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

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Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu disease, is a relatively common "rare" vascular disease with an estimated prevalence of 1 in 5000–8000.[1,2] Inheritance is autosomal dominant. Genetic findings include germline mutations primarily in *ENG*, encoding endoglin (HHT type 1, OMIM#187300), and *ACVRL1* encoding activin receptor-like kinase-1 (HHT type 2, OMIM#600376), whereas mutations in *SMAD4* (juvenile polyposis/HHT overlap syndrome, OMIM#175050) are found only in a small proportion of cases, and mutations in *GDF2*, encoding the activin receptor-like kinase-1-ligand BMP9 (HHT5, OMIM#615506) so far in a few cases only.[1,2] Mutations in these genes, all linked to TGFβ signaling pathways, lead to the development of large visceral arteriovenous malformations (AVMs; mainly in the lungs, liver, and brain) and smaller telangiectasia of mucosa and skin, which are typically found on fingers, lips, tongue, buccal, and gastrointestinal mucosa. The clinical phenotype is very variable but usually dominated by hemorrhages (ie, epistaxis and gastrointestinal bleeding) from these abnormal vascular structures and consequences of chronic bleeding, primarily iron deficiency anemia.

Large AVM in the pulmonary circulation may cause right-left shunts associated with dyspnea, hypoxia, and can be the origin of preventable transient ischemic attacks, ischemic strokes, and cerebral abscesses. Hepatic AVMs can be associated with considerable intrahepatic shunting that can lead to high-output cardiac failure, portal hypertension, hepatic encephalopathy, and mesenteric ischemia, while cerebral AVMs may be caused with seizures and ischemic and hemorrhagic strokes.

The broad spectrum of clinical presentation of HHT, from asymptomatic patients with known germline mutations up to life-threatening conditions in others, is demanding specialized care to prevent future complications and to increase the quality of live and life-expectancy.

Patients with HHT are best managed in specialized centers with interdisciplinary multisystem teams including specialists of internal medicine, angiology, hematology, otolaryngology, gastroenterology, hepatology, radiology, neurology, genetics, and pediatrics. Next to these specialists, it is crucial to involve nurses, healthcare workers, psychologists, and patient advocates and to provide education programs for care givers and for patients and their families. This has been realized in recent years by implementing the European Reference Networks (ERN) networks in countries of the European community, one of them having a working group for HHT, the VASCERN: https://vascern.eu/expertise/rare-diseases-wgs/hht-wg/. Another example of such a network is Cure HHT: https://curehht.org, predominantly working in North America. However, not all countries are yet partners or have the possibility to become partners in these programs. Then, national reference centers, such as Bern University Hospital, Inselspital in Bern, Switzerland, have to elaborate programs themselves and/or try to get connected to the networks.

Taken the above into account, guidelines for diagnosis and treatment of HHT are extremely important and regular updates very helpful. Recently, an international panel from 15 countries, including 64 authors from the VASCERN and the Cure HHT published the Second International Guidelines on the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia in the *Annals of Internal Medicine*.[3] This excellent guideline demonstrates the successful multidisciplinary collaboration of medical experts, HHT patients, and patient advocates. The guidelines were developed using the AGREE (Appraisal of Guidelines for Research and Evaluation) II framework and the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology and focused on areas not previously addressed in guidelines, or where significant new information had been published. Six priority topics were identified and addressed:

- Epistaxis management
- Gastrointestinal bleeding management
- Anemia and anticoagulation
- Liver venous malformations in HHT
- Pediatric care
- Pregnancy and delivery

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Other topics, such as clinical diagnosis of HHT, which is commonly based on the Curaçao criteria,[4] diagnosis and management of cerebral vascular malformations or of pulmonary AVMs were not reassessed. Here, recommendations of the First International HHT Guidelines remain valid. All currently valid recommendations are nicely summarized in a detailed table at the beginning of the article.

While international and multidisciplinary collaborations in the past have helped to define a good standard of care for HHT patients,[5,6] the Second International HHT Guidelines add an important value on the screening recommendations for nonsymptomatic HHT patients, especially in the pediatric age.[3,7] The input of patients and patient advocates in this area is an innovative and strong aspect and resulted in proposing brain MRI in children to identify AVM, a diagnostic approach which was apparently favored more by patients than by medical experts.

In summary, the Second International Guidelines for the Diagnosis and Management of HHT provide practical evidence-based guidance for clinicians and expert centers. It will help to further improve management of HHT patients and harmonize the diagnostics and therapeutic procedures internationally.

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Disclosures

JAKH is a member of Guidelines Committee, European Hematology Association (area: Blood Coagulation and Hemostatic Disorders). The other authors have no conflicts of interest to disclose.

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