

An Epistaxis Severity Score for Hereditary Hemorrhagic Telangiectasia

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Objectives/Hypothesis: Hereditary hemorrhagic telangiectasia (HHT)-related epistaxis leads to alterations in social functioning and quality of life. Although more than 95% experience epistaxis, there is considerable variability of severity. Because no standardized method exists to measure epistaxis severity, the purpose of this study was to determine factors associated with patient-reported severity to develop a severity score.

Study Design: Prospective, survey-based study.

Methods: HHT care providers and a focus group of patients were interviewed to determine epistaxis-associated factors. From this, an electronic survey was developed and administered to patients with HHT. Descriptive analyses were performed with calculations of means and medians for continuous and proportions for categorical variables. Multiple ordinal logistic and linear regression models were developed to determine risk factors for epistaxis severity.

Results: Nine hundred respondents from 21 countries were included. Eight hundred fifty-five (95%) subjects reported epistaxis. The mean (standard deviation) age was 52.1 (13.9) years, and 61.4% were female. Independently associated risk factors for self-reported epistaxis severity included epistaxis frequency (odds ratio [OR] 1.57), duration (OR 2.17), intensity (OR 2.45), need for transfusion (OR 2.74), anemia (OR 1.44), and aggressiveness of treatment required (OR 1.53, $P < .001$ for all).

Conclusions: Risk factors for increasing epistaxis severity in patients with HHT include frequency, duration, and intensity of episodes; invasive-

ness of prior therapy required to stop epistaxis; anemia; and the need for blood transfusion. From these factors, an epistaxis severity score will be presented.

Key Words: Epistaxis, hereditary hemorrhagic telangiectasia, Osler-Rendu-Weber severity score.

Level of Evidence: 1b.

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INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disease characterized by epistaxis, telangiectases, and visceral arteriovenous malformations that has nearly 100% penetrance by age 40 years. As this disease afflicts an estimated one in 10,000 to 15,000 individuals,¹ it represents a significant health burden. Epistaxis related to HHT is a major complaint in up to 90% of patients with HHT,² and has a significantly negative impact on quality of life.^{3,4}

Many studies^{5–7} have described methods of assessing epistaxis severity (Table I), although none have directly addressed the validity of the scoring system itself. These instruments share several factors, such as epistaxis frequency measured as number of bleeds per unit time as well as the need for blood transfusions specifically related to epistaxis. Similarly, duration of bleeding episodes, intensity, and changes in quality of life have served as factors to calculate epistaxis severity. Al-Deen and Bachmann-Harildstad⁷ published a study in which experts in the field of HHT-related epistaxis were polled as to their impressions of factors that best correlated with epistaxis severity. They determined that a need for blood transfusions, ease of comprehension by both patients and care providers, and frequency of bleeds were the most important factors to calculate severity of bleeding in this patient population.

Although HHT care providers have extensive experience treating epistaxis in these complex patients, and individual HHT centers of excellence utilize their particular systems for grading epistaxis severity, there has been resistance to adopt any particular severity scoring system as a universal, standardized system. Some of this resistance may be due to particular care providers' comfort with their own systems. Another possible reason

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TABLE I.

Summary of HHT-Related Epistaxis Factors Used to Assess Overall Severity Published in the Literature.⁵⁻⁷

Frequency
Duration
Intensity
Need for blood transfusion
Anemia and/or iron replacement therapy
Quality of life
Patient satisfaction with therapy
Duration of therapeutic effect
Side effects of therapy

See also online supplemental references.

for not adopting a single system of grading may stem from a lack of statistical support for any given system.

Several lines of evidence support the need for a standardized severity scoring system in HHT. First, in an informal survey of 100 patients with HHT (Terry 2007, unpublished data), epistaxis was the primary issue that the patients wanted improvement in therapy. Second, the Scientific Medical Advisory Board (SMAB) of the HHT Foundation International, Inc. came to the conclusion that epistaxis treatment is the highest priority for future research. Finally, the SMAB issued a consensus statement from the recent International HHT Clinical Guidelines Conference⁸ that there is insufficient evidence on how to measure the severity of HHT-related epistaxis.

Therefore, the purpose of this investigation was to determine factors associated with epistaxis severity, and to utilize these factors to develop a standardized, validated epistaxis severity score (ESS).

MATERIALS AND METHODS

This study was approved by the institutional review boards of both Johns Hopkins University School of Medicine and Drexel University College of Medicine.

Development of Survey

A comprehensive list of covariates including demographics and clinical characteristics related to epistaxis severity was obtained through discussions with care providers from HHT centers of excellence, informal discussions with HHT patients, and review of previously published studies utilizing measures of epistaxis severity. From this comprehensive list, a cross-sectional survey was developed that utilized 120 questions to gather demographic information, disease specific data, and treatments received for epistaxis. The survey also contained 19 open-ended questions to allow for more detailed responses and clarifications by the participants.

Only respondents with HHT were included in the analysis. Diagnosis of HHT was determined using the Curaçao Criteria,⁹ in which subjects with three or four criteria have a definite diagnosis. In those patients with two criteria (possible HHT), specific survey responses and open-ended questions were evaluated for potentially omitted diagnostic criteria. From these 253 respondents, more than 90% had other corroborating evidence for the diagnosis of HHT and were thus included in the analysis of factors correlating to epistaxis severity. Table II describes the diagnostic criteria to support HHT in the subject cohort.

Subject Recruitment

The survey was compiled and distributed using an internet-based tool (SurveyMonkey, www.surveymonkey.com). Subjects were recruited from the membership registry of the HHT Foundation International, Inc. through an email blast advertisement of the project and through posting of the survey on the HHT Foundation International, Inc.'s website (www.HHT.org). The survey was anonymous and deidentified. Imbedded in the survey were questions to confirm the diagnosis of HHT by the Curaçao Criteria as described by Shovlin et al.⁹ Subjects were included in the analysis if they completed a series of mandatory response questions that included those used to confirm the diagnosis of HHT, information about epistaxis-related clinical factors, and treatments received for epistaxis.

Statistical Analysis

Data are presented as absolute numbers, percentages, and means (\pm standard deviation) where appropriate. A descriptive analysis was performed with calculation of mean and medians for continuous variables and percentages for categorical variables. Multiple ordered logistic regression models and linear regression models were constructed to evaluate the association between covariates and epistaxis severity. Analysis of variance and Fisher exact testing were used where appropriate. Values were considered statistically significant for $P < .05$. All statistical calculations were performed using STATA SE version 10 statistical software (STATA Corp., College Station, TX).

Validation

Internal validation was performed through bootstrapping methods.¹⁰ External validation was performed by comparing ESS calculations with invasiveness of treatment received for epistaxis. Treatments were divided into minimally invasive (topical or oral medications, nasal packing), moderately invasive (endoscopic procedures including laser therapy, electrocautery, argon plasma coagulation), and most invasive (Young's Procedure, septal dermoplasty, arterial ligation, or embolization).

RESULTS

Demographics and HHT Diagnostic Criteria

Nine hundred fifteen survey responses were collected for a 6-month period of time from March 2008 through August 2008. Fifteen subjects were excluded due to age outside the range approved by the

TABLE II.

Distribution of Study Subject Curaçao Criteria for Diagnosis of HHT and Specific Factors Leading to Diagnosis.

Description of HHT Criteria	No.	%
Curaçao Criteria		
4	229	25.7
3	386	43.4
2	253	28.4
1	21	2.4
Epistaxis	855	98.5
Visceral AVMs (diagnosed)	505	58.1
Family history	763	87.9
Telangiectasia	382	44.0

HHT = hereditary hemorrhagic telangiectasia; AVMS = arteriovenous malformations.

TABLE III.
Demographic Data of Respondents.

Descriptions of Respondents	No. (%)
No.	894
Gender	
Female	561 (61.4)
Male	353 (38.6)
Age, yr	
Diagnosis	32.0±16
Current	52.6±13.9
Location of respondents	
North America	813 (89)
Europe	46 (5)
Australia	37 (4)
Asia	9 (1)
South America	7 (0.8)
Africa	2 (0.2)

institutional review board protocol (age <18 or >89). Table III shows the demographic data of the cohort of respondents. The average age of the cohort was 52.6 (±13.9) years, and there were more female respondents (61.4%) than male. Most of the respondents from this cohort were from North America, with approximately 80% from the United States, reflecting the membership of the HHT Foundation International, Inc.

Descriptive Distribution of Epistaxis-Related Factors

Approximately 45% of the cohort self-reported epistaxis severity in the moderate range, with 29.9% self-classifying above and 26.2% below (Fig. 1). Factors leading to particular self-classification were similar to factors previously described in the literature as being important predictors of epistaxis. Epistaxis episode duration ranged from <1 minute to >30 minutes, with a mean duration of about 6 to 15 minutes of bleeding per epistaxis episode. There was considerable variability in the frequency of epistaxis episodes ranging from several per day to more than a month between episodes of bleeding. Of the patients, 13.7% described their epistaxis

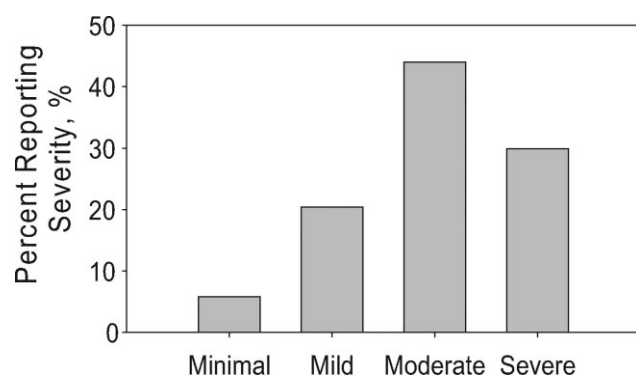


Fig. 1. Self-reported epistaxis severity and general factors leading to severity characterization.

TABLE IV.
Correlation of Factors With Self-Reported Severity of Epistaxis.

Variable	Coefficient	SE	P Value
Intensity	0.25	0.07	<.001
Frequency	0.14	0.02	<.001
Duration	0.25	0.02	<.001
Need for medical attention	0.30	0.07	<.001
Transfusion related to epistaxis	0.31	0.07	<.001
Anemia	0.20	0.06	.001

SE = standard error.

intensity as either gushing or pouring. Of notable interest, 17.5% of this cohort had never sought medical attention related specifically to epistaxis. Furthermore, more than 30% of respondents had never seen an otolaryngologist, suggesting that a significant percentage of these individuals are seeking epistaxis therapy from other types of care providers. Of the study subjects, 59.8% reported a prior history of anemia, whereas 35.9% reported anemia at the time of the survey. Red cell transfusions were also common, with 26.6% receiving a blood transfusion related to blood loss from epistaxis at some point in life; however, only 22.6% of study subjects knew their current hemoglobin (9.9 ± 2.1 mg/dL; range, 3.5–16.5).

Epistaxis Severity Score

Six factors were independent predictors of self-described epistaxis severity (Table IV). Using these six predictors of epistaxis severity, we developed an ESS (Table V). The responses are weighted by respective

TABLE V.
Data Sheet for the Calculation of the Epistaxis Severity Score for Hereditary Hemorrhagic Telangiectasia.

How often do you TYPICALLY have nose bleeding? (coefficient 0.14)	
0 — Less than monthly	3 — Several per week
1 — Once per month	4 — Once per day
2 — Once per week	5 — Several each day
How long do your TYPICAL nose bleeds last? (coefficient 0.25)	
0 — <1 minute	3 — 16–30 minutes
1 — 1–5 minutes	4 — >30 minutes
2 — 6–15 minutes	
How would you describe your TYPICAL nose bleeding intensity? (coefficient 0.25)	
0 — Not typically gushing	1 — Typically gushing or pouring
Have you every sought medical attention for nose bleeding? (coefficient 0.30)	
0 — No	1 — Yes
Are you anemic (low blood count) currently? (coefficient 0.20)	
0 — No	1 — Yes
Have you ever received a red blood cell transfusion specifically because of nose bleeding? (coefficient 0.31)	
0 — No	1 — Yes

Six questions are answered, the number of the response is multiplied by the respective coefficient, and the sum of these gives the raw epistaxis severity score.

Question	Response	Multiplied by:		Coefficient	Result
1	Less than monthly	0	x	0.14 (0.70 Den)	
	Once per month	1			
	Once per week	2			
	Several per week	3			
	Once per day	4			
	Several per day	5			
2	< 1 minute	0	x	0.25 (1.00 Den)	
	1-5 minutes	1			
	6-15 minutes	2			
	16-30 minutes	3			
	> 30 minutes	4			
3	No	0	x	0.25	
	Yes	1		(0.25 Den)	
4	No	0	x	0.30	
	Yes	1		(0.30 Den)	
5	No	0	x	0.20	
	Yes	1		(0.20 Den)	
6	No	0	x	0.31	
	Yes	1		(0.31 Den)	
TOTAL =				Denominator (Sum Den)	Raw Score

Fig. 2. Calculation of the raw and normalized epistaxis severity score (ESS). The responses to each of the six questions are assigned a weighted integer that is multiplied by the question's coefficient. These are added to yield the raw score. The raw score is then normalized by dividing the raw score by the maximum possible score (2.71), then multiplied by 10 to give the normalized ESS. HHT = hereditary hemorrhagic telangiectasia.

$$\text{Normalized HHT-ESS} = \left[\frac{\text{Raw Score}}{\text{Denominator (2.71)}} \right] \times 10$$

coefficients from the model, and these are added together yielding a raw ESS. This is then divided by the range of the raw score (2.71) and multiplied by 10 to give the normalized ESS within a range of 0 (no epistaxis) to 10 (most severe epistaxis) (Fig. 2).

Validation of the ESS

Bootstrapping resampling using 1,000 replications was performed to obtain variance of the independent predictor variables in the final ESS model to ensure internal model validation.¹⁰ The standard errors of the predictor variables presented in the final ESS are those obtained through bootstrapping resampling. Logistic regression models were also fit to evaluate the association between ESS and prior invasiveness of treatment for epistaxis as a means of external validation. The ESS was found to be a significant predictor of invasiveness of treatment (Fig. 3), as patients with higher ESS had a much greater risk of requiring surgical procedures for epistaxis (odds ratio, 1.61; 95% confidence interval, 1.46-1.78).

DISCUSSION

This is the first paper to propose a statistically validated ESS based on a comprehensive survey of a large cohort of HHT patients. Through review of a comprehensive list of possible related factors derived from information obtained from otolaryngologists with extensive experience with HHT, non-ear, nose, and throat HHT center of excellence care providers, and patients

with HHT, we were able to identify six factors with the highest correlation to epistaxis severity. The resulting ESS questionnaire is easy to administer and comprehend, and it should provide an effective tool in assessing epistaxis severity.

We sought to develop a scoring system that can be administered by either care providers or self-administered by patients. The questions are easy to understand by both medical and lay persons. Because of this it may serve as an adjunct for therapeutic algorithms. Treating physicians may utilize the questionnaire or individual

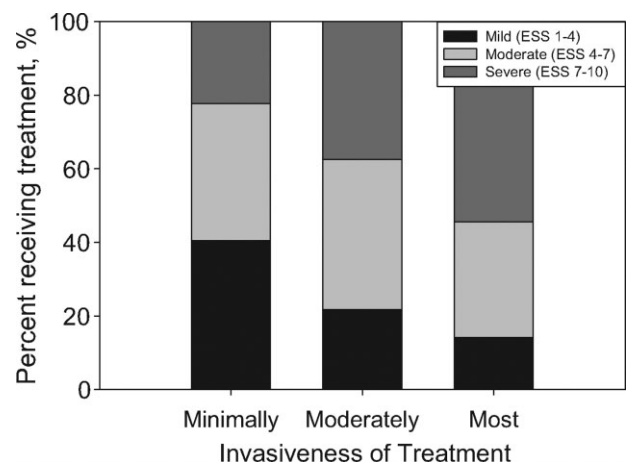


Fig. 3. Correlation between invasiveness of therapy and normalized epistaxis severity score (ESS). Trends were statistically significant ($P < .0001$; Fisher exact test).

scores to gauge patient responses to various epistaxis therapies. This scoring system is not meant to supplant expert evaluation; however, as we demonstrated in this survey, a significant number of HHT patients are not seeing experienced otolaryngologists (40%). Many of these patients are frequently visiting emergency rooms and primary care providers. Such a score may help to identify unrecognized epistaxis severity that should be referred to more appropriate providers. Second, this scoring system, through its ease of interpretation, may help patients to monitor their own symptoms with an objective measurement. Many patients with chronic disease have improved outcomes through utilization of patient-centered treatment aids.^{11,12} This may serve as a benchmark for epistaxis in this group of patients who have a lifetime of experience caring for the nasal bleeding complications of the illness.

Finally, this ESS fills an unmet need as an accurate, reproducible, and validated objective measure of epistaxis severity to be used to compare existing and new therapeutics. Several reports⁵⁻⁷ have utilized epistaxis severity scoring systems to assess treatment efficacy; however, they all suffer from an important limitation, a lack of systematic evaluation of validity of the score itself. Nevertheless, it is important to point out that our system was derived, in part, by the tremendous experience compiled by these earlier investigators. Very few randomized clinical trials have been performed in HHT, and moreover, almost no multicenter trials have been undertaken. Part of the inability to pool patients from multiple centers and conduct these necessary trials comes from the lack of standardized measurement tools for standardization among centers.

Al-Deen and Bachmann-Harildstad determined that ease of understanding for both care providers and patients, inclusion of transfusion needs, and association for a fixed time interval were important attributes of an epistaxis severity survey.⁷ Their proposed scoring scale shares measures of intensity, frequency, and transfusion needs, although their scale was not been systematically validated.

Despite the many strengths of this investigation, there are several limitations that warrant mentioning. First, data included in the project were derived from survey responses to an anonymous, deidentified survey. This adds potential misclassification of study subjects without disease. We believe that we overcame this limitation by targeting membership of the disease-specific foundation for inclusion and by using questions embedded into the questionnaire that accurately predict the diagnosis of HHT.¹³

Another piece of information that is lacking from this analysis stems from the cross-sectional nature of the data used to calculate the ESS. Future studies could collect data longitudinally from this patient group to determine measures such as minimum clinically relevant changes.

A possible criticism to this scoring system may center on the ease of calculation. With the inclusion of weighted factors, on-the-spot calculations may be difficult without a computer program or calculator. Although

this is a valid argument, as the ease of calculation is improved, the robust, statistically supported nature of this score is weakened. This score is analogous to other clinical scoring systems, like the lung allocation score, used for lung transplantation listing.¹⁴ Although a computerized method of calculating the score may be necessary, we believe the fear of using a labor-intensive system can be overcome with only six questions requiring single selection responses.

Finally, this ESS has not yet been correlated with existing grading of nasal telangiectases. Mahoney and Shapshay¹⁵ developed objective grading of nasal involvement of telangiectases, which described a range from small, punctuate telangiectases to confluent, large nasal arteriovenous malformations. Although this grading system did not correlate epistaxis severity with the particular lesions, there could be a linear correlation that could be corroborated with further analysis using this study's proposed ESS.

CONCLUSION

Through the evaluation of a comprehensive list of factors related to epistaxis severity in patients with hereditary hemorrhagic telangiectasia, we determined six factors associated with self-reported severity, including: frequency, duration, intensity, need for medical attention, anemia, and need for transfusion. By compiling responses to six questions focused on these factors, an ESS can be generated that is accurate and validated. This ESS can serve as a clinical and therapeutic outcome measure for epistaxis in HHT.

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