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Keynote Speaker

The NHLBI Support Mechanisms: What to know to get funding

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ORAL COMMUNICATIONS

SESSION 1: DIAGNOSIS OF HHT

High incidence of hepatic encephalopathy in HHT

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Objective: Arteriovenous malformations of the liver are common in HHT, but symptoms from liver AVM have been thought to be uncommon. Hepatic encephalopathy can result from portosystemic shunts that lead to a failure to metabolize and remove gut-based toxins (such as ammonia) from the blood. Blood in the GI tract is a potent stimulus for ammonia production. By virtue of hepatic vascular malformations and frequent presence of blood in the gut, we hypothesized that HHT patients may be at risk for hepatic encephalopathy.

Methods: Starting in January 2015 serum ammonia analysis was recommended for all patients at our center, together with hepatic function chemistries, ESS, measures of heart failure, anemia, iron stores, and vitamin D, and these were compared for all patients with confirmed HHT at the time of the highest recorded ammonia level.

Results: 193 unique patients had ammonia samples available for analysis (ACVRL1: 130, ENG: 52, SMAD4: 1, negative genotype: 2, and unknown gene: 8). A total of 18 patients had elevated ammonia levels (9.3%). Elevated ammonia was much more common in patients with ACVRL1 mutations (17/130, 13.1%) than ENG (0/51, 0%). We observed moderately strong correlations between ammonia level and cardiac index, bilirubin and age, and weak correlations with B-natriuretic peptide and alkaline phosphatase. Of those with elevated ammonia levels, 3/18 had no other indicator of liver AVM.

Conclusion: Hepatic encephalopathy is common and underappreciated in HHT, and particularly affects patients with ACVRL1 mutations. In 17% of cases, elevated ammonia was the only indicator of liver involvement.

Subaortic membranes in HHT patients and liver vascular malformations

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Objective: To describe the clinical features of subaortic membranes (SAoM) in the left ventricular outflow tract (LVOT) in HHT patients with liver vascular malformations (VMs) and high-output heart failure.

Method: Retrospective analysis of HHT patients evaluated at a single center with known liver AVMs and high-output heart failure. Clinical features, genotype, echocardiographic, and hemodynamic data were analyzed in 28 patients who had undergone transthoracic echocardiograms and right heart catheterization.

Results: There were 9 patients with SAoM identified (mean age of 65 ± 4 years). Patients with SAoM were female and had ACVRL1 mutations. SAoM were discrete and located in the LVOT 1.1 ± 0.1 cm below the aortic annular plane. They caused turbulent flow and mild obstruction (peak velocity 2.8 ± 0.2 m/s, mean gradient 17 ± 2 mmHg). No SAoM patient had more than mild aortic insufficiency. SAoM patients had higher cardiac outputs (12.1 ± 1.3 vs 9.3 ± 0.7 L/min, $p < 0.04$) and mean pulmonary artery pressures (36 ± 3 vs 28 ± 2 mm Hg, $p < 0.04$) during right heart catheterization. They also had higher LV stroke volumes, cardiac outputs, and ejection fractions on echocardiography.

Conclusion: SAoM develop in patients with type 2 HHT who have high-output heart failure due to liver VMs. They are mildly obstructive and not associated with significant aortic insufficiency. They contribute to the high velocities and may confound the measurement of cardiac output based on LVOT measurements. We postulate that they may result from increased shear stress in the LVOT.

A comparative study between MR angiography and CT in the detection of pulmonary arteriovenous malformations

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Objective: To assess the diagnostic performance of Magnetic Resonance Angiography (MRA) compared to Computed Tomography (CT) in the detection of Pulmonary Arteriovenous Malformations (PAVM).

Methods: Fifty patients suspected of having untreated or recanalized PAVMs based on transthoracic contrast echocardiography underwent both CT and contrast-enhanced MRA of the pulmonary arteries. MRA was performed on a 1.5T scanner: spatial resolution $0.57 \times 0.57 \times 1.5$ mm. CT scans were performed on a 256- or 64-slice scanner with 1-mm reconstructions. MRAs and CT scans were assessed for the presence of PAVMs and scored per lobe and segment. Two observers independently scored the scans. A third observer matched and selected PAVMs with a feeding artery diameter of at least 2 mm. In addition, the third observer acted as an adjudicator in case of discrepancy between the first two observers.

Results: 65 PAVMs were detected both on MRA and CT. With MRA, 8 PAVMs were missed with an indication for treatment resulting in an accuracy of 57/65 (88%). Of these 8 PAVMs, 3 were untreated, 4 previously embolized, and 1 with systemic perfusion.

Conclusions: Compared to CT, MRA angiography has an accuracy of 88% in detecting treatable PAVMs. These results are promising but improved detection is warranted should MRA replace CT in the work-up of patients suspected of having PAVMs.

The use of gray-scale image intensity to quantify pulmonary right-to-left shunt measured with transthoracic contrast echocardiography

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Objective: To assess a novel method of pulmonary right-to-left shunt (RLS) evaluation with transthoracic contrast echocardiography (TTCE) using a change in gray-scale image intensity (e.g., change in echo density) following contrast injection.

Methods: Retrospective analysis of all patients diagnosed or suspected of HHT, who visited the St. Antonius Hospital between January 2017 and December 2017, and underwent a TTCE for the detection of a RLS. Using ImageJ, a scientific image processing program, the image intensity of different frames was reviewed for each patient. The image intensity with maximum contrast in the left ventricle was subtracted from the image intensity of a baseline measurement of the left ventricle without any contrast present. This change was converted to percentage of change in image intensity (e.g., increase in whiteness). In addition, the RLS grade, chest computed tomography (CT) scan if applicable and demographic parameters were extracted from the medical files.

Results: In total, 214 patients (56% female, mean age 48 ± 17 years) were included. TTCE revealed no RLS in 75 patients (35%), grade I in 50 patients (23%), grade II in 39 patients (19%), and grade III in 50 patients (23%). A pulmonary arteriovenous malformation (PAVM) was detected with chest CT in 95 (44%) patients and embolotherapy recommended in 38 patients. The mean change in image intensity was $-0.4\% \pm 1.3\%$ in patients without RLS; $+1.3\% \pm 1.6\%$ in RLS grade I; $+6.5\% \pm 4.0\%$ in RLS grade II; and $+25.8\% \pm 13.3\%$ in RLS grade III. Both methods were strongly correlated: Spearman's Rho 0.89, $p < 0.0001$. The mean change in image intensity was $+0.9 \pm 3.7\%$ in patients without macroscopic PAVM versus $+15.5 \pm 14.6\%$ in patients with macroscopic PAVM visualized on chest CT. This was $+23.3\% \pm 14.7\%$ in patients that required embolotherapy versus $+3.9 \pm 8.7\%$ in those not requiring embolotherapy. The sensitivity and specificity of the current quantification method for the detection of treatable PAVMs were 100% and 71%, respectively. Using a cut-off value of $+5.2\%$ change in image intensity (sensitivity 100%, specificity 80%), 16 chest CT scans (18%) were not required without missing any treatable PAVM.

Conclusions: This novel method shows promising results for the evaluation of pulmonary RLS with TTCE but should be validated in another study population.

SESSION 2: ENG/ALK1 SIGNALING

BMP10 has a unique function for the development of proper arteriovenous network

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Objective: While numerous biochemical and cellular experiments have shown that both BMP9 and BMP10 can signal through ALK1-ENG in endothelial cells and regulate angiogenic properties, the extent to which overlapping and unique functions of these ligands control arteriovenous (AV) network formation remains to be determined.

Methods: Using a novel *Bmp10*-inducible knockout (iKO) mouse strain that we have generated, we induced global deletion of *Bmp10* at neonatal and adult stages, and compared gross and vascular phenotypes of *Bmp10*-iKO with *Bmp9*-KO and *Bmp9/10*-double KO (dKO) mice at both stages.

Result: While *Bmp9* deletion did not affect vitality, BMP10 depletion at a neonatal or adult stage resulted in lethality with anemia and bleeding in gastrointestinal tract. *Bmp9/10*-dKO mice exhibited the phenotypes similar to *Bmp10*-iKOs, but their phenotypes were more pronounced and they reached lethality 2–3 days sooner compared with *Bmp10*-iKOs. In the development of retinal vasculature, *Bmp9*-KO did not display any noticeable defects, but *Bmp10*-iKO showed AV shunting vessels at varying degrees. While retinal vascular expansion was moderately affected in *Bmp10*-iKO, it was severely impaired in *Bmp9/10*-dKO retinas. Nonetheless, the number of AVMs developed in *Bmp9/10*-dKO retinas was not significantly different from that in *Bmp10*-iKO. Wound-induced AVMs in subdermal vessels were detected in adult *Bmp10*-iKO as well as *Bmp9/10*-dKO mice.

Conclusion: BMP10 is indispensable for the development of proper AV network, indicating that BMP9 has limited compensatory functions for the loss of BMP10. Taken together, these data suggest that BMP10 is the most relevant physiological ligand of the ENG-ALK1 signaling pathway pertinent to HHT pathogenesis.

BMP10 is the sole required ligand for endothelial ALK1 signaling

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Objective: Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant vascular disorder characterized by development of high-flow arteriovenous malformations (AVMs) that can lead to stroke or high-output heart failure. HHT2 is caused by heterozygous mutations in *ACVRL1*, which encodes an endothelial cell morphogenetic protein (BMP) receptor, ALK1. BMP9 and BMP10 are established ALK1 ligands. However, the unique and overlapping physiological roles of these ligands remain poorly defined.

Methods: To probe spatiotemporal ALK1 ligand requirements, we generated zebrafish mutants in *bmp9* and duplicate paralogs, *bmp10* and *bmp10-like*, which encode putative Alk1 ligands expressed primarily in liver and heart, respectively.

Results: Combined loss of *bmp10* and *bmp10-like* results in embryonic cranial AVMs indistinguishable from *acvr1l* mutants, confirming functional redundancy of these paralogs during embryonic vascular development. In contrast, Bmp10 is the only necessary Alk1 ligand in the juvenile-to-adult period, with mutants exhibiting hemorrhagic and/or enlarged vessels in anterior skin and liver, heart dysmorphology, and premature death. Heart dysmorphology correlates with severity of vascular defects, and *bmp10* mutant hearts show increased cardiac output. This same phenotype occurs with low penetrance in *acvr1l* heterozygous adults.

Conclusions: Taken together, these data support the conclusion that BMP10 is the sole required ligand for endothelial ALK1 signaling, and that vascular defects lead to low systemic vascular resistance and high-output heart failure in *bmp10* mutants. As such, we believe that *bmp10* mutants will be a valuable model for dissecting the mechanism of AVM-associated high-output heart failure, which is an increasingly recognized complication of severe liver involvement in HHT.

Enhanced ALK1 signaling inhibits arteriovenous malformations caused by endoglin deficiency

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Objective: Hereditary hemorrhagic telangiectasia (HHT) has been considered a disease caused by defects in TGF- β /BMP signaling, mediated by ENG and ALK1. Since ALK1 is downstream of ENG in the signaling pathway, it is speculated that induced-ALK1 overexpression (OE) or activation may overcome ENG deficiency as well as ALK1 deficiency.

Method: We have generated a novel mouse allele (*ROSA26^{Alk1}*) in which expression of HA-tagged ALK1 and bicistronic eGFP can be induced by Cre-recombinase. We examined whether ALK1-OE or ENG-OE could inhibit the development of AVMs in wounded skin and developing retinas of *Alk1*- and *Eng*-inducible knockout (iKO) mice.

Result: Biochemical and immunofluorescence analyses confirmed the Cre-dependent overexpression of HA-ALK1 transgene. Ubiquitous, smooth muscle cell (SMC), or endothelial cell (EC)-specific overexpression of ALK1 in post-natal stages did not affect the vitality nor the development/homeostasis of vascular network. ALK1-OE prevented the development of retinal AVMs and wound-induced skin AVMs in *Eng*-iKO as well as *Alk1*-iKO mice. On the other hand, ENG-OE could not inhibit the AVM development in *Alk1*-iKO models. ALK1-OE normalized aberrant vascular smooth muscle cell coverage, loss of artery–vein identities, the reduced expression of SMAD and NOTCH target genes, enhanced AKT phosphorylation, and randomized EC polarity in *Eng*-iKO mice. Supplementation of BMP10, but not BMP9, could inhibit AVM development in *Eng*-iKO retinas.

Conclusion: These data suggest that ENG and ALK1 form a linear signaling pathway for the formation of proper arteriovenous network during angiogenesis, and that ALK1 overexpression or activation can be an effective therapeutic strategy for HHT.

BMP9 is a paracrine factor controlling liver sinusoidal endothelial cell fenestration and protecting from hepatic fibrosis

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Objective: Bone morphogenetic protein 9 (BMP9) is a circulating factor produced by hepatic stellate cells that plays a critical role in vascular quiescence via its endothelial receptor ALK1. Mutations in the gene encoding ALK1 cause HHT2 (Hereditary Hemorrhagic Telangiectasia type 2), whose patients present hepatic vessel malformations. However, the molecular mechanism that links BMP9 with liver malformations is still unknown.

Results: Here, we report that *Bmp9* gene deletion in 129/Ola mice triggers hepatic perisinusoidal fibrosis from 15 weeks of age. An inflammatory response appeared within the same time frame, whereas sinusoidal vessel dilation developed later on. mRNA analyses of primary liver sinusoidal endothelial cells (LSECs) revealed that the expression of the LSEC-specifying transcription factor GATA4 was strongly reduced in *Bmp9*-KO mice as compared to wild-type mice. LSECs from *Bmp9*-KO mice also lost the expression of several terminal differentiation markers. They gained CD34 expression and deposited a basal lamina, indicating that they were capillarized. Another main characteristic of differentiated LSECs is the presence of permeable fenestrae. LSECs from *Bmp9*-KO mice had a significantly reduced number of fenestrae. This was already observable in 2-week-old pups. Moreover, we could show that addition of BMP9 to primary cultures of LSECs prevented the loss of their fenestrae and maintained the expression levels of *Gata4* and *Plvap*.

Conclusion: Taken together, our observations show that BMP9 is a key paracrine regulator of liver homeostasis, controlling LSEC fenestration and protecting from perivascular hepatic fibrosis and that *Bmp9*-KO mice in the 129/Ola background could be an interesting preclinical model for HHT.

SESSION 3: SYSTEMIC TREATMENT OF HHT

Intravenous bevacizumab in HHT-related bleeding: significant inter-individual variability in the need for maintenance therapy

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Objective: Systemic (IV) bevacizumab is a well-established treatment option for severe HHT-related bleeding. Most patients receive

an initial ‘induction’ dosing regimen of 4–8 doses of IV bevacizumab. The need for further ‘maintenance’ therapy with IV bevacizumab as well as the optimal maintenance dosing strategy is undefined (regular prophylactic maintenance dosing vs. as-needed dosing only after recurrent bleeding). We present our center’s experience with maintenance dosing of IV bevacizumab.

Method: We reviewed all patients treated with IV bevacizumab from Jan 2013 to Jan 2019 at the Mayo Clinic HHT center of excellence in Rochester, Minnesota. Patients with ≥ 2 years of follow-up after completion of initial induction IV bevacizumab therapy were included. Data regarding subsequent bevacizumab dosing were carefully abstracted.

Result: A total of 61 unique HHT patients received IV bevacizumab from 2013 to 2019 with 52 patients receiving this treatment primarily for HHT-related bleeding. A total of 44 patients were followed for ≥ 1 year from date of initial bevacizumab dosing and 35 patients were followed for ≥ 2 years. There was substantial variability (data not shown) in the need for maintenance dosing among patients with only a very small fraction (4 patients) receiving regular maintenance doses every 4–6 weeks.

Conclusion: We present our center’s experience with ‘as-needed’ maintenance dosing for IV bevacizumab. Our data demonstrate significant inter-individual variability in the need for IV bevacizumab. A more personalized and individualized re-dosing strategy may likely result in significant cost savings without compromising patient safety or quality of life.

Experience with bevacizumab as treatment in HHT patients with severe hepatic affection and refractory anemia: ambispective cohort study

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Objective: To report our clinical experience with bevacizumab in a cohort of HHT patients.

Methods: Observational, ambispective cohort study of our Institutional Registry of HHT. Patients were treated with bevacizumab due to high-output cardiac failure (HOCF) and/or iron deficiency refractory anemia (IDRA) secondary to nasal/gastrointestinal bleeding. We describe basal clinical data, bevacizumab schedules, efficacy outcomes, and adverse events. Comparison between groups (before-after) was performed using Signed-rank test.

Results: Eighteen patients were included from July 2013 to January 2019. Mean age was 60.2, 11 females. Clinical indications were 3 for HOCF, 12 for IDRA, and 3 for both. For HOCF, pretreatment median cardiac index (CI) was 5.6 L/min/m² (IQR_{25–75}: 5.1–5.9) and cardiac output (CO) was 8.6 L/min (IQR_{25–75}: 8.1–9). For IDRA group, median pretreatment hemoglobin in the previous quarter was 8.1 g/dl (IQR_{25–75}: 7.5–9.2) while median transfusional requirement was 3.5 units (IQR_{25–75}: 1.3–6). Bevacizumab 5 mg/kg/dose every 2 weeks for 6 applications (reference drug or biosimilar) was scheduled. By the end of treatment, median CI was 4 L/min/m² (IQR_{25–75}: 3.6–4.2) and cardiac output was 6.6 L/min (IQR_{25–75}: 5.6–6.7) ($n = 4$). For IDRA group, median hemoglobin after 3 months was 12 g/dl (IQR_{25–75}: 9.8–12.8) ($p < 0.05$) and median transfusional requirement 0 units (IQR_{25–75}: 0–0.5) (ns). No serious adverse events were registered.

Conclusion: Bevacizumab is a promising line of treatment for HHT patients with IDRA. More power is needed for HOCF subcohort to strengthen previous published results.

Efficacy and safety of oral itraconazole as treatment for severe epistaxis in hereditary hemorrhagic telangiectasia patients: results of a prospective phase II clinical trial

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Background: Severe epistaxis in hereditary hemorrhagic telangiectasia (HHT) patients is a frequently observed and difficult to treat problem. Recently, potent vascular endothelial growth factor (VEGF) inhibiting effects of oral itraconazole have been discovered in vitro and in vivo. In addition, itraconazole is currently being repurposed as anti-cancer drug in human clinical trials because of the VEGF inhibition. Since VEGF levels are elevated in HHT patients and VEGF-inhibiting antibodies decrease epistaxis, the hypothesis states that oral itraconazole may decrease epistaxis as well in HHT patients.

Objectives: A prospective phase II clinical trial was designed to assess the safety and efficacy of oral itraconazole in HHT patients with severe epistaxis.

Methods: Patients received once daily 200 mg oral itraconazole for sixteen weeks. The primary outcome was the epistaxis severity score (ESS) measured at the beginning and the end of the trial. Secondary outcomes included adverse events, monthly epistaxis duration, and epistaxis number measured with a epistaxis diary, hemoglobin levels, and quality of life.

Results: Sixteen HHT patients, 4 females (25%), 12 males (75%) with a median age of 58.6 years (interquartile range (IQR) 49.7–70.4) were enrolled. Of these 16 patients, 9 (56%) were diagnosed with HHT type I, 6 (38%) with HHT type II, and in one patient (6%) no mutation was found. The median ESS significantly decreased from 6.1 (IQR 5.1–7.2) to 3.8 (IQR 3.1–5.2) ($p = 0.006$). The monthly epistaxis number decreased with 27 epistaxis episodes ($p = 0.004$) and the monthly duration with 335 min ($p = 0.005$). However, in two patients, either argon plasma coagulation or nasal embolization were still required to treat epistaxis despite itraconazole treatment. Hemoglobin levels did not significantly change. The quality of life showed a tendency of improvement. In this trial, 3 patients (19%) prematurely terminated due to temporary side effects including fatigue, polyneuropathy, and mild congestive heart failure.

Conclusions: Oral itraconazole significantly improved epistaxis in HHT patients. However, moderate side effects have occurred during treatment, probably related to itraconazole. The potential therapeutic benefit of oral itraconazole should be further investigated.

Pomalidomide in HHT: design of a randomized, placebo-controlled trial

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Objective: Based on the results of a pilot study, we have developed a randomized, placebo-controlled study to further examine the efficacy and safety of pomalidomide in HHT. This abstract describes the development and primary features of the study.

Methods: With the support of a U34 award from NHLBI, a group of experienced HHT investigators was convened and met biweekly to develop this trial. Assistance in trial design was provided by Research Triangle Institute (RTI). Participating sites were selected with the guidance of CureHHT.

Results: One hundred fifty-nine study subjects will be randomized 2:1 to six four-week cycles of pomalidomide or placebo. The primary endpoint will be the difference in the mean change of the Epistaxis Severity Score (ESS) from baseline to week 24 between placebo- and pomalidomide-treated groups. Eligible patients will have a clinical diagnosis of HHT, a requirement for parenteral infusion of at least 250 mg of iron or transfusion of 1 unit of blood over the preceding 24 weeks, and an ESS of ≥ 3 measured over the preceding 3 months. All patients will undergo genotyping, the cost of which will be paid by the study in the absence of third-party coverage. Samples for exploratory mechanistic analyses and to define biomarkers of response will be obtained before and during treatment.

Conclusion: The study has been approved by NHLBI and milestones developed. Efforts are underway to finalize the protocol and obtain the IND. We expect this study to begin accrual in August, 2019.

Pomalidomide in HHT: results of a pilot study*

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Objective: A broader therapeutic portfolio is needed for HHT. Based on studies demonstrating efficacy of thalidomide, we examined the efficacy and safety of pomalidomide in a single-arm pilot study.

Methods: Eligible patients had 1) GI bleeding requiring transfusion of ≥ 4 units PRBC or 4 iron infusions, or 2) epistaxis with epistaxis severity score (ESS) ≥ 4 requiring ≥ 2 units PRBC or 500 mg intravenous iron, each within the preceding 4 months. The primary endpoint was a 50% reduction in parenteral iron or transfusion. The secondary endpoint was to define the effect of pomalidomide on the ESS. Treatment was initiated with 1 mg, increasing to 5 mg of pomalidomide/daily, which was continued for 4 months then tapered.

Results: Nine patients provided consent. One was not treated due to an intervening cardiac event. Two developed a drug-related AE (rash) within 3 weeks of treatment and were removed, thus we report on 6

patients. Two patients were on study for only 5 months and removed for non-drug-related AEs; both had primarily GI bleeding. One of these met the primary endpoint while the other did not; however, this patient significantly reduced the ESS. The remaining four patients completed the study and all met the primary endpoint and demonstrated significant reductions in the ESS. Decreased levels of plasma MMPs and/or HB-EGF were observed in responders.

Conclusions: This pilot study demonstrates safety and suggests efficacy of pomalidomide in HHT, and provides support for a randomized, placebo-controlled study that will open August, 2019.

*This study was supported by Celgene, Summit NJ

SESSION 4: GENETICS OF HHT

Unraveling the mystery: genome sequencing reveals deep intronic splice variants that cause HHT

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Objective: Hereditary hemorrhagic telangiectasia (HHT) is a genetically heterogeneous disorder caused by mutations in the genes *ENG*, *ACVRL1*, and *SMAD4*. Yet, the genetic cause remains unknown for some families even after exhaustive exome analysis. We hypothesized that non-coding regions of the known HHT genes may harbor variants that disrupt splicing in these cases.

Methods: DNA from 35 individuals with clinical findings of HHT and 2 healthy controls from 13 families underwent whole genome sequencing. Additionally, 87 unrelated cases suspected to have HHT were evaluated using a custom designed next-generation sequencing (NGS) panel to capture the coding and non-coding regions of *ENG*, *ACVRL1*, and *SMAD4*. Individuals from both groups had tested negative previously for a mutation in the coding region of known HHT genes. Samples were sequenced on a HiSeq2500 instrument and data were analyzed to identify novel and rare variants.

Results: Eight unrelated cases had a novel non-coding *ACVRL1* variant that disrupted splicing. One family had an *ACVRL1* intron 9:chromosome 3 translocation, the first reported case of a translocation causing HHT. The other 7 cases had a variant located within a ~ 300 bp CT-rich “hotspot” region of *ACVRL1* intron 9 that disrupted splicing. Finally, one additional case had a deep intronic *ENG* c.524-210T>G variant that was confirmed to disrupt splicing using cDNA sequencing.

Conclusions: Despite the difficulty of interpreting deep intronic variants, our study highlights the importance of non-coding regions in the disease mechanism of HHT, particularly, the CT-rich hotspot region of *ACVRL1* intron 9. The addition of this region to HHT molecular diagnostic testing algorithms will improve clinical sensitivity.

Common genetic variants associated with immune or inflammatory traits and disease severity phenotypes in hereditary hemorrhagic telangiectasia

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Objectives: Hereditary hemorrhagic telangiectasia (HHT) patients have variable phenotypes including bleeding and organ vascular malformations (VM), which can lead to stroke. Genetic modifier effects and inflammatory processes may contribute to phenotypic heterogeneity. We hypothesized that genetic variants associated with other immune or inflammatory traits are associated with HHT phenotypes.

Methods: We genotyped 760 Caucasian HHT patients from the Brain Vascular Malformation Consortium (Affymetrix UK Biobank array) and selected 5081 variants (or proxies) associated with immune and inflammatory traits from the Genome-Wide Association Study Catalog. Association with 6 phenotypes: VM (brain, liver, lung, any), anemia, and stroke (ischemic or intracerebral hemorrhage) were evaluated using additive models adjusted for age, sex, and 20 principal components.

Results: Six variants were associated with brain VM, 6 with lung AVM, 3 with liver VM, 4 with any VM, 6 with anemia, and 10 with stroke ($p < 0.001$), however, none achieved FDR-corrected statistical significance. The strongest associations were any VM with a *MAZ* variant, previously associated with multiple sclerosis (OR 2.36, $p = 0.000054$), brain VM with a *MSI2* variant (OR 1.88, $p = 0.000095$), associated with coronary artery calcification, and lung VM with an *IGF1R* variant (OR 1.57, $p = 0.00034$), associated with endometriosis. *MAZ* is a transcription factor involved in TGF β signaling, cell proliferation, and carcinogenesis. *MSI2* is an RNA-binding protein that modulates cell proliferation and IL6 signaling. *IGF* signaling has been implicated in HHT VMs.

Conclusions: Variants associated with immune or inflammatory traits may also be associated with HHT phenotypes. We will replicate top associations in a second cohort of 800 HHT patients.

HHT telangiectases contain biallelic mutations in *ENG/ACVRL1*

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Objective: HHT is caused by constitutional heterozygous mutation of *ENG*, *ACVRL1*, or *SMAD4*. Despite the systemic presence of the mutation, vascular malformations associated with HHT occur focally, rather than manifesting as a systemic vascular defect. Mouse models of HHT only develop AVMs after an angiogenic stimulus and only with homozygous loss of the causal genes. Based on these observations, we investigated the hypothesis that one trigger for HHT-associated vascular malformation is a localized somatic mutation resulting in biallelic loss of endoglin or ALK1.

Methods: We performed targeted deep sequencing on 18 fresh-frozen telangiectases, 2 FFPE telangiectases, and 3 FFPE liver AVMs. The

presence of each mutation was confirmed by independent amplification and resequencing.

Results: Somatic mutations were identified in 9/23 lesions; 5 in *ENG* and 4 in *ACVRL1*. Mutations were identified in 8/18 fresh-frozen telangiectases, 1/2 FFPE telangiectases, and 0/3 FFPE liver AVMs. Somatic mutations were exclusively present in the same gene as the pathogenic constitutional mutation, with frequencies ranging from 0.5 to 9%. The mutations consisted of 5 indels causing frameshifts, 3 in-frame deletions, and 1 variant predicted to impact splicing; all predicted to cause loss-of-function. Currently, we have confirmed that 3/9 constitutional and somatic mutation pairs are biallelic with no evidence that any pairs occur on the same allele. Additionally, multiple lesions taken from singular patients contain unique somatic mutations.

Conclusion: These data support the long-standing but unproven hypothesis that biallelic loss of endoglin or ALK1 is a critical event in the development of an HHT-associated vascular malformation.

A threshold of endoglin expression in endothelial cells explains the vascular etiology of hereditary hemorrhagic telangiectasia

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Objective: HHT shows considerable variation in clinical manifestations within and between families. Only specific vascular beds are found affected suggesting environmental and genetic modifier effects.

Methods: We took advantage of *Eng* \pm mutant mice that exhibit HHT1 vascular lesions including poor mural cell attachment to the vessel walls and compared the expression levels of endoglin in different organs to the severity of the phenotype observed. We investigated how variations in endoglin expression levels affect endothelial cell responses to TGF- β 1 and BMP9, in vitro. Finally, HHT1 biopsies were analyzed to determine whether the mechanism evident in mice is conserved in humans.

Results: We report that a minimum threshold of endoglin is required to control endothelial cell responses to TGF- β 1 and BMP9 activation. Endothelial cells exhibited abnormal responses if endoglin levels fell below a critical threshold. We also revealed an association between the expression levels of endoglin and the general prevalence of clinical manifestations in various organs and specific vascular beds. Endoglin levels were particularly low in skin, a tissue typically associated with early lesions in HHT1 and only vascular beds with the lowest levels of endoglin showed vascular abnormalities.

Conclusions: Endothelial cells only exhibit abnormal responses if endoglin expression is below a certain threshold and predict that vascular lesions typical of HHT1 develop primarily in vascular beds where mutations reduce endoglin expression below this threshold. These provide a mechanism that could explain the specificity of the vascular beds that are affected as well as the variability between HHT individuals and confirm that *ENG* is modifier gene.

Genotype–phenotype correlation in children with HHT

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Objective: To investigate genotype–phenotype correlations in a pediatric cohort of patients with Hereditary Hemorrhagic Telangiectasia (HHT).

Methods: Clinical manifestations of HHT were examined in the first 176 children (0–18 years old) enrolled with and without brain arteriovenous malformation (AVM) in the multicenter Brain Vascular Malformation Consortium (BVMC) HHT Project. HHT gene mutation results were assessed for correlation with clinical phenotypes.

Results:

Table 1 Genotype–phenotype characteristics in children with HHT

	Number of patients	Mean age ± SD (years)	Epistaxis (%)	GI bleed (%)	PAVMs (%)	BAVMs (%)	LAVMs (%)
ENG	84	11.9 ± 4.8	70 (83.3%)	1 (1.2%)	32 (38.1%)	43 (51.1%)	1 (1.2%)
ALK-1	54	9.8 ± 4.9	47 (87.1%)	0 (0.0%)	4 (7.4%)	8 (14.8%)	2 (3.7%)
SMAD4	11	11.0 ± 4.2	10 (91.0%)	6 (54.5%)	1 (9.1%)	0 (0.0%)	0 (0.0%)
Overall	176	10.8 ± 4.9	127 (72.2%)	8 (4.5%)	48 (27.3%)	61 (34.7%)	3 (1.7%)

Patients with an endoglin mutation were significantly more likely to have PAVMs ($P < 0.001$) and BAVMs ($P < 0.0001$) in comparison to those with ALK-1 mutations. Most patients with GI bleeding (75%) carried a SMAD4-disease causing mutation.

Conclusion: These data represent one of the largest genotype–phenotype pediatric cohorts to date. Endoglin mutation was associated with higher prevalence of both PAVMs and BAVMs in children with HHT, which is similar to known adult observations. Though rare, GI bleeding and liver vascular malformations were reported in this pediatric series.

SESSION 5: TREATMENT OF HHT

Treatment of recanalized pulmonary arteriovenous malformations with the proximal versus distal embolization technique

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Objectives: To compare the success of proximal versus distal embolization technique for treatment of previously embolized, recanalized pulmonary arteriovenous malformations (PAVMs).

Methods: Between July 2007 and October 2018, 24 consecutive patients underwent embolization of 52 previously treated recanalized PAVMs within a single Hereditary Hemorrhagic Telangiectasia (HHT) Center of Excellence with imaging follow-up. PAVM angioarchitecture was classified as either simple (1 feeding artery) or complex (≥ 2 feeding arteries). Repeat embolization was performed either by embolizing proximal to or within the existing embolic (proximal embolization technique), or by embolizing distal to the existing embolic within the distal feeding artery or PAVM sac (distal embolization technique). Costs of embolic agents were calculated from manufacturer list prices. Follow-up CT angiography was reviewed to determine the presence or absence of persistent PAVM perfusion. Success rates of the embolization techniques were compared.

Results: Mean patient age was 45.6 years (range 22–70 years) and 58.3% were female. 22 patients (91.7%) had definite HHT. Persistent PAVM occlusion following repeat embolization was 61.5% at a mean follow-up time of 576.9 days. Success following re-treatment was significantly more likely with distal embolization technique (13/14, 92.9%) than with proximal embolization technique (19/38, 50.0%) ($p = 0.0085$). However, distal embolization was associated with longer fluoroscopy time (58.1 vs. 47.6 min, $p = 0.0181$) and higher average cost per PAVM (\$9,025.71 vs. \$4,753.92, $p = 0.0031$).

Conclusion: Recanalized PAVMs have high rates of recurrence following repeat embolization. Distal embolization technique requires longer fluoroscopy time and higher cost, but is more likely to produce durable occlusion than proximal embolization.

Safety of catheter embolization of pulmonary AVMs in Osler patients—evaluation of peri-interventional complications on pre- and post-interventional MRI

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Objectives: The recommended treatment of PAVMs in HHT is catheter embolization either with coils or by the use of vascular plugs. The purpose of our study was to prospectively evaluate patients undergoing embolization therapy of pulmonary AVMs pre- and post intervention by MRI for detection of clinical insignificant cerebral infarctions.

Methods: 94 HHT patients (male/female = 40/54; mean age 45.7 ± 16.7 (range 5–86)) with pre-diagnosed PAVMs on CE-MRA underwent embolization therapy. The number of PAVMs treated in each patient ranged from one to 8 PAVMs. Depending on the size of the feeding vessel and the anatomical situation, either Nester Coils (Cook, USA) or Amplatzer plugs were used for embolization therapy. During the procedure, each patient received IV injection of 2500 IE heparin. MRI was performed immediately before and 4-h and 3-month post-embolization therapy.

Results: DWI post-interventional therapy only showed small, diffuse emboli in one patient that underwent re-embolization after initial treatment with tungsten coils. He already before treatment had several episodes of brain emboli, and re-embolization had to be performed in the

already placed coils for anatomic reasons. After successful re-embolization, the patient did not experience any further brain emboli over a follow-up period of 8 years. All other patients, either primary embolization or re-embolization, did not show any periinterventional brain ischemia.

Conclusions: This prospective study in 94 patients undergoing interventional treatment of PAVMs shows that catheter embolization is a safe method for treatment and does not even result in clinical inconspicuous cerebral ischemia, which was not demonstrated previously.

Tacro study: efficacy and safety of a 0.1% tacrolimus nasal ointment as a treatment for epistaxis in hereditary hemorrhagic telangiectasia (HHT). A double-blind, randomized, placebo-controlled, multicenter trial

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Objectives: Improvement in epistaxis has been shown in HHT patients after a liver transplantation. Furthermore, Albiñana et al. reported that the immunosuppressor FK506 increases the protein and mRNA expression of ENG and ALK1 in cultured endothelial cells, and enhances the TGF- β 1/ALK1 signaling pathway and endothelial cell functions such as tubulogenesis and migration. It was thus hypothesized that the immunosuppressive treatment (FK506) used to prevent rejection may have an anti-angiogenic effect and may be an interesting drug for use in patients with HHT. The main objective was to evaluate the efficacy of a tacrolimus (FK506) nasal ointment treatment, on nosebleeds duration in HHT patients.

Methods: Multicentric, randomized, phase 2, double-blind placebo-controlled study with an allocation ratio of 1:1. The treatment tested, Protopic[®] (tacrolimus at 0.1%) or placebo, is self-administered by the patient in each nostril twice a day for 6 weeks. Patients were monitored for 12 weeks: 6-week treatment and 6-week follow-up. The percentage of patients experiencing improvement in their nosebleeds will be computed in each group. An improvement is defined as a 30% reduction in the total duration of nosebleeds over 6 weeks after treatment, compared with the duration of the nosebleeds in the 6 weeks before the treatment.

Conclusion: A total of 50 patients were randomized and treated. Statistical analysis is ongoing. The results on efficacy and safety will be presented.

Trial Registration: #NCT03152019

This study has been promoted and granted by Hospices Civils de Lyon, and by patients' association (AMRO).

Topically applied etamsylate, new orphan drug for HHT-derived epistaxis

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Hereditary Hemorrhagic Telangiectasia (HHT) is a vascular dysplasia characterized by recurrent and spontaneous epistaxis (nose bleeds), telangiectases on skin and mucosa, internal organ arteriovenous malformations, and dominant autosomal inheritance. Mutations in Endoglin and ACVRL1/ALK1, genes mainly expressed in endothelium, are responsible in a 90% of the cases for the pathology. These genes are involved in the TGF- β signaling pathway.

Epistaxis remains as one of the most common symptoms impairing the quality of life of patients, becoming life-threatening in some cases. Different strategies have been used to decrease nose bleeds, among them antiangiogenesis. The two main angiogenic pathways in endothelial cells are depending on VEGF (vascular endothelial growth factor) and on FGF (fibroblast growth factor).

The present work has used etamsylate, the diethyleneamine derivative of 2,5-dihydroxybenzene sulfonate, also known as dobesilate, as FGF signaling inhibitor.

In endothelial cells, in vitro experiments show that etamsylate acts as anti-angiogenic factor, inhibiting wound healing and matrigel tubulogenesis. Moreover, etamsylate decreases phosphorylation of Akt and ERK1/2.

A pilot clinical trial EudraCT: 2016-003982-24 was carried out with 12 HHT patients who were using a topical spray of etamsylate twice a day for 4 weeks. The epistaxis severity score (HHT-ESS) and other pertinent parameters were registered in the clinical trial. The significant reduction of at least 1 point in the ESS scale, together with the lack of significant side effects, allowed the designation of topical etamsylate as a new orphan drug for epistaxis in HHT EMA/OD/135/18.

Pulsed dye laser surgery for bleeding mucocutaneous telangiectasia in hereditary hemorrhagic telangiectasia

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Objective: There is limited evidence regarding the treatment of bleeding mucocutaneous telangiectasia outside of the nasal mucosa. The objective of this series is to describe the lesional characteristics in HHT patients presenting with non-nasal, mucocutaneous telangiectasia, complicated by significant bleeding and to describe our experience in the treatment of these lesions.

Method: Retrospective chart review of HHT patients presenting to the Yale HHT Program's Cutaneous Vascular Anomalies Clinic (CVAC) for treatment of bleeding mucocutaneous telangiectasia during the 5-year period from 2013 to 2018.

Result: There were 23 evaluable HHT patients comprising 69 distinct laser treatment sessions. The median age at first presentation to the Yale CVAC was 61 years with 61% female. The most frequent sites of involvement were, in decreasing order, vermilion lips, tongue, fingertips, cheeks, upper alveolar gingiva, and toes. There were rare cases involving the hard palate, buccal mucosa, ears, nasal skin, and palpebral conjunctiva. Several patients presented with multiple sites of involvement. Nearly all lesions stopped bleeding after one or two laser surgeries. One bled more but subsequently ceased after the second laser session. Another telangiectasia on the palpebral conjunctiva bled once five days after laser then completely resolved. Patients were generally pleased with the results. There were no serious complications and no scarring. Various laser parameters were employed, however, a smaller spot size (5 mm) and higher fluences ($\sim 12.5 \text{ J/cm}^2$) were most effective.

Conclusion: Pulsed dye laser surgery is an effective and safe treatment modality to control problematic bleeding of mucocutaneous telangiectasia associated with HHT.

Sclerotherapy on demand. Treating nosebleeds in HHT**Marcos S, MD¹; Borelli LM² PhD, de Rosales AM³ PhD, Mr Muñoz B⁴**¹ENT surgeon. Hospital Universitario Alcorcón²Biological Doctor. Researcher. Centro de Investigaciones Biológicas CSIC³Pharmaceutical Doctor. HUFA Alcorcón⁴President of the Spanish HHT Association Till June 2019

Objectives: Epistaxis is the most frequent clinical manifestation of hereditary hemorrhagic telangiectasia (HHT). Since July 2013, more than 150 HHT patients have been treated with nasal sclerotherapy for epistaxis in our center. The attention is at the office and on demand, according to patient symptoms and needs. At the beginning of 2016, we added a propranolol nasal cream to inhibit the evolution of old and new lesions. In 2017, a study was undertaken to evaluate whether the combined treatment of sclerotherapy with topical propranolol (in a 0.5% nasal cream formulation) would reduce HHT epistaxis and improve patient's quality of life. This study has been recently updated in view of the 13th HHT World Conference.

Methods: In 2017, an observational cross-sectional study on 38 HHT patients treated with sclerotherapy and topical propranolol was carried out. The study was updated in 2019 and carried out in 105 patients. We used the Epistaxis Severity score to measure frequency and severity of epistaxis at baseline (4 weeks before therapy) and at least 4 weeks after the treatment was implemented. Quality of life was analyzed before and after treatment using EuroQol-5D (EQ-5D) scale and a visual analog scale (VAS) on health status.

Results: Among the 150 patients who were susceptible to evaluation at the time (52% women), 105 completed the study. According to the ESS, and prior to treatment, 22 patients had mild nasal bleedings, 35 patients had moderate nasal bleedings, and 47 presented with severe epistaxis. We found that sclerotherapy significantly reduced frequency and severity of epistaxis with a mean improvement of the total ESS in 4.6 points (SD 2.3, $p < 0.05$), from 6.23 ± 2.3 to 1.64 ± 1.6 . On the 22 patients with mild ESS, the improvement was of 2.1 points (from 2.79 to 0.7), on the 35 patients with moderate EES the improvement was of 4.12 points, from 5.52 pre to 1.4 post, and on the 47 patients with severe epistaxis the mean improvement of their ESS achieved 6.1 points (from 8.4 pre to 2.3 post). On the other hand, the EQ-5D scale increased from 0.7 ± 0.26 pre treatment to 0.92 ± 0.16 post treatment ($p < 0.05$). The difference in health status VAS mean value showed an increase from 4.38 ± 2.4 to 8.35 ± 1.2 ($p < 0.05$). This improvement of the quality of life was in line with the drop in ESS.

Conclusion: The study demonstrates that sclerotherapy performed at the office and on demand significantly reduces HHT epistaxis and greatly improves patients' quality of life.

SESSION 6: CELL BIOLOGY OF HHT**Alk1-deficient endothelial cells form vascular malformations in a microphysiological disease model of hereditary hemorrhagic telangiectasia****Fang JS; Phan DT; Andrejcsk J; Zhao D; Lee AP; Hughes CCW**

During embryonic development, the blood vasculature forms by the coalescence of primordial endothelial cells (EC) into a primitive blood vessel network that undergoes subsequent organization into arteries, capillaries, and veins. Mutations in endothelial-expressed genes such as *ACVRL1* (Alk1) and *ENG* (Endoglin)—which occurs in a majority of patients with Hereditary Hemorrhagic Telangiectasia (HHT)—disrupts this process leading to the appearance of vascular malformations (VMs) including microvascular overgrowths (telangiectasias) and arteriovenous

shunts. HHT affects 1 in 5000 births, and VM associated with this disease affects blood vessels of the liver, brain, lung, and skin; rupture of these aberrant vessel structures compromises patient quality-of-life and can even be fatal. There is currently no cure for HHT, and efforts to develop such treatments are challenged by the lack of available in vitro models that can mimic the tissue-specific microenvironment in which healthy and diseased blood vessels form. Here, we present a microfluidic vascularized micro-organ (VMO) system wherein application of fluid flow induces primary human EC and co-seeded stromal cells to spontaneously self-organize into a perfused blood vessel network. Further application of high-flow conditions induces apparent arteriovenous specification in this model. Using the VMO platform, we show that primary human ECs engineered (via siRNA or shRNA) to lack *ACVRL1* expression form aberrant blood vessel networks characteristic of HHT. Inclusion of stromal cells from brain (astrocytes, neurons) produces a vascularized micro-organ that exhibits specific characteristics of the blood–brain barrier, and in this “brain” model, we find that use of Alk1-deficient EC again results in the formation of VMs. We are also developing a liver model by the inclusion of hepatocytes.

Conclusion: In conclusion, we demonstrate that our in vitro VMO platform supports the appearance of VMs, and that these VMs can be induced in an organ-specific model, mimicking the tissue-specific vascular signs of HHT. These findings represent significant progress towards development of the first robust, scalable tissue-specific microphysiological disease model of HHT, which will both support further studies into the pathophysiology of HHT as well as significantly improve the drug discovery and testing pipeline for HHT patients.

Mutant endothelial cells undergo clonal expansion and the number of mutant endothelial cells correlates with avm severity**Shaligram S, PhD¹; Zhang R, PhD¹; McDougall CM, MD¹; Zhu W, PhD¹; Lawton MT, MD²; Santander N, PhD³; Arnold T, MD³; Su H, MD¹**¹Center for Cerebrovascular Research, Department of Anesthesia and Perioperative Care, University of California, San Francisco, CA, USA²Neurosurgery, Barrow Neurological Institute, Phoenix, AZ, USA³Department of Pediatrics, University of California, San Francisco, CA, USA

Mutation of arteriovenous malformation (AVM) causal genes in the endothelial cells (ECs) is essential for AVM formation. We tested whether the number of the mutant ECs correlates with AVM severity and mutant ECs undergo clonal expansion using HHT2 mouse models. Model 1 is *PdgfbiCreER;Alk1^{2fl/2fl}* mouse that expresses an EC-specific estrogen inducible cre and has floxed *Alk1* gene. The mice with different doses of tamoxifen. Model 2 is *PdgfbiCreER;Alk1^{2fl/2fl}; R26R-confetti* mouse. The R26R-confetti transgene has a loxP-flanked STOP cassette between CAG promoter and Confetti sequence. Upon TM treatment, cells carrying Confetti locus will express 1 of the 4 confetti colors (cytoplasm RFP or YFP, nuclear GFP or membrane CFP), which are stably propagated within progeny. *Alk1* gene deletion and activation of confetti genes were induced by treating the mice with TM. BAVMs were induced through intra-brain injection of AAV-VEGF 2 weeks before TM treatment. Gene deletion efficiency was quantified by immunostaining and western blot analysis. AVM phenotypes were analyzed by immunostaining and latex vascular casts. EC-clonal expansion was analyzed by confocal microscopy. Reduction of TM dose increased Alk1 expression in the brain, reduced the number of Alk1-null ECs and abnormal vessels in the brain, arteriovenous shunts in the intestine, and mouse mortality. Roughly equal distribution of the four confetti colors were detected in the normal brain. In bAVM, we found obvious predominance of individual

confetti colors, indicating clonal expansion of mutant ECs. Our data indicated that mutant ECs undergo clonal expansion and reduction of mutant ECs reduces bAVM severity.

Endoglin silencing in endothelial colony forming cells (ECFC) decreases their vasculogenic activity and ECFC-dependent permeability through the LIMK/Cofilin signaling pathway

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Hereditary Hemorrhagic Telangiectasia type 1 (HHT1) is a vascular disease associated with abnormal angiogenesis and originated by mutations in endoglin (Eng) gene. Eng is an endothelial cell (EC) transmembrane glycoprotein, whose function has been studied in mature EC, but not in endothelial progenitors such as endothelial colony forming cells (ECFC), implicated in vascular repair.

Objective: To study Eng role in ECFC tubulogenesis, cytoskeleton reorganization, and vessel permeability.

Methods: ECFC were from human cord blood. Eng was inhibited by siRNA (Eng-siRNA). Mouse lung ECs (MLEC) were isolated from Eng +/+ (MLEC +/+) or Eng +/- (MLEC +/-) mice. ECFC actin-tubulin distribution/co-localization was analyzed by confocal microscopy and cofilin levels, implicated in actin filament assembly/disassembly, by Western blot. ECFC proliferation, wound healing (WH), tubulogenesis/sprouting in matrigel/cytodex, permeability with iCELLigence under inflammatory (\pm TNF α 20 ng/ml), or inhibitory (\pm LIMK/COFILIN inhibitor; LIMKi) conditions, and Ca ++ flux were also measured.

Results: Eng silencing in ECFC did not impact cell proliferation, but reduced their migration/transmigration ($p < 0.05$), tubulogenesis ($p < 0.001$)/sprouting ($p < 0.005$) capacity, as well as the actin-tubulin redistribution ($p < 0.05$), and this latter finding was confirmed in MLEC +/-/. In the absence of Eng, cofilin phosphorylation in ECFC was decreased, suggesting that Eng acts on the cytoskeleton through the cofilin signaling pathway. Under inflammatory conditions, ECFC Eng-siRNA revealed an increased permeability ($p < 0.01$) and a higher Ca ++ flux compared to controls ($p < 0.05$).

Conclusion: Eng plays a critical role in ECFC angiogenic properties and, under inflammatory conditions, influences ECFC-related permeability through LIMK/cofilin signaling pathway. These data suggest that ECFC might be a potential therapeutic cell target in HHT.

Endoglin is involved in cholesterol-induced endothelial/vascular dysfunction in mice and human aortic endothelial cells

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Objective: Endoglin expression was demonstrated to be affected during atherogenesis suggesting its role in atherosclerosis. In this study, we aimed to investigate the effect of cholesterol (hypercholesterolemia/7-ketocholesterol) on endoglin expression and regulation with respect to endothelial/vascular dysfunction and monocyte adhesion/transmigration prior formation of atherosclerotic changes in vivo and in vitro.

Methods: In vivo experiments were performed in two-month-old ApoE^{-/-}/LDLR^{-/-} female mice and their wild-type C57BL/6 J littermates. In vitro experiments, Human Aortic Endothelial Cells (HAECs) were treated with 7-ketocholesterol (7 K).

Results: ApoE^{-/-}/LDLR^{-/-} mice developed hypercholesterolemia accompanied by increased levels of sP-selectin, sEng, and a disruption of NO metabolism. Functional analysis of aorta demonstrated impaired vascular reactivity and Western blot analysis revealed downregulation of membrane Eng/Smad2/3/eNOS signaling in ApoE^{-/-}/LDLR^{-/-} mice. 7 K increased endoglin expression via KLF6, LXR, and NF- κ B in HAECs. 7 K-induced endoglin expression was prevented by the treatment with 2-hydroxypropyl- β -cyclodextrin, PHA-408 or by KLF6 silencing. 7 K-induced increased adhesion and transmigration of monocytic THP-1 cells was prevented by endoglin silencing.

Conclusion: Hypercholesterolemia altered endoglin expression and signaling, followed by endothelial/vascular dysfunction before formation of atherosclerotic lesions in ApoE^{-/-}/LDLR^{-/-} mice. By contrast, 7-ketocholesterol increased endoglin expression, and induced inflammation in HAECs, which was followed by an increased adhesion and transmigration of monocytes via endothelium, which was prevented by endoglin inhibition. Thus, we propose a relevant role for endoglin in endothelial/vascular dysfunction/inflammation when exposed to cholesterol.

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Role of soluble endoglin in BMP9 signaling

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Objective: Loss-of-function mutations in endoglin (ENG) are causal for type I HHT. The extracellular domain (ECD) of ENG, also known as soluble ENG (sENG), can be found in the circulation and is important in pre-eclampsia. BMP9 binds sENG with high affinity, and

augmentation of BMP9 reverses pulmonary arterial hypertension in rodent models. The objective of this study is to investigate how sENG participates in BMP9 signaling to shed light on the function of cell surface ENG and its role in HHT.

Methods: sENG was purified from human tissues (plasma from pre-eclampsia patients and ex vivo cultured full-term placenta) and HEK cells expressing human sENG. The circulating form of BMP9, which is prodomain-bound BMP9 (pro-BMP9), was produced using HEK cells. ALK1 ECD was produced from E.coli. Protein–protein interactions between sENG, pro-BMP9, and ALK1 were investigated using native-PAGE, gel filtration, and pull-down experiments. Ligand activity was monitored by signaling assays and microarray in human pulmonary artery endothelial cells and ENG-KO mouse endothelial cells.

Results: sENG purified from human tissues is primarily in the monomeric form. Incubating monomeric sENG with pro-BMP9 in solution leads to the release of the prodomain and formation of an sENG:BMP9 complex. The binding of sENG to BMP9 is not inhibitory and sENG:BMP9 complex has a comparable signaling potency and specificity to that of BMP9 on primary endothelial cells. Full signaling activity by sENG:BMP9 complex requires transmembrane ENG.

Conclusion: Soluble ENG is not a ligand trap for BMP9. Cell surface ENG is required for efficient BMP9 signaling.

SESSION 8: EMERGING ISSUES IN HHT

Development and launch My HHT Tracker app

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Objective: To describe the launch of My HHT Tracker App. The overall goal is to improve the health of HHT patients through utilization of a mobile device to track their disease, educate doctors, and improve quality of life.

Methods: My HHT Tracker is designed on the iOS platform to track HHT health issues while ensuring privacy, compliance, and security. The App allows HHT patients to track their disease, treatments, and outcomes. Patient data are stored on their phones. They can add medical providers' address, specialty, hospital, and contact information. Nosebleeds can be tracked daily or at intervals determined by the patient. Blood loss can be viewed graphically over time. Patients can follow data points of hematocrit, hemoglobin, and ferritin levels graphically over time and assess energy and oxygen saturation levels. Data on interventions, procedures, and new medications can be added as well as scheduling of testing appointments. The app contains hyperlinks to educational content on Cure HHT website. Patients can email a copy of the HHT data to themselves and physicians.

Results: Over the first 6 months, 881 people downloaded the App. 702 (79%) U.S., 76 (9%) Canada, 54 (6%) UK, 44 (5%) Australia, and 5 (1%) Norway. 94% of patients rated the app as helpful; 7% said it was not. HHT patients and physicians have been surveyed to determine benefits and utility as well as improvements in the next version.

Conclusion: Managing and tracking HHT data with an easy to use app is a novel approach to improve care for patients and health care providers.

Development and performance of a hereditary hemorrhagic telangiectasia specific quality of life instrument

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Objective: Hereditary Hemorrhagic Telangiectasia (HHT) negatively impacts health-related quality of life (HR-QoL), however, previous tools to measure HR-QoL are not HHT-specific. Our objective was to develop an HHT-specific HR-QoL (HHT-QoL) instrument and evaluate its performance in a cross-sectional survey of individuals with HHT.

Methods: Four HHT-specific questions were developed to evaluate the impact of HHT on productivity, social, and personal interactions. An anonymous email survey was conducted through the Cure HHT Foundation. Participants also indicated their perceived HHT severity and completed three Patient-Reported Outcomes Measurement Information System (PROMIS) short-form questionnaires (A: Discretionary social activities; B: Social roles; and C: Emotional distress).

Results: Complete data were available for 290 participants who self-identified their HHT severity as mild (29%), moderate (46%), or severe (25%). The HHT-QoL scale was reliable (Cronbach's- α , 0.83). Principal components analysis indicated the instrument was unidimensional. Participants had low levels of satisfaction with their ability to participate in discretionary social activities (PROMIS A mean [SD] = 36.4 [14.3]) and perform in social roles (PROMIS B 41.5 [17.2]), and a high level of emotional distress (PROMIS C 64.8 [24.2]). The HHT-QoL score was negatively correlated with PROMIS A ($r = -0.65$) and B ($r = -0.68$), and positively correlated with PROMIS C ($r = 0.51$).

Conclusion: We developed a 4-question, HHT-specific QoL instrument and demonstrated that it is reliable and correlates well with PROMIS tools assessing productivity, social interactions, and emotional distress. The HHT-QoL provides valuable insight and may be a useful addition to future clinical research in HHT.

A double-blind placebo-controlled study assessing the safety and efficacy of topical propranolol for moderate–severe epistaxis in patients with hereditary hemorrhagic telangiectasia (HHT)

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Background: Severe epistaxis in patients with Hereditary Hemorrhagic Telangiectasia (HHT) may be difficult to control. Propranolol was shown to have anti-angiogenic properties in vitro and in vivo and is in widespread use to treat infantile hemangiomas. Propranolol improved epistaxis in HHT patients in an uncontrolled study. We designed a controlled study to assess the safety and efficacy of topical propranolol treatment for moderate to severe epistaxis in HHT.

Methods: a double-blind placebo control (DBPC) study followed by an open-label study. 24 HHT patients with moderate–severe epistaxis (Epistaxis severity score (ESS) ≥ 4), refractory to conventional

treatment, were recruited. Patients were randomized 1:1 to treatment or placebo group for 2 months followed by 2 months of treatment with the active medication. 0.5 cc of propranolol gel 1.5% or placebo were applied to the nasal mucosa of each nostril twice daily for 2 months followed by an open-label study—all patients were treated with propranolol gel 1.5% 0.5 cc each nostril twice daily for 2 months. Blood pressure and heart rate were monitored during the study period. Side effects were recorded. Primary outcomes were—change in ESS, epistaxis duration, and severity. Secondary outcomes—Quality of life (QOL), Hemoglobin and iron levels, and transfusion requirement.

Results: The DBPC study is due to be finalized in April 2019. Results will be presented at the conference.

Towards an integrated approach for screening for complications of HHT, JPS, and connective tissue disorder in SMAD4

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Objective: To describe clinical findings in patients with SMAD4 mutations to expand the phenotype and to establish a standardized approach to screen for possible complications.

Methods: A retrospective chart review was performed of 12 patients from 5 families with identified SMAD4 mutations.

Results: All 12 patients met clinical criteria for HHT; 10 of 10 screened had pulmonary AVM, 4/12 had hepatic AVM, and 0/9 had brain AVM. All 10 of 10 patients screened for JPS had polyps, with 2 patients undergoing gastrectomy and 2 colectomy due to polyp burden. Two patients developed colon cancer, one in her 30 s and 1 at age 10y. In addition, these patients showed evidence of connective tissue disorder. Two of 8 patients evaluated for aortopathy had dilatation of the aortic root or sinotubular junction and ascending aorta. In addition, 7 of 7 evaluated had evidence of dysmorphism including long fingers, Marfanoid facies, and pectus excavatum. Finally, 3 patients had evidence of vasculopathy involving intracranial arteries only in 2 patients including 1 with discrete aneurysm of the ACA, with a 3rd patient having numerous intracranial and intraabdominal aneurysms.

Conclusions: Based on these findings of a connective tissue disorder phenotype, including aneurysms and tortuosity, we now recommend imaging from head to pelvis to assess for vasculopathy in patients with a confirmed SMAD4 mutation. We have partnered with our cardiovascular genetics team, who follows patients with similar disorders such as Marfan and Loeys–Dietz Syndromes, to help us fully assess and manage this very complicated group of patients.

Correlation of oxygen saturation and serious adverse events in pediatric patients with HHT and documented or suspected pulmonary arteriovenous malformations—update (2014–2018)

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Objective: To identify baseline demographics for pediatric patients who had a serious adverse event (SAE) related to pulmonary arteriovenous malformation (PAVM).

Methods: Two hundred and twenty-two patients up to 16 years of age were evaluated for PAVM over a 16-year period (2002–2018). Based on clinical criteria and genetic testing, patients were categorized as having hereditary hemorrhagic telangiectasia (HHT), probable HHT, or doubt HHT. Clinical evaluation and pulse oximetry were performed. Additional studies were reserved for patients with exertional dyspnea or significant hypoxemia. Other information collected included the presence of migraine, epistaxis, telangiectasia, and cerebral AVM.

Results: The average age was 9.7 years (range 2 months–16), with 93 male (53%) patients. HHT was present in 161 (73%) and probable HHT in 52 (23%). Pulse oximetry data were available for 176 (79%) with an average of 97% (range 64–100%). Fatal and non-fatal SAEs occurring under 16 years old occurred in 11(6%). Non-fatal SAEs in 9(5%) consisted of hemoptysis 2 (1%), cerebral hemorrhage in 4 (2%), brain abscess 1 (0.5%), seizure in 1 (0.5%), and intestinal bleeding in 1 (0.5%). Fatal events occurred in 2 (1%) both consisted of hemoptysis. SAE attributable to PAVM occurred in (3%) included hemoptysis (4) and brain abscess (1). Average pulse oximetry in patients with any SAE was 90.6% (range 68–95%, median 95%), while in those with an SAE attributable to PAVM was 82.4% (range 68–92%, median 90%).

Conclusion: Children less than 16 years old without prior embolization with clinically assessed pulse oximetry equal to or greater than 93% had no PAVM-related SAE, supporting the use of clinical pulse oximetry as an objective screening tool to help exclude further evaluation of PAVMs until the age of 16 years.

Efficacy and tolerability of nasal septal splints for the treatment of recurrent epistaxis in patients with Hereditary Hemorrhagic Telangiectasia

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Objective: To evaluate the efficacy and tolerability of nasal splints for recurrent epistaxis in patients with Hereditary Hemorrhagic Telangiectasia (HHT), as determined by patient complaints, quality of life metrics, and Epistaxis Severity Score (ESS).

Methods: Retrospective chart review of HHT patients with recurrent epistaxis who underwent operative management that included splint placement between 2012 and 2018 at a single academic center, followed by a prospectively administered questionnaire.

Results: Twenty-eight patients underwent splint placement (mean age 59.4 years, 46% male). On retrospective review, 85% of patients reported that their splints were effective in reducing epistaxis symptoms. Splints were left in for a median of 6 months (maximum 56 months, minimum 1 week), and were removed due to side effects in 27%, dislodgement in 22%, and ineffectiveness in 2%. Common patient complaints included nasal obstruction (56%), nasal pain (41%), and nasal crusting/drainage (37%). On prospective follow-up (N = 13), patients rated the efficacy of splints in reducing nasal bleeding as 8.23/10, and 85% stated they would use a splint again.

The most bothersome complaints included nasal obstruction (54%), crusting/drainage (23%), pain/irritation (15%), and splint dislodgment (8%). Of note, dislodgement occurred with the size 0.51-mm-diameter splints but not with the 1.02 mm splints.

Conclusion: Septal splints reduce the ESS from 7.37 to 2.35 in patients with epistaxis from HHT. Septal splints are a simple, effective, and generally well-tolerated treatment option. Eighty-five percent of patients would use a nasal splint again. Crusting, nasal obstruction, and pain can occur. Dislodgement risk may be reduced by using thicker diameter splints.

SESSION 9: INTERACTING PATHWAYS AND DRUG DISCOVERY IN HHT

Angiopoietin-2 inhibition rescues arteriovenous malformation in a SMAD4 hereditary hemorrhagic telangiectasia mouse model

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Objective: To identify potential targets of the TGFβ pathway that promote AVM pathogenesis and assess their therapeutic potential in a Smad4-AVM mouse model of HHT.

Methods: RNA- and ChIP-sequencing experiments were conducted on isolated endothelial cells (ECs) from a Smad4 inducible, EC-specific knockout (*Smad4*-iECKO) mouse model that develops retinal AVMs and on BMP9 stimulated ECs, respectively. Integration of these datasets revealed the Angiopoietin-Tek signaling pathway as a downstream target of SMAD4. Monoclonal blocking antibodies against ANGIOPOIETIN-2 (ANGPT2) were utilized to evaluate their effects on AVM development.

Results: We identified 212 potential biological targets involved in AVM formation, including the EC surface receptor, TEK (TEK receptor tyrosine kinase), and its antagonistic ligand, ANGPT2. *Angpt2* expression was robustly increased in *Smad4*-iECKO ECs, while *Tek* levels were decreased resulting in an overall reduction in Angiopoietin-Tek signaling. Our data demonstrated that SMAD4 directly represses *Angpt2* transcription and that blockade of ANGPT2 function, either before or after AVMs form, prevents and ameliorates AVM formation and normalizes vessel diameters in *Smad4*-iECKO mice. These rescue effects are attributed to a reversion in EC morphological changes, such as size and shape.

Conclusions: Our studies point to a novel mechanism whereby loss of *Smad4* causes increased *Angpt2* transcription in ECs leading to AVM formation, increased blood vessel calibers, and changes in EC morphology. Inhibition of ANGPT2 function in *Smad4*-iECKO mice alleviated these vascular phenotypes further implicating ANGPT2 as an important TGFβ downstream mediator of AVM pathogenesis. Therefore, approaches that target ANGPT2 function may have therapeutic value for the improvement of HHT symptoms, such as AVMs.

Sirolimus reduces AVM pathology in mice

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Objectives: HHT is caused by loss-of-function mutations in ALK1/ENG-Smad1/5/8 signaling and leads to arteriovenous malformations (AVMs). In our previous attempt to repurpose FDA-approved drugs, we identified tacrolimus as a potential blocker of HHT pathology that could rescue Smad1/5/8 signaling in vitro and in vivo in a retinal HHT mouse model. However, even though tacrolimus showed significant efficacy at preventing the abnormal increase in vascular density, it did not substantially reduce AVM number in this model. To improve this aspect, we tested sirolimus, an analog of tacrolimus reported to act as a Smad1/5/8 signaling activator in endothelial cells (ECs).

Methods: HHT pathology was induced at post-natal day 3 (P3) and pups were treated with sirolimus from P3 to P5. The P6 retinal vasculature was then analyzed using histology techniques and Western blots.

Results: Sirolimus significantly and substantially reduced AVM number and diameter in HHT mice. As we observed previously for tacrolimus, sirolimus prevented vein dilation and the increase in density of the vascular plexus. Furthermore, sirolimus prevented endothelial overactivation of mTOR signaling in ECs of the AVMs, and significantly rescued Smad1/5/8 signaling in vitro in ECs and in vivo in the retinal vasculature of the HHT mice. Lastly, ALK inhibition and gene silencing showed that ALK2 was required for the stimulatory effect of sirolimus on Smad1/5/8 signaling.

Conclusions: Sirolimus treatment significantly improved HHT vascular pathology in mice by strongly reducing AVM number through a mechanism implicating mTOR inhibition and Smad1/5/8 signaling activation. We propose that sirolimus has therapeutic potential in HHT.

Sonic hedgehog signaling pathway: a novel player in the pathogenesis of arteriovenous malformations

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The Sonic hedgehog (SHH) pathway is a crucial regulator of angiogenesis both in embryonic and post-natal life. It is also a player in the determination of arteriovenous phenotype of endothelial cells. In this study, we show that SHH is expressed in the endothelial layer of human brain arteriovenous malformations (AVMs), while it is not detectable in the endothelium of normal human brain vessels. Also Gli-1, the major transcription factor of the SHH pathway, is present in the endothelium of human brain AVMs and absent in the endothelium of normal human brain vessels. Next, we show that SHH has the ability to induce the growth of an arteriovenous angiogenic process in vivo. First, we used

ephrinB2-lacZ mice, which carry the lacZ reporter gene under the control of the ephrinB2 gene, which is expressed selectively in arteries but not in veins. We found that the implantation into the mouse cornea of pellets containing SHH induces an angiogenic process characterized by the presence of both arteries and veins, interconnected by complex sets of arteriovenous shunts, without an interposed capillary bed. Then, we performed stereotactical intracranial injection of a plasmid containing the human Shh gene (phShh) in the brain of Sprague–Dawley rats. This resulted in the formation of a vascular network with distinct arterial and venous structures and arteriovenous shunts and fistulas. Our findings demonstrate that SHH is aberrantly expressed in human brain AVMs and that SHH-induced angiogenesis has characteristics similar to those seen in AVMs in humans.

Decreased expression of VEGFR1 contributes to the pathogenesis of hereditary hemorrhagic telangiectasia type 2

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Objectives: How ALK1 haploinsufficiency leads to pathological angiogenesis is unknown. Here, we have examined the role of VEGFR1 in HHT2 pathogenesis. We focused on the neonatal *Acvr11*^{+/-} mouse retina and on the airway system after *Mycoplasma pulmonis* infection as physiological and pathological models of angiogenesis, respectively. We generated the *Acvr11*^{+/-} mouse embryonic stem cell lines (ESCs) as in vitro model of sprouting angiogenesis and performed genetic complementation experiments. Finally, HHT2 plasma samples and skin biopsies were analyzed to determine whether the mechanisms evident in mice are conserved in humans.

Methods: *Acvr11*^{+/-} retinas at post-natal day 7 showed excessive angiogenesis and numerous endothelial “tip cells” at the vascular front that displayed migratory defects. VEGFR1 levels were reduced in *Acvr11*^{+/-} mice and HHT2 patients suggesting similar mechanisms in humans. In sprouting angiogenesis, soluble VEGFR1 is secreted creating a VEGF gradient that promotes orientated sprout migration. *Acvr11*^{+/-} ESCs recapitulated the vascular anomalies in *Acvr11*^{+/-} mice. Genetic insertion of VEGFR1 into the ROSA26 locus of *Acvr11*^{+/-} ESCs prevented the vascular anomalies suggesting that high VEGFR2 activity in *Acvr11*^{+/-} endothelial cells induces HHT2 vascular anomalies. To confirm our hypothesis, *Acvr11*^{+/-} mice were

infected by *Mycoplasma pulmonis* to induce sustained airway inflammation. Infected *Acvr11*^{+/-} tracheas showed excessive angiogenesis with the formation of multiple telangiectases that were prevented by VEGFR2 blocking antibodies.

Results: Our findings demonstrate a key role of VEGFR1 in HHT2 pathogenesis and provide mechanisms explaining why HHT2 blood vessels respond abnormally to angiogenic signals. This supports the case for using anti-VEGF therapy in HHT2.

Amplified responses to VEGF signaling following loss of endothelial Endoglin leads to peripheral arteriovenous shunting and high-output heart failure

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Background: Endoglin is a co-receptor for BMP9/10, and is strongly expressed in endothelial cells. Mutations in endoglin lead to the inherited vascular disorder, Hereditary Hemorrhagic Telangiectasia type I. Preclinical models of this disease have primarily focussed on angiogenic vasculature either in development or in response to an external angiogenic stimulus. Little is known about the role of endoglin in adult life, in quiescent mature blood vessels.

Methods/Results: We used endoglin inducible knockout (Eng-iKO) mice, where endoglin was depleted only in adults. These mice reproducibly developed peripheral AVMs in close association with the pelvic cartilaginous symphysis leading to a rapid reduction in mean aortic blood pressure, increased cardiac preload, and high stroke volumes, resulting in high-output heart failure (HOHF). The pelvic location of these AVMs, although initially unexpected, was due to the close proximity of the affected vasculature to non-capsulated cartilage with high endogenous expression of vascular endothelial growth factor (VEGF). Complementary in vitro experiments showed that loss of endoglin in endothelial cells leads to increased sensitivity to VEGF and amplified pAKT and pERK responses. Treatment of Eng-iKO mice with anti-VEGFR2 antibody completely blocked development of AVMs and reduced progression to HOHF.

Conclusions: We conclude that Endoglin attenuates VEGF signaling in quiescent endothelial cells to maintain vessel caliber, an essential function when VEGF expression increases in conditions such as local hypoxia or inflammation. Increased sensitivity to VEGF in the absence of endoglin drives endothelial proliferation at sites of high VEGF expression, leading to AVM formation and a rapid injurious impact on heart function.

SESSION 11: GENOTYPE/PHENOTYPE CORRELATIONS AND OTHER VASCULAR SYNDROMES

HHT and capillary malformation-arteriovenous malformation type 2 (CM-AVM2): how much overlap?

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Objective: To investigate the clinical overlap between HHT and the newly described syndrome CM-AVM2 disorder caused by mutations in the *EPHB4* gene.

Method: Exome sequencing or a next-generation sequencing panel including *EPHB4* was performed on > 100 individuals with previously negative molecular genetic testing for the HHT genes and/or *RASA1*. Detailed clinical description and pictures of cutaneous lesions were gathered for positive cases.

Results: An *EPHB4* variant considered pathogenic or suspicious for being pathogenic was identified in ten unrelated cases; including one with germline mosaicism. The majority had epistaxis (6/10 cases), and the punctate, 1–2 mm telangiectases (8/10 cases) characteristic of HHT, as well as the 0.5–4 cm CMs considered the classic lesion of CM-AVM. However, the onset, location, and number of telangiectases in these cases are distinct from HHT. In particular, the cutaneous telangiectases were often haloed, had pediatric onset, were more diffuse/numerous, and occurred frequently on the trunk and extremities. Two of ten cases had a central nervous system AVM.

Conclusions: These findings suggest that CM-AVM2 should be included in the differential diagnosis for HHT, but also highlight noteworthy differences in the presentation of cutaneous telangiectases.

A comparative study suggests a defective hemostasis and different mechanisms underlying severe bleeds in HHT-1 and HHT-2 animal models

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Objectives: HHT patients present recurrent and difficult to stop bleeds that compromise patients' life. The aim of this study is to assess possible alterations in hemostasis mechanisms in animal models of HHT.

Methods: Two different heterozygous murine models of HHT-1 (*Eng*^{+/-}) and HHT-2 (*ALK1*^{+/-}) were used to study different phases of hemostasis in vivo and ex vivo. Moreover, primary culture lung endothelial cells were obtained from these mice and in vitro platelet adhesion was assayed under static or shear stress conditions.

Results: Our results show that bleeding time is increased in both animal models of HHT, whereas endothelial-independent hemostasis shows normal activity. Endoglin deficiency impairs platelet-endothelial adhesion, in agreement with a recent report. In addition, thrombus stabilization is reduced in *Eng*^{+/-} animals, while it is increased in human endoglin transgenic mice (*hEng*⁺). On the other hand, the HHT-2 model presents alterations in fibrinolysis, as PAI-1 plasma level is decreased while t-PA is increased.

Conclusions: Both HHT murine models have defects in hemostasis, but the pathophysiological mechanism underlying this effect seems to be different in HHT-1 and HHT-2. Endoglin deficiency leads to an impaired interaction between platelets and endothelium in HHT-1, resulting in a defective thrombus stabilization that associated with more severe hemorrhages. However, HHT-2 increased susceptibility to bleeding seems to be due to the acceleration of thrombus lysis due to an increased fibrinolysis. Both mechanisms would explain the common bleeding phenotype and should be considered as potential therapeutic targets in future investigations.

An international survey to assess use of systemic bevacizumab for high-output cardiac failure in hereditary hemorrhagic telangiectasia

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Objective: Systemic bevacizumab has demonstrated effectiveness in treating high-output cardiac failure (HOCHF) in HHT. This study assessed administration, effectiveness, and safety of systemic bevacizumab for HOCHF in HHT via survey.

Methods: A 27-item HOCHF survey was sent to center directors of 29 international HHT centers and results were analyzed.

Results: Survey response rate was 59%. Approximately half of centers had treated 11 or more HHT patients with bevacizumab primarily for HOCHF. All centers utilize a 5 mg/kg dose for induction treatment and most administer 6 doses (range 4–10) every 2 weeks. Following induction treatment, 50% utilized a continuous maintenance regimen of 5 mg/kg either every 4 weeks (75%) or every 12 weeks (25%) and 50% utilized intermittent maintenance of 5 mg/kg with a variable interval between doses (median 2 weeks, range 2–4 weeks) for 1–6 doses. Bevacizumab was reported to be effective in reducing heart failure symptoms and improving or normalizing cardiac index (Fig. 1) with rare adverse effects (Fig. 2). 87% of centers perform right heart catheterization in all patients being considered for systemic bevacizumab. Threshold for initiation of bevacizumab was highly variable (Table 1) and it is typically prescribed and managed by hematologists (53% of centers) or pulmonologists (40% of centers).

Conclusions: Systemic bevacizumab is widely used for HOCHF in HHT and respondents report high degrees of effectiveness and safety. There is wide variability in maintenance regimens and disease severity threshold to initiate bevacizumab. Further study is necessary to determine the optimal maintenance approach and magnitude of benefit.

Table 1 Threshold for respondents to initiate bevacizumab for HOCF based on clinical scenario. CO, cardiac output; CI, cardiac index; NT-proBNP, N-terminal pro-brain natriuretic peptide

Clinical scenario	Would initiate bevacizumab (%)	Would not initiate bevacizumab (%)
Elevated CO/CI, normal NT-proBNP Moderate left atrial enlargement, no arrhythmias No signs or symptoms of HF or activity restriction	13	87
Elevated CO/CI, elevated NT-proBNP Moderate left atrial enlargement, no arrhythmias No signs or symptoms of HF or activity restriction	13	87
Elevated CO/CI, elevated NT-proBNP Severe left atrial enlargement, no arrhythmias No signs or symptoms of HF or activity restriction	20	80
Elevated CO/CI, elevated NT-proBNP Severe left atrial enlargement, paroxysmal atrial fibrillation No signs or symptoms of HF or activity restriction	60	40
Elevated CO/CI, elevated NT-proBNP Severe left atrial enlargement, paroxysmal atrial fibrillation Mild dyspnea on exertion, exercise limitation	80	20

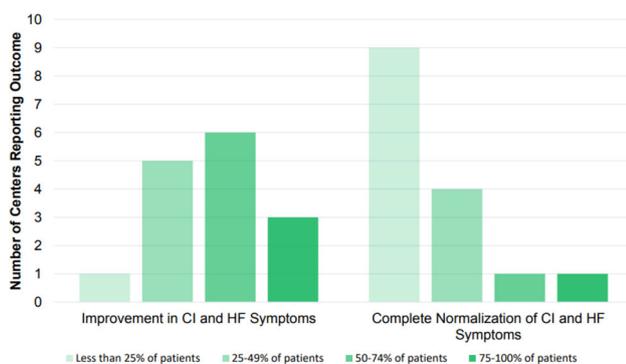


Fig. 1 Reported efficacy of bevacizumab to manage HOCF by HHT centers. Bar color represents response selected by respondent (e.g., 75–100% of patients treated at their center had improvement CI and HF symptoms) and bar height reports the number of centers responding with that category for a given question

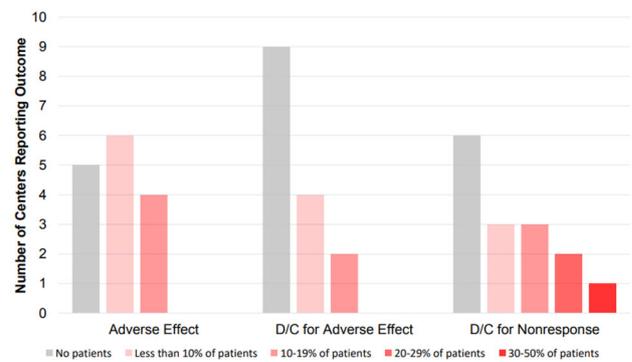


Fig. 2 Rates of bevacizumab adverse effects (such as hypertension, proteinuria, or poor wound healing) and discontinuation reported by HHT centers in patients treated for HOCF. Bar color represents response selected by respondent (e.g., 10–19% of patients treated at their center had an adverse event) and bar height reports the number of centers responding with that category for a given question

Cyclo-oxygenase 2 is expressed in the wall brain AVM vessels and associates with inflammation—a putative mediator of vessel wall remodeling in brain AVMs

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Objective: Hemorrhagic hereditary telangiectasia (HHT) predisposes to arteriovenous malformations in the brain (bAVM) that may rupture causing disability or death. BAVMs are characterized by pathological vessels with abnormally high flow triggering expansive remodeling in vessels. This flow-driven inflammatory remodeling is mediated by cyclo-oxygenase-2 (COX2), an induced enzyme that is the target of non-steroidal anti-inflammatory drugs. We investigated whether COX2 is expressed in bAVMs and whether it associates with inflammation and hemorrhage.

Methods: Tissue was obtained from surgery of 110 bAVMs and 10 normal Circle of Willis samples from autopsy. The tissue samples were studied with immunohistochemistry.

Results: Although no COX2 expression was found in normal brain arteries, COX2 was expressed in 72% (73/102) of bAVMs and localized to the endothelium in 48% of the bAVMs, and in smooth muscle cells of some bAVM vessels. COX2 was also expressed by inflammatory cells, and correlated with inflammatory cell infiltration ($r = 0.4$, $p = 0.001$). COX2 expression did not associate with clinical or histological hemorrhage (hemosiderin) nor with epilepsy. bAVM vessels expressed receptors for COX2-derived mediators of vessel remodeling. Analysis of the association of COX2 expression with bAVM genotype (HHT +/-) is undergoing.

Conclusion: COX2 is induced in bAVMs, and likely participates in regulation of vessel wall remodeling and inflammation ongoing in the bAVM. This possible role of COX2 signaling as a target for medical therapy stabilizing bAVMs merits further studies, especially since safe COX2 inhibitors are available. Patients predisposed to AVM formation (such as HHT patients) could benefit from these.

SESSION 12: BRAIN VASCULAR MALFORMATIONS

Increase VEGF level and venous hypertension exacerbates hemorrhage in mouse brain arteriovenous malformation

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High level of VEGF has been implicated in bAVM bleeding and rupture through analyzing patients' blood and surgically resected bAVMs. The direct evidence is missing. Using a mouse bAVM model, we tested the hypothesis that elevation of focal VEGF level exacerbates the severity of bAVM hemorrhage. Brain AVMs were induced in adult mice that have *Alkl* exons 4–6 floxed by injection of an adenoviral vector expressing Cre-recombinase and an adeno-associated viral vector expressing VEGF (AAV-VEGF) into the brain. Two doses of AAV-VEGF, 5×10^9 (high) or 2×10^9 (low) viral genomes were used. In addition, the common carotid artery and jugular vein were anastomosis in a group of mice treated with low-dose AAV-VEGF 6 weeks after the model induction to induce venous hypertension (VH), because VH increases VEGF level in the brain. Hemorrhages in the bAVM lesions were quantified on brain sections stained with Prussian blue, which detect iron deposition 8 weeks after model induction. VEGF levels were quantified by ELISA. Compared to mice in low-dose AAV-VEGF group, mice in high-dose AAV-VEGF group had a higher level of VEGF, larger Prussian blue positive areas in the bAVM lesion ($p < 0.0001$). VH increased bAVM hemorrhage in low-dose AAV-VEGF group. The overall mortality of bAVM in the high-dose AAV-VEGF group was 26.7%, while no mouse died in the low AAV-VEGF group. VH caused a 50% mortality in low-dose AAV-VEGF group. Our data provide direct evidence that increase of VEGF level or VH increases bAVM hemorrhage and mouse mortality.

Comparison of angiographic features in sporadic and HHT-related brain AVMs

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Objective: Brain arteriovenous malformations (AVMs) can occur sporadically or associated with hereditary hemorrhagic telangiectasia (HHT), but little is known about hemodynamic differences underlying these pathologies. This study compares associations between clinical and angiographic features, including quantitative measures derived from parametric color-coded angiography (PCCA), in these two patient populations.

Methods: Cerebral angiograms of AVM patients were retrospectively reviewed for size, anatomic location, and associated angiographic findings. PCCA was applied with regions of interest measuring the diameter and contrast dynamics of the main feeding artery and draining vein of each AVM. We compared patient and AVM characteristics using Fisher's exact tests and two-sample t-tests. We used linear mixed models to test whether PCCA measures were associated with clinical and imaging characteristics.

Results: 158 sporadic AVMs and 41 AVMs in 20 HHT patients were reviewed. Sporadic AVMs averaged triple the diameter of HHT-related AVMs ($p < 0.001$). HHT-related lesions were more likely to have superficial venous drainage, more likely to be in an eloquent anatomic location, and less likely to be associated with venous stenosis or ectasia ($p < 0.05$ for all). Hemorrhagic presentation occurred in 41% of patients with sporadic AVMs but only 5% of patients with HHT-related AVMs ($p = 0.002$). HHT-related AVMs demonstrated more rapid arterial upslope ($p = 0.001$) and venous downslope ($p < 0.001$) than sporadic lesions. After adjusting for size, patients with hemorrhagic presentation demonstrated lower arterial upslope ($p < 0.002$).

Conclusion: PCCA provides hemodynamic parameters such as arterial upslope that are correlated with clinically significant outcomes. Further exploration is necessary to determine whether these metrics have predictive value.

Evaluation of cerebral arteriovenous malformations (AVMs) and detection of micro-AVMs in HHT with silent MRA; arterial spin labeling magnetic resonant angiography with ultra-short time echo comparing with TOF MRA

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Objective: Cerebral arteriovenous malformations (CAVMs) have little evidence to determine the standardized therapy. Treatment policy for each CAVM depends on its clinical course and vascular complexity. TOF MRA which is a most commonly used modality for CAVM has been demonstrated to be insufficient to assess some certain groups of CAVMs. Silent MRA being newly developed MRI sequence, have potential advantages over TOF MRA because they employ the combination of arterial spin labeling method and ultra-short time echo. We compared TOF MRA and silent MRA focusing on the goodness of detection for micro-AVM which is less than 10 mm and visualization for CAVM.

Methods: Consecutive 27 CAVM patients including 6 HHT patients, diagnosed by CT-DSA or DSA, who underwent both TOF MRA and silent MRA from August 2015 to August 2018 in Keio University Hospital (Tokyo, Japan), were enrolled. Two experienced interventional neurosurgeons independently assessed the silent and TOF images of CAVMs patients without any information from DSA or CT-DSA. The detection of lesions, Spetzler-Martin Grading (S-M Gr.) of CAVMs, and visibility scoring of the components (feeder, nidus, and drainer) using subjective 5-point scales; Grade1, not visible (no signal at all); Grade2, slightly visible (can be detected but highly blurring or artifacts); Grade3, acceptable (enough to discern the diagnostic information with moderate image quality); Grade4, good (can give clinicians good quality diagnostic information with slight blurring or artifacts); Grade5, excellent (the visibility is very high without few artifacts) were

performed, respectively, and they are compared in use of statistical software R. The value $p < .05$ was statistically significant.

Results: The sensitivity for detecting CAVMs was 79% in TOF MRA and 100% in silent MRA, respectively. In TOF MRA image, both observers could not detect 6 micro-AVMs in 10 cases which are defined as the size being less than 10 mm being frequent in HHT. The accuracy rates for AVM grading of TOF MRA and silent MRA imaging were 69% (20/29) and 93% (27/29), respectively. There was of significant difference ($p = 0.04$) between them. As for visibility, the mean scores of the feeder, nidus, and drainer were 3.48 ± 1.00 , 2.07 ± 0.84 , and 1.86 ± 1.06 by TOF MRA and 3.93 ± 0.91 , 4.24 ± 0.72 , and 3.17 ± 1.47 by silent MRA, respectively. There was no significant difference of feeder visibility between the TOF MRA and silent MRA ($p = 0.07$). By contrast, the visibility of the other components, nidus and drainer were significantly different between the modalities, with both p values being < 0.001 .

Conclusions: Silent MRA can more effectively detect micro-AVMs and more clearly visualize variously directional flow of AVM components than 3D TOF MRA. Especially for nidus and drainer, there are significantly huge differences of visibility between those modalities. In the medical practice for HHT, silent MRA seems to be exclusively effective for patients with the allergy against contrast agent or with chronic kidney disease and is also useful for the outpatient follow-up which needs repeated image acquisitions. Additionally, in theory, Silent MRA does not delineate CVM which exists frequently in HHT but has few probabilities to bleed. This phenomenon is specific to silent MRA having a trait to employ subtraction method. This trait may give clinicians the opportunity to tell it from other high-risk dangerous arteriovenous lesions easily and definitely.

SESSION 13: EPIDEMIOLOGY OF HHT

Circulating biomarkers associated with HHT phenotypes

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Objective: The objective of this pilot study was to screen a panel of angiogenic and inflammatory proteins to identify candidate circulating biomarkers of HHT phenotypes.

Methods: The levels of 60 proteins related to angiogenesis and inflammation were assessed in heparin plasma samples from HHT patients ($n = 15$) and sporadic brain arteriovenous malformation (AVM) patients ($n = 13$) using the Quantibody Human Angiogenesis Array 1000 (Raybiotech). Concentrations of each marker were determined using the Quantibody Q-Analyzer tool. Log-transformed marker levels were evaluated for associations with phenotypes (brain AVM, pulmonary AVM) in multivariable interval regression models adjusting for age, sex, and ethnicity; interval regression allowed for readings below and above the limits of detection.

Results: Levels of activin A, IFG-1, and PDGF-BB differed between HHT patients and sporadic brain AVM controls. Among HHT patients, decreased levels of activin A, AGRP, bFGF, INFg, IL-1a, TNFa, and FGF-4 were associated with the presence of brain AVM in HHT patients. Interestingly, a nearly distinct set of proteins comprised of FGF-4, Follistatin, MMP-9, Tie-2, VEGFR3, and VEGFD

was associated with pulmonary AVMs (PAVM). Finally, circulating levels of FGF-4, Tie2, and VEGFR2 were significantly reduced in patients with differing levels of organ involvement ($p < 0.05$).

Conclusions: This pilot study identified fifteen proteins with significant differences in circulating levels between HHT patients with BAVMs and/or PAVMs that may be useful for identifying patients at risk for HHT phenotypes. We will validate these findings in additional HHT patient and healthy control samples to identify the most robust biomarkers for managing HHT.

Predictors of mortality in patients with hereditary hemorrhagic telangiectasia

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Objective: Retrospective questionnaire and healthcare administrative data suggest reduced life expectancy in untreated HHT. Prospective data suggest similar mortality to the general population, in Denmark's center-treated HHT patients. However, clinical phenotypes vary widely in HHT, likely affecting mortality. We aimed to measure predictors of mortality among center-treated HHT patients.

Methods: HHT patients were recruited at 14 HHT centers to the Brain Vascular Malformation Consortium (BVMC) since 2010, and followed annually. Vital status, organ vascular malformations (VMs), and clinical symptoms data were collected at baseline and during follow-up ($N = 1219$). We tested whether organ VMs, HHT symptoms, and HHT gene were associated with increased mortality using Cox regression analysis, adjusting for patient age.

Results: 56 deaths occurred over average follow-up time of 3.3 years (max 8.1 years). GI bleeding was associated with increased mortality (HR = 2.7, 95% CI 1.5–4.8, $p = 0.001$), as were symptomatic liver VMs (HR = 2.1, 95% CI 1.1–3.7, $p = 0.016$). Brain arteriovenous malformations (AVM) and pulmonary AVMs were not associated with mortality ($p > 0.05$). Patients with SMAD4 mutation had significantly higher mortality (HR = 15.9, 95% CI 4.1–61.4, $p < 0.001$) compared to patients with ACVRL1/ENG mutations, but the estimate is imprecise given the rarity of SMAD4 patients ($n = 30$, 3 deaths).

Conclusion: Mortality in HHT patients is associated with chronic GI bleeding and symptomatic liver VMs, independent of age, and in keeping with the limited treatment options for these aspects of HHT. Conversely, mortality does not appear to be associated with pulmonary AVMs, for which patients are routinely screened and treated preventatively at HHT Centers.

Nationwide call for screening by dentists for hereditary hemorrhagic telangiectasia—first results

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Objective: Hereditary hemorrhagic telangiectasia (HHT) is a rare inherited disease. Nosebleeds and mucocutaneous telangiectases are frequent manifestations. Predilection sites of the latter include oral mucosa, face, and lips. Diagnosis after first manifestation is often delayed for decades. However, early diagnosis and screening for visceral manifestations are desirable to avoid serious complications.

Method: The German HHT self-help group prospectively noted first contacts of affected persons by phone. On June 16, 2018, a case report about a serious infectious complication after professional dental cleaning due to lung shunting in HHT was published in an interdisciplinary approach in the journal of the German dental association and the Federal Association of Fund Dentists in Germany. This was connected with a call to search for typical telangiectases and if in combination with nosebleeds to connect the patient with the self-help group. A reminder was published on September 16, 2018 in the same journal.

Result: Within 17.5 months before the call, 3 spontaneous first contacts by phone were registered (0.17/month). Within 3.5 months after the call 9 were counted (2.57/month). Two of the latter could be connected directly to the publication. Data collection continues; evaluation of other communication channels (email, etc.) and of the national diagnosis database are further planned steps.

Conclusion: First results indicate a moderate efficacy of the call presented by a rise of the frequency of contacts (initially more than tenfold). An interdisciplinary cooperation seems to be a way for screening and—in consequence—for reducing morbidity in patients with this complex disease.

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Hereditary hemorrhagic telangiectasia (HHT) and cardiovascular risk: Is HHT cardioprotective?

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Objective: Our objective was to compare the cardiovascular risk of HHT patients to a control group through coronary artery calcification (CAC) assessment. CAC is a strong predictor of incident coronary heart disease and provides risk factor stratification beyond that provided by standard risk prediction algorithms. We hypothesized that CAC severity would be less in HHT patients than in age- and sex-matched controls.

Method: We performed a retrospective review of non-contrast CT studies performed for the evaluation of pulmonary AVMs between November 2013–November 2018 in adult HHT patients aged between 40 and 80 ($n = 218$). We assessed the burden and severity of CAC by

calculation of the Agatston score in these patients and compared these scores with randomly selected age-matched controls ($n = 218$) from other patients of the St. Michael's Hospital respiratory division. A χ^2 test was performed to assess for statistical variation in CAC between the HHT and control group, and a linear regression was performed to assess an association between age and severity.

Results: We assessed 218 HHT patients and 218 control patients. The mean age in both groups was 58 (range 40–80). 56% of both groups were female. In the HHT group, 59% ($n = 127$) had an ENG gene mutation and 41% ($n = 90$) had an ACVRL1 mutation. CAC increased significantly with increasing age, as expected, in the HHT and control groups ($p < 0.01$). However, the severity of CAC was significantly less in HHT patients compared with the control group ($p = 0.037$). There was no significant difference in the severity of CAC between the HHT1 (ENG gene) and HHT2 (ACVRL1) cohorts. **Conclusion:** Severe CAC is less frequent in HHT patients compared to an age and sex match control group, suggesting that the risk of cardiovascular events in HHT patients may be less than that of the general population. However, there is no significant difference in the CAC severity between HHT1 and HHT2 patients.

Embolotherapy outcomes in 272 pulmonary arteriovenous malformations at an HHT center of excellence: a cost–benefit analysis

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Purpose: To evaluate the effectiveness and comparative costs of coil and plug embolotherapy for pulmonary arteriovenous malformations (PAVMs).

Methods: 272 previously untreated PAVMs embolized between 2008 and 2018 were retrospectively evaluated. 82/103 patients (79.6%) had a diagnosis of definite hereditary hemorrhagic telangiectasia (HHT). PAVM angioarchitecture was reported as either simple (1 feeding artery) or complex (≥ 2 feeding vessels). PAVMs were embolized via coils, plugs, or both. Coils were classified as soft versus standard, and detachable versus pushable. Costs of embolic materials were calculated from the current manufacturer's list prices. Treatment success was defined as lack of contrast opacification of the sac and/or draining vein on follow-up CT angiography.

Results: The overall success rate was 239/272 (87.9%) with average embolic cost of \$4,270.00 per PAVM (range \$164.00–\$27,937.00). Success for simple PAVMs was 167/181 (92.3%) versus 72/91 (79.1%) for complex ($p = 0.002$), with costs of \$2,961.93 and \$5,969.16 per PAVM, respectively ($p < 0.001$). With regard to embolic material, success was achieved in 201/231 PAVMs (87.0%) treated with coils only (\$4,284.10/PAVM), 18/20 (90.0%) with plugs only (\$2,539.55/PAVM), and 20/21 (95.2%) for both (\$5,762.86/PAVM). Plugs were cheaper than coils ($p = 0.012$) or both ($p < 0.001$), though success did not differ significantly.

Conclusions: In previously untreated PAVMs, we found no significant difference between success rates with respect to the type of embolotherapy utilized. However, the lower costs of treating PAVMs with plugs alone may help to reduce healthcare costs without compromising treatment outcomes.

Comorbidities and end-of-life complications in patients with hereditary hemorrhagic telangiectasia (HHT)

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Objective: There are only a few published studies that demonstrate associations between severe comorbidities and their complications in patients with hereditary hemorrhagic telangiectasia (HHT).

Method: Relatives of 73 deceased patients with suspected HHT completed a questionnaire about causes of death, symptoms, and comorbidities that patients had developed. In 55 cases with clinically confirmed HHT, data have been compared to the German population.

Result: Patients suffering from HHT lost, on average, 19 years (standard deviation of 11 years) of potential life compared to the general population. Among the deceased HHT patients, 35% (95%CI 23–48%) died from sepsis, 26% (95%CI 16–38%) from cardiac failure, 20% (95%CI 9–28%) from a severe bleeding episode, and 13% (95%CI 6–24%) suffered from terminal cancer. Congestive heart failure (69%, 95%CI 56–80%) and pulmonary hypertension (23%, 95%CI 14–36%) were the main non-fatal comorbidities in patients with HHT. Patients with HHT appear to have a lower life expectancy than the general population. Sepsis and cardiac failure were the main causes of death.

Conclusion: Optimized and targeted screening programs for the most frequent comorbidities followed by improved management of infectious complications may increase life expectancy.

POSTER PRESENTATIONS

CLINICAL MANIFESTATIONS OF HHT

Anemia is associated with reduced cardiac index in HHT patients with liver AVMs

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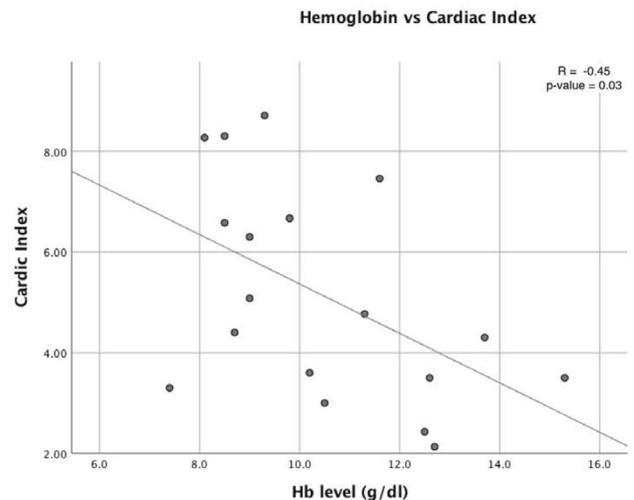
Objective: Patients with hereditary hemorrhagic telangiectasia (HHT) and liver arteriovascular malformations (AVMs) may develop high-output cardiac failure. Iron deficiency anemia is common in HHT patients and is believed to adversely impact cardiac index (CI) but has not been systemically studied in this population. We performed a retrospective study to assess the relationships among hemoglobin, iron, and CI.

Method: Chart records were reviewed of HHT patients with liver AVMs who were seen in the Yale HHT Center from 2003 to 2019 and who had undergone cardiac catheterization with calculation of CI. For each patient, clinical history, laboratory studies, and CI were recorded. All variables were categorized according to median of interquartile range and analyzed using Spearman's correlation coefficients.

Result: Seventeen patients with HHT and liver AVMs were identified who had undergone cardiac catheterization. Median age was 68 years (range 36–85); 15 were female and 2 male. Median values of

hemoglobin, ferritin, and CI were 10.6 g/dL, 35 ng/mL, and 4.77L/m², respectively. A statistically significant, inverse correlation between hemoglobin and CI was observed ($R = -0.45$, $p = 0.03$). Serum iron and CI were also negatively correlated although the association was not significant ($R = -0.3$, $p = 0.17$). No significant correlation of serum ferritin with CI was seen ($R = 0.05$, $p = 0.8$).

Conclusion: Anemia is negatively correlated with CI in HHT patients with liver AVMs. The impact of iron indices on CI is uncertain and partly limited by our small sample size. Larger studies incorporating multivariable analyses are warranted.



Screening a pediatric population with brain AVM/FS for HHT and CM-AVM

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Objectives: The objective of this study was to identify patients who need additional screening for HHT and CM-AVM in a pediatric brain AVM population.

Methods: The genetic counselor (GC) involved with the HHT Center screened patients with brain AVM/Fs (bAVM) for genetic conditions by taking a targeted medical and family history during appointments in Cerebrovascular Clinic with neurosurgery and neurology. Previously, a retrospective chart review of 12 patients screened by the GC was conducted, identifying that 33% met the Curacao Criteria for definite ($n = 2$) or possible ($n = 2$) HHT. An additional 23 patients with bAVM were identified in the current study. They were screened and a retrospective chart review was conducted.

Results: Patients ranged from 6 months to 20 years at the time of evaluation by the GC. Of the 23 patients screened, 11 pursued additional work-up. Seven patients completed genetic testing, with 5 negative

results and 2 variants of uncertain significance identified. Nine patients pursued an appointment in the HHT Center or with a Geneticist, including a physical exam. Six patients pursued bubble echo to screen for pulmonary AVMs. Of the 23 patients, 2 eventually met criteria for definite HHT (ages 7 and 17 years), 3 for possible HHT (ages 12, 16, and 17 years), and 1 for CM-AVM (6 years). An additional patient (11 years) has 2 telangiectasias and a brother with telangiectasias (3) and epistaxis that do not yet meet criteria for HHT. Overall, while only 47% of patients pursued additional work-up after seeing the GC, 26% of patients qualified for a clinical genetic diagnosis.

Conclusions: This study provides further evidence that a standard algorithm for evaluating patients for HHT and CM-AVM in the pediatric brain AVM setting should be implemented. Genetic counseling, skin evaluation, and appropriate imaging should be considered at diagnosis of a brain AVM/F in the algorithm.

Aortic valve replacement in a patient affected by Osler–Rendu–Weber disease with a brain arteriovenous malformation

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We report the case of 70-year-old man affected by Hereditary Hemorrhagic Telangiectasia (HHT), hypertension with severe aortic valve regurgitation and left ventricular dilatation in need of aortic valve replacement.

He had recurrent episodes of epistaxis and gastrointestinal bleeding, chronic iron deficiency anemia, and a brain arteriovenous malformation (bAVM) in the left cingulate gyrus.

This report is unique because only four cases of open-heart valve replacement in HHT patients are reported in the literature [1–4], but none of these had a bAVM.

Our case was discussed and managed in a multidisciplinary manner. The treatment of the bAVM before the valve replacement was ruled out because of the size and location of the AVM, the intrinsically high hemorrhagic risk and uncertain benefits. In order to avoid the lifelong anticoagulant therapy needed in case of mechanic prosthesis, the team chose for a bioprosthesis. Also, we decided to perform a brain CT scan immediately after the conclusion of cardiac surgery, with the patient still under anesthesia, with the goal to early identify signs of bleeding from the bAVM and, if needed, to perform urgent neurological surgery.

The intervention was performed in May 2018, without intraoperative hemorrhagic complications. The brain CT scan excluded signs of bleeding.

In the post-operative period, the patient was treated with Fondaparinux 2.5 mg for 3 months with no major or minor bleedings, nor worsening of anemia.

After 8 months of follow-up, the patient is in good clinical condition and has no symptoms of heart failure and echocardiogram showed proper functionality of the bioprosthesis.

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Influence of climate on epistaxis in HHT

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Objective: Epistaxis is the most frequent clinical manifestation of HHT. A wide variety of factors that could act as triggers have been postulated: climatology (temperature, humidity), physical activity, spicy foods, alcohol, etc. However, in no study a direct relationship has been demonstrated with epistaxis. The objective of this study is to evaluate:

1. If there is a climate influence on the appearance of epistaxis.
2. If there is influence, determine which climatic conditions are the ones that favor the most bleeding.

Method: Cross-sectional study which includes 515 patients with HHT, attended at the HHT Unit of Hospital Sierrallana (Cantabria), over 14 years (2003–2017). 430 of whom had epistaxis. Statistical test used was Chi-square method. Variables analyzed were the *presence of epistaxis* (present or absent), its *severity* (mild, moderate, or severe), and the *origin* of the individuals depending on the climate (atlantic, Mediterranean and continental). In a first analysis, we studied the relationship between the variables *origin* with *presence of epistaxis*. A second analysis was performed with the *origin* and *severity* variables.

Results: There is a strong association between *origin (climatic conditions)* and *prevalence of epistaxis*.

There is also a relationship between climate and the severity of epistaxis.

The regions with the highest prevalence of nose bleeding and with greater severity of bleeding are Mediterranean ones.

Conclusions: We could say that there is an influence between climate and epistaxis in HHT. The higher prevalence and severity of bleeding is seen in those climates with a higher percentage of humidity and a greater thermal variability.

Epistaxis triggered by pulmonary function testing

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Objective: Toronto HHT Centre physicians are pulmonologists and manage co-morbid airways disease in HHT patients. As 30% of Canadian adults have chronic airways disease, pulmonary function testing (PFT) is routinely required in the HHT Center. In our experience, epistaxis can be triggered in HHT patients during and after PFTs, likely related to forced maneuvers and/or the use of nose clips.

Our aim was to improve care through education of PF lab staff about HHT, prevention and management of epistaxis.

Method: Staff was educated, regarding HHT and epistaxis. An emergency epistaxis management kit was created for each testing room. A protocol was established to enquire about epistaxis: severity, frequency, recent episode, date of nasal interventions, and if nose clips have triggered epistaxis. Patients were surveyed after their testing to determine if protocol was followed.

Result: In 2018, over 10 clinic days, 19 HHT patients had PFTs. Of the 19 patients, 15 patients were surveyed, 5 reported that the protocol was followed. Eight indicated PF staff did not inquire about HHT/epistaxis prior to testing. One patient indicated a preference to hold their own nose (vs clips), 1 declined testing.

Conclusion: There was poor uptake of the HHT protocol in the PF lab. Factors likely included familiarity with return patients, we assumed full time staff had knowledge about nasal interventions. Moving forward we will re-educate all staff, simplify the protocol to be direct, i.e., “are you ok to use a nose clip?” understanding that pressure could trigger a nosebleed. Also, we will ask patients to inform staff of any recent bleeds/interventions.

Neurological manifestations of hereditary hemorrhagic telangiectasia (Osler–Weber–Rendu disease)

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Objective: Hereditary Hemorrhagic Telangiectasia (HHT) (Osler–Weber–Rendu Syndrome) is an autosomal dominant genetic disorder with vascular malformations in different organs: brain, heart, skin, lungs, and liver. Its prevalence is estimated to be 1 in 5000–10,000 individuals. Its diagnosis is based on Curacao criteria; spontaneous and recurrent epistaxis, mucocutaneous telangiectasias, visceral lesions in either brain, lung, and/or liver, and family history (a first-degree relative with the disease). AVM complications are the major cause of morbidity and mortality among these patients. In the present study, we sought to describe the cerebrovascular disease burden in patients with HHT.

Methods: HHT patients were identified from the National Inpatient Sample (NIS) database for the year 2014, using ICD-9 codes. Comorbidities including intracerebral hemorrhage, cerebrovascular anomaly including AVM's, headache, seizures, and migraine were also identified using ICD-9 coding system. Descriptive and inferential statistical analyses were performed using SAS (version 9.4, SAS Institute Inc., Cary, NC, USA).

Results: We identified 842 HHT patients for the year 2014. The estimated prevalence was approximately 1 in every 8000 individuals. These HHT patients were mostly females (59.4%) and predominantly Whites (74.3%). The neurological manifestations (with prevalence), associated with HHT were headaches (1.31%, $p = 0.61$), seizures (0.71%, $p = 0.42$), migraines (4.51%, $p < 0.0001$), intracerebral hemorrhage (0.48%, $p = 0.39$), and cerebrovascular anomaly (including arteriovenous malformations-AVMs) (0.83%, $p < 0.0001$). The multivariable logistic regression analyses show that the HHT patients were 3.2 and 30 times more likely to experience migraines and cerebrovascular anomaly as compared to the patients without the disease.

Conclusion: This study describes a higher prevalence of migraine and cerebrovascular anomaly in HHT patients. Interestingly, we did not find statistical significance for seizures and intracerebral hemorrhage in HHT population, even though higher prevalence of cerebral AVM is reported. Prospective observational studies are needed to authenticate these findings.

Pulmonary arteriovenous malformations and their vascular and non-vascular mimics

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Objective: The primary objective of this case review series is to describe imaging characteristics that differentiate PAVM from their vascular and non-vascular mimics.

Methods: Accurately diagnosing pulmonary arteriovenous malformations (PAVM) in patients with hereditary hemorrhagic telangiectasia (HHT) is critical due to the high rates of paradoxical embolism resulting in stroke or cerebral abscess. CT is the gold standard for diagnosis of PAVM, characterized by paired, parallel-running abnormal vessels that course through a singular pulmonary segment. Characteristic imaging findings between PAVM and their mimics can be distinguished via CT.

Results: Vascular mimics of PAVM include pulmonary artery aneurysms (PAA), pulmonary venous varices (PVV), meandering pulmonary veins (MPV), pulmonary artery to pulmonary artery collaterals (PAC), and hepatopulmonary syndrome (HPS).

PAA typically occur at a bifurcation and lack draining veins. PVV and MPV have an absent feeding pulmonary artery and/or a non-parallel and detoured course through more than one pulmonary segment. PAC are seen in pulmonary hypertension or chronic thromboembolic disease as peripheral, subpleural, irregular pulmonary arteries without draining veins. Finally, HPS is characterized by focal arterial dilation at the lung bases, without draining veins.

Non-vascular mimics are primarily either bronchoceles or tumors. Bronchoceles are lobular, branching, and low density with surrounding air trapping and absent enhancement. Hypervascular metastases, carcinoid, or pleural fibrous tumors can enhance avidly, though less than adjacent pulmonary arteries, and lack feeding/drainage vessels.

Conclusions: CT imaging features characteristic of PAVM and their mimics are described to allow physicians to make an accurate diagnosis in high-risk HHT patients.

Single-center experience of a long-term follow-up of pulmonary arteriovenous malformations (PAVM) in hereditary haemorrhagic telangiectasia (HHT)

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Background: According to recommendations, HHT patients need a chest computed tomography (CT) every 5 years to screen PAVM.

Objective: To assess radiological outcomes of PAVM in HHT patients with at least a 5-year follow-up.

Methods: Retrospective analysis of medical and radiological records of all patients referred to our HHT center from 2005 to 2018. All CT were analyzed by one chest radiologist. PAVM was defined as simple, complex, and mini-PAVM.

A single feeding artery size ≥ 3 mm was described as simple PAVM. More than one feeding artery was described as complex PAVM.

Artery sizes ≤ 2 mm were considered as mini-PAVM. Among the mini-PAVM, we individualized a diffuse pattern with numerous mini-PAVM within lung parenchyma.

Results: 84/393 patients (20.5%) had PAVM. Twenty-six patients with definite HHT met our criteria with CT available for at least a 60-month follow-up. In those patients, 129 PAVM were observed and were classified in simple ($n = 36$), complex ($n = 14$), mini ($n = 34$), and diffuse ($n = 30$). Fifteen PAVM were already embolized before the first CT. Transcatheter embolization (TCE) was performed for 29/36 (80.5%) simple PAVM, 12/14 (85.7%) complex PAVM, in 2/34 (5.9%) mini-PAVM. During a 107(± 39) month follow-up, 11/29 (33%) simple PAVM and 10/12 (83.3%) complex PAVM were re-permeabilized. Among non-embolized PAVM, enlargement was observed in none of the diffuse pattern and in only 2 of the mini-PAVM (but not enough to undergo TCE).

Conclusion: Our results demonstrate that PAVM progression is slow. We suggest a 10-year follow-up for PAVM with an artery size ≤ 2 mm.

Rendu–Osler–Weber syndrome: the dangerousness of pulmonary vascular malformations.

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Objective: Pulmonary arteriovenous malformations (PAVMs) that are associated with Rendu–Osler–Weber syndrome (ROWS) may cause paradoxical embolism to the brain.

Methods/Results: A 51-year-old woman presented to PSCUH with a history of week-long blurred vision. Medical history: AH, Hashimoto's thyroiditis and PAVMs on both sides. On examination, the temperature was 37.8 °C, HR 110 bpm, BP 135/70 mmHg, and the SpO₂ was 88% while breathing ambient air, GCS—15 points. There was pain and hotness in the anterior aspect of the left proximal forearm with a visible enlargement. Ophthalmologically—no pathology. Neurologically—homonymous hemianopia. MR angiography showed a hyperintense lesion on FLAIR and T2-weighted images, measuring 2.5 × 3 cm, with a hypointense zone around the structure on T1-weighted image in the right temporal lobe's *crus posterior capsulae interna* continuing to the *thalamus*—with the utmost probability signs of abscess. Lung CTA showed a big varicose left-sided PAVM, 15 mm in diameter, and several bilateral PAVMs. US of the left hand revealed a phlegmon. Drainage was performed. The patient was discharged on TMP-SMX 430 mg BID, but did not improve, neurological deficit became more apparent. The patient was admitted to the hospital again for the abscess drainage. Cultures were negative. The patient's status improved.

Conclusions: The brain abscess was most likely caused by septic emboli that migrated through the PAVM. The only known infection's source is the phlegmon. ROWS is suspected, because 2 of 4 Curaçao's diagnostic criteria are met—skin telangiectasias and organ vascular lesions present.

Clinical characteristics and outcomes of patients with hereditary hemorrhagic telangiectasia and symptomatic gastrointestinal bleeding: a single-center prospective study

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Objective: Main objective was to compare clinical characteristics and outcomes during long-term follow-up of HHT patients according to severity of symptomatic gastrointestinal (GI) involvement.

Method: In this prospective non-interventional study, we included HHT patients attended at our HHT referral Unit with objectively confirmed GI involvement. GI telangiectasias were classified according to number in few or multiple ($<$ or ≥ 10 telangiectasia) and depending on the size in small or large (≤ 3 mm or > 3 mm). Patients were divided in two groups according to the presence of severe anemia (hemoglobin levels < 8 gr/dL or blood transfusion requirement).

Results: Symptomatic GI involvement was objectively confirmed in 39 (21.4%) out of 221 patients. The most frequent location of telangiectasia was gastroduodenal. After a follow-up of 45.9 \pm 38.5 months, those with severe anemia were significantly older, with older age at GI symptoms presentation, higher Epistaxis Severity Score (ESS), higher systolic Pulmonary artery pressure at TTE and higher endoscopic fulguration of GI telangiectasia with argon plasma coagulation (APC) requirement, therapy with iron and octreotide, and ED visits and hospital admissions than patients without severe anemia. Moreover, patients with severe anemia had larger telangiectasia (> 3 mm), without statistically significant differences between both groups in the location or number of GI telangiectasia.

Conclusions: Patients with GI involvement and severe anemia are older, with more hospital admissions and larger telangiectasia than patients without severe anemia. In HHT patients with severe anemia, a high suspicion of GI involvement is needed, despite a high ESS.

Prevalence and diagnostic value of nail fold capillary microscopy in hereditary hemorrhagic telangiectasia: a retrospective study

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Objective: Abnormal vasculature is a key feature of hereditary hemorrhagic telangiectasia (HHT), and is also found in the nailfold capillary beds. The nail fold can be easily and non-invasively inspected by a capillary microscope. The exact prevalence and diagnostic value of abnormal nailfold capillaries in the diagnosis of HHT are still largely unknown. Therefore, we designed this study to further assess the prevalence and diagnostic value of abnormal nailfold capillaries in HHT.

Methods: All patients who were screened between January, 2000 and July, 2017 for the presence of HHT and underwent capillary microscopy in the St. Antonius Hospital were included. Capillary microscopy results and patient characteristics were extracted from medical files. The prevalence of abnormal nailfold capillaries was calculated and diagnostic value of the Curacao criteria with and without capillary microscopy results was assessed.

Results: Of the 1,761 individuals screened, 923 (52%) were diagnosed with a clinical and/or genetic HHT diagnosis. In these patients, capillary microscopy was normal in 23% ($n = 218$), enlarged loops were seen in 11% ($n = 99$) and giant loops in 66% ($n = 606$). The sensitivity and specificity of the Curacao criteria for the diagnosis of HHT without capillary microscopy results were 96% and 90%, respectively. The addition of the presence of giant loops to the Curacao criteria led to a small increase in sensitivity to 97% without affecting the specificity.

Conclusions: The prevalence of nailfold abnormalities in HHT patients is high. Capillary microscopy can be a useful, easy and non-invasive diagnostic tool in HHT.

Incidence of thromboembolic disease in hereditary hemorrhagic telangiectasia

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Objective: To report the incidence of venous thromboembolism (VTE) in the HHT population.

Methods: Ambispective adult cohort based on the Institutional Registry of HHT. VTE was defined as the first episode of pulmonary embolism (PE), deep venous thrombosis (DVT), or the progression of a prior event after its first 48 h despite anticoagulation.

Result: Over 524 patients, 394 adults with HHT confirmed and complete data were included. There were 18 VTE events 4.6% (CI95% 2.7–6.8%), 9 DVT (2.3% CI95% 1.2–4.4%), 3 PE (0.7% CI95% 0.13–2%), and 6 DVT + PE (1.5% CI95% 0.6–3.2%). Thirteen (72%) were female. The median age at the event was 67 (IQR 25–75% 56–73). Five patients (27%) were on ACO prior to the event, mainly for atrial fibrillation, and 3(18%) suffered from previous VTE.

The most frequent risk factors were recent hospitalization (44%) and iron deficiency anemia (44%); next, immobility (33%), recent surgery (18%), as well as cancer (5%) and recent travel (5%) patient each. Fifteen (83%) patients received ACO, 10(55%) received LMH followed by acenocoumarol, 3(30%) of which had to be stopped due to nose or gastrointestinal bleeding. In 5 (27%), a cava vein filter was inserted, of which 3 are under anticoagulation therapy.

Conclusion: VTE incidence in our study was significantly higher than reported in general population at similar age. However, the inclusion of more symptomatic and serious HHT patients could be selection bias. The low number of patients may influence the results. IDA and hospitalization were the most important associated conditions.

Acute aortic dissection in a patient with HHT associated with juvenile polyposis due to SMAD4 mutation

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Objective: SMAD4 mutations have been associated with collagen defects, hyperlaxitude, and a higher aortic root aneurysm prevalence than other types of HHT. We report a novel case of an HHT-JP patient who suffered from fatal aortic dissection.

Methods/Results: A 64-year-old female patient has been followed at our HHT center for the last 7 years. She was urgently hospitalized due to sudden chest, back, and abdominal pain; diarrhea and hematochezia. She presented pallor and low blood pressure, hemoglobin of 7 g/dl. An urgent CT scan was performed showing a type A aortic dissection with extensive compromise of carotids, mesenteric, renal, and iliac arteries. She underwent an aortic replacement (Bentall de Bono technique) progressing with high doses of inotropics, dialysis requirements, and coagulopathy. Seven days later, she presented an extensive ischemic stroke and passed away. Concerning HHT, she had 3 treated PAVMs, hepatic telangiectases, and marked tortuosity of the celiac artery branches despite a lack of hepatic fistulae, renal arteries aneurysms, mild-to-moderate epistaxis, digestive compromise with telangiectases, and large gastric non-dysplastic juvenile polyps, under endoscopic surveillance. A CT scan performed 3 years earlier, showed a normal aortic diameter though her carotids were very sinuous (kinkings). She did not present aortic dissection risk factors apart from HHT-JP. SMAD4 mutations were confirmed by deletion in exons 12–13.

Conclusion: Despite a high prevalence of aortic aneurysms has been recently described in HHT-JP (SMAD4), no aortic dissection has been reported. Finally, we would like to warn about this severe complication and reinforce the screening of aortic anomalies in this group.

EPIDEMIOLOGY

Descriptive analysis of hospitalization in a cohort of HHT patients at a reference center

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Objective: To describe the hospitalization data and the principal causes in a cohort from an HHT Reference Center.

Methods: A cross-sectional study from our Institutional HHT Registry, from January 2012 to December 2017. Ambulatory consultations were excluded.

Results: We analyzed 550 adults of which 119 (60% female) had been hospitalized, at least, once. The median age was 48.5 (18–83). The number of hospitalization episodes was 331. The median of hospitalization episodes per patient was 3.31 (1–24) and the median of duration of hospitalization stay was 46 h (3–2160). Thirty-two of these (10%) corresponded to admissions in critical care units of which 12 occurred more than once. Emergency Department (ER) consultations were 783 corresponding to 121 patients and the mean of ER consultations per patient was 3(1–36), 112/783(14%), corresponding to 78/121 patients, determined admissions. Hospitalization causes were 53 pulmonary embolization, 40 ENT procedures, 35 infections, 30 symptomatic anemia, 30 epistaxis, 32 gastrointestinal bleeding or therapeutics, 20 surgical causes, 18 hepato-cardiovascular, 17 gynecologic-obstetrics, and 18 for neurological or neurovascular treatment. Five patients were admitted due to trauma, 4 liver transplantation assessment and liver transplantation, 3 oncological causes, 3 bevacizumab infusion, 1 chemotherapy, and 18 due to miscellaneous. Eighty-three patients underwent surgery, at least, once, 24 more than once (2–11) and 29 were unscheduled surgeries. Of 151 surgeries, 31 were ambulatory.

Conclusion: A high number of patients were hospitalized or consulted at the ER. The most common causes were related to HHT

though other unrelated causes were recorded. This report aims at highlighting the important role of an HHT Reference Center.

Launching OUR HHT Registry

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Objective: To describe the initial launch of the Outcomes Registry in HHT (OUR HHT Registry), including recruitment success, time required for data collection, and initial patient population. The overarching aim of the Registry is to prospectively and longitudinally characterize the major outcomes of HHT and identify their predictors.

Methods: OUR HHT Registry is a large prospective relational database, implemented with the Geisel School of Medicine at Dartmouth and co-designed with Cure HHT. The Registry contains 4500 data fields regarding all aspects of HHT (symptoms, diagnostic testing, treatments, complications, genetics, comorbidities, etc.). Ultimately, the goal is to recruit 10,000 patients from across North America and follow them for 10 + years. The Registry was launched first at the Toronto HHT Centre on June 1, 2018 with the goal to recruit 100 patients in year one.

Results: Over 8 months, of the 102 patients approached, 100 consented (98% participation). Of the 100 participants, 10% were new patients to the Center within 1 year, 63% were women and mean age was 56 years (range 25–90 years). HHT manifestations included epistaxis (94%), pulmonary AVMs (40%), brain AVM (10%), clinically evident liver VM (20%), and GI bleeding (33%). After initial training, and then experience gained during the first 16 recruits, time required for data collection and entry improved by 30–50%. Total time required per recruit (including consent, data collection and entry, sample collection) ranged from 1.7 h to 4.7 h for the most complex patients with longest retrospective data. Saliva sample was collected from 95% of recruits for DNA extraction. Patients were provided a secure log-into the “HHT Patient Portal” to enter their own data about epistaxis, migraine symptoms, self-management, quality of life, and knowledge of their disease.

Conclusion: HHT Centre Recruitment to OUR HHT Registry is highly successful and exceeded recruitment expectations, with feasible comprehensive data and saliva collection.

Epidemiology of HHT in Cantabria (Spain)

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Objective: To describe the clinical, genetic, and epidemiological characteristics of the HHT population from the region of Cantabria (northern Spain), one of the best studied cohorts in the country due to the existence of the local HHT Unit in Hospital Sierrallana.

Methods: Between January 2003 and December 2017, 252 locals from Cantabria with suspected HHT were evaluated in the unit in Hospital Sierrallana through interview, physical examination, genetic test, and screening protocol to disclose internal organ affectation.

Results: Out of the 252 patients, 121 were diagnosed (clinically and/or genetically) of HHT. Carriers of mutation in *ACVRL1* were predominant and most frequent clinical sign was nose bleeding. Lungs were the most frequent affected organs. In HHT1 patients, pulmonary and brain affectation were predominant, while liver disease was more prevalent in HHT2. Capillaroscopy was pathological in 66.67% of patients, mainly in HHT1 individuals. Prevalence of the disease in the region was of 1:4960 but there were several municipalities over 1:2000 (in the range of non-rare disease).

Conclusion: HHT is a condition with a low prevalence in the region of Cantabria but with several areas of high aggregation. Internal organ involvement ranges are similar to those described in previous series showing also a significant relation between pulmonary affectation and carriers of mutations in *ENG*. Nevertheless, there was a higher number of HHT2 individuals.

Epidemiological study of hereditary hemorrhagic telangiectasia from 2016 to 2018

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Hereditary Hemorrhagic Telangiectasia, HHT (also referred to as Osler–Weber–Rendu disease) is a rare genetic disorder that causes malformed blood vessels and can affect multiple organs in the body. We present our experience at Metropolitan Hospital, Greece, between January 2016 and December 2018. Our department is the first and so far the only center in Greece that treats patients with HHT in a systematic manner.

A total of 22 patients (8 men, 14 women) were treated during the period of the study. The mode of presentation and the type of genetic mutations of the patients are shown in the table below.

	Male	Female
Epistaxis	8	14
Telangiectasia	8	14
Lung AVM’s	2	0
Liver AVM’s	2	1
Brain AVM’s	2	0
Priapism	1	0
Heart failure	1	1
Genetic mutation		
ACVRL1	4	8
ENG	1	—*

*Six women and 3 men did not have genetic testing

One woman had ACVRL1 heterozygosity of mutation c1114A > C(p.Thr372Pro). Another woman had ACVRL1 heterozygosity of mutation C1411T > C(p.Cys471Arg) and one man had ENG gene in heterozygosity c.297_298delCA(p.Ser100Cysfs). These mutations have never been reported previously.

In terms of treatment, all patients were given Vitamin D PO, 4 patients were given Propranolol PO, 1 patient was given Tranexamic acid PO, and 4 patients were given Bevacizumab IV.

Previously reported genetic variants do not detect all mutations that might be present. An improvement of the distribution of HHT variant classification and their clinical significance should be considered.

Psychological study of the dimensions affected in patients with HHT

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Summary: The main objective of this study was to identify the dimensions affected in the lives of patients with HHT, and the consequences of this pathology, both as conditioning and response mechanisms. A qualitative descriptive method with a cognitive approach was deliberately chosen for this study. It consisted on the observation of a group of people affected by a chronic disease, and the revaluing of self-care as a determining factor in contributing with the search for alternatives, from the perspective of prevention and promotion of health, aimed at improving their quality of life. We propose a set of guidelines for self-care, as well as raising awareness of the different dimensions affected on those who have been diagnosed with this condition.

Objectives: To generate new knowledge about the subjective construction of patients with HHT. To develop a positive, constructive, and patient-oriented input.

Methods: During the first phase, an ad hoc questionnaire was administered, with questions related to the condition, the situational environment, and personal characteristics. During the second phase, an in-depth interview was conducted based on the data extracted from the questionnaire. A situational diagnosis of each participant was provided. Currently, there are seven participants.

Results: It was observed that patients were affected in multiple dimensions. The dimensions affected were the following: somatic, psychic, affective, family, and social.

Conclusions: Seeking that this pathology has a minimal effect on the dimensions mentioned above, we emphasize that the improvement in the quality of life of affected patients should not only be reduced to the treatment of symptoms, but an integral approach of their life should be included as well.

Demographics and clinical characteristics of HHT patients diagnosed in the Optum database from 2007 to 2017

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Objective: To establish the demographics and clinical characteristics of HHT patients diagnosed between 2007 and 2017 in a large national database of patients.

Method: We conducted a retrospective cohort analysis using OptumLabs[®] Data Warehouse, which includes administrative claims data from a large national U.S. health plan. We identified HHT patients diagnosed between 2007 and 2017 using ICD-9 and ICD-10 diagnosis codes. Comparisons were assessed using χ^2 tests.

Result: A total of 19267 unique HHT patients were identified with a mean age of 55.3 years (SD 17.4). Females accounted for 60.2% of the cohort. The mean duration of follow-up was 2.4 years (SD 2.0). Within 1 year prior to HHT diagnosis, the following comorbidities were identified in this cohort: CHF in 4259 (22.1%) patients; anemia in 9676 (50.2%); epistaxis in 9987 (51.8%); and gastrointestinal bleeding in 6943 (36.0%). At least one comorbidity was present in 13,055 (67.8%) of subjects. Males had significantly higher proportions of anemia (54% vs 48%; $p < 0.01$) and epistaxis (58% vs 48%; $p < 0.01$) than females. Older patients had a significantly higher comorbidity burden.

Conclusion: We present preliminary findings from a large national database of commercially insured patients. We report on the largest HHT cohort to date and find the presence of substantial comorbidities in this patient population. Further analyses regarding utilization of invasive ENT procedures, blood transfusions, iron infusions, gastrointestinal endoscopies, and use of anti-angiogenic agents will result in a better understanding of the true health care burden and comorbidities associated with HHT.

Table 1 Patient sex versus comorbidities

	Female	Male	Total	<i>p</i> value
CHF	2568 (22.2%)	1691 (22.0%)	4259 (22.1%)	0.8373
Anemia	5565 (48.0%)	4111 (53.6%)	9676 (50.2%)	< 0.0001
Epistaxis	5539 (47.8%)	4448 (58.0%)	9987 (51.8%)	< 0.0001
GI bleed	4367 (37.7%)	2576 (33.6%)	6943 (3.0%)	< 0.0001
Any comorbidity	7490 (64.6%)	5565 (72.5%)	13055 (67.8%)	< 0.0001

Table 2 Patient age versus comorbidities

	Age < 50 years	Age 50 + years	Total	<i>p</i> value
CHF	454 (7.5%)	3805 (28.8%)	4259 (22.1%)	< 0.0001
Anemia	2107 (34.7%)	7569 (57.3%)	9676 (50.2%)	< 0.0001
Epistaxis	2407 (39.7%)	7580 (57.4%)	9987 (51.8%)	< 0.0001
GI bleed	1525 (25.1%)	5418 (41.0%)	6943 (3.0%)	< 0.0001
Any comorbidity	3184 (52.5%)	9871 (74.8%)	13055 (67.8%)	< 0.0001

HHT in Uruguay

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Introduction: Uruguay is a country of 3 million inhabitants. The health system presents difficulties in the care of less prevalent diseases. Since 2011, a multidisciplinary team has been trying to cover all aspects of the disease, with the main objective of an HHT unit recognized by local and international entities, which favors the quality care of patients.

Methods: Observational and descriptive study of clinical characteristics of patients diagnosed with HHT, according to the criteria of Curaçao, from January 2011 to January 2019 in Montevideo Uruguay.

Results: 54 patients, 32 women (59%) and 22 men (41%), with a range between 11 and 70 years. 95% of patients present with epistaxis and cutaneomucosal telangiectasias. Two patients have nasal septodermoplasty. More than 50% of patients with epistaxis have anemia. Less than 50% of patients are adequately studied. There are 5 patients with pulmonary AVMs of which 4 were embolized. Two patients present MAVs in the CNS that have not required treatment. Genetic studies were carried out in 42% of the patients, of which 78% were HHT 2. We found a *de novo* mutation not reported in the literature to date.

Conclusions: In Uruguay, since 2011, it has been possible to make a patient registry that is still insufficient. There are difficulties for the correct study and treatment of these patients, but the work is in continuous growth.

GENETICS

New genetic mutation found in HHT

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De novo mutations in HHT are rare and open doors to diagnosis in suspected cases that do not meet the criteria of Curaçao.

A 68-year-old-man with no history of family or personal hereditary hemorrhagic telangiectasia (HHT) begins with spontaneous and recurrent epistaxis. He required emergency assistance where anterior and posterior tamponade was performed without success and ends in a surgical procedure with vascular ligation.

Multiple cutaneous–mucosal telangiectasias were evidenced in face, oral cavity, upper respiratory tract, trunk, and hands; so HHT was suspected. It was studied with angioresonance of the brain and chest angiotomography that showed no arteriovenous malformations. Fibrocolonoscopy; only telangiectasia in the colon.

A genetic study was carried out using the technique (MLPA) to confirm HHT and shows a signal decrease compatible with a heterozygous deletion corresponding to 1 exon 6 of the ALK1 gene. This change has not been previously described in the literature. By the genetic alteration the patient has HHT type 2.

Clinical manifestations according to ENG/ACVRL1 mutations in Spain: data from the riHHTa registry

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Objective: To compare clinical characteristics of HHT patients included in the riHHTa Registry (Registry of the Hemorrhagic Hereditary Telangiectasia) according to ENG or ACVRL1 mutations. **Methods:** The riHHTa is a prospective, observational registry from multiple Spanish hospitals since June 2016. All patients with positive genetic test for ENG and ACVRL1 mutations were included.

Results: 104 out of 217 patients were included, 34 (32.6%) with ENG and 70 (67.4%) with ACVRL1 mutations. There were no significant differences between ENG and ACVRL1 patients in age (47 years vs 52 years), female gender (61.7% vs 68.5%), ≥ 3 Curaçao criteria (94% vs 82%), recurrent epistaxis (100% Vs 94.3%), ESS (3.1 vs 3.5), mucocutaneous telangiectasia (82.3% vs 82.8%), family history (94.1% vs 92.8%), cerebral vascular malformations (4/17 (23.5%) vs 3/47 (6.3%)) or GI involvement (7/10 (70%) vs 6/12 (50%)), respectively. ENG patients were statistically significant younger at diagnosis (36 years vs 45 years), had more arteriovenous (AV) pulmonary malformations at CT than ACVRL1 patients [19/29 (65.5%) vs 9/42 (21.4%)] and lower hepatic involvement at CT [10/23 (43.4%) vs 27/32 (84.3%), but not at ultrasound test (2/10 (20%) vs 6/36 (16.6%)]. Hepatic telangiectasia, AV and arterioportal shunts, and focal nodular and nodular regenerative hyperplasia were more frequent in ACVRL1, while portovenous shunts were more frequent in ENG patients.

Conclusions: ACVRL1 mutations are more frequent in Spanish riHHTa Registry. ENG patients were younger at diagnosis, had more AV pulmonary malformations and hepatic portovenous shunts than ACVRL1 patients. Abdominal CT detects more hepatic involvement than ultrasound, especially in patients with ACVRL1 mutations.

ClinGen HHT variant curation expert panel

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Objective: The Clinical Genome Resource (ClinGen) is an NIH-funded program that works to standardize and implement clinical relevance criteria for genes and variants used in clinical medicine and research. A ClinGen HHT Variant Curation Expert Panel (VCEP) began the approval process in 2018, with final approval and the start of active work expected in 2019. This panel includes individuals with diverse areas of expertise related to HHT. In 2015, the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG-AMP) provided a systematic scoring process for analyzing evidence and classifying variants (Richards et al., Genetics in Medicine). Many clinical laboratories have implemented these guidelines but there is still reviewer subjectivity without gene/disease rule specifications, leading to discrepancies between how laboratories classify variants. To aid in this, ClinGen expert panels are adapting the ACMG-AMP guidelines and providing rule specifications for particular genes/diseases. The HHT VCEP will provide assessment regarding the pathogenicity of variants in *ACVRL1*, *ENG*, and *SMAD4* with respect to HHT disease. **Methods:** Adapt/Specify ACMG-AMP guidelines for more standardized HHT variant interpretation.

1. Resolve ClinVar classification discrepancies for variants in *ENG*, *ACVRL1*, and *SMAD4*.
2. Curate internal database variants and submit to ClinVar for one centralized HHT variant database.

Conclusion: The work of the ClinGen HHT VCEP will aid in the standardization of variant interpretation and data sharing of HHT variants, which will provide a centralized curated resource where

clinicians and researchers can go to find the significance of variants associated with HHT.

Monozygotic twins with endoglin mutations

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Objective: Although genetic mutations are identical among the affected HHT family members, their phenotypes are not always similar even they share considerable degree of the common genomes. We report a case of monozygotic twins with endoglin mutations, which was the third case in the literature.

Methods/Results: Twin A: a 51-year-old man presented with epistaxis from age around 5 years old, continued thereafter and once a week at present. Telangiectases were observed at tongue, hard palate, and lip. He had asymptomatic four micro-AVMs in the brain, but no AVM in lung, liver, or spinal cord. Twin B: a 51-year-old man presented with epistaxis from the same age as Twin A, continued thereafter, and every day at present. Telangiectases were only observed at tongue. He had no AVM in the brain, spinal cord, lung, liver, or upper and lower GI tracts. Genetic analysis showed endoglin mutation in both twins as well as their proband father. Clinical manifestations in these twins were considerably similar in epistaxis, telangiectasia, and absence of AVMs in lungs and liver in terms of chronological and spatial standpoints, but they were not identical (brain AVMs were found only in twin A). In the literature, there were two other cases of monozygotic HHT twins with the similar characteristics. As expected from genetic commonality, clinical characteristics of three twins are considerably similar, but not identical.

Conclusion: Genetic influence for phenotypic presentation is profound, but the other factors including environments also have a certain effect on clinical manifestations.

Child with juvenile colonic polyposis and variant of unknown significance in SMAD4 proves to have complicated HHT

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Objective: A majority of HHT cases are caused by variants in *ENG* or *ACVRL1*. We report a pediatric case underlying the importance of initiating comprehensive screening for HHT in asymptomatic patients who have *SMAD4* variants.

Method: Case report.

Result: A 3-year-old female presented with a 2-month history of fatigue and easy bruising. She was noted to have anemia, thrombocytopenia, and hepatomegaly. A bone marrow examination showed no dysplasia or malignancy. Liver ultrasound was consistent with portal hypertension and liver biopsy showed sinusoidal congestion and fibrosis. She underwent an orthotopic liver transplant at 4 years of age and pathology of explant liver was similar to previous biopsy. A colonoscopy completed at 8 years of age for a history of hematochezia and anemia showed numerous colonic polyps. Subsequent exome sequencing revealed a missense novel *SMAD4* variant of unknown clinical significance (c.989A > T). She had no clinical symptoms or family history of HHT, though her father reportedly has a history of

polyposis. Brain magnetic resonance imaging showed 3 punctate foci of supratentorial susceptibility. Bubble echocardiogram was positive and chest computed tomography angiogram confirmed multiple large bilateral pulmonary arteriovenous malformations. Patient underwent pulmonary embolization and is clinically doing well.

Conclusion: We have identified a new variant of unknown significance in *SMAD4* associated with juvenile polyposis and complicated HHT with large pulmonary arteriovenous malformations.

Whole genome sequencing of 13 HHT families reveals novel biological insights into the etiology of HHT

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Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant genetic disorder of the vasculature featuring arteriovenous malformations. Around 85% of HHT can be explained by rare or novel variants in the known HHT genes *ENG*, *ACVRL1*, and *SMAD4*. This suggests that variants in novel genes may also contribute to the heritability of HHT and may give rise to clinically nuanced disease presentations.

Objective: Based on this understanding, there is a need to further identify and interpret variants in known associated genes as well as in new HHT genes.

Method: Here we used whole genome sequencing (WGS) in 13 HHT families who lacked genetic findings following HHT panel and whole exome sequencing. Using WGS and novel genomic analysis methods (GEMINI, RUFUS, smooove, and others), we sought to define potentially causal genetic variants in new HHT genes and/or genomic regions.

Results: Using these methods, we identified several high-impact (stop gain, frameshift, missense) coding-sequence variants in loss-of-function intolerant (high pLI) genes that are involved in a variety of molecular functions including miRNA processing, protein phosphorylation, and signal transduction. We also found variants in genes that make protein: protein interactions with *SMAD4*, suggesting these variants may contribute to HHT through a connected or similar pathway to that of the known HHT genes.

Conclusion: Performing WGS on 13 HHT families revealed biologically intriguing novel variants for HHT. Further functional studies and validation will be needed to determine how these candidate gene variants may contribute to HHT.

Identification of Genetic Variants Associated with Hereditary Hemorrhagic Telangiectasia in a Puerto Rican Cohort

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Introduction: Hereditary Hemorrhagic Telangiectasia (HHT) is a rare autosomal dominant multisystem disorder. HHT is characterized by the presence of skin vascular lesions, epistaxis, and arteriovenous

malformations (AVMs). HHT-associated genes are *ACVRL1*, *ENG*, *GDF2*, *RASA1*, and *SMAD4*. To date, no data are available about the frequency of genetic variants present in Puerto Rican subjects with HHT. Identification of HHT genetic variants in Puerto Rico is crucial in order to determine genotype/phenotype associations in our population.

Objective: To explore the genetic variants, clinical manifestations, and outcomes of HHT Puerto Rican subjects.

Methods: A descriptive retrospective chart review of *n* = 15 subjects with HHT was completed. Genetic HHT testing was performed on 10 Puerto Rican subjects with HHT. Whole gene sequencing and deletion/duplication testing were conducted for the following genes: *ACVRL1*, *ENG*, *GDF2*, *RASA1*, and *SMAD4*.

Results: Cohort median age was 22-year old and 66%(10/15) were females. Eighty percent (8/10) of all subjects presented *ENG* heterozygous and pathogenic variants. Most common genetic variants were deletion of the entire *ENG* coding sequence and [c.277C > T (p.Arg93*)]. Additional pathogenic *ENG* variant was [c.1326C > A (p.Cys442*)]. A family with [c.1427A > G (p.Gln476Arg)], a variant of uncertain significance, has three members with severe CNS bleeding. HHT-related clinical findings were noted as follows: Epistaxis 60%(9/15), CNS bleeding 20%(3/15), Pulmonary AVMs 13%(2/15), and Genitourinary bleeding 13%(2/15).

Conclusion: *ENG* genetic variants are the most common in Puerto Rico. A better understanding of the genetic variants, prevalence, clinical manifestations, and natural history of HHT patients in Puerto Rico is essential for healthcare needs assessment, planning, and resources allocation.

Table 1 Genetic variants, clinical characteristics, and outcomes in subjects with HHT in Puerto Rico (*n* = 15). Subjects 1–3, 4–6, and 7–8 belong to a single family, respectively. Subjects 9–13 are related to a single family, genetic analysis conducted only in subjects 9 and 10

Case #	Age/ Gender	HHT gene	Genetic variant	Patient zygosity	Variant classification	Symptoms	Findings	Outcome
1	9/M	ENG	Deletion (Entire coding sequence)	Heterozygous	PATHOGENIC	Epistaxis		
2	22/M	ENG	Deletion (Entire coding sequence)	Heterozygous	PATHOGENIC	Epistaxis		
3	49/F	ENG	Deletion (Entire coding sequence)	Heterozygous	PATHOGENIC	Epistaxis		
4	9/F	ENG	c.277C > T (p.Arg93*)	Heterozygous	PATHOGENIC	Epistaxis		
5	14/M	ENG	c.277C > T (p.Arg93*)	Heterozygous	PATHOGENIC	Epistaxis		
6	27/F	ENG	c.277C > T (p.Arg93*) resection	Heterozygous	PATHOGENIC	Shortness of breath, dizziness, epistaxis	Pulmonary AVM	Surgical
7	7/M	ENG	c.1326C > A (p.Cys442*)	Heterozygous	PATHOGENIC	Epistaxis		
8	30/F	ENG	c.1326C > A (p.Cys442*)	Heterozygous	PATHOGENIC			Healthy
9	11/F	ENG	c.1427A > G (p.Gln476Arg) malformations	Heterozygous	VUS	Severe CNS and gum bleeding neurological deficit	Multiple CNS	
10	36/F	ENG	c.1427A > G (p.Gln476Arg) transfused	Heterozygous	VUS	Epistaxis, gum bleeding, recurrent vaginal bleeding during pregnancy		Healthy, never
11	22/M					Severe CNS bleed		Deceased, 1988
12	56/F					Epistaxis		
13	60/F					Syncope	Multiple CNS	
14	12/F		malformations resection	Successful		Embolization High hemoglobin (> 95%) for age	Pulmonary AVM	Surgical
15	22/F					Severe intra-partum bleeding		Deceased, 2016

HHT Hereditary hemorrhagic telangiectasia, CNS Central nervous system, VUS Variant of uncertain significance, AVM Arteriovenous malformation, ENG Endoglin

IMAGING

Triple-phase liver CT scan changes in HHT patients with high-output cardiac failure (HOCF)

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Objective: Liver vascular involvement in HHT patients (identified by triple phase liver CT scanning) can result in high-output cardiac failure (HOCF) and need for systemic anti-angiogenic therapy or liver transplantation. There are currently no liver imaging parameters that can predict the presence of HOCF. We performed this study to identify CT-based liver morphological changes in HHT patients with HOCF.

Method: We reviewed all HHT patients with available echocardiograms and triple phase liver/abdomen CT scanning seen at the Mayo Clinic from Jan 2013 to Jan 2019. Patients were classified into HOCF (cardiac index > upper limit of normal) and non-HOCF categories. A detailed evaluation was undertaken to detect vascular involvement and dimensions of the celiac artery, hepatic arteries, IVC as well as type of anatomic shunting etc.

Result: We identified 18 HOCF patients and compared them to a randomly chosen cohort of 18 patients without HOCF. Patients with HOCF had significantly larger median values for celiac artery diameter (9.5 mm vs. 7.5 mm, $p = 0.005$); common hepatic artery (9 vs. 6 mm, $p < 0.0001$); right hepatic artery (8.5 vs. 5 mm, $p < 0.0001$) and left hepatic artery (7 vs. 4 mm, $p = 0.0006$). Arteriovenous shunting ($n = 14$ vs. 4, $p = 0.0002$) was also more prevalent in the HOCF group.

Conclusion: HHT patients with HOCF have significantly larger dimensions of the celiac and hepatic arteries and higher rates of arteriovenous shunting. Incorporation of these findings into a clinical score may allow for identification of patients with HOCF.

Validation of ultra-low-dose unenhanced chest CT for pulmonary arteriovenous malformations diagnostic in hereditary hemorrhagic telangiectasia: a phantom study

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Objective: Chest X-ray exposure is a worrisome drawback of an early diagnosis and long-term follow-up of hereditary hemorrhagic telangiectasia (HHT). We aim to validate an ultra-low-dose (ULD) chest CT for pulmonary arteriovenous malformations (PAVM) diagnosis in HHT, in comparison to the reference clinical routine CT.

Method: A last-generation CT was used (iQon, Philips, Israel) for performing an ULD protocol on CT performance (ACR Gammex) and chest anthropomorphic (Kyoto Kagaku Torso) phantoms.

Acquisition parameters were set to reach the lower achievable dose at 10 mAs and 80, 100, 120, 140 kVp, in comparison to the reference at 33 mAs and 120 kVp. Iterative reconstruction algorithms (iDose 6, IMR 1–3) in combination to appropriate Kernel were tested. Quantitative physical metrics (noise power spectrum-NPS, task-based transfer function-TTF), including detectability indexes of simulated 2-mm-diameter solid non-calcified lesions simulating a PAVM contrast were measured. Computed tomography dose index (CTDIvol) was recorded for radiation doses comparison. Subjective image quality and image noise of the chest phantom acquisitions will be assessed by two radiologists for intra and inter-agreement analysis.

Result: ULD CT allows a 90%, 81%, 72%, 60% radiation dose decrease, respectively, at 80, 100, 120 and 140 kVp (CTDIvol: 0.3, 0.6, 0.9, 1.3 mGy vs 3.3 mGy). NPS analysis demonstrated higher peak with lower kVp. For the same dose, the range of NPS and the spatial frequency of the peak were lower with higher IMR. TTF benefited from higher KVp and use of IMR. Detectability indexes and subjective analysis are work in progress.

Conclusion: This study aim to validate suitable ULD chest CT protocol suitable for upcoming PAVM diagnosis clinical studies.

Detection of reperfused pulmonary arteriovenous malformations using ultrafast contrast enhanced magnetic-resonance-angiography

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Objectives: To evaluate time-resolved contrast-enhanced MR Angiography for detection of reperfused PAVM.

Methods: 56 patients with previous treatment of PAVMs by either coil embolization or implantation of Amplatzer vascular plugs underwent follow-up studies for detection of reperfused PAVM by contrast-enhanced MRA.

A time-resolved MRA study was performed with injection of a small contrast medium bolus (0.025 mmol/kg BW MultiHance, Bracco). The temporal resolution of the sequence was < 3 s/dataset with a total number of 72 slices. Thereafter, a high-resolution CE-MRA (0.075 mmol/kg BW MultiHance) with bolus timing based on the time-resolved study was performed. Images were evaluated regarding time of enhancement of the draining vein. Recanalization was considered when a simultaneous enhancement of feeding artery and draining vein or aneurysm sac was observed.

Results: MR Angiography was technically adequate in 51 of 56 cases. In 26 patients, reperfused PAVM were diagnosed based on both time-resolved and high-resolution MRA. If findings were unclear on high-resolution images, evaluation of the enhancement kinetics of the draining vein was helpful to distinguish between retrograde filling, filling of the still dilated draining vein via normal lung tissue, and reperfusion by reopening of shunt vessels or new collateral supply. All reperfused PAVM were confirmed by DSA and underwent re-embolization. Reperfusion was detected both after coil embolization and implantation of Amplatzer vascular plug 4.

Conclusions: Time-resolved dynamic contrast-enhanced MR Angiography is a helpful adjunct to anatomic imaging, allowing for the evaluation of the enhancement kinetics of the draining vein as an indicator of recanalization of PAVM.

Unenhanced MRI of the pulmonary vasculature for detection of pulmonary AV-malformations (PAVM) in patients with hereditary hemorrhagic telangiectasia

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Objectives: To compare the detection rate of pulmonary AV-Malformations (PAVMs) in Gd-enhanced MR angiography with unenhanced MR imaging techniques in patients with hereditary hemorrhagic telangiectasia (HHT).

Methods: 128 patients with proven HHT or first-degree relatives underwent a total of 188 MR examinations between 01/2011 and 12/2017. The patients' age varied from 8 month to 83 years (mean 48 years). Each examination included an unenhanced free breathing SPACE (3D TSE-sequence/TR 4.733 ms/TE 101 ms/FLIP 150°) and a contrast-enhanced 3D GRE MRI sequence (TR 2,87 ms/TE 1,07 ms/FLIP 25°, 0.075 mmol/kg BW MultiHance).

Examinations were read by two experienced radiologists and the number of detected.

AV-Malformations were reported in agreement for each examination. The contrast-enhanced images were read first and after an interval of 6 weeks, the SPACE was read by the same radiologists; blinded to the results of the first reading. In patients undergoing therapy catheter angiography and in all other cases, CE-MRA served as the gold standard. A paired t-test was utilized for statistical evaluation.

Results: 68 AV-malformations requiring therapy were reported in 39 patients. Using contrast-enhanced images, an overall significantly higher number of AV-malformations was detected (174 vs. 102, $p < 0.001$) but none of the AV-malformations requiring therapy (feeding vessel larger 2 mm) were missed on unenhanced imaging.

Conclusions: Using a SPACE sequence, detection of clinically relevant PAVM can be safely performed in patients with contraindications for i.v. contrast medium (e.g., pregnancy) or patients that are not able to follow a breathing command (pediatric patients).

Where is the origin of the last normal branch from feeding artery of pulmonary arteriovenous malformations?

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Objective: Reperfusion via pulmonary-to-pulmonary arterial anastomoses is known as one type of recurrence of pulmonary arteriovenous malformations (PAVMs) after embolization. It is important to occlude the fistulous portion beyond the origin of the last normal branch from feeding artery of PAVMs to prevent recurrence. In this study, we evaluate the origin of the last normal branch by CT as well as its visibility on pulmonary arteriography (PAG).

Method: We reviewed forty patients with 77 PAVMs who underwent coil embolization between October 2007 and December 2017. All patients underwent MDCT before embolization. Axial and MPR CT lung images were reviewed with special interests in the origin of the last normal branch from feeding artery of PAVMs. The origin was classified into three portions, including sac, junction (portion just proximal to the sac), and proximal feeder (more than 5 mm proximal to the sac). We also evaluated whether PAG can depict the normal branches detected by MDCT.

Result: MDCT showed that the last normal branch originated from sac in 30 PAVMs (39.0%), junction in 39 (50.6%), and proximal feeder in 8 (10.4%).

On selective PAG, the last normal branch could be visualized in 30 PAVMs (39.0%), although it could not be visualized due to high-flow shunt in the other 47 PAVMs.

Conclusion: Selective PAG frequently fails to demonstrate the last normal branch from feeding artery of PAVM, which often originates from the sac. Pretherapeutic evaluation of CT image of the last normal branch is important to prevent reperfusion of PAVMs.

Quantitative texture analysis of lung parenchyma: Can it be imaging biomarker of telangiectasia and pulmonary AVM in HHT patients? A preliminary result

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Objective: In HHT patient, lung is commonly affected by telangiectasia and arteriovenous malformation (AVM) leading to hypoxemia and paradoxical embolism. In some cases, de novo AVM due to aggravation of telangiectasia can also be observed in long-term follow-up period. The macroscopic arteriovenous malformation can be diagnosed by CT as well as pulmonary angiography; however, telangiectasia is difficult to be identified on the conventional CT. In this study, the CT texture analysis was applied to diagnose telangiectasia and the feasibility was evaluated whether it can depict microscopic vascular change and can be an imaging biomarker to predict the risk of AVM in HHT patients.

Methods: In this retrospective single-center analysis, ten cases including 5 HHT patients and 5 normal subjects were identified. In each subject, histogram-based CT textures on one selected lung field image with less area of vascular and bronchial tree were analyzed with focusing on various textural features. These features were statistically compared between HHT group and normal group.

Results: Between the two groups, sum-Average, sum-Variance, entropy, kurtosis, and skewness showed significantly different between the two groups ($p < 0.05$). These differences of texture might be affected by telangiectasia of lung parenchyma.

Conclusion: Texture analysis of lung parenchymal CT could be one of useful imaging biomarkers to predict the pulmonary telangiectasia.

Structural and angiographic optical coherence tomography (OCT) for quantitative analysis of hereditary hemorrhagic telangiectasia (HHT) skin lesions: preliminary findings

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Objectives: To develop and optimize a set of quantitative metrics for characterization of telangiectasia in patients with HHT, using structural and speckle variance optical coherence tomography (OCT and SV-OCT).

Methods: Patients' lesions were imaged at different time intervals according to protocol design using a Health Canada approved swept-source OCT system. The Gabor OCT Angiography (GOCTA) algorithm was used on fringe data to create angiographic images at various depths up to 2.5 mm from scans. Image processing and analysis was used to determine vascular lesional area (VLA), epidermal fraction (EF), vascular fraction (VF), fractal dimension (FD), and the proxy measure of "Vascular Area Lesional Value" (VALV) from structural and angiographic data. The data were plotted, and analyzed for relationships between metrics and imaging.

Results: Initial observations suggest that it may be possible to categorize lesion vasculature density through parameters including the VALV coefficient, with dense lesions having a VALV > 0.40, and diffuse lesions having a VALV < 0.40. Also, we categorized lesions as superficial versus deep with EF measures, with superficial having an EF > 0.55 and deep an EF < 0.55. In one patient, we observed, an average VF of 0.058 and average VLA = 1.47mm² at a baseline time point, compared to average VF = 0.012 and average VLA = 0.04mm² 11 weeks later, suggesting these measures may be useful for measuring lesion response to interventions. Variations in imaging caused by re-localization error and skin lesion temperature were seen to influence imaging results, with specific effects to variance in VF and FD. Currently, we are working on standardization of imaging methods to minimize effects of the impact of these factors, including repeated reimaging of the same local regions and controlling of region temperature before imaging, with control studies underway to show consistency in measures through these steps.

Conclusions: We report here a potentially useful set of quantitative metrics gathered from OCT, for classification of telangiectasia and potentially for measuring lesion response.

MECHANISMS OF DISEASE

Decreased levels of MIR-19A-3P and MIR-132-3P in myeloid angiogenic cells from patients with hereditary hemorrhagic telangiectasia

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Objective: Myeloid angiogenic cells (MACs), also known as early endothelial progenitor cells, support angiogenesis through the secretion of various angiogenic factors. MAC dysfunction has been identified in hereditary hemorrhagic telangiectasia (HHT), but their

exact role in HHT pathogenesis remains unclear. MicroRNAs (miRs) regulate gene expression post-transcriptionally and have not been fully explored in HHT pathogenesis. The goal of this study was to profile and characterize miRs in MACs from HHT patients.

Methods: Eighteen clinically and genetically confirmed HHT patients and 11 controls were recruited. MACs were cultured from peripheral blood for total RNA isolation and subsequent miR expression profiling with array analyses. Select dysregulated miRs were validated with RT-qPCR. Significant differences were determined using a two-tailed *t* test.

Results: Of the 384 miRs screened, 34 dysregulated miRs were identified. Selected miRs (miRs-19a-3p, -29b-3p, -126-3p, -133a-3p, -132-3p, -139-5p, -155-5p, -221-3p, -301a-3p, 424-5p, and 454-5p) were validated with RT-qPCR. MiR-19a-3p, known to target IGF1, a potent angiogenic factor, and miR-132-3p, a pro-angiogenic miR, were found to be significantly decreased compared to controls ($p < 0.05$). The other miRs were not found to be significantly dysregulated by RT-qPCR. IGF1 messenger RNA (mRNA) levels were also significantly increased in HHT patients compared to controls ($p < 0.05$).

Conclusion: Our results indicate that miR-19a-3p and -132-3p are significantly decreased in MACs from HHT patients. The interaction between increased IGF1 mRNA and decreased miR-19a-3p may play a critical role in the pathogenesis of HHT. Future work will continue to characterize the roles of these dysregulated miRs in MAC dysfunction in patients with HHT.

Angiogenic T lymphocytes expansion in hereditary hemorrhagic telangiectasia

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Objective: T angiogenic lymphocytes (Tang) are known to participate to angiogenesis via VEGF secretion and interactions with endothelial progenitor cells (EPC). Their role in Hereditary Hemorrhagic Telangiectasia (HHT) has never been described, which constitute the aim of our study.

Method: Tang (CD3+CD31+CXCR4+), Tang subsets, and EPC (CD45-CD34+CD31+CD133+) were quantified by flow cytometry from peripheral blood samples. Intracytoplasmic-VEGF was assessed by flow cytometry after stimulation by PMA-Ionomycin. Patients with infection, auto-immune disease or cancer, and those treated by specific drugs (immunosuppressors, beta-blockers, tranexamic acid, bevacizumab) were excluded.

Results: Nine-teen HHT patients and 10 matched controls were included with a median age of 50.8 years and a 15/14 sex ratio. Among HHT patients, the medians of hemoglobin, ferritin, and Epistaxis Severity Score (ESS) were, respectively, 13.7 g/dl, 31 µg/l, and 2.32. Ten patients were ENG-mutated and 9 were ACVRL1-mutated.

In the HHT group, the Tang frequency was significantly increased (median: 43% vs 26%, $p = 0.0345$), mainly concerning the TCD8 + subset (median: 73% vs 37%, $p = 0.0093$), contrasting with an absolute T lymphopenia (median: 1057/mm³ vs 1522/mm³, $p = 0.0185$). The proportions of VEGF-secreting Tang and EPC were increased (median: 78% vs 41% $p = 0.0389$, 0.089% vs 0.036%, $p = 0.0057$) in the HHT group. A negative correlation appeared between ESS and VEGF-secreting Tang ($r = -0.68$, $p = 0.0013$).

Age, sex, mutation, hemoglobin, and ferritin did not influence these findings.

Conclusion: This study demonstrates for the first time a significant increase of circulating Tang in HHT patients, including the VEGF-secreting subset. Circulating Tang could be considered as potential biomarkers and therapeutic targets.

Opposing roles for endoglin and bone morphogenetic protein 9 (BMP9) in cardiac remodeling after a heart attack

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Objectives: Acute myocardial infarction (AMI) is a major cause of heart failure. Transforming growth factor beta (TGF- β 1) promotes cardiac fibrosis and myocyte hypertrophy after AMI. We previously reported that endoglin promotes cardiac fibrosis in heart failure and further that BMP9 negatively regulates endoglin activity and loss of BMP9 promotes heart failure. No studies have explored an interaction between BMP9 and endoglin in AMI. We hypothesize that endoglin and BMP9 play opposing roles in cardiac remodeling after AMI. To test this hypothesis, we subjected BMP9 $^{-/-}$, BMP9 $^{+/-}$, and endoglin (Eng $^{+/-}$) haploinsufficient mice to left coronary artery ligation.

Results: We report that all BMP9 $^{-/-}$ mice failed to survive past 6 days after AMI ($n = 5$) due to cardiac rupture. Next, BMP9 $^{+/-}$ and Eng $^{+/-}$ mice demonstrated 50% and 90% survival 4 weeks after AMI, respectively. We observed that compared to wild-type (WT) controls, left ventricular (LV) mass was increased among BMP9 $^{+/-}$, but unchanged among Eng $^{+/-}$ after AMI. LV function was impaired among BMP9 $^{-/-}$, but unchanged among Eng $^{+/-}$ after AMI. Compared to WT, LV fibrosis was increased among BMP9 $^{+/-}$, but reduced among Eng $^{+/-}$. We are now quantifying molecular indices of maladaptive cardiac remodeling and canonical and non-canonical TGF β 1 and BMP signaling pathways.

Conclusion: Our results identify that loss of BMP9 promotes mortality and impaired cardiac function in murine models of AMI. We further show that reduced endoglin activity may be protective in AMI. Further studies of molecular signaling pathways will provide key mechanistic insight into the role of BMP9 and endoglin signaling in AMI.

Phosphatidylinositol 3-kinase (PI3 k) activation in cutaneous telangiectasia biopsies of patients with hemorrhagic hereditary telangiectasia type 1

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Objective: HHT2 patients have increased activation of PIK3 signaling in telangiectasia. The objective is to evaluate the activation of PI3 K pathway in cutaneous telangiectasia of HHT1 patients.

Method: A punch biopsy from a digital hand telangiectasia was performed in HHT1 patients from our HHT referral Unit. The study was approved by the Clinical Research Ethics Committee of our center. The possible activation of the PI3 K pathway was studied by immunohistochemistry, specifically, activation of pAKT, pNDRG1, and pS6 was analyzed with appropriate antibodies, and compared with controls. Clinical data and findings from screening tests were also recorded.

Results: A cutaneous biopsy of a digital hand telangiectasia was performed in 7 HHT1 patients. Mean age was 50.9 (38–66) years and 4 (57%) were female. Five (71.4%) had pulmonary arteriovenous malformations and 2 (28.5%) had hepatic involvement. Mean Epistaxis Severity Score (ESS) was 3.7 (1.2–7.5) points. Mean % of positive vessels with pNDRG1 and pAKT in HHT1 patients versus controls were 34.2 (14–57.8) versus 7.2 (1.25–14.3), $p = 0.034$; 20.7 (6.5–46.5) versus 8.9 (3.3–13.3), non-significant, respectively. Mean % of positive endothelial cells with pS6 and Ki67 staining for HHT1 patients Vs controls were 7.4 (4.1–9.4) versus 3.1 (1.9–3.8), $p < 0.03$; and for Ki67 were 3.9 (1.3–7.4)% versus 0.7 (0.5–1.02)%, $p = 0.039$.

Conclusions: In cutaneous telangiectasia biopsies of patients with HHT1, we detected an increase in endothelial cell proliferation linked to an increase on the PI3 K pathway. Our results suggest that PI3 K inhibitors could be used as novel therapeutic agents for HHT.

Soluble endoglin has choleric effect in mice liver

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Objective: Increased plasma levels of soluble endoglin (sEng) are observed in patients with cardiovascular and metabolic diseases including hypercholesterolemia, atherosclerosis, and type II diabetes mellitus, which affect liver functions and metabolism. Therefore, we hypothesized that high levels of sEng will affect cholesterol and bile acids (BA) turnover in liver.

Method: Six-month-old transgenic male mice overexpressing human sEng and control mice underwent bile collection study. Spectra of BA in

the bile and stool were evaluated by LC–MS. Expressions of enzymes and transporters in liver were assessed by qRT-PCR and Western blot.

Results: sEng mice demonstrated decreased plasma total and LDL cholesterol concentrations due to upregulation of hepatic Sr-b1 and Ldlr receptors, increased liver cholesterol content, and increased Abcg8-mediated cholesterol efflux into bile. sEng also increased conversion of cholesterol into bile acids (BA) via upregulation of Cyp7a1 and increased Mdr1 expression. Plasma concentrations of BA were increased in sEng mice due to their enhanced reabsorption via ileum. Increased hepatic disposition of BA led to their increased biliary excretion coupled with choleric activity.

Conclusion: In conclusion, we demonstrate here for the first time that high levels of sEng affect cholesterol and bile acid metabolism in liver. We propose that choleric effect and modulation of Mdr1 expression by sEng might modify effects of drugs used in therapy of disorders with sEng accumulation, suggesting its role in pathology and pharmacotherapy of cardiometabolic diseases.

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Dysregulation of mitochondrial quality control mechanisms during in vitro ischemia reperfusion injury

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Objective: Approximately 50% of HHT patients are affected by pulmonary arteriovenous malformations (PAVM), with 85% of endoglin mutation carrying patients demonstrating right-to-left shunt on electrocardiography. Ischemic brain injury caused by paradoxical embolic stroke is a serious and common concern for patients with PAVM's. While restoration or reperfusion of blood flow is essential to salvage ischemic tissue, reperfusion paradoxically exacerbates damage via the excessive production of reactive oxygen species (ROS) from mitochondria. Mitochondria are the key regulators of cell fate during ischemia–reperfusion (I/R) injury. They promote cell survival through the production of ATP that fuels cellular processes and, conversely, cell death through the production of ROS and the release of pro-apoptotic factors such as cytochrome C. Therefore, stringent quality control mechanisms are critical to ensure a healthy mitochondrial network.

Method: We characterized mitophagic flux utilizing primary cortical neurons isolated from mitochondrial quality control (mito-QC) reporter transgenic mice (C57BL/6- Gt(ROSA)26Sortm1(CAG-mCherry/GFP)Ganl/J) using an *in vitro* oxygen–glucose deprivation (OGD) system. The reporter allele contains a CAG promoter and mCherry- GFP-mtFIS1 fusion protein inserted into the *Gt(ROSA)26Sor* locus on chromosome 6. mCherry is stable in acidic pH (pKa 4.5) while GFP (pKa 5.9) is quenched in the acidic lysosomal environment, allowing identification of mitochondria inside autolysosomes.

Results: Mito-QC mice show an increase in mitophagic flux after in vitro OGD/Reoxygenation.

Conclusion: These novel findings provide key evidence for the role of mitophagy in neuronal death following I/R injury. These evidence could provide the foundation for creating novel neuroprotective therapies.

TREATMENT OF HHT

Treatment of brain arteriovenous malformations in children with HHT

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Objective: To describe the patterns of treatment of brain arteriovenous malformations (BAVMs) in a pediatric cohort of patients with HHT.

Methods: Children with BAVMs were identified among the first 176 pediatric patients (0–18 years old) with HHT enrolled in the multi-center Brain Vascular Malformation Consortium (BVMC) HHT Project. The frequency of treatment and modalities (embolization, gamma knife, surgery) used were calculated. Data were then compared to all adult patients in the BVMC database.

Results:

Table 1 Treatment rates and modalities used in children and adults with BAVMs and HHT

	No. of patients	Mean age (years)	No. with BAVMs	Initial hemorrhage	BAVMs treated	Embolization (%)	Gamma knife (%)	Surgery (%)
Children	176	11.2 ± 4.8	61 (34.7%)	14 (23%)	27 (44%)	43.3	10.0	46.7
Adults	1465	50.1 ± 5.0	280 (19.1%)	34 (12%)	161 (57.5%)	28.1	27.1	44.8

Surgical resection was the most common BAVM treatment modality in both children and adults. The majority (65%) of children treated surgically had intracranial hemorrhage on initial presentation. Embolization was more commonly used in children compared to adults ($p < 0.0001$), while the opposite held true for gamma knife technique ($p < 0.0001$). Two children had BAVMs that were treated multiple times using different modalities.

Table 2 Comparison of treatment rates children with single versus multiple BAVMs

	No. of patients	BAVMs treated	BAVMs not treated	Initial hemorrhage
Single BAVM	18	9 (50%)	9 (50%)	6 (33.3%)
Multiple BAVMs	10	0 (0%)	10 (100%)	0 (0%)
		$p < 0.01$	$p < 0.01$	$p < 0.05$

Conclusions: 44% of children with HHT and BAVMs underwent treatment Surgical resection was commonly used, as well as embolization. Children with multiple BAVMs were significantly less likely to undergo treatment or have intracranial bleeding on presentation. Practice guidelines are still needed for the treatment of BAVMs in children.

Combined KTP laser + radiofrequency ablation for HHT epistaxis control

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Objective: To describe surgical outcomes from combined-technique management of HHT epistaxis, utilizing radiofrequency instruments (Coblator device).

Methods: Single institution retrospective review of surgical cases for HHT epistaxis management from 2016 to 2019. Inclusion criteria: combined KTP laser + radiofrequency ablation technique. Patient demographics, HHT genetic testing results, non-surgical adjunct treatments (IV bevacizumab, etc.), adverse effects, and overall surgical outcomes are described.

Results: 30 patients underwent combined-technique surgical management. 5 of 30 patients underwent a second surgical procedure for repeat epistaxis control sometime within the 3-year period. The remaining patients demonstrated symptomatic control of epistaxis to varying degrees, but without yet requiring repeat surgical intervention. Genetics: 10 Endoglin, 12 ACVRL1, 8 unknown. Intraoperative blood loss was minimal, usually less than 20 mL, although occasional exceptions did occur as expected.

Conclusions: Combined-technique surgical management of HHT epistaxis offers the advantages of selective vascular ablation of small telangiectasias via KTP laser, plus the advantages of radiofrequency ablation for large exophytic telangiectasias and active bleeding. This technique minimizes damage to adjacent mucosa while controlling any sites of acute epistaxis. Radiofrequency ablation with the Coblator device permitted excellent surgical visualization of actively bleeding lesions, with favorable control of total intraoperative blood loss. Moderate-term results within the 3-year study period compare favorably with previous techniques and approaches thus far.

Sublabial approach for management of HHT epistaxis behind intact Young's nasal closure

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Objective: To describe a unique surgical approach for epistaxis control in HHT patients with prior Young's nasal closure.

Methods: Case report

Results: A pt with HHT experienced recurrent epistaxis from a single telangiectasia located high on the dorsal nasal septal mucosa, beginning 15 months after Young's nasal closure. In order to preserve the intact Young's closure, a sublabial intraoral approach was used, bringing the nasal endoscopy and radiofrequency ablation instruments (Coblator device) via the gingivobuccal sulcus and the premaxillary soft tissue of the nasal floor. 1 year later, recurrent symptoms were again controlled via the same sublabial approach. No adverse post-operative concerns were noted with regard to the incision site.

Conclusion: Although clinically significant epistaxis behind an intact Young's nasal closure is rare, surgical access via traditional approaches has not been possible without re-incising the skin flaps of the Young's procedure. Instead, a sublabial approach permits access to the nasal lumen and to any bleeding sites within the nasal septal mucosa without requiring re-incision of the Young's closure. This minimizes the risk of subsequent dehiscence or breakdown between the skin flaps of the Young's procedure, preserving the intact closure while still providing control of acute or recurrent blood loss.

Nasal-self packing on youtube—evaluation of video-assisted instructions in patients with hereditary hemorrhagic telangiectasia (HHT)

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Objective: Inserting nasal self-packings is a secure method leaving patients more self-confident. In HHT centers, patients often learn how to use them, but these centers are rare. Providing a video on <https://www.youtube.com/watch?v=LaiOLYfSJ-E> demonstrating how to use nasal self-packings may also help patients without access to HHT centers.

Method: After seeing the video about using pneumatic nasal self-packings (RapidRhino[®]), a questionnaire was answered. The Curaçao criteria and Epistaxis Severity Score (ESS) were documented. The consultation time was compared to patients who did not see the video.

Result: 33 patients with HHT with an average ESS of 5.4 (SD ± 2.1) were evaluated. 11 patients saw the video on YouTube. 10 patients (10/11, 91%) were regularly online using a smartphone or tablet. During the last year, patients stated that due to heavy nosebleeds they consulted their practitioner three times (m = 2.5, SD ± 2.2) and were admitted once to hospital (m = 0.8, SD ± 1.1). 42% (5/11) knew already about nasal packings but none had used the pneumatic ones. There was no significant difference in their consultation time between patients who saw the video and those who did not (*t* test: − 0.683, *p* = 0.509). Before clicking on the video, 8 out of 11 patients (82%) had at least sometimes the feeling of losing control, and 64% (7/11) patients felt more secure afterwards. All patients (11/11, 100%), who saw the video, understood the instructions and evaluated it as very helpful.

Conclusion: Teaching with YouTube is user-friendly; no additional time is needed and especially those, who are not able to visit an HHT center can be reached.

Hepatic transplantation in patients with hereditary hemorrhagic telangiectasia. Experience of two cases at an Argentine HHT referral center

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Objective: To describe two cases of liver transplantation in HHT with severe hepatic involvement

Results: Patient 1 (P1) is a 47-year-old male and patient 2 (P2) is a 37-year-old female multiple HVMs. Cardiac index (CI) and cardiac output were 6.8, 9.5 (L/min/m²), and 5.8, 9.3 (L/min) in P1 and P2, respectively; associated with dilated cardiomyopathy with mean pulmonary hypertension of 60 mmHg in P1 and 45 mmHg in P2. In addition, both presented portal hypertension and ischemic biliopathy refractory to medical treatment. They also received bevacizumab 1 year before transplantation, showing marked clinical improvement. P1 was anticoagulated due to mechanical aortic valve. After intensive diuretic therapy, the mean pulmonary pressure was 35 mmHg in P1. Natural MELD was 11 in both patients and additional MELD was 26 and 28, respectively. A 6-h liver transplantation was performed in both

patients. The piggyback technique was carried out. Only 1 and 3 units of red cells were transfused, respectively. No hemorrhagic perioperative events were observed. Post-transplant complications in P1 included vasoplegic shock, splenic steal (solved with artery embolization), and reversible renal failure due to hypotension and calcineurin inhibitors; while P2 presented a mild reversible cellular rejection. Tacrolimus was prescribed for both cases as immunosuppression strategy. After 18 months, P1 is in good clinical conditions with mild remnant ascites, CI of 5.6 (L/min/m²) and low doses of diuretic requirements. P2 was discharged 10 days post transplantation and after 3 months is in excellent performance with a CI of 3.31 (L/min/m²).

Conclusion: This is the first Latin American report of liver transplantation in HHT. Perioperative transfusion requirement was very low despite anticoagulation in one. We reinforce the applicability and timing of liver transplantation in selected patients with HHT with severe hepatic involvement.

Multidisciplinary HHT care through hemophilia treatment centers: a pilot project

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Objective: Increase patient access to expert HHT multidisciplinary care through evaluation of a pilot study to evaluate the feasibility of providing HHT care at established Hemophilia Treatment Centers (HTC's) in underserved areas.

Methods: Cure HHT was successful in obtaining a funding appropriation from the United States Congress for the project. A subaward agreement was created between the CDC, Cure HHT, and American Thrombosis & Hemostasis Network (ATHN). An RFA was sent to all 140 federally funded HTC's in the U.S. Centers were scored according to a maximum number of points available for each criterion: potential to provide care to a large number of underserved persons with HHT, availability of expertise for management of HHT-related manifestations and complications, and a plan for organizing and providing multidisciplinary care within the HTC.

Results: Six applications were reviewed and scored. Two applicants were selected—Indiana Hemophilia and Thrombosis Center and University of Michigan HTC. A work plan was developed for training, education, recruitment of patients, and collaboration with Cure HHT. Annual site visits will be conducted by Cure HHT and Mentor Center to assess care and provide HHT education. Quarterly collaboration goals were identified to assess patient enrollment, review of study-related outcomes data, opportunities for discussions, and troubleshooting of any anticipated issues. Specific outcome performance measures including data analysis, evaluation, and quality of life will be evaluated.

Conclusion: Exploration of collaborations with Hemophilia Treatment Centers is a novel approach to enable HHT patients seeking access to expert care in underserved areas.

Integrating psychosocial care into HHT Centers

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Objective: To identify the psychosocial needs of patients with HHT and describe the psychosocial care provided within the clinical setting.

Methods: A retrospective chart review was conducted of the program coordinator, social worker, and psychologist's notes/contacts of 95 patients seen in the Cincinnati HHT Center over the course of 1 year.

Results: Of the 95 patients seen in the HHT Center in 2018, all patients had at least one contact with the program coordinator and based on identified needs through intake, genetic counselor or physician assessment, the social worker met with 57 patients for further assessment. Fourteen patients required travel/lodging assistance, including mileage reimbursement, airfare assistance, insurance lodging benefits, Ronald McDonald House reservations, and discounted lodging through hospital concierge service. Nine were referred for financial assistance resources, and 13 were referred to state Title V program. In addition, the social worker assisted with school issues (IEP/504 plan/referrals) for 4 patients, custody/guardianship for 4 patients, and living will/medical power of attorney forms for 1 patient. Five patients met with a psychologist in conjunction with HHT clinic, 4 of whom were recommended for follow-up services. The Psychosocial Assessment Tool (PAT 2.0) screener was utilized to identify psychosocial risks and connect patients/families to appropriate services.

Conclusion: Psychosocial needs are common among the HHT patient population. A multidisciplinary approach, including pre-screening for psychosocial needs during intake, as well as an embedded social worker and psychologist to address these needs allows for a holistic assessment and treatment of the patients in the clinic setting.

Pulmonary arteriovenous malformation embolization with the microvascular plug system (MVP): a single institutional experience

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Objective: Pulmonary arteriovenous malformations (pAVMs) are anomalous connections between a pulmonary artery and pulmonary vein without an intermediary capillary bed, and are seen in Hereditary Hemorrhagic Telangiectasia. These can manifest with dyspnea, exercise intolerance, headache, stroke/transient ischemic attack, and pulmonary hemorrhage. Embolization therapy traditionally has utilized coils or Amplatzer plugs (St. Jude Medical). However, the newest embolic device is the microvascular plug (MVP) (Medtronic). In this abstract, we describe our institution's experience with MVPs in treating 119 pAVMs.

Method: This IRB-approved retrospective study examined fifty-two patients with 119 pAVMs treated exclusively with MVPs (70 procedures) between July 2014 and July 2018. Patient consent requirement was waived. Patient demographics, procedural attributes, and technical success rate were collected and analyzed.

Result and Conclusion: All procedures were technically successful without major complications as defined by SIR criteria for outcomes complications. Average feeding artery diameters of treated pAVMs were 3.3 mm (SD 1.2 mm, range 2–7.9 mm). Average fluoroscopy time per procedure was 35 min (SD: 16 min) with contrast volume 217 cc (SD: 101 cc). An average of 1.3 (SD: 0.8) MVPs were used per pAVM. The mean follow-up time was 328 days (SD: 258 days). No instances of pAVM flow persistence were observed in the follow-up periods. MVPs are safe and effective options for pAVMs given their high technical success rates and lack of observed persistence.

While upfront costs may be higher than other embolization devices, this may be offset by avoidance of repeat intervention.

Transcardiac retrograde transvenous embolization for recurrent pulmonary arteriovenous malformation: report of two cases

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Objective: To report two cases of successful transcardiac retrograde transvenous embolization (TVE) for recurrent pulmonary arteriovenous malformations (PAVMs).

Methods/Results: Case 1: A 7-year-old male with HHT1 presented with multiple PAVMs. Right S3 and 4 lesions were treated by feeding artery occlusion with coils. Six years later, recurrent PAVMs caused shortening of breath on exertion. Transcardiac retrograde TVE for the larger S4 lesion was performed. After introduction of an 8F sheath from right-to-left atrium by Brockenbrough method, a 7F catheter was advanced to the draining pulmonary vein of the lesion. Then, the microcatheter was retrogradely navigated to the arterial segment of the lesion through the venous sac. Deposition of coils from arterial segment to venous sac resulted in disappearance of this lesion and improvement of his symptom. Case 2: A 5-year-old female with HHT1 underwent coil embolization for PAVMs in the right S3 and 6 regions. 15 years later, both lesions recurred due to previous proximal feeding artery occlusion. Transcardiac retrograde TVE resulted in disappearance of both lesions.

Conclusion: Coil embolization is currently a standard treatment for PAVMs. However, recurrence is not uncommon, especially in the cases of proximal feeding artery occlusion. Re-treatment is not feasible when a microcatheter cannot pierce the previously deposited coils. Transcardiac retrograde TVE is only the solution for such recurrent PAVMs treated by proximal feeding artery occlusion.

Reperfusion of pulmonary arteriovenous malformations following embolotherapy: a randomized controlled trial of the interlock™ fibered IDC™ occlusion system versus nester coils

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Objective: To compare 1-year post-embolization reperfusion rates in pulmonary arteriovenous malformations (PAVMs) treated with the Interlock™ Fibered IDC™ Occlusion System coils (IDC) versus Nester coils.

Methods: A single-blinded randomized controlled trial was performed randomizing individual PAVMs to treatment with IDC vs Nester coils at the Toronto HHT Centre. The primary outcome was CT evidence of reperfusion at 1 year. Secondary outcomes included peri-procedural complications, fluoroscopy time, and contrast volume.

Results: A total of 46 PAVMs in 25 patients (mean age = 49.0 ± 16.2, 16 females (64%)) were included in our study; 26 randomized to Nester coils and 20 randomized to IDC. One patient was lost to follow-up. At a mean follow-up of 421.2 ± 215.7 days, no significant difference in PAVM reperfusion was detected between Nester and IDC coils (Nester: 0%, IDC: 5.6%, $p > 0.05$). There was no significant difference in mean follow-up time between groups (Nester:

423.9 ± 251.4 days, IDC: 417.6 ± 163.2 days, $p > 0.05$). No major peri-procedural complications were noted in either group. Fluoroscopy time (Nester: 15.0 ± 11.8 min, IDC 16.0 ± 5.4 min, $p > 0.05$) and contrast volume utilized (Nester: 80.3 ± 36.5 ml, IDC 87.3 ± 51.7 ml, $p > 0.05$) did not differ between groups.

Conclusion: No significant difference was detected in PAVM reperfusion rates, peri-procedural complication rates, contrast volume utilization, or fluoroscopy time following embolization with IDC and Nester coils.

Hemoptysis from pulmonary arteriovenous malformation after coil embolization during a long follow-up period: a case report

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Objectives: Pulmonary arteriovenous malformations (PAVMs) are the abnormal communications between the pulmonary arteries and veins without any intervening capillary beds. PAVMs cause hypoxemia, cyanosis, and dyspnea, and can be associated with hereditary hemorrhagic telangiectasia (HHT). Previously, they were initially treated with pneumonectomy, but transcatheter embolization has become the first-line therapy for this condition, obviating the need for surgery in most cases.

Results: Here, we report a rare complication of hemoptysis following coil embolization for PAVM during a long follow-up period. A 28-year-old man presented with hemoptysis at 11 years after undergoing coil embolization for PAVM. Chest radiographs during the follow-up period showed that the form of coils placed for the PAVM in the left upper lobe deformed gradually. CT revealed the coils located inside the cavity close to the PAVM and inflammation around the cavity.

Conclusion: To control the hemoptysis, bronchial arterial embolization was attempted at first. Thereafter, lobectomy was performed as a curative treatment.

Does embolization of pulmonary arteriovenous malformations complicate pulmonary hypertension? Examination of pulmonary haemodynamics in patients with pulmonary arteriovenous malformations

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Objective: The prevalence of pulmonary hypertension (PH) in patients with pulmonary arteriovenous malformations (PAVMs) and whether or not transcatheter coil embolization of PAVMs complicates pulmonary hypertension were determined.

Methods: Thirty-five patients (7 males [mean age, 51 years; age range, 17–89 years]) underwent right heart catheterization (RHC) to measure haemodynamics prior to PAVM coil embolization. Twenty-eight patients who completed therapy underwent RHC after coil embolization and the changes in haemodynamics before and after coil embolization were examined.

Results: Fourteen (40%) patients had hereditary hemorrhagic telangiectasia. The mean pulmonary arterial pressure (mPAP), pulmonary arterial wedge pressure (PAWP), cardiac index, and pulmonary vascular resistance (PVR) were 16.0 mmHg (10–26 mmHg), 6.8 mmHg (3–14 mmHg), 3.79 L/min.m² (2.07–5.97 L/min.m²), and 1.6 Woods Units (WU) (0.7–3.5 WU), respectively. Seven (20%) patients had a mPAP > 20 mmHg, and 3 (9%) patients met the criteria of pre-capillary PH (pc-PH [mPAP > 20

mmHg, PAWP \leq 15 mmHg and PVR \geq 3 WU). Among 28 patients who completed therapy, mPAP significantly decreased from 16.3 ± 5.2 mmHg to 14.6 ± 4.7 mmHg ($p < 0.05$). Two patients with pc-PH before embolization had improved mPAP < 20 mmHg after therapy. Six patients had increased mPAP after embolization, but only 1 patient had a mPAP > 20 mmHg; the PVR improved after embolization (2.2 WU to 2.0 WU). One patient had a mPAP > 20 mmHg after embolization, and the PVR improved (2.2 WU to 1.6 WU).

Conclusion: Coil embolization of PAVMs may not complicate pulmonary hypertension.

DRUG TREATMENTS OF HHT

Pomalidomide in HHT: results of a pilot study

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Objective: A broader therapeutic portfolio is needed for HHT. Based on studies demonstrating efficacy of thalidomide, we examined the efficacy and safety of pomalidomide in a single-arm pilot study.

Methods: Eligible patients had (1) GI bleeding requiring transfusion of ≥ 4 units PRBC or 4 iron infusions, or (2) epistaxis with epistaxis severity score (ESS) ≥ 4 requiring ≥ 2 units PRBC or 500 mg intravenous iron, each within the preceding four months. The primary endpoint was a 50% reduction in parenteral iron or transfusion. The secondary endpoint was to define the effect of pomalidomide on the ESS. Treatment was initiated with 1 mg, increasing to 5 mg of pomalidomide/daily, which was continued for four months then tapered.

Results: Nine patients provided consent. One was not treated due to an intervening cardiac event. Two developed a drug-related AE (rash) within three weeks of treatment and were removed, thus we report on 6 patients. Two patients were on study for only 5 months and removed for non-drug-related AEs; both had primarily GI bleeding. One of these met the primary endpoint while the other did not; however, this patient significantly reduced the ESS. The remaining four patients completed the study and all met the primary endpoint and demonstrated significant reductions in the ESS. Decreased levels of plasma MMPs and/or HB-EGF were observed in responders.

Conclusions: This pilot study demonstrates safety and suggests efficacy of pomalidomide in HHT, and provides support for a randomized, placebo-controlled study that will open August, 2019. This study was supported by Celgene, Summit NJ

Pomalidomide in HHT: design of a randomized, placebo-controlled trial

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Objective: Based on the results of a pilot study, we have developed a randomized, placebo-controlled study to further examine the efficacy and safety of pomalidomide in HHT. This abstract describes the development and primary features of the study.

Methods: With the support of a U34 award from NHLBI, a group of experienced HHT investigators was convened and met biweekly to develop this trial. Assistance in trial design was provided by Research Triangle Institute (RTI). Participating sites were selected with the guidance of CureHHT.

Results: One hundred fifty-nine study subjects will be randomized 2:1 to six four-week cycles of pomalidomide or placebo. The primary endpoint will be the difference in the mean change of the Epistaxis Severity Score (ESS) from baseline to week 24 between placebo- and pomalidomide-treated groups. Eligible patients will have a clinical diagnosis of HHT, a requirement for parenteral infusion of at least 250 mg of iron or transfusion of 1 unit of blood over the preceding 24 weeks, and an ESS of ≥ 3 measured over the preceding 3 months. All patients will undergo genotyping, the cost of which will be paid by the study in the absence of third-party coverage. Samples for exploratory mechanistic analyses and to define biomarkers of response will be obtained before and during treatment.

Conclusion: The study has been approved by NHLBI and milestones developed. Efforts are underway to finalize the protocol and obtain the IND. We expect this study to begin accrual in August, 2019.

An international survey to assess use of systemic bevacizumab for chronic bleeding in hereditary hemorrhagic telangiectasia

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Objective: Systemic bevacizumab has demonstrated effectiveness in treating chronic epistaxis and gastrointestinal bleeding in HHT. This study assessed administration, effectiveness, and safety of systemic bevacizumab for chronic bleeding in HHT via survey.

Methods: A 27-item bleeding survey was sent to center directors of 29 international HHT centers and results were analyzed.

Results: Response rate was 72%. Approximately half of centers had treated 15 or more HHT patients with bevacizumab primarily for chronic bleeding. All centers utilize a 5 mg/kg dose for induction treatment and most administer 6 doses (range 4–8) every two weeks. Following induction treatment, 60% utilized a continuous maintenance regimen of 2.5 mg/kg (9%) or 5 mg/kg (91%) with a variable interval between doses (median 4 weeks, range 2–12 weeks) and 40% utilized intermittent maintenance of 5 mg/kg with a variable interval between doses (median 4 weeks, range 2–8 weeks) for 1–8 doses. There was wide variation in modification of maintenance over time (e.g., tapering and modification of dose and interval based on clinical response). Bevacizumab was reported to be highly effective in reducing bleeding symptoms and improving or normalizing hematologic parameters (Fig. 1) with rare adverse effects (Fig. 2). Threshold

for initiation of bevacizumab was highly variable (Table 1) and it is typically prescribed and managed by hematologists (71% of centers). **Conclusions:** Systemic bevacizumab is widely used for chronic bleeding in HHT and respondents report high degrees of effectiveness and safety. There is wide variability in maintenance treatment practices and disease severity threshold to initiate bevacizumab.

Table 1 Threshold for respondents to initiate bevacizumab for bleeding based on clinical scenario. Nasal procedures described in clinical scenarios include laser treatment and sclerotherapy

Clinical scenario	Would initiate bevacizumab (%)	Would not initiate bevacizumab (%)
Normal hemoglobin		
Iron deficiency controlled with oral iron		
Moderate epistaxis, not attempted nasal procedures	0	100
Normal hemoglobin		
Iron deficiency controlled with oral iron		
Moderate epistaxis, failure of nasal procedures	18	82
Mild anemia (Hgb 10–12 g/dL)		
Iron deficiency controlled with occasional iron infusion		
Severe epistaxis, failure of nasal procedures	59	41
Moderate anemia (Hgb 8–10 g/dL)		
Iron deficiency controlled with monthly iron infusion		
Severe epistaxis, failure of nasal procedures	77	23
Severe anemia (Hgb 6–8 g/dL)		
Iron deficiency requiring multiple iron infusions per month and occasional red cell transfusions		
Severe epistaxis, failure of nasal procedures	88	12

Hgb hemoglobin concentration

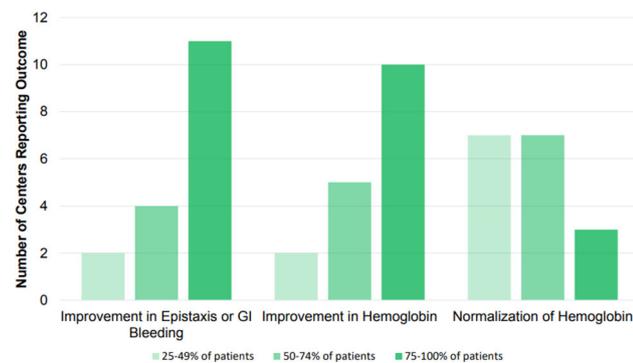


Fig. 1 Reported efficacy of bevacizumab for chronic bleeding by HHT centers. Bar color represents response selected by respondent (e.g., 75–100% of patients treated at their center had improvement in hemoglobin) and bar height reports the number of centers responding with that category for a given question

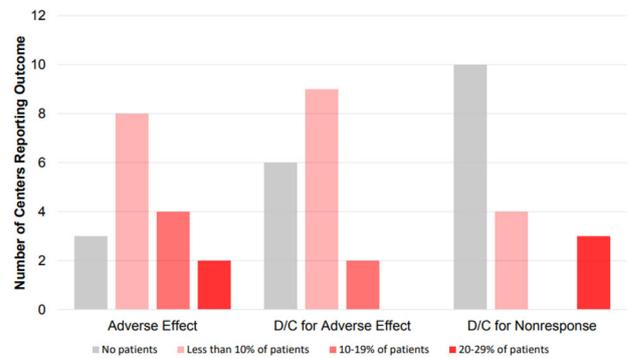


Fig. 2 Rates of bevacizumab adverse effects (such as hypertension, proteinuria, or poor wound healing) and discontinuation reported by HHT centers. Bar color represents response selected by respondent (e.g., 10–19% of patients treated at their center had an adverse event) and bar height reports the number of centers responding with that category for a given question

Mobile mitral and aortic valvular masses in HHT patients receiving intravenous bevacizumab for severe bleeding

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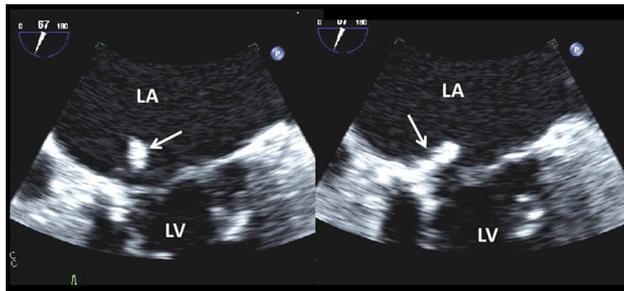
Objective: Bevacizumab is now a well-established treatment option for severe HHT-related bleeding including epistaxis and GI bleeding. The impact of long-term IV bevacizumab therapy on cardiac structure and function is unknown.

Method: We reviewed all transthoracic (TTE) and trans-esophageal echocardiography (TEE) images of patients treated with IV bevacizumab from Jan 2013 to Jan 2019 at the Mayo Clinic HHT center of excellence in Rochester, Minnesota.

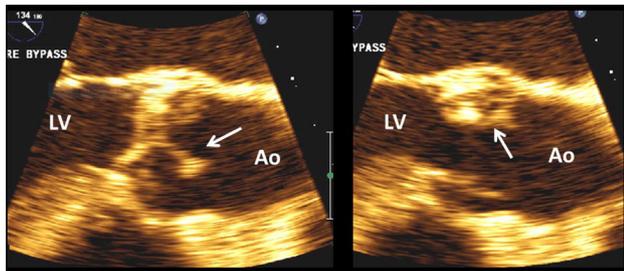
Result: We present 3 patients receiving IV bevacizumab therapy for severe HHT-related bleeding who were found to have abnormal mobile calcifications on the mitral valve (n = 2) and aortic valve (n = 1). Case 1 (aged 74) was found to have multiple mobile round echodensities on the aortic valve (6 mm diameter) attached to the cuspal edges of the left and non-coronary cusps. Case 2 (aged 88) had a mobile (12 × 14 mm) echodensity on the atrial side of the posterior mitral annulus. There was severe mitral annular calcification along with mild–moderate mitral valve regurgitation. Case 3 was found to have a mobile echodensity (11 × 5 mm) arising from a heavily calcified posterolateral mitral annulus. All patients had prior echocardiography images before treatment with bevacizumab that did not show these abnormalities. No patient had an embolic event or significant valvular pathology associated with these lesions.

Conclusion: We present 3 cases with a novel cardiac valvular pathology temporally associated with IV bevacizumab therapy that was being administered for severe HHT-related bleeding. The etiopathogenesis, clinical significance, and evolution of these lesions require further study.

Representative image 1:



Representative image 2:



Bevacizumab treatment for hepatic manifestations secondary to liver involvement in patients with hereditary hemorrhagic telangiectasia (HHT)

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Objectives: Liver involvement in HHT can manifest clinically as high-output cardiac failure, portal hypertension, or biliary disease. There is increasing evidence that treatment with Bevacizumab can improve high cardiac output (CO) heart failure secondary hepatic involvement but there is scant data regarding Bevacizumab treatment for other manifestations of liver involvement in HHT.

The aim of this study is to describe the outcome of patients treated with Bevacizumab for hepatic manifestations of HHT.

Method: Retrospective case series.

Results: Eleven HHT patients were treated with Bevacizumab for clinically significant liver involvement. Ten patients had high CO failure and one—liver decompensation only (portal hypertension—ascites and encephalopathy). One patient with high CO failure had severe hepatic encephalopathy, one had severe ischemic cholangiopathy, and one had refractory ascites with features compatible with portal hypertension. All patients were treated with Bevacizumab 5 mg/kg every 2 weeks for 6 courses and then every 4–8 weeks for up to 3 years (range: 3 months–3 years). All patients demonstrated significant clinical improvement in heart failure parameters as well as in other hepatic manifestations (ascites and encephalopathy).

Conclusion: Bevacizumab may be beneficial for the treatment of hepatic manifestation of HHT other than high cardiac output.

Systemic Avastin in hereditary hemorrhagic telangiectasia (HHT): case report and review of literature

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Objectives: Currently, treatment options for patients with HHT who experience severe chronic bleeding are limited. Prior studies have shown intravenous Avastin, an anti-VEGF monoclonal antibody, to be beneficial in managing systemic HHT manifestations. This report provides objective and qualitative efficacy measures of systemic Avastin from longitudinal follow-up of several patients with HHT treated at our institution.

Methods: Three HHT patients were given intravenous Avastin due to severe, chronic bleeding. Their main manifestations were high-output heart failure due to arteriovenous malformations, epistaxis, and GI bleeding resulting in severe anemia, fatigue, and need for hospitalizations. Patients received 5 mg/kg doses every 2 weeks for 6 total doses with two patients continuing as maintenance or repeat treatment cycles due to refractory bleeding.

Results: All patients showed overall symptomatic improvement after treatment with increased hemoglobin values and decreased need for blood transfusions. One patient showed particularly significant improvement with complete resolution in epistaxis, measured by epistaxis severity scores with a period of sustained effect (Fig. 1), and heart failure symptoms and decrease in AVM size demonstrated on imaging. No significant adverse effects from Avastin were experienced.

Conclusions: Intravenous Avastin appears to markedly decrease symptoms from systemic manifestations of HHT. These results are consistent with findings from prior studies and are promising for improved treatment options for patients experiencing refractory symptoms. Larger prospective studies are needed to assess long-term adverse effects, optimal maintenance dosing, additional objective measurements, and identification of patients most likely to benefit from treatment. This may require a multicenter effort.

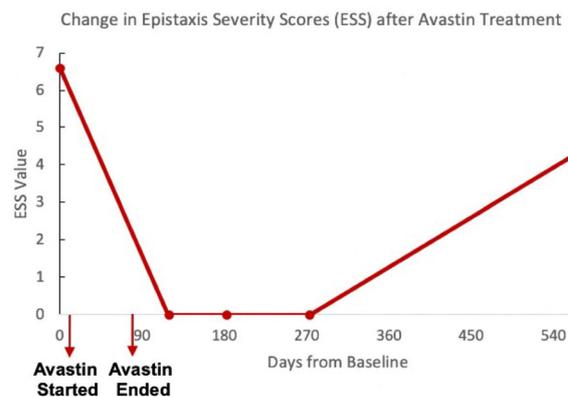


Fig. 1 Plot of epistaxis severity scores (ESS) against time in patient treated with Avastin. ESS dropped dramatically from 6.59 to 0 while on Avastin with sustained effect for at least 6 months after treatment cessation, before rising to 4.9

Phenotypic drug discovery using machine learning to identify novel treatments for hereditary hemorrhagic telangiectasia

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Objective: Recursion has developed a drug discovery platform that consists of high-content immunofluorescence image analysis and sophisticated computational techniques to identify changes in hundreds of cellular and subcellular features. The aim is to utilize this unbiased, target-agnostic approach to identify novel treatments for HHT.

Method: Using siRNA-targeting *ACVRL1* in HUVECs, a unique phenotypic fingerprint ('phenoprint') has been identified and screened against a repurposing library. Based on the initial active hits, an expansion screen was conducted. Hit compounds were further validated in in vitro and in vivo validation assays.

Results: A cluster of hits were identified as receptor tyrosine kinase inhibitors, in particular those with activity towards vascular endothelial growth factor receptor. An expansion screen of the class revealed that not all VEGFRs were able to rescue the phenomodel, suggesting the platform may be able to distinguish compounds with a unique polypharmacology. Evaluation of a lead compound in an *ACVRL1*-GI bleeding model demonstrated it was able to prevent GI bleeding and declining hemoglobin levels.

Impact of antithrombotic therapy in patients with hereditary hemorrhagic telangiectasia

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Subjects with Hereditary Hemorrhagic Telangiectasia (HHT) may require antithrombotic therapy (AT)—for reasons ranging from atrial fibrillation (AF) to venous thromboembolism (TEV) and primary and secondary cardiovascular prevention. Nonetheless, the safety of AT in HHT remains uncertain and there is diffuse perception that AT is contraindicated in HHT, because of the increased risk of bleeding^{1,2}. Using the database of the Gemelli HHT Center, we identified 23 patients who had received (or were still receiving) AT and were willing to participate in this study. They all completed a questionnaire to retrospectively assess the bleeding complications that they experienced while they were on AT (mean time on AT was 19.9 ± 23.5 months). Nine of these patients—those who were still receiving AT—also entered a prospective study in order to intercept new bleeding events. In our retrospective analysis, worsening of epistaxis was reported by 34.8% of patients. A major gastrointestinal bleeding was reported by 4.3%. Blood transfusion or severe worsening of anemia was reported by 13.0% of patients. No pulmonary or cerebral hemorrhages were recorded. No fatal hemorrhages were recorded. In the prospective analysis (mean follow-up 10.8 ± 5.7 months), two patients (18.1%) reported worsening of epistaxis and one patient (11.1%) reported a major gastrointestinal bleeding. Our study shows that the rate of bleeding complications is relatively low among HHT patients who receive AT, with no fatal hemorrhages. These findings support the

concept that AT in HHT patients is feasible and that AT should not be withheld from HHT patients when strongly indicated.

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Indications and tolerance of anticoagulation in hereditary hemorrhagic telangiectasia

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Objective: To describe relevant clinical data, indications, tolerance, and withdrawal causes for anticoagulation in a cohort of HHT patients.

Methods: Observational retrospective cohort study from our HHT Institutional Registry. Patients with HHT confirmed and under anticoagulation therapy were included between January 2006 and January 2019.

Results: Twenty-three of 347 (6.6%) HHT patients received anticoagulants. Median age at initiation of anticoagulation was 64 years old (IR 61–70), 17 were females (74%), all of them had epistaxis, 15 (65%) had gastrointestinal telangiectases of which 4 (17%) suffered from overt gastrointestinal bleeding; 19 (83%) had arteriovenous malformations (18 hepatic, 16 lung, 14 central nervous system), 12 patients (52%) were anticoagulated due to venous thromboembolic disease (VTE), and 5 (22%) for atrial fibrillation. Eight (35%) patients received enoxaparin and 15 (65%) acenocoumarol or warfarin. Overall, 11 patients (48%) continued lifelong anticoagulation, 6 (26%) of them withdrew treatment due to increased bleeding frequency from usual sites, especially epistaxis and 6 (26%) because they completed the treatment. We highlight the withdrawal was stated by non-HHT specialists who do not belong to our Center. No deaths or major bleeding were recorded during follow-up.

Conclusion: Anticoagulation among HHT patients poses a clinical challenge. The most frequent indication for anticoagulation in our cohort was VTE. Anticoagulation seems to be safe in our cohort since two-thirds of our population tolerated the anticoagulation. No severe events were recorded in the rest of the patients. 74% of patients continued treatment with no major side effects and nobody died or had major complications in the rest of the study population. Although anticoagulation seems to be safe among HHT patients and there were no episodes of major bleeding, 26% of patients had to stop anticoagulation.

High efficacy with propranolol in patient with hereditary hemorrhagic telangiectasia and refractory epistaxis

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Objective: To report the quick epistaxis cessation in an HHT patient after treatment with propranolol.

Method: We reported a 54-year-old woman with a severe longtime epistaxis and multiple blood transfusions. She has multiple large macular telangiectases in her hands, tongue, palate, and macular lineal and araneiform in her face. An Internal organs assessment revealed asymptomatic hepatic telangiectases and portovenous fistulae, with no PAVMs, CVMs, or gastrointestinal bleeding. The genetic test shows a novel variant in ACVRL intron 5 (c.626-1G > A). As a first therapy, we prescribed high doses of tranexamic acid and raloxifene afterwards, but they were not effective. We performed an endonasal laser treatment that was ineffective. After that, we carried out a bilateral nasal closure (Young's Procedure) with which the epistaxis stopped, recovering a normal hematocrit. One year after surgery, the hematocrit fell 10% due to a moderate daily bleeding through a new opening in her nostrils. Due to the extreme thinness of the vestibular skin, the surgical closure of the opening was initially unsuccessful. We prescribed propranolol 40 mg daily and 2 days later, the epistaxis stopped completely normalizing the blood parameters which kept normal after 18 months, presenting a mild and sporadic epistaxis. Finally, we carried out a nostril closure with an ear graft, harvested from the cavum of her concha cartilage. Nowadays, she is under treatment with 120 mg of propranolol (1.71 mg/kg) and her ESS is 0.

Conclusion: Propranolol might help to reduce the epistaxis in some HHT patients due to anti-angiogenic and vasoconstriction effects. More data are necessary to confirm the role of propranolol in HHT patients.

Propranolol assessment as therapy for epistaxis in hereditary hemorrhagic telangiectasia: a preliminary report of a large retrospective observational cohort study

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Objective: To compare the epistaxis severity in patients with and without systemic propranolol.

Methods: Retrospective observational cohort study from our Institutional Registry of HHT, started in June 2012. We included HHT patients with completed data at the moment of this report. Propranolol consumption was considered in those patients who complete at least 1 month of treatment. Propranolol was prescribed due to different causes. Epistaxis was assessed with the Sadick Scale and the Epistaxis Severity Score (EES). Improvement was defined as a decrease in at least one category in the Sadick Scale (in intensity and/or frequency) between the first measurement registered and the last measurement in non-propranolol consumers (NPC), and between the first measurement before treatment and the three last ones in the propranolol consumers (PC). Categorical variables were compared with the chi-square test and numerical variables with Wilcoxon test. We will adjust by confounders and the prescription bias. The tolerance and adverse events will be also recorded.

Results: We included 141 patients, 88(62%) females. The median age was 55 (IQR 41–68) Fifty-nine (41%) patients received propranolol. PC were older and had greater median values in the first Sadick Scale (frequency and intensity), while hemoglobin was slightly lower, Table 1. The last epistaxis was assessed, so far, in 62 patients, 31 PC and 31 NPC. Both groups showed the same improvement in the frequency of the Sadick score, 18 PC (58%) had a slightly improvement in the intensity domain (64% vs 58%).

Conclusion: PC were older with a higher morbidity and more severe epistaxis than those untreated. Although these are preliminary results,

it seems that propranolol could be a good choice of treatment in selected patients since they could reach the same improvement than less severe patients. A low rate of adverse events was recorded.

Table 1 Patients characteristics

	PC (n = 59)	NPC (n = 82)	p value
Age ^a	60 (51–71)	49 (36–65)	<0.001
Gender ^b	39 (66%)	49 (59%)	0.443
First Sadick ^a intensity	2(1–3)	1(1–2)	0.0247
First ESS ^a	2.43 (1.89–3.6)	1.96 (1–3.7)	0.2641
Hemoglobin g% ^a	11 (8–12)	12 (9–13)	0.077

^a Median and interquartile range

^b Absolute frequency and relative frequency %

Effectiveness and safety of the treatment with oral propranolol in patients with hereditary hemorrhagic telangiectasia and blood hypertension or atrial fibrillation: A possible anti-angiogenic treatment in epistaxis

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Objectives: To study the efficacy and safety of oral propranolol (OP) in the treatment of epistaxis in patients with Hereditary Hemorrhagic Telangiectasia (HHT) and another pathology with therapeutic indication for OP.

Methods: It is a prospective intervention study in patients with arterial hypertension and/or atrial fibrillation at the Ramón y Cajal University Hospital in Madrid. The patients accepted the substitution or implementation of their previous antihypertensive or antiarrhythmic treatment with OP. In our cohort, OP was used for the original indication. Epistaxis was evaluated by Sadick scale and the Epistaxis Severity Score (ESS). Analysis was performed 1 month before and 3 and 6 months after the treatment.

Results: The first 7 patients who had an indication for beta-blockers and signed the consent were studied. Six were women and 1 man. The mean age was 62.71 years. Five women had hypertension, 1 woman and the man had atrial fibrillation. The mean follow-up was of 8.5 months. ESS decreased more than 1 point in 5 of 7. No adverse events were recorded. Neither hypotension nor bradycardia occurred in any case. The average daily dose of propranolol was 80.41 mg (SD 22). The number of transfusions was reduced by 15% and hemoglobin levels improved significantly.

Conclusion: This study demonstrates that the administration of OP in our patients reduced the number and frequency of epistaxis with good tolerance and improvement of the quality of life. OP could be effective as an “off-label” medicine in patients with HHT.

Doxycycline for the treatment of hereditary hemorrhagic telangiectasia (HHT)-related epistaxis

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Objective: To evaluate the safety and efficacy of an inexpensive and non-invasive treatment for HHT-related epistaxis, the most common symptom of HHT.

Methods: This is a retrospective, uncontrolled, single-center study of doxycycline for the management of HHT-related epistaxis. Patients with definite or possible HHT who were prescribed doxycycline in 2018 were interviewed by standardized survey to assess efficacy and safety.

Results: We analyzed 41 courses of treatment (100 mg bid in 36; 100 qd in 5) in 38 patients for efficacy. Demographics: Mean age, 63.6 years; 46% male; 98% white; 95% definite; 54% with GI AVM. Prior to doxycycline, 90% had tried cautery/laser and 68% had tried a mean of 1.4 ± 1.2 drugs. On doxycycline, 66% noted improved nosebleeds at a mean onset of 16.7 ± 14.5 days. ESS fell from 5.2 ± 2.0 at baseline ($n = 41$) to 2.9 ± 1.2 at 3 months ($n = 30$, $p = 0.00001$) and 3.2 ± 1.5 at final check (18.5 ± 10.9 weeks, $p = 0.000002$). On a scale of 1–5, QOL improved moderately at 3.2. Hemoglobin rose from 9.7 to 11.1 ($n = 26$, $p = 0.006$). At the time of the survey, 13 (32%) had stopped doxycycline after 10.2 ± 8.5 weeks, 7 from side effects and 4 due to lack of efficacy. 47% had one or more side effects: diarrhea 22%, abdominal pain 12%, stuffy nose 12%, superinfection 5% (vaginal and penile yeast 1 each), sun sensitivity 9%, and others in 28%. There were no serious side effects.

Conclusions: In this uncontrolled retrospective study, doxycycline showed a significant improvement in ESS and hemoglobin, and a moderate improvement in QOL.

Tacrolimus treatment for two rare complications caused by hereditary hemorrhagic telangiectasia: a description of two cases

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Objective/Methods: We present two cases of hereditary hemorrhagic telangiectasia (HHT) patients treated with tacrolimus for two different HHT sequelae: abdominal angina due to high-output heart failure, and severe gastrointestinal blood loss requiring frequent blood transfusions.

Results: A 54-year-old female suspected of HHT and hepatic arteriovenous malformations (HAVMs) was referred to our department. She suffered from abdominal angina, mild, spontaneous epistaxis, and characteristic. Magnetic resonance imaging of the liver revealed several HAVMs and an enlarged hepatic artery of 12 mm. Right heart catheterization (RHC) showed increased cardiac output of 9.4 L/min without pulmonary hypertension. The abdominal angina was believed to be caused by shunting from the gastric artery and presumably the superior mesenteric artery. Genetic testing showed a *ACVLR1* mutation. Following tacrolimus treatment initiation, dyspnea and abdominal angina were no longer present. The cardiac output decreased to 8.2 L/min measured with RHC. Epistaxis markedly decreased and 16 months after initiation. The second case is 10-month-old boy, who presented with abdominal cramps, melena,

and severe anemia. Genetic testing revealed an *ENG* mutation. Abdominal angiography and video capsule enterography showed abnormal vascularization and several telangiectasias in the digestive tract. The boy required 13 blood transfusions in 504 days to treat anemia. Following start of tacrolimus treatment until today (327 days), no blood transfusions were needed, and the abdominal cramps and melena have disappeared. There were no side effects in either case.

Conclusions: Tacrolimus seems a good therapeutic option for treatment of several HHT-associated symptoms without numerous side effects. Clinical trials assessing efficacy and safety of tacrolimus should be performed.

Epicure: efficacy of nintedanib as a treatment for epistaxis in HHT disease. A national, randomized, multicenter phase II study

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Objectives: Anti-VEGF treatments have shown therapeutic efficacy in HHT disease. Tyrosine kinase inhibitors are anti-angiogenic molecules which are available orally and could therefore overcome the difficulties encountered with bevacizumab. The tyrosine kinase inhibitor nintedanib targets growth factor receptors involved in angiogenesis. Most importantly it inhibits the platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), and vascular endothelial growth factor receptor (VEGFR). Therefore, we hypothesize that nintedanib acts by indirect inhibition of the VEGF receptor and should allow a reduction of epistaxis in HHT patient. Published results on pazopanib in HHT and a case report on a HHT patient treated with nintedanib encouraged us to set up this study. The main objective was to evaluate the efficacy of a nintedanib treatment on nosebleeds duration.

Method: multicentric, randomized, phase 2, double-blind placebo-controlled study with an allocation ratio of 1:1. Patients will be monitored for 24 weeks: 12-weeks treatment and 12-weeks follow-up. A total of 60 HHT patients (ESS score > 4) will be randomized and treated. The treatment tested, Ofev[®] soft capsules (nintedanib

150 mg) or placebo, is self-administered by patient, oral route twice daily (i.e., 300 mg per day).

Results: Inclusions will start in 2019 upon receipt of regulatory agreements.

This study is promoted by Hospices Civils de Lyon, and has been granted by the French Ministry of Health (PHRCN 2018). Boehringer Ingelheim supports the study and will provide experimental drug.

Tempo: efficacy of timolol nasal spray as a treatment for epistaxis in hemorrhagic hereditary telangiectasia. A double-blind, randomized, placebo-controlled trial

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Objective: Epistaxis is the most frequent and disabling manifestation and timolol appears to be a new therapeutic option in HHT since non-selective beta-blockers have in vitro and in vivo anti-angiogenic properties. The main objective was to evaluate the efficacy of TIMOLOL nasal spray as a treatment for epistaxis in HHT.

Method: Single-center, randomized, phase 2, double-blind placebo-controlled study with an allocation ratio of 1:1. People aged over 18 years diagnosed with HHT and epistaxis (total duration > 60 min/3 months prior to inclusion) were included. A total of 58 patients were randomized and treated. The treatment is self-administered by the patient with a posology of one spray (50 µL) of timolol 0.5% or placebo in each nostril twice a day for 28 consecutive days. The primary efficacy endpoint was mean monthly epistaxis duration assessed by monitoring epistaxis grids completed by the patient for 3 months after the treatment.

Results: Epistaxis duration measured at 3 months was not significantly different in the 26 patients receiving the drug in comparison with the placebo group ($p = 0.54$). Toxicity was low and no severe adverse events were reported.

Conclusion: Timolol administered by nasal spray at a dose of 0.25 mg in each nostril twice a day (1 mg/day) for 28 consecutive days did not improve epistaxis in patients with HHT at 4 months after the beginning of the treatment.

Case report of combination therapy for severely refractory HHT

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Objective: Pazopanib (Votrient) has recently shown success in treatment of anemia and epistaxis in HHT patients [1]. Pazopanib is a tyrosine kinase inhibitor acting on multiple targets, including several VEGF receptors. Low-dose bevacizumab has also been shown to be effective in HHT [2]. The combination of these two medications for refractory HHT-related bleeding has not been studied.

Method: The 75-year-old male patient was diagnosed with hereditary hemorrhagic telangiectasia (HHT) in 2000, after presenting with gastrointestinal bleeding, lifelong frequent epistaxis, and family history. Refractory gastrointestinal bleeding required transfusions of up to 3 units twice a week and weekly iron infusions. Bevacizumab at 5 mg/kg was effective, but resulted in progressive renal dysfunction. Tranexamic acid was discontinued after a myocardial infarction. Thalidomide caused intolerable emotional lability and malaise. Neither tranexamic acid nor thalidomide was effective. A novel regimen was introduced, using pazopanib 100 mg daily with intermittent low-dose bevacizumab administered biweekly at 1 mg/kg, as tolerated by renal function.

Result: The patient's hemoglobin level, transfusion requirement, and therapeutic regimen over the first 4 years of treatment are displayed in Fig. 1. Figure 2 charts the following 56 weeks of combination pazopanib and bevacizumab therapy. 109 units of blood were required in the year prior to combination therapy, while 47 units of blood were required in the year after combination therapy was started. Hemoglobin level averaged 7.7 in 2017, compared to 7.8 in 2018.

Conclusion: The combination of maintenance pazopanib and periodic low-dose bevacizumab shows potential for controlling bleeding in severely refractory HHT.

References:

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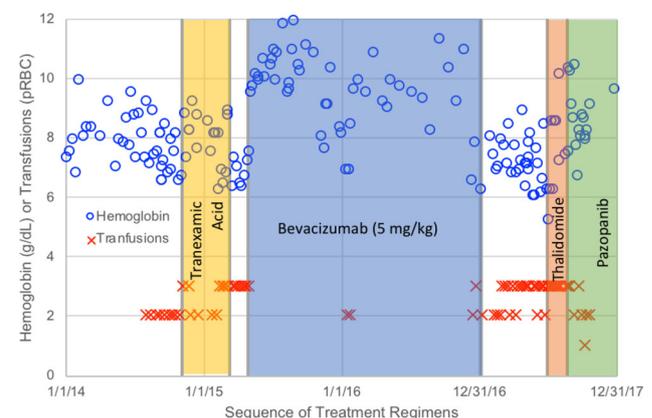


Fig. 1 Prior treatment regimens

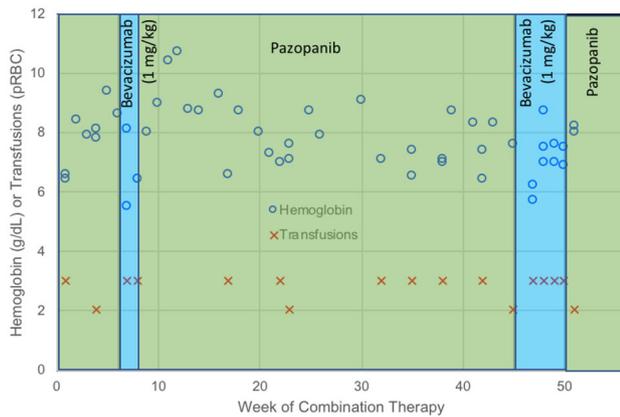


Fig. 2 Combination therapy: pazopanib interspersed with low-dose bevacizumab

Efficacy and safety of octreotide as treatment for severe gastrointestinal bleeding in hereditary hemorrhagic telangiectasia patients: results of a prospective phase II clinical trial

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Background: Gastrointestinal telangiectases in hereditary hemorrhagic telangiectasia (HHT) patients can cause recurrent bleeding with refractory anemia. Treatment for gastrointestinal bleeding in HHT is mostly symptomatic due to lack of effective treatment options. Octreotide, a somatostatin analog, has shown to inhibit angiogenesis and modifies splanchnic blood flow which may decrease gastrointestinal bleeding in these patients.

Objectives: A prospective phase II clinical trial was designed to assess safety and efficacy of octreotide in HHT patients with refractory gastrointestinal bleeding.

Methods: Patients received 20 mg octreotide long-acting release (LAR) monthly for 6 months. The primary outcome was the change in number of blood transfusions and change in iron infusions required during the study period compared to six months prior to inclusion. Secondary outcomes included adverse events, quality of life, fatigue symptoms, hemoglobin, and ferritin levels.

Results: Eleven patients of which 6 (55%) female, with a median age of 61.2 years (interquartile range (IQR) 53.9–65.2), were enrolled. Of these 11 patients, 10 (91%) were diagnosed with HHT type I, and one patient (9%) with HHT type II. The median number of blood transfusions decreased significantly from 13.5 (IQR 8.0–26.5) before inclusion to 8.0 (IQR 4.5–13.8) during treatment ($p = 0.049$) and the median number of iron infusions showed a non-significant decrease from 4.0 (IQR 2.0–10.8) to 3.0 (IQR 2.0–9.3) during treatment ($p = 0.66$). Patients reported significantly less fatigue complaints. The quality of life and the epistaxis severity score showed a tendency of improvement. Hemoglobin and ferritin did not significantly change. No serious side effects were observed.

Conclusions: Octreotide significantly reduced the number of blood transfusions in HHT patients with gastrointestinal bleeding and might be good therapy in this specific group.