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Review Article

# Overview of Bleeding Disorders

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## Abstract

**Introduction:** Bleeding disorders are usually a group of conditions that occur due to the inability of the blood to clot properly. Platelets are the blood cell fragments that are responsible for providing the base for coagulation. Since bleeding is a common symptom and it need not always indicate the presence of an underlying pathological condition. Identification of a bleeding disorder can be challenging, especially because clinical bleeding can be of varying severity. The application of molecular sciences has improved the diagnostic and treatment aspects of the disease. Even though knowledge of the clinical presentation, appropriate diagnostic measures, and therapeutic options of bleeding disorders have been problematic to attain, there has been progressing with more evidence-based information to control or treat the conditions. The last two decades have seen advanced and translational investigations that have improved the clinical management of the disorders.

**Aim of the Work:** The review aims to focus and highlight the latest advances in understanding, diagnosis and treatment of Bleeding disorders.

**Methodology:** The review is comprehensive research of PUBMED from the year 1976 to 2019.

**Conclusion:** The early detection of the potential hallmarks of the underlying disorder can help in early control and treatment of the severity of the disease. Adequate laboratory and hematological tests should be performed to provide an accurate picture of the disease so that the appropriate treatment strategy can be adapted. A definitive diagnosis of a bleeding disorder will require individualized long-term hemostatic management.

***Keywords:*** *Prothrombin Time; Platelets; Coagulation Time; Clotting*

## Introduction

The human body has an inbuilt mechanism to control the bleeding pertaining to an injury. Hemostasis is started by any injury to the vascular wall, which can lead to the deposition of platelets that adheres to the components of the sub-endothelium [1]. The bone marrow megakaryocytes are where the platelets are derived from. They are a nuclear cellular fragments whose complex internal structure represents their hemostatic function. The platelets have two major intracellular bodies, which are the alpha granules and dense bodies, which are released through an open canalicular system when they are stimulated [2,3].

The hemostatic system, with the help of prostacyclin, antithrombin III and nitric oxide within the endothelial cells, keeps the blood in its fluid state without platelet aggregation or thrombus formation. These innately present substances help in clot prevention by converting plasminogen into plasmin for promoting fibrinolysis. An injury or damage to the endothelium initiates a cascade of events for controlling the bleeding. Local vasoconstriction, which limits the blood flow sets the primary hemostatic action in play where the platelets

release the von Willebrand factor (vWf) and glycoproteins. A plug is formed at the site of injury by the combination of platelets and vWf. Collagen and factor VII binds with the circulating vWf which further enhances the adhering of the platelet plug to the area of injury. Bleeding disorders occur when there is a deficiency in any of the essential clotting factors [4].

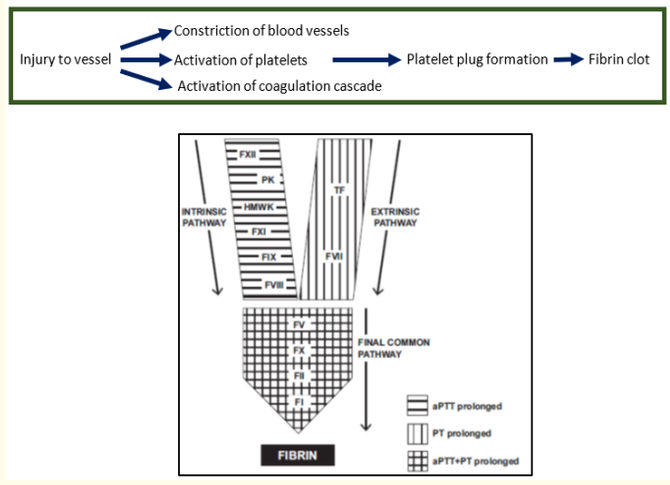


***Figure 1:*** *Simplified schematic presentation of a coagulation cascade [5].*

Bleeding disorders can be present during childhood (severe bleeding disorders or congenital bleeding disorders) or during adulthood (bleeding after a hemostatic condition like surgery/trauma, hemophilia or Von Willebrand disease). Coagulation factor inhibitors seen in acquired disorders are seen more in adults than in children. It is usually detected in adults during an abnormal laboratory test or an early consultation due to the presence of an inherited disorder in the family [6].

Understanding the pathophysiology of impaired hemostasis of any bleeding disorder can help to choose the correct treatment and avoid unnecessary or contraindicated therapies [6].

The impact of molecular biology on inherited bleeding disorders has continued to grow over the years. There has been an improved influence in terms of basic knowledge of gene biology of the clotting factors and therapeutic options seen in forms of gene transfer for bleeding disorders like hemophilia B [7].

The usage of prophylactic treatment protocols for hemophiliacs are being widely used because of routine molecular diagnosis. This helps in the long-term musculoskeletal health of such patients. The most common inherited bleeding disorder is Von Willebrand's disorder (VWD). The cloning of the VWF gene in the 1980s helped in gaining knowledge of the disease pathogenesis. There has been an establishment of a rare bleeding disease registry, which has widened the information that is available for the development of a more evidence-based approach for the management of these diseases. Benign hematology has evolved due to substantial advances in clinical management [7].

## Platelet function and its disorder

The abnormality in platelet function can be acquired or hereditary. Usually, mucocutaneous bleeding or excessive hemorrhage is seen in patients following surgery or trauma. Careful examination of the peripheral smear must be done to account for the size of the platelets in all patients who presents with mucocutaneous bleeding. The presence of large platelets can indicate the following [1,8].

The primary hemostatic response can be assessed by the bleeding time (BT). However, it can be nonspecific and insensitive in many cases. There still appears to be a substantial variation in the Bleeding times between the individuals who perform it. Initially, along with this the Rumpel-Leede test was used to evaluate the platelet/vascular response to injury [9]. An important component of laboratory testing in a patient with clinical findings is platelet aggregation suggestive of a primary hemostatic abnormality. ADP, epinephrine, or collagen can be added to normal platelet-rich plasma, which can produce an aggregation pattern showing a biphasic pattern when an agonist like epinephrine is used. A 'release reaction' of dense bodies is seen, which is abnormal in diseases like Hermansky-Pudlak, Che´diak-Higashi,

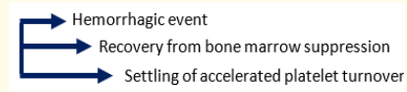


***Figure 2***

Wiskott-Aldrich syndromes, and thrombocytopenia with absent radii. Tests like flow cytometry, prothrombin consumption test, receptor occupancy and electron microscopy for evaluating ultrastructural anatomy can also help in evaluating platelet function [1].

## Diagnostic considerations

### Bleeding symptoms

- Bleeding as a symptom does not necessarily indicate a bleeding disorder. Gum bleeding, epistaxis, menorrhagia, petechiae and bruising are commonly seen in 22 - 85% of an asymptomatic population [10].

### Clinically significant mucocutaneous bleeding is defined as either of the following:

- Spontaneous or elicited bleeding from 2 or more separate mucocutaneous sites;
- Bleeding from a single site necessitating blood transfusions; or
- Bleeding from a singular site on 3 or more separate instances.

For physical examination, skin and mucous membranes should be inspected for bruising, petechiae, etc. Skin or conjunctival pallor, tachycardia, or a cardiac flow murmur should also be assessed for which could indicate possible anemia. Patients with quantitative or qualitative platelet disorders may show [10]:

- Excessive bruising,
- Epistaxis,
- Bleeding after dental extraction, and
- Menorrhagia.

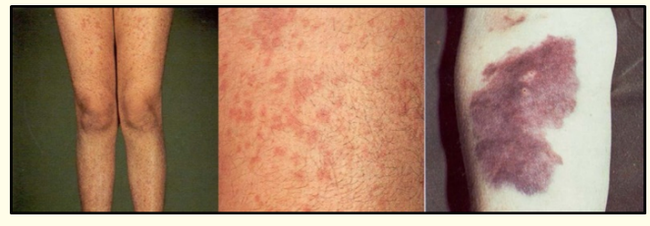

***Figure 3:*** *Scattered petechiae, purpura and large ecchymosis [11].*

### Laboratory tests

Suggested preliminary laboratory tests includes complete blood count, pregnancy test, prothrombin time (PT), aPTT, fibrinogen, and if feasible, VWF levels. The liver or platelet function or specific factor levels can be tested additionally. Acquired or congenital clotting factor deficiency or an inhibitor of one or more coagulation factors can be indicated by the Prolongation of the aPTT or PT [10].

### Types of bleeding disorders

Broadly platelet disorders can be qualitative or quantitative. Quantitative platelet abnormalities seen in adults are usually acquired; autoimmune (i.e. isolated thrombocytopenia's like idiopathic thrombocytopenic purpura [ITP]) and drug-induced thrombocytopenia). Others include disseminated intravascular coagulation [DIC] and thrombotic thrombocytopenic purpura [TTP] may be seen in acutely ill or asymptomatic patients [12]. Qualitative platelet disorders seen in adults are triggered by medication (e.g. aspirin and nonsteroidal anti-inflammatory drugs [NSAIDs]), uremia, cirrhosis, and myeloproliferative disorders [13]. von Willebrand's disease (a disorder of platelet adhesion due to the decrease in the vWf) shows clinical signs and symptoms similar to other platelet disorders. Specific tests like (VWF antigen, VWF ristocetin cofactor activity, and factor VIII activity assays) can be done for confirmation [5].

## Haemophilia

Congenital coagulation factor deficiencies like Hemophilia A (deficiency in factor VIII- 1:5000 male births) and hemophilia B (deficiency in Factor IX- 1:30,000 male births). Apart from bleeding into the deep tissue, joints and muscles (suggesting a coagulation factor defect), the most important and life-threatening types of bleeding to be considered here are [14]:

- Intracranial hemorrhage which can eventually lead to death in patients
- Bleeding into the iliopsoas muscle
- Bleeding may occur in the neck when the retropharyngeal space is expanded by a hematoma, occluding the airway.

The laboratory findings show a prolongation of the PTT with normal PT, bleeding time, and thrombin time. Severe hemophilia will show the PTT 2 to 3 times longer than the reference range. With the help of amniocentesis or chorionic villus sampling, prenatal diagnosis is available using chromosomal analysis of cells [14].

The treatment of hemophilia is by factor replacement, which can be done at the time of the bleeding episode or as a prophylactic measure. Since there are no specific guidelines for the optimal time to initiate prophylaxis, dosing of factor concentrate and the length of treatment prophylaxis can be initiated before the occurrence of repeated hemarthroses. Factors are usually given 1 to 4 times per week with a central catheter or peripheral venipuncture. Monitoring of the trough levels of the factor activity must be done several times in a year. Desmopressin can be used to treat mild to moderate hemophilias.it is usually administered intranasally, intravenously, or subcutaneously. The responses of patients to the desmopressin intake may vary; a response may also decrease with repeated administration [14].

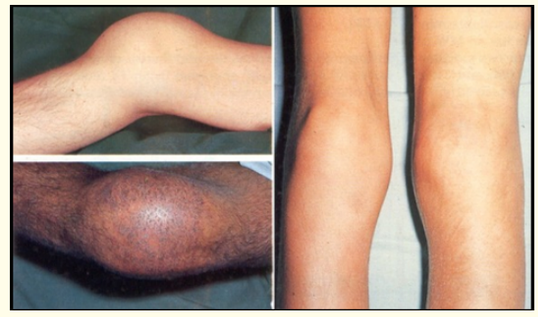

***Figure 4:*** *Hemarthroses in haemophilia [11].*

An important iatrogenic complication of developing factor inhibitors (specific antibodies like (IgG) against factor VIII or IX) is seen more with hemophilia A. Chronic arthropathy, Joint deformity, muscle atrophy, and soft tissue contractures can develop die to repeated hemarthroses. Erythrocytes release hemoglobin, which can get deposited into affected joint spaces and subsequently leads to inflammatory synovitis. destruction of the bone and cartilage can result due to subsequent bleeding into a joint [14].

## Thrombocytopenia

It is a condition when the platelet count is below the lower limit of the normal range (i.e. < 150,000/μL). It occurs due to impaired production, destruction, consumption, or sequestration of platelets. Immune thrombocytopenias, which could be idiopathic (primary) or secondary to an autoimmune disease, maybe seen along with asymptomatic, isolated thrombocytopenia. Medications, infectious agents such as Epstein-Barr, human immunodeficiency, or hepatitis C virus, or primary marrow failure could be the other causes.

Few thrombocytopenic conditions can be excluded due to the lack of specific predisposing factors or acute illness (e.g. Shiga toxin-induced hemolytic uremic syndrome or DIC). The bleeding intensity in thrombocytopenic conditions generally depends on the platelet count.

When platelet counts exceed 20,000/μL, bleeding is usually mild and limited to easy bruising [15].

Only when the platelet count decreases to < 10,000/μL, the risk for spontaneous bleeding increases except in ITP, in which the increased presence of young, hyper-functional platelets can retain hemostasis even when the platelet counts are below this level [16].

### Other conditions

Acquired deficiencies of single coagulation factors should be differentiated from congenital deficiencies. Prolongation of aPTT and PT can be due to deficiencies of multiple factors from both the intrinsic and extrinsic pathways or from all 3 pathways. Liver disease, supratherapeutic warfarin doses resulting in a deficiency of vitamin K–dependent factors, or consumptive coagulopathy (i.e. DIC) multiple factor deficiencies are seen [7].

Prolongation of PT or, in more advanced stages, of both PT and aPTT are seen in Vitamin K deficiency and liver disease. Due to malabsorption, prolonged antibiotic use, or warfarin therapy depletion of the vitamin K–dependent coagulation factors (II, VII, IX and X) are seen. It is unlikely to see in patients with liver disease asymptomatic coagulation laboratory irregularities and often has concurrent physical signs (e.g. jaundice, hepatomegaly) or other laboratory abnormalities indicative of impaired hepatic function (e.g. thrombocytopenia, hypoalbuminemia, transaminitis) [7].

## Therapeutic strategies

### Preventive measures

Universally medications that impair function, such as aspirin and NSAIDs, should be avoided, particularly during bleeding episodes. screening for common age-related comorbidities and related risk factors must be performed routinely as a part of preventive care. Invasive procedures must be performed with minimal bleeding risks, which should only be attempted after consultation with the hematologist. Topical measures to prevent bleeding from wounds by applying pressure or packing the wounds can control epistaxis [17].

### Platelet transfusion

Usually done in patients with thrombocytopenias when the situation is life-threatening to reduce risk of internal bleeding to major organs. leukocyte-depleted concentrates may be used if human leukocyte antigen–matched platelets are not available [5].

### Hemostatic therapies

Consultation with the hematologist is of utmost importance before any of the transfusion of any blood products. The transfusion of defective of missing hemostatic components may not work for all patients. Other specialized treatment modalities can be used if the disease is specifically known (e.g. plasma exchange for TTP) [18].

### Coagulation factor replacement

In cases of active bleeding or for hemostatic coverage before surgery, the suspected coagulation factor replacement can be done. The decision will be influenced by assessing the patient's bleeding tendency, severity, and anticipated risk of bleeding. However, the prophylactic transfusion of FFP has not shown to correct coagulation abnormalities. Fresh frozen plasma (FFP) and cryoprecipitate are used worldwide for factor replacement. FFP contains all the clotting factors and is obtained from whole blood. Cryoprecipitate FVIII, VWF, FXIII, and fibrinogen are obtained by thawing a single unit of FFP at $4^0$ Celsius [5].

### Nontransfusional hemostatic therapies

Nontransfusional therapies can be used for the treatment or prevention of these conditions with antifibrinolytics like e-aminocaproic acid or tranexamic acid, desmopressin, and vitamin K. It can also be administered as an adjunct to transfusional therapies when there is more severity of bleeding or if any major surgery requires hemostatic coverage.

Antifibrinolytics and hormone therapy can be used in menorrhagia of women along with combination or progestin-only contraceptives for maintenance therapy. Even in refractory cases, transfusional therapies can be used [5].

## Conclusion

Since bleeding disorders have a wide spectrum of possible clinical presentations, the primary care provider plays an important role in an early identification process of an undiagnosed bleeding disorder. The ability to recognize the signs and symptoms will help in the accurate diagnosis of the underlying pathological condition. The correct diagnosis can be validated by appropriate laboratory findings and understanding of the coagulation abnormality. Practical guidance must be inculcated in every clinician's practice for the rightful evaluation of the symptoms of bleeding and abnormal hematological tests. Every clinician must have adequate knowledge about preventive care and hemostatic management of patients who have been conclusively diagnosed with a bleeding disorder.

The management of the bleeding disorders is a multidisciplinary approach where a consultation with the hematologist can help in proper treatment and evaluation, especially in adults with rare bleeding disorders.it is recommended to avoid systemic interventions for minor bleeding.

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