World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

Check for updates

Bleeding disorders unveiled: An in-depth analysis

Iván Alfredo De Ávila Consuegra [1,*], Abel Enrique Manjarres Guevara [2], Andrés Felipe García Osorio [1], Huber Alvarado Castell [1], William Albeiro Caicedo Solarte [1] and Juan Manuel Pretelt Gazabón [1]

[1] *Department of Internal Medicine, Faculty of Health Sciences, Universidad Libre, Barranquilla, Colombia.*
[2] *Department of Medicine and Health Sciences, Universidad del Norte, Barranquilla, Colombia.*

World Journal of Advanced Research and Reviews, 2024, 22(02), 1658–1665

Publication history: Received on 14 April 2024; revised on 20 May 2024; accepted on 23 May 2024

Article DOI: https://doi.org/10.30574/wjarr.2024.22.2.1587

Abstract

Bleeding constitutes a frequent reason for consultation and can stem from various causes, both congenital and acquired, thereby presenting a diagnostic challenge. Understanding the physiological foundations of hemostasis is crucial, alongside conducting a detailed yet focused patient medical history, to enable timely diagnostic and therapeutic interventions. This review provides an overview of the approach to patients presenting with bleeding from a global perspective.

Keywords: Bleeding disorders; Coagulation; Hemostasis; Von Willebrand disease; Hemophilia

1. Introduction

Bleeding constitutes a common reason for visits to emergency departments, outpatient clinics, and hospital admissions, stemming from both congenital and acquired issues. In evaluating a patient with a bleeding disorder, understanding, and comprehending hemostasis are imperative, as its management can pose a challenge for the medical team.

Hemostasis is a tightly regulated physiological process occurring through complex interactions among endothelial cells, platelets, von Willebrand factor, and coagulation factors. Traditionally, hemostasis has been dichotomized into primary and secondary phases (Fig 1); however, platelet plug formation and coagulation are two processes that initiate simultaneously upon vessel injury, signifying their interplay throughout the coagulation cascade. Hemostasis commences following vascular wall injury, triggering rapid platelet adhesion, activation, and aggregation to the exposed subendothelial extracellular matrix. Concurrently, coagulation factors bind to the procoagulant surface of activated platelets to reinforce the platelet plug, consolidating its formation and creating a meshwork of cross-linked fibrin [1].

Primary hemostasis relies on the integrity of the vascular system and platelet function (both qualitative and quantitative). Upon endothelial injury, a local reflex vasoconstriction is elicited [2], followed by platelet adhesion to tissue factor, collagen, von Willebrand factor (vWF), and fibronectin within the exposed subendothelial matrix. Following this initial contact, platelets undergo activation, leading to significant surface protein expression and granule release, promoting platelet aggregation and plug formation [3].

Secondary hemostasis pertains to the role of the coagulation cascade, wherein plasma proteins (coagulation factors) interact with each other, undergoing activation in a series of cascading reactions [2], culminating in thrombin and fibrin generation, further reinforcing the initial platelet plug [3]. Its onset occurs almost simultaneously with primary hemostasis. Following vascular injury and exposure of tissue factor within the subendothelial tissue or extracellular matrix, circulating activated factor VII (FVIIa) binds to this tissue factor, forming the FVIIa-tissue factor complex (initiation phase), which activates factors IX and X. Factor Xa (FXa) can then generate thrombin, which activates factors

* Corresponding author: Iván Alfredo De Ávila Consuegra

V and VIII, promotes platelet activation, and activates factor XI, which in turn activates factor IX (amplification phase). Following activation of factors IX and VIII, the tenase complex (FIXa-FVIIIa) forms, converting FX into FXa, subsequently forming the prothrombinase complex (FXa-FVa), triggering a burst of thrombin that can cleave fibrinogen into fibrin to stabilize the clot (propagation phase) [1].

To regulate this coagulation cascade, fibrinolysis is initiated, a process aimed at removing excess fibrin, ultimately resulting in vascular repair and restoration of blood flow [2]. An appropriate balance in platelet function and the coagulation process is crucial for maintaining stable blood circulation. If any of these element's malfunction, it can lead to impaired bleeding cessation, clinically reflected in hemorrhagic complications [1]. Subsequently, important aspects in the management of patients presenting with bleeding are described.

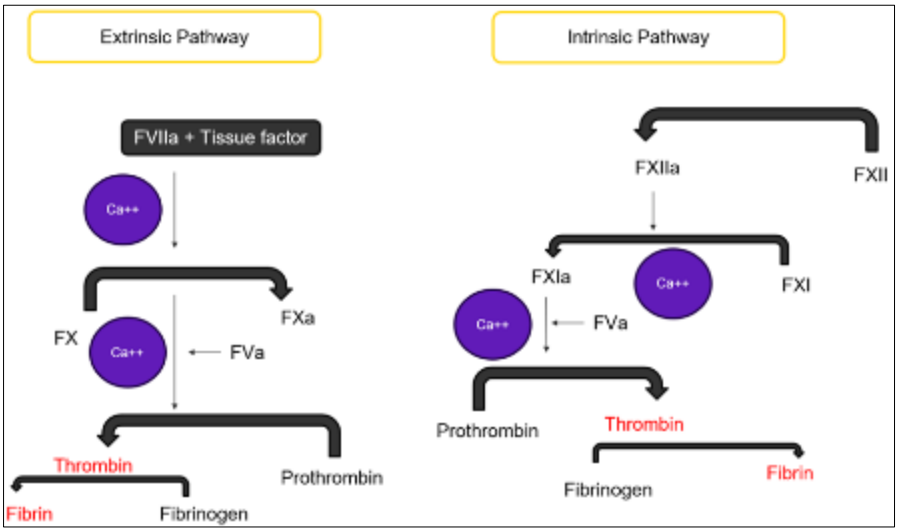

Figure 1 Adapted from Vayne C. Hemostasis: physiology and main exploration tests. EMC - Medical Treatise. 2021. [2]

1.1. Medical History

Thorough yet targeted questioning remains one of the primary tools in the clinical history when encountering a patient with bleeding. A meticulous review of the patient's medical history is conducted, including any prior bleeding episodes and family history. It is essential to assess whether the patient's bleeding is abnormal, for which various objective bleeding assessment tools have been developed [3]. Inquiry is made about previous bleeding events, their onset, severity, frequency, need for medical intervention, associated complications, and whether any studies have been conducted [4]. The age of onset of bleeding manifestations is crucial, as it helps distinguish between a congenital disorder and an acquired one [3]. For instance, bleeding from the umbilical cord, episodes of bleeding during childhood (excessive bleeding during the shedding of deciduous teeth), during adolescence (menstruation, trauma requiring surgical intervention, or transfusion requirement) [1]. Inquiring about pharmacological history is important, as different medications (Table 1) can alter hemostasis and predispose to bleeding. The presence of comorbidities that may manifest with bleeding [3]. A family history of bleeding in first-degree and second-degree relatives increases the likelihood of a congenital bleeding disorder. However, the absence of family history does not rule out a bleeding disorder, as in disorders such as hemophilia type A, approximately 30-40% have negative family histories [5].

Table 1 Pharmaceuticals associated with heightened risk of bleeding

Pharmaceuticals associated with heightened risk of bleeding
Anticoagulants
Nonsteroidal antiinflammatory drugs (NSAIDs
Steroids
Antiplatelets
Selective serotonin reuptake inhibitors (SSRI)
Herbal supplements

The International Society on Thrombosis and Haemostasis Bleeding Assessment Tool (ISTH-BAT) (Table 2) is a screening tool for individuals undergoing investigation for a potential bleeding disorder. It provides a standardized method for describing disease characteristics and assessing overall bleeding severity. Comprising 14 items, each scored on a scale of 0-4, the normal range is <4 in adult males and <6 in adult females [6,7].

Table 2 (ISTH-BAT). Taken from: Chaigneau M. Approach to the patient with bleeding. Hematol Oncol Clin North Am. 2021. [4]

	International Society of Thrombosis and Haemostasis Bleeding Assessment Tool (ISTH-BAT)		
1	Epistaxis	8	Surgery
2	Cutaneous bleeding	9	Menorrhagia
3	Bleeding from minor wounds	10	Postpartum hemorrhage
4	Oral cavity	11	Muscle hematoma
5	Gastrointestinal bleeding	12	Hemarthrosis
6	Hematuria	13	Central nervous system bleeding
7	Tooth extraction	14	Other bleeding

1.2. Physical Examination

Physical examination may be challenging as bleeding manifestations are often transient and may not be evident upon evaluation. Bleeding manifestations (Table 3) can occur in any organ or system of the body. Adequate inspection of the skin is essential to identify cutaneous bleeding manifestations such as petechiae, ecchymosis, peripheral hemorrhages, and telangiectasias. Signs of anemia such as pallor, tachycardia, among others, should also be evaluated. Additionally, assessing the joints for abnormalities, facial and skeletal anomalies, joint hypermobility, and other signs such as cardiac murmurs, lymphadenopathy, splenomegaly, and hepatomegaly is crucial. Clinical characteristics of bleeding disorders can be categorized into primary hemostasis defects (bleeding from skin and mucous membranes), secondary hemostasis impairment (deep tissues like joints, muscles), and connective tissue abnormalities. Observed signs may be attributed to other medical conditions and/or medication use, or may only become evident after a hemostatic challenge, such as menstruation, surgical procedures, or trauma. The most common primary hemostasis defects include von Willebrand disease and platelet function disorders, while hemophilia A and hemophilia B are predominant in secondary hemostasis defects [4,8].

Table 3 Characteristics of Primary and Secondary Hemostasis

Divergent Clinical Presentations in Primary and Secondary Hemostasis		
Characteristics	**Primary hemostasis alteration**	**Secondary hemostasis alteration**
Onset of post-traumatic bleeding	Immediate	Later (hours or days)
Location of bleeding	Mucocutaneous bleeding	Deep tissue bleeding
Physical Examination	Petechiae, ecchymoses	Intramuscular hematomas, hemarthrosis
Family history	Autosomal dominant	Autosomal recessive

1.3. Laboratory Tests

Relatively common hereditary bleeding disorders can present with spontaneous or trauma-induced bleeding. Qualitative platelet disorders often manifest with mucocutaneous bleeding. Patients with dysfibrinogenemia may present with bleeding or thrombosis. Therefore, diagnosing a patient with bleeding represents a diagnostic challenge, which may initially go unnoticed until it presents as severe hemorrhage [9]. Hence, there is a need for targeted laboratory testing following a structured and cost-effective approach tailored to each patient. Starting from a complete blood count and potentially progressing to the quantification of coagulation factors, laboratory tests are categorized into first, second, and third-line tests [5].

1.3.1. First-Line Tests

Initial laboratory tests include a complete blood count, peripheral blood smear, and initial assessment of coagulation with prothrombin time (PT) and activated partial thromboplastin time (aPTT). These tests will identify many patients with abnormal bleeding, including thrombocytopenia and common factor deficiencies [3]. The aPTT assesses the integrity of the intrinsic and common pathways, while the PT evaluates the extrinsic pathway. Prolongation of PT may result from factor VII deficiency, vitamin K antagonist use (e.g., warfarin), and vitamin K deficiency. It is important to note that the international normalized ratio (INR) obtained from PT is only useful for monitoring vitamin K antagonist doses and does not assess bleeding risk in other contexts. Prolongation of aPTT can have various causes, including deficiencies of factors VIII, IX, XI, XII, anticoagulant effect of heparins, and lupus anticoagulant presence [3,4].

Bleeding time serves to assess platelet function. It is the period between making a small incision in a specific area of the skin and the cessation of bleeding. It is the only global test that measures in vivo platelet-endothelium reaction and demonstrates the hemostatic capacity of platelets. Normal bleeding time is between 8 and 10 minutes. Additionally, we can perform PFA, which measures platelet function under high shear conditions. While it is less specific than bleeding time, it is less expensive and faster [4].

Table 4 Interpretation of Coagulation Tests. Taken from: Rydz N. Why is my patient bleeding or bruising? Hematol Oncol Clin North Am. 2012. [5]

Coagulation tests				
PT	**PTT**	**Thrombin time**	**Fibrinogen**	**Interpretation**
Normal	Normal	Normal	Normal	Normal profile, can be seen with mild factor deficiencies
Increased	Normal	Normal	Normal	FVII deficiency, warfarin therapy
Normal	Increased	Normal	Normal	Deficiencies of FVIII, FIX, FXI, XII, VWD if FVIII is significantly decreased.
Increased	Increased	Normal	Normal	Deficiencies of FII, FV, FX; supratherapeutic warfarin.
Increased	Increased	Increased	Decreased	Dysfibrinogenemia or afibrinogenemia; late DIC or liver failure.
Increased	Increased	Increased	Normal	Large amounts of heparin (reptilase time is normal)
Normal	Increased	Increased	Normal	Heparin (reptilase time is normal)

Overall, challenges in maintaining operator performance and reproducibility during the Ivy bleeding time test, coupled with its low sensitivity and invasiveness, have led to its replacement over time by some in vitro tests [10]. One such test is the Platelet Function Analyzer (PFA-100), which measures the citrated whole blood's ability to occlude two capillary tubes coated with collagen and either ADP or epinephrine. The sample is aspirated into two separate capillary tubes, and platelets adhere to the surface, aggregate, and ultimately stop blood flow [11]. While not specific to any clinical situation, the PFA-100 serves as a screening test to detect most platelet functional abnormalities (thrombocytopenias), whether congenital or acquired. It also allows for the monitoring of antithrombotic therapies (useful prior to surgical procedures) and therapeutic response in von Willebrand disease. An abnormal finding on the PFA-100 would prompt further second line testing for specific diagnoses of primary hemostasis disorders [10, 11].

Table 5 Adapted from: Cheves TA et al. Laboratory methods in the assessment of hereditary hemostatic disorders. Hematol Oncol Clin North Am. 2021;35(6):1051–68 [11]

Interpretation of platelet agonist using the common chemical agonists		
ADP	**Decreased or absent**	**Hereditary deficiency of ADP P2Y12 receptor. Glanzmann disease; such drugs as P2Y12 inhibitors.**
Collagen	Decreased or absent	Gray platelet syndrome or Glanzmann disease.
Arachidonic	Decreased or absent	Cyclooxygenase-1 deficiency; thromboxane A2 receptor defect.
Ristocetin	Decreased or absent	Von Willebrand disease. Bernard-Soulier síndrome.
Epinephrine	Decreased or absent	Disorder of platelet α2-receptor; highly variable in normal patients.

1.3.2. Second-Line Tests

Second-line tests aim to identify the two most common bleeding disorders: von Willebrand disease and platelet function disorder.

Levels of von Willebrand factor (antigen) and ristocetin cofactor (functional activity of von Willebrand) are measured. Platelet function tests include light transmission aggregometry (LTA), the gold standard test for evaluating platelet function, and electron microscopy to assess platelet granule ultrastructure [4].

1.3.3. Third-Line Tests

Third-line tests are requested when first and second-line tests have been performed, yet a definitive diagnosis has not been obtained.

Prolongation of both PT and aPTT together, or isolated prolongation of aPTT, may suggest a coagulation cascade abnormality, warranting a mixing study. This involves mixing normal plasma with patient plasma in a 1:1 ratio, measuring PT or aPTT immediately, followed by incubation for 60 to 120 minutes at 37°C. Interpretation considers the correction of aPTT and the timing of that correction. Immediate correction upon mixing, which remains corrected in the incubated sample, suggests a deficiency of a factor replaced by normal plasma. If immediate correction upon mixing is followed by prolongation after incubation, it suggests the presence of an acquired factor VIII inhibitor with time-dependent binding. Finally, if aPTT does not correct after mixing, lupus anticoagulant presence should be considered, which is associated with a prothrombotic state rather than bleeding disorders. It is noteworthy that in patients with severe liver disease causing dysfunctional fibrinogen, both tests may be prolonged due to fibrinogen dependence for clot formation [3].

Table 6 Laboratory Tests. Adapted from: Chaigneau M. Approach to the patient with bleeding. Hematol Oncol Clin North Am. 2021. [4]

Laboratory tests	
First line	CBC, PT, aPTT, TT, peripheral blood smear (PBS), fibrinogen, ferritin, renal function, liver test, TSH, Bleeding time (BT) and platelet function analyzer 100 (PFA-100).
Second line	VWD Testing: VWF:Ag, VWF:GPIbM, FVIII. Platelet function testing (PFT): LTA.
Third line	Factor assays (II, V, VII, IX, XI, XIII), mixing studies, inhibitor assays, α_2-Antiplasmin level and plasminogen activator inhibitor activity, reptilase time.

At this stage, levels of coagulation factors (II, V, VII, XI, XIII), fibrinolysis, and thrombin generation are requested. Additionally, the reptilase time, similar to the thrombin time (TT), is measured. It assesses the conversion of fibrinogen

to fibrin, but instead of thrombin, reptilase, an enzyme similar to thrombin but resistant to inhibition by drugs like heparin, is added. Therefore, it is used to rule out heparin contamination [4].

2. Differential Diagnoses

2.1. Von Willebrand Disease

Von Willebrand disease (VWD) is an inherited bleeding disorder characterized by a quantitative or qualitative defect in von Willebrand factor (vWF). VWD affects 0.1-1.3% of the general population, making it the most common inherited bleeding disorder. Von Willebrand factor (vWF) is a high molecular weight glycoprotein synthesized and stored in megakaryocytes and endothelial cells. The gene encoding this factor is located on chromosome 12p13.2. VWD involves a decrease in von Willebrand factor, either in its function (vWF:RCo, ristocetin cofactor) or concentration (vWF:Ag), defining several subtypes of the disease [12].

- Type 1: This is the most common form, accounting for approximately 70% of reported cases. It is characterized by a quantitative decrease in vWF, which is functionally normal, representing a highly heterogeneous group of disorders.
- Type 2: Characterized by qualitative deficiencies of von Willebrand factor. It is estimated that 20-30% of all types of von Willebrand disease belong to type 2. Being such a heterogeneous group, it is divided into 4 subtypes: 2A, 2B, 2M, and 2N.
- Type 3: This variety was originally reported in 1926 by Erick von Willebrand and is defined as the absence of circulating vWF:Ag and decreased concentrations of Factor VIII by approximately 1-5%. It is the most severe form of the disease and is inherited in an autosomal recessive manner [3].

Treatment choice depends on the subtype of von Willebrand disease and the severity of bleeding. There are two treatment options for von Willebrand disease: desmopressin and transfusion therapy with blood products [12].

2.2. Hemophilia A and B

Hemophilia is a coagulation disorder attributed to a genetic origin, with a recessive X-linked inheritance pattern, where factors VIII and IX are altered, causing a functional and quantitative deficit known as hemophilia A and B, respectively [13].

Type A represents 80% of hemophilia cases, making it the most common X-linked disorder and the second most common genetic bleeding disorder after von Willebrand disease.

In Colombia, according to the latest global survey by the World Federation of Hemophilia in 2016, 2059 people were reported diagnosed with this blood deficiency (1705 with hemophilia A and 354 with hemophilia B), with patients aged 19 to 44 being the most frequently affected age group (38% of hemophilia A and B cases). Due to its low prevalence and being a chronically debilitating and life-threatening condition, hemophilia is classified as an orphan disease and even appears on the list of high-cost diseases for the Colombian health system. Depending on factor levels, it is classified as severe (<1% of normal value), moderate (1-5% of normal value), or mild (>5% of normal value).

The main clinical manifestation of hemophilia is bleeding, the degree of which depends on the level of factors VIII or IX present in the plasma, usually secondary to trauma in deep-seated locations such as joints, muscles, and the central nervous system, unlike other coagulopathies such as von Willebrand disease and platelet dysfunction, where bleeding predominates in mucous membranes. Coagulation tests commonly reveal prolonged activated partial thromboplastin time (aPTT) with normal prothrombin time (PT).

The primary goal of treatment is to prevent long-term joint damage and improve the quality of life of patients. Additionally, treatment aims to prevent and treat bleeding with deficient coagulation factors. Current management of severe hemophilia is based on prophylactic replacement of the missing factor or timely treatment when required.

2.3. Acquired Hemophilia

Acquired hemophilia, or acquired inhibitor against factor VIII, is a rare autoimmune disease, but slightly more common in individuals over 85 years old. Although it is more frequently found in men over 85 years old, it can occur in young women with autoimmune diseases, associated with paraneoplastic syndromes, during pregnancy, and postpartum [13].

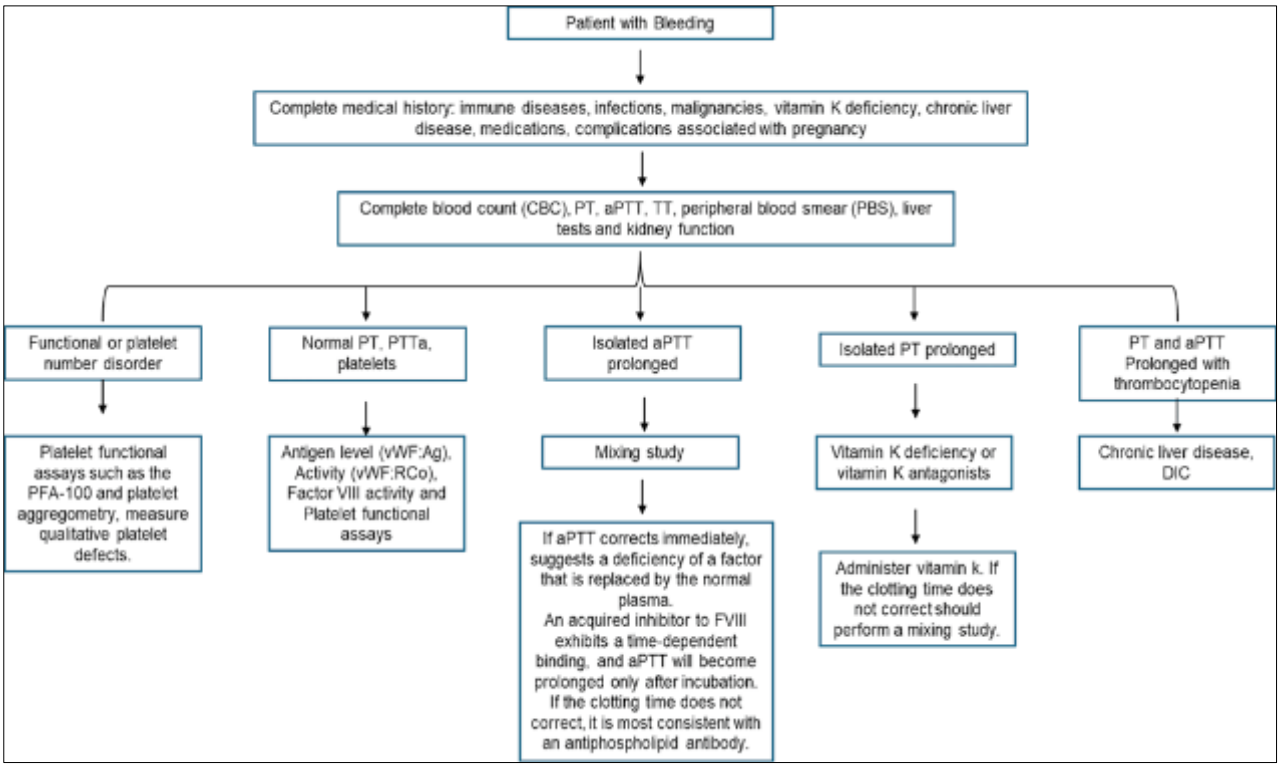

Figure 2 Diagnostic Algorithm

3. Treatment

Treatment options largely depend on the underlying bleeding disorder, the severity of the condition, presenting symptoms, and anticipated hemostatic challenges. It can be roughly classified into four areas: [4,5]

3.1. Patient Education on Bleeding

The use of local measures to control bleeding, including direct pressure on the wound and the application of cold compresses. Likewise, avoiding medications that increase the risk of bleeding and clearly understanding the need to seek urgent medical attention for any significant bleeding.[4,5]

3.2. Evaluation/Treatment of Common Consequences of Bleeding Disorders

This involves screening for hepatitis B, hepatitis C, and HIV, especially in patients who received blood products or plasma-derived coagulation factor concentrates before 1985. [4,5]

For female patients, gynecological evaluation for heavy menstrual bleeding and follow-up for iron deficiency and iron deficiency anemia.[4,5]

3.3. Indirect Therapies

Fibrinolytic inhibitors, such as tranexamic acid, may be useful for a wide range of bleeding disorders, either as adjunctive therapy or primary treatment. [4,5]

Hormonal treatment with oral contraceptives, intrauterine devices, and endometrial ablation can be effective for treating heavy menstrual bleeding in patients with bleeding disorders. Desmopressin therapy stimulates the release of VWF from endothelial cells and may provide adequate hemostatic coverage for most invasive procedures. [4,5]

3.4. Direct/Replacement Therapy

This refers to directly increasing plasma levels of the specific hemostatic defect, such as in hemophilia A or hemophilia B. In cases of refractory bleeding or the presence of an inhibitor, bypassing agents may be considered. [4,5]

4. Conclusion

A comprehensive clinical history with appropriate anamnesis, objectively reporting clinical manifestations, onset, frequency, and severity of symptoms, referencing relevant personal history, associated complications, and the need for medical intervention, coupled with timely and organized laboratory testing, is key to determining the underlying cause of the bleeding disorder. This approach allows for early and accurate therapeutic interventions.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Sang Y, Roest M, de Laat B, de Groot PG, Huskens D. Interplay between platelets and coagulation. Blood Rev. 2021; 46:100733.

[2] Vayne C, Gruel Y, Pouplard C. Hemostasis: Physiology and main exploration tests. EMC - Treatise Med. 2021;25(1):1–10.

[3] Paddock M, Chapin J. Bleeding diatheses. Prim Care. 2016;43(4):637–50.

[4] Chaigneau M, James PD. Approach to the patient with bleeding. Hematol Oncol Clin North Am. 2021;35(6):1039–49.

[5] Rydz N, James PD. Why is my patient bleeding or bruising? Hematol Oncol Clin North Am. Hematol Oncol Clin North Am. 2012; 26:321–44.

[6] Fasulo MR, Biguzzi E, Abbattista M, Stufano F, Pagliari MT, Mancini I, et al. The ISTH Bleeding Assessment Tool and the risk of future bleeding. J Thromb Haemost. 2018;16(1):125–30.

[7] Deforest M, Grabell J, Albert S, et al. Generation and optimization of the self- administered bleeding assessment tool and its validation as a screening test for von Willebrand disease. Haemophilia. 2015;21(5):e384–8.

[8] Hayward CPM. How I investigate for bleeding disorders. Int J Lab Hematol. 2018;40 Suppl 1:6–14.

[9] Bannow BS, Konkle BA. How I approach bleeding in hospitalized patients. Blood. 2023;142(9):761–8.

[10] Campuzano-Maya G. PFA-100: a new platelet function test replacing the bleeding time. The clinic and the laboratory. 2013; 19:511–48.

[11] Cheves TA, DeMarinis S, Sweeney JD. Laboratory methods in the assessment of hereditary hemostatic disorders. Hematol Oncol Clin North Am. 2021;35(6):1051–68.

[12] Martínez-Murillo C. The challenge in diagnosis and treatment. Hematol Mex. 2018; 19:61–72.

[13] Martínez-Sánchez LM, Universidad Pontificia Bolivariana, Álvarez-Hernández LF, Ruiz-Mejía C, Jaramillo-Jaramillo LI, Builes-Restrepo LN, et al. Hemophilia: diagnostic and therapeutic approach. Rev Fac Nac Salud Pública. 2018;36(2):85–93.