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Coagulation Monitoring

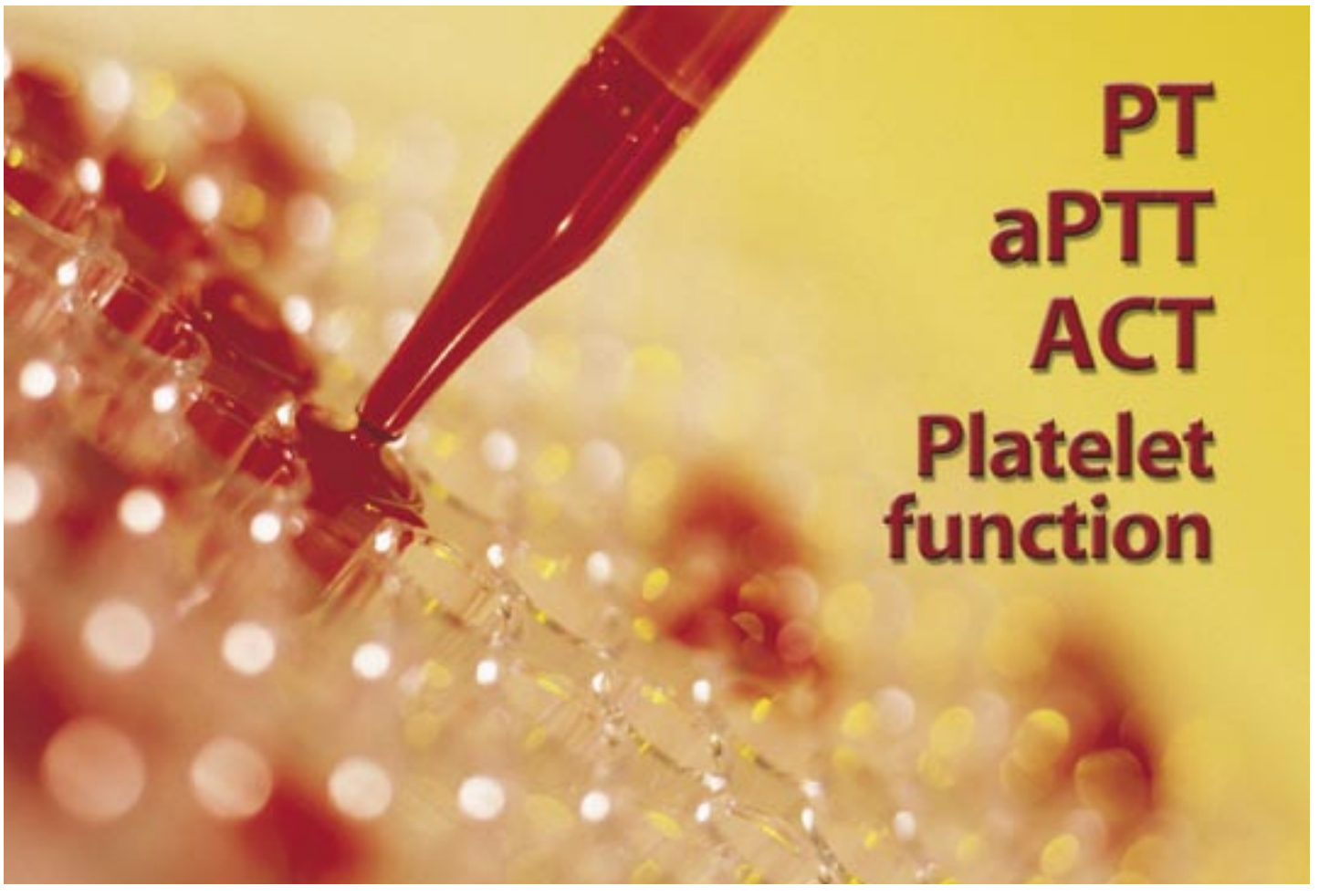
How Labs Can Meet the Demand for Point-of-Care Testing

BY TAK-SHUN CHOI, MD

The management of bleeding patients requires close monitoring of rapidly changing hemostatic parameters. These patients are typically on a number of antiplatelet and anticoagulant drugs, and clinicians need the results of coagulation tests quickly in order to guide critical anticoagulant dose adjustments or blood transfusion therapy in surgical and other critical care settings. Consequently, the demand for coagulation monitoring at the point of care (POC) has soared in hospitals. In addition, the availability of POC methods for coagulation monitoring has led to the growth of patient self-testing at home for management of oral anticoagulant therapy.

Coupled with the increasing demand for POC coagulation testing in hospital and home settings, diagnostic manufacturers have recently developed a new, superior generation of POC coagulation instruments based on advances in microelectronics, microfluidics, and microfabrication. Today, many IVD companies offer POC coagulation testing systems that measure various components of hemostasis—including whole-blood prothrombin time (PT), activated partial thromboplastin time (aPTT), activated clotting time (ACT), and platelet function tests— as well as other tests of hemostatic function (Table 1).

Clearly, the increasing demand for these tests and their growing sophistication necessitates greater involvement from laboratorians in overseeing a POC coagulation monitoring program. This article will describe the clinical uses of various coagulation tests, provide an overview of POC coagulation instruments, and discuss how laboratorians can provide a comprehensive POC program that delivers rapid and accurate test results that are comparable to lab methods.



Overview of POC Coagulation Instruments

Compared to larger coagulation analyzers, the technologies employed in POC coagulation instruments are less precise and a 10% coefficient of variation (CV) is generally considered clinically acceptable for POC coagulation instruments. A correlation coefficient of r=0.88 (not r^2) is considered acceptable for comparison studies between POC and lab coagulation methods. For some tests, however, the POC coagulation tests are not directly comparable to any test performed in the central lab, most notably ACT.

Furthermore, although many POC coagulation tests have the same name as central lab tests, they are not comparable. Differences in sample type (fresh or citrated whole blood versus citrated plasma), reagent sensitivity to heparin, and methodology all affect test results, and mathematical conversions do not correct for all these variables. While the International Normalized Ratio (INR) has improved comparability between PT results that use different reagents and assay systems, there is no INR-like system for normalizing differences in heparin response curves observed with different reagents and test systems. Laboratorians therefore must interpret the results of PT, aPTT, and ACT tests using the normal and therapeutic ranges determined specifically for either the POC or the central lab method.

Platelet Function Analyzers

Traditional testing of platelet function or von Willebrand factor (vWF) function is not commonly available in primary care hospitals as it takes several hours to perform and requires a skilled technologist. In contrast, POC platelet function analyzers are easy to use and provide results in less than an hour. These instruments are most useful for monitoring the effect of antiplatelet therapy and for assessing the need for platelet transfusion in post-cardiac bypass surgery patients.

Table 2 lists some of the currently available POC platelet function analyzers, which differ primarily in the parameters tested and the applicability of the test for detecting platelet and/or vWF abnormalities.

Home PT/INR Monitoring

Bleeding is a major complication of warfarin therapy that is often associated with supratherapeutic drug levels. These complications can be reduced as much as 76% if patients maintain their PT/INR values within the therapeutic range. Furthermore, in one study, researchers showed that management of anticoagulation therapy based on self-testing was superior to management by a physician-directed anticoagulation clinic. Patients achieved an 84.5% success rate for keeping their PT/INR values in the target range, compared to 73.8% for the physician-directed group.

Table 3 lists the currently available home PT/INR monitoring instruments. All these instruments have been FDA cleared for at home use by patients.

POC Instruments for Heparin Monitoring

Despite the superiority of low-molecular-weight heparin, unfractionated heparin (UFH) remains the standard of care for inhibiting thrombus and clot formation in many clinical settings. Clinicians must monitor heparin therapy closely, however, due to heparin's short half-life (average 90 minutes) and the great variability in an individual's response to the drug. Particularly in the critical care settings where clinicians need to achieve therapeutic heparin levels rapidly in patients, this is especially difficult

Table 1

Examples of POC Coagulation Instruments

Company	Instrument	Tests
Abbott (Abbott Park, Ill.) www.i-stat.com	i-STAT	ACT, PT
Accumetrics (San Diego, Calif.) www.accumetrics.com	VerifyNow (Ultegra)	Aspirin Assay; IIb/IIIa Assay; Clopidogrel Assay (research use only)
Chrono-log Corporation (Havertown, Pa.) www.chronolog.com	Whole Blood Aggregometer (WBA)	Platelet function test
Dade-Behring (Deerfield, Ill.) www.dadebehring.com	Platelet Function Analyzer PFA-100	Platelet function test
Haemoscope, Inc. (Niles, Ill.) www.haemoscope.com	Thromboelastogram (TEG)	Global assessment of clot formation including platelet function and resolution of clot
Helena Laboratories (Beaumont, Tex.) www.helena.com	Actalyke	ACT
	PlateletWorks	Platelet funtion test
Hemodyne, Inc. (Bethesda, Md.) www.hemodyne.com	Hemostasis Analysis System	Assessment of platelet activity and clot quality
Instrumentation Laboratory (Lexington, Mass.) www.ilus.com	GEM PCL Plus (Portable Coagulation Laboratory)	PT, aPTT, ACT-LR, ACT, Citrated PT
International Technidyne Corporation (Edison, N.J.) www.itcmed.com	Hemochron Signature +	PT, aPTT, Citrated PT, Citrated aPTT, ACT-LR, ACT+
	ProTime	Home PT/INR
	Hemochron Response	PT, citrate PT, APTT, citrate aPTT, ACT, TT, HNTT, HiTT, Fibrinogen, PDAO, RxDx
Medtronic Perfusion Systems (Minneapolis, Minn.) www.medtronic.com	ACT Plus Automated Coagulation Timer System	PT, aPTT, ACT, high-range heparinase test (HRHTC)
	HMS Plus Hemostasis Management System	ACT, HDR, HPT, HemoSTATUS Platelet Function Test
Pentapharm GmbH (Munich, Germany) www.pentapharm.de	ROTEG 05	Global assessment of clot formation
Roche Diagnostics Corporation (Indianapolis, Ind.) www.roche.com	CoaguChek S	PT/INR
	CoaguChek	Home PT/INR
Sienco, Inc. (Arvada, Colo.) www.sienco.com	SonoClot	Global assessment of clot formation including platelet function and resolution of clot

Abbreviations used: ACT, activated clotting time; aPTT, activated partial thromboplastin time; HDR, heparin dose response; HiTT, high dose thrombin time; HMT, heparin management test; HNTT, heparin neutralized thrombin time; HPT, heparin protamine titration; HTT, heparin titration test; LHMT, low heparin management test; PDAO, protamine dose assay; PRT, protamine response test; PT, prothrombin time; RxDx (heparin and protamine response tests); TT, thrombin time.

due to the narrow therapeutic window between thrombus suppression and excessive bleeding. Because of these requirements, the turnaround time for aPTT, the standard test for monitoring heparin therapy in patients with thromboembolic disease, frequently does not meet clinicians' needs. However, POC coagulation instruments can provide fast results that facilitate rapid titration of a patient's heparin dose.

Table 4 lists some of the currently available POC instruments for monitoring heparin anticoagulation therapy. These instruments can also provide coagulation results to guide plasma therapy and cryoprecipitate transfusion in perioperative or bleeding patients.

Heparin is also the drug of choice for high-dose anticoagulation during cardiopulmonary bypass surgery or invasive vascular procedures. For heparin levels >1.0 U/mL, ACT is the standard test because when the aPTT exceeds 200 seconds the clotting tests available in the lab are not suitable. Table 5 lists the POC instruments that offer low-heparin range and/or high-range ACT. These instruments can be divided into those that provide a full range of heparin monitoring and those that provide only high- or low-range monitoring.

Global Assessment of Clot Formation

Predicting microvascular bleeding in surgical and trauma patients by using the PT or aPTT is imprecise because *in vitro* conditions cannot adequately mimic the complex *in vivo* interplay of platelets, procoagulants, anticoagulants, and the fibrinolytic system. Fortunately several alternatives to the *in vitro* clot formation tests are available. The thromboelastogram was originally described for global assessment of clot formation and resolution in the 1940s, and more recently, in 1990, Sienco Inc. (Arvada, Colo.) developed the Sonoclot Coagulation & Platelet Function Analyzer. These instruments monitor the viscoelastic properties of clot formation and provide a clot signature that traces the processes of clot formation and clot resolution. By analyzing the tracing produced by the instruments, clinicians can obtain a global assessment of the function of platelets, procoagulants, anticoagulants, and fibrinolysis. Other instruments available to assess global clot formation include the ROTEG 05 by Pentapharm GmbH (Munich, Germany) and the Hemostasis Analysis System by Hemodyne (Bethesda, Md.).

In the Sonoclot system, a hollow tube vibrates up and down within a cup containing the whole blood sample, and the resistance to oscillation provides a measure of sample viscosity. Once clotting of the sample begins, changes in the signal, or clot signature, correlate with structural events within the clot. The Sonoclot system has also been used to assess qualitative or quantitative platelet abnormalities.

These instruments require a highly skilled technologist to perform the test and analyze the result, but recently, Haemoscope Corp. (Niles, Ill.) developed the Computerized Thrombelastograph Coagulation Analyzer that automates the test and provides more reproducible and interpretable measurements. The analyzer measures the coupling of a moving outer cup with a centrally placed piston during clotting of whole blood samples. As the clot forms, it connects the inner piston and outer wall, causing the piston to move. Adhesion and clot strength are determined by the degree of coupling. The system also documents the interaction of platelets with procoagulants and anticoagulants from the time blood is placed in the analyzer until initial fibrin formation and eventual clot lysis. Measured parameters are defined by changes in the kinetic curve.

Hypothermia and Coagulation

A commonly overlooked factor in coagulation monitoring is the temperature at which the coagulation cascade takes place. In the lab, coagulation testing is performed at 37° C and the results reflect the amount of coagulation factors present in the blood specimen. However, in patients experiencing hypothermia after massive blood transfusion or undergoing cardioplegia during cardiac bypass surgery, body temperature can be as low as 25° C. Since the coagulation enzyme cascade does not function well below 37° C, it is important to warm the patient when the test results show the presence of adequate coagulation factors but the patient still has microvascular bleeding.

A Critical Role for Laboratorians: Method Validation

The availability of POC coagulation monitoring does not automatically translate into better patient care. Inaccurate test results can easily jeopardize patient management, and therefore laboratorians need to take a leadership role in designing appropriate studies when a hospital or health care system is assessing the validity of POC methodology in comparison to methodology used in the lab.

In a study conducted at my institution, POC results for aPTT showed poor agreement with the lab method. Although previously published studies demonstrated acceptable correlation coefficients of 0.79–0.83, we found that the correlation coefficient was insufficient to fully evaluate the acceptability of a method. Using the lab method as a

Table 2

Platelet Function Analyzers

Instrument	Platelet Works	HemoSTATUS Platelet Function Test	PFA-100	VerifyNow (Ultegra)	WBA
Company	Helena	Medtronic	Dade Behring	Accumetrics	Chrono-log
Method	Platelet count differential after activation by choice of activators	Platelet activating factor (PAF)-induced shortening of the kaolin-ACT; a clot ratio= 1-(PAF-ACT/control ACT) reflects platelet function	Occlusion of an aperture under high shear condition in a COL/EPI or COL/ADP test cartridge	Turbidimetric-based optical detection measuring platelet-induced aggregation of fibrinogen-coated microbeads	WB electrical impedance with disposable electrodes; AA, collagen, ristocetin, ADP agonists may be used
Sample	WB	VWB	CWB	CWB	CWB
Patient ID	Yes	Yes	Yes	Yes	No
Reagent ID	Yes	Yes	Yes	Yes	No
EQC	Yes	Yes	No	Yes	Yes
Liquid QC	No	Yes	No	Yes	No
AED	Yes	Yes	Yes	Yes	No
Result TAT	<5 min	>12 min	<5 min	2–8 min depending on the test	6 min
Capability of Data Transfer to LIS	Yes	Yes	Yes	Yes	No
Capability of Data Management	Yes	Yes	No	No	No

Abbreviations used: AA, arachidonic acid; AED, automated error detection; COL/ADP, collagen/adenosine diphosphate; COL/EPI, collagen/epinephrine; CWB, citrated whole blood; EQC, electronic quality control; VWB, venous whole blood.

Table 3

Home PT/INR Monitoring Instruments

Instrument	CoaguChek	INRatio	ProTime
Company	Roche	Hemosense	ITC
Test	PT/INR	PT/INR	PT/INR
Method	Optical detection of cessation of movement of paramagnetic iron particles as clot forms	Electronic detection of change in impedance on clot formation	Optical detection of clot formation by interruption of blood flow
Sample	Fingerstick (FS)	FS	FS or venous
Electronic QC	Yes	Yes–internal	Yes–internal
Liquid QC	Yes–external only	Internal only	Yes–internal and optional external
AED	Yes	Yes	Yes
Result (TAT)	2 min	2 min	3–4 min
Data storage	30 tests	60 tests	30 tests
Capability of Data Transfer to LIS	No	No	No
Capability of Data Management	No	No	No
CLIA waived	Yes	Yes	Yes

Abbreviations used: AED, automated error detection; FS, fingerstick.

Table 4

POC Coagulation Instruments That Perform Multiple Tests

Instrument	i-STAT	GEM PCL Plus	Hemochron Signature +	Hemochron Response
Company	Abbott	IL	ITC	ITC
Tests	PT, ACT	PT, ACT-LR, ACT, aPTT	PT, ACT-LR, ACT, aPTT	PT, APTT, ACT, TT, HNTT, HiTT, Fibrinogen, PDAO, RxDx
Sample (assay dependent)	Fingerstick (FS) VWB	FS CWB VWB	FS CWB VWB	CWB VWB
Method	Amperometric detection of cleavage of artificial thrombin substrate	Optical detection of cessation of blood movement pumped back and forth across a window as clot forms	Optical detection of cessation of blood movement pumped back and forth across a window as clot forms	Electromagnetic method: shifting of magnet in the sample test tube and magnet detector within the instrument test well as clot forms
Patient ID	Yes	Yes	Yes	Yes
Reagent ID	Yes	Yes	Yes	Yes
EQC	Yes	Yes	Yes	Yes
Liquid QC	Yes	Yes	Yes	Yes
AED	Yes	Yes	Yes	Yes
Result TAT	1–20 min depending on test & result	~1–9 min depending on test & result	~1–9 min depending on test & result	1–20 min depending on test & result
Capability of Data Transfer to LIS	Yes	Yes	Yes	Yes
Capability of Data Management	Yes	Yes	Yes	Yes

Abbreviations used: AED, automated error detection; CP, citrated plasma; CWB, citrated whole blood; EQC, electronic quality control; FS, fingerstick; VWB, venous whole blood.

reference, the regression analysis between the POC and lab instruments should be linear; however in our study, the POC instrument lost linearity at prolonged aPTT values. For example, the difference between the methods was -2.7% at 30 sec, but -41.1% at 71.2 sec. Therefore, we concluded that the correlation coefficient alone was insufficient to fully evaluate the acceptability of a method.

Laboratorians also need to examine the regression data for studies comparing lab and POC coagulation methods. Significant deviations from zero for the y-intercept are acceptable; however, slopes that fall greatly below 1.0 are not. Low slopes (<0.85) indicate loss of analytical sensitivity, which makes the test of limited value. In addition, laboratorians need to evaluate the CV of the POC method and reject assays that have large CVs.

A Well-Run POC Coag Program

The development of a successful POC coagulation monitoring program requires cooperation between laboratorians and clinicians. Once the POC coagulation methods and instruments have been selected, laboratorians continue to play a critical role in delivering accurate results. A program must be established to calibrate and maintain equipment, train non-technician users of the instruments, review quality control data, organize documentation and quality assurance, and ensure documentation of output and cost-effective operation.

Quality Control Issues

According to the CLIA guidelines, quality control (QC) of coagulation testing requires that at least two levels of control material, either electronic or liquid, be tested every 8 hours on each day of patient testing. Most manufacturers have electronic QC for their instruments that satisfies this requirement, but laboratorians also need to verify the performance of the disposables using liquid QC materials, which are also available from each manufacturer. Last year, the Centers for Medicare and Medicaid Services published extensive guidelines on QC for POCT, which all laboratories need to follow.

A Future of Better Patient Care

The demand for POC coagulation monitoring will continue to grow as new and better instruments enable clinicians to access real-time, objective data when making critical decisions about anticoagulant drug dosing or blood transfusion therapy. In addition, positive data on the benefits of patient self-testing in the management of oral anticoagulant therapy will also stimulate growth in this area. With this growth, laboratorians will have more opportunities to contribute their expertise in directing the POC coagulation monitoring programs in hospitals by ensuring the validity of methods and guiding compliance for regulatory and accrediting agencies.

SUGGESTED READINGS

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Table 5

High-range Heparin POC Monitoring Instruments

Company	Abbott	Helena	IL	ITC – Hemochron		Medtronic	
Instrument	i-STAT	Actalyke	GEM PCL	Jr Signature+	Response	ACT Plus	HMS Plus
ACT Tests	LR: None HR: Celite ACT, Kaolin ACT	LR: G-ACT, MAX ACT HR: C-ACT, K-ACT	LR: ACT-LR HR: ACT	LR: ACT-LR HR: ACT+	LR: Glass-ACT, HR: C-ACT, K-ACT Heparin and protamine dosing	LR: LR-ACT HR: HR-ACT	HR ACT Heparin and protamine dosing
Method	See Table 4	Electromagnetic method: shifting of magnet in the sample test tube and magnet detector within the instrument test well as clot forms		See Table 4		Photo-optical detection of slowing of a flag movement on one end of a plunger assembly through the reaction chamber as fibrin forms on the other "daisy" end of the plunger	
Patient ID	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Reagent ID	Yes	Yes	Yes	Yes	Yes	Yes	Yes
EQC	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Liquid QC	Yes	Yes	Yes	Yes	Yes	Yes	Yes
AED	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Capability of Data Transfer to LIS	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Capability of Data Management	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Abbreviations used: LR, low range; HR, High range; AED, automated error detection; EQC, electronic quality control

Tak-Shun Choi, MD, is Medical Director of Transfusion Medicine Unit, Pathology and Laboratory Medicine Service, Veteran's Administration North Texas Health Care System, and Assistant Professor of Pathology, University of Texas Southwestern Medical Center at Dallas.

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