HAMILTON REGIONAL LABORATORY MEDICINE PROGRAM

LAB CONNECTIONS

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IN THIS ISSUE

The Effect of New Oral Anticoagulants on Laboratory Testing

WHAT'S NEW

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Coagulation Laboratory Testing and New Oral Anticoagulant Therapy

Recently, a number of new oral anticoagulants have been introduced into clinical practice, including Dabigatran, Rivaroxaban and Apixaban. Dabigatran is an oral, reversible direct thrombin inhibitor that has been approved for use in the prevention of strokes and systemic emboli in patients with non-valvular atrial fibrillation.[1,2] Rivaroxaban and apixaban are oral direct factor Xa inhibitors that have been developed for prophylaxis and treatment of thrombotic disorders [2,3] and for the prevention of venous thromboembolism in patients undergoing major orthopaedic surgery and the prevention of stroke in patients with non-valvular atrial fibrillation.[2,4] While none of these new anticoagulants are reported to require routine laboratory monitoring [2], all have an effect on coagulation laboratory tests, dependent on their respective modes of action and the individual laboratory test principles.[1-4]

Effect on Coagulation Laboratory Tests

Activated partial thromboplastin time (APTT) reagents are considered more sensitive to dabigatran than prothrombin time (PT) reagents, whereas the opposite is reported with rivaroxaban, with PT reagents being more sensitive than APTT reagents.[2] As with rivaroxaban, apixaban also demonstrates a concentration dependent response with the APTT and PT.[4] In-vitro experiments have demonstrated the effects of the new anticoagulants on the PT and APTT are variable and dependent on the reagent and instrument combination used in the laboratory.[1,3,4] This makes it challenging to compare results between laboratories and also to determine if one of these drugs is present using PT and APTT results.[1,3,4]

While there is limited information available on the effect of these new anticoagulants on the more specialized coagulation tests for thrombophilia, there are interferences [1-5] that should be considered.

In Table 1, we summarize the effect of the various anticoagulants on laboratory test results based on individual laboratory test principles. Clinicians are reminded that thrombophilia laboratory testing should not be performed when a patient is on anticoagulant therapy or at the time of an acute thrombotic event. Furthermore, thrombophilia testing is generally not recommended as the results rarely influence treatment decisions, and non-genetic risk factors predominate in older patients.[6,7,8]

Table 1. Potential effect of various anticoagulants on coagulation tests, based on test principle, performed in the HRLMP Special and Core Coagulation laboratories.

Test	Principle	Potential effect of the anticoagulant drug on results				
		Warfarin	**UFH**	**LMWH**	**Dabigatran (or other DTI)**	**Factor Xa Inhibitors (i.e. Rivaroxaban, Apixaban, Edoxaban)**
PT/INR	Clot based	↑	No effect or ↑ (reagent neutralizes up to ~ 0.6 U/mL)	N	N - ↑	N - ↑
APTT	Clot based	↑	↑	N - ↑	N - ↑	N - ↑
TCT TCTPS	Clot based	N	↑ Shortens with protamine (neutralizes up to ~ 1.0 U/mL)	N - ↑ Minimal to no change with protamine	↑ No change with protamine	N
Clauss Fibrinogen	Clot based	N	N (very high concentration of thrombin used)	N	falsely ↓ if DTI concentration is very high	N
Antithrombin	Chromogenic anti Xa activity assay. Inverse relationship – decreased residual FXa; increased AT	N	↓ (due to increased clearance)	↓ to N (due to possible increased clearance)	N	False ↑
Protein C Functional	Clot based. Plasma diluted in PC deficient plasma; an APTT + Protac performed. Direct relationship – increased APTT; increased PC level	↓	N (PC deficient plasma neutralizes heparin up to 2 U/mL)	N	False ↑	False ↑
Protein S Free	Latex Immunoassay. Ag (PSF) + Ab (on latex bead) Direct relationship – more light detected; the more agglutination; higher the PSF level	↓	N	N	N	N
APCR	<u>In house</u> clot based ratio. Plasma diluted in FV deficient plasma. 2 APTT's run – 1 with Calcium only (regular APTT); 1 with Calcium + APC. APCR ratio calculated (dividing the Calcium only APTT into the Calcium + APC APTT.) Below cut point – "positive" for FVL	Unknown	Unknown	Unknown	Unknown but potentially falsely normal **[1]**	Unknown but potentially falsely normal due to a dose dependent effect on APTT **[4]**
LA - Lupus Sensitive APTT	2 clot based assays. Lupus sensitive APTT and DRVVT. APTT 1:1 mixing study and PL dependency (DRVVT) performed to follow up on abnormal results. Times that are ↑ indicate above cut point.	False ↑ APTT that may correct on mixing	False ↑ that generally shows no correction on mixing	Possible false ↑ that may not correct on mixing	False ↑ that generally shows no correction on mixing	False ↑ that generally shows no correction on mixing
LA – dRVVT		False ↑ dRVVT that doesn't show phospholipid correction; demonstrates presence of a coagulopathy	N (dRVVT reagent neutralizes heparin at therapeutic doses)	Typically N (dRVVT reagent neutralizes heparin activity at therapeutic doses)	False ↑ dRVVT that doesn't show phospholipid correction; demonstrates presence of a coagulopathy	False ↑ dRVVT that doesn't show phospholipid correction; demonstrates presence of a coagulopathy

Legend: ↑ = increased; ↓ = decreased; N = no effect

If you have any questions regarding this or any other coagulation laboratory issue, please contact Karen Moffat, Technical Specialist, Coagulation by email, moffat@hhsc.ca or by phone, 905-521-2100 ext. 73124.

References

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5. Martinuzzo ME, Barrera LH, D'Adamo MA, Otaso JC, Gimenex MI, Oyhamburu J. Frequent false-positive results of lupus anticoagulant tests in plasmas of patients receiving the new oral anticoagulants and enoxaparin. Int Jnl Lab Hem. 2014, 36:144-150.
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Education News

Congratulations to General Pathology resident, Deepti Ravi. Deepti has won the new **American Society for Clinical Pathology (ASCP) 40 Under 40 award**, which recognizes future leaders in pathology and laboratory medicine.

The **Laboratory Medicine Resident Research Day** was a success again this year!

Congratulations to all of our award winners.

Original Research/Best Platform Presentation:

Linda Kocovski (GP PGY3)
Yang Yu (MM PGY4)

Best Case Report/Case Series:

Aisling O'Meara (AP PGY4)
Jeremy Daniels (AP PGY3)

Laboratory Medicine/All Specialties:

Jay Maxwell (AP PGY2)
Ipshita Kak (GP PGY2)
Caroline Lemieux (AP PGY1)

Fellowship Program/Best Paper:

Lori Beach (Clinical Chemistry)

Postdoctoral Research Fellowship Program:

Sam Workenhe (Molecular Medicine Postdoc)

HRLMP Award for Quality Assurance:

Syed Abedi (AP PGY3)

The Medical Microbiology Training Program is proud to announce that **Dr. Salaheddin Abouanaser** has passed his Royal College examination.

The Medical Biochemistry Training Program is proud to announce that **Dr. John Sievenpiper** has passed his Royal College examination.

Welcome to our new residents for 2014/15

Medical Biochemistry **Hala Kufaishi**

Clinical Chemistry **Jolene Read**

Anatomical Pathology	**Benfeng Zhang**
	Brigette Courteau
	Ian Brain
	Nermin ElMaghraby
General Pathology	**Akash Gupta**
	Katherine Chang
	Esmail Safiya

For information and the latest news on our residency training programs follow the link:
http://fhs.mcmaster.ca/pathres/news/index.html

Information on the postdoctoral fellowship:
http://fhs.mcmaster.ca/pathology/education/postdoctoralfellowshiptraining.html

News from the HRLMP

We have recently completed our **OLA/ISO Surveillance visit** and once again had a very successful assessment.

Members of the Quality Teams and the many individuals who contributed to the very many small and large projects deserve our special thanks.

Some of the comments from the assessors during the summation meeting speak to the HRLMP larger team and to the commitment, enthusiasm, and true professionalism demonstrated by everyone in the program:

> "Very forward-thinking organization"
> "Great team work and a passion to show what they do"
> "Staff provided open and honest dialogue"
> "Staff were readily available and accommodating"
> "Patient focused"
> "Evidence of great team work"

Great work everyone!

LRC Integration Update

The Microbiology and Core Laboratories are working together toward an integrated LRC specimen receiving area to handle our LRC specimens. This innovative project has drawn on the knowledge and experience of both departments. The planning process has involved mapping workflow and specimen volume, standardizing processes, organizing schedules and creating training documents.

Once this integrated model is in place, all LRC work will be received into LRC on the same day that it arrives, nothing will go in the fridge. There will be no division of duties between Core lab and LRC work, it will all be handled by a team effort. Everyone will follow an established priority list to ensure that work is handled effectively.

Training has already started and the goal is to have this model in place by the end of this month.

News from Genetics

Our molecular protocols for **BCL1 (also known as CCND1)** and **BCL2** testing are being replaced with FISH (fluorescence in situ hybridization) assays. PCR testing will not be maintained after May 15, 2014.

Benefits of FISH:

- Can be applied to both fresh material (e.g. marrow aspirates, touch preps), as well as FFPE sections.
- Fewer false negatives (higher test accuracy for diagnostic specimens).
- Better robustness and reliability.
- Scoring of FFPE sections is selective to regions identified by the referring pathologist.

The specific probe sets applied depend upon the test request:

BCL1 (CCND1) break-apart probe set: detects virtually all BCL1 translocations (used for FFPE specimens in particular).

BCL1(CCND1)-IGH dual fusion probe set: specifically detects 11;14 translocations associated with mantle cell lymphomas; not used for FFPE sections except as reflex test.

BCL2 break-apart probe set: detects virtually all BCL2 translocations (used for FFPE specimens in particular).

IGH-BCL2 dual fusion probe set: specifically detects 14;18 translocations, e.g. follicular lymphoma; not used for FFPE sections except as reflex test.

Other FISH probe sets are also available to identify marginal zone, Burkitt's type, and ALK positive lymphomas. Request a combination of BCL2 and CMYC probe sets to identify "dual-hit" lymphomas. BCL6 FISH testing is also available.

Please note: Testing marrow specimens is usually uninformative unless prior testing on a lymph node has established that the tumour is positive for a rearrangement.

Requisition forms can be downloaded from: ***http://www.lrc.hrlmp.ca***

Questions: Call Laboratory Genetic Services,
HRLMP
(905-521-2100) Ext. 73707

News from Hematology

Congratulations to **Malignant Hematology** on their 1 year Anniversary (June 4, 2014) of moving to 10-colour flow cytometry.

Congratulations to **Dr. Cathy Hayward**, Head of HRLMP's Regional Coagulation Laboratory, for recently becoming President of the International Society for Laboratory Hematology (ISLH).

News from Pathology

Dr. Asghar Naqvi is a cytopathologist and pulmonary pathologist who was recently recruited to the HRLMP at the St. Joseph's Healthcare site. Welcome Dr. Naqvi!

On July 18, **Dr. Jeff Terry** is leaving the HRLMP to take a job as pathologist in BC Children's Hospital. We are sad to see him go but wish him all the best in Vancouver. The search for his successor is work in progress.

News from Microbiology

When a patient presents with fever and pneumonia or Adult Respiratory Distress Syndrome (ARDS) with one of the following, immediately place patient in **Airborne AND Contact Precaution with Eye Protection for the Health Care Provider:**

1. Travel in the past 14 days from countries in or near the Arabian Peninsula or China
2. Close contact with an ill traveler who has fever and acute respiratory illness (not necessarily pneumonia) with the travel history to the above region
3. Close contact with a confirmed or probable MERS / H7N9 case within 14 days

There are reported cases of MERS in the US in returning travelers from Saudi Arabia and secondary case of laboratory evidence of infection but no symptoms in a contact to one of the imported cases. Information on emerging viruses and the geographic areas at risk can be found at:

http://www.cdc.gov/coronavirus/mers/US.html
http://www.phac-aspc.gc.ca/tmp-pmv/notices-avis/index-eng.php

Immediately notify the Infection Prevention & Control and the Microbiology laboratory

whenever there is a potential case of MERS-CoV or novel strains of influenza (H7N9).

News from Chemistry

The laboratory is offering two new order codes within the blood gas panel for use in critically ill patients. These new order codes, labeled CRITABG and CRITVBG, offer a complete panel of tests with a faster turnaround time. In an effort to maintain the integrity for their use and the decreased turn-around time associated with them, **please restrict the use of these new test panels to critically ill patients**. These new order codes will become available on May 27, 2014.

If you have any questions, please contact Dr. Tony Chetty at chetty@hhsc.ca or Dr. Cynthia Balion at balion@hhsc.ca.

Test	Test Specific Orders	Order Codes for Panels				Critical Values (Adults)
		ABG	CRITABG	VBG	CRITVBG	
Hemoglobin			✓		✓	≤ 60 g/L ≥ 200 g/L
Glucose Random	✓		✓		✓	≤ 2.5 mmol/L ≥ 25 mmol/L
Sodium			✓		✓	≤ 120 mmol/L ≥ 160 mmol/L
Potassium			✓		✓	≤ 2.5 mmol/L ≥ 6.5 mmol/L
Chloride			✓		✓	-
Lactate	✓		✓		✓	≥ 4.0 mmol/L
Hydrogen Ion		✓	✓	✓	✓	nmol/L
pH		✓	✓	✓	✓	≤ 7.00 ≥ 7.70
PCO2		✓	✓	✓	✓	≤35 mmHg*
PO2		✓	✓	✓	✓	-
Bicarbonate (Calc)		✓	✓	✓	✓	≤ 10 mmol/L
Base Excess		✓	✓	✓	✓	-
O2 Sat Measured		✓	✓	✓	✓	-
Ion Calcium	✓					≤ 0.6

* Denotes arterial blood

*Please note, potassium values measured on the whole blood balanced heparin syringe have a **slight negative bias (about 5%)** compared to plasma potassium values measured from a lithium heparin Vacutainer.*

The laboratory recently offered two new order codes within the blood gas panel for use in critically ill **pediatric** patients (CRITABG and CRITVBG). These orders require collection with a blood gas syringe. Effective June 16, a further test order code will be added to allow the expanded test panel to be offered for samples collected on critically ill children using capillary collection.

Test	Test Specific Orders	CRITCBG	Pediatric Critical Values
Hemoglobin		√ May not be available, depending on sample volume	
Random Glucose	√	√	≤ 1.7 mmol/L (< 3 days old) ≥ 16.7 mmol/L (< 3 days old) (1st occurrence) ≤ 2.5 mmol/L (> 3 days old) ≥ 20 mmol/L (> 3 days old) (1st occurrence)
Sodium		√	≤ 125 mmol/L ≥ 150 mmol/L
Potassium		√	≤ 2.0 mmol/L (neonates) ≥ 7.0 mmol/L (neonates) ≤ 2.5 mmol/L (children) ≥ 6.0 mmol/L (children)
Chloride		√	
Lactate	√	√	≥4.0 mmol/L
Hydrogen Ion		√	
pH		√	≤ 7.25 ≥ 7.60
pCO_2		√	
pO_2		√	≤ 40 mmHg
Bicarbonate (Calc)		√	≤ 10 mmol/L
Base Excess		√	
O_2 Sat Measured		√ May not be available, depending on sample volume	
Ionized Calcium	√		≤ 0.8 mmol/L ≥ 1.6 mmol/L

*Please note, potassium values measured on whole blood balanced heparin capillary tubes have a **slight negative bias (approximately 4%)** compared to potassium samples from lithium heparin collection devices.*

If you have questions, contact Dr. T. Chetty at chetty@hhsc.ca or Dr. Stephen Hill at hillstev@hhsc.ca.