Medical treatment of epistaxis in hereditary hemorrhagic telangiectasia: an evidence-based review

Ashleigh A. Halderman, MD[1], Matthew W. Ryan, MD[1], Christopher Clark, MD[1], Raj Sindwani, MD[2], Douglas D. Reh, MD[3], David M. Poetker, MD[4], Rosangela Invernizzi, MD[5] and Bradley F. Marple, MD[1]

Background: **Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant hereditary disorder resulting in vascular dysplasia and formation of arteriovenous malformations. Recurrent epistaxis is a hallmark of the disease. An array of medical therapies are used in this patient population, but robust evidence-based recommendations regarding the medical treatment of epistaxis are lacking. This systematic review was performed to look at the current literature and make meaningful evidence-based recommendations.**

Methods: **A search of the Ovid MEDLINE, Embase, and Cochrane databases was conducted by a research librarian. Abstracts in the English language and published in a peer-review journal were reviewed for relevance and inclusion. PRISMA guidelines were followed.**

Results: **Eighteen studies met the inclusion criteria. In a few small studies, thalidomide was shown to consistently improve severity and frequency of epistaxis and improve hemoglobin concentrations while decreasing the need for transfusion. Tranexamic acid appeared to only impact the epistaxis severity score and not other clinical outcomes. Selective estrogen modulators (SERMs), propranolol, rose geranium oil, and *N*-acetylcysteine, have demonstrated promising efficacy in small trials.**

Conclusion: **Appropriate medical therapies for epistaxis outcomes in HHT remain undefined, and there is no "gold standard." Many of the studies are small and the data reported are heterogeneous, and therefore the ability to make strong evidence-based recommendations is limited. However, many different medications appear to be promising options.** © 2018 ARS-AAOA, LLC.

Key Words:
epistaxis; hereditary; hemorrhagic disorders; evidence-based medicine

***How to Cite this Article*:**
Halderman AA, Ryan MW, Clark C, et al. Medical treatment of epistaxis in hereditary hemorrhagic telangiectasia: an evidence-based review. *Int Forum Allergy Rhinol.* 2018;8:713–728.

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disease leading to the development of arteriovenous malformations (AVMs) in afflicted patients. The prevalence of this disease has been estimated at between 1 in 5000–18,000 individuals, depending on the population studied.[1–4] The Curacao Criteria published in 2000 established diagnostic criteria necessary for the diagnosis of HHT, including: (1) recurrent epistaxis; (2) multiple telangiectasias of the face, lips, oral cavity, nasal cavity, and/or fingers; (3) visceral AVMs, typically found in the lungs, liver, gastrointestinal tract, or brain; and (4) a first-degree relative with HHT.[5] The presence of 3 or more criteria is considered a "definite" diagnosis, whereas 2 criteria equate to a "possible or suspected" diagnosis. One or zero criterion makes a diagnosis of HHT unlikely.

HHT is believed to be a haploinsufficiency where 1 functioning copy of the gene is not sufficient to produce the amount of protein to preserve function. Two genes have been implicated in the majority of HHT cases, ACRLV1, which codes for activin receptor-like kinase 1 (ALK1), and ENG, which codes for endoglin.[6,7] These mutations appear

[1]*Department of Otolaryngology–Head and Neck Surgery, University of Texas Southwestern, Dallas, TX;* [2]*Head and Neck Institute, Cleveland Clinic Foundation, Cleveland, OH;* [3]*Department of Otolaryngology–Head and Neck Surgery, Johns Hopkins Hospital, Baltimore, MD;* [4]*Department of Otolaryngology and Communication Sciences, Medical College of Wisconsin, Milwaukee, WI;* [5]*Department of Internal Medicine, University of Pavia, Pavia, Italy*

Correspondence to: Ashleigh A. Halderman, MD, Department of Otolaryngology–Head and Neck Surgery, University of Texas Southwestern, 5303 Harry Hines Boulevard, Dallas, TX 75390; e-mail: ashleigh.halderman@utsouthwestern.edu

Potential conflict of interest: None provided.
Presented as a poster at the American Rhinologic Society meeting at the Combined Otolaryngologic Spring Meeting, on April 27, 2017, in San Diego, CA.

Received: 18 November 2017; Revised: 2 January 2018; Accepted: 10 January 2018
DOI: 10.1002/alr.22094
View this article online at wileyonlinelibrary.com.

to alter signaling by the transforming growth factor-beta (TGF-β) superfamily, leading to abnormal vessel formation during angiogenesis and an inability of blood vessels to mature appropriately.[5,8–10] These abnormal blood vessels, otherwise known as telangiectasias, are characterized by dilation of the vascular lumen and thinning of the vessel wall, making them more prone to rupture and hemorrhage.

Epistaxis secondary to telangiectasias of the nasal mucosa is the primary complaint in 90%-96% of HHT patients.[11,12] Typically, the incidence of epistaxis increases with age, leading to anemia, significantly reduced quality of life (QoL), need for iron and blood transfusions, and extensive healthcare resource utilization.[12–16] Surgical procedures, although typically effective, have only a temporary impact on the frequency and severity of epistaxis episodes. Thus, there is an urgent need for improved medical treatment of this condition.

A large number of published reports have described the various medical approaches to treating epistaxis in HHT. However, evidence-based treatment guidelines are lacking. The purpose of this study was to systematically review the available literature on medical management of epistaxis in HHT with the ultimate goal of improving patient care. This review is not a formal clinical guideline. Rather, it is an evidence-based review with recommendations as described by Rudmik and Smith.[17] The process was devised by Rudmik and Smith to provide objective evidence-based findings on topics that would, for a variety of reasons, likely never be evaluated in a formal clinical guideline.

Materials and methods

An electronic search was performed by a research librarian on September 30, 2016 and updated on November 7, 2017 of the following databases: Embase; MEDLINE; MEDLINE InProcess/Epub; and Cochrane. The search methodology with the terms and related terms searched can be found in the Appendix.

All included abstracts were written in the English language. Each abstract was independently reviewed by 2 authors (A.A.H. and M.W.R.). The following inclusion criteria were used: published in a peer-review journal; diagnosis of HHT; 5 or more subjects included; and clinical outcomes on epistaxis following medical intervention reported. Duplicates, single case reports, or case series with fewer than 5 subjects, abstracts, and studies that did not report epistaxis outcomes were excluded. Studies evaluating the efficacy of bevacizumab in HHT are not included in this review due to manuscript length restrictions. Also, due to length limits, the focus of this review was topical or oral therapeutics. After independent review, wherever there was disagreement regarding inclusion, both authors reviewed these together and came to a consensus. Following the process devised by Rudmik and Smith,[17] quality of included studies was assessed based on the Oxford levels of evidence[18] and an aggregate grade of evidence was determined based on the American Academy of Pediatrics Steering Committee on Quality Improvement and Management.[19]

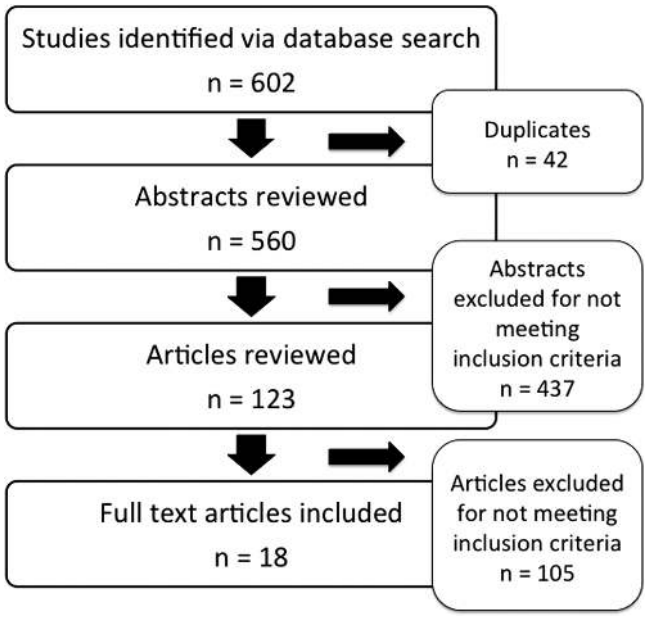

FIGURE 1. Search strategy based on PRISMA guidelines. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

Included studies used a variety of methods to assess the severity of epistaxis. The Epistaxis Severity Score (ESS), developed in 2010 by Hoag et al, is the only standardized and validated scoring system for epistaxis in HHT.[20] If the ESS was not used, data regarding frequency, intensity, duration, quality-of-life assessments, hemoglobin concentrations, and other scales was matched as best as possible for comparisons among studies.

Statistical analysis was performed using GraphPad software (GraphPad Software, Inc, La Jolla, CA). Categorical data were analyzed using the Wilcoxon signed rank test and statistical analysis was defined as $p < 0.05$. The search strategy is demonstrated in Figure 1 and was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[21] Risk for bias for level 1 and 2 studies was evaluated using the Cochrane Collaboration tool,[22] as shown in Table 1. Quality of level 3 and 4 studies was assessed using the Newcastle-Ottawa Quality Assessment Scale,[23] as shown in Table 2.

Results

A total of 123 abstracts met inclusion criteria and the full-text articles were reviewed. Of these, 18 were included in the current systematic review. The manuscripts were divided into subgroups depending on the specific medical treatment studied. Two separate authors analyzed the articles in each subgroup and a standardized review form was filled out by each author. A third author then analyzed each review and where differences were noted; these were discussed with both authors and a consensus was

TABLE 1. Quality assessment of level 1 and 2 evidence studies using the Modified Cochrane Collaboration tool for assessing risk of bias

Potential source of bias	Scoring per item	Yaniv et al[30]	Whitehead et al[35]	Geisthoff et al[53]	Gilliard et al[54]
Was there random allocation of subjects?	Random = 0; not random = 1	0	0	0	0
Was the allocation scheme concealed?	Concealed = 0; not concealed = 1	0	0	0	0
Were the interventions concealed from study personal and participants?	Complete blinding = 0; incomplete blinding = 1	0	0	0	0
Was incomplete data adequately addressed?	Addressed = 0; not addressed = 1	0	0	0	0
Did the sponsoring company participate in any way?	No involvement = 0; involvement = 1	0	0	1	0
Were there any other sources of bias?	None = 0; yes = 1	0	0	0	0
Total score		0	0	1	0

Interpretation of results: 0–1 = low risk of bias; 2–3 = medium risk of bias; 4–6 = high risk of bias.

TABLE 2. Quality assessment of level 3 and 4 evidence studies using the Newcastle-Ottawa Scale

	Selection grade (max 4 asterisks)	Comparability grade (max 1 asterisk)	Outcome (max 3 asterisks)	Total
Albinana et al[29]	**	NA	**	****
Yaniv et al[31]	**	NA	*	***
Minami et al[34]	**	NA	*	***
Lebrin et al[41]	****	*	**	******
Invernizzi et al[42]	**	NA	**	****
Peng et al[43]	**	NA	**	****
Fang et al[44]	**	NA	*	***
Fernandez et al[51]	**	NA	**	****
Zaffar[52]	*	NA		*
Contis et al[63]	**	NA	**	****
Mei-Zahav et al[64]	**	NA	**	****
de Gussem et al[66]	**	NA	**	****
Reh et al[67]	**	NA	**	****

NA = not available.

reached. Data regarding epistaxis outcomes in response to each treatment was extracted and, when possible, evidence-based recommendations were made.

Hormonal therapy

Estrogen therapy for the treatment of HHT has been proposed since the early 1950s after identification of fluctuations in epistaxis symptoms associated with the menstrual cycle. Investigators initially reported a case series of female patients with worsened epistaxis symptoms following menarche and resolution of epistaxis after radiotherapy-induced menopause.[24] Later, reports described improvement in epistaxis with oral contraceptive use as well as temporary improvement in symptoms during pregnancy.[25] The proposed mechanism of action of estrogen therapy is the development of squamous metaplasia of respiratory mucosa in response to treatment in conjunction with enhanced infiltration of mucopolysaccharides in arterial walls and perivascular connective tissue believed to provide improved coverage and protection of delicate vascular tissues.[26]

Early reports of systemic hormonal therapy used starting doses as high as 0.5 mg ethinyl estradiol twice daily with subsequent taper after decrease in epistaxis symptoms, or in response to untoward side effects.[24] These high doses were noted to have substantial adverse effects (especially in men), and included symptoms such as breast tenderness/enlargement, anorexia, fluid retention, flushing, loss of libido, and weight gain.[25] Establishment of a direct link between estrogen/estradiol or estrogen/progesterone combinations and breast and gynecologic cancers led to the eventual abandonment of these therapeutics. Selective estrogen receptor modulators (SERMs), such as raloxifene and tamoxifen, have replaced these older forms. In addition, topical estriol ointment is available and associated with a much more favorable risk profile.

Five articles reporting on the use of hormone therapy for epistaxis in HHT were reviewed by 2 authors (A.A.H. and C.C.) and included in this review. They are summarized in Table 3 and were broken down into oral SERMs and topical therapy.

Selective estrogen receptor modulators

SERMs were initially developed as contraceptives but are now used in the treatment of breast cancer and osteoporosis. These agents have anti-angiogenic properties that make

TABLE 3. Systematic review of hormonal therapies

Author/year	Type of study	LOE	Intervention	n	Measurements	Outcomes on epistaxis	Other HHT-related outcomes	Follow-up	Duration of benefit	Adverse reactions
Selective Estrogen Receptor Modulators										
Albinana et al 2010[29]	PCS	3b	60 mg Raloxifene daily for 6 mo	19	Sadick Scale, Hgb	Average frequency improved from 2.36 to 1.31 $p = 0.05$, and quantity from 2.26 to 1.42 $p = 0.05$	Average increase in Hgb of 9.25% (11.18+/- 0.1 to 12.08+/- 0.15)	6 mo	Unknown	Transaminase levels double normal level, no impact on hepatic function
Yaniv et al 2009[30]	DBRPCT	1b	Group 1: 20 mg Tamoxifen daily Group 2: Placebo daily	Group 1: 10 Group 2: 11	Frequency and severity of epistaxis, Hgb, QOL	9/10 patients Group 1 showed improvement in self reported epistaxis grades and on endoscopy. At 6 mo, Group 1 showed improved frequency ($p = 0.01$) and severity ($p = 0.049$) compared to placebo.	Significant improvement in QOL ($p = 0.0001$) in tamoxifene group. No differences in Hgb	6 mo	2-6 weeks after stopping therapy	Ovarian cyst
Yaniv et al 2011[31]	PCS	3b	20 mg Tamoxifen daily	38	Frequency, intensity, RDL, Hgb, transfusions	Severity significantly improved ($p = 0.0001$)	RDL significantly improved ($p = 0.0001$) and Hgb significantly improved ($p = 0.0001$)	23.4 +/- 16 mo	Unknown	None

(*Continued*)

TABLE 3. Continued

Author/year	Type of study	LOE	Intervention	n	Measurements	Outcomes on epistaxis	Other HHT-related outcomes	Follow-up	Duration of benefit	Adverse reactions
Topical Estriol										
Minami et al 2016[34]	PCS	3b	0.1% Estriol ointment BID	5	ESS, Hgb	ESS decreased from mean 5.26 to 2.34 after 3 mo ($p = 0.043$)	Hgb increased in 4/5 patients but not significantly ($p = 0.097$). No change in serum estriol levels	3 mo	Unknown	None
Whitehead et al 2016[35]	DBRPCT	1b	Bevacizumab 1% (4mg/d) for 1wk followed by 0.9% saline for 11wks, Estriol 0.1% (0.4 mg/d) for 12 wks, Tranexamic acid 10% (40 mg/d) for 12 wks, Placebo (0.9% saline) for 12 wks	120 total: 24 beva-cizumab, 25 estriol, 30 tranexamic acid, 27 placebo	Median weekly epistaxis frequency for weeks 5–12, mean duration of epistaxis weeks 5–12, ESS, Hgb and ferritin levels, need for transfusion, ED visits, and treatment failure	Frequency: No significant drug effect ($p = .97$) Duration: No drug effect Median ESS: No drug effect Placebo: decreased from 5.71 (95%CI, 5.04 to 6.38) to 3.74 (95%CI, 3.17 to 4.31) Estriol: decreased from 5.19 (95%CI, 4.71-5.68) to 3.56 (95%CI, 2.81-4.30)	No significant differences between groups for Hgb or ferritin levels, treatment failure, need for transfusion or ED visits	3 mo	Unknown	None reported with estriol

Key: PCS-Prospective case series, Mo-Month, Hgb-Hemoglobin, DBRPCT-Double blind randomized placebo controlled trail, QOL-Quality of life, RDL- Rhinosinusitis disability index, BID- twice daily, ESS-Epistaxis severity score, Wk-Week, ED-Emergency department.

them potentially beneficial in HHT. Two SERMs have been evaluated in HHT patients: raloxifene and tamoxifen.

Raloxifene is used for prevention of osteoporosis and to reduce the risk of invasive breast cancer in postmenopausal women. It has been shown to create a procoagulant state and increase the risk of venous thromboembolism (VTE) in some women.[27,28] In a prospective study, Albinana et al investigated the effect of 60 mg/d raloxifene in 19 postmenopausal women with HHT for 6 months. Statistically significant improvements in the frequency and quantity of epistaxis ($p = 0.05$) were observed.[29] The molecular mechanisms behind these clinical improvements were in part explained by the demonstration of an increased expression of the protein and mRNA of ENG and ALK1 and improved endothelial cell functions in vitro.[29] As HHT is a haploinsufficiency, drugs that increase protein expression would help decrease the disease burden. No adverse events or changes in coagulation studies were observed; however, transaminase levels were found to be double their typical values without an associated impact on hepatic function.[29] Unfortunately, this study did not have a control group.

Tamoxifen is a SERM used for the treatment of breast cancer. Yaniv et al performed a small, double-blind, randomized, placebo-controlled trial (DBRPCT) involving 25 subjects, comparing 6 months of 20 mg/d tamoxifen with placebo. Adult men and women with HHT were included. They found that both frequency ($p = 0.01$) and severity ($p = 0.049$) of epistaxis improved significantly in the treatment group compared with placebo.[30] No significant difference in hemoglobin concentrations was identified. In a follow-up prospective study that followed 38 patients (20 men and 18 women) for an average of 23.4 months, ESS ($p = 0.0001$) and hemoglobin ($p = 0.0001$) improved significantly.[31] In the first study, 1 patient was noted to develop an ovarian cyst while on tamoxifen, but no other adverse events were identified.[30,31]

Selective estrogen receptor modulators may be an effective treatment for epistaxis in HHT based on small early studies. The side-effect and safety profiles of raloxifene and tamoxifen offer substantial benefits over other oral forms of hormonal therapy; however, they may be restricted to use in postmenopausal women, yet appear to be associated with a favorable side-effect profile in men.

Aggregate grade of evidence: Grade C (level 1b: 1; level 3b: 2).
Benefit: Potential improvement in frequency, severity, and number of epistaxis episodes.
Harm: Elevated transaminase levels and risk of VTE with raloxifene, and development of ovarian cyst with tamoxifen.
Cost: Moderate.
Benefits-harm assessment: Potential benefits appear to outweigh harm.
Value judgments: Improvement in patient symptoms may occur without significant side effects.
Policy level: Option.
Intervention: Larger, well-designed studies could further establish the efficacy of SERMs in HHT.

Topical estriol ointment

Topical estriol ointment represents an option in which the beneficial properties of estrogen can be attained without the undesirable side effects of the systemic form. Histopathologic studies have shown that 6 months of estriol application to the nasal mucosa results in metaplastic changes to the epithelium with thickening of the mucous membrane.[32] After 12 months of use, the ciliated columnar epithelium changes to stratified keratinized squamous epithelium.[33] It is hypothesized that this change leads to better vessel protection and less rupture.

Two studies evaluating estriol ointment in HHT patients were included in this review. Minami et al reported a small case series of 5 patients who were given 0.1% estriol ointment that was applied intranasally on a cotton-tipped applicator, twice daily for 3 months. After 3 months, ESS had improved significantly ($p = 0.043$), and no change was noted in serum estriol levels to suggest systemic absorption of topical estriol.[34] Unfortunately, the study did not include a control group. Given that metaplastic changes were seen in other studies at 6 months, it is unclear whether the benefit to epistaxis after 3 months was from a moisturizing or emollient effect of the topical ointment or from actual histologic changes to the mucosa. In a DBRPCT by Whitehead et al, topical 0.1% estriol compared with placebo nasal saline spray failed to show any significant benefit or drug effect of estriol compared with placebo after 3 months of use.[35] The authors concluded that the 3-month treatment period was not long enough to appreciate the added therapeutic benefit of estriol-induced changes to the nasal mucosa, if one truly exists. Ultimately, the true efficacy of 0.1% estriol remains unclear, warranting additional randomized trials of longer duration. In the aforementioned studies, none of the side effects associated with systemic estrogen, including decreased libido, gynecomastia, breast tenderness, or development of either breast or gynecologic cancers, were noted.

Aggregate grade of evidence: Grade C (level 1b: 1; level 3b: 1).
Benefit: Potential improvement in ESS.
Harm: Local irritation of the mucosa.
Cost: Low.
Benefits-harm assessment: Potential benefits appear to outweigh harm.
Value judgments: Improvement in patient symptoms may occur without significant side effects.
Policy level: Option.
Intervention: The determination of efficacy should not be made until after topical ointment has been used for 6 months, as studies have determined mucosal changes are present at this time.

Thalidomide

Thalidomide was originally introduced in the 1950s to treat nausea in pregnancy. It was removed from the market when a link between the drug and severe birth defects was established. Thalidomide-associated birth defects were later found to be a result of antiangiogenic activity reducing blood supply to fetal organs and tissue.[36] The exact mechanism for this activity is largely unknown, but thought to be an interference with signaling pathways involved in stimulating or inhibiting angiogenesis.[37] It is this antiangiogenic mechanism that has led to a resurgence of thalidomide to treat gastrointestinal bleeding caused by different disease states as well as in the treatment of various cancers.[38,39] Its use in the treatment of bleeding secondary to HHT came about, much like other discoveries in medicine, by the observation of improved epistaxis in HHT patients receiving thalidomide as an antiangiogenic cancer treatment.[40]

Lebrin et al studied changes in abnormal blood vessels in a mouse model of HHT treated with thalidomide. They demonstrated that thalidomide modulated recruitment and activation of mural cells, increasing both their proliferation and formation of protrusions that enveloped blood vessels, something thought to aid in vessel stabilization.[41] They also showed that blood vessels in nasal mucosal biopsies in patients with HHT treated with thalidomide were surrounded by more smooth muscle cell layers than in HHT patients not treated with thalidomide, thereby showing the mechanisms at work in the mouse model were present in humans as well.[41]

To investigate whether these vessel-stabilizing mechanisms impart a clinical benefit in HHT patients, 4 prospective studies were identified and reviewed. These are summarized in Table 4. There were a number of similarities between the studies. Each study evaluated the response in HHT patients on low-dose thalidomide (50-200 mg/d) for a duration of around 3 months. Outcomes included frequency, duration, and intensity of epistaxis in the form of parameter grades and ESS. In addition, 2 studies reported on hemoglobin concentrations before and after starting treatment.

To enable meta-analysis of the frequency, intensity, and duration scores from each of these studies, the raw data for the Invernizzi et al[42] study were requested and obtained. These data are shown in Table 5. For the pooled data, treatment with thalidomide resulted in a significant improvement in the frequency ($p \leq 0.01$), intensity ($p \leq 0.01$), and duration ($p < 0.01$) of epistaxis. The Lebrin et al[41] and Peng et al[43] studies reported hemoglobin levels before and after treatment. Analysis of the pooled hemoglobin data showed a significant increase in hemoglobin levels with treatment ($p = 0.0011$; 95% confidence interval, −4.98 to −1.79). Two studies also reported significant decreases in the need for transfusion in their study populations.[41,42] At a median follow-up time after the end of treatment of 14.1 months, Invernizzi et al reported that 27% of their patients maintained a response and 70% of patients had relapsed.[42] The median relapse-free period was 7 months.[39] Fang et al conducted a prospective case series on 7 patients at doses of between 50 and 100 mg. Over a mean treatment period of 12.9 weeks, the mean ESS improved from 5.03 ± 2.05 pretreatment, to 0.90 ± 0.84 ($p = 0.0003$) at the end of treatment.[44] Three months after stopping thalidomide, the ESS had increased somewhat to 1.98 + 1.33, but remained as a significant improvement from pretreatment values ($p = 0.006$).[44]

In the study by Invernizzi et al, patients were started on a dose of 50 mg for 4 weeks. If a complete or partial response (defined as cessation of epistaxis or reduction of epistaxis, respectively) was achieved by 4 weeks, patients continued on 50 mg for an additional 8 weeks. If no response was achieved, the dose was increased by 50 mg every 4 weeks until a response was achieved. Interestingly, 81% of patients had a clinical response at 50 mg after only 4 weeks of treatment. The remaining patients achieved a response at 100 mg (5 patients) and 150 mg (1 patient). The ability to achieve a response at lower doses is of great importance as higher doses are associated with a number of side effects such as peripheral neuropathy. At the doses studied in the 3 reviewed studies (50-200 mg), a number of mild side effects, most commonly constipation, drowsiness, lethargy, and peripheral edema, were recorded.[41,42] Of note, a total of 10% of patients had paresthesias/peripheral neuropathy typically at doses over 100 mg. In 3 of these patients, it was documented that these symptoms resolved by decreasing the dose.[42] For the fourth patient, it is not clear whether these symptoms resolved. Also, slight increases in thyroid-stimulating hormone were detected in 5 patients.[42] Finally, it must be noted that there has been 1 report in the literature of a patient with HHT developing deep vein thrombosis shortly after starting thalidomide.[45]

In summary, based on 4 prospective studies, thalidomide appears to provide a significant improvement in the frequency, intensity, and duration of epistaxis, as well as hemoglobin levels, in patients with HHT. In 1 study, a majority of patients responded in 1 month to the lowest dose possible (50 mg), whereas minor side effects, including constipation, drowsiness, lethargy, and peripheral edema, were reported. Peripheral neuropathy still occurred in around 10% of patients, but the majority of these cases resolved by lowering the dose of thalidomide. Based on the available data, patients could be started on a dose of 50 mg with the option to increase the dose by 50 mg at 4 weeks if minimal or no response had been achieved. The fact that a treatment period ranging from 12 to 28 weeks resulted in an average 7-month relapse-free period after the cessation of treatment suggests that intermittent dosing of thalidomide may be feasible. Ultimately, the efficacy of thalidomide must be established through adequately powered high-quality DBRPCTs before this can become a widely used therapeutic option. Finally, the severe teratogenic effects of this medication cannot be ignored and its use in female HHT patients of childbearing age must be avoided.

TABLE 4. Systematic review of thalidomide

Author/year	Type of study	LOE	Intervention	n	Measurements	Outcomes on epistaxis	Other HHT-related outcomes	Follow-up	Duration of benefit	Adverse reactions
Lebrin et al 2010[41]	PCCS	3b	Thalidomide 100mg daily	7 thalidomide, 3 controls	Severity, frequency, duration	Frequency decreased in 6/7 subjects ($p<0.05$) and duration decreased in 3/4 subjects	Need for transfusion significantly decreased. Hgb significantly improved in 5/6 patients.	12 mo	Frequency/duration: 3 mo. Transfusions and mean Hgb: 12 mo	Constipation, loss of libido, drowsiness and lethargy, peripheral neuropathy
Invernizzi et al 2015[42]	PCS	3b	Thalidomide 50 mg/daily for 4 wks. Increased dose by 50mg/day increments of 4 wks until partial/complete response seen.	30	Epistaxis parameter grades, need for transfusion	Frequency ($p = 0.00031$), intensity ($p<0.0001$), and duration ($p = 0.019$) decreased. Complete or partial response achieved in 81% of pts at 50mg/day.	Hgb concentrations increased ($p = 0.00011$), need for transfusion decreased ($p<0.0001$)	median 14.1 mo	Median time to relapse 6 mo	Constipation, drowsiness, temporary paresthesia, asthenia, dizziness. Slight increases in TSH detected in 5 pts without clinical significance.
Peng et al 2016[43]	PCS	3b	Thalidomide 100mg daily	5	ESS, parameter grades, Hgb, need for transfusions or medical attention	ESS at 6 mo of therapy significantly decreased from an average 6.966 (SD = 3.093) to 1.799 (SD = 0.627) ($p = 0.009$). Frequency and duration improved in all patients.	Telangiectatic spots on the tongue decreased in size in all case. Hgb improved in all patients.	6 mo	Unknown	Not commented on
Fang et al 2017[44]	PCS	3b	Thalidomide 50–100mg daily	7	ESS	Mean pretreatment ESS 5.03 +/- 2.05 decreased to 0.90 = /- 0.84 ($p = 0,0003$) with treatment and 1.98 +/- 1.33 ($p = 0.006$)	None	3 mo	Unknown	Drowsiness, dizziness, constipation, nausea, peripheral neuropathy

Key: PCCS-Prospective case-control series, Hgb-hemoglobin, Mo-month, PCS-Prospective case series, TSH-Thyroid stimulating hormone, ESS-Epistaxis severity score, SD-Standard deviation.

International Forum of Allergy & Rhinology

TABLE 5. Meta-analysis of thalidomide studies

Patient	Frequency pre	Frequency post	Intensity pre	Intensity post	Duration pre	Duration post
1	3	3	2	1		
2	3	2	2	1	2	1
3	3	3	2	2	2	2
4	3	3	3	1	2	1
5	3	2	2	1		
6	3	2	2	2		
7	3	3	3	2	2	2
8	2	1	3	1	3	1
9	3	1	3	1	2	1
10	2	1	1.5	1	1	1
11	2	1	1.5	1	1	1
12	3	1	3	1	2	1
13	2	1	2	1	2	1
14	3	3	3	1	2	1
15	2	1	1	2	1	1
17	2	1	2	1	2	1
18	2	2	3	2	2	2
19	1	2	3	1	2	1
20	3	3	3	3	3	2
21	3	1	3	1	3	1
22	2	2	3	1	3	1
23	2	2	3	1	2	1
24	2	2	3	3	3	2
25	3	0	3	0	2	0
27	3	2	3	2	1	1
29	3	2	3	3	3	2
30	3	0	3	0	2	0
31	2	2	3	1	1	1
32	3	1	2	1	1	1
33	3	1	3	1	2	1
34	2	1	3	1	3	1
35	3	1	3	1	2	1
36	2	1	3	1	2	1
37	3	2	3	2	3	1
38	3	1	3	1	3	1
39	3	1	3	2	2	1
40	3	1	3	1	2	1
41	3	1	3	1	2	1
42	1	1	2	1	1	1
43	3	2	3	1	3	1
	$p < 0.01$		$p < 0.01$		$p < 0.01$	

Aggregate grade of evidence: Grade C (level 3b: 4).
Benefit: Potential improvement in frequency, intensity, and duration of epistaxis and hemoglobin levels.
Harm: Side effects including constipation, drowsiness, lethargy, peripheral edema, and peripheral neuropathy. Serious teratogenic effects.
Cost: Moderate.
Benefits-harm assessment: Potential benefits appear to outweigh harm in patients not of childbearing age.
Value judgments: Improvement in patient symptoms may occur without serious side effects at lower doses.
Policy level: Option.
Intervention: Start at the lowest dose (50 mg) and increase after 4 weeks only if a response has not occurred in an attempt to avoid more serious side effects associated with higher doses.

Tranexamic acid

Tranexamic acid (TXA) is a derivative of the amino acid lysine that binds to plasminogen and decreases the conversion of plasminogen to plasmin.[46–48] Plasmin acts to degrade fibrin clots (a process called fibrinolysis), fibrinogens, and other plasma proteins. TXA enters into and accumulates within tissues and acts there to stabilize clots.[49] Increased fibrinolytic activity has been demonstrated on the walls of telangiectasias in HHT,[50] and it was postulated that TXA could be effective in the treatment of this disease state. An in-vitro study by Fernandez et al added another layer of understanding to the effect of TXA in HHT. Their study showed that TXA appears to trigger an increase in ALK1 and endoglin protein levels and consequent stimulation of the ALK1/endoglin pathway, which is impacted by HHT.[51]

This review included a total of 5 studies looking at oral and topical TXA and are summarized in Table 6. A retrospective survey of multiple regimens (oral TXA, topical TXA, or a combination) conducted by Zaffar[52] is included in Table 6, but was not discussed at length.

Oral tranexamic acid

Oral doses of TXA range between 500 mg to 1 gm dosed either 2 or 3 times daily for a total daily dose of between 1 and 3 gm. Three studies looking at oral TXA for the treatment of epistaxis in HHT were identified and included. Two were double-blind, randomized, placebo-controlled crossover trials (DBRPCCTs) and 1 was a prospective

TABLE 6. Systematic review of tranexamic acid

Author/year	Type of study	LOE	Intervention	n	Measurements	Outcomes on epistaxis	Other HHT-related outcomes	Follow-up	Duration of benefit	Adverse reactions
Oral Tranexamic Acid										
Geisthoff et al 2014[53]	DBRPCCT	1b	1g PO TXA TID	20 (Group 1-TXA first: 9, Group 2-Placebo first: 11)	Hgb, epistaxis score (combination of duration and intensity)	Epistaxis score significantly reduced on TXA vs placebo ($p = 0.0031$)	No significant difference in Hgb ($p = 0.33$)	3 mo	Not reported	Pruritus, diarrhea and dyspnea occurred in TXA group only
Gaillard et al 2014[54]	DBRPCCT	1b	1.5 g PO TXA BID	118 (57 TXA-then-placebo, 61 placebo-then-TXA)	Mean duration of epistaxis, number of nosebleeds, Hgb, QOL	17.3% decrease in duration of epistaxis/month on TXA compared to placebo ($p = 0.005$); 5.5% decrease in number of episodes with TXA compared to placebo ($p = 0.0005$)	No significant difference for Hgb, QOL	3 mo	Only while on treatment	Diarrhea, vertigo significantly increased in treatment group
Fernandez et al 2007[51]	PCS	3b	500mg PO TXA TID	14	Need for transfusions, epistaxis severity, satisfaction	Improvement on all measures in all patients reported		2 - 24 mo	loss of benefit immediately after discontinuation	Not noted
Topical Tranexamic Acid										
Whitehead et al 2016[35]	DBRPCT	1b	topical bevacizumab 1% (4 mg/d); estriol 0.1% (0.4 mg/d); tranexamic acid 10% (40 mg/d); or placebo (0.9% saline), 1 spray bid x 12 weeks intranasally	120 total: 24 bevacizumab, 25 estriol, 30 tranexamic acid, 27 placebo	Median weekly epistaxis frequency, Mean duration, ESS, Hgb, Ferritin, need for transfusion, ED visits, Treatment failure	Frequency: No significant drug effect ($p = .97$) Duration: No drug effect Median ESS: No drug effect Placebo: decreased from 5.71 (95%CI, 5.04 to 6.38) to 3.74 (95%CI, 3.17 to 4.31)$$$$TXA: decreased from 5.43 (95%CI, 4.94-5.91) to 4.06 (95%CI, 3.50-4.61)	No significant differences between groups for Hgb or ferritin, treatment failure, need for transfusion or ED visits	3 mo	Not reported	Abdominal pain and nausea/vomiting seen most commonly in patients receiving TXA ($p<0.05$)

(*Continued*)

TABLE 6. Continued

Author/year	Type of study	LOE	Intervention	n	Measurements	Outcomes on epistaxis	Other HHT-related outcomes	Follow-up	Duration of benefit	Adverse reactions
Combined Oral and Topical Tranexamic Acid										
Zaffar et al 2014[52]	RCS	4	1-4 g PO TXA daily oral, nasal or oral topical solution, both PO TXA and oral or nasal topical solution	29 (27 patients reported epistaxis) 72.4% (21) PO TXA only, 17.2% (5) topical solution only, 7% (2) both PO and topical solution	ESS, duration of epistaxis, need for transfusion, need for intervention, need for hospitalization for bleeding, frequency of anemia	Significant improvement in ESS ($p<0.001$)	Trend towards a reduction in need for transfusion ($p = 0.095$) and hospitalizations for bleeding ($p = 0.08$)	NA	Not reported	Headache, nasal dryness, anxiety, insomnia, venous thrombosis

Key: DBRPCCT-Double blind randomized placebo controlled crossover trial, PO-oral, TXA-Tranexamic acid, TID-three times daily, Hgb-Hemoglobin, Mo-Month, BID-twice daily, QOL-Quality of life, PCS-Prospective case series, DBRPCT-Double blind randomized placebo controlled trial, ESS-Epistaxis severity score, ED-Emergency department, CI-Confidence interval, RCS-Retrospective case series

study. Both DBRPCCTs treated patients with 3 gm/d of oral TXA or placebo for 3 months, followed by a crossover and an additional 3 months of treatment. Neither study was able to show a significant change in average hemoglobin levels in their study groups.[53,54] Both studies did, however, show a significant benefit in various epistaxis parameters. Geisthoff et al devised an epistaxis score, which multiplied the self-reported total daily duration by the self-reported daily mean intensity. They found a significant reduction in this score during treatment with TXA compared with placebo ($p = 0.0031$).[53] Galliard et al measured the mean duration of epistaxis per month and the mean number of episodes per month and found mean duration shortened significantly ($p = 0.0005$) and rate decreased significantly ($p = 0.0005$) while on TXA.[54] Interestingly, assessment of QoL revealed no significant difference despite these improvements.[54]

Fernandez et al conducted a prospective case series treating patients with doses of oral TXA of between 1 and 3 gm/d. During treatment, all subjects reported significantly improved frequency ($p < 0.05$) and intensity ($p < 0.05$) of epistaxis.[51] Clinical improvement was seen in all patients after 1 week of treatment and the amount of epistaxis immediately increased after cessation of therapy.[51] Therefore, it appears that improvements only occur while patients are actively taking TXA.

No adverse events were noted in the Fernandez et al study, whereas Geisthoff et al noted headache, nausea, diarrhea, and abdominal pain occurring at similar frequencies in both treatment and placebo groups.[53] Gaillard et al reported significantly increased rates of adverse events in the TXA treatment group, including vertigo ($p = 0.01$) and diarrhea ($p = 0.04$).[54] One particularly concerning adverse event previously described in patients taking TXA is venous thrombosis. No episodes of venous thrombosis were reported in the 3 studies included in this review and this is further supported by the findings of others.[55,56] However, venous thrombosis has been reported in HHT patients on TXA in other studies.[52,57] Patients with HHT have been found to have elevated concentrations of factor VIII and von Willebrand factor antigen compared with normal controls and these elevated levels are associated with increased risk of venous thromboemboli (VTE).[5] Careful monitoring of all patients on systemic TXA for VTE should be performed.

To summarize, in 2 DBRPCCTs, daily duration and intensity, monthly duration, and monthly number of episodes improved significantly with treatment, whereas hemoglobin and QoL did not. Of note, in the Geisthoff et al study, it was shown that the treatment effect was quite heterogeneous and, upon further analysis, they could not identify a relevant factor of influence.[53] Therefore, it may be that a yet unidentified variable predicts those patients who will receive the greatest therapeutic benefit from oral TXA. Ultimately, further high-quality studies are needed to elucidate this before a true judgment can be made about the efficacy of oral TXA.

Aggregate grade of evidence: Grade C (level 1b: 2; level 3b: 1).
Benefit: Potential improvement in frequency, intensity, and duration of epistaxis.
Harm: Side effects, including vertigo and diarrhea and potential for venous thrombosis.
Cost: Low.
Benefits-harm assessment: Potential benefits appear to outweigh harm.
Value judgments: Improvement in patient symptoms may occur without serious side effects.
Policy level: Option.
Intervention: Screen for elevated levels of factor VIII and von Willebrand factor antigen prior to initiating oral TXA to prevent possible VTE.

Topical tranexamic acid

One DBRPCT looking at the efficacy of TXA in the form of a topical nasal spray was identified and included in this review. Whitehead et al studied topical nasal sprays for the treatment of epistaxis in HHT in a DBRPCT with 4 arms. For the TXA arm, they used a concentration of 10% TXA (40 mg/d). For epistaxis frequency and duration, the TXA group did not do significantly better than the placebo or other treatment groups.[35] Each of the 4 arms showed improvements in ESS; however, the improvement with TXA was not significantly better than that seen with placebo or any of the other treatments.[35] Upon review of the adverse events experienced during the trial, the authors identified an overall increased risk for gastrointestinal side effects (abdominal pain, nausea, and vomiting) in the topical TXA group compared with the other groups ($p < 0.05$).[35] It was surprising that only 1 trial evaluating topical TXA met inclusion for this review. The demonstrated lack of increased efficacy of topical TXA over alternative topical therapies along with an associated significantly increased risk for adverse side effects dictates that further DBRPCTs are needed to provide more complete information.

Aggregate grade of evidence: Grade C (level 1b: 1).
Benefit: Potential improvement in ESS.
Harm: Higher rate of gastrointestinal side effects than with placebo.
Cost: Low.
Benefits-harm assessment: Unclear whether benefits are provided while there is evidence for increased rate of gastrointestinal side effects.
Value judgments: Unclear whether patients experience added benefit over placebo/saline with topical TXA.
Policy level: No recommendation.
Intervention: Efficacy, or lack thereof, needs to be determined in large, well-designed studies before further use can be promoted.

Propranolol

Vascular endothelial growth factor (VEGF) is an angiogenic factor that is part of the TGF-β pathway. It is found at elevated levels in both the serum and nasal mucosa of patients with HHT, suggesting its possible role in pathogenesis.[58,59] The expression of VEGF is controlled by adrenergic stimulation. Through their anti-adrenergic effects, β-blockers can reduce the expression of VEGF and restrict VEGF-stimulated angiogenesis.[60] Further, β-blockers can increase the rate of apoptosis of endothelial cells[60]; specifically, propranolol can inhibit the proliferation and migration of endothelial cells.[61] These properties have led to the application of propranolol for treating infantile hemangiomas.[62]

Propranolol has been tested in the treatment of epistaxis in HHT in both oral and topical forms. Two studies, one evaluating oral propranolol and one a topical formulation, were identified and are summarized in Table 7. A retrospective, then prospective case series by Contis et al treated a total of 21 patients on oral propranolol with doses of between 80 and 160 mg/d. In the retrospective arm, 10 patients treated for a median duration of 16.5 months had a significant decrease in ESS from 8.3 (7.98-9.44) to 4.5 (4.31-6.61) ($p = 0.003$).[63] Median duration ($p = 0.003$) and frequency ($p = 0.0015$) also improved significantly.[63] In the prospective arm, 11 patients were treated with propranolol for 3 months. Median cumulative duration of epistaxis per month decreased significantly ($p < 0.0001$).[63] In addition, median number of episodes per month ($p < 0.0001$) and number of days without epistaxis per month ($p = 0.01$) decreased significantly.[63] Regarding side effects, only 1 subject had to discontinue propranolol use secondary to hypotension.[63] Other side effects included asthenia, nightmares, and erectile dysfunction.[63]

Topical propranolol was evaluated by Mei-Zahav et al in a retrospective case series. With twice-daily application of 1.5% propranolol gel, their 6 subjects had a significant benefit in mean ESS, from 6.4 ± 2.1 to 3.5 ± 1.7 ($p = 0.028$), and an improvement in mean hemoglobin, from 8.4 ± 3.1 gm/dL to 11 ± 1.8 gm/dL ($p = 0.043$).[64] Similar to the aforementioned studies that evaluated topical treatment, without a control group in their study it is unclear whether there was a significant drug effect from the topical propranolol, or if the improvements observed were simply from better moisturization of the sinonasal passages.

Those 2 small studies have significant limits from both a size and design standpoint, but both offer evidence for a potential benefit of propranolol in the treatment of epistaxis in HHT. It is important to note that β-blockers are contraindicated in certain populations and their use would require regular follow-up of blood pressure and heart rate. Ultimately, further studies are required to evaluate the efficacy of propranolol in these patients.

Aggregate grade of evidence: Grade C (level 3b: 1, level 4: 1) (oral and topical delivery combined due to limited number of studies).
Benefit: Potential improvement in ESS, hemoglobin, and duration of epistaxis.

TABLE 7. Systematic review of propanolol

Author/year	Type of study	LOE	Intervention	n	Measurements	Outcomes on epistaxis	Other HHT-related outcomes	Follow-up	Duration of benefit	Adverse reactions
Contis et al 2016[63]	R/PCS	3b	80-160mg PO daily for retrospective, 80 mg PO daily for prospective	10 retrospective, 11 prospective	ESS, intensity via Sadick scale, duration and number of episodes	Retrospective: ESS decreased- median 8.3 (7.98-9.44) to 4.5 (4.31-6.61) (p = 0.003); Median duration decreased- 30 min (27.5-37.5) to 10 min (5-15) (p = 0.003). Prospective: Duration decreased from median 2.8h (2.28-7.56) to 0.71h (0.27-3.76) (p<0.0001)	Prospective-days without epistaxis improved from 9 (5-18) to 17 (11.5-23.5) (p = 0.01)	3 mo	Unknown	Hypotension, asthenia, nightmares, erectile dysfunction
Mei-Zahav et al 2017[64]	RCS	4	0.5cm of 1.5% propranolol gel BID x 12 weeks	6	ESS, Hgb, need for transfusion	ESS decreased from mean 6.4 +/- 2.1 to 3.5 +/- 1.7 (p = 0.028)	Mean Hgb increased from 8.4 +/- 3.1 g/dL to 11 +/- 1.8 g/dL (p = 0.043). No significant difference in need for transfusion.	Mean 30 wks	Unknown	None reported

Key: R/PCS-Retrospective then prospective case series, ESS-Epistaxis severity score, RCS-Retrospective case series, Cm-Centimeter, Hgb-Hemoglobin

Harm: Hypotension and bradycardia, and β-blockers are contraindicated in certain populations.

Cost: Low.

Benefits-harm assessment: Unclear whether benefits outweigh harm given small number of studies.

Value judgments: Unclear whether propranolol significantly benefits epistaxis in HHT over other interventions.

Policy level: No recommendation.

Intervention: Efficacy, or lack thereof, needs to be determined in large, well-designed studies before further use can be promoted.

Additional therapies

Two additional studies met the inclusion criteria. The first study evaluated the effect of *N*-acetylcysteine (NAC) on epistaxis in HHT patients. Toporsian et al demonstrated that the production of free oxygen (O_2^-) radicals led to endothelial dilation and impaired myogenic response in $ENG^{+/-}$ mice.[65] As stated previously, ENG is one of the genes implicated in HHT, specifically HHT1. The O_2^--driven dysfunction in $ENG^{+/-}$ mice appears to lead to increased pressure on vessels and ultimately results in the development of telangiectasias.[65] NAC is a known scavenger of O_2^- radicals and, for this reason, de Gussem et al performed a pilot study on NAC as a potential therapeutic in HHT. Fifty patients were treated with 600 mg of NAC 3 times daily for a total of 12 weeks. Patients kept a diary in which they scored the severity, duration, and frequency of epistaxis as well as the impact of epistaxis on QoL and on work. NAC significantly improved frequency ($p < 0.01$) and severity ($p = 0.02$) but not duration ($p = 0.07$) of epistaxis.[66] The impact of epistaxis on ability to work significantly improved ($p = 0.02$); however, the changes in both impact on personal life and hemoglobin concentration did not reach significance ($p = 0.14$ and $p = 0.5$ respectively).[66] No adverse events were reported. Patients with the ENG mutation showed a greater degree of improvement on all parameters.[66] Interestingly, the male patients showed greater overall benefit as well.[66] The release of O_2^- radicals has not been demonstrated in patients with the ALK1 mutation and, in the study, as a subgroup, patients with the ALK1 mutation did perform differently than those with the ENG1 mutation.[66] Therefore, NAC may represent one therapy in which genotype needs to be specifically considered.

Another study assessed the impact of a combination of topical sesame/rose geranium oil (RGO) on epistaxis. Reh et al prospectively followed 20 patients who used 3 or 4 drops of RGO topically in each nostril twice daily for at least 3 months. They found a significant improvement in ESS from a pretreatment mean of 5.3 to a posttreatment mean of 3.5 ($p < 0.0001$).[67] Overall satisfaction with the treatment was rated at an average of 7.8 out of 10 points.[67] No adverse events were reported.[67] RGO is a viscous liquid and likely provides benefit on epistaxis through providing a durable moisturizing layer preventing drying of the

nasal mucosa. Further investigation is necessary to determine whether RGO exerts other mechanisms of action.

Both NAC and RGO showed promise in single, small studies. Further research is necessary to better understand the potential benefit of each of these therapies. As only 1 study was identified for each treatment, no evidence-based recommendations have been developed.

Discussion

As our understanding of the genetic basis and molecular mechanisms of this disease state grows, so will our ability to adequately treat its manifestations. Currently, the literature on medical treatment of HHT consists of a few small DBRPCTs, but mostly prospective and retrospective case series. Consequently, the depth of our understanding regarding the efficacy of various therapies is limited. In an effort to reach meaningful conclusions from which to base recommendations, a systematic review was performed and an in-depth look into the available literature was performed. Through this, a few notable conclusions were made.

Only 1 study looking at topical TXA compared with placebo failed to show added efficacy with the addition of TXA. Because only 1 study has shown this, topical TXA remains an option at this time. If, however, further DBRPCTs validate the previous findings and fail to find a significant drug effect for topical TXA, ongoing use of this medication for epistaxis prevention should be questioned. Similarly, more study is required before strong recommendations can be made for topical estriol. Currently, a benefit from topical estriol has been demonstrated in 1 DBRPCT (when combined with argon plasma coagulation [APC]) and 1 level 3b study. Another DBRPCT failed to show a significant drug effect with topical estriol over placebo. The authors of that study were careful to point out their treatment period was only 3 months, and that mucosal changes from estriol therapy have been observed closer to 6 months. Therefore, the treatment period may have been too short and thus underestimated the clinical efficacy of topical estriol. This review identified a need for future large DBRPCTs (>6 months in length in the case of estriol) to establish the true efficacy (or lack thereof) of topical TXA and estriol over placebo.

The oral therapeutic SERMs, TXA and thalidomide, represent options with exciting potential but they also need further exploration. Based on small studies, the SERMs raloxifene and tamoxifene represent well-established antiangiogenic agents with favorable side-effect profiles that appear to provide improvements in epistaxis frequency and severity as well as hemoglobin levels. These early findings must be validated with further study. Similarly, oral TXA has shown some potential benefit in epistaxis parameters. Oddly, significant improvements were not likewise seen in hemoglobin levels or QoL scores, which raises concern as to the true clinical efficacy of these improvements. The side-effect profile appears to be more significant than for SERMs, for example, and may represent a true limitation to regular use.

Oral thalidomide represents an intriguing option. Surely, it is not without major side effects, but the significant clinical response of most patients to the lowest dose appears to offset some of the consequences. Over 3 separate trials, thalidomide significantly improved frequency, intensity, and duration of epistaxis, and in 2 trials that assessed hemoglobin levels these increased significantly with treatment. In addition, with a reported average relapse-free interval of 7 months after stopping therapy, there is potential for intermittent dosing to also help decrease the risk of side effects. As with the topical agents, moving forward, more investigational work is necessary to establish the true efficacy of these oral agents on the treatment of epistaxis in HHT, which represents another need identified in this review.

Regarding β-blockers, propranolol has proven efficacious in other vascular growth disorders such as infantile hemangiomas. The use of propranolol in HHT is largely restricted to small case series or case reports. This represents an area where active research could improve the understanding of the true impact and efficacy of β-blockers in HHT and may provide yet another treatment option for this patient population. Finally, emerging evidence has shown promise in both NAC and RGO, with NAC representing perhaps the first genotype-directed medical therapy in HHT.

Conclusion

No "gold standard" of medical therapy for the treatment of epistaxis in HHT currently exists. At this time, the selection of a particular therapeutic must be made after careful consideration of the potential benefits weighted against possible adverse events. With relatively limited evidence behind treatments currently utilized in treating epistaxis in this patient population, strong evidence-based recommendations cannot be made.

Acknowledgments

The authors thank Helen Mayo, MLS, for design and execution of the database search.

References

1. Kjeldsen AD, Vase P, Green A. Hereditary hemorrhagic telangiectasia: a population-based study of prevalence and mortality in Danish patients. *J Intern Med*. 1999;245:31–39.
2. Brunet G, Lesca G, Genin E. Thirty years of research into Rendu-Osler-Weber disease in France: historical demography, population genetics and molecular biology. *Popul Engl Ed*. 2009;64:273–291.
3. Dakeishi M, Shioya T, Wada Y, et al. Genetic epidemiology of hereditary hemorrhagic telangiectasia in a local community in the northern part of Japan. *Hum Mutat*. 2002;19:140–148.
4. Westermann CJJ, Rosina AF, de Vries V, de Coteau PA. The prevalence and manifestations of hereditary hemorrhagic telangiectasia in the Afro-Caribbean population of the Netherlands Antilles: a family screening. *Am J Med Genet A*. 2003;116:324–328.
5. Shovlin CL, Guttmacher AE, Buscarini E, et al. Diagnostic criteria for hereditary hemorrhagic

telangiectasia (Rendu-Osler-Weber syndrome). *Am J Med Genet*. 2000;91:66–67.
6. Johnson DW, Berg JN, Baldwin MA, et al. Mutations in the activin receptor-like kinase 1 gene in hereditary haemorrhagic telangiectasia type 2. *Nat Genet*. 1996;13:189–195.
7. McAllister KA, Grogg KM, Johnson DW, et al. Endoglin, a TGF-beta binding protein of endothelial cells, is the gene for hereditary haemorrhagic telangiectasia type 1. *Nat Genet*. 1994;8:345–341.
8. Begbie ME, Wallace GMF, Shovlin CL. Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome): a view from the 21st century. *Postgrad Med J*. 2003;79:18–24.
9. Park S, Wankhede M, Lee Y, et al. Real-time imaging of de novo arteriovenous malformation in a mouse model of hereditary hemorrhagic telangiectasia. *J Clin Invest*. 2009;119:3487–3496.
10. Mahmoud M, Allinson K, Zhai Z, et al. Pathogenesis of arteriovenous malformations in the absence of endoglin. *Circ Res*. 2010;106:1425–1433.
11. Guttmacher AE, Marchuk DA, White RI Jr. Hereditary hemorrhagic telangiectasia. *New Engl J Med*. 1995;333:918–924.
12. Plauchu H, de Chadarevian JP, Bideau A, Robert JM. Age-related clinical profile of hereditary hemorrhagic telangiectasia in an epidemiologically recruited population. *Am J Med Genet*. 1989;32:291–297.
13. Ingrand I, Ingrand P, Gilbert-Dussardier B, et al. Altered quality of life in Rendu-Osler-Weber disease related to recurrent epistaxis. *Rhinology*. 2011;49:155–162.
14. Loaec ML, Morineiere S, Hitier M, et al. Psychosocial quality of life in hereditary haemorrhagic telangiectasia patients. *Rhinology*. 2011;49:164–167.
15. Pasculli G, Resta F, Guastamacchia E, et al. Health-related quality of life in a rare disease: hereditary hemorrhagic telangiectasia (HHT) or Rendu-Osler-Weber disease. *Qual Life Res*. 2004;13:1715–1723.
16. Lennox PA, Hitchings AE, Lund VH, Howard DH. The SF-36 health status questionnaire in assessing patients with epistaxis secondary to hereditary hemorrhagic telangiectasia. *Am J Rhinol*. 2005;19:71–74.
17. Rudmik L, Smith TL. Development of an evidence-based review with recommendations using an online iterative process. *Int Forum Allergy Rhinol*. 2011;1:431–437.
18. Oxford Centre for Evidence-based Medicine (CEBM)—Levels of Evidence. 2009. http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/. Accessed September 30, 2016.
19. American Academy of Pediatrics Steering Committee on Quality ImprovementManagement. Classifying recommendations for clinical practice guidelines. *Pediatrics*. 2004;114:874–877.
20. Hoag JB, Terry P, Mitchell S, et al. An epistaxis severity score for hereditary hemorrhagic telangiectasia. *Laryngoscope*. 2010;120:838–843.
21. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009;62:e1–e34.
22. Chandler J CM, Higgins J, eds. Cochrane methods. *Cochrane Database Syst Rev*. 2012;(1):1–56.
23. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25:603–605.
24. Koch HJ, Escher GC, Lewis JS. Hormonal management of hereditary hemorrhagic telangiectasia. *JAMA*. 1952;149:1376–1380.
25. Harrison DF. Use of estrogen in treatment of familial hemorrhagic telangiectasia. *Laryngoscope*. 1982;92:314–320.
26. Vase P, Lorentzen M. Histological findings following oestrogen treatment of hereditary haemorrhagic telangiectasia: a controlled double-blind investigation. *J Laryngol Otol*. 1983;97:427–429.
27. Azevedo GD, Franco FV, Baggio MS, et al. Procoagulant state after raloxifene therapy in postmenopausal women. *Fertil Steril*. 2005;84:1680–1684.
28. Mosca L, Grady D, Barrett-Connor E, et al. Effect of raloxifene on stroke and venous thromboembolism according to subgroups in postmenopausal women at increased risk of coronary heart disease. *Stroke*. 2009;40:147–155.
29. Albinana V, Bernabeu-Herrero ME, Zarrabeitia R, et al. Estrogen therapy for hereditary haemorrhagic telangiectasia (HHT): effects of raloxifene, on endoglin and ALK1 expression in endothelial cells. *Thromb Haemost*. 2010;103:525–534.
30. Yaniv E, Preis M, Hadar T, et al. Antiestrogen therapy for hereditary hemorrhagic telangiectasia: a double-blind placebo-controlled clinical trial. *Laryngoscope*. 2009;119:284–288.
31. Yaniv E, Preis M, Shvero J, et al. Anti-estrogen therapy for hereditary hemorrhagic telangiectasia-a long-term clinical trial. *Rhinology*. 2011;49:214–216.
32. Sadick H, Naim R, Oulmi J, et al. Plasma surgery and topical estriol: effects on the nasal mucosa and long-term results in patients with Osler's disease. *Otolaryngol Head Neck Surg*. 2003;129:233–238.
33. Sadick H, Bergler WF, Oulmi-Kagermann J, et al. Estriol induced squamous metaplasia on the nasal mucosa in patients with hereditary hemorrhagic telangiectasia. *Arch Med Res*. 2005;36:468–473.
34. Minami K, Haji T. Intranasal topical estrogen in the management of epistaxis in hereditary hemorrhagic telangiectasia. *Acta Otolaryngol*. 2016;136:528–531.
35. Whitehead KJ, Sautter NB, McWilliams JP, et al. Effect of topical intranasal therapy on epistaxis frequency in patients with hereditary hemorrhagic telangiectasia; a randomized clinical trial. *JAMA*. 2016;316:943–951.
36. Therapontos C, Erskine L, Gardner ER, et al. Thalidomide induces limb defects by preventing angiogenic outgrowth during early limb formation. *Proc Natl Acad Sci USA*. 2009;106:8573–8578.
37. Melchert M, List A. The thalidomide saga. *Int J Biochem Cell Biol*. 2007;39:1489–1499.
38. Bauditz J, Schachschal G, Wedel S, Lochs H. Thalidomide for treatment of severe intestinal bleeding. *Gut*. 2004;53:609–612.
39. Kamalaporn P, Saravanan R, Cirocco M, et al. Thalidomide for the treatment of chronic gastrointestinal bleeding from angiodysplasias: a case series. *Eur J Gastroenterol Hepatol*. 2009;21:1347–1350.
40. Kurstin R. Using thalidomide in a patient with epithelioid leiomyocarcoma and Osler-Weber-Rendu disease. *Oncology*. 2002;16:21–24.
41. Lebrin F, Srun S, Raymond K, et al. Thalidomide stimulates vessel maturation and reduces epistaxis in individuals with hereditary hemorrhagic telangiectasia. *Nat Med*. 2010;16:420–428.
42. Invernizzi R, Quaglia F, Klersy C, et al. Efficacy and safety of thalidomide for the treatment of severe recurrent epistaxis in hereditary haemorrhagic telangiectasia: results of a non-randomised, single-centre phase 2 study. *Lancet Haematol*. 2015;2:e465–473.
43. Peng HL, Yi YF, Zhou SK, et al. Thalidomide effects in patients with hereditary hemorrhagic telangiectasia during therapeutic treatment and in Fli-EGFP transgenic zebrafish model. *Chin Med J*. 2015;128:3050–3054.
44. Fang J, Chen X, Zhu B, et al. Thalidomide for epistaxis in patients with hereditary hemorrhagic telangiectasia: a preliminary study. *Otolaryngol Head Neck Surg*. 2017;157:217–221.
45. Penaloza A, Vekemans MC, Lambert C, et al. Deep vein thrombosis induced by thalidomide to control epistaxis secondary to hereditary haemorrhagic telangiectasia. *Blood Coagul Fibrinol*. 2011;22:616–618.
46. Mannucci PM. Hemostatic drugs. *New Engl J Med*. 1998;339:245–253.
47. Thorsen S. Differences in the binding to fibrin of native plasminogen and plasminogen modified by proteolytic degradation. Influence of omega-aminocarboxylic acids. *Biochim Biophys Acta*. 1975;393:55–65.
48. Hoylaerts M, Lijnen HR, Collen D. Studies on the mechanism of the antifibrinolytic action of tranexamic acid. *Biochim Biophys Acta*. 1981;673:75–85.
49. Verstraete M. Clinical application of inhibitors of fibrinolysis. *Drugs*. 1985;29:236–261.
50. Kwaan HC, Silverman S. Fibrinolytic activity in lesions of hereditary hemorrhagic telangiectasia. *Arch Dermatol*. 1973;107:571–573.
51. Fernandez A, Garrido-Martin EM, Sanz-Rodriguez F, et al. Therapeutic action of tranexamic acid in hereditary haemorrhagic telangiectasia (HHT): regulation of ALK-I/endoglin pathway in endothelial cells. *Thromb Haemost*. 2007;97:254–262.
52. Zaffar N, Ravichakaravarthy T, Faughnan ME, Shehata N. The use of anti-fibrinolytic agents in patients with HHT: a retrospective survey. *Ann Hematol*. 2015;94:145–152.
53. Geisthoff UW, Seyfert UT, Kubler M, et al. Treatment of epistaxis in hereditary hemorrhagic telangiectasia with tranexamic acid—a double-blind placebo-controlled cross-over phase IIB study. *Thromb Res*. 2014;134:565–571.
54. Galliard S, Dupuis-Girod S, Boutitie F, et al. Tranexamic acid for epistaxis in hereditary hemorrhagic telangiectasia patients: a European cross-over controlled trial in a rare disease. *J Thromb Haemost*. 2014;12:1494–1502.
55. Gluud LL, Klingenberg SL, Langholz SE. Systematic review: tranexamic acid for upper gastrointestinal bleeding. *Aliment Pharmacol Ther*. 2008;27:752–758.
56. Shakur H, Roberts I, Bautista R, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomized, placebo-controlled trial. *Lancet*. 2010;376:23–32.
57. Riviere S, Pelenc D, Dupuis-Girod S, et al. Hereditary hemorrhagic telangiectasia and venous thromboembolism. Hematology meeting reports. In: Proceedings of the 8th International Hereditary Hemorrhagic Telangiectasia Scientific Conference in Santander, Spain, 2009;3:54.
58. Sadick H, Riedel F, Naim R, et al. Patients with hereditary hemorrhagic telangiectasia have increased plasma levels of vascular endothelial growth factor and transforming growth bactor-beta1 as well as high ALK1 tissue expression. *Haematologica*. 2005;90:818–828.
59. Sadick H, Naim R, Sadick M, et al. Plasma level and tissue expression of angiogenic factors in patients with hereditary hemorrhagic telangiectasia. *Int J Mol Med*. 2005;15:591–596.
60. Storch CH, Hoeger PH. Propranolol for infantile haemangiomas: insights into the molecular mechanisms of action. *Br J Dermatol*. 2010;163:269–274.
61. Albinana V, Recio-Poveda L, Zarrabeitia R, et al. Propranolol as antiangiogenic candidate for the therapy of hereditary haemorrhagic telangiectasia. *Thromb Haemost*. 2012;108:41–43.
62. Leaute-Labreze C, Dumas de la Roque E, Hubiche T, et al. Propranolol for severe hemangiomas of infancy. *New Engl J Med*. 2008;358:2649–2651.
63. Contis A, Gensous N, Viallard JF, et al. Efficacy and safety of propranolol for epistaxis in hereditary haemorrhagic telangiectasia: a retrospective, then prospective study, in a total of 21 patients. *Clin Otolaryngol*. 2017;42:911–917.
64. Mei-Zahav M, Blau H, Bruckheimer E, et al. Topical propranolol improves epistaxis in patients with hereditary hemorrhagic telangiectasia—a preliminary report. *J Otolaryngol Head Neck Surg*. 2017;46:58.
65. Toporsian M, Gros R, Kabir MG, et al. A role for endoglin in coupling eNOS activity and regulating vascular tone revealed in hereditary hemorrhagic telangiectasia. *Circ Res*. 2005;96:684–692.
66. de Gussem EM, Snijder RJ, Disch FJ, et al. The effect of N-acetylcysteine on epistaxis and quality of life in patients with HHT: a pilot study. *Rhinology*. 2009;47:85–88.
67. Reh DD, Hur K, Merlo CA. Efficacy of topical sesame/rose geranium oil compound in patients with hereditary hemorrhagic telangiectasia associated epistaxis. *Laryngoscope*. 2013;123:820–822.

Appendix

Search methodology with terms and related terms

1 epistaxis/dm, dt, pc, rt, su, th [Disease Management, Drug Therapy, Prevention, Radiotherapy, Surgery, Therapy] (2354)
2 Rendu Osler Weber disease/ (4508)
3 (hereditary hemorrhagic telangiectasia or hereditary haemorrhagic telangiectasia).tw. (2685)
4 Rendu Osler Weber.tw. (544)
5 2 or 3 or 4 (4745)
6 1 and 5 (297)
7 Rendu Osler Weber disease/dm, dt, pc, rt, su, th [Disease Management, Drug Therapy, Prevention, Radiotherapy, Surgery, Therapy] (609)
8 epistaxis/ (17407)
9 epistaxis.tw. (7658)
10 8 or 9 (18603)
11 7 and 10 (296)
12 6 or 11 (448)
13 *Rendu Osler Weber disease/ and *epistaxis/ (377)
14 Rendu Osler Weber disease/ and epistaxis/ (1231)
15 (hereditary hemorrhagic telangiectasia or hereditary haemorrhagic telangiectasia or Rendu Osler Weber).tw. (3010)
16 epistaxis.tw. (7658)
17 14 and 15 and 16 (654)
18 13 or 17 (787)
19 exp therapy/ (7349761)
20 exp drug therapy/ (2361080)
21 exp "administration of drugs, food and chemicals"/ (2194646)
22 exp surgery/ (4146522)
23 ((therap* or treat* or drug* or surg* or operat*) adj5 (epistaxis or hereditary hemorrhagic telangiectasia or hereditary haemorrhagic telangiectasia or Rendu Osler Weber)).tw. (1428)
24 19 or 20 or 21 or 22 or 23 (10547641)
25 18 and 24 (577)
26 12 or 25 (776)
27 limit 26 to english language (633)
28 limit 27 to human (588)
29 limit 27 to animals (3)
30 27 not 29 (630)
31 28 or 30 (630)
32 remove duplicates from 31 (606)
33 limit 32 to embase (271)