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Title:

Managing Epistaxis in Hereditary Hemorrhagic Telangiectasia (HHT): A Comprehensive Narrative Review of Therapeutic Horizons

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Abstract:

Introduction:

Hereditary Hemorrhagic Telangiectasia (HHT) is an autosomal dominant vascular disorder characterized by mucocutaneous telangiectasia, leading to recurrent epistaxis in nearly all affected individuals. Treatment strategies are broadly categorized into conservative, medical, and surgical approaches.

Objective:

To provide a concise summary of the existing literature on epistaxis associated with HHT.

Methods:

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The MEDLINE/PubMed database was searched for relevant articles using the keywords HHT, Osler-Weber-Rendu, and epistaxis.

Results:

Out of 93 reviewed articles, 59 contained pertinent information. Interventions are categorized into self-delivered therapy, intravenous treatment, in-office procedures, and surgical intervention.

Conclusion:

A stepwise approach is essential. Topical oils can be efficient, and intranasal Bevacizumab injection shows promise. However, more data is needed. Surgical options range from bipolar cautery and laser therapy to complete closure of the nasal cavity. Proper patient selection remains crucial.

Keywords:

Hereditary Hemorrhagic Telangiectasia, Osler-Weber-Rendu, epistaxis, hemostasis.

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Introduction:

Hereditary Hemorrhagic Telangiectasis (HHT) is an autosomal dominant vascular disorder with incomplete penetrance. It is characterized by mucocutaneous telangiectasis. Involvement of the nasal lining leads to recurrent treatment-resistant nose bleeds. Additional diagnostic criteria include; disease in a first-degree relative and visceral Arterio-Venous Malformations (AVMs)[1]. The Curacao criteria are summarized in Table 1[2]. When the clinical picture is incomplete, identification of a heterozygous pathogenic variant in *ACVRL1, ENG, GDF2*, and *SMAD4* genes is diagnostic[3].

The highest prevalence, 1 in 1331, is seen in the Afro-Caribbean residents of the Netherlands Antilles[4]. The prevalence in North America, Europe, and Japan ranges between 1 in 5000-10 000 [1,5–7].

Almost all patients will suffer from epistaxis during their lifespan and more than half will do so before the age of 20[4,8,9]. The recurrent nose bleeds will lead eventually to anemia with a significant increase in medical cost and a decrease in Quality Of Life (QOL)[3,10]. A strong correlation was found between age and poor QOL highlighting the increasing burden of the disease over time[10].

Since its description by Osler[11], Weber[12], and Rendu[13] more than a hundred years ago, a myriad of HHT-related epistaxis (HRE) management strategies has been reported. In the acute setting the ABC approach should be implemented and packing with resorbable material is preferred[3]. This article aims to review and summarize the recent literature.

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Methods:

We thoroughly searched MEDLINE/PubMed to identify relevant articles published in the last 15 years. Keywords included: HHT, Osler-Weber-Rendu, and epistaxis. Abstracts were reviewed and those focusing on epistaxis management were selected.

Overall, 59 articles were examined in depth by 2 reviewers independently. The pertinent findings are summarized in this article.

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Self-delivered therapy:

Droege et al. published a survey about self-packing. Out of the 588 responders, almost two-thirds self-performed nasal packing, 52% of them used medical packing, and the rest only tissues. The highest score on the Glasgow Benefit Inventory was achieved when using a pneumatic packing device despite being more painful[14].

Since turbulent airflow is believed to be traumatic to the telangiectasis, reversible nasal occlusion is considered when other therapy fails. Woolford et al. reported on 3 patients with recalcitrant epistaxis that decreased significantly after using a Silastic nasal obturator. While they didn't specify how long the obturator was applied throughout the day, patients commented that they preferred to remove the obturator while eating to restore their sense of smell[15]. In a study, 20 patients undergoing laser therapy at regular intervals performed nasal occlusion with a hypoallergenic tape 5 hours a day. After 3 months, the epistaxis severity scores (ESS) decreased by 1.16 points and hemoglobin remained stable[16].

When 20 patients were prescribed sesame/rose geranium oil topical compound for a minimal duration of 3 months, ESS decreased by 1.81 ($P < 0.0001$). Although the mechanism of action is not quite clear, the benefit seems to be coming from the combination of nasal hydration and the formation of a durable protective layer[17].

Bevacizumab spray didn't show superiority to placebo in a Meta-analysis of 3 RCTs[18].

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In an RCT, intranasal Tranexamic acid (TXA) and estriol showed no decrease in epistaxis frequency or duration. All groups, including placebo, improved the ESS at weeks 12 and 24[19]. TXA stabilizes blood clots by inhibiting fibrinolysis. The mechanism of action of estriol is by inducing squamous metaplasia[19].

Tacrolimus exhibits anti-angiogenic properties by targeting the BMP9/ALK1/ENG/SMAD pathway[20]. In a study, 50 patients were randomized for treatment with 0.1g intranasally of 0.1% Tacrolimus twice a day vs. placebo for 6 weeks. No significant difference in epistaxis duration and frequency was found 6 weeks after cessation of therapy. However, during treatment, this difference was significant. Since the toxicity of topical Tacrolimus is not known, the authors didn't recommend a longer treatment duration to maintain the observed benefit[20].

De Jel et al. reported their experience with topical 5-FU, known for its ability to promote the formation of scar tissue. 6 patients with HRE were treated on the side that bleeds the most with a 4.5 cm nasal tampon with 1 cc of 50 mg/g 5-FU and 1 cc of normal saline. The same protocol was repeated once a week for 4 weeks. After treatment, there was a significant improvement in nasal mucosa score as described by Mahoney et al., ESS, and Hb levels. No significant side effects were reported. The patient described a bad smell and dry sensation in the throat at the end of the treatment. The study did not include a control arm[21].

Non-selective beta blockers, namely propranolol, are used routinely to treat infantile hemangiomas. The possible mechanisms of action include both vasoconstrictive and antiangiogenic effects by reducing vascular endothelial growth factor (VEGF) stimulated angiogenesis[22]. In an RCT, twice daily Propranolol nasal gel showed superiority to placebo after 8

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weeks of treatment. In the treatment group (10 participants), ESS decreased from a mean of 6.50 ± 1.84 to 4.47 ± 1.75, p = 0.004, Hb numbers increased significantly and transfusion requirements decreased. None of these parameters changed significantly in the placebo group (10 participants). This period was followed by an open-label 8-week study, where 7 participants from the treatment group and 8 from the placebo group used propranolol gel twice daily for an additional 8 weeks. The beneficial effect was preserved in the previously treated group and the ESS score improved significantly in the former placebo group (−1.99 ± 1.41, p = 0.005). No systemic side effects were observed. The most common side effect was a burning sensation that decreased with continued treatment[22]. Thermosensitive intranasal timolol (0.1%) gel for 8 weeks did not show definitive superiority to placebo. ESS and quality of life improved in both groups. The authors concluded that the use of a thermosensitive gel with or without Timolol is appropriate for patients with HHT[23]. Dupuis-Girod et al used timolol spray and found no significant difference between treatment and control groups[24].

In a randomized, double-blind, placebo-controlled, cross-over Phase IIIB study involving 22 patients, the effects of 1 gram of tranexamic acid administered three times daily were compared to a placebo over a period of 6 months. Despite the treatment, hemoglobin levels remained statistically unchanged. However, a significant 54% reduction in epistaxis was observed. It is important to note that the treatment effect was heterogenous, and the distribution of epistaxis scores was notably skewed[25] In a similar study with 118 patients, tranexamic acid led to a 17.3% reduction in the duration of epistaxis, though there was no significant change in the frequency of epistaxis compared to placebo[26]. A 2019 Meta-Analysis found no statistically significant difference between TXA and placebo[18].

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Oral Estrogen for 3 months showed no improvement in HRE frequency or duration[18].

Antiestrogen agents are used in HHT patients because it is believed that estrogen, when binding to its receptors, triggers the formation of blood vessels. Blocking this interaction aims to halt or reverse the formation of telangiectasis. In a Double-Blind Placebo-Controlled Clinical Trial aiming to investigate the effectiveness of tamoxifen in treating HRE, twenty-five patients were randomly assigned to receive tamoxifen 20 mg daily or a placebo for 6 months. Based on the grading system suggested by Bergler et al.[27] tamoxifen was significantly more effective in reducing the frequency (p=.01) and severity (p=.049) of epistaxis compared to the placebo. Additionally, tamoxifen led to a non-significant increase in hemoglobin levels in some patients. One patient in the treatment arm developed an ovarian cyst that resolved spontaneously[28].

Contis et al. reported on their experience with systemic Propranolol. The study included a retrospective group of 10 patients already on Propranolol for cardiac or neurologic reasons and another prospective group of 11 patients. In the former group, ESS significantly decreased from a median of 8.3 [7.98–9.44] to 4.5 [4.31–6.61] (P=0.003) with a median duration of treatment of 16.5 months [12–22.75]. In the latter group, with a dose of 40 mg twice daily, the median cumulative duration of epistaxis per month was reduced from 2.8 h [2.28–7.56] to 0.71 h [0.27–3.76] after 3 months of treatment (P<0.0001). The median number of epistaxis episodes per month decreased from 27 [15–56] to 14.5 episodes/month [8–27] (P<0.0001) at 3 months and the median number of days without epistaxis per month increased from 9 days [5–18] to 17 days [11.5–23.5] after 3 months of treatment (P=0.01). The ESS is not reported in the prospective group[29].

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Oral Itraconazole, an antifungal drug with inhibiting effects on VEGF, 200 mg daily for 16 weeks, significantly decreased ESS and monthly epistaxis frequency. However, Hb levels did not significantly change. 4 out of 21 patients prematurely interrupted the study, 3 of them for mild or moderate side effects[30].

Intravenous treatment:

The pathogenic effects of HHT are largely driven by VEGF. Research has shown that normalizing VEGF levels can effectively prevent AVMs in mice lacking Acvrl1[31]. Consequently, Bevacizumab, a monoclonal antibody that blocks VEGF signaling, has become a promising therapeutic candidate[32]. The InHIBIT-bleed international multicenter study evaluated the efficacy of intravenous Bevacizumab on HRE and GI bleed. 143 patients were included in the epistaxis analysis. Mean ESS decreased by 3.37 points after treatment and clinically meaningful reduction in epistaxis, defined as an ESS decrease of ≥0.71 post-treatment, was achieved in 92% of patients. The reduction was noticeable after 3 months of treatment. Mean hemoglobin increased and the need for transfusion decreased after treatment. However, this is the effect of a combined reduction in epistaxis and GI bleeding. Overall, 12(5%) of patients discontinued Bevacizumab because of adverse events[33]. Adverse effects of bevacizumab may include hypertension, proteinuria, venous thromboembolism, intestinal perforation, and poor wound healing. Paradoxically, Bevacizumab is associated with a significant risk of epistaxis in non HHT patients[32].

A cost-effectiveness analysis of systemic bevacizumab therapy in HHT found that, regardless of willingness to pay, the addition of long term IV bevacizumab to the current standard of care

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improves the quality-adjusted life expectancy of patients with HHT and appears to be a cost-saving intervention, compared with the current standard of care alone[34].

The Dutch HHT expertise center evaluated to efficacy of Tacrolimus on HRE. 25 patients received 1 mg of Tacrolimus a day for 20 weeks. The daily dose was adjusted for a trough level between 2 and 3 µg/L. 2 patients did not continue the study due to serious side effects and 2 due to non-serious side effects. ESS, duration, and severity of epistaxis decreased significantly, especially in the group with no GI bleeding. Hb levels did not change significantly in patients with epistaxis or GI bleeding alone[35].

Pazopanib, a highly selective VEGF receptor inhibitor, dramatically improved epistaxis in a patient with HRE not responding to multiple courses of IV Bevacizumab[36].

In-office procedures:

Multiple regimens of submucosal Bevacizumab injections have been suggested, most ranging between 25-100 mg. In an RCT on 15 patients (9 treatment arm, 6 placebo arm) receiving a single injection of 100 mg submucosal Bevacizumab, there was a trend at 3 months towards better Visual Analogue Scale scores, ESS and a decrease in daily minutes of epistaxis. None of these changes reached statistical significance when compared to placebo. The study was underpowered since the required number of participants, in theory, cannot be reached in practice. Side effects(number of events) included high blood pressure(1), rhinitis(1), 3 days of whole body tingling(1), and nasal tip itching(1)[37]. Another recent RCT compared Bevacizumab to saline injections in patients undergoing surgical cauterization for HRE. The minimal clinically important difference (MCID) of the ESS was set at 0.71. 37 patients were included, all received a single

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injection. The additive benefit of bevacizumab over saline exceeded the MCID at 1, 2, and 4 months, but the difference was not statistically significant[38]. Karnezis et al. published efficacy data on 10 patients receiving 100 mg submucosal and 5 patients with both submucosal and intranasal bevacizumab. 12 of them were treated concurrently with KTP laser. After a mean period of follow-up of 4.1 months (range=1.15–19.15), ESS decreased from 7.0 (SD =2.1) to 2.9 (SD = 1.7), $p<0.0001$[39]. The same group reported safety data showing that combined treatment of the cartilaginous septum with Bevacizumab injections and laser therapy results in high rates of septal perforation[40]. A recent Meta-analysis of 7 studies [nasal spray (3); intranasal injection only (3); intranasal injection + laser (1)] showed improvement in ESS [WMD = −0.22,95%CI (−0.38, −0.05), p = .01]. There was no significant effect on epistaxis duration and frequency[41].

In a recent systematic review totaling 196 patients, sclerotherapy led to improvement in HRE in all of the 7 included studies. 3/7 reported outcome on an ESS scale, 3/7 used the Bergler-Sadick scale, and 1/7 through subjective surveys. This heterogeneity in reporting outcomes precluded formal meta-analysis[42]. In a retrospective chart review of 36 adults and 153 treatment sessions, no postprocedural visual loss, deep venous thrombosis/pulmonary embolus, transient ischemic attack/stroke, or anaphylaxis were encountered. Reported complications included per-procedure bleeding, mostly mild, and some postinjection nasal, cheek, and eye pain. Less frequent complications include nasal congestion, sneezing, and vasovagal responses[43].

Surgical intervention:

Ghaheri et al. described their experience with bipolar electrocautery. Over 8 years, 42 bipolar procedures were performed over 18 patients. The laser was used as an adjunct in 22 procedures.

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9 patients required more than one intervention. The average time interval to follow-up surgery was 7.5 months. No septal perforation or synechia were noted[44].

In a systematic review in 2020 with a total of 362 patients, Argon and Nd: YAG laser therapy was around 90% effective in reducing HRE frequency and severity. Nd: YAG seems to be more efficient for severe epistaxis than Argon. Diode laser therapy was significantly inferior with a 71.1% success rate[45].No post-operative complications were described with these 3 laser types[46–48].

In an RCT, coblation and KTP laser were found to be equally effective in controlling HRE. Nasal obstruction VAS scores were significantly lower in the coblation group[49]. Rotenberg et al. had equally good results in 37 patients they treated with coblation over 3 years. 3 of their patients suffered from a septal perforation. They all had multiple septal cauterizations in the past[50]. In a case series of 5 patients, hemostasis was found to be difficult to achieve with coblation in a patient with severe disease[51].

For severe refractory disease, septodermoplasty is an option. It has the advantage of replacing a large area of diseased mucosa. Telangiectasias can re-grow on the skin graft[9]. However, the need for laser therapy after septodermoplasty decreased significantly, from (1.83 [±1.99]) to (0.78 [±0.85]), in a study spanning over 60 months[52]. To balance the risks of septal perforation, increased crusting, decreased cessation of airflow, loss of olfaction, and the precipitation of atrophic rhinitis, Harvey et al. felt like a septodermoplasty is suitable for patients with less than 6 months of epistaxis control after three laser treatments[52].

Super-selective embolization of branches of the external carotid artery achieved immediate hemostasis in 12/14 patients with refractory HRE. 11/12 patients available for the 24 months

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follow-up reported reduction in frequency and severity of epistaxis[53]. Compared to idiopathic epistaxis, HRE requires multiple endovascular and surgical treatments over time[54].

In a study by Dabiri et al. where bilateral endonasal cauterization of branches of the sphenopalatine, anterior, and posterior ethmoids was performed, ESS decreased by > 50% in 4/5 participants at 9 months. The one patient that did not fall into this category had the posterior ethmoid cauterized only on one side because of a CSF leak. The contralateral artery was shown to be involved in the epistaxis at pre-operative angiography. 1/5 patients maintained a more than 50% reduction of ESS 12 months after the surgery. All patients had embolization of the SPA before the surgical intervention[55].

43 patients with severe intractable HRE underwent surgical nasal closure [38 bilateral; 5 unilateral (patient's choice)]. 7 patients were lost to follow up. 30/36 experienced a complete cessation of epistaxis. 5 patients experienced minor posterior epistaxis. Post-operative Hb data was available for 16 patients. There was an average increase of 4.68 g/dl. 36/36 patients reported feeling better after the surgery and that they would rather have the side effects of Young's procedure (xerostomia, anosmia, or decreased taste) than epistaxis[56]. Another article examined the outcome of surgical nasal closure in 100 patients (87 bilateral, 13 unilateral). Ten patients developed small pinholes that led to bleeding. These were managed successfully with primary closure and nasolabial flap (2 patients). Two cases were less successful, one due to prior radiotherapy and surgery for basal cell carcinoma of the external nose. Postoperative follow-up ranged from 6 months to 22 years, with a mean of 8.4 years. Of the 87 patients who underwent bilateral closure, 79 (91%) achieved complete cessation of bleeding. Epistaxis score as proposed by Al-Deen at al.[57] was available for 50 of the patients who underwent bilateral closure. It dropped

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from a mean of 9.42 pre-operatively to 0.54 post-operatively, with a high effect size indicating substantial improvement. Common postoperative complaints included decreased sense of smell and taste (40%), fatigue (14%), sleep disturbances (12%), and ear fullness (10%). Nasal obstruction was less common (14%), and some patients required additional treatments for mouth dryness (10%). 12% mentioned embarrassment even though the closure was not usually visible. Every patient interviewed indicated that they would choose to undergo the procedure again and would recommend it to others in similar situations[58].

In a case report, a patient had an epistaxis episode despite Young's procedure. Even with bilateral embolization hemostasis could not be achieved. Reversal of the Young's procedure had to be performed so traditional packing could be done[59].

- HHT is a genetic vascular disorder with recurrent epistaxis, anemia, and decreased quality of life, prevalent in Afro-Caribbean populations of the Netherlands Antilles.
- The Curacao criteria are essential for diagnosis.
- Self-treatments like nasal packing, occlusion, and topical oils vary in success; Bevacizumab and intranasal TXA sprays are less effective.
- Submucosal Bevacizumab injections are a promising, minimally invasive option for managing epistaxis, balancing efficacy with manageable side effects. Further research is needed.

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- Intravenous Bevacizumab and Tacrolimus improve epistaxis and hemoglobin levels; Pazopanib shows dramatic improvement in refractory cases.
- Effective surgical interventions include laser therapies, coblation, septodermoplasty, super-selective embolization, and bilateral nasal closure, with laser therapy most recommended.

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Conclusion:

Almost all patients with HHT will suffer from epistaxis that could range from mild to severe life-threatening. The disease is progressive, hence the importance of a step-wise approach. Simple measures like topical oils can be efficient. More disease-specific medical therapy like Bevacizumab injections offers a great balance between efficiency, ease of access, and side effects. However, data in the literature is limited due to the rare nature of the disease. When surgical intervention is indicated, the consensus in the literature is to rely on laser therapy although bipolar cautery is a reasonable option. As a last resort, surgical closure of the nasal cavity is a highly efficient treatment accepted by a carefully selected group of patients.

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Criteria	
Epistaxis	spontaneous, recurrent nose bleeds
Telangiectasis	multiple, at characteristic sites:
	Lips, oral cavity, fingers, nose
Visceral lesions	Gastrointestinal telangiectasia (with or without bleeding)
	Pulmonary AVM
	Hepatic AVM
	Cerebral AVMs
	Spinal AVM
Family history	a first degree relative with HHT according to these criteria
Diagnosis	
Definite	3 criteria are present
Possible or suspected	2 criteria are present
Unlikely	if fewer than 2 criteria are present

Table 1. The Curaçao Diagnostic Criteria for HHT.
HHT: Hereditary Hemorrhagic Telangiectasia
AVM: Arterio-Venous Malformation

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