Hematology in the Adolescent Female

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Part I

Bleeding Disorders and Heavy Menstrual Bleeding

1 Evaluation of the Adolescent with Heavy Menstrual Bleeding

Ayesha Zia and May Lau

Introduction

Adolescence is a time of change, and this change is often reflected in their menstrual bleeding. Heavy menstrual bleeding (HMB) is common in adolescents [1]. In a large insurance claims database of more than 200,000 females aged 10–17 years in the United States, 27% had an outpatient diagnostic code consistent with HMB at least once during the study period [2]. The complaint of HMB is subjective. Beliefs derived from personal experience and cultural, social, and educational influences give rise to a sense of what constitutes "normal" blood loss during menses. HMB is qualitatively defined as blood loss that interferes with a woman's physical, social, emotional, and/or material quality of life, irrespective of the volume lost [3]. School absenteeism and interruption in sports or social activities frequently occur in adolescents with HMB [4]. Given the consequences of HMB, physicians and other healthcare providers should be able to evaluate an adolescent presenting with HMB competently.

Normal Menstruation and Terminologies

The median age of menarche is 12 years old, with a range of 10–15 years [5]. Typically menstrual cycles should occur every 21–45 days and last ≤7 days [6, 7]. Average blood loss during menses for an adolescent female is approximately 30–40 ml, which translates to six menstrual pads/tampons on the heaviest day of bleeding [8]. Many terms have been used to describe abnormal uterine bleeding. The International Federation of Gynecology and Obstetrics (FIGO) recommends against using terms such as menorrhagia, dysfunctional uterine bleeding, or hypermenorrhea [9]. Abnormal uterine bleeding is the umbrella term to describe menstrual bleeding that is abnormal with regard to frequency, volume, duration, and cycle regularity [9]. While blood loss of >80 mL is broadly used in clinical studies and trials to define HMB, this measurement (involving

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extracting hemoglobin from sanitary wear) is impractical outside of research settings; therefore, a requirement to change sanitary pads or tampons more often than hourly, clots at least 1 inch in diameter, and a low ferritin level are clinical predictors of heavy periods [10]. FIGO recommends that HMB in women be classified according to the PALM–COEIN system: polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not otherwise classified [11].

The Association of HMB and Bleeding Disorders

The frequency of bleeding disorders in the general population is approximately 1–2%, but bleeding disorders are found in about ~30% of adolescent girls who are referred for evaluation of HMB to a specialty [12]. Low von Willebrand factor (VWF) levels or von Willebrand disease (VWD) and platelet functional disorders (PFD) are the most common type of bleeding disorders encountered in adolescents [12]. Importantly, bleeding disorders coexist with anovulation and non-hemostatic disorders (Table 1.1). HMB confers a significantly lower perceived quality of life in terms of the ability to fully participate in school, work, and athletic and social activities [13]. It is, therefore, imperative that bleeding disorders resulting in HMB are diagnosed without delay. Additional key points in history taking and screening tools for HMB in adolescents that point toward an underlying bleeding disorder are discussed in Chap. 2.

Table 1.1 Frequency of non-hemostatic and concomitant disorders in adolescents with heavy menstrual bleeding

	Anovulatory HMB		Ovulatory HMB	
	BD (n = 31)	No BD (n = 69)	BD (n = 36)	No BD (n = 64)
PCOS	3	3	0	0
BJH[a]	3	7	6	4
Uterine structural ab.	1[f]	1[g]	3[h]	0
Systemic disorders	6[b]	10[c]	1[d]	4[e]
VWF exon 28 polym.	0	1	0	3

Table adapted from Zia et al. [12]
Ab. abnormalities, *BD* bleeding disorder, *PCOS* polycystic ovarian syndrome, *BJH* benign joint hypermobility, *polym.* polymorphism. [a]BJH assessment was performed only on 100 participants
No differences in the prevalence of bleeding disorders according to menstrual bleeding pattern (31% in anovulatory pattern bleeding vs. 36% ovulatory pattern bleeding; $p = 0.45$)
Systemic or medical disorders = [b]depression (n = 4), remote history of cancer (n = 1) and hypothyroidism (n = 1); [c]depression (n = 3), asthma requiring medications (n = 3), remote history of cancer (n = 3), hypothyroidism (n = 1); [d]one had juvenile rheumatoid arthritis; [e]depression (n = 1), diabetes mellitus (n = 2); celiac disease (n = 1)
Uterine structural abnormalities: [f]One had endometriosis; [g]one had erosive vaginitis from tampon use; [h]two were diagnosed with endometriosis, and one was diagnosed with uterine polyps

Laboratory Evaluation of the Adolescent with HMB: The Hematology Perspective

General Perspectives on Laboratory Evaluation of Bleeding Disorders The laboratory evaluation of an underlying bleeding disorder in an adolescent with HMB does not differ from the assessment in any patient presenting with unusual bruising or bleeding. Table 1.2 reviews the estimated sensitivity and specificity of various hemostasis assays in the evaluation of a bleeding phenotype. There are certain caveats specific to the testing approach in adolescents due to acute HMB and concomitant hormonal use that we will highlight below. There is no simple diagnostic strategy or testing algorithm that can adequately cover all possible bleeding disorders when the presenting complaint is HMB, but a proposed algorithm that the authors have used prospectively to diagnose bleeding disorders in HMB is covered elsewhere [14, 15]. As an educational book chapter, this work does not reflect a systematic review methodology but instead serves as an overview of laboratory evaluation of bleeding disorders in adolescents with HMB. While efforts

Table 1.2 Estimated sensitivities and specificities of hemostasis assays used to evaluate bleeding problems

	Estimated sensitivity (%)	Estimated specificity (%)
PTT	2.1	98
PT	1.0	>99
TT	1.0	86
Clauss fibrinogen	1.0	>99
VWD screen	6.7	>98
Light transmission aggregometry	26	96
Factor assays	Not reported	Not reported

Table adapted from Hayward and Moffat [37]. The estimated sensitivities and specificities reported in this table for a bleeding problem have not been tested specifically in the setting of HMB. PTT indicates partial thromboplastin time; *PT* prothrombin time, *TT* thrombin time, *VWD* von Willebrand disease

were taken to highlight pertinent evidence without bias, the interested reader is encouraged to conduct an additional review of the literature.

The initial laboratory evaluation of patients with a suspected bleeding disorder should include a complete blood count, a review of peripheral blood smear for platelet morphology, prothrombin time, partial thromboplastin time (PTT), and either fibrinogen or thrombin time [16]. These routine coagulation studies can suggest whether a severe coagulation factor deficiency or thrombocytopenia might be the reason for clinical bleeding but will neither rule in nor rule out VWD or PFD, the most common bleeding disorders encountered in adolescents with HMB. When using the PTT in the diagnosis of VWD, the results of this test are abnormal only if the coagulation factor (F) VIII is sufficiently reduced [17]. Some centers add a platelet function analyzer (PFA-100) assay to their initial laboratory screening tests to "loosely" screen for either VWD or PFD. A clinician, faced with an individual with a personal and family history of bleeding, should not use the results of a normal PFA-100 to influence his/her decision to undertake more specific laboratory testing. Thus, irrespective of an abnormal or normal PFA-100 result, VWF and platelet function testing are still warranted to assess the possibility of these disorders in patients with HMB; so in this context, the PFA-100 has a limited utility [18].

VWD Testing in HMB The laboratory diagnosis of VWD can be complicated. The initial tests commonly used to detect VWD or low VWF are determinations of plasma levels of (i) VWF:Antigen (Ag); (ii) VWF:Ristocetin Co-factor activity (RCo); and (iii) FVIII [17]. These three tests, readily available in most larger hospitals, measure the amount of VWF protein present in plasma (VWF:Ag), the function of the VWF protein that is present as VWF:RCo, and the ability of the VWF to serve as the carrier protein to maintain normal FVIII survival. New options for laboratory assessment of VWF activity include a new platelet-binding assay, the VWF:GPIbM, which is subject to less variability than VWF:RCo assay, and collagen-binding (CB) assays that provide insight into a different function of VWF. Because the VWF:RCo uses the nonphysiologic agonist ristocetin to bridge VWF and platelet glycoprotein (GP) Ibα, there is the potential for false results due to defects in VWF's ability to bind ristocetin. The most common of these is the p.D1472H variant, which affects ristocetin binding but not VWF function [19]. The VWF:GPIbM assay introduces gain-of-function mutations into GPIbα, allowing it to bind VWF spontaneously in vitro without the requirement for ristocetin [20]. The VWF:GPIbM allows higher precision, with a reported lower limit of detection of 2 IU/dL and a coefficient of variation of 5.6% [21]. There is a reasonable correlation between VWF:RCo and VWF:GPIbM results [20].

VWF also binds to exposed collagen at sites of injury, which requires specific testing. Collagen binding is dependent on the presence of high-molecular-weight VWF multimers [22]. There may be a dual role for collagen-binding assays in VWD diagnosis, to evaluate multimer status and to screen for a possible collagen-binding defect. Assays using either type I, type III, or a combination of the two will suffice to detect specific A3 domain collagen-binding variants [23]. Specific A1 binding defects are more common, although binding to types IV and VI collagen is rarely assessed in clinical practice [24]. Research from the Zimmerman Program, a large multicenter

US study on patients with all types of VWD, has shown a relatively high incidence of type IV and VI collagen-binding defects in patients with both type 1 (5%) and type 2 M VWD (27%) [24]. The presence of a collagen-binding variant was associated with an increased bleeding score compared with similar subjects without a collagen-binding defect in this cohort. Adolescents with HMB and other unexplained bleeding symptoms or a strong family history of HMB may benefit from collagen-binding testing to explore the possibility of an undiagnosed collagen-binding defect in VWF.

The increased availability and lower cost of genetic testing enable increased use in the diagnosis of VWD. An impediment to the routine use of genetic analysis for VWD is the weak correlation between VWF sequence variants and type 1 VWD, the most common VWD type. A large study of VWD subjects in the United States showed a relatively low rate of probably causative VWF variants in those subjects with VWF:Ag >30 IU/dL [25]. Genetic analysis is most useful in type 2 VWD. Genetic analysis either specifically for the p.D1472H variant or of VWF exon 28 is helpful when the VWF:RCo/VWF:Ag ratio is decreased in the setting of a normal multimer distribution. Sequencing can either verify that the low ratio is caused by p.D1472H or, in patients with suspected type 2 M VWD, reveal a causative variant [26].

VWF levels will increase in the setting of stress, inflammation, and illness and are often found to be quite elevated when measured in adolescents hospitalized for severe HMB [17]. Recent data suggest that VWF levels >100 IU/dL in the pediatric population may not need repeat testing to rule out the diagnosis of VWD [27]; however, a relatively small proportion (18%) of the included patient population in this study tested for VWD had HMB. Patients with blood group type O have VWF levels that are approximately 25% lower than non-O blood group individuals [28]; however, current guidelines recommend against using blood-type-specific reference values and suggest instead using either absolute cutoffs or population-based reference ranges in conjunction with personal and family history of bleeding in making a diagnosis of VWD [17, 29]. High-dose estrogen therapy also elevates VWF levels, but the influence of standard dose (30–35 mcg) estrogen is less clear and unlikely to affect the laboratory diagnosis of VWD. The majority of studies in healthy women who use standard dose combined hormonal contraceptives have shown no significant increase in VWF [30, 31]; however, there have been no studies in women with VWD or low VWF levels at baseline. Patients on a taper of combined hormonal contraceptives or a high-dose pill (estrogen dose >50 mcg) should not undergo testing for VWD until the patient has been tapered down to standard dose for ~3 months [32]. To avoid continued or recurrent HMB, treatment with combined hormonal contraceptives should not be delayed or withheld to complete testing for VWD [32].

PFD Testing in HMB PFD are clinically important bleeding disorders that are particularly challenging for clinical laboratories to diagnose. Many PFD are associated with increased bleeding scores and increased risks for bleeding. Often, laboratory testing for PFD is done after VWD is excluded [33], although testing for PFD and VWD at the same time may improve the evaluation of suspected bleeding disorders. Most PFD tests require rapid processing and testing of freshly collected, hand-delivered blood samples, using assays with validated reference intervals, derived from an adequate number of female and male healthy control samples [34]. The performance characteristics of PFD tests, and the control of pre-analytical, analytical, and post-analytical factors (including ingestion of drugs that inhibit platelet function) and procedures, influence their overall diagnostic usefulness [34].

Beyond complete blood count to assess disorders of platelet numbers and peripheral smear for platelet morphology for platelet storage pool and membrane deficiencies, platelet aggregation is the gold-standard platelet func-

tion testing method. It began with light transmittance aggregometry in 1965 and continues to be used extensively [35]. In light transmittance aggregometry, the operator prepares platelet-rich plasma, adds a platelet agonist to the platelet-rich plasma, and records the rise in light transmission as platelets aggregate and the suspension clears [34, 36]. Whole blood impedance lumiaggregometry represents an updated methodology and is technically more straightforward, wherein the operator prepares a whole blood suspension, adds an agonist, and records the rise in impedance as platelets coat electrodes suspended in the blood. Both whole blood and light transmission aggregation may be enhanced with a luminescence channel to measure and detect platelet-dense granule ATP secretion after in vitro platelet activation [34, 36].

Inherited PFD include platelet membrane receptor abnormalities, secretion disorders related to internal enzyme deficiencies, and storage pool defects, whereas acquired defects are seen with medications and liver and renal disease [36]. Abnormalities on platelet aggregation should be repeated to help rule out false positives, particularly if the findings suggest a drug-induced defect, and should be reproducible. Single agonist abnormalities are usually a false positive and are much less predictive of a bleeding disorder than multiple agonist abnormalities. Many PFD encountered in practice are uncharacterized inherited disorders with abnormal aggregation responses to multiple agonists that do not fit a well-described pattern of abnormal findings [37]. A lack of standardized reference ranges for delta granules/platelets in children and adolescents limits the upfront utilization of platelet electron microscopy in the workup of HMB at this time. Recent strides, however, have been made to establish references and ranges and validate the methodology [38]. Newer technologies such as high-throughput DNA sequencing are low yield unless the clinical picture suggests a probable etiology [33]. The most recent guidance, from the SSC of the ISTH, recommends many tests for the diagnosis of inherited PFD, including assays validated for diagnostic purposes and assays predominantly used for research investigations [33].

Coagulation Factor Deficiencies in HMB Coagulation factor assays may be considered in the presence of a significant bleeding phenotype if the tests mentioned above are normal, but a suspicion of a bleeding disorder remains high. Evidence of abnormal bleeding in factor XI deficiency not confined to severely deficient patients and a previously reported 26% prevalence of HMB in FXIII-deficient women with FXIII levels <70 IU dL justify testing FXI and FXIII levels in select patients [39, 40].

Laboratory Evaluation for "Bleeding Tendencies" It is not infrequent for hematologists to care for adolescents with HMB and other bleeding tendencies such as easy bruising but for whom available hemostatic testing does not reveal a diagnosis [41]. For such patients, it is important to consider a bleeding tendency that may result from a benign joint hypermobility syndrome and to assess for hypermobility [42]. Joint hypermobility is more common in females, and patients with joint hypermobility syndromes (Ehlers-Danlos syndrome being the most common) may bleed because of increased capillary fragility, alterations in collagen protein interactions in platelet function, or changes in the interaction between exposed collagen in endothelial walls and platelet receptors or VWF [43]. Prolonged menses, irregular menses, and dysmenorrhea are all commonly reported by women with Ehlers-Danlos syndrome [44]. Although many of these patients will have prolonged bleeding times [45], results from hemostatic tests are typically normal [46].

Identifying and Managing Iron Deficiency in HMB Hematologists play a key role in diagnosing and managing concomitant iron deficiency or iron deficiency anemia in adolescents with HMB. A CBC and iron panel should be part of the diagnostic evaluation of adolescents with

HMB. This aspect of assessment in HMB is discussed in Chap. 17.

Laboratory Evaluation of the Adolescent with Heavy Menstrual Bleeding: The Adolescent Medicine and Gynecology Perspective

The most frequent cause of HMB in an adolescent medicine or gynecology practitioner's office is anovulatory bleeding. This is a diagnosis of exclusion. Two years post-menarche, over half of menstrual cycles are anovulatory, whereas by 5 years, about one-tenth of menstrual cycles are anovulatory [47]. Anovulation cannot be based on cycle frequency, given that despite irregularity in their cycle frequency, most adolescent females are ovulating [48]. Polycystic ovarian syndrome (PCOS) is an important diagnosis to consider when anovulatory cycles are present. It occurs when hyperandrogenism results in anovulatory cycles. Approximately 1/3 of adolescent female patients admitted for HMB and anemia were diagnosed with PCOS in one study [49]. It is important to remember that either hypothyroid or hyperthyroid states can cause HMB [50].

An often-overlooked reason for HMB is combined hormonal contraceptives due to medication adherence issues, prolonged menstrual suppression, inadequate estrogen dose [51, 52], or the inability of progesterone to regulate shedding of the endometrium [53, 54]. Trauma and foreign bodies are additional causes of HMB [55]. There are a few essential non-hematological tests to evaluate for HMB [56]. These include urine pregnancy test to rule out any pregnancy-related causes, urine for sexually transmitted diseases such as gonorrhea and chlamydia, thyroid studies including thyroid-stimulating hormone and free T4 to evaluate for thyroid disease, and free testosterone to assess for PCOS.

Speculum and pelvic examinations depend on the age of the patient, diagnostic suspicion, and the clinician's judgment [57]. Papanicolau test, endometrial biopsy, or endocervical/vaginal swab for *Chlamydia* and gonorrhea depends on the age of the patient and other features in history. In a virginal adolescent, an abdominal ultrasound may be substituted for the pelvic examination. The transabdominal approach is the procedure of choice for any nonsexually active female, and the transvaginal approach is the procedure of choice for those females who are emotionally mature and sexually active [58]. Intrauterine saline instillation at the time of transvaginal ultrasound (sonohysterography) increases the sensitivity for abnormalities of the uterine cavity but is usually reserved for the evaluation of acquired uterine abnormalities in perimenopausal bleeding [59].

A systematic review examined the use of ultrasound, sonohysteroscopy, and hyteroscopy in the setting of HMB [60]. This review found a wide variation in published results on the accuracy of the various imaging modalities. Ultrasound is an accurate method for identifying uterine pathology with sensitivity ranging from 48% to 100% and specificity 12% to 100% in the setting of HMB. Furthermore, ultrasound is better at identifying fibroids than hysteroscopy but is less accurate for identifying polyps or endometrial disease when compared with hysteroscopy. Saline infusion sonography accurately identifies uterine pathology, with a sensitivity of 85–100% and a specificity of 50–100%. For hysteroscopy, the sensitivity was 90–97% and the specificity was 62–93%. MRI has no advantage over ultrasound as the firstline investigation for HMB but may be reserved for problem-solving where ultrasound provides indeterminate results.

References

1. Friberg B, Orno AK, Lindgren A, Lethagen S. Bleeding disorders among young women: a population-based prevalence study. Acta Obstet Gynecol Scand. 2006;85(2):200–6.
2. Jacobson AE, Vesely SK, Koch T, Campbell J, O'Brien SH. Patterns of von Willebrand disease screening in girls and adolescents with heavy menstrual bleeding. Obstet Gynecol. 2018;131(6):1121–9.
3. National Collaborating Centre for Women's and Children's Health (UK). Heavy menstrual bleeding. London: RCOG Press; 2007.
4. Nur Azurah AG, Sanci L, Moore E, Grover S. The quality of life of adolescents with menstrual problems. J Pediatr Adolesc Gynecol. 2013;26(2):102–8.

5. ACOG Committee Opinion No. 651: Menstruation in girls and adolescents: using the menstrual cycle as a vital sign. Obstet Gynecol. 2015;126(6):e143–6.
6. Screening and management of bleeding disorders in adolescents with heavy menstrual bleeding: ACOG Committee Opinion, Number 785. Obstet Gynecol. 2019;134(3):e71–e83.
7. World Health Organization multicenter study on menstrual and ovulatory patterns in adolescent girls. II. Longitudinal study of menstrual patterns in the early postmenarcheal period, duration of bleeding episodes and menstrual cycles. World Health Organization Task Force on Adolescent Reproductive Health. J Adolesc Health Care. 1986;7(4):236–44.
8. Bennett AR, Gray SH. What to do when she's bleeding through: the recognition, evaluation, and management of abnormal uterine bleeding in adolescents. Curr Opin Pediatr. 2014;26(4):413–9.
9. Fraser IS, Critchley HO, Broder M, Munro MG. The FIGO recommendations on terminologies and definitions for normal and abnormal uterine bleeding. Semin Reprod Med. 2011;29(5):383–90.
10. Warner PE, Critchley HO, Lumsden MA, Campbell-Brown M, Douglas A, Murray GD. Menorrhagia I: measured blood loss, clinical features, and outcome in women with heavy periods: a survey with follow-up data. Am J Obstet Gynecol. 2004;190(5):1216–23.
11. Munro MG, Critchley HO, Fraser IS. The FIGO systems for nomenclature and classification of causes of abnormal uterine bleeding in the reproductive years: who needs them? Am J Obstet Gynecol. 2012;207(4):259–65.
12. Zia A, Jain S, Kouides P, Zhang S, Gao A, Salas N, et al. Bleeding disorders in adolescents with heavy menstrual bleeding in a multicentre prospective US cohort. Haematologica. 2019 Oct 17:haematol.2019.225656. https://doi.org/10.3324/haematol.2019.225656. Online ahead of print. PMID: 31624107.
13. Shankar M, Chi C, Kadir RA. Review of quality of life: menorrhagia in women with or without inherited bleeding disorders. Haemophilia. 2008;14(1):15–20.
14. Zia A, Lau M, Journeycake J, Sarode R, Marshall J, De Simone N, et al. Developing a multidisciplinary young women's blood disorders program: a single-centre approach with guidance for other centres. Haemophilia. 2016;22(2):199–207.
15. Zia A, Rajpurkar M. Challenges of diagnosing and managing the adolescent with heavy menstrual bleeding. Thromb Res. 2016;143:91–100.
16. James AH, Kouides PA, Abdul-Kadir R, Edlund M, Federici AB, Halimeh S, et al. Von Willebrand disease and other bleeding disorders in women: consensus on diagnosis and management from an international expert panel. Am J Obstet Gynecol. 2009;201(1):12e1–8.
17. Nichols WL, Hultin MB, James AH, Manco-Johnson MJ, Montgomery RR, Ortel TL, et al. von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) expert panel report (USA). Haemophilia. 2008;14(2):171–232.
18. Favaloro EJ. Clinical utility of the PFA-100. Semin Thromb Hemost. 2008;34(8):709–33.
19. Flood VH, Gill JC, Morateck PA, Christopherson PA, Friedman KD, Haberichter SL, et al. Common VWF exon 28 polymorphisms in African Americans affecting the VWF activity assay by ristocetin cofactor. Blood. 2010;116(2):280–6.
20. Patzke J, Budde U, Huber A, Mendez A, Muth H, Obser T, et al. Performance evaluation and multicentre study of a von Willebrand factor activity assay based on GPIb binding in the absence of ristocetin. Blood Coagul Fibrinolysis. 2014;25(8):860–70.
21. Graf L, Moffat KA, Carlino SA, Chan AK, Iorio A, Giulivi A, et al. Evaluation of an automated method for measuring von Willebrand factor activity in clinical samples without ristocetin. Int J Lab Hematol. 2014;36(3):341–51.
22. Favaloro EJ. Diagnosis and classification of von Willebrand disease: a review of the differential utility of various functional von Willebrand factor assays. Blood Coagul Fibrinolysis. 2011;22(7):553–64.
23. Riddell AF, Gomez K, Millar CM, Mellars G, Gill S, Brown SA, et al. Characterization of W1745C and S1783A: 2 novel mutations causing defective collagen binding in the A3 domain of von Willebrand factor. Blood. 2009;114(16):3489–96.
24. Flood VH, Schlauderaff AC, Haberichter SL, Slobodianuk TL, Jacobi PM, Bellissimo DB, et al. Crucial role for the VWF A1 domain in binding to type IV collagen. Blood. 2015;125(14):2297–304.
25. Flood VH, Christopherson PA, Gill JC, Friedman KD, Haberichter SL, Bellissimo DB, et al. Clinical and laboratory variability in a cohort of patients diagnosed with type 1 VWD in the United States. Blood. 2016;127(20):2481–8.
26. Sharma R, Flood VH. Advances in the diagnosis and treatment of Von Willebrand disease. Hematology Am Soc Hematol Educ Program. 2017;2017(1):379–84.
27. Doshi BS, Rogers RS, Whitworth HB, Stabnick EA, Britton J, Butler RB, et al. Utility of repeat testing in the evaluation for von Willebrand disease in pediatric patients. J Thromb Haemost. 2019.
28. Gill JC, Endres-Brooks J, Bauer PJ, Marks WJ Jr, Montgomery RR. The effect of ABO blood group on the diagnosis of von Willebrand disease. Blood. 1987;69(6):1691–5.
29. Laffan MA, Lester W, O'Donnell JS, Will A, Tait RC, Goodeve A, et al. The diagnosis and management of von Willebrand disease: a United Kingdom Haemophilia Centre Doctors Organization guideline approved by the British Committee for Standards in Haematology. Br J Haematol. 2014;167(4):453–65.
30. Dumont T, Allen L, Kives S. Can von Willebrand disease be investigated on combined hormonal contraceptives? J Pediatr Adolesc Gynecol. 2013;26(3):138–41.

31. Zia A, Callaghan MU, Callaghan JH, Sawni A, Bartlett H, Backos A, et al. Hypercoagulability in adolescent girls on oral contraceptives-global coagulation profile and estrogen receptor polymorphisms. Am J Hematol. 2015;90(8):725–31.
32. O'Brien SH. Evaluation and management of heavy menstrual bleeding in adolescents: the role of the hematologist. Blood. 2018;
33. Gresele P. Subcommittee on Platelet Physiology of the International Society on T, Hemostasis. Diagnosis of inherited platelet function disorders: guidance from the SSC of the ISTH. J Thromb Haemost. 2015;13(2):314–22.
34. Harrison P, Mackie I, Mumford A, Briggs C, Liesner R, Winter M, et al. Guidelines for the laboratory investigation of heritable disorders of platelet function. Br J Haematol. 2011;155(1):30–44.
35. Born GV. Aggregation of blood platelets by adenosine diphosphate and its reversal. Nature. 1962;194:927–9.
36. Hayward CPM, Moffat KA, Brunet J, Carlino SA, Plumhoff E, Meijer P, et al. Update on diagnostic testing for platelet function disorders: what is practical and useful? Int J Lab Hematol. 2019;41(Suppl 1):26–32.
37. Hayward CP, Moffat KA. Laboratory testing for bleeding disorders: strategic uses of high and low-yield tests. Int J Lab Hematol. 2013;35(3):322–33.
38. Sorokin V, Alkhoury R, Al-Rawabdeh S, Houston RH, Thornton D, Kerlin B, et al. Reference range of Platelet Delta granules in the pediatric age group: an ultrastructural study of platelet whole mount preparations from healthy volunteers. Pediatr Dev Pathol. 2016;19(6):498–501.
39. Bolton-Maggs PH, Patterson DA, Wensley RT, Tuddenham EG. Definition of the bleeding tendency in factor XI-deficient kindreds–a clinical and laboratory study. Thromb Haemost. 1995;73(2):194–202.
40. Sharief LA, Kadir RA. Congenital factor XIII deficiency in women: a systematic review of literature. Haemophilia. 2013;19(6):e349–57.
41. Quiroga T, Goycoolea M, Panes O, Aranda E, Martinez C, Belmont S, et al. High prevalence of bleeders of unknown cause among patients with inherited mucocutaneous bleeding. A prospective study of 280 patients and 299 controls. Haematologica. 2007;92(3):357–65.
42. van der Giessen LJ, Liekens D, Rutgers KJ, Hartman A, Mulder PG, Oranje AP. Validation of beighton score and prevalence of connective tissue signs in 773 Dutch children. J Rheumatol. 2001;28(12):2726–30.
43. Kendel NE, Haamid FW, Christian-Rancy M, O'Brien SH. Characterizing adolescents with heavy menstrual bleeding and generalized joint hypermobility. Pediatr Blood Cancer. 2019;66(6):e27675.
44. Hurst BS, Lange SS, Kullstam SM, Usadi RS, Matthews ML, Marshburn PB, et al. Obstetric and gynecologic challenges in women with Ehlers-Danlos syndrome. Obstet Gynecol. 2014;123(3):506–13.
45. Mast KJ, Nunes ME, Ruymann FB, Kerlin BA. Desmopressin responsiveness in children with Ehlers-Danlos syndrome associated bleeding symptoms. Br J Haematol. 2009;144(2):230–3.
46. De Paepe A, Malfait F. Bleeding and bruising in patients with Ehlers-Danlos syndrome and other collagen vascular disorders. Br J Haematol. 2004;127(5):491–500.
47. Apter D. Serum steroids and pituitary hormones in female puberty: a partly longitudinal study. Clin Endocrinol. 1980;12(2):107–20.
48. Pena AS, Doherty DA, Atkinson HC, Hickey M, Norman RJ, Hart R. The majority of irregular menstrual cycles in adolescence are ovulatory: results of a prospective study. Arch Dis Child. 2018;103(3):235–9.
49. Maslyanskaya S, Talib HJ, Northridge JL, Jacobs AM, Coble C, Coupey SM. Polycystic ovary syndrome: an under-recognized cause of abnormal uterine bleeding in adolescents admitted to a children's hospital. J Pediatr Adolesc Gynecol. 2017;30(3):349–55.
50. Bourne AW. Hyperthyroidism in functional menorrhagia. Proc R Soc Med. 1922;15(Obstet Gynaecol Sect):24–30.
51. Endrikat J, Muller U, Dusterberg B. A twelve-month comparative clinical investigation of two low-dose oral contraceptives containing 20 micrograms ethinylestradiol/75 micrograms gestodene and 30 micrograms ethinylestradiol/75 micrograms gestodene, with respect to efficacy, cycle control, and tolerance. Contraception. 1997;55(3):131–7.
52. Rosenberg MJ, Meyers A, Roy V. Efficacy, cycle control, and side effects of low- and lower-dose oral contraceptives: a randomized trial of 20 micrograms and 35 micrograms estrogen preparations. Contraception. 1999;60(6):321–9.
53. Salamonsen LA, Butt AR, Hammond FR, Garcia S, Zhang J. Production of endometrial matrix metalloproteinases, but not their tissue inhibitors, is modulated by progesterone withdrawal in an in vitro model for menstruation. J Clin Endocrinol Metab. 1997;82(5):1409–15.
54. Galant C, Berliere M, Dubois D, Verougstraete JC, Charles A, Lemoine P, et al. Focal expression and final activity of matrix metalloproteinases may explain irregular dysfunctional endometrial bleeding. Am J Pathol. 2004;165(1):83–94.
55. Pennesi CM, Kenney B, Thakkar R, Ching C, Hewitt G, McCracken K. Prolonged vaginal bleeding in an adolescent secondary to a foreign body: need for a comprehensive assessment and complex surgery. J Pediatr Adolesc Gynecol. 2018;31(6):640–3.
56. Deligeoroglou E, Karountzos V, Creatsas G. Abnormal uterine bleeding and dysfunctional uterine bleeding in pediatric and adolescent gynecology. Gynecol Endocrinol. 2013;29(1):74–8.
57. James AH. Heavy menstrual bleeding: work-up and management. Hematology Am Soc Hematol Educ Program. 2016;2016(1):236–42.

58. Arbel-DeRowe Y, Tepper R, Rosen DJ, Beyth Y. The contribution of pelvic ultrasonography to the diagnostic process in pediatric and adolescent gynecology. J Pediatr Adolesc Gynecol. 1997;10(1):3–12.
59. American College of O, Gynecologists. ACOG Technology Assessment in Obstetrics and Gynecology No. 5: sonohysterography. Obstet Gynecol. 2008;112(6):1467–9.
60. Farquhar C, Ekeroma A, Furness S, Arroll B. A systematic review of transvaginal ultrasonography, sonohysterography and hysteroscopy for the investigation of abnormal uterine bleeding in premenopausal women. Acta Obstet Gynecol Scand. 2003;82(6):493–504.

2 Screening Tools for Evaluating the Bleeding Adolescent

Kalinda Woods and Sue Kearney

Introduction

Bleeding has always been a distressing and obvious clinical symptom, a fact which is demonstrable through many eras in history and across cultures. Because bleeding is a common human experience, it can be challenging to differentiate normal versus pathologic bleeding. Historically, clinicians have relied heavily on a thorough assessment of the patient (including the interview and physical exam) to determine if further diagnostic testing is appropriate. However, when it comes to bleeding, approximately 1/3 of healthy individuals may report at least one hemorrhagic symptom by 30 years of age [1]. The significant overlap of lifetime cumulative bleeding incidence in normal and mild bleeding disorder patients highlights the challenges in discriminating between normal and abnormal hemostasis using an "individualized approach" to the bleeding history.

The adolescent population presents unique challenges when it comes to diagnosing abnormal bleeding. Adolescents have had less time to manifest bleeding symptoms, and as a group, they may have had less exposure to surgical and other hemostatic challenges. In addition, bruising and epistaxis are frequently reported at this age in the absence of a bleeding disorder [2] and may be erroneously attributed to their high level of activity. Finally, adolescents with heavy menstrual bleeding (HMB) are often loathe to seek medical attention. Estimates suggest that 5–44% of adolescents with HMB have an associated underlying and undiagnosed bleeding disorder [3].

Given these issues, investigators have sought to standardize the bleeding history in the form of bleeding assessment tools (BATs) in order to objectively quantify bleeding severity and increase diagnostic accuracy.

This chapter will:

(a) Review the bleeding assessment tools (BATs) used for both pediatric and adult populations with emphasis on those applicable to the adolescent.
(b) Review the application of these tools with reference to the published data on specific study populations and disease states.
(c) Review the opportunities and challenges of BATs.
(d) Discuss strategies for administration and data collection of future BATs.

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The Bleeding Assessment Tool

Over many years, clinician-researchers have developed a variety of questionnaires to evaluate bleeding, which are collectively referred to as bleeding assessment tools or BATs. Bleeding assessment tools were designed and developed initially as research tools for the quantification of bleeding symptoms and the study of phenotype/genotype correlations. A BAT typically includes a specific set of questions to illicit the bleeding history and an interpretation grid to score the severity of each bleeding symptom [1]. The ideal BAT will provide a bleeding score (BS) based not only on incidence of bleeding but also on severity, frequency, and need for intervention. These tools have proven helpful not only for researchers but also for clinicians diagnosing and treating bleeding disorders. Clinicians can utilize these tools to establish an objective score or quantitative benchmark by which to determine the need for further diagnostic tests, to evaluate severity of bleeding symptoms, and to track patient response to therapy. Given the complexity and nuances of differentiating normal vs abnormal bleeding and the desire to reduce unnecessary testing, there has been a renewed interest in the use of BATs in recent years.

The Evolution of BAT

In the mid-1990s, the International Society on Thrombosis and Hemostasis (ISTH) Scientific and Standardization Committee (SSC) established a set of provisional criteria for the diagnosis of von Willebrand disease (vWD) type I which included thresholds for mucocutaneous bleeding symptoms to be considered significant [4]. The establishment of the ISTH vWD consensus criteria provided a platform for investigators to develop and validate BATs with the goal of an objective, quantitative assessment of bleeding and a standardized approach to diagnosis. Minimal criteria for significant bleeding were defined. See Table 2.1 [5].

Much of the initial work on the modern BAT was done by a group of investigators from Vicenza, Italy. Led by Rodegheiro, the "Vincenza BAT" has undergone several iterations [6]. The original Vincenza BAT queried bleeding symptoms including epistaxis, menstrual bleeding, and postsurgical bleeding. For each bleeding symptom, a score was given depending on the bleeding severity (0 for absent or trivial; 3 for those

Table 2.1 Criteria for nontrivial bleeding

Epistaxis	Any nosebleed that causes interference or distress with daily or social activities. Significant features include bleeding greater than 10 minutes, a frequency of greater than five episodes/year, and no other identifiable cause
Cutaneous bleeding	Five or more bruises (>1 cm) in exposed areas; petechiae; hematomas without trauma
Minor cutaneous wound	Two or more bleeding episodes caused by superficial cuts lasting more than 10 minutes requiring frequent bandage changes
Oral cavity bleeding	Causes frankly bloody sputum or a swollen tongue or mouth and lasts greater than 10 minutes on more than one occasion
Hematemesis	Unexplained gastrointestinal bleeding
Hematuria	Unexplained macroscopic hematuria
Tooth extraction	Any unexpected bleeding requiring intervention by a dentist
Surgical bleeding	Any abnormal bleeding judged by the surgeon that causes a delay in discharge or that requires supportive treatment
Menorrhagia	Any bleeding that interferes with daily or social activities. Significant features include changing pads more than every 2 hours; lasting more than 7 days; large clots >1 cm combined with a history of flooding; or a PBAC score higher than 100
Postpartum bleeding	Bleeding lasting for more than 6 weeks that causes progressive anemia or is judged to be abnormal by the obstetrician
Muscle hematomas or hemarthrosis	Any spontaneous joint/muscle bleeding (not related to traumatic injuries) is considered significant
CNS bleeding	Any subdural or intracerebral hemorrhage requiring intervention
Other	Bleeding symptoms that occur during infancy

Adapted from Rodeghiero et al. [6]

symptoms requiring medical intervention). The approximate time of administration of the original Vincenza BAT was 40 minutes. The Vincenza BAT was first studied in 42 obligatory carriers of type I vWD. The results of this study demonstrated that having at least three hemorrhagic symptoms or a BS of 3 in men and 5 in women was supportive of type I VWD (high specificity, moderate sensitivity) [7]. The Vincenza BAT was later revised in an attempt to improve the sensitivity. In this version, the scoring system reflected the absence of symptoms in the setting of significant hemostatic challenges (scoring −1), all the way up to a score of 4 if infusion of clotting factors or surgery were required. Version 2 of the Vincenza BAT was used to evaluate patients in the European Molecular and Clinical Markers for the Diagnosis and Management of Type 1 VWD Study (MCMDM-1 VWD), and the BS was strongly inversely correlated with vWF level [8]. A condensed version (version 3) of the MCMDM1-VWD Bleeding Questionnaire was subsequently developed, removing all details that did not directly affect the BS. This reduced the time of administration from 40 minutes to 5–10 minutes [9]. These tools have been studied in other bleeding disorders with good validity [10, 11]. See Table 2.2 for further details.

Table 2.2 Scoring comparison for BATs

Symptom	Score					
	−1	0[a]	1[a]	2	3	4
Epistaxis	–	No or trivial	Present	Packing, cauterization	Blood transfusion or replacement therapy	–
	–	No or trivial (≤5)	>5 or more than 10′	Consultation only	Packing or cauterization or antifibrinolytics	Blood transfusion or replacement therapy or desmopressin
	–	No or trivial	>5 or more than 10′	Consultation only	Packing or cauterization	Blood transfusion or replacement therapy
	–	No/trivial	> 5/y or more than 10′	Consultation only[b]	Packing or cauterization or antifibrinolytics	Blood transfusion or replacement therapy (use of hemostatic blood components and rFVlla) or desmopressin
Cutaneous	–	No or trivial	Petechiae or bruises	Hematomas	Consultation	–
	–	No or trivial (<1 cm)	>1 cm and no trauma	Consultation only	–	–
	–	No or trivial	> 1 cm and no trauma	Consultation only	–	–
	–	No/trivial	For bruises 5 or more (> 1 cm) in exposed areas	Consultation only[b]	Extensive	Spontaneous hematoma requiring blood transfusion
Minor wounds	–	No or trivial	Present (1–5 episodes/year)	Consultation	Surgical hemostasis	–
	–	No or trivial (<5)	>5 or more than 5′	Consultation only or Steri-Strips	Surgical hemostasis or antifibrinolytics	Blood transfusion or replacement therapy or desmopressin

(continued)

Table 2.2 (continued)

Symptom	Score					
	–	No or trivial	>5 or more than 5′	Consultation only	Surgical hemostasis	Blood transfusion or replacement therapy or desmopressin
	–	No/trivial	> 5/year or more than 10′	Consultation only[b]	Surgical hemostasis	Blood transfusion, replacement therapy, or desmopressin
Oral cavity	–	No or trivial	Present	Consultation only	Surgical hemostasis or blood transfusion	–
	–	No	Reported at least one	Consultation only	Surgical hemostasis or antifibrinolytics	Blood transfusion or replacement therapy or desmopressin
	–	No	Referred at least one	Consultation only	Surgical hemostasis or antifibrinolytics	Blood transfusion or replacement therapy or desmopressin
	–	No/trivial	Present	Consultation only[b]	Surgical hemostasis or antifibrinolytics	Blood transfusion, replacement therapy, or desmopressin
Gastrointestinal	–	No or trivial	Present	Consultation	Surgery or blood transfusion	–
	–	No	Identified cause	Consultation or spontaneous	Surgical hemostasis, antifibrinolytics, blood transfusion, replacement therapy, or desmopressin	–
	–	No	Associated with ulcer, portal hypertension, hemorrhoids, anglodysplasia	Spontaneous	Surgical hemostasis, antifibrinolytics, blood transfusion, replacement therapy, or desmopressin	–
	–	No or trivial	Present but not associated with ulcer, portal hypertension, hemorrhoids, anglodysplasia	Consultation only[b]	Surgical hemostasis, antifibrinolytic	Blood transfusion, replacement therapy, or desmopressin
Hematuria	–	–	–	–	–	–
	–	–	–	–	–	–
	–	–	–	–	–	–
	–	No or trivial	Present (macroscopic)	Consultation only[b]	Surgical hemostasis, antifibrinolytic	Blood transfusion, replacement therapy, or desmopressin
Tooth extraction	–	No or trivial	Present	Suturing or packing	Blood transfusion	–

Table 2.2 (continued)

Symptom	Score					
	No bleeding in at least 2 extractions	None done or no bleeding in 1 extraction	Reported, no consultation	Consultation only	Resuturing, repacking, antifibrinolytics	Blood transfusion, replacement therapy, or desmopressin
	No bleeding in at least 2 extractions	None done or no bleeding in 1 extraction	Reported, no consultation	Consultation only	Resuturing or packing	Blood transfusion, replacement therapy, or desmopressin
	–	No/trivial or none done	Reported in <25% of all procedures, no intervention[c]	Resuturing or packing	Blood transfusion, replacement therapy, or desmopressin	
Surgery	–	No or trivial	Present	Suturing or resurgery	Blood transfusion	–
	No bleeding in at least 2 surgeries	None done or no bleeding in 1 surgery	Reported, no consultation	Consultation only	Surgical hemostasis or antifibrinolytics	Blood transfusion, replacement therapy, or desmopressin
	No bleeding in at least 2 extractions	None done or no bleeding in 1 extraction	Reported, no consultation	Consultation only	Surgical hemostasis or antifibrinolytic	Blood transfusion, replacement therapy, or desmopressin
	–	No/trivial or none done	Reported in <25% of all procedures, no intervention[c]	Surgical hemostasis or antifibrinolytics	Blood transfusion, replacement therapy, or desmopressin	
Menorrhagia	–	No or trivial	Present	Consultation, pill use, iron therapy	Blood transfusion, hysterectomy, D&C	–
	–	No	Reported or consultation only	Antifibrinolytics or pill use	D&C, iron therapy	Blood transfusion or replacement therapy or desmopressin or hysterectomy
	–	No	Consultation only	Antifibrinolytics or pill use	D&C, iron therapy, endometrial ablation	Blood transfusion or replacement therapy or desmopressin or hysterectomy
	–	No/trivial	Consultation only[b] or changing pads more frequently than every 2 h or clot and flooding or PBAC score > 100[d]	Time off work/school >2/year or requiring antifibrinolytics, hormonal or iron therapy	Requiring combined treatment with antifibrinolytics and hormonal therapy or present since menarche and > 12 month	Acute menorrhagia requiring hospital admission and emergency treatment or requiring blood transfusion, replacement therapy, desmopressin, D&C, endometrial ablation, hysterectomy
Postpartum	–	No or trivial	Present, iron therapy	Blood transfusion, D&C, suturing	Hysterectomy	–

(continued)

Table 2.2 (continued)

Symptom	Score					
	No bleeding in at least two deliveries	None done or no bleeding in one delivery	Reported or consultation only	D&C, iron therapy, antifibrinolytics	Blood transfusion, replacement therapy, or desmopressin	Hysterectomy
	No bleeding in at least two deliveries	None done or no bleeding in one delivery	Consultation only	D&C, iron therapy, antifibrinolytics	Blood transfusion, replacement therapy, or desmopressin	Hysterectomy
	–	No/trivial or no deliveries	Consultation only[b] or use of Syntocinon or IV oxytocin >6 week	Iron therapy or antifibrinolytics	Requiring blood transfusion, replacement therapy, desmopressin, or requiring examination under anesthesia and/or the use of uterine balloon/package to tamponade the uterus	Any procedure requiring critical care of surgical intervention (e.g., hysterectomy, internal iliac artery ligation, uterine artery embolization, uterine brace suture)
Hemarthrosis	–	No or trivial	Present	Consultation only	Blood transfusion, surgery	–
	–	Never	Posttrauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic requiring desmopressin, or replacement therapy	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
	–	Never	Posttrauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic requiring desmopressin, or replacement therapy	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
	–	Never	Posttrauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic requiring desmopressin, or replacement therapy	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
Central nervous system	–	–	–	–	–	–
	–	Never	–	–	Subdural, any intervention	Intracerebral, any intervention
	–	Never	–	–	Subdural, any intervention	Intracerebral, any intervention
	–	Never	–	–	Subdural, any intervention	Intracerebral, any intervention
Other bleeding[e]	–	–	–	–		

Table 2.2 (continued)

Symptom	Score					
	–	No	Reported	Consultation only	Surgical hemostasis, antifibrinolytics, iron therapy	Blood transfusion, replacement therapy, or desmopressin
	–	–	–	–	–	–
	–	No/trivial	Present	Consultation only[b]	Surgical hemostasis, antifibrinolytics	Blood transfusion, replacement therapy, or desmopressin

Notes: The white rows are the scoring system for the original Vicenza Bleeding Questionnaire,[5] the light gray rows for the EU MCMDM-1VWD Bleeding Questionnaire (the "Other" category is not scored) and Pediatric Bleeding Questionnaire,[18] the medium gray rows for the Condensed MCMDM–1VWD Bleeding Questionnaire,[7] and the dark gray rows are for the scoring used for both the ISTH-BAT[10] and Self-BAT[14]

[a]Distinction between 0 and 1 is of critical importance. Score 1 means that the symptom is judged as present in the patient's history by the interviewer but does not qualify for a score of 2 or more (as provided for ISTH-BAT scoring[10])

[b]Consultation only: the patient sought medical evaluation and was either referred to a specialist or offered detailed laboratory investigation (as provided for ISTH-BAT scoring[10])

[c]Example: 1 extraction/surgery resulting in bleeding (100%): the score to be assigned is 2; 2 extractions/surgeries, 1 resulting in bleeding (50%): the score to be assigned is 2; 3 extractions/surgeries, 1 resulting in bleeding (33%): the score to be assigned is 2: 4 extractions/surgeries, 1 resulting in bleeding (25%): the score to be assigned is 1

[d]If already available at the time of collection

[e]Includes umbilical stamp bleeding, cephalohematoma, cheek hematoma caused by sucking during breast/bottle feeding, conjunctival hemorrhage, or excessive bleeding following circumcision or venipuncture. Their presence in infancy requires detailed investigation independently from the overall score

In 2008, the ISTH/SSC Joint Working Group met to establish a consensus BAT. The group proposed a standardized bleeding questionnaire with a defined scoring system for calculating the overall bleeding for use in children and adults with inherited bleeding disorders [5]. Based heavily on the foundations of the Vincenza BAT, the ISTH-BAT was proposed as a consensus BAT and was recommended for universal adoption.

Modern Bleeding Assessment Tools

The ISTH-BAT

Launched in 2010, the ISTH-BAT was designed to achieve greater accuracy by considering not only the severity but also the frequency of bleeding episodes. The scoring system for this tool removed the −1 score for categories including dental extraction and surgery. Administration time for the ISTH-BAT is approximately 10–20 minutes. Normative values for adults and pediatrics were established by collating data from the prior Vincenza-based BAT studies including data from more than 1000 normal adults and 328 children. Abnormal bleeding is defined as a BS of > = 4 in adult males, > = 6 in adult females, and > =3 in children [12]. The ISTH-BAT has subsequently been coupled with an electronic repository, at the Rockefeller University Center for Clinical and Translational Science, with the goal of an expansive dataset on bleeding symptoms in different patient populations [5]. The ISTH-BAT can be found at https://www.isth.org/page/reference_tools [13], and its scoring system is depicted in Table 2.2.

The ISTH-BAT has not been extensively studied and validated in all populations or bleeding disorders, but research using this tool is ongoing. Using the ISTH-BAT, the resultant BS was able to discriminate between patients with vWD and those