INVITED ARTICLE

Approach to the Coagulopathic Patient in the Intensive Care Unit

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Key learning objectives:
- Evaluating patients with coagulopathy in intensive care
- Managing coagulopathy in intensive care
- Understand the complications and limitations of various therapies

Keywords: Bleeding and hemorrhage, Coagulation reversal, Coagulation tests, Coagulopathy, Factor concentrate, Fresh frozen plasma, Haemostasis, Recombinant coagulation products

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Introduction

A critical care physician often has to manage patients who either present with or develop coagulation abnormalities in intensive care unit, and they are a predictor of both, the need for massive transfusion and mortality.[1] These abnormalities can range from something as simple as isolated thrombocytopenia to more complex multisystem coagulation defects. Table 1 shows the common causes of coagulopathy in critically ill patients. Moreover, in critically ill patients, assessing bleeding risk is one of the key management strategies to minimize any procedural or perioperative bleeding. Critically ill patients can be prone to bleeding for a wide variety of reasons including hereditary or acquired bleeding disorders (platelet function abnormalities, factor deficiencies and factor inhibitors), underlying medical conditions such as hepatic or renal disease and concomitant anticoagulation medications. Besides, certain connective tissue disorders can impact on the integrity of blood vessels, which make them more prone to bruising/bleeding.

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Understanding Normal Hemostasis

Hemostasis is a complex process and involves multiple steps (Fig. 1). It is subdivided into four phases. The first phase of primary hemostasis involves vasoconstriction and platelet plug formation and is triggered when the subendothelial collagen is

Table 1: Common causes of coagulopathy in critically ill

Secondary disruption of hemostasis	*Deranged hemostasis*		
	Deranged coagulation	*Thrombocytopenia*	*Hyperfibrinolysis*[2]
• Hypothermia (Temp <34°C) • Severe acidosis (pH <7.25) • Hypocalcemia (iCa^{++} <1 mmol/L)	*Consumption*		*Acquired secondary*
	• Sepsis • DIC • Cardiac surgery	• Sepsis • DIC • Extracorporeal circuits (CRRT), • Enlarged spleen	• Trauma • Thrombolytic therapy • Cardiopulmonary bypass • Systemic amyloidosis • Placental disorders
	Blood Loss		*Acquired Primary*
	• Multiple trauma and major blood loss	• Multiple trauma and major blood loss	• End-stage liver cirrhosis • Acute promyelocytic leukaemia
	Decreased generation/Drugs		*Inherited secondary*
	• Vitamin K deficiency • Vitamin K antagonists • Liver disease and renal failure • Hemophilia • FXIII deficiency • Dysfibrinogenemias • Drugs: Heparin, novel oral anticoagulants, direct thrombin inhibitors, direct Xa inhibitors.	• Bone marrow suppression • Vitamin B_{12} and folate deficiency • Myelosuppression • Drugs: Acetaminophen, carbamazepine, hydrochlorothiazide, cimetidine, ranitidine, quinidine, quinine, bactrim, etc	• Hemophilia • FXIII deficiency • Dysfibrinogenemias

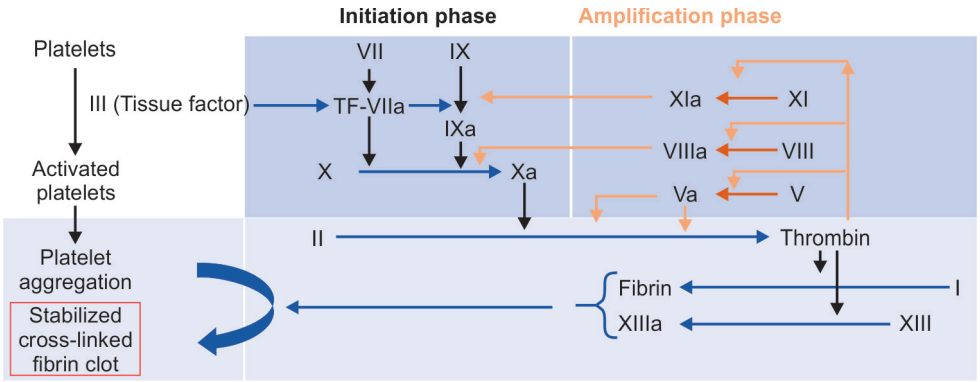

Fig. 1: Simplified diagram of Hemostasis

Table 2: Screening and confirmatory test for hemostasis

	Screening test	*Confirmatory test*
Coagulation	aPTT, PT, Thrombin time (TT)	FII, V, VII, VII, IX, X, XI, XII, XII activity Fibrinogen activity
vWF	Platelet function analyzer, vWF antigen	Antigen and platelet activity, genetic testing, propeptide testing
Platelet function	• Platelet count • Bleeding time (BT) • Platelet function analyzer	Light transmission aggregometry with arachidonic acid, thrombin receptor-activating peptide, collagen, adenosine diphosphate
Fibrinolysis	Euglobulin lysis time	tPA, plasminogen activity inhibitor, alpha-2 antiplasmin
Anticoagulation	aPTT, PT, TT, BT, anti-FXa activity, thrombin inhibition time (TTI), reptilase time	

exposed after vessel wall injury. This leads to platelet adhesion to the subendothelial layer via von Willebrand and glycoprotein Ib and subsequent platelet aggregation. Next comes secondary hemostasis, which involves the activation of coagulation factors and thrombin formation. Phase 3 requires fibrin clot formation and stabilization, and the final step requires inhibition of thrombin generation and fibrinolysis. Traditionally, this process has thought to occur via three pathways. The intrinsic pathway (uses factors VIII, IX, XI, XII), extrinsic pathway (uses factor VII), and common pathway where both converge to activate factor X (uses factors II, V, fibrinogen). In the new proposed coagulation cascade, this complete process does not occur continuously but instead requires three consecutive phases: namely, an initial phase, an amplification phase and the propagation phase.

The liver is responsible for the production of most of the factors, namely; I, II, V, VII, VII, IX, X, XI, XIII and protein C (FXIV) and protein S. Thus, patients with advanced liver disease often have coagulopathy. The coagulation system also has a negative feedback mechanism to prevent overcoagulation and thrombosis. Thrombin also acts by activating plasminogen (to plasmin, which is an active enzyme in fibrinolysis) and stimulating the production of antithrombin (which decreases the production of thrombin and decreases the output of FXa).

Evaluating Coagulation

The most obvious indications that a patient has coagulopathy are an unusual drop in hemoglobin or persistent bleeding. This often manifests as the presence of ecchymosis, petechiae, haematuria, hematomas or prolonged bleeding from puncture sites. Excessive bleeding from surgical drains or incision sites may also occur. If the bleeding is significant and allowed to continue, it may lead to hypovolemic shock, hypoperfusion and organ failure. Apart from above physical signs of bleeding, one should also look for jaundice, splenomegaly, arthropathy, joint and skin laxity (Marfans or Ehlers-Danlos syndrome) as signs of systemic or connective tissue disorder. The other causes of easy bruising like alcohol abuse, purpura simplex, Cushing's disease, vitamin C deficiency should also be screened for. One should also take a detailed medication history to check if the patient is taking medications such as antiplatelet agents, anticoagulants (warfarin or NOVACs) and complementary medications that affect coagulation. Drugs like cephalosporins, ginkgo-biloba, interferon, SSRI, TCA are rare causes that can cause bleeding and bruising.[3]

The screening tests for hemostasis are summarized in Table 2. Despite their limitations, both prothrombin time (PT) and activated partial thromboplastin time (aPTT) remain the most common screening test to evaluate coagulation. PT measures the integrity of extrinsic and common pathway while aPTT measures the integrity of the intrinsic and common pathway. They assess the time it takes for both the pathways to generate cellular plasma and thus only investigate a narrow part of the coagulation system. Figure 2 highlights the factors involved in each pathway. These tests are designed for clinical monitoring of anticoagulation and not coagulopathy and thus only serve as useful starting points of investigation of coagulation. Mixing studies are done to determine whether a prolonged PT or aPTT or both are affected by the presence of a factor deficiency or a factor inhibitor. If the test normalises when plasma is added, it is due to factor deficiency, and if not, it is secondary to the presence of an inhibitor like lupus anticoagulant.

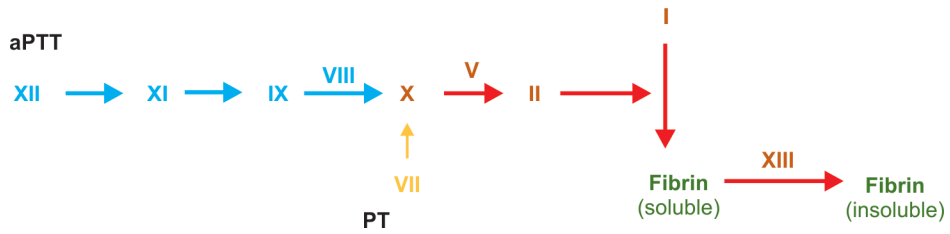

Fig. 2: Factors involved in the extrinsic (yellow), intrinsic (blue) and common pathways (red)

Table 3: Initial assessment of prolonged PT and aPTT in a patient with bleeding

PT	*aPTT*	*Causes*	
Normal	Normal	von Willebrand's disease FXIII deficiency, Dysfibrinogenemia	Platelet dysfunction α-antiplasmin deficiency
		Mixing study corrects	*Mixing study does not correct*
Prolonged	Normal	*Hereditary* • Isolated FVII deficiency *Acquired* • Vitamin K deficiency/ antagonists • Severe liver impairment	Inhibitors • Lupus anticoagulant • FVII inhibitor (rare)
Normal	Prolonged	*Bleeding* • FVIII/vWD deficiency, FIX/XI deficiency *No bleeding* • FXII, HMWK, prekallikrein	*Bleeding* • FVIII, FIX, FXI inhibitor, heparin *No bleeding* • FXII inhibitor, lupus anticoagulant HMWK, prekallikrein
Prolonged	Prolonged	• FII, FV, FX deficiency • FV and FVIII deficiency • Severe liver impairment • Vitamin K deficiency/antagonist • DIC	• FII, FV, FX inhibitor • Lupus anticoagulant

Table 4: Assessment of coagulation for patients on anticoagulants

Test	*Anticoagulant*				*Reference range*
	LMWH/ Fondaparinux	*Thrombin inhibitors* • Argatroban • Bivalirudin • Dabigatran	*Vitamin K antagonist* • Warfarin	*FXa inhibitors* • Rivaroxaban • Apixaban	
PT	Normal	Prolonged	Prolonged	Prolonged	<35 sec
aPTT	Normal	Prolonged	Normal	Prolonged	<13.5 sec
TT	Normal	Prolonged	Normal	Normal	<21 sec
BT	Normal	Normal	Normal	Normal	<21 sec
Anti-FXa	Detectable	Not detectable	Not detectable	Detectable	<0.1
TTI	No inhibition	Inhibition	No inhibition	No inhibition	

TT, thrombin time; BT, bleeding time; TTI, tissue thromboplastin inhibition

These tests should accompany a detailed history, including medication and clinical examination. It is also essential to get the peripheral smear examination as it also helps in looking at the morphology of platelets and also identify systemic illness and other hematological disorders. Table 3 highlights the causes of abnormality in these tests and Table 4 highlights the defect associated with the use of anticoagulants.

Evaluation of Preexisting Coagulation Disorder

The British Committee for Standards in hematology and various Anesthesiology Society guidelines for perioperative assessment recommend evaluation of bleeding risk before surgery or invasive procedures for all patients.[4–6] Bleeding assessment tools (BATs) were developed to offer a simple, structured screening tool to improve the diagnostic accuracy of bleeding disorder with symptom severity, minimise investigations, predict the risk of bleeding and inform about the treatment strategies (Table 5).

It is easy to diagnose major bleeding disorders like hemophilia and vWD but challenging to diagnose or classify some of the mild bleeding disorders. In a prospective Indian study, Kotru et al. reported that of the 164 patients who presented with slight bleeding, epistaxis was the most common presentation with cutaneous bleeding, the next common site. A family history of bleeding was present in only 11 patients. Only 25% of the patients were confirmed to have a bleeding disorder based on the investigation, and the rest labeled as unclassified bleeding disorder.[7]

Table 5: Commonly used BAT scores to assess bleeding risk in bleeders

Tool	*Year developed*	*Scores allotted*	*Target condition*	*Time taken*	*Comments*[8,9]
Vincenza bleeding score	2005	0 to +3	Type 1 vWD	40 min	Sensitivity (64%) Specificity (99%)
European molecular and clinical markers for diagnosis and management of type 1 vWD (MCMDM- 1 vWD)	2006	–1 to +4	Type 1 vWD	40 min	Sensitivity (59%) Specificity (96%)
Condensed MCMDM vWD-1	2008	–1 to +4	Type 2B vWD	5–10 min	Sensitivity (76%) Specificity (100%)
			Bleeding disorders		Sensitivity (85%) Specificity (90%)
ISTH-BAT	2010	0 to +4	Type 1 vWD	20 min	Sensitivity (49%) Specificity (47%)
HEMSTOP	2015	0 to 1	Bleeding disorder	5–10 min	Sensitivity (89.5%) Specificity (98.6%)

Table 6: Advantages and disadvantages of blood and pharmacological products

Blood Products		*Factor concentrates*	
Advantages	*Disadvantages*	*Advantages*	*Disadvantages*
• FFP contains all factors including vWF and factor XIII • Well studied and included in standardized massive transfusion protocols (MTP) • Effective volume therapy in shock patients • Relatively cheap	• Low concentration • Transfusion related risks • Requires cross matching • Large fluid load • Shorter storage life • Thawing takes time and not immediately available	• High concentration of factors • Few transfusion related complications • No cross match required • Small fluid volumes and hence no hemodilution	• Not all factors available • High costs • Point of care testing required • Need parallel fluid resuscitation for volume loss

Reversal of Coagulopathy

When managing a patient with coagulopathy, it is essential to consult a hematologist. It is also crucial to monitor the response to the treatment given by checking targeted tests. One can correct the factor deficiencies using fresh frozen plasma (FFP) when the coagulopathy is undifferentiated or secondary to causes like severe sepsis and DIC. Factor concentrates are used when one knows the coagulopathy is secondary to specific factor deficiency and or anticoagulant (e.g. warfarin). Table 6 highlights the advantages and disadvantages of each.[10]

Plasma transfusion may be useful in a patient who requires volume resuscitation along with multiple factors to correct the coagulopathy (e.g. patients with trauma and or one with massive exsanguination). It is also important to maintain temperature >35°C, ionized calcium levels >1.1 mmol/L and pH >7.25 in these patients. One also needs to activate a systematic transfusion therapy with local massive transfusion protocol to improve the delivery of blood products (packed blood cells, fresh frozen plasma, platelets in fixed ratios along with cryoprecipitate if the fibrinogen is <2.0 g/L). One gram of tranexamic acid followed by an infusion of 1 gram over 8 hours is also used in such scenarios. FFP is effective in correcting high PT as it has a dilution factor secondary to the volume. However, it is uncertain that prophylactically correcting INR decreases the incidence of bleeding. The TOPIC trial, which was an RCT, failed to show that transfusion of FFP (12 mL/kg) to correct the INR (>1.5–3.0) prevented bleeding complications in patients undergoing central venous catheter placement, percutaneous tracheostomy, chest tube or abscess drainage.[11] The amount of FFP needed to increase the desired level of factor concentration also varies. Chowdary et al. found that one may need volume as high as 30 mL/kg to achieve the target.[12]

Table 7: Reference for blood component and factor concentrate administration based on factor deficiency

Factor deficient	*Blood Component*	*Factor concentrates*
FI (fibrinogen)	Cryoprecipitate (cryo), fresh frozen plasma (FFP)	FI concentrate
Factor V (labile factor)	FFP	
Factor VII (stable factor/ proaccelerin)	FFP	Factor VII concentrate
Factor VIII (antihemophilic factor)	Cryo, FFP	Factor VIII concentrate
von Willebrand's disease	Cryo, FFP	Factor VIII concentrate
Factor IX (Christmas factor)	FFP	Factor FIX concentrate
Factor X (Stuart–Prower factor)	FFP	Factor FX concentrate
Factor XI (plasma thromboplastin antecedent)	FFP	Factor IX complex (II, VII, IX, X)
Factor XIII (fibrin-stabilizing factor)	FFP	Factor FXIII concentrate

The common risks associated with FFP transfusion are transfusion-related acute lung injury (TRALI), transfusion-related circulatory overload, allergic or anaphylactic reactions. The less frequent complications include risk of transmission of infections, febrile nonhemolytic reactions, hemolytic reactions and red blood cell (RBC) alloimmunization. Factor concentrate therapy (Table 7) guided by viscoelastic testing (TEG or ROTEM) has been tried to

minimize the use of blood products in patients undergoing major surgery and trauma but the benefits of this approach has not been demonstrated in big multicentre randomized control trials (RCT).[13,14]

Prothrombin complex concentrate (PCC) has variable concentrates of 4 factors, namely II, VII, IX, and X and are mainly approved for reversal of coagulopathy secondary to vitamin K antagonist. They are also used in the prevention and treatment of bleeding in patients with hemophilia B. Certain PCC also contain small levels of activated FVII. When compared to FFP, PCCs reverse INR faster and are easier to administer as do not need cross-matching. In scenarios when the INR is not corrected post PCC infusion, one should treat the patient with FFP.

Recombinant coagulation products are proteins which are now more readily available for managing bleeding patients on anticoagulants or with specific coagulation deficiencies. These proteins can be modified and can be used in patients with acquired antibodies and inhibitors to various factors. Recombinant activated factor VIIa is approved for patients with hemophilia with inhibitors but increasingly used in patients with life-threatening massive hemorrhage where conventional blood component therapy is unsuccessful. It only works once hypothermia, hypocalcemia, acidosis are corrected, and PT/aPTT optimized. Its significant side-effects are thromboembolic complications. Inactivated-zhzo recombinant FXa (Andexxa) has recently been approved for reversal of the anticoagulation effect of direct FXa inhibitors (apixaban and rivaroxaban). The limitation of this product is that the anticoagulant effect lasts while the infusion is ongoing (2 hours) and its high costs.

Factor XIII plays a vital role in the final step of clot formation and stabilization. Many studies have shown a reduction in factor FXIII in patients put on cardiopulmonary bypass and FXIII replacement, along with antifibrinolytic therapy reduces the risk of postoperative bleeding and in patients with major trauma.[15,16] However, the presence alpha-2 antiplasmin protein (which inactivates plasmin) and other clotting factors (VIII, XIII, vWF) in addition to fibrinogen in the cryoprecipitate makes them more effective in terms of their duration and mode of action when compared to factor FXIII concentrates.

In the event when the coagulopathy is secondary to anti-coagulants, it is ideal first to use specific anticoagulation reversing agents and it is also necessary to consult a haematologist. Table 8 highlights the specific reversal agents of various anticoagulants.[17]

Summary

Coagulopathy is common in intensive care and can be multifactorial. It is crucial to find the underlying cause and understand the limitations of various tests to assess them. Early hematology referral is vital. FFPs remain the broad-spectrum therapy to correct coagulopathy.

Table 8: Anticoagulant and the reversal agents

Anticoagulant	*Evaluation test*	*Half-life (hours)*	*Reversible*	*Reversal agent(s) Consult hematologist*	*Reversal agent Half-life*
			Antithrombin III activator (FII and FX inhibitor)		
IV Heparin	aPTT	1.5	Yes	Protamine (1mg/100 units heparin)	7–8 minutes
			Vitamin K inhibitor		
Warfarin	PT/INR	40	Yes	Vitamin K 10 mg Prothrombin complex concentrate 20–50 units/kg rFVIIa 90 µg/kg FFP	2 hours 4–12 hours 2.3 hours 4–12 hours
			Factor X inhibitor		
LMWH Enoxaparin	Anti-FXa	7	Partial	*Protamine* *If received <2 hours (60–80%)* 1mg protamine/1mg enoxaparin *If received >8 hours before:* 0.5 mg protamine/1 mg enoxaparin *If received >12 hours* before: Nil rFVIIa (70–90 mg/kg) in severe bleeds	7–8 minutes 2.3 hours
LMWH Dalteparin	Anti-FXa	3-5	Partial	*Protamine* *If received <2 hours:* (60%) 1 mg protamine/1 mg dalteparin rFVIIa (70–90 mg/kg) in severe bleeds	7–8 minutes 2.3 hours
			Direct FXa inhibitors		
Apixaban	Anti-FXa	8–15	No	Andexxa (rXa, inactivated-zhzo) <8 hours:400 mg–800 mg at 30 mg/minute; >8 hours 400 mg Prothrombin complex concentrate 25–50 units/kg	1 hour 4–60 hours
Rivaroxaban	Anti-FXa	7–11	No	Andexxa (rXa, inactivated-zhzo) <8 hours:400 mg–800 mg at 30 mg/minute; >8 hours 400 mg Prothrombin complex concentrate 25–50 units/kg rFVIIa 90 mg/kg	1 hour 4–60 hours 2.3 hours

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			Direct FIIa inhibitors		
Dabigatran	Limited value except TT, TEG, anti-FIIa	12–17	No	Idarucizumab (if TT is prolonged) 5 mg bolus or infusion over 5–10 minutes Prothrombin complex concentrate 50 units/kg	Biphasic: 45 minutes, 4–8 hours 4–12 hours
Argatroban	Limited value except TEG anti-FIIa	0.75	No	rFVIIa 90 µg/kg	2.3 hours
			Tissue plasminogen activator		
Alteplase	D-dimer	0.5–0.75	Yes	Tranexamic acid 10 mg/kg	2 hours

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