Coagulation Assays in Critical Care

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LEARNING OBJECTIVES

1. Analyze coagulation assays available in clinical practice and their relevance in critical care settings.
2. Evaluate coagulation assays in critically ill patients to assess critical care-associated coagulopathy.
3. Develop a pharmacotherapy plan for a critical care-associated coagulopathy based on coagulation assay results.

ABBREVIATIONS IN THIS CHAPTER

AFIIa	Anti-factor IIa
AFXa	Anti-factor Xa
aPTT	Activated partial thromboplastin time
ARU	Aspirin reaction unit
DIC	Disseminated intravascular coagulation
DOAC	Direct oral anticoagulant
dTT	Dilute thrombin time
FFP	Fresh frozen plasma
FVII	Coagulation factor VII
FVII	Coagulation factor VIII
FIX	Coagulation factor IX
FXa	Coagulation factor Xa
GP	Glycoprotein
INR	International normalized ratio
LMWH	Low molecular-weight heparin
LTA	Light transmission aggregometry
PCC	Prothrombin complex concentrate
PFA	Platelet function analyzer
PRU	Platelet reaction unit
PT	Prothrombin time
ROTEM	Rotational thromboelastometry
T[C]T	Thrombin (clotting) time
TGA	Thrombin generation assay
TEG	Thromboelastography
UFH	Unfractionated heparin
VET	Viscoelastic test

Table of other common abbreviations.

INTRODUCTION

Coagulopathy, defined as coagulation impairment that leads to thrombosis or bleeding, is a common medical complication in critically ill patients and contributes to high morbidity and mortality (Hunt 2014). The resulting clinical manifestations include thrombosis and bleeding because of hypercoagulable and hypocoagulable conditions, respectively. For example, patients with severe sepsis may develop hypercoagulability with the activation of tissue factors (TFs) and inactivation of antithrombin, protein C, and TF pathway inhibitor (Levi 2008). In contrast, hypocoagulable conditions may result from antithrombotic drug use, coagulation factor deficiencies from either consumption or decreased production, thrombocytopenia, blood loss, trauma, and uremia (Hunt 2014). In the common setting of coagulopathy in critically ill patients, an understanding the balance between coagulation and fibrinolysis is essential. Unfortunately, no such test exists with high specificity and sensitivity for prognostic value. This chapter will review components of common coagulation assays as well as their strengths and limitations. Understanding the evolutionary course of coagulation assays and their future pathways can equip clinicians with the knowledge necessary to formulate informative decisions on patient care in the critical care setting.

Coagulopathies in Critical Care

The incidence of coagulopathy in critically ill patients is about 30%. Known independent predictors of mortality are sepsis-induced coagulopathy, hemorrhage or trauma-induced coagulopathy, acute burn-induced coagulopathy, and disseminated intravascular coagulation (DIC) (Duque 2021; Iba 2017; Sherren 2013; Stanworth 2011). Unlike other coagulopathies, DIC is common in patients with sepsis (30%–60%), head trauma (30%–40%), cardiac arrest (10%–30%), solid tumors (10%), and complicated pregnancy (≤1.1%) (Adelborg 2021). Overall, DIC develops in 10%–30% of critically ill patients and is associated with 30–day mortality rate of 45%.

Critically ill patients are at high risk of developing venous thromboembolism because of the presence of additional risk factors such as central venous catheters, sepsis, mechanical ventilation, suboptimal

pharmacologic thromboprophylaxis, and use of vasoactive medications (Tran 2022). In corollary, critically ill patients are also at higher risk of developing bleeding because of their disease acuity, including sepsis, shock, and acidosis, can lead to organ dysfunction, including renal dysfunction and liver dysfunction (Neuenfeldt 2021). Although it is difficult to predict which coagulopathy critically ill patients will develop, currently available coagulation assays may provide a comprehensive overview of hemostasis status.

Development of coagulopathy is multifactorial, and a diagnosis may be challenging because of the ongoing changes in physiologic conditions in critically ill patients. Common factors in critically ill patients that further impair hemostasis include acidosis (pH ≤7.1), hypocalcemia (ionized calcium <0.9 mmol/L), and hypothermia (temperature ≤34°C) (Meybohm 2013; Lier 2008). Other causes of coagulopathy include antithrombotic drug use, vitamin K deficiency, end stage liver disease, mechanical circulatory support devices (e.g., extracorporeal membrane oxygenation, or left ventricular assist devices), sepsis, hemodilution, uremia, thrombocytopenia (defined as platelet count less than 150,000/mm^3), major trauma, acute burn, and DIC (Neuenfeldt 2021; Bashaw 2017). Ultimately, the goals are to prevent these coagulopathies and reduce morbidity and mortality, for which serial coagulation assays may be helpful and provide insight into current medical therapies.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of coagulation cascade and a cell-based model of hemostasis
- General knowledge of coagulopathy in critically ill patients
- General knowledge of anti-thrombotic assays and their parameters
- Drug knowledge of anti-thrombotic drugs
- Effect of anti-thrombotic drugs on coagulation assays

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Hoffman M, Monroe III DM. A cell-based model of hemostasis. Thromb Haemost 2001;85:958-65.
- Samama MM, Guinet C. Laboratory assessment of new anticoagulants. Clin Chem Lab Med 2011;49:761-72.
- Tripodi A. Thrombin generation assay and its application in the clinical laboratory. Clin Chem 2016;62:699-707.
- Selby R. TEG talk: expanding clinical roles for thromboelastography and rotational thromboelastometry. Hematology Am Soc Hematol Educ Program 2020:67-75.
- Neuenfeldt FS, Weigand MA, Fischer D. Coagulopathies in intensive care medicine: balancing act between thrombosis and bleeding. J Clin Med 2021;10:5369.
- Hunt BJ. Bleeding and coagulopathies in critical care. N Engl J Med 2014;370:847-59.

COAGULATION ASSAYS: METHODS AND CONSIDERATIONS

Many coagulation assays were developed around similar times, but ease of use and continued work in inherited bleeding disorders contributed to some of these assays becoming a part of clinical workflow in the health care setting. Coagulation assays either identify problems with components of hemostasis, including prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin (clotting) time (T[C]T), light transmission aggregometry (LTA), platelet function analyzer (PFA), or identify hypo- or hypercoagulable conditions, including thrombin generation assay (TGA), thromboelastography (TEG), rotational thromboelastometry (ROTEM), TEG or ROTEM platelet. Other assays only measure anticoagulant or antiplatelet effect with drug therapies, including chromogenic assays (e.g., anti-factor IIa (AFIIa) or anti-factor Xa (AFXa)), rapid PFA. Table 1 outlines the components of common coagulation assays, including factors that contribute to abnormal results and their use in therapeutic drug monitoring.

Pre-analytic and analytic issues that must be considered when interpreting coagulation assays include the sample collection, sample handling, reagent and instrument, normal reference ranges, and calibration (McCraw 2010). Blood sampling for coagulation assays should be obtained in citrate-containing tubes and gently mixed to avoid activation of the coagulation process. This sample should be handled at room temperature and tested as soon as possible. Many of the analytic issues may be minimized by performing periodic internal and external quality control by the central laboratory that holds the accreditation certificates. Interpretation of the coagulation assays should always accompany the clinical evaluation, and the central laboratory should provide reference manuals after assay review, such as the indications, limitations, and result interpretation. Common biological factors that may affect coagulation assays are shown in Box 1. False elevation in PT/international normalized ratio (INR) have been documented with daptomycin and argatroban whereby the prolonged PT/INR is dependent on the drug concentration and on the type of thromboplastin reagent (Webster 2008; Gosselin 2004).

Table 1. Coagulation Assays

Assay Characteristic	PT/INR	aPTT	TT/dTT	TGA	Thromboelastography/ Thromboelastometry	AFIIa	AFXa
Hemostasis phase	Clot initiation	Clot initiation	Clot initiation	Clot initiation Clot amplification Clot resolution	Clot initiation Clot amplification Clot inhibition	—	—
Assay type	Clot-based	Clot-based	Clot-based	Clot-based global	Clot-based viscoelastic	Chromogenic	Chromogenic
Sample[a]	Citrated PPP	Citrated PPP	Citrated PPP	Citrated PPP	Citrated whole blood	Citrated PPP	Citrated PPP
Medium	Thromboplastin (phospholipid and TF) Calcium	Partial Thromboplastin (phospholipid) Activator (celite, ellagic acid, kaolin, or silica) Calcium	Factor IIa Calcium	Phospholipid TF Calcium Fluorogenic substrate	TEG: kaolin, calcium Rapid TEG: kaolin, TF, calcium MA_{ff}/CFF: kaolin, TF, abciximab, calcium ROTEM INTEM: ellagic acid, calcium EXTEM: recombinant TF, polybrene, calcium FIBTEM: recombinant TF, polybrene, cytochalasin D, calcium	Factor IIa Chromogenic substrate	Factor Xa Chromogenic substrate
Reference range for normal hemostasis[b]	PT 10–13 sec INR 0.9–1.1	25–40 sec	<20 sec	Lag time 2.5–4.5 min Thrombin peak 200–450 nmol/L Thrombin peak time 5–8 min ETP 1200–2400 nmol/L/min	See Table 2	NA	NA
Reference range during anticoagulant drug therapy for treatment of VTE[c]	INR 2–3	Calibrated to chromogenic AFXa level 0.3–0.7 IU/mL	50–90 sec	Lag time increased Thrombin peak decreased ETP decreased	TEG R or ROTEM CT: prolonged	$Dabigatran_{mean,peak}$ 175 ng/mL (117–275)[e] $Dabigatran_{mean,trough}$ 60 ng/mL (39–95)[e] UFHss 0.2–0.4 IU/mL	UFH_{ss} 0.3–0.7 IU/mL $LMWH_{peak}$ daily 1.0–2.0 IU/mL $LMWH_{peak}$ twice daily 0.5–1.0 IU/mL $Fondaparinux_{peak}$ 0.6–1.5 mg/L $Rivaroxaban_{mean,peak}$ 270 ng/mL (189–419)[f] $Rivaroxaban_{mean,trough}$ 26 ng/mL (6–87)[f] $Apixaban_{median,peak}$ 132 ng/mL (59–302)[f] $Apixaban_{median,trough}$ 63 ng/mL (22–177)[f] $Edoxaban_{median,peak}$ 234 ng/mL (149–317)[e] $Edoxaban_{median,trough}$ 19 ng/mL (10–39)[e]

(*continued*)

Table 1. Coagulation Assays (*continued*)

Assay Characteristic	PT/INR	aPTT	TT/dTT	TGA	Thromboelastography/ Thromboelastometry	AFIIa	AFXa
Factor(s) causing abnormal assay	FI, FII, FV, FVII, FX	FI, FII, FV, FVIII, FIX, FX, FXI, FXII, VWF (with low FVIII), LA	FI	FII	Coagulation factors Fibrinogen Platelets Tissue plasminogen activator	FIIa inhibiting drug	FXa inhibiting drug
Therapeutic drug monitoring	Warfarin[d] (INR)	UFH[d] Argatroban[d] Bivalirudin[d]	UFH (TT) Argatroban (TT) Bivalirudin (TT) Dabigatran (dTT)	None	None	FIIa inhibiting drug	UFH LMWH Fondaparinux Direct FXa inhibiting drug

[a]Citrate chelates the calcium in the blood sample and prevents the activation of coagulation.

[b]Varies depending on the reagent and the sample used to establish control.

[c]Therapeutic drug monitoring should be performed after achieving steady state drug concentration.

[d]Routine monitoring recommended for dose adjustment.

[e]25th–75th percentile, ng/mL.

[f]5th–95th percentile, ng/mL.

α = angle (rate of clot development); AFIIa = anti-factor IIa; AFXa = anti-factor Xa; aPTT = activated partial thromboplastin time; CFF = citrated functional fibrinogen; CFT = clot formation time; (ROTEM) CT = clotting time; dTT = dilute thrombin time; ETP = endogenous thrombin potential; FVII = coagulation factor VII; FVIII = coagulation factor VIII; FIBTEM = fibrin-based thromboelastometry; FIX = coagulation factor IX; INR = international normalized ratio; IQR = interquartile range; K = kinetic time (rate of clot development); LA = lupus anticoagulant; MA = maximum amplitude; MA_{ff} = maximum amplitude functional fibrinogen; LMWH = low molecular-weight heparin; MCF = maximum clot firmness; NA = not applicable; PPP = platelet-poor plasma; PRP = platelet-rich plasma; PT = prothrombin time; (TEG) R = reaction time; ROTEM = rotational thromboelastometry; ss = steady state; TEG = thromboelastography; TGA = thrombin generation assay; TF = tissue factor; T(C)T = thrombin (clotting) time; UFH = unfractionated heparin; VTE = venous thromboembolism; VWF = von Willebrand factor.

Information from: Volod O, Bunch CM, Zackariya N, et al. Viscoelastic hemostatic assays: a primer on legacy and new generation devices. J Clin Med 2022;11:860; Bozic Mijovski M. Advances in monitoring anticoagulant therapy. Adv Clin Chem 2019;90:197-213;127:13-6; Gosselin RC, Adcock DM, Bates SM, et al. International Council for Standardization in Haematology (ICSH) recommendations for laboratory measurement of direct oral anticoagulants. Thromb Haemost 2018;118:437-50; Kintigh J, Monagle P, Ignjatovic V. A review of commercially available thrombin generation assays. Res Pract Thromb Haemost 2018;2:42-8; Tripodi A. Thrombin generation assay and its application in the clinical laboratory. Clin Chem 2016;62:699-707; Favaloro EJ, Lippi G. Coagulation update: what's new in hemostasis testing? Thromb Res 2011;127:S13-5; Wheeler AP, Rice TW. Coagulopathy in critically ill patients: part 2—soluble clotting factors and hemostatic testing. Chest 2010;137:185-94.

Clot-Based Assays

Clot-based assays, including PT, aPTT, TT, and dTT are simple and quick tests that detect the initial fibrin clot formation with a small, initial concentration of thrombin (see Table 1). These assays' results represent the clot initiation phase of hemostasis and specifically focus on coagulation factors as they interact with a respective contact activator, such as thromboplastin for PT and celite, silica, ellagic acid, or kaolin for aPTT. Results depend on the reagent used because reagents have different sensitivities to the degree and the number of coagulation factor deficiencies. For example, coagulation factors VII (FVII), VIII (FVIII), and IX (FIX) sensitivities ranged from 25%–50%, 38%–50%, and less than 10%–35%, respectively, when PT and aPTT tests were performed using six different reagent lots (Murray 1999). It is important to recognize that coagulation factor value of 20%–30% is required to form a clot, and coagulation factor value of 40%–50% may result in prolonged PT or aPTT (Dzik 2004). Therefore, these tests are helpful screening tools for patients at risk of bleeding primarily from coagulation factor deficiencies. In contrast, TGA, TEG, and ROTEM are global hemostasis tests because it describes clot initiation, clot amplification, and clot resolution.

Prothrombin Test/INR

The PT primarily assesses the FVII functionality and is a common screening tool used to identify patients at risk of bleeding, indicated by a prolonged PT (Wheeler 2010). Common causes for a prolonged PT are either the presence of a FVII inhibitor or a decrease in coagulation factor production, such as from vitamin K deficiency because of poor nutrition, use of a

Box 1. Common Biological Factors That May Affect Coagulation Assays

- Elevated hematocrit values
  - Hematocrit > 55%; prolonged PT and aPTT
- Antithrombin deficiency
  - Shortened aPTT and decreased AFXa assay
- End-stage liver disease
  - Prolonged PT/international normalized ratio and aPTT
- Lupus anticoagulant
  - Prolonged aPTT
- Increased factor VIII and fibrinogen
  - Shortened aPTT
- Hypertriglyceridemia
  - Triglycerides > 360 mg/dL; increased AFXa assay
- Elevated bilirubin values
  - Bilirubin > 6.6 mg/dL; decreased AFXa assay

aPTT = activated partial thromboplastin time; AFXa = antifactor Xa; PT = prothrombin time.

Information from: Vandiver JW, Vondracek TG. Antifactor Xa levels versus activated partial thromboplastin time for monitoring unfractionated heparin. Pharmacotherapy 2012;32:546-58; Kamal AH, Tefferi A, Pruthi RK. How to interpret and pursue an abnormal prothrombin time, activated partial thromboplastin time, and bleeding time in adults. Mayo Clinic Proceedings 2007;82:864-73.

vitamin K antagonist or antibiotic, or liver disease (Favaloro 2020; Wagenman 2009). A subsequent PT mixing study may be performed to differentiate these two main causes, in which the patient's plasma sample is mixed with a control plasma sample (Figure 1). Use of PT with direct oral anticoagulant (DOAC) therapy is limited because prolonging of PT result depends on the drug and reagent used. A prolonged PT result may also depend on drug concentration; for example, a marked increase in PT may occur with on-therapy concentrations of rivaroxaban (120 ng/mL), dabigatran (200 ng/mL), and edoxaban (97–296 ng/mL) as well as with supratherapeutic concentrations of apixaban (480–1000 ng/mL) (Gosselin 2018).

The INR was developed to assist in monitoring warfarin therapy; however, despite a lack of supporting evidence, the INR is often used to monitor other disease states, including end-stage liver disease, DIC (Ng 2009). In these case scenarios, trending INR over time may better assist in clinical diagnosis and treatment rather than obtaining INR only at one time.

Activated Partial Thromboplastin Time

The aPTT assesses the functionality of FI, FII, FV, FVIII, von Willbrand factor (with low FVIII), FIX, FX, FXI, FXII, and contact activators, including high molecular-weight kininogen, and prekallikrein. A prolonged result may be caused by coagulation factor deficiency, coagulation factor inhibitors, or the presence of lupus anticoagulant (Ng 2009). A shortened aPTT result may suggest a hypercoagulable state because of a high concentration of FVIII, which is associated with increased thrombotic events. Presence of phospholipid antibody, such as lupus anticoagulant syndrome, prolongs aPTT, and it may also lead to a clinically significant thrombotic disorder. Deficiencies in high molecular-weight kininogen, prekallikrein, or FXII prolong aPTT; however, this effect does not lead to clinically significant bleeding disorders (McCraw 2010; Kamal 2007). Deficiencies in FVIII, FIX, or FXI also prolong aPTT and are associated with clinically significant bleeding (Kamal 2007). Similar to PT, a mixing aPTT study can be performed when an initial aPTT result is prolonged to help identify the cause for its abnormal result (see Figure 1).

To standardize aPTT results at different laboratories, the American College of Chest Physicians and the College of American Pathologists recommended a therapeutic aPTT target range for UFH therapy correlating to heparin concentrations of 0.3–0.7 IU/mL using an AFXa assay. Although the AFXa assay has less pre-analytic, analytic, and biological interference compared with aPTT, use of the AFXa assay has not surpassed that for aPTT because of higher cost and unfamiliarity (Vandiver 2012). In addition, frequent discordance between aPTT and AFXa assay has made it difficult to prioritize one assay over another (Takemoto 2013).

Use of aPTT is not reliable for monitoring DOAC therapy. Supratherapeutic concentration of dabigatran (400 ng/mL) and therapeutic concentration of apixaban (200 ng/mL) can significantly prolong aPTT, but only a modest change in aPTT is observed with edoxaban (Gosselin 2018). Therapeutic concentration of rivaroxaban may prolong aPTT, but its dose–response relationship is unpredictable (Kaserer 2019).

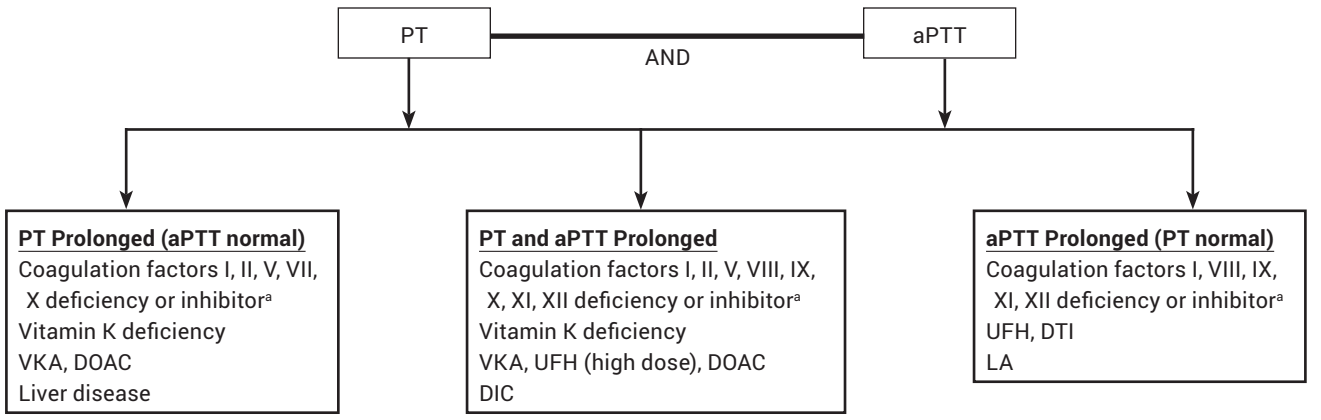
Thrombin (Clotting) Time and dTT

The thrombin (clotting) time (T[C]T) and dTT evaluate the speed of the conversion of fibrinogen to fibrin in the presence of exogenous thrombin. Therefore, this test is helpful to identify patients with *dysfibrinogenemia*, which is a rare inherited coagulation disorder, or to monitor UFH or direct thrombin inhibitor therapies. However because of ease of use and wide availability of aPTT, neither the TT nor dTT are routinely used for monitoring UFH, argatroban, or bivalirudin therapy. The TT is very sensitive to subtherapeutic concentrations of dabigatran (30 ng/mL); thus, dTT is a modified version of TT that is preferred for monitoring dabigatran therapy (Gosselin 2018). The dTT can detect dabigatran peak and trough concentrations between 70–275 ng/mL and 17–35 ng/mL, respectively, as well as low as 8 ng/mL (Bozic Mijovski 2019). In this test, patient plasma is diluted first before adding it to normal plasma. Thrombin is added later, and the time to fibrin clot formation is measured. Monitoring of dTT correlates highly with direct thrombin inhibitors, including dabigatran, and has been used to evaluate clinical efficacy and reversibility (Pollack 2017; Hawes 2013).

Global Hemostasis Assays

Thrombin generation assay and viscoelastic tests (VETs) are considered *global hemostasis tests* because they can describe clot initiation, clot amplification, clot stability (Depasse 2021,

Step 1: Screening Coagulation Tests



Step 2: Global Hemostasis Test

- Order if coagulation process cannot be adequately assessed using PT/aPTT
- TEG ± Platelet test may be preferred to assess for overall coagulation and/or platelet function
- TEG ± Platelet test may assist with targeted transfusion therapy
- TEG Reaction time or Clotting Time (or TGA EPT) may guide anticoagulant drug reversal therapy (e.g., PCC)

[a]Mixing study	PT result	aPTT result	Causes for abnormal results
PT	Normal/corrected	NA	Factor deficiency, VKA, vitamin K deficiency
	Prolonged/not corrected	NA	Factor VII inhibitor, DOAC
PT and aPTT	Normal/corrected	Normal/corrected	Factor deficiency
	Prolonged/not corrected	Prolonged/not corrected	Factor inhibitor, DOAC, UFH
	Normal/corrected	Prolonged/not corrected	UFH
aPTT	NA	Normal/corrected	Factor deficiency
	NA	Prolonged/not corrected	Factor inhibitor, dabigatran, UFH, LA

Figure 1. Clinical use of coagulation assays in critical care—the 2-step process. Step 1: Screen for coagulation issues with PT and aPTT and identify the cause for the abnormal result. Step 2: If PT or aPTT are abnormal, then confirm hypo- or hypercoagulable condition with global hemostasis test.

[a]Mixing Study is performed to differentiate abnormal PT/aPTT resulting from either coagulation deficiency or from coagulation inhibitor.

aPTT = activated partial thromboplastin time; DIC = disseminated intravascular coagulation; DOAC = direct oral anticoagulant; DTI = direct thrombin inhibitor; FVIII = factor VII; FIX = factor IX; LA = lupus anticoagulant; NA = not applicable; PT = prothrombin time; TEG = thromboelastography; TGA = thrombin generation assay; UFH = unfractionated heparin; VKA = vitamin K antagonist.

Information from Favaloro EJ. Coagulation mixing studies: Utility, algorithmic strategies and limitations for lupus anticoagulant testing or follow up of abnormal coagulation tests. Am J Hematol 2020;95:117–28.

Selby 2020). VETs provide additional information about fibrinolysis or clot resolution; whereas TGA only provides information about formation and subsequent cessation of thrombin generation. Although VET considers platelet interaction in the coagulation process, platelet function may be underrepresented because of the burst generation of

thrombin. Therefore, a separate test is used to assess platelet function, called TEG or ROTEM platelet.

Thrombin Generation Assay

The TGA provides detailed information about the time to thrombin generation (lag time), time to and degree of peak thrombin generation (thrombin peak time and thrombin peak), and the total amount of thrombin generation (endogenous thrombin potential). This test reflects coagulation initiation and amplification phases. Improvements to the sampling techniques and methods of measuring thrombin led to the marketing of several commercial products, and further standardization in reagents led to its widespread use. Theoretically, this assay can be used to identify either hyper- or hypo-coagulable conditions (shortened or prolonged thrombin peak time, respectively) and as well as to diagnosis inherited or acquired coagulation disorders. Reagents such as TF, phospholipid, or celite may be tailored to detect different coagulation-associated disorders, including the following: FVIII or FIX deficiencies; hypercoagulable state from conditions, such as deep vein thrombosis, cancer, smoking, or contraceptive use; and coagulation status during anticoagulation therapy (Depasse 2021). During anticoagulant drug therapy, thrombin generation is reduced and is reflected by increased lag time, decreased thrombin peak, and decreased endogenous thrombin potential. The TGA has been valuable to demonstrate the restoration of thrombin generation in anticoagulation reversal studies; thus TGA may be useful to guide hemostatic drug therapy in critically ill patients. Thrombin generation assay is currently available for research use only.

TEG and ROTEM

Both TEG and ROTEM are similar to routine coagulation assays. These tests use TF as an agonist to mimic PT, a kaolin agonist to mimic aPTT, functional fibrinogen test to provide degree of fibrinogen contributing to clot strength, and the lysis 30 test to provide similar information as the D-dimer (Thomas 2018). Although TEG and ROTEM report similar parameters, they are not interchangeable because their devices, operations, and reagents differ. Reagents with various activators may be used to provide overall status of hemostasis (see Table 1).

Table 2 outlines their measurements, representation of different hemostasis phases, and the option for VET-directed transfusion therapy. The use of VET is helpful to identify patients with hyperfibrinolysis, which may be common in critically ill patients with trauma and is associated with 53%–75% mortality (Howley 2018). The VET tests may also be beneficial if the overall hemostasis status cannot be adequately assessed using PT or aPTT. For example, a patient with liver disease may present with prolonged PT and aPTT because of coagulation factor deficiencies. In this case, TEG may be ordered to assess if and where the issue is within the different hemostasis phases.

Thromboelastography or ROTEM may be used to analyze effects of drugs that disrupt clot formation or clot lysis (see Table 1). Time to clot formation (TEG R-time) or extrinsic thromboelastometry clotting time (ROTEM EXTEM CT) is prolonged with anticoagulant drugs, with varying degrees depending on the type of VET test used. During warfarin therapy, INR was correlated better with EXTEM CT than TEG R-time (Schmidt 2015). This relationship was also not reliable when TEG R-time was measured in patients receiving rivaroxaban or apixaban therapy, suggesting that TEG R-time is not useful to monitor these medications (Jenrette 2022). However, EXTEM CT was strongly correlated with edoxaban concentrations in healthy volunteers (Havrdova 2021). In other studies, rapid TEG activated clotting time showed better dose–response relationship than TEG R-time for dabigatran, rivaroxaban, and apixaban concentrations in healthy volunteers (Artang 2019; Dias 2015). Percent clot reduction after reaching maximum clot strength may be helpful to identify patients with hyperfibrinolysis and to initiate antifibrinolytic drug therapy.

TEG Platelet Mapping or ROTEM Platelet Test

The TEG platelet mapping or ROTEM platelet test may be useful in guiding platelet transfusion therapy in patients with major trauma or in patients undergoing major surgery, including cardiac or hepatic surgery (Tantry 2022). The VET platelet assay may also be used to assess antiplatelet drug therapy with different mechanisms of actions, including arachidonic acid for aspirin and glycoprotein (GP) IIb/IIIa inhibitor therapy, adenosine diphosphate for P2Y12 inhibitor and GPIIb/IIIa inhibitor therapy, and thrombin receptor-activating peptide for protease-activated receptor-1 antagonist or GPIIb/IIIa inhibitor therapy (Volod 2022). In particular, TEG platelet mapping has been validated using light transmission aggregometry (LTA), which is the gold standard of platelet function tests. Its use in the clinical setting for either of these indications is not well established because of a sparsity of clinical outcomes data, except in patients who undergo percutaneous coronary intervention. An American College of Cardiology Foundation consensus statement suggests a TEG platelet mapping maximum amplitude (MA) range of 31–47 mm as therapeutic range to tailor P2Y12 inhibiting drug therapy in patients undergoing percutaneous coronary intervention and at high risk of thrombotic or bleeding complications (Sibbing 2019).

Chromogenic Assays

Chromogenic assays measure the effect of specific anticoagulant drugs by indirectly measuring drug concentration by light absorbance at 450 nm (Samama 2011). This assay is useful to predict therapeutic efficacy with DOACs (FXa and FIIa inhibitors) and is preferred instead of the traditional clot-based assays. This test should not be confused with the FII or

Table 2. TEG and ROTEM Assay Results

Hemostasis Phase	Coagulation Parameter	TEG Parameter	ROTEM Parameter	Parameter Change Indicating a Hypo-coagulable Condition	General Transfusion Guidance
		Reference Range for Normal Hemostasis	Reference Range for Normal Hemostasis		
Clot initiation (coagulation activation)	Time to clot formation of 2 mm	Kaolin reaction time, R (min) Rapid TEG activated clotting time, ACT (sec)	Clotting time (sec), CT	Increased	FFP PCC
		R 4.6–9.1 min ACT 86-118 sec	INTEM 137–246 sec EXTEM 42–74 sec		
Clot amplification (fibrin polymerization)	Speed of clot development	Angle (°), a	Angle (°), a	Decreased	Cryoprecipitate Fibrinogen
		Kaolin 53°–72° Rapid TEG 64-80°	INTEM 71–82° EXTEM 63–81°		
Clot amplification	Time for clot to reach 20 mm from 2 mm	Kinetic time (min), K	Clot formation time (sec), CFT	Increased	Cryoprecipitate Fibrinogen
		Kaolin 0.8–2.1 min Rapid TEG 1-2 min	INTEM 40–100 sec EXTEM 46–148 sec		
Clot strength (fibrinogen and platelet activation)	Maximum clot strength	Maximum amplitude (mm), MA Maximum amplitude functional fibrinogen (mm), MA_{ff}	Maximum clot firmness (mm), MCF	Decreased	Cryoprecipitate Fibrinogen Platelet[a] Desmopressin[a]
		Kaolin 50–70 mm Rapid TEG 52-71 mm MA_{ff}/CFF 15-32 mm	INTEM 52–72 mm EXTEM 49–71 mm FIBTEM 9–25 mm		
Clot resolution	% Reduction in area under the curve 30 min after reaching MA	Lysis 30 (%), LY30	Lysis index 30 (%), LI30	Increased	Tranexamic acid Aminocaproic acid
		Kaolin 0%–7.5% Rapid TEG 0-7.5%	LI30 94%–100%		

[a]TEG platelet mapping is preferred to assess platelet function and guide treatment.

EXTEM = extrinsic thromboelastometry; FFP = fresh frozen plasma; FIBTEM = fibrin-based thromboelastometry; INTEM = intrinsic thromboelastometry; PCC = prothrombin complex concentrate; ROTEM = rotational thromboelastometry; TEG = thromboelastography.

Information from: Volod O, Bunch CM, Zackariya N, et al. Viscoelastic hemostatic assays: a primer on legacy and new generation devices. J Clin Med 2022;11:860; Selby R. "TEG talk": expanding clinical roles for thromboelastography and rotational thromboelastometry. Hematology Am Soc Hematol Educ Program 2020:67-75.

FX level assay because the latter assay quantifies the coagulation factor level rather than a drug concentration.

Anti-factor IIa Assay

Anti-factor IIa (AFIIa) assay can be used to monitor patients receiving a drug that inhibits FIIa, such as argatroban, bivalirudin, and dabigatran. It requires the addition of chromogenic substrate for thrombin and a thrombin reagent to the patient plasma (Gosselin 2018). This test requires a direct AFIIa drug-calibrated assay, and it has been well correlated with mass spectrometry measurement. However, it has limited clinical use because argatroban and bivalirudin are monitored based aPTT level and the use of dabigatran is very low compared with other DOACs (Wheelock 2021).

Anti-factor Xa Assay

Anti-factor Xa (AFXa) assay can be used to monitor patients receiving a drug that inhibits FXa. AFXa assay is now more

widely used with the improvement of operator usability, automated instrument availability, and decreased cost. This test may be favored for the management of UFH because of less laboratory interference compared with aPTT, which may translate to a decrease in the number of blood draws, nursing time, number of dose adjustments, and overall drug therapy-associated costs (Guervil 2011; Levi 2008; Rosborough 1999). There are two types of AFXa assays, one in which antithrombin is added exogenously (high antithrombin level) and one in which an endogenous supply from the patient's blood sample is used (low antithrombin level) (Wool 2013). The latter test is preferred for monitoring UFH and low molecular-weight heparin (LMWH) therapy to accurately analyze the anticoagulant effect.

In several specific cases AFXa assay is preferred over aPTT during UFH therapy due to the presence of biological factors that causes shortened aPTT (see Box 1). For example, a hospitalized patient with severe coronavirus disease 2019 (COVID-19) infection may benefit from AFXa monitor during UFH IV therapy instead of aPTT because COVID-19 infection may elevate FVIII level (Barnes 2020). In this case, there will be little to no changes in aPTT with increasing doses of heparin. This is referred to as heparin resistance when the heparin dose exceeds 35,000 units/day (Smythe 2016; Wool 2013). In order to determine whether AFXa assay may be used as an alternative method to aPTT, first AFXa assay and aPTT should be performed simultaneously to distinguish the difference between true drug resistance or laboratory interference. If both aPTT and AFXa assays are low despite multiple UFH dose increases, then drug resistance is suspected and an alternative anticoagulant drug therapy is recommended (Smythe 2016).

Anti-factor Xa assays are not recommended for routine monitoring or dose adjustments for direct FXa-inhibiting drugs (Smythe 2016). However, AFXa assays may be clinically useful to monitor for medication adherence, suggest a reason for therapy failure, and guide anticoagulant reversal therapy. Therapy failure may result from higher-than-expected AFXa levels observed in patients with older age, major drug–drug interactions (e.g., combined P-glycoprotein and strong CYP3A4 inhibitors), low estimated glomerular filtration rate, or low BMI (<18.5 kg/m2) (Rottenstreich 2018). Reversal therapy may be warranted if patients present with major bleeding or are at high risk of bleeding and the direct FXa-inhibiting drug concentration is greater than 50 ng/mL or greater than 30 ng/mL, respectively (Levy 2016). Laboratory standards for monitoring direct FXa-inhibiting drugs are available from International Council for Standardization in Haemotology, and clinicians should consider the sensitivity of the assay to low levels of drug concentration to ensure appropriate clinical application (see Table 1) (Gosselin 2018). This is especially true when heparin-calibrated AFXa assay is used to estimate a direct FXa inhibiting drug concentration (Gosselin 2015). For example, the lower limit of quantitation (LLQ) and upper limit of quantitation (ULQ) is less than 5–35 ng/mL and 24–greater than 200 ng/mL, respectively, for rivaroxaban with correlation of the LLQ and ULQ for the heparin-calibrated AFXa level of 0–0.03 U/mL and 0.6–1.86 U/mL, respectively.

Anti-factor Xa assay must be calibrated for each of the anticoagulant drugs. Alternatively, heparin-calibrated AFXa assay may be used in urgent situations for patients on direct FXa-inhibiting drugs. An abnormal result of an heparin-calibrated AFXa assay for a patient taking a direct FXa-inhibiting drug suggests the presence of a direct FXa-inhibiting drug. A normal result, however, may not be clinically useful because it does not imply absence of the drug based on the poor sensitivity of the assay. For example, a comparative test using three different AFXa assays (heparin-calibrated) showed that the AFXa assay showed minimal response (0.5 IU/mL or less) for drug concentrations less than 100 ng/mL of rivaroxaban, apixaban, and edoxaban (Sabor 2017). In addition, AFXa assay responses were different among the three AFXa assays tested. Recently, a universal heparin-calibrated AFXa assay for both indirect and direct FXa-inhibiting drugs has been tested against rivaroxaban-, apixaban-, and edoxaban-calibrated AFXa assay and showed strong correlation (Meihandoest 2022; Willekens 2021). Clinicians should be aware of the drug-specific AFXa assays used at their institution and ensure that the appropriate AFXa assay is ordered for accurate interpretation. Currently, prognostication for clinical outcome-based dose-response has yet to be determined (Onundarson 2019).

Platelet Aggregometry

Platelet function tests measure the degree of platelet aggregation and clinical uses include identification of bleeding disorders or evaluation of antiplatelet drug therapy. Table 3 outlines the components of common antiplatelet assays used to evaluate hemostasis.

Light Transmission Aggregometry

The gold standard test for evaluating platelet function is LTA. This test uses platelet-rich plasma and measures platelet aggregation with the addition of an agonist. The result is reported as degree of platelet aggregation, ranging from 0%–100% (Hvas 2017; Paniccia 2015). Because LTA uses numerous agonists, it is useful to identify various platelet function impairments including those from antiplatelet drug therapy. In addition, LTA is useful to identify patients at risk of bleeding disorders resulting from platelet dysfunction. However, routine use of LTA in the clinical settings is limited because of the lack of standardization of its technique (Cattaneo 2013).

Platelet Function Analyzer

The platelet function analyzer (PFA) is a point-of-care test that mimics shear stress in vitro and analyzes platelet adhesion and aggregation; thus, this test has often been referred to as *in vitro bleeding time*. The PFA uses a cartridge that includes an agonist that requires transfer of blood sample to a chamber (Hvas 2017). The result is reported as *closure*

Table 3. Platelet Function Tests

Test Characteristic	LTA	PFA	Rapid PFA	TEG/ROTEM Platelet
Assay	Platelet aggregation	Platelet adhesion/ aggregation	Platelet aggregation	Platelet viscoelastic
Sample	Citrate PRP	Citrated WB	WB	Citrated WB
Agonist	AA ADP Collagen Ristocetin Epinephrine TRAP	CADP CEPI	AA ADP and PGE_1 TRAP	Kaolin (TEG platelet) AA ADP TRAP (ROTEM platelet)
Reference level indicating nonresponse to antiplatelet therapy for PCI	Aspirin-LTA_{AA}: ≥ 20% Aspirin-LTA_{ADP}: ≥ 70% Aspirin-$LTA_{collagen}$: ≥ 70% P2Y12-LTA_{ADP}: ≥ 46%	Aspirin-CADP/CEPI: ≤ 193 sec	Aspirin: > 550 ARU P2Y12 inhibitor: > 208 PRU GPIIb/IIIa inhibitor: > 330 PRU	TEG platelet Aspirin: TEG_{AA} ≥ 50% P2Y12 inhibitor: MA_{ADP} > 47 mm
Point-of-care testing	No	Yes	Yes	No
Screening tool for bleeding disorder	vWD Bernard-Soulier syndrome Glanzmann thromboasthenia	vWD Bernard-Soulier syndrome Glanzmann thromboasthenia	None	None
Therapeutic drug monitoring	Aspirin P2Y12 inhibitor GPIIb/IIIa inhibitor	Aspirin Desmopressin (in vWD)	Aspirin P2Y12 inhibitor GPIIb/IIIa inhibitor	TEG platelet: Aspirin, P2Y12 inhibitor
Comments	Gold standard for platelet function test Prone to preanalytic error Operator dependent	In vitro bleeding time Cartridge includes agonist Reference range varies per institution	Automated (cartridge, aggregometer) Correlates with LTA	Global hemostasis test TEG platelet mapping correlates with LTA Cartridge with agonist available for TEG platelet mapping

AA = arachidonic acid; ADP = adenosine phosphate; ARU = aspirin reaction unit; CADP = collagen plus adenosine phosphate; CEPI = collagen plus epinephrine; GP = glycoprotein; LTA = light transmission aggregometry; PCI = percutaneous coronary intervention; PGE1 = prostaglandin E1; PFA = platelet function analyzer; PRP = platelet-rich plasma; PRU = platelet reaction unit; ROTEM = rotational thromboelastometry; TEG = thromboelastography; TRAP = thrombin receptor-activating peptide; VWD = von Willebrand disease; WB = whole blood.

Information from: Volod O, Bunch CM, Zackariya N, et al. Viscoelastic hemostatic assays: a primer on legacy and new generation devices. J Clin Med 2022;11:860; Sibbing D, Aradi D, Alexopoulos D, et al. Updated expert consensus statement on platelet function and genetic testing for guiding P2Y12 receptor inhibitor treatment in percutaneous coronary intervention. JACC Cardiovasc Interv 2019;12:1521-37; Hvas AM, Grove EL. Platelet function tests: preanalytical variables, clinical utility, advantages, and disadvantages. Methods Mol Biol 2017;1646:305-20; Paniccia R, Priora R, Liotta AA, et al. Platelet function tests: a comparative review. Vasc Health Risk Manag 2015;11:133-48; Bonello L, Tantry US, Marcucci R, et al. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. J Am Coll Cardiol 2010;56:919-33; Gurbel PA, Bliden KP, DiChiara J, et al. Evaluation of dose-related effects of aspirin on platelet function: results from the Aspirin-Induced Platelet Effect (ASPECT) study. Circulation 2007;115:3156-364.

time in seconds, which is the time for platelets to aggregate and block blood flow. Because this test uses a whole blood sample, it can be affected by levels of von Willbrand factor, hematocrit, platelet count, and white blood cells. The interference with von Willbrand factor levels makes this test useful to screen for von Willebrand disease. The degree of platelet reactivity is shown by prolonged (low platelet reactivity) or shortened (high platelet reactivity) closure time, and the PFA may be used to identify patients at high risk of thrombotic or bleeding events in those undergoing major surgery (Paniccia 2015). In addition, the PFA can also be used to monitor responsiveness to aspirin therapy (Favaloro 2008). Aspirin non-responsiveness is defined as PFA-$100_{\text{collagen plus adenosine phosphate/collagen plus epinephrine}}$ of 193 seconds

Patient Care Scenario

A 56-year-old man is admitted to the intensive care unit for a major gastrointestinal bleed and hypotension that requires norepinephrine therapy. His medical history includes hypertension, type 2 diabetes mellitus, ischemic stroke, and mechanical heart valve placement. His home drugs include lisinopril/hydrochlorothiazide 20–12.5 mg daily, insulin glargine 30 units daily, apixaban 5 mg twice daily, and aspirin 81 mg daily. The patient is intubated and opens eyes to pain but does not follow commands. Which coagulation assays are needed to assess this patient's coagulopathy?

ANSWER

The initial work-up should include obtaining a thorough medication history. Adherence to apixaban therapy should be assessed, including the time of the most recent dose and whether the pharmacokinetic properties of apixaban have been altered because of unexpected drug–drug interaction. The option of reversing the effects of apixaban should be discussed with the primary care team. The goal of reversal therapy in the setting of an apixaban-associated major bleed is restoring normal hemostasis. Thus, the first step is to identify if there are any underlying coagulation factor deficiencies that may be contributing to coagulopathy. Second step is to determine the presence of or quantify anticoagulant effect from apixaban therapy and, if possible, the overall hemostasis status. Therefore, PT, aPTT, AFXa assay, and rapid TEG should be obtained.

Anti-factor Xa assay—calibrated for apixaban, if available, otherwise calibrated for heparin—should be ordered together with routine coagulation assays, including PT/INR, aPTT, and platelet count. Other laboratory tests, such as pH, temperature, calcium, serum creatinine, liver function test, hemoglobin, should be ordered to provide a comprehensive overview of patient's current hemostatic condition. If platelet count is less than 50,000/mm^3, PT is 6 seconds or more, and INR is greater than 1.4, then fibrinogen and D-dimer should be ordered promptly to assess for the development of DIC. Rapid TEG may also be ordered, if available, to determine the current state of coagulopathy and to monitor the anticoagulant effect of apixaban with or without reversal therapy. These coagulation assays should serve as a baseline and may be followed as patient deteriorates or improves over time. Although platelet function test may be performed to determine the effects of antiplatelet effect from aspirin therapy, it is unnecessary since its correlation with clinical outcome has not been validated.

1. Sabor L, Raphaël M, Dogné JM, et al. Heparin-calibrated chromogenic anti-Xa assays are not suitable to assess the presence of significant direct factor Xa inhibitors levels. Thrombosis Research 2017;156:36-8.
2. Gosselin RC, Adcock DM, Bates SM, et al. International Council for Standardization in Haematology (ICSH) recommendations for laboratory measurement of direct oral anticoagulants. Thromb Haemost 2018;118:437-50.

or less (Gurbel 2007). Theoretically, aspirin dose may be increased to decrease risk of atherothrombosis in high-risk patents; however, this approach is not routine because aspirin non-responsiveness may be caused by many other factors and its clinical outcomes has not been well established. Because of the lack of sensitivity to other antiplatelet drugs, the PFA is not useful for monitoring P2Y12 or GPIIb/IIIa inhibiting drugs.

Rapid PFA

The rapid PFA (RPFA) is a point-of-care test that uses fibrinogen-coated beads and an activator to show the deg ree of platelet aggregation, similar to LTA. The RPFA was developed as a tool for therapeutic drug monitoring in patients receiving antiplatelet drug therapy. Many studies have evaluated RPFA to correlate hypo- or hyper-responsiveness to clopidogrel therapy and thrombotic or bleeding events, respectively, in different clinical settings, such as percutaneous coronary intervention and intracranial stent placement. The cutoff values to determine responsiveness to P2Y12 inhibitor therapy are available for patients undergoing percutaneous coronary intervention (Sibbing 2019). For example, American College of Cardiology Foundation suggests cutoff values for identifying hypo- and hyper-responders to clopidogrel therapy using RPFA at 208 platelet reaction unit (PRU) and 85 PRU, respectively. Hypo-responsiveness (defined as ≥208 PRU) may necessitate an increase in clopidogrel dose (e.g., 150 mg/day) to reduce the risk of thrombosis, whereas hyper-responsiveness (defined as ≤85 PRU) may warrant a decrease in clopidogrel dose (e.g., 37.5 mg/day) to prevent bleeding. If the patient is unresponsive despite the increase in clopidogrel dose, then clopidogrel may be switched to either prasugrel or ticagrelor to exert the appropriate antiplatelet effect. Although a similar cutoff value for hypo-responsiveness to aspirin therapy exist, dose titrate is not routinely done since its correlation with clinical outcome has not been validated.

The RPFA reference range is not well established in other patient populations, and routine use of RPFA is not recommended because of variable clinical outcomes observed with different RPFA results. Furthermore, RPFA-guided platelet transfusion practice has not been well studied, and it should not be used to justify reversal of antiplatelet drug therapy. Instead, reversal of antiplatelet drug associated major bleeding should be individualized. For example, a routine platelet transfusion in patients receiving antiplatelet drug therapy for at least 7 days and presenting with intracerebral hemorrhage

resulted in higher rate of death or dependence at 3 months compared with patients who did not receive platelet transfusions (Baharoglu 2016). Although RPFA was not performed as part of this study, it suggests that clinical outcome may be determined by other factors independent of RPFA results because resistance to antiplatelet drug is 5%–44%.

CLINICAL APPLICATION OF COAGULATION ASSAYS IN CRITICAL CARE

Coagulation assays provide information about different coagulation phases, and their interpretation and application to critically ill patients should be made with caution. A combination of assays should be used to identify issues with hemostasis in these patients. See Figure 1 for a two-step process for screening and confirming coagulation issues; the clinical use of coagulation assays in critical care is reviewed in the following text.

Coagulation Assay Use in DIC

Acute DIC is an ongoing activation of the coagulation system with hypofibrinolysis. The incidence rate of thrombosis and bleeding may differ based on the cause of DIC; thrombosis may be more prevalent in sepsis-induced DIC (70%), whereas bleeding may be more prevalent in malignancy-induced DIC (30%–50%) (Adelborg 2021). Common coagulation assays predictive of DIC include low platelet count, elevated D-dimer value, prolonged PT, and low fibrinogen value (Levi 2014; Taylor 2001). Some of these individual laboratory parameters may be confounded by other factors, so VET together with plasminogen activator inhibitor-1 (PAI-1) tests may assist in the diagnosis and in the treatment of DIC. Hypofibrinolysis is a prominent feature of sepsis-induced DIC because of increased release of PAI-1; however, PAI-1 testing is not often available (Levi 2014). Overall, the prognostic value of VET and PAI-1 tests have not been validated in DIC, and these tests should be used with caution.

Coagulation Assay Use in Thrombocytopenia

Thrombocytopenia is a common complication in critically ill patients and can contribute to coagulopathy and lead to a high mortality rate. The incidence of thrombocytopenia (less than 150,000/mm^3) in critically ill patients is up to 40%. Up to 20% of critically ill patients may have a platelet count lower than 100,000/mm^3, and 10%–15% may have a platelet count of less than 50,000/mm^3 (Levi 2016). Thrombocytopenia may develop because of decreased production, increased use, or destruction of platelets. A prompt evaluation for causes of thrombocytopenia should be initiated to reverse the process, if possible. A platelet count less than 100,000/mm^3 is associated with an increased risk of bleeding, and spontaneous bleeding may occur with platelet counts less than 10,000–20,000/mm^3. In clinical practice, the threshold for platelet transfusion for most critically ill patients is less than 50,000/mm^3 in those actively bleeding or undergoing an invasive procedure and less than 10,000–20,000/mm^3 for those not actively bleeding but at high risk (Vlaar 2020; Kaufman 2015).

Coagulation Assay Use in Blood Transfusion

Patients who are at high risk of bleeding based on prolonged PT or aPTT or low platelet count may require fresh frozen plasma (FFP) or platelet transfusion to correct these laboratory parameters. The main goal of blood transfusion is to supply respective blood components to maintain normal hemostasis. Normal hemostasis can be successfully achieved with a coagulation factor concentration of at least 20%–30% and a fibrinogen concentration of at least 75 g/dL (ASA 1996). The associated INR with this amount of coagulation factors is about 2.0. At least 10–15 mL/kg FFP is recommended to raise coagulation factor concentrations by 30%, but the most common dose (2–3 units of FFP) is often insufficient to normalize and maintain hemostatic balance (Dzik 2004).

Thromboelastography-directed blood transfusion therapy has been studied in patients with cirrhosis, liver transplant, trauma, cardiac surgery, and extracorporeal membrane oxygenation (Vlaar 2021). This method was shown to significantly improve overall mortality (RR 0.52; 95% CI, 0.28–0.95) compared with the usual transfusion protocol in patients with bleeding; however, the level of evidence remains low because of heterogeneity among studies (Wikkelso 2016). The benefit of this method is likely from reducing complications associated with transfusion, which includes transfusion-related acute lung injury, coagulopathy, circulatory overload, sepsis, or transfusion reactions, including fever, anaphylaxis, and hemolytic reactions. Currently, VET-directed blood transfusion is only recommended in patients undergoing cardiac surgery, and its use is limited in other clinical settings, including major trauma (Baksaas-Aasen 2021; Thomas 2018). Examples of TEG-guided transfusion protocols are shown in Box 2. Its use in other patient population is growing because of overall benefit observed with VET-guided transfusion therapy.

Coagulation Assay Use for Therapeutic Drug Monitoring

Critically ill patients are already at high risk of thrombotic and/or bleeding events during their acute illness, so a comprehensive bedside coagulation assay that reliably monitors and predicts clinical outcomes during antithrombotic therapy would be favorable. Currently, INR, aPTT, and AFXa assay are reliable coagulation assays for monitoring anticoagulant drugs; however, the cutoff values predicting bleeding events is not well established. For therapeutic drug monitoring for anticoagulants, see Table 1; and for antiplatelets, see Table 3.

Coagulation assay results may be helpful in deciding and guiding hemostatic drug therapy in patients who present with

Box 2. TEG-guided Transfusion Protocol

Cardiac surgery with excessive microvascular bleeding (using TEG kaolin)

- Heparinase TEG R >12 min: FFP 10–15 mL/kg or PCC low-dose
- MA <40 mm and MA_{ff} <8 mm: cryoprecipitate or fibrinogen concentrate
- MA <40 mm and MA_{ff} >8 mm: platelets with or without desmopressin 0.3 mcg/kg
- LY30 >7.5%: aminocaproic acid or tranexamic acid

Massive transfusion protocol for trauma (using rapid TEG)

- Rapid TEG ACT >128 sec: 2 units FFP
- Angle <65°: 10 units cryoprecipitate
- MA <55 mm: 1 unit platelet
- LY30 ≥5%: 1 Gm TXA

ACT = activated clotting time; FFP = fresh frozen plasma; LY30 = lysis 30; MA = maximum amplitude; MA_{ff} = maximum amplitude functional fibrinogen; PCC = prothrombin complex concentrate; R = reaction time; TEG = Thromboelastography.

Information from: Raphael J, Mazer CD, Subramani S, et al. Society of Cardiovascular Anesthesiologists clinical practice improvement advisory for management of perioperative bleeding and hemostasis in cardiac surgery patients. J Cardiothorac Vasc Anesth 2019;33:2887-99; Gonzalez E, Moore EE, Moore HB, et al. Goal-directed hemostatic resuscitation of trauma-induced coagulopathy: a pragmatic randomized clinical trial comparing a viscoelastic assay to conventional coagulation assays. Annals of Surgery 2016;263:1051-109.

anticoagulant drug-associated major bleeding, including GI hemorrhage and intracranial hemorrhage. Use of PCC for warfarin-associated major bleeding considers the coagulation factor values required to promote and maintain hemostasis, and the dose is calculated based on body weight and INR level (Sarode 2013). Although INR reliably decreases with PCC therapy, it may not always reach the desired INR value (e.g., < 1.4 or < 2.0), and clinicians debate whether a second dose of PCC should be administered. In this case, or VET (or TGA) may be helpful to identify patients who are hypercoagulable and avoid any unnecessary administration of PCC. A similar method is not available for the reversal of FXa-inhibiting drugs, but drug-specific AFXa (or universal AFXa assay) along with VET may be used to guide hemostatic therapy. The use of drug-specific or universal AFXa assay is limited with DOACs because of limited availability and few data on the relationship between drug concentration and clinical outcomes.

CONCLUSION

Hemostasis is maintained with a fine balance between the coagulation and fibrinolysis systems. Critically ill patients often present with or develop coagulopathy that increases their risk of thrombotic or bleeding events. Coagulation assays may be used to screen for patients with coagulopathy, and further testing is often required to make a definitive diagnosis. Clinicians should be familiar with the availability of coagulation assays at their respective institutions and understand the limitations of these assays. One or more coagulation assays may be used to diagnose and monitor coagulopathy. An initial coagulation assay with PT and aPTT may not be sensitive to small changes in coagulation factors and may not be sufficiently sensitive or specific to monitor coagulopathy. Treatment response to the correction of coagulopathy may be monitored using coagulation assays, but further studies are needed to validate their use. Clinical trials are currently ongoing or recently completed that evaluate the use of VET in different patient populations, and increased use in critically ill patients is anticipated. Therapeutic drug monitoring using INR and aPTT is well established for older anticoagulant drugs. The use of drug-specific or universal AFXa assay is limited with DOACs because of limited availability and limited data on the relationship between drug concentration and clinical outcomes. During anticoagulant drug therapy in patients who may require hemostatic therapy or when determining the degree of responsiveness to anticoagulant drug therapy is important, VET (or TGA) may be helpful.

Practice Points

- **Standard coagulation assays (e.g., PT/INR, aPTT) and platelet parameters can be used to screen for coagulation disorders.**
- **Critically ill patients often develop coagulopathy, which has been associated with increased mortality.**
- **Clot-based and global hemostasis assays are used to diagnose coagulopathy but do not correlate with clinical outcomes. Instead, these assays describe current status of hemostasis.**
- **The PT, aPTT, dTT, AFXa assay, PFA, RPFA, TGA, and TEG/ROTEM with or without platelet assay may be used to assess antithrombotic drug therapies.**
- **The VET may be helpful to identify hypo- or hypercoagulable conditions and to guide blood transfusion therapy.**

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Self-Assessment Questions

Questions 1 and 2 pertain to the following case.

A.B. is a 79-year-old man with medical history of dementia, benign prostate hyperplasia, hepatitis C with cirrhosis, esophageal varices, chronic obstructive pulmonary disease, and gastroesophageal reflux disease. He is admitted to the medical ICU for an exacerbation of chronic obstructive pulmonary disease and work up for community-acquired pneumonia. Pertinent baseline coagulation laboratory values include international INR 1.9, PT 21.7 seconds, activated partial thromboplastin time (aPTT) 36 seconds, and Plt 37,000/mm^3.

1. Which one of the following tests would best evaluate A.B.'s current hemostasis state to assess balance between coagulation and fibrinolysis?

   A. Thrombin generation assay (TGA)
   B. Anti-factor IIa (AFIIa) assay
   C. Thromboelastography (TEG)
   D. TEG platelet test

2. Two days after admission, A.B. is intubated. He is suspected to have upper GI bleeding or esophageal variceal bleeding. A.B. is hypotensive with blood pressure 81/45 mm Hg and is initiated on norepinephrine intravenous at 5 mcg/min. Pertinent laboratory test results include Hgb 6.4 g/dL (decrease from 10 g/dL), INR 2.2, PT 24 seconds, aPTT 49 seconds, Plt 25,000/mm^3, and fibrinogen 2.5 g/dL (normal reference range 1.5–4.5 g/dL). Rapid TEG reveals activated clotting (ACT) time 135 seconds, k time 2.2 minutes, angle 67 degrees, maximum amplitude (MA) 50 mm, and lysis at 30 minutes 0%. Which one of the following combinations of blood products is best to recommend for A.B.?

   A. Fresh frozen plasma (FFP) and platelets
   B. Cryoprecipitate and desmopressin
   C. FFP and cryoprecipitate
   D. Fibrinogen and platelets

3. A 50-year-old man with a medical history that includes coronary artery disease, type 2 diabetes, congestive heart failure, and hyperlipidemia is admitted to the ICU after being found down. He is noted to be bleeding from his forehead. A CT scan of the head shows subdural hematoma. The patient's medication history, based on outpatient pharmacy fill history, includes aspirin 325 mg daily, carvedilol 25 mg twice daily, clopidogrel 75 mg daily, insulin glargine 35 units daily, atorvastatin 40 mg daily, and levofloxacin 500 mg daily. The patient is not a good historian and is confused. Rapid platelet function test (RPFA) result shows 585 aspirin reaction unit (ARU) and 195 platelet reaction unit (PRU). Which one of the following blood transfusions is best to recommend for this patient based on the RPFA?

   A. FFP
   B. Cryoprecipitate
   C. Platelets
   D. No blood transfusion

4. A 38-year-old man is admitted to ICU with a major GI bleed after 4 weeks of apixaban therapy. The patient was recently diagnosed with non-valvular atrial fibrillation. He states that he took his last dose 8 hours ago. The patient is currently hypotensive on norepinephrine intravenously 10 mcg/min and received 2 units FFP and 2 packed red blood cells. Which one of the following coagulation tests would be best to recommend for this patient to show presence of apixaban?

   A. PT
   B. TEG R time
   C. Rapid TEG ACT
   D. AFXa assay, heparin-calibrated

Questions 5–7 pertain to the following case.

C.D., a 71-year-old woman, is diagnosed with pulmonary embolism and started on intravenous unfractionated heparin (UFH) therapy. Her medical history includes HIV infection, asthma, non-valvular atrial fibrillation, HTN, coronary artery disease after percutaneous coronary intervention, and small cell lung cancer. C.D. states that she has not been taking her medications consistently since she was having flu-like symptoms 5 days ago. Pertinent laboratory values include baseline PT 12 seconds and aPTT 51 seconds, and subsequent aPTT mixing study shows prolonged/not corrected aPTT.

5. Which one of the following is the most likely cause of C.D.'s coagulopathy?

   A. Factor X inhibitor
   B. Lupus anticoagulant
   C. Vitamin K deficiency
   D. Disseminated intravascular coagulation (DIC)

6. Which one of the following is the best to recommend as a monitoring coagulation test to titrate intravenous UFH doses in C.D.?

   A. aPTT
   B. Thromboelastography
   C. AFIIa assay
   D. AFXa assay

7. On day 3, the medical team decides to switch the C.D. to rivaroxaban for ease of administration and dosing. Which one of the following is best to recommend regarding routine coagulation monitoring for C.D.?

   A. PT
   B. aPTT
   C. No routine monitoring
   D. AFXa assay, calibrated for heparin

8. A 59-year-old woman is currently receiving UFH IV 36,000 units/day for the treatment of acute DVT. The UFH dose has been increased three consecutive times with minimal increase in aPTT. Which one of the following is best to recommend as the next step for this patient?

   A. Increase UFH dose to 50,000 units/day.
   B. Change UFH to enoxaparin 1 mg/kg subcutaneous every 12 hours.
   C. aPTT and AFIIa assay should be performed simultaneously to assess for UFH resistance.
   D. aPTT and AFXa assay should be performed simultaneously to assess for UFH resistance.

Questions 9 and 10 pertain to the following case.

E.F. is a 76-year-old man with medical history that includes coronary artery disease after stent placement, and CABG (2019), congestive heart failure, HTN, and type 2 diabetes. His home drugs include warfarin and aspirin. E.F. is found down and discovered to be hyperglycemic (glucose 500 mg/dL) and hypoxic (oxygen saturation 87%). Because of respiratory failure, he is emergently intubated, and a CT scan of the head shows evidence of a large subdural hematoma. Pertinent laboratory test results include Hgb 9.1 g/dL, INR 2.9, aPTT 35 seconds, and Plt 195,000/mm^3. Four-factor prothrombin complex concentrate (4F-PCC) is administered to reverse warfarin-associated coagulopathy and major bleeding.

9. Which one of the following coagulation tests is best to recommend for E.F. to monitor for efficacy after administering 4F-PCC?

   A. PT
   B. INR
   C. TGA
   D. AFIIa assay

10. Which one of the following is the best platelet function test to assess antiplatelet effect in E.F.?

    A. TEG MA
    B. Rapid PFA
    C. Platelet count
    D. TEG platelet test, adenosine phosphate agonist

11. A 77-year-old woman with a medical history of HTN and chronic obstructive pulmonary disease has been in the ICU for 7 days for the management of acute ischemic stroke. The patient is now diagnosed with hospital-acquired pneumonia and septic shock. Pertinent laboratory test results include PT 25 seconds, INR 2.1 and platelet count 65,000/mm^3, TEG parameters are R time 10 min, K time 4.5 min, angle 51 degrees, MA 48 mm, lysis at 30 minutes 1%. Which one of the following is the most likely cause of this patient's coagulation abnormality?

    A. DIC
    B. Pneumonia
    C. Ischemic stroke
    D. Chronic obstructive pulmonary disease

12. A 59-year-old man is undergoing percutaneous coronary intervention and is started on aspirin 81 mg daily and clopidogrel 75 mg daily. After 7 days of dual antiplatelet therapy, a RPFA test shows 450 ARU and 230 PRU. Which one of the following is best to recommend regarding this patient's antiplatelet therapy?

    A. Discontinue aspirin therapy.
    B. Increase aspirin to 325 mg daily.
    C. Decrease clopidogrel to 37.5 mg daily.
    D. Increase clopidogrel to 150 mg daily.

13. A clinical pharmacist is consulted on whether aPTT monitoring should be replaced by AFXa assay for UFH intravenous therapy in the ICU. Which one of the following patient-specific factors would be most likely to improve with use of the AFXa assay?

    A. Hypertriglyceridemia (triglycerides greater than 360 mg/dL)
    B. Increase in acute phase reactant, factor VII (FVIII)
    C. Hyperbilirubinemia (bilirubin greater than 6.6 mg/dL)
    D. Antithrombin deficiency

14. A 60-year-old woman with a medical history of nonvalvular atrial fibrillation on apixaban, congestive heart failure, chronic kidney disease on hemodialysis, and asthma is brought to the ED with altered mental status. She is emergently intubated, and further testing reveals spontaneous intracerebral hemorrhage. A dose of 4F-PCC is administered, and the patient is transferred to ICU for further care. The medical team decides to send AFXa assay (heparin-calibrated) 12 hours after the 4F-PCC dose, and the result is 1.81 IU/L. The medical team consults the clinical pharmacist about whether a second dose of 4F-PCC may be given because the patient is still at high risk for hematoma expansion. Which one of the following is best to recommend regarding a second dose of 4F-PCC for this patient?

    A. Yes, but only if PT is also prolonged.
    B. No, AFXa assay is not sensitive for apixaban.
    C. Yes, AFXa assay indicates the presence of apixaban.
    D. No, AFXa assay must be greater than 2 IU/L to show apixaban therapy.

15. A 76-year-old man is admitted to the ICU with osteomyelitis and altered mental status. His medical history includes stroke, coronary artery disease, congestive heart failure, type 2 diabetes, gastroesophageal reflux disease, hyperlipidemia, HTN, obstructive sleep apnea, obesity, and benign prostate hyperplasia. Pertinent laboratory test results include ALT 5 U/L, AST 15 U/L, total bilirubin 0.6 mg/dL, Hgb 9.5 g/dL, INR 1.6, PT 19.6 seconds, aPTT 79 seconds, and Plt 210,000/mm^3. Which one of the following tests is best to recommend to further work up this patient's coagulopathy and identify if coagulation factor disturbances exist?

    A. TGA
    B. TEG
    C. PT and aPTT mixing study
    D. AFXa assay