



Saint Luke's Regional Laboratories Clinical Laboratory Letter



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Excessive Esoteric Test Ordering

With the expectation of decreasing reimbursement, physicians need to make certain that all tests ordered during inpatient visits are absolutely necessary for immediate care of the patient. Physicians should discriminate between those tests that are necessary for care of the patient during the hospital stay versus those that are important for guiding treatment or follow-up after discharge. For example, many esoteric tests, especially molecular and/or genetic tests, are not performed at Saint Luke's Hospital and are very expensive to purchase from an outside laboratory. During an inpatient stay, Saint Luke's Hospital receives no additional reimbursement for these tests, but bears the full expense. These tests should be delayed until post-discharge. For this reason, clinical pathologists have begun calling physicians ordering esoteric tests to determine their acuity.

Bleeding Associated with New Oral Anticoagulants

The September issue of the Clinical Laboratory Letter reviewed Dabigatran (Pradaxa), which is an oral direct thrombin inhibitor. More recently, rivaroxaban, (Xarelto), which is a factor Xa inhibitor, has been approved by the FDA. Some of the pharmacokinetic properties of these drugs are compared in the following table.

	Dabigatran	Rivaroxaban
GI absorption	7%	80%
Time to Peak	1-2 h	2-4 h
Half life	12-17 h	7-11 h
Excretion	80% renal, 20% bile	33% renal, 66% CYP
Protein binding	33%	80%

Data from many phase III clinical trials of dabigatran and rivaroxaban indicated that the bleeding rate was approximately 3%. Unfortunately, if bleeding does occur, no specific antidote is available. Fresh frozen plasma will **not** be very effective in reversing the anticoagulant effect of these drugs because of its relatively low

concentration of coagulation factor II (thrombin) and factor X. Most articles written on this topic have suggested that Prothrombin Complex Concentrate (PCC) would be useful in reversing the anticoagulant effect of these drugs because it contains large doses of coagulation factors II, VII, IX and X. However, a recent publication demonstrated that PCC corrected the anticoagulant effect of rivaroxaban but not dabigatran (Circulation 2011; 124:1573-79). The authors concluded that PCC is a viable treatment for reversing the anticoagulant effect of rivaroxaban but has no role in the reversal of dabigatran.

The only remaining option for treating the bleeding associated with dabigatran is recombinant activated factor VII (rFVIIa), which achieves hemostasis by directly activating thrombin on the surface of platelets. However, the use of rFVIIa has had inconsistent results with other direct thrombin inhibitors. Other options include activated charcoal to absorb recently ingested drug and dialysis. Clearly, more research is needed in this area.

Dipstick Proteinuria to Identify Rapid Renal Decline

A recent prospective observational study followed 3371 participants longitudinally with yearly blood and urine samples to determine the most efficient and effective method to detect rapid kidney function decline (J Am Soc Nephrol. 2011;22:1729-1736). Random urine specimens were collected yearly and tested for abnormal protein excretion using two different methods: urine dipstick and microalbumin to creatinine ratio (ACR). Estimated glomerular filtration rate was calculated using the annual serum creatinine. The rate of loss of kidney function was derived for each participant over 3 years. Participants who lost more than 5% per year were designated as having rapid kidney function decline (RKFD).

Among the entire cohort, the likelihood of developing RKFD was 3.2 times greater among those with an elevated ACR as compared with those with normal ACR. When persons with at least trace proteinuria were compared with those without

proteinuria by dipstick, the likelihood of RKFD was 3.7 times greater in those with trace proteinuria. Thus, urine dipstick performed comparably to ACR as a screening test. Although, the likelihood of developing RKFD increased with higher urine dipstick protein levels to a maximum of 7.8 with a protein level > 3 g/L, trace proteinuria represented a clinically relevant threshold to consider as a positive test.

These results suggest that even in the age of expensive biomarkers, the urine dipstick is an effective screening tool to identify individuals who are likely to lose significant kidney function in the short term. The number needed to screen in the overall population to find one positive test was 18 using a dipstick with at least a trace protein reading.

TEG for Liver Transplantation

Thromboelastography (TEG®) measures the mechanical properties of a developing blood clot. An aliquot of citrated blood is pipetted into a sample cup, and a stationary pin attached to a torsion wire is immersed in the blood. The sample cup oscillates back and forth constantly at a set speed. When fibrin and platelet aggregates form, they connect the inner wall of the cup with the pin, causing the pin to oscillate in phase with the clot. The magnitude of pin motion is directly proportional to the strength of the clot. Lysis or retraction of the clot diminishes transfer of cup motion to the pin. Pin motion is converted by a transducer to an electrical signal which can be monitored by a computer. This information is displayed graphically as a tracing.

Five major parameters are measured:

- **R** - Reaction time is the time that elapses between placing blood in the sample cup and formation of the first measurable clot. The time of the first measurable clot has been designated as the time required for the TEG tracing to reach amplitude of 2 mm. R-time is prolonged by coagulation factor deficiencies and anticoagulant medications, such as heparin, and is shortened by hypercoagulable conditions.
- **K** - K time is the elapsed time from the beginning of clot formation until a fixed level of clot strength is detected as defined by amplitude of 20 mm. This parameter is a measure of the speed at which a clot achieves

this level of strength or firmness. Elevated fibrinogen levels, and to a lesser extent, hyperactive platelets shorten K. Fibrinogen deficiency prolongs K.

- **Alpha Angle (α)** - Alpha angle is the slope of the TEG tracing drawn between the R and K values. It reflects the speed of fibrin accumulation and polymerization and is closely related to K-time. Alpha angle is decreased by fibrinogen deficiency and anticoagulants.
- **MA** - Maximum Amplitude is the highest vertical amplitude of the TEG tracing and is an indication of platelet function. MA is similar to PFA-100 platelet function and aggregation studies. Thrombocytopenia and abnormal platelet function will decrease MA.
- **LY30** - LY30 measures the rate of amplitude reduction 30 minutes after the MA is reached. It represents the degree of fibrinolysis and breakdown of the clot during this time interval. Fibrinolysis increases the value of LY30, while the use of antifibrinolytic agents, such as Amicar, will shorten it.

Reference ranges for each of these parameters using citrated blood are summarized in Table 1.

TEG Parameter	Reference Range
R time	5 – 10 minutes
K	1 – 3 minutes
Alpha Angle	53 – 72 degrees
MA	50 – 70 mm
LY30	0 – 8% lysis

TEG is primarily used to assess coagulation during liver transplantation. Hemostasis is affected in all three stages of liver transplantation: hypo-coagulable state during pre- and early operative period, hyperfibrinolysis during anhepatic phase, and hypercoagulability during postoperative state. TEG can be used to guide transfusion therapy as summarized in Table 2.

TEG Value	Hemostasis State	Suggested Therapy
R >11	↓coag factors	FFP
MA <45	↓platelet function	Platelet
Alpha <45	↓fibrinogen	Cryoprecipitate
LY30 >8.0	Fibrinolysis	Amicar