Received 3.15.05 | Revisions Received 4.7.05 | Accepted 4.12.05

Prothrombin Time Testing Practices in the Pacific Northwest

Monitoring voluntary practice guidelines and indicators of quality*

Kathleen M. LaBeau, MT(ASCP),[1] Shahram Shahangian, PhD, DABCC, FACB[2]

([1]Washington State Department of Health, Office of Laboratory Quality Assurance, Shoreline, WA, [2]Laboratory Practice Evaluation and Genomics Branch, Centers for Disease Control and Prevention, Atlanta, GA)

**Use of trade names are for identification purposes only, and it does not imply any endorsement by the United States Department of Health and Human Services or the Centers for Disease Control and Prevention.*

DOI: 10.1309/YE6MK65XTOQAGMPR

- In October 2003, the Washington State Department of Health and the Centers for Disease Control and Prevention used prothrombin time testing to develop a model to reduce medical errors by identifying steps that are vulnerable to errors and comparing current laboratory practices with voluntary practice standards.
- Laboratory personnel can use the study results and references to voluntary practice standards to reduce their opportunities for error for prothrombin time testing.
- Professional societies can use this model to systematically assess other error-prone tests to both establish and harmonize best practices among laboratories.

Medical mistakes and errors are unacceptably high, despite a longstanding focus on activities carried out in the name of quality assurance, quality improvement, total quality management, and quality assessment. In 1999, a report by the Institute of Medicine revealed the magnitude of medical errors and concluded that most were the result of systematic failures and were preventable.[1]

One approach to reducing serious medical errors is by identifying quality indicators and developing systems for best practices. Practice standards and guidelines are developed through a consensus process that identifies specific essential requirements for materials, methods, and practices. They are designed to both establish and harmonize best practices among the health care community. However, studies have shown that despite required and voluntary standards of practice, many laboratory professionals fail to use them.[2]

Purpose of the Study

In October 2003, the Washington State Office of Laboratory Quality Assurance (LQA) and the Centers for Disease Control and Prevention (CDC) created a model to collect and monitor laboratory quality indicators from a broad spectrum of clinical laboratories.

To develop our model, we established the following objectives:

- Select a common, error-prone laboratory test.
- Identify the steps that are vulnerable to errors.
- Investigate voluntary practice standards to determine best practices.
- Gather information about current practices from a variety of testing sites.
- Share the findings.
- Recognize inherent differences between testing settings and methods.
- Make recommendations about quality indicators and best practices.

We selected the prothrombin time (PT) test to develop this model since it is a very common test that is vulnerable to errors and adverse patient outcomes. Patients on oral anticoagulation therapy must be monitored carefully to prevent dangerous complications of bleeding or thrombosis.

Methods

To gather information about current laboratory testing practices, a questionnaire was developed in October to December 2003 by the LQA and CDC, and was pilot-tested in 5 laboratories in Washington State in December 2003. We researched numerous voluntary practice standards addressing PT testing that served as the basis for our questionnaire. Questions were developed to address the areas we identified to be vulnerable to errors for PT testing. These included:

- Selection of the thromboplastin reagent.
- Concentration of the anticoagulant in collection tubes.
- Specimen acceptance and rejection policies.
- Implementation of new lots of reagents.
- Contents of patient test report to clinicians.

Table 1_Questionnaire Respondents

	Total	Site Type			Laboratory Classification			Location	
		POL*	Hospital	IL**	Waived/ PPMP	Moderate/ High***	Accredited	Urban	Rural
Targeted (N)	591	333	198	60	119	247	225	324	267
Respondent (N)	297	152	117	28	45	140	112	159	138
Response rate (%)	50	46	59	47	38	57	50	49	52

*POL includes the following types of sites: physician office laboratories, clinics, community health clinics, home health agencies, health maintenance organizations, and ambulatory surgical centers.
**IL, independent laboratory.
***Moderate/High, moderate or high complexity testing, but not accredited.

Using the Washington Medical Test Site (MTS) data base and licensure application forms, testing sites performing PT by either waived or non-waived test complexity methods were identified and targeted to receive the questionnaire. Laboratories located in Alaska, Idaho, and Oregon, performing proficiency testing for PT, were identified using the CLIA (OSCAR) data base. Questionnaires were mailed to 591 laboratories in the Pacific Northwest region on January 27, 2004.

Results

Respondents

Two hundred ninety-seven completed questionnaires were returned by March 19, 2004, resulting in an overall response rate of 50% (**Table 1**).

Table 2_PT Test Methods

Site Type	Traditional Methods		POC Devices	
	Number	Percent	Number	Percent
Hospital	108	61	5	7
Independent laboratory	22	13	1	1
POL	46	26	69	92

Table 3_Testing Personnel

Testing Personnel Background	Sites Employing Testing Personnel With the Background			
	Traditional Methods		POC Devices	
	Number	Percent	Number	Percent
Medical technologist	171	98	34	46
Medical laboratory technician	99	57	27	36
Medical assistant	2	1	33	45
Registered nurse	3	2	23	31
On the job trained	9	5	13	18
Licensed practical nurse	0	0	12	16
Pharmacist	3	2	4	5
Phlebotomist	3	2	4	5
Laboratory assistant	3	2	2	3
Physician assistant	0	0	3	4
Advanced registered nurse practitioner	1	1	1	1
Non-registered technologist	2	1	0	0
Emergency medical technician	0	0	1	1

We further categorized respondents according to the test reagent/system used. Seventy percent indicated they used a reagent associated with a traditional PT test method and 30% indicated the use of reagent test strips or cartridges associated with point of care (POC) testing devices (**Table 2**).

A wide variety of backgrounds for testing personnel were given. Different patterns were seen in testing personnel between the sites using traditional test methods and those using POC devices (**Table 3**).

Selection of the Thromboplastin Reagent

When using the PT test to monitor oral anticoagulation therapy, the sensitivity of the thromboplastin reagent to the depletion of vitamin K dependent coagulation factors is reflected as the international sensitivity index (ISI). All thromboplastins are calibrated against standards with sensitivities comparable to the WHO International Reference Plasma, which is assigned an ISI of 1. Commercial manufacturers of thromboplastin reagents calculate the ISI and include it in the product package insert.

Several voluntary practice standards and other publications recommend the use of thromboplastin reagents that have a low ISI value.[3-7] Thromboplastins with low ISIs are more responsive or "sensitive." The variability of international normalized ratio (INR) values produced by different test systems is reduced by the universal use of highly responsive reagents. While sensitive thromboplastin reagents with lower ISI values may offer the potential for improved precision in determining the INR [due to the fact that INR = $(\text{PT ratio})^{ISI}$ where PT ratio = patient PT/mean normal PT], some studies have suggested that low-ISI reagents may be less precise.[6] The following recommendations have been made for the selection of reagent ISI values:

- 0.9 to 1.70 College of American Pathologists[3]
- <1.50 NCCLS[4] (Clinical and Laboratory Standards Institute)
- Close to 1.00 American Society of Health System Pharmacists[5]
- ≤1.20 Hirsch[6]
- ≤1.50 American Heart Association[7]

For sites using traditional methods (**Table 4**), the range of ISI values for their reagents was 0.85 to 2.33, with an average ISI of 1.34 and median ISI of 1.15. **Table 5** shows a frequency distribution of the reagents used according to ISI values.

Sites using POC devices and the ISI values of their reagents are summarized in **Table 6**.

Concentration of the Anticoagulant in Collection Tubes

Several voluntary practice standards or guidelines recommend the use of collection tubes containing sodium citrate in the concentration of 3.2%.[3,8-10] The INR can be affected by

Table 4_PT Reagents – Traditional Methods (N=176 sites)

Reagent Manufacturer	Number of Respondents	Examples of Brand Names	Range of ISI Values
Dade Behring	58	Innovin Thromborel S	0.90 to 1.13
		Thromboplastin C+	1.77 to 2.21
Beckman Coulter/ Instrumentation Laboratory	50	IL PT-Fibrinogen Recombinant IL PT-Fibrinogen HS+	0.85 to 1.13
		IL PT-Fibrinogen HS	1.35 to 1.44
		IL PT-Fibrinogen IL Thromboplastin	>2.00
BioMerieux	24	HTF	1.15 to 1.26
		Simplastin Excel	1.81 to 1.91
Diagnostica Stago	13	Neoplastin Neoplastin C1+	1.26 to 1.35
Hemoliance	11	Recombiplastin RTF	0.94 to 1.03
		Brain thromboplastin	2.00 to 2.33
Sigma Diagnostics/Sigma Trinity Biotech	10	Thrombomax HS Thromborel HS	1.15 to 1.31
		Thrombomax	1.69 to 1.71
Pacific Hemostasis	6	None given	1.16 to 2.04
Ortho	3	None given	0.85 to 1.00
Other	1	MLA Recombiplastin	1.03
Total	176	———————	0.85 to 2.33

the citrate concentration. The specimen osmolarity is closer to plasma and decreases the variability in clotting times related to the variability in the hematocrits and filling volumes of the tubes when using 3.2% sodium citrate. Many of the manufacturers determine their ISI values using 3.2% citrate and the same citrate concentration should be used in individual laboratories. Low ISI reagents yield higher INR values when under-filled samples are collected in 3.8% citrate.

Participants were asked if they collected samples for PT by venipuncture. Of the 260 respondents to this question, 216 (83%) indicated they did. The majority of respondents (92%) used only the recommended citrate concentration of 3.2%. Four percent used a concentration of 3.8%, and 1% used both 3.2% and 3.8% sodium citrate concentrations.

Table 5_Distribution of Traditional PT Reagents by ISI Values (N=172 sites)

ISI Values	Number of Sites	Percent of Sites
<1.20	91	53
>1.20 and <1.50	36	21
>1.50 and <1.70	3	2
>1.70 and ≤2.00	20	12
2.01 to 2.40	22	13

Specimen Acceptance and Rejection Policies

There are several voluntary practice standards that address the proper collection and handling of specimens for coagulation testing and PT testing in particular.[4,8,11]

Of the 216 respondents that collected samples by venipuncture, 202 (94%) said they had a written policy addressing specimen acceptability and rejection for PT testing. Participants were given a list of issues that are commonly recommended for inclusion in specimen acceptability and rejection policies for coagulation testing. They were asked to acknowledge those they included in their written policy (**Table 7**).

It should be noted that depending on the setting or the methodology, some of these issues may not apply. For example, the collection of samples from patient lines and heparinized specimens may be applicable for patients in hospitals but not for most patients in outpatient settings. Specimens that are icteric or lipemic

Table 6_PT Reagents – POC Devices (N=75 sites)

Manufacturer	Examples of Brand Names	Number of Respondents	ISI Values
Roche Diagnostics	CoaguChek CoaguChek S	61	29 sites = 2.00 2 sites = 1.00 30 sites did not give a value
International Technidyne Corporation	Hemochron Jr Protime Protime 3	8	1.00
Bayer Diagnostics	PT-NC RapidPoint Thrombocard	5	1.00 to 1.20
Hemosense	INRatio	1	1.00

Table 7_Specimen Acceptance and Rejection Policies

Specimen Acceptance/Rejection Issue	Percent of Sites That Included the Issue in Their Written Policies	Number
Properly anticoagulated specimen	98	194
Correct volume of blood	98	194
Appropriate storage temperature	97	189
Adequate labeling of specimen	96	190
Time delays prior to testing	96	187
Adequate centrifugation (speed and time)	92	178
Information on requisition and specimen label match	90	174
Adequate information on requisition	90	173
Hemolysis	90	170
Appropriate transport times	89	168
Order of multiple tubes	86	166
Lipemia	79	146
Drawing specimens from patient lines	73	136
Icterus	71	131
Collection of samples in a syringe	67	129
Difficult draws	67	127
Abnormal hematocrits	65	123
Heparinized specimens	60	113

may affect test methods based on optical clot detection but may not be a concern for mechanical clot detection methodologies.

Of the 259 respondents, 85 (33%) stated that they collected samples by finger stick or capillary collection. Of those, 87% indicated that they had a written policy addressing the proper collection of capillary specimens for PT testing.

Implementing New Lots of Reagents

Various practice standards address issues associated with implementing new lots of testing reagents. Some address general activities such as establishing or verifying patient reference ranges and mean of normal, and some are specific for handling new lots of thromboplastin reagents.[3-5,11,12] Given a list of 8 indicators of quality practices associated with the evaluation of new lots of thromboplastin reagents for PT testing, participants were asked which they performed (**Table 8**).

Contents of Patient Test Report to Clinicians

The ISTH and the WHO recommend that reporting of PT results for patients on oral anticoagulation therapy include the use of INR values.[10,13] Other practice standards and publications suggest this as well.[3,4,6,11]

Given a list of choices, participants were asked which test values and other information they provide in the patient report to clinicians. Nearly all respondents reported the INR value (**Table 9**).

Discussion

Adherence to the standards we studied was relatively high for sites performing traditional PT methods. For those collecting venipuncture samples, 92% used the generally recommended concentration of sodium citrate, and 94% had a written specimen acceptance/rejection policy. The majority of these sites used a reagent with an ISI of ≤1.70 (76%), verified their reference range (92%), and established their mean of normal (95%) for new lots of thromboplastin reagents. For sites using POC devices, specimens were primarily obtained by capillary collection methods. Therefore, issues related to collection tubes and transport, processing, and storage of samples are not applicable in those cases. Respondents using POC devices relied more on information provided by the manufacturer for reference ranges and mean of normal values, rather than establish their own. Nearly all testing sites reported INR values.

Table 8_Evaluation of New Lots of Reagents

	Sites That Perform			
	Traditional Methods		POC Devices	
Quality Practice	Percent	Number	Percent	Number
Establish patient mean of normal	95	158	35	19
Conduct parallel testing between lots	93	156	35	19
Verify reference (normal) range	92	153	62	36
Confirm calculations of INR	89	148	34	19
Verify that the ISI is correct for instrument/reagent combination	89	147	60	35
Alert clinicians when a new reagent or reagent with a different ISI is placed into use	66	107	33	19
Perform correlation studies with another method or site	42	67	40	22
Establish ISI with calibrators	20	32	30	17

Because clinicians compare INR values against standardized therapeutic ranges and monitor trends in an individual patient's INR values over time, consistency in test values from an individual laboratory and agreement in values between different laboratories are issues of key importance. Errors can occur when a laboratory changes to a new lot of testing reagents. Testing personnel may not recognize that their reagent sensitivity has changed and may not do studies to verify their test results are consistent and calculations are accurate. Therefore, personnel should adhere to the following best practices when introducing new lots of reagents, test strips, or cartridges:

- Verify the ISI value in the product insert.
- Establish their own patient mean of normal using the new reagent.
- Perform parallel testing between the old and new lots.
- Assure that ISI value and patient mean of normal value are correctly entered into their instrument and laboratory information system where the INR calculation occurs.

Errors can also occur when a patient moves from one setting to another due to a lack of correlation between methods. Agreement of test results between laboratories can be improved when personnel follow these best practices:

- Use reagents with low ISI values.
- Use specimen collection tubes with 3.2% sodium citrate.
- Report INRs.

As part of this study, we also determined if laboratory testing personnel used voluntary practice standards to develop their PT testing policies and procedures. We found that a minority of respondents used voluntary practice standards, and that the most common reason given for not using standards was a "lack of awareness." By publishing this report, sharing it with study participants, and posting it on the CDC Web site, we hope to raise awareness of recommended standards of practice and references that may help to harmonize practices among all sites performing PT testing. It is also hoped that testing personnel may investigate and adopt new practices based on a comparison to their peers.

To review the results of the entire study, go to http://www.phppo.cdc.gov/MLP/SurveyReports/Prothrombin_2004.aspx

Acknowledgements: Assistance in on-site data collection was done by Susan Walker, MA, MT(ASCP), Gary Utter, DrPH, MT (ASCP), Lori Hudson, MT (ASCP), and Leonard Kargacin, MA, CLS (NCA). Thanks to the Office of Laboratory Quality Assurance Washington State Department of Health. Funding for this study was provided by Centers for Disease Control and Prevention, Cooperative Agreement U10/CCU023393-01.

Table 9_Patient Test Reports

	Percent of Sites That Report	Number
Test values		
PT as INR	99.6	232
PT in seconds	89	204
PT ratio	7	14
Other responses were: patient mean of normal value (N=4), normal control value/quality control value (N=3), therapeutic range (N=1), and last dose of medication (N=1).		
Interpretation or comments		
Reference (normal) ranges	84	211
Specimen comments	79	195
Therapeutic ranges	74	182
Interpretation	30	66
Other responses were: dose of medication (N=5), clinician sees patient and knows what ranges are (N=2), extenuating circumstances (N=1), and normal patient mean (N=1).		

1. Committee on Quality of Health Care in America, Institute of Medicine. *To Err is Human: Building a Safer Health System*. Washington, DC: National Academy Press, 2000.
2. Shahangian S, Stankovic´ AK, Lubin IM, et al. Results of a survey of hospital coagulation laboratories in the United States, 2001. *Arch Pathol Lab Med.* 2005;129:47-60.
3. Fairweather RB, Ansell J, van der Besselaar AM, et al. College of American Pathologists Conference XXXI on Laboratory Monitoring of Oral Anticoagulation therapy: laboratory monitoring of oral anticoagulation therapy. *Arch Pathol Lab Med.* 1998;122:768-781.
4. NCCLS. *One-Stage Prothrombin Time (PT) Test and Activated Partial Thromboplastin Time (APTT) Test; Approved Guideline*. NCCLS document H47-A; 1996.
5. American Society of Health System Pharmacists. ASHP therapeutic position statement on the use of the international normalized ratio system to monitor oral anticoagulant therapy. *Am J Health Syst Pharm.* 1995;52:529-531.
6. Hirsh J, Dalen JE, Deykin D, et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest.* 1995;108(Supplement):231S–246S.
7. Ansell J, Hirsh J, Wenger NK. *Management of Oral Anticoagulant Therapy: Principles and Practice*. American Heart Association, Postgraduate Education Committee, Council on Clinical Cardiology; 1999.
8. NCCLS. *Collection, Transport, and Processing of Blood Specimens for Coagulation Testing and General Performance of Coagulation Assays; Approved Guideline–Third Edition*. NCCLS document H21-A3; 1998.
9. Hassett AC. *Optimizing the INR to improve anticoagulant monitoring: Transfusion Medicine Update*. The Institute for Transfusion Medicine; 1998.
10. Loeliger EA. International Committee for Standardization in Haematology/International Committee for Thrombosis and Haemostasis recommendations for reporting prothrombin time in oral anticoagulation control. *Thromb Haemost.* 1985;54:155-156.
11. The Ontario Association of Medical Laboratories, Quality Assurance and Clinical Laboratory Practice Committee. *CLP 014 Guidelines for the Laboratory Monitoring of Oral Anticoagulants*; 1997.
12. NCCLS. *How to Define and Determine Reference Intervals in the Clinical Laboratory; Approved Guideline–Second Edition*. NCCLS document C28-A2; 2000.
13. World Health Organization Expert Committee on Biological Standardization. *28th Report: WHO Technical Report Series 610*, Geneva, Switzerland: WHO; 1977.