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EC EMERGENCY MEDICINE AND CRITICAL CARE

Mini Review

Approach to Patients with Bleeding Disorders in the Emergency Department

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Received: November 22, 2018; **Published:** December 28, 2018

Abstract

Bleeding due to abnormal haemostasis, although rare, is a crucial pathology to grasp for an emergency physician. Clinical presentation varies as bleeding can be minor or life-threatening depending on the site and the underlying haemostasis defect. Since the emergency medicine physician is probably the first to assess and manage the patient, having knowledge regarding the underlying pathophysiology, the aetiology and a structured approach to a patient with bleeding disorder in the emergency department is essential because the workup and management are different from those used for patients with injury-related, normal haemostatic bleeding.

Keywords: *Bleeding Disorders; Emergency Department; Haemostasis; Bleeding; Coagulation; Thrombin Time; Transfusion; Haemophilia*

Abbreviations

ED: Emergency Department; FFP: Fresh Frozen Plasma; TTP: Thrombotic Thrombocytopenic Purpura; TT: Thrombin time; PT: Prothrombin Time; aPTT: Activated Partial Thromboplastin Time; LMWH: Low Molecular Weight Heparin

Introduction and Pathophysiology

Patients who bleed due to abnormal haemostasis often present to the emergency department, and it is important to recognise these patients through careful history-taking and examination and to have essential knowledge regarding the underlying pathophysiology because the workup and management could be different from those used for patients with injury-related, normal haemostatic bleeding.

Haemostasis is a complex physiological mechanism that consists of the following major events (Figure 1 and Table 1) [1-4]:

1. **Primary haemostasis:** platelet aggregation at the site of vessel endothelial injury.
2. **Secondary haemostasis:** consolidation of a platelet plugs through the activation of coagulation factors.
3. **Fibrin clot formation:** thrombin-dependent process fibrinogen is converted into fibrin.
4. **Inhibition of coagulation:** endogenous or exogenous inhibition of thrombin, resulting in clot breakdown.

Haemostasis event	Disorders	
Primary haemostasis disorders [2]	Vascular abnormalities	Hereditary haemorrhagic telangiectasia
		Disorders of the connective tissue (including Ehlers–Danlos disease and osteogenesis imperfecta)
		Small vessel vasculitis
	Von Willebrand disease	
	Thrombocytopenia	Decreased production: bone marrow dysfunction or inadequate precursors such as vitamin B12 and folic acid
		Destruction or consumption as in disseminated intravascular coagulation (DIC), infection, drugs most commonlyheparin and then some antimicrobials, anti-arrhythmic, anticonvulsant, and antifungal agents and H2 receptor antagonists, toxins, systemic illness such as liver or renal disease, immune diseases such as ITP and TTP
		Sequestration: hypersplenism
	Platelet dysfunction	Hereditary: VWB, Ehlers–Danlos syndrome, Bernard–Soulier syndrome, Glanzmann's thrombocytopenia, Congenital fibrinogen disorders Congenital platelet disorders
		Acquired: drug effect such as antiplatelet
		Systemic illness: uraemia, cirrhosis, SLE
		Surgery-related: cardiac surgery, liver transplant
Secondary haemostasis disorders [3]	Haemophilias Liver disease Vitamin K deficiency Acquired inhibitors of coagulation (antibodies) Consumptive processes (e.g. DIC)	
Fibrin clot formation [4]	Hyperprothrombinaemia Haemophilia (A and B) Hereditary fibrinogenaemia Drugs Systemic illness (chronic liver disease)	
Inhibition of coagulation	Coagulation factor deficiency	Idiopathic Rheumatic diseases Postpartum period Malignancy Drugs SLE Antiphospholipid Congenital Surgery Malignancy

Table 1: *Classification based on haemostasis defect mechanism.*

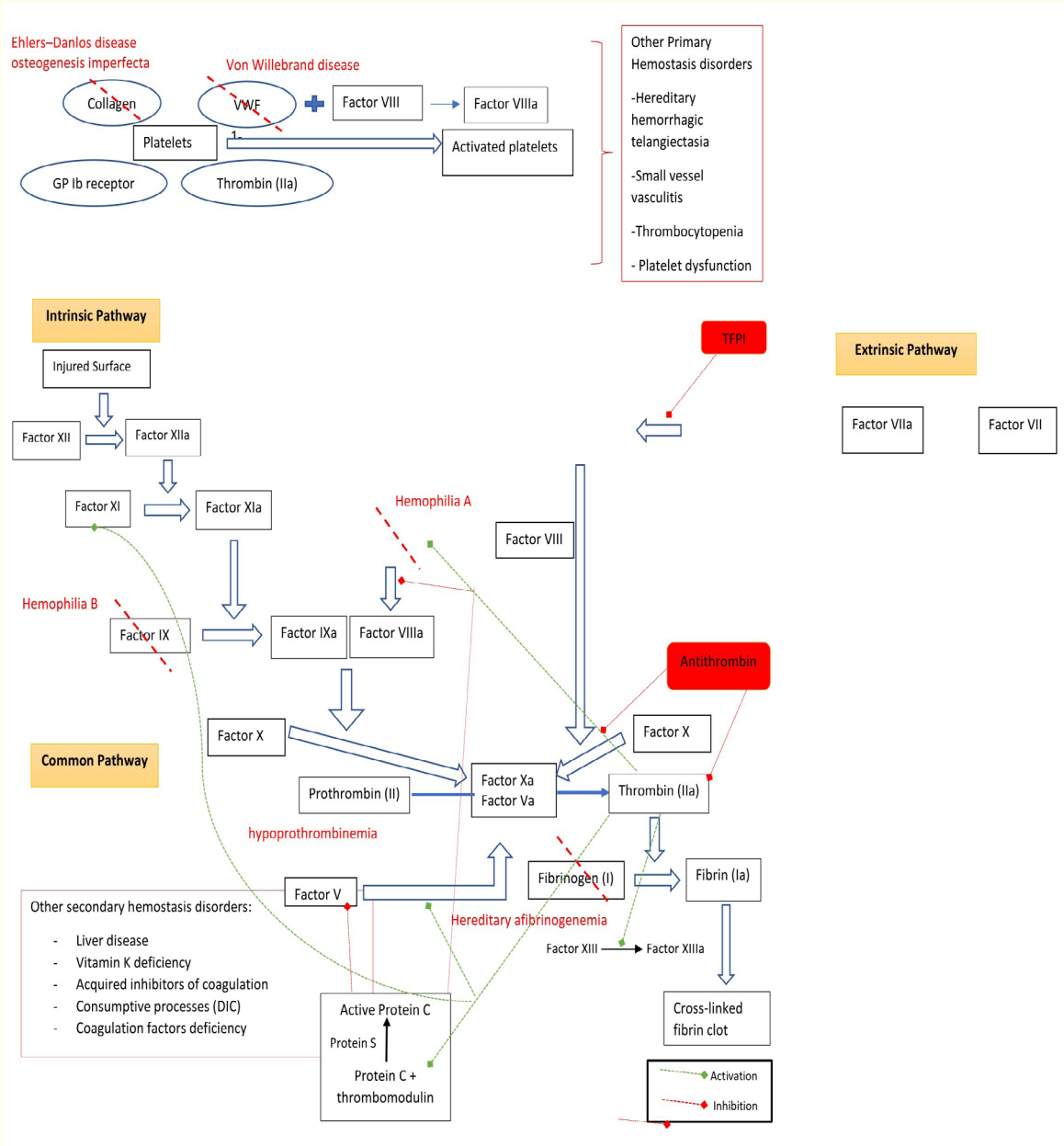


Figure 1

Aetiology

The aetiology of bleeding disorders can be either congenital or acquired (Table 2) [5,6]. Bleeding disorders can be generally classified as either platelet disorders or coagulation factor deficiencies, or they could be caused due to both disorders such as in disseminated intravascular coagulation as outlined in table 3 [7].

Congenital	Acquired
Haemophilia A (factor VIII deficiency)	Disseminated intravascular coagulopathy
Haemophilia B (Factor IX deficiency)	Liver disease
Von Willebrand disease	Vitamin K deficiency
Fibrinogen disorders	Massive transfusion of stored blood
	Acquired inhibitors of coagulation
	Heparin or oral anticoagulant therapy
	Renal disease
	Hypersplenisim

Table 2: *Classification of bleeding disorders based on aetiology [5,6].*

Platelet disorder	Low platelet number	Congenital thrombocytopenia	Wiskott–Aldrich syndrome
		Impaired bone marrow production	Impaired bone marrow production aplastic anaemia, megaloblastic anaemia and bone marrow infiltration
		Increased platelet destruction/consumption.	Immune-related conditions such as autoimmune thrombocytopenia (ITP), systemic lupus erythematosis, drugs and non-immune conditions such as DIC, TTP
		Splenic sequestration	hypersplenism
	Platelet dysfunction	Inherited	Glanzmann's thrombasthenia, Bernard–Soulier syndrome and Von Willebrand disease
		Acquired	Aspirin ingestion, uraemia and in myeloproliferative disorders
Disorders of the Coagulation Cascade	Inherited bleeding disorders	Haemophilia A (Factor VIII deficiency) Haemophilia B (Factor IX deficiency) Von Willebrand disease Congenital fibrinogen deficiency	
	Acquired bleeding disorders	Liver disease Renal disease Vitamin K deficiency DIC Anticoagulant therapy Massive transfusion Hyperfibrinolysis	

Table 3: *Simplified classification of bleeding disorders based on underlying haemostasis pathophysiology [7].*

History and physical examination

Patients with an underlying diagnosed bleeding disorder will probably be aware of their illness or would carry a document indicating their diagnosis. Physicians should enquire about previous ED presentations, previous medications received, or previous hospital admissions and procedures performed. For patients who present with non-injury-related bleeding, specific yet detailed history-taking is essential to exclude possibilities of underlying undiagnosed bleeding disorders. Important historical factors in patients with de novo bleeding episodes are outlined in table 4 [8-10]. Bleeding disorders caused due to platelet pathology would manifest generally as petechiae, bruises and mucous membrane bleeding, whereas those caused due to dysfunction of the coagulation cascade may present with deep tissue bleeding such as haemarthrosis and deep muscle and soft tissue bleeding. Considering that several systemic illnesses cause haemostasis dysfunction, examination for signs of chronic illness such as chronic liver disease, signs of anaemia such as pale mucous membranes, and signs of end-stage renal disease is an important component of physical examination. The International Society on Thrombosis and Haemostasis published a definition of a major bleeding episode in 2005 based on the following objective data [11].

1. Fatal bleeding, and/or
2. Symptomatic bleeding in a critical area or an organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or
3. Bleeding causing a fall in haemoglobin level of 20g L^{-1} (1.24 mmol L^{-1}) or more or leading to transfusion of two or more units of whole blood or red cells.

History of current presentation	Onset Location Severity Amount estimation Skin manifestation (bruises, petechiae) Systemic symptoms (dizziness, syncope, dyspnoea, palpitation, abdominal or back or chest pain) Spontaneous bleeding or provoked Gum bleeding when brushing teeth.
Past medical and surgical history	Prolonged or recurrent bleeding from wounds, lasting more than 15 min or recurring spontaneously during the 7 days after the wound, or after surgical procedures such as tonsillectomy, history of blood transfusion. Bruises, after minimal or no apparent trauma Spontaneous nosebleeds that lasted more than 10 min or required medical attention to stop.
Medication history	Prescribed and over the counter medications, including herbal medications or teas. Common drugs to enquire about are the 5 A's: 1. ASPIRIN 2. ANTICOAGULANTS 3. ANTIBIOTICS 4. ALCOHOL 5. ANTICANCER
Gynaecology and obstetrics history	History of menorrhagia. History of post-partum haemorrhage. Recurrent abortions.
Occupational history	Animal exposure (Crimean–Congo haemorrhagic fever). Working in industries that use fibrous glass material.
Travel history	Ask about travel to countries at risk of haemorrhagic fever.

Table 4: *History elements in a bleeding patient [8,9,10].*

Any bleeding symptoms that do not meet the above-mentioned criteria can perhaps be called a minor bleeding.

Investigations

The laboratory evaluation for bleeding includes conducting initial screening tests. The most common screening tests that can be performed in the emergency room are platelet counts, prothrombin time (PT) and activated partial thromboplastin time (aPTT). For an individual with known haemophilia, routine laboratory investigations (PT, PTT, factor levels) are not indicated for a routine bleeding episode unless requested by the patient's haematologist. The clinical severity of a patient's haemophilia is gauged by his or her baseline clotting factor level, a value that remains constant throughout that person's life [12].

Alternatively, an individual with an undiagnosed bleeding disorder may present with abnormal haematologic laboratory results obtained as a part of routine evaluation or an evaluation for surgery or for some other reason. A prolongation of aPTT or PT of a patient who is not on any prescribed anticoagulants may indicate an acquired or congenital clotting factor deficiency or an inhibitor of one or more coagulation factors (Figures 2–4).

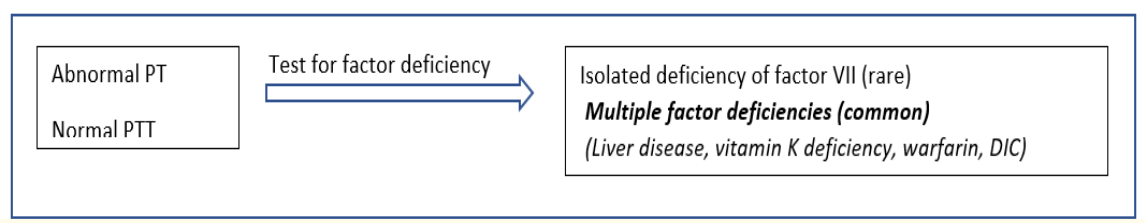
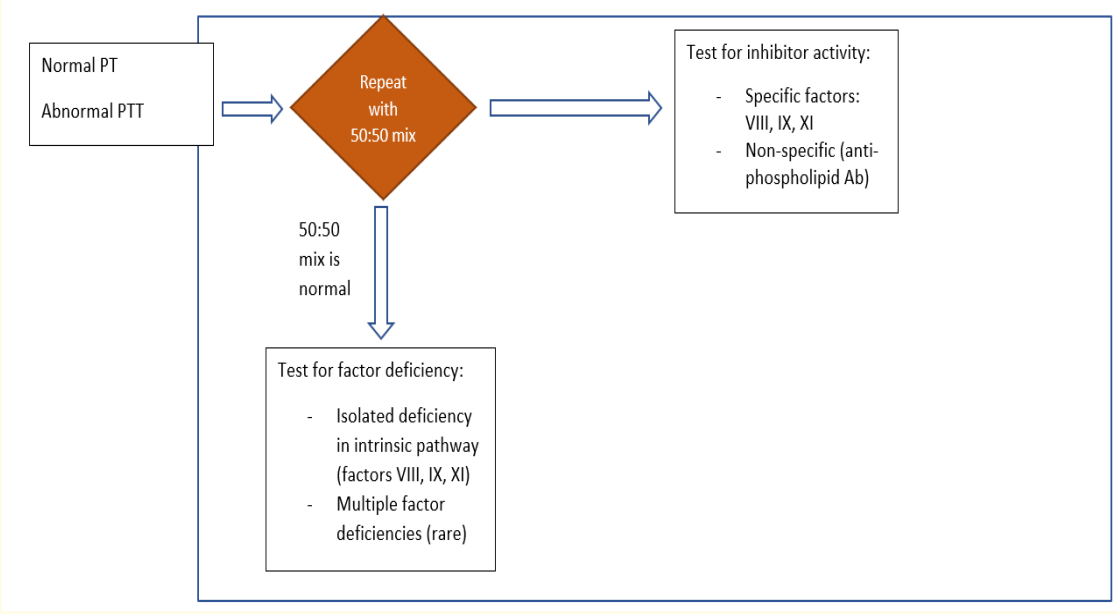


Figure 2: *Illustration to laboratory investigation of bleeding disorders.*



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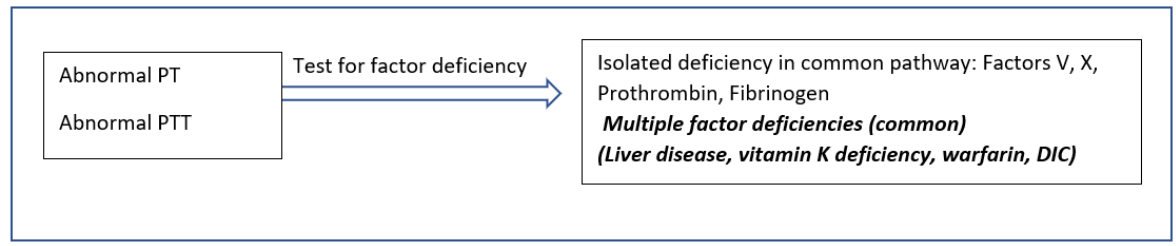

Figure 4: *Illustration to laboratory investigation of bleeding disorders.*

Thrombin time (TT) is of novel interest to emergency physicians as it helps them assess the bleeding tendency in patients using new anticoagulants. The TT is the time required to convert fibrinogen into a fibrin clot, bypassing the intrinsic, extrinsic and common pathways. Dabigatran (Pradaxa) was licensed for the treatment of non-valvular atrial fibrillation. Routine monitoring of TT in patients using dabigatran is not required; however, testing for drug clearance may be needed in select circumstances such as emergencies. TT is highly sensitive to the presence of any thrombin inhibitors in the plasma, which include oral thrombin inhibitors such as dabigatran as well as parenteral thrombin inhibitors such as heparin (both unfractionated and LMWH), argatroban, lepirudin and bivalirudin. TT shows a minimal value in the context of overdose assessment where aPTT and PT-INR may be of more use. Another cause for a prolonged TT that may be encountered is a low fibrinogen level which can occur with massive haemorrhage, disseminated intravascular coagulation or post-thrombolytic therapy. In this context, measurement of the fibrinogen level would be particularly useful. Uncommon causes of TT prolongation include dysfibrinogenaemia, some par proteins and high levels of fibrinogen degradation products.

Approach to Patients with a Possible Bleeding Disorder in the ED

Considering the above-described pathophysiology, the clinical presentation and the investigation discussed above, we recommend following a 5-step approach for evaluating patients presenting to ED with non-traumatic bleeding who may potentially have an underlying acquired or congenital bleeding disorder. The 5-step approach will help define the type of bleeding and in providing the basis for planning management, including the initial decisions regarding administration of blood products.

Step 1: Is there a problem with the patient's platelets?

- Look for petechial haemorrhage, easy bruising, mucous membrane bleeding, epistaxis and menometrorrhagia.
- Perform screening laboratory tests (platelet counts, PT and aPTT).
- Platelet aggregation would be assessed by the haematologist.

Step 2: Does the patient have a single factor deficiency?

- Such as haemophilia A (FVIII) or B (FIX) or very common or rare deficiencies such as FVII, FX, FV and FXI.
- Look for purpura, haemarthrosis, muscle haematoma and bleeding of large vessels.
- Screening test for PT and aPTT.
- Factor assays.

Step 3: Does the patient have deficiency of several vitamin K-dependent coagulation factors?

- Indicated by history of poor nutrition, vitamin K malabsorption, warfarin ingestion, symptoms and signs of liver disease.
- Warfarin and liver disease produce multiple factor deficiencies involving the extrinsic and common pathways.
- Screening for PT and aPTT.
- Factor assays.

Step 4: Is there a circulating anticoagulant?

- Such as heparin, FVIII or IX antibody and lupus anticoagulant.
- Check aPTT, 1:1 mixing, aPTT, TT and reptilase time.

Step 5: Does the patient have consumptive coagulations?

- Such as TTP, HUS, vasculitis, sepsis, obstetrical complications, trauma and liver disease.
- Check platelet count, PT, aPTT, TT, fibrinogen, D-dimer and blood smear.

Treatment

The principles of managing a patient with active bleeding in the ED are the same irrespective of whether the aetiology is trauma-related or there is an underlying bleeding disorder [13]. Beginning with haemodynamic assessment is important; management of a haemodynamically unstable patient focuses on controlling the source of bleeding while simultaneously resuscitating with red blood cell transfusion initially and then adding other blood products that will help maintain haemostasis, such as FFP, platelets, cryoprecipitate, prothrombin complex concentrate, tranexamic acid and calcium, as well as maintaining normothermia [4]. Table 5 outlines the management priorities of an actively bleeding patient in the ED. If the patient presents with recent bleeding or non-major bleeding and is haemodynamically stable, it is recommended to consult haematology before transfusing blood products to avoid harmful transfusion therapy (such as transfusion of platelets to a thrombocytopenic patient with possible heparin-induced thrombocytopenia or thrombotic thrombocytopenic purpura (TTP) may induce thrombosis) and to collect required blood samples for diagnosis as results will not be accurate once the patient is transfused [10].

1. Assess haemodynamic stability.
2. Control the source of bleeding.
3. Activate local massive transfusion protocol if major bleeding or haemodynamic instability is believed to be caused due to haemorrhage.
4. If haemodynamically stable, replace PRBC as per estimated blood loss if needed and replace platelets and coagulation factors based on platelet count, PT and PTT result and expected underlying aetiology of bleeding disorder whether congenital or acquired.
5. Serial assessment of ongoing bleeding and response to resuscitation by repeated serum lactate, vital signs and coagulation profile (PT, PTT, INR, fibrinogen level, blood pH and ionised Ca).
6. Definitive diagnostic test to identify the bleeding source based on the presenting complaints of the patient (POCUS, CT, endoscopy, angiogram).
7. Definitive bleeding site management once the bleeding source/aetiology is identified.
PRBC: Packed red blood cell POCUS: Point-of-care ultrasound CT: Computed tomography

Table 5: *Priorities of managing actively bleeding in the ED [20].*

Conclusion

Bleeding disorders are common specially the acquired one. Having understanding of etiology, clinical presentation and management is essential for safe emergency medicine practice. The five step approach described above will help the emergency physician to assess patients presenting with non-traumatic bleeding in order to detect possible acquired or inherited bleeding disorders. Preparing our EDs to patient with bleeding disorders will facilitate their management and enhance safety of therapy provided in ED.

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Volume 3 Issue 1 January 2019