hepatic artery embolization in certain patients, such as a patient with heart failure who has failed to respond to optimal medical therapy and who does not have biliary ischemia or portovenous shunting and who is not a transplant candidate. The risks and benefits of embolization and transplant should be considered on an individualized basis, based on type of shunting, clinical syndrome, patient characteristics and patient preference.

MY NOSEBLEED (EPISTAXIS) CARE CHECKLIST

USING THE HHT GUIDELINES

The HHT Epistaxis (Nosebleed) Guidelines are detailed on the next pages

Date: _____

Name: _____

Please check all that apply

☐ I HAVE NOSEBLEEDS (EPISTAXIS) THAT BOTHER ME AND I RATE MY NOSEBLEED SEVERITY TO HELP GUIDE MY NOSEBLEED CARE:

☐ I rate my usual nosebleeds (circle one) as: mild – moderate -severe.

☐ My epistaxis severity score (ESS) = _____ which is (circle one): mild-moderate-severe.

My score was computed at this link:
https://www2.drexelmed.edu/HHT-ESS/

☐ TALK TO MY DOCTOR ABOUT MOISTURIZING TOPICAL THERAPIES FOR MY NOSE.

☐ MY NOSEBLEEDS STILL BOTHER ME DESPITE MOISTURIZING TOPICAL THERAPY.

☐ See my doctor about treatment with tranexamic acid tablets.

☐ See an HHT-experienced ENT doctor about ablative therapies, like laser, radio frequency, electrosurgery and sclerotherapy.

☐ MY NOSEBLEEDS ARE AFFECTING MY QUALITY OF LIFE AND/OR ARE LIFE-THREATENING, DESPITE TRANEXAMIC ACID AND/OR ABLATIVE THERAPIES.

☐ See an HHT expert about systemic antiangiogenic therapy, such as bevacizumab.

☐ Talk to an HHT-experienced ENT doctor about septodermoplasty surgery.

☐ Talk to an HHT-experienced ENT doctor about nasal closure surgery (Young's procedure).

☐ I HAVE A BAD NOSEBLEED AND I AM IN THE EMERGENCY ROOM.

☐ If I need packing: Ask for packing that won't likely make my nose rebleed, such as liquid packing, dissolvable packing or lubricated low-pressure packing.

INTERNATIONAL HHT GUIDELINES

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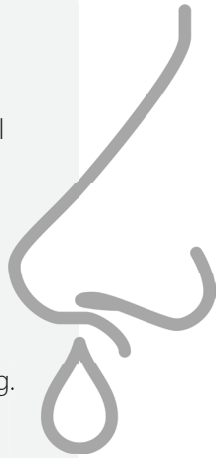
WHAT IS MY ROLE AS SOMEONE LIVING WITH HHT?

- Be aware of the Guidelines. Share them with your care team. Ideally you should be seen at an HHT Center of Excellence or your care team may want to consult with one.
- Read up on your condition and know what care is available for HHT.
- **Prepare ahead of time for your appointments**: Bring your HHT Care Checklists and a family member or friend. They can help you communicate your questions and priorities, as well as act as a second set of ears. Share your experiences, worries and priorities to help your care team better understand your needs and provide individualized care.

EPISTAXIS IN HHT



Epistaxis is the most common symptom of HHT, developing in 90% of adults with the disease, affecting quality of life and often leading to iron deficiency and anemia. Typically, turbulent nasal airflow with breathing leads to mucosal dryness and bleeding from telangiectases of the nasal mucosa. Topical moisturizing helps prevent the telangiectases from cracking and bleeding and is a mainstay of epistaxis care. When epistaxis doesn't respond to moisturizing, other therapies are considered, including oral antifibrinolytics, ablative therapies, systemic antiangiogenic therapy and surgical management, with the approach as recommended below.

HHT GUIDELINES RECOMMENDATIONS

EPISTAXIS IN HHT

Epistaxis is the most common symptom of HHT, developing in 90% of adults with the disease, affecting quality of life and often leading to iron deficiency and anemia. Typically, turbulent nasal airflow with breathing leads to mucosal dryness and bleeding from telangiectases of the nasal mucosa. Topical moisturizing helps prevent the telangiectases from cracking and bleeding and is a mainstay of epistaxis care. When epistaxis doesn't respond to moisturizing, other therapies are considered, including oral antifibrinolytics, ablative therapies, systemic antiangiogenic therapy and surgical management, with the approach as recommended below.

The expert panel recommends:

A1 **PATIENTS WITH HHT-RELATED EPISTAXIS USE MOISTURIZING TOPICAL THERAPIES THAT HUMIDIFY THE NASAL MUCOSA TO REDUCE EPISTAXIS.**

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

A2 **CLINICIANS CONSIDER THE USE OF ORAL TRANEXAMIC ACID FOR THE MANAGEMENT OF EPISTAXIS THAT DOES NOT RESPOND TO MOISTURIZING TOPICAL THERAPIES.**

Clinical Considerations: Prescribing and safety monitoring guidance for oral tranexamic acid is detailed in Supplement Table 4 (see www.HHTGuidelines.org)

A3 **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.**

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

A4 **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.**

Clinical Considerations: Prescribing and safety monitoring guidance for IV bevacizumab is detailed in Supplement Table 4 (see www.HHTGuidelines.org)

A5 **CLINICIANS CONSIDER A SEPTODERMOPLASTY FOR PATIENTS WHOSE EPISTAXIS HAS FAILED TO RESPOND SUFFICIENTLY TO MOISTURIZING TOPICAL THERAPIES, ABLATIVE THERAPIES, AND/OR TRANEXAMIC ACID.**

Clinical Considerations: Clinicians and patients should consider septodermoplasty when epistaxis affects QOL or is life-threatening, considering risks and benefits, as well as alternatives, such as nasal closure and anti-angiogenic medications.

A6 CLINICIANS CONSIDER A NASAL CLOSURE FOR PATIENTS WHOSE EPISTAXIS HAS FAILED TO RESPOND SUFFICIENTLY TO MOISTURIZING TOPICAL THERAPIES, ABLATIVE THERAPIES, AND/OR TRANEXAMIC ACID.

Clinical Considerations: Clinicians and patients should consider nasal closure when epistaxis affects QOL or is life-threatening, considering risks and benefits, as well as alternatives, such as septodermoplasty and anti-angiogenic medications.

From the First HHT Guidelines:

A7 PHYSICIANS ADVISE PATIENTS WITH HHT-RELATED EPISTAXIS TO USE AGENTS THAT HUMIDIFY THE NASAL MUCOSA TO PREVENT EPISTAXIS.

A8 CLINICIANS REFER HHT PATIENTS WITH EPISTAXIS AND WHO DESIRE TREATMENT TO OTORHINOLARYNGOLOGISTS WITH HHT EXPERTISE FOR EVALUATION AND TREATMENT.

Clinical Considerations: Primary physicians are key players in the care of HHT patients, especially in the emergency situation. In the patient with epistaxis problematic enough to warrant consideration of treatment, consultation with an otorhinolaryngologist with HHT expertise should help guide the intervention choice, to maximize effectiveness and reduce risk, in this life-long rare disorder.

A9 WHEN CONSIDERING NASAL SURGERY FOR REASONS OTHER THAN EPISTAXIS, THE PATIENT AND CLINICIAN OBTAIN CONSULTATION FROM AN OTORHINOLARYNGOLOGISTS WITH EXPERTISE IN HHT-RELATED EPISTAXIS.

Clinical Considerations: In the patient with HHT and an unrelated ENT problem requiring surgery, consultation with an otorhinolaryngologist with HHT expertise should help guide the procedural interventions to minimize risk of worsening epistaxis.

A10 THE TREATMENT FOR ACUTE EPISTAXIS REQUIRING INTERVENTION INCLUDE PACKING WITH MATERIAL OR PRODUCTS THAT HAVE A LOW LIKELIHOOD OF CAUSING RE-BLEEDING WITH REMOVAL (E.G., LUBRICATED LOW-PRESSURE PNEUMATIC PACKING).

Clinical Considerations: In order to perform atraumatic packing, the clinician can lubricate the packing or use a pneumatic packing which allows insertion and removal of the packing in a deflated size. When using pneumatic packing, a low pressure packing would be preferable. This recommendation is specifically addressing nasal packing performed by physicians, though the expert panel is aware that patients often choose to self-pack the nose.

MY PREGNANCY & DELIVERY CARE CHECKLIST

USING THE HHT GUIDELINES

The HHT Pregnancy and Delivery Guidelines are detailed on the next pages

Date: _____

Name: _____

Please check all that apply

☐ I AM EXPECTING A CHILD OR PLANNING A FAMILY, AND I OR MY PARTNER HAVE HHT.

☐ Talk to my doctor about the range of options for genetic diagnosis, from pre-conception to post-delivery.

☐ I HAVE HHT AND I HAVE HAD A PREVIOUS BRAIN HEMORRHAGE OR HAVE OTHER SYMPTOMS THAT SUGGEST I MIGHT HAVE BRAIN VASCULAR MALFORMATIONS (VMs).

☐ Talk to my doctor about planning a brain MRI in second trimester.

☐ I HAVE HHT AND I AM PREGNANT, AND I HAVE NOT RECENTLY BEEN SCREENED FOR LUNG ARTERIOVENOUS MALFORMATIONS (AVMs)

☐ Ask my doctor about planning lung AVM screening tests in second trimester, with bubble echo or non-contrast CT scan, if I am asymptomatic.

☐ Ask my doctor about planning an ASAP diagnostic non-contrast CT scan, if I am having symptoms of lung AVMs.

☐ I HAVE LUNG AVMs AND I AM PREGNANT.

☐ Ask for referral to a center with high-risk pregnancy care and HHT expertise.

☐ Plan to have my lung AVMs treated in early second trimester, at an expert center.

☐ I HAVE BRAIN VMs AND I AM PREGNANT.

☐ Ask for referral to a center with high-risk pregnancy care and HHT expertise.

☐ Talk to an expert multidisciplinary neurovascular team about my brain VMs and my risk of bleeding, to decide if I can proceed with vaginal delivery.

☐ Talk to an expert multidisciplinary team about my brain VMs and my risk of bleeding, to decide if I should have brain VMs treated after delivery.

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- **Prepare ahead of time for your appointments**: Bring your HHT Care Checklists and a family member or friend. They can help you communicate your questions and priorities, as well as act as a second set of ears. Share your experiences, worries and priorities to help your care team better understand your needs and provide individualized care.

PREGNANCY & DELIVERY

A pregnant woman with HHT should be assessed for their risk of pregnancy and delivery related complications and have access to, as needed, a multidisciplinary maternal-fetal medicine team that includes HHT experts. Screening for pulmonary AVMs and brain VMs should be considered, as detailed below, and unscreened patients may need to be considered high-risk. In addition, since offspring are at 50% risk of inheriting the pathogenic mutation, pre-pregnancy consultation with an obstetrician is recommended, for consideration of options for genetic diagnosis.

HHT GUIDELINES RECOMMENDATIONS

PREGNANCY & DELIVERY

A pregnant woman with HHT should be assessed for their risk of pregnancy and delivery related complications and have access to, as needed, a multidisciplinary maternal-fetal medicine team that includes HHT experts. Screening for pulmonary AVMs and brain VMs should be considered, as detailed below, and unscreened patients may need to be considered high-risk. In addition, since offspring are at 50% risk of inheriting the pathogenic mutation, pre-pregnancy consultation with an obstetrician is recommended, for consideration of options for genetic diagnosis.

The expert panel recommends:

F1 **THAT CLINICIANS DISCUSS PRE-CONCEPTION AND PRE-NATAL DIAGNOSTIC OPTIONS INCLUDING PRE-IMPLANTATION GENETIC DIAGNOSIS WITH HHT AFFECTED INDIVIDUALS.**

Clinical Considerations: Once the causative familial mutation is identified in an affected parent, then it can be screened for in future off-spring. Available options, including pre-implantation, post-conception and post-delivery testing (online supplement, see www.HHTGuidelines.org), vary internationally. The discussion will be influenced by local legislation pertaining to pre-implantation diagnosis and termination of pregnancy.

F2 **TESTING WITH UNENHANCED MRI IN PREGNANT WOMEN WITH SYMPTOMS SUGGESTIVE OF BRAIN VMs.**

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

F3 **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 non-contrast 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 non-contrast 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.

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 mode, minimizing 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.

F4 **THAT PREGNANT WOMEN WITH HHT BE MANAGED AT A TERTIARY CARE CENTER BY A MULTI-DISCIPLINARY TEAM, IF THEY HAVE UNTREATED PULMONARY AVMs AND/OR BRAIN VMs OR HAVE NOT BEEN RECENTLY SCREENED FOR PULMONARY AVMs.**

Clinical Considerations: Pregnant women with untreated pulmonary AVMs or brain VMs, and 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.

F5 NOT WITHHOLDING AN EPIDURAL BECAUSE OF A DIAGNOSIS OF HHT, AND THAT SCREENING FOR SPINAL VASCULAR MALFORMATIONS IS NOT REQUIRED.

Clinical Considerations: Patients should meet with an anesthetist during early third trimester to discuss anesthesia options. The risk of complications from spinal VM during epidural anesthesia are unsubstantiated and only theoretical.

F6 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.

Clinical Considerations: If a brain VM has not previously ruptured, patients may proceed with mode of delivery based on obstetrical indications and discussion with their obstetrical care provider. Vaginal delivery is not contra-indicated. Patients with "high risk" brain VMs should be considered for Cesarean section, OR epidural, to allow passive descent of the presenting part, with consideration for an assisted second stage. Diligent management of blood pressure is imperative, in these higher risk cases, and obtaining the opinion a multi-disciplinary neuro vascular team is prudent.

MY PULMONARY AVM CARE CHECKLIST

USING THE HHT GUIDELINES

Pulmonary AVMs= pulmonary arteriovenous malformations (lung AVMs). The HHT Pulmonary AVM Guidelines are detailed on the next pages.

Date: _____

Name: _____

Please check all that apply

☐ I HAVE HHT OR MIGHT HAVE HHT (THE HHT DIAGNOSIS HAS NOT BEEN RULED OUT).

- ☐ Ask my doctor to screen me for lung arteriovenous malformations (AVMs), typically with contrast echocardiography ("bubble echo").
- ☐ Consider having my screening done at an HHT Center of Excellence.

☐ I HAVE LUNG (PULMONARY) AVMs.

- ☐ Request preventative treatment (embolization) of my AVMs, even if I have no symptoms and my oxygen levels are normal.
- ☐ Ask my doctor to refer me to an HHT Center of Excellence for the preventative treatment (embolization) of my AVMs.
- ☐ Talk to my dentist and all my health care professionals about my need for lung AVM precautions, lifelong.
- ☐ Avoid SCUBA diving, lifelong.
- ☐ Plan regular long-term follow-up for the lung AVMs, even once they are treated.

☐ I HAVE TINY LUNG AVMs WHICH HAVE NOT BEEN TREATED.

- ☐ Plan for long-term follow-up to monitor for growth of the lung AVMs.

☐ I HAVE UNDERGONE SCREENING AND I DO NOT HAVE LUNG AVMs.

- ☐ Plan with my doctor for re-screening in 5 years' time.

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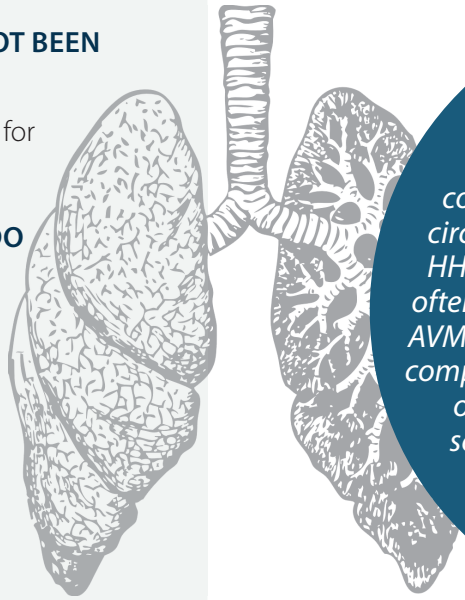
- The HHT Guidelines help ensure that people living with HHT get the best care possible.

WHAT IS MY ROLE AS SOMEONE LIVING WITH HHT?

- Be aware of the Guidelines. Share them with your care team. Ideally you should be seen at an HHT Center of Excellence or your care team may want to consult with one.
- Read up on your condition and know what care is available for HHT.
- **Prepare ahead of time for your appointments**: Bring your HHT Care Checklists and a family member or friend. They can help you communicate your questions and priorities, as well as act as a second set of ears. Share your experiences, worries and priorities to help your care team better understand your needs and provide individualized care.

PULMONARY AVMs IN HHT



Arteriovenous malformations (AVMs) are direct artery to vein connections in the lung (pulmonary) circulation. At least 40% of people with HHT have pulmonary AVMs. People are often unaware that they have pulmonary AVMs until they develop a life-threatening complication, such as stroke, brain abscess or lung hemorrhage. With the right screening and treatment, these life-threatening complications can be prevented.

HHT GUIDELINES RECOMMENDATIONS

PULMONARY AVMs IN HHT

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The expert panel recommends that:
(all recommendations are from the First HHT Guidelines)

I1 CLINICIANS SCREEN ALL PATIENTS WITH POSSIBLE OR CONFIRMED HHT FOR PULMONARY AVMs.

Clinical Considerations: Screening should be performed at the time of initial clinical evaluation for HHT. Although less evidence exists in children, the expert panel included children in the screening recommendation, since they are also at risk of life-threatening complications and treatment appears to be similarly effective. In patients with negative initial screening, repeat screening should be considered after puberty, after pregnancy, within 5 years preceding planned pregnancy and otherwise every 5-10 years.

I2 CLINICIANS USE TRANSTHORACIC CONTRAST ECHOCARDIOGRAPHY AS THE INITIAL SCREENING TEST FOR PULMONARY AVMS.

Clinical Considerations: Screening should be performed by clinicians with significant expertise in HHT, usually in an HHT center of excellence, to achieve the accuracy and low risks reported in the literature. Transthoracic contrast echocardiogrpahy (TTCE) is considered positive if there is detection of any bubbles in the left atrium. Positive screening should be confirmed with unenhanced multidetector thoracic CT with thin-cut (eg. 1-2mm) reconstructions. CT was not recommended as a screening test, due to the associated radiation exposure, but could be considered for screening in centers without expertise in TTCE for pulmonary AVM screening.

I3 CLINICIANS TREAT PULMONARY AVMS WITH TRANSCATHETER EMBOLOTHERAPY.

Clinical Considerations: The selection of pulmonary AVMs for embolization is based on feeding artery diameter, generally 3mm or greater, though targeting AVMs with feeding artery diameter as low as 2 mm may be appropriate. This procedure should be performed by clinicians with significant expertise in embolizing pulmonary AVMs, usually in an HHT center of excellence, to achieve the effectiveness and low-risks reported in the literature. This is particularly relevant when considering embolization in rare or higher risk situations, such as during pregnancy and in patients with mild-moderate pulmonary hypertension. The panel agrees there is no role for surgical management of pulmonary AVMs, other than in the management of life-threatening bleeding in a center where embolization expertise is unavailable.

I4 CLINICIANS PROVIDE THE FOLLOWING LONG-TERM ADVICE TO PATIENTS WITH DOCUMENTED PULMONARY AVMS (TREATED OR UNTREATED):

- Antibiotic prophylaxis for procedures with risk of bacteremia
- When IV access is in place, take extra care to avoid IV air
- Avoidance of SCUBA diving

Clinical Considerations: The rationale for recommending prophylactic antibiotics for bacteremic procedures in people with pulmonary AVMs, is based on expert opinion that cerebral abscess is frequent in these patients (approximately 10% before pulmonary AVM diagnosis), that cerebral abscess in these patients occurs primarily as a complication of bacteremic procedures, the fact that cerebral abscess is associated with considerable morbidity and mortality and that this precaution is low-risk. The AHA guidelines for prevention of bacterial endocarditis should be followed for choice of antibiotics. Similarly, careful avoidance of intravenous air bubbles is recommended to prevent cerebral air embolism, and this could include an in-line filter. There are only theoretical arguments for avoidance of SCUBA suggesting that there may be an increased risk of complications of decompression in patients with pulmonary AVMs. These precautions should be followed life-long, regardless of size of pulmonary AVMs, even once AVMs are treated. These precautions should also be considered in HHT patients in whom pulmonary AVMs have not been excluded or in whom microscopic pulmonary AVMs are suspected (for example, detected on TTCE but not detectable on CT).

I5 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.

Clinical Considerations: Follow-up allows the identification of embolized pulmonary AVMs that have re-perfused and other pulmonary AVMs that have grown large enough to be considered for embolization. Multidetector thoracic CT with thin-section reconstruction (1-2mm) should be undertaken within 6-12 months after embolization and then approximately every 3 years after embolization. For patients with only small untreated pulmonary AVMs and in patients with suspected microscopic pulmonary AVMs (for example, detected on TTCE but not detectable on CT), the follow-up period should be determined on a case by case basis (approximately every 1-5 years) with CT (as above), with consideration for limiting radiation exposure.

MY TEEN YEARS HHT CARE CHECKLIST

USING THE HHT GUIDELINES

The HHT Pediatric Care Guidelines are detailed on the next pages

Date: _____

Teen's Name: _____

Please check all that apply

☐ ONE OF MY PARENTS HAS HHT AND I DON'T KNOW IF I HAVE IT.

- ☐ Talk to my doctor about genetic testing to check if I carry my family's HHT mutation.

☐ I HAVE HHT OR I MIGHT HAVE HHT (THE HHT DIAGNOSIS HAS NOT BEEN RULED OUT).

- ☐ Ask my doctor for screening for lung arteriovenous malformations (AVMs).
- ☐ Ask my doctor for screening (usually MRI) for brain vascular malformations (VMs).

☐ I HAVE LUNG (PULMONARY) AVMs.

- ☐ Consider preventative treatment (embolization) for large AVMs or if I have low oxygen levels.
- ☐ Talk to my dentist and other health care professionals about my need for lung AVM precautions, lifelong.
- ☐ Plan regular follow-up for the lung AVMs, whether or not they are treated.

☐ I HAVE BRAIN VMs.

- ☐ Ask for a referral to an expert multi-disciplinary neurovascular team for assessment of my risk of bleeding from the VM(s) and for consideration for treatment.

☐ MY SCREENING FOR LUNG AVMs AND BRAIN VMs WAS DONE AND IT IS NEGATIVE.

- ☐ Talk to my doctor about re-screening in 5 years' time.

INTERNATIONAL HHT GUIDELINES

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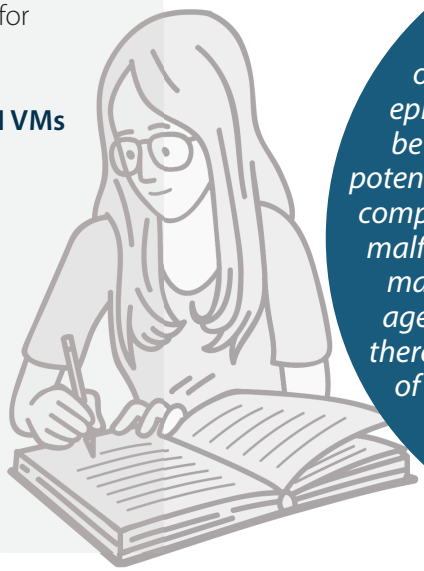
WHAT IS MY ROLE AS SOMEONE LIVING WITH HHT?

- Be aware of the Guidelines. Share them with your care team. Ideally you should be seen at an HHT Center of Excellence or your care team may want to consult with one.
- Read up on your condition and know what care is available for HHT. **The Pediatric HHT Guidelines apply up to age 18.**
- **Prepare ahead of time for your appointments**: Bring your HHT Care Checklists and a family member or friend. They can help you communicate your questions and priorities, as well as act as a second set of ears. Share your experiences, worries and priorities to help your care team better understand your needs and provide individualized care.

PEDIATRIC CARE *(up to age 18)*



While some manifestations of HHT, such as telangiectasia and epistaxis, are age dependent and may be absent in young children with HHT, potentially serious and even life-threatening complications of pulmonary arteriovenous malformations (AVMs) and brain vascular malformations (VMs) can occur at any age. The pediatric HHT guidelines focus therefore on screening and management of pulmonary AVMs and brain VMs in children.

HHT GUIDELINES RECOMMENDATIONS

PEDIATRIC CARE

While some manifestations of HHT, such as telangiectasia and epistaxis, are age dependent and may be absent in young children with HHT, potentially serious and even life-threatening complications of pulmonary arteriovenous malformations (AVMs) and brain vascular malformations (VMs) can occur at any age. The pediatric HHT guidelines focus therefore on screening and management of pulmonary AVMs and brain VMs in children.

The expert panel recommends:

E1 THAT DIAGNOSTIC GENETIC TESTING BE OFFERED FOR ASYMPTOMATIC CHILDREN OF A PARENT WITH HHT.

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

E2 SCREENING FOR PULMONARY AVMs IN ASYMPTOMATIC CHILDREN WITH HHT OR AT RISK FOR HHT AT THE TIME OF PRESENTATION / DIAGNOSIS.

Clinical Considerations: Screening may be performed with either chest X-ray and pulse oximetry OR transthoracic contrast echocardiography (TTCE). Screening with CT is not recommended, though CT chest remains the confirmatory diagnostic test when screening tests are positive.

E3 THAT LARGE PULMONARY AVMs AND PULMONARY AVMs ASSOCIATED WITH REDUCED OXYGEN SATURATION BE TREATED IN CHILDREN TO AVOID SERIOUS COMPLICATIONS.

Clinical Considerations: Pulmonary AVMs with feeding arteries ≥3 mm 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 TTCE), as do intervals.

E4 REPEATING PULMONARY AVM SCREENING IN ASYMPTOMATIC CHILDREN WITH HHT OR AT RISK FOR HHT; TYPICALLY AT 5 YEAR INTERVALS.

Clinical Considerations: Typically, negative screening is repeated every 5 years. In children with indeterminate or borderline screening results, either based on imaging or oximetry, screening should be repeated sooner.

E5 SCREENING FOR BRAIN VM IN ASYMPTOMATIC CHILDREN WITH HHT, OR AT RISK FOR HHT, AT THE TIME OF PRESENTATION / DIAGNOSIS.

Clinical Considerations: First-line screening is MRI (contrast enhanced more sensitive) to identify brain VM 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 of hemorrhage. As such, the decision to screen the child should be a shared decision among clinicians, caregivers and the child (where possible). There are important differences in clinical practice across countries: from screening asymptomatic children with MRI in infancy, to no routine screening of asymptomatic children for brain VM. Patient representatives felt strongly that children should be screened for brain VMs citing anecdotal evidence of disastrous outcomes in unscreened patients.

E6 THAT BRAIN VMS WITH HIGH RISK FEATURES BE TREATED.

Clinical Considerations: Given the need to balance natural history risk with treatment risk, children with HHT who have brain VM 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.