Bleeding of Unknown Etiology

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When a patient is actively and rapidly bleeding, it may need to be managed before making a diagnosis of bleeding etiology. The bleeding may be due to coagulopathy, overdose of anticoagulant, accidental/suicidal ingestion of rat poisoning, anatomical bleeding, or surgical bleeding, or the etiology may remain unknown. In an emergency, blood specimens may not have been drawn; however, treatment should be started without knowing the cause of bleeding. The work-up for bleeding usually starts with laboratory testing for prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, and platelet count, included in complete blood count (CBC), as first-tier (Table 16.1) testing. In the setting of anemia, if both the MCV and MCH are decreased and red blood cell distribution width (RDW) is increased, it suggests chronic iron deficiency anemia. If PT, aPTT, fibrinogen, and platelet count are normal, second-tier testing may be performed, including coagulation factor assays, platelet aggregation studies, rotational thromboelastometry (ROTEM™) or thromboelastography (TEG™), PFA-100™, and factor XIII assay (Table 16.1).

Unclassified bleeding disorders may be defined as within normal limits in all tests listed in Table 16.1. Even in tertiary care hospitals, tests shown in Table 16.1 may not be performed in-house. If the tests listed in Table 16.1 are all normal, bleeding can only be defined as an unknown bleeding disorder.

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Hemophilia Carrier and Diagnostic Difficulty in Hemophilia A

Even if the PTT is within the normal range and factor VIII is normal, hemophilia carriers may experience excessive bleeding after surgery, hemarthrosis, or postpartum hemorrhage [1, 2]. Recently it had been shown that hemophilia carriers with normal baseline factor VIII levels but with abnormal bleeding scores had lower and less sustained factor VIII increase to DDAVP, suggesting an impaired ability to respond to hemostatic stress [3]. Diagnosis of hemophilia A is also dependent on the method of factor VIII assay. Even if one-stage clotting assay for factor VIII activity is normal, chromogenic factor VIII assay may give a low value or vice versa [4].

Factor XIII Deficiency

ROTEM™ or TEG™ may be used as a screening test for factor XIII deficiency. It may show normal clotting time and low maximal clot firmness in ROTEM™, or normal reaction time with low maximum amplitude in TEG™, with evidence of fibrinolysis [5, 6]. However, unless the factor XIII level is below 10–15%, TEG™ or ROTEM™ may be normal, while factor XIII less than 30% was already associated with a high variability of bleeding severity, and XIII >15% is a proposed target to start prophylaxis for prevention of major bleeding [7]. Factor XIII deficiency or acquired factor XIII inhibitor may cause delayed bleeding or intramuscular hematomas. A factor XIII assay is needed to make a diagnosis; however, before the result is available, factor XIII concentrate or recombinant factor XIII may be given based on the finding of ROTEM™ or TEG™ if the factor XIII assay is not performed in-house. The classic symptom of congenital homozygous factor XIII deficiency is bleeding from the umbilical cord on days 5–7 following birth. Still, patients with heterozygous factor XIII deficiency may not bleed until surgical procedure or dental extraction is performed [8]. If the patient has no bleeding history, but has developed

J. Teruya (ed.), *Management of Bleeding Patients*, https://doi.org/10.1007/978-3-030-56338-7_16

Table 16.1 Laboratory tests related to hemostasis

First tier
PT
aPTT
Fibrinogen
Platelet count
Second tier
Thrombin time
Coagulation factor assay
Factor XIII assay
Viscoelastometry (ROTEM™ or TEG™)
PFA-100™
Von Willebrand panel (factor VIII, VWF activity, VWF antigen, activity/antigen ratio, VWF multimer assay). VWF collagen binding assay may also be included in the panel.
Third tier
Euglobulin lysis time
α2-Antiplasmin (α2AP)
Tissue plasminogen activator (tPA)
Plasminogen activator inhibitor-1 (PAI-1)
Plasmin–antiplasmin complex (PAP)
Tissue factor pathway inhibitor (TFPI)
Chromogenic factor VIII
Thrombin generation assay (TGA)
Bleeding time[a]

[a]In collagen disorder, bleeding time may be prolonged with a normal platelet aggregation study or PFA

new onset of bleeding such as intramuscular bleeding, a factor XIII inhibitor should be suspected [9]. If the patient has compartment syndrome due to intramuscular bleeding, fasciotomy should be performed after giving factor XIII concentrate or recombinant factor XIII and an increase in factor XIII level has been confirmed, or there is improvement of ROTEM™ or TEG™ parameters [10].

Acquired von Willebrand Syndrome

Acquired von Willebrand syndrome (AVWS) may not cause serious spontaneous bleeding; however, it may cause bleeding during invasive procedures or anticoagulation. Also, occasional spontaneous gastrointestinal bleeding due to AVWS and angiodysplasia (Heyde syndrome) occurred in dysfunctional prosthetic heart disease [11]. Since AVWS is under-recognized, knowledge of underlying conditions associated with AVWS is necessary (Table 16.2).

It should be noted that ROTEM™ or TEG™ cannot detect von Willebrand disease unless it is the severe type, i.e., Type 3. In the setting of Type 3 von Willebrand disease, clotting time in ROTEM™, or reaction time in TEG™, is prolonged due to a low factor VIII level. Since it is unlikely that factor VIII level is decreased enough to prolong clotting time (or reaction time) in acquired von Willebrand disease, ROTEM™ or TEG™ cannot accurately detect this condition. PFA-100™ may be useful to detect undiagnosed von Willebrand disease or acquired von Willebrand syndrome [12]. However, the PFA-100™ has several limitations. PFA-100™ may be prolonged by thrombocytopenia, anemia, high erythrocyte sedimentation rate, or medication. Therefore, this test is of limited utility in sick patients due to thrombocytopenia or the acute phase response. ROTEM™ and TEG™ are useful for moderate to severe platelet function defects in entities such as Glanzmann thrombasthenia or Bernard–Soulier syndrome [13]. Since they are not sensitive to mild to moderate platelet dysfunction, they cannot be used to monitor antiplatelet medication.

Table 16.2 Etiology of acquired von Willebrand syndrome

Autoantibody against VWF	Lymphoproliferative disorders
	Neoplastic disorders
	Immunologic disorders
Adsorption of VWF	Lymphoproliferative disorders
	Neoplastic disorders
	Myeloproliferative disorders
Increased shear stress	Congenital cardiac defects
	Aortic stenosis
	Mitral valve regurgitation
	Endocarditis
	Malformation of vessels (Kasabach–Merritt syndrome)
	Severe atherosclerosis
	β-Thalassemia
	VAD
	ECMO
Decreased synthesis	Hypothyroidism
Increased proteolytic degradation of VWF	Myeloproliferative disorders
	Uremia
	Ciprofloxacin
	Hyperfibrinolysis
Unknown mechanism	Wilms' tumor
	Valproic acid
	Cefotaxime
	Viral disease
	Liver transplantation
	Mixed cryoglobulinemia
	Amyloidosis
	Glycogen storage disease type 1
	Turner syndrome

VAD ventricular assist device, *ECMO* extracorporeal membrane oxygenation

Acute Bleeding but No Laboratory Test Results Are Available

When pediatric patients or newborns present with active bleeding, blood specimens may be difficult to draw from veins due to vasoconstriction. Whenever possible, blood specimens should be collected for first-tier testing, PT, aPTT,

Table 16.3 Available blood components

Red blood cells
Platelets
Fresh frozen plasma, thawed plasma, liquid plasma
Cryoprecipitate

fibrinogen, and platelet count. While the results are pending, or if specimens are unable to be collected, the patient needs to be managed empirically. When family history is available, such as known hemophilia or platelet disorders, targeted therapy may be initiated. Common causes of acquired coagulopathy include liver failure, disseminated intravascular coagulation (DIC), and vitamin K deficiency. Transfusion of plasma or platelets may be started. Red blood cells should also be transfused in order to prevent hemorrhagic shock or ischemic organ damage if bleeding is continuous. Table 16.3 shows possible blood component therapy and medications that may be employed. If the patient has liver failure, plasma transfusion and antifibrinolytics may be useful since hyperfibrinolysis is known to be associated with liver failure due to less inactivation of tissue plasminogen activator (see Chapter 11). TEG™ or ROTEM™ can show only moderate to severe hyperfibrinolysis, especially when associated with trauma or liver transplant surgery. Therefore, without evidence of hyperfibrinolysis in TEG™ or ROTEM™, clinically significant hyperfibrinolysis cannot be ruled out [14]. Individual laboratory tests for hyperfibrinolysis may not be readily available. Of note, antifibrinolytics may be beneficial without significantly increasing thrombotic risk (see Chapter 34).

Continuous Bleeding from the Catheter Insertion Site After Diagnostic Catheterization Without Pertinent Laboratory Data

If there is a suspicion of heparin overdose, such as after cardiac catheterization, it is prudent to give protamine for reversal. Although activated clotting time, also known as ACT, is not considered to be accurate or precise, if it is unreasonably prolonged, heparin or a heparin-like substance such as heparan sulfate or dermatan sulfate may be circulating. When aPTT is prolonged, but PT is normal, heparin overdose is likely. In this setting, protamine may be administered (Chap. 34 for dosing). PT is not usually affected by heparin up to 1–2 units/mL, depending on the reagent used [15], since PT reagent contains a heparin neutralizer such as polybrene.

Rare Bleeding Disorders

There are rare bleeding disorders which have been reported by very sophisticated evaluations. Work-up may be performed in a research laboratory. Table 16.4 shows examples of rare bleeding disorders. Finding the etiology of bleeding requires consultation with specialized laboratories, usually research laboratories. Tables 16.3 and 16.5 show available blood components and medications used to treat these disorders.

Table 16.4 Examples of rare bleeding disorder

Disease condition	Management
East Texas bleeding disorder [16]	
Factor V Amsterdam [17]	
Thrombomodulin (p.Cys537Stop) mutation [18]	Protein C concentrate
Antithrombin Pittsburgh [19]	
Ehlers–Danlos syndrome (connective tissue disorders) [20, 21]	DDAVP, antifibrinolytics
Quebec platelet disorder [22]	Antifibrinolytics
Scott syndrome [23]	Platelet transfusion

Table 16.5 Available medication for hemostasis

Desmopressin (DDAVP)
ε-Aminocaproic acid (Amicar™)
Tranexamic acid
Von Willebrand factor/factor VIII concentrate (Humate-P™)
Prothrombin complex concentrate (Kcentra™)
Recombinant activated factor VII (NovoSeven™)
Activated prothrombin complex concentrate (FEIBA™)
Vitamin K
Protamine

Usual dose and renal dose are stated in Chap. 34

Platelet transfusions are useful for not only thrombocytopenia or platelet function defects but also in other non-platelet-related disease conditions such as acquired factor V inhibitor or thrombomodulin mutation, which causes elevated levels of circulating activated protein C. It is explained that factor V stored in α-granules of platelets is sheltered from inhibition by activated protein C [24] or antibody against factor V [25, 26]. Likewise, platelet transfusions may be also effective for AVWS since von Willebrand factor is also stored in α-granules [27].

Among available medication, the administration of DDAVP and tranexamic acid may be considered since there are numerous platelet function defects which are not identified.

Suspected Overdose of Anticoagulant

If overdose of unknown anticoagulant is suspected, PT, aPTT, and thrombin time may be performed. Warfarin overdose may be managed by vitamin K administration, plasma transfusion, and/or prothrombin complex concentrate (Kcentra™), depending on the urgency of warfarin

reversal and INR. Hemodialysis may be performed for overdose of dabigatran, but is not effective for rivaroxaban and apixaban [28]. Idarucizumab for the reversal of the anticoagulant effect of dabigatran is already available; however, repeated dose of this drug is necessary for complete inactivation in patients with renal failure due to extravascular accumulation of dabigatran [29, 30]. There is not much data regarding the use of plasma exchange in order to remove direct oral anticoagulant [31]. Fibrinogen concentrate, antifibrinolytics, and oral charcoal can be considered as an additional therapy for direct anticoagulants-associated bleeding [32].

Anticoagulant Rodenticide (Superwarfarin) Poisoning

"Superwarfarin" includes derivatives of 4-hydroxycoumarin, such as difenacoum, bromadiolone, flocoumafen, and brodifacoum, and indanedione derivatives, such as chlorophacinone, pindone, and diphacinone. It is usually seen in suicide attempts [33]; however, recent outbreak of multiple (more than 150 cases) intoxications due to synthetic cannabinoids adulteration with different superwarfarins was reported [34]. If an accidental/intentional intoxication with superwarfarin is suspected, PT/INR should be measured. If only a very small amount of rat poisoning was ingested, PT/INR should be normal, and bleeding symptoms may not occur. If the patient has bleeding symptoms, INR >4 is a very common finding. Mild bleeding may be corrected with oral vitamin K1 at 25–100 mg daily; however, sometimes up to 400 mg is required [35]. Because of the very long half-life of superwarfarin in humans (brodifacoum 15–33 days, flocoumafen 6.7 days), the long-term treatment with vitamin K1 for several weeks to months is required to normalize PT/INR. Since these compounds are lipid soluble, plasma exchange is not effective. Severe bleeding should be managed with 3-factor or 4-factor prothrombin complex concentrate (PCC) or fresh frozen plasma (initial dose 15–30 mL/kg), plus intravenously 10–15 mg of vitamin K1 [36]. Rarely paradoxical thrombosis complicates superwarfarin bleeding, and the management in these cases is very challenging [37]. Thrombotic episodes were attributed to the administration of prothrombin complex concentrate, or if concomitant thrombosis and hemorrhage happened prior to any blood product infusion, thrombotic phenomenon was postulated to be provoked by rapid depletion of proteins C and S within the initial period of toxicity and, therefore, a transient thrombophilia that was later followed by a tendency for hemorrhage as other vitamin K-dependent factors became depleted.

Heparin-Like Effect

Described as early as 1951 [38], multiple case reports have surfaced regarding the production of an endogenous heparin-like anticoagulant associated with clinically significant bleeding. These compounds have been identified in numerous settings, but are most commonly reported in the setting of hematologic malignancy and liver disease [39]. The etiology of this disorder remains obscure; however, several pathogenic mechanisms have been proposed.

The heparin-like effect is mediated by heparin-like substances, i.e., glycosaminoglycans. These include heparan sulfate, dermatan sulfate, chondroitin sulfate, keratan sulfate, and hyaluronic acid. Anticoagulant activity has been observed associated with heparan sulfate, dermatan sulfate, and chondroitin sulfate. Heparan sulfate is a glycosaminoglycan found naturally on the surface of endothelial cells and produced by mast cells [40]. It is structurally similar to unfractionated heparin, though its anticoagulant effects are mediated mostly via complexing with antithrombin to inhibit factor Xa [41]. Dermatan sulfate is found primarily in the skin, blood vessels, and heart valves and plays roles in wound repair and fibrosis. The anticoagulant effects of dermatan sulfate are mediated via inactivation of thrombin by forming a complex with heparin cofactor II [41]. Both heparan sulfate and dermatan sulfate are less potent inhibitors of coagulation than pharmaceutical heparin, which is likely due to decreased sulfation of saccharide units [42, 43].

The heparin-like effect of endogenous glycosaminoglycans has been associated with multiple myeloma [39, 44], B-cell and T-cell lymphomas [39], systemic mastocytosis [45, 46], suramin therapy [47], metastatic transitional cell carcinoma [48, 49], metastatic breast cancer [50], systemic candidiasis [51], renal cell carcinoma [52], hepatocellular carcinoma [53], and mucormycosis [54]. This effect has been further described in patients with liver disease including in the setting of bacterial infection in cirrhotic patients [55], in portal hypertension [56], in acute variceal bleeding [57], and in the setting of liver transplantation [58–60]. The heparin-like effect is more commonly seen in patients with acute liver failure undergoing transplantation and is more pronounced at the time of reperfusion [59, 60]. More recently, this effect has been described in pediatric patients following liver transplantation [61, 62] and in patients receiving extracorporeal membrane oxygenation (ECMO) therapy [63, 64]. Heparan sulfate from mast cells may be produced in excess or released from the vascular endothelium in the setting of systemic inflammatory response syndrome (SIRS) and sepsis [65, 66]. Like heparin, heparan sulfate is metabolized by the liver and may build up in the setting of liver disease [47]. Increased production or systemic circulation of free glycosaminoglycans in

conjunction with decreased metabolism likely is responsible for coagulopathy associated with this disorder.

Patients may present with a variety of signs and symptoms listed in Table 16.6. Laboratory identification of heparin-like substance is difficult. Though we often identify heparin in association with a prolonged aPTT, this test may not always reliably demonstrate a heparin-like effect. The thrombin time has been reported to be the most reliable test when assessing for this disorder [67]. A reptilase time may be used in conjunction with the thrombin time to demonstrate the heparin-like effect. One would expect to find a prolonged thrombin time and normal reptilase time in this setting [67] (see Table 16.7). In addition, specific lyases can be used to help identify the glycosaminoglycan associated with the heparin-like effect. Hepzyme™ (heparinase, heparin lyase I), commonly used in the coagulation laboratory, may correct, or partially correct, the heparin-like effect associated with heparan sulfate. Other lyases such as heparin lyase III and chondroitinase B provide additional specificity for the glycosaminoglycans heparan sulfate and dermatan sulfate, respectively [47]. Prolongation of the clotting time on TEG™ or ROTEM™ can also demonstrate the heparin-like effect [52, 55, 58–60, 64] (Fig. 16.1).

Table 16.6 Signs and symptoms of heparin-like effect

Mucocutaneous bleeding
Petechiae
Ecchymosis
Bleeding from venipuncture sites/prolonged bleeding from surgical sites
Gastrointestinal bleeding
Deep-seated hematomas

Table 16.7 Tests for identification of heparin-like inhibitor

Prothrombin time	Normal or prolonged
Activated partial thromboplastin time	Normal or prolonged
Thrombin time	Prolonged
Reptilase time	Normal
aPTT with Hepzyme	Normal (may only see partial correction)
TEG/ROTEM	Prolonged clotting time
Anti-Xa	Normal or elevated

Appropriate treatment for heparin-like effect is not well defined. Some patients have been successfully treated with protamine sulfate [67]. A slow continuous infusion of protamine at 1 mg/min has resolved bleeding in some patients; however, protamine therapy does not always appear to work [51]. Plasma exchange in this setting has been described, but is of questionable benefit [67]. In our own recent case, protamine had a small, transient effect, while plasma exchange was successfully used to resolve bleeding [62]. The only reliable treatment appears to be eradication of the underlying disorder [67]. The prognosis for patients with bleeding associated with heparin-like effect is generally poor, as it typically presents in the terminal stages of disease when associated with malignancy or end-stage liver disease. However, the heparin-like effect identified in the setting of liver transplantation or ECMO appears to be transient [63, 64]. Ongoing research indicates that circulating glycosaminoglycans may be a marker for the development of critical illness [63, 64, 68]. A high index of suspicion is critical to identify this disorder.

Summary

Occasionally, patients present with bleeding without any apparent cause. Laboratory testing algorithms may be used to help guide treatment and determine the underlying etiol-

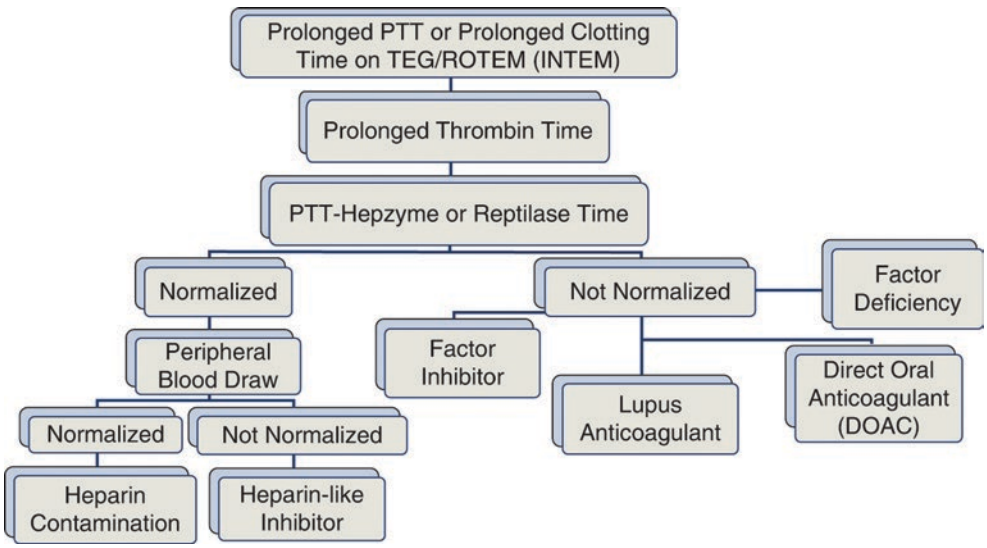

Fig. 16.1 Diagnostic algorithm. *PTT* activated partial thromboplastin time, *TEG* thromboelastography, *ROTEM* rotational thromboelastometry

ogy. When laboratory testing is incomplete or unavailable, patients must be treated empirically. There are a variety of blood components and medications available for treatment in an emergency. Of these, the use of DDAVP and/or tranexamic acid is the most important consideration when the cause of bleeding is unclear. Extended laboratory work-ups and expert consultation may be necessary to identify rare bleeding disorders.

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