An Update on the Use of the D-Dimer

Introduction

The D-dimer assay is an important part of multiple clinical prediction tools and algorithms. It is frequently used in the evaluation of acute venous thromboembolism (VTE), and is also used in the diagnosis of disseminated intravascular coagulation (DIC). In this update we will review the D-dimer assay used in the Hamilton Regional Laboratory Medicine Program (HRLMP) Core Laboratories, discuss the utility of D-dimer assays in clinical prediction rules for VTE and disseminated intravascular coagulation (DIC), and mention other investigational uses of the test that have been described in the literature.

Background

D-dimer formation requires the generation of thrombin, activated factor XIII (XIIIa), and plasmin, as D-dimer is one of the products formed when factor XIIIa cross-linked fibrin is digested by plasmin. The D-dimer is thus named because it is composed of two cross linked D domains and one E domain of fibrin.1 In young, healthy individuals, D-dimer levels are generally low to undetectable. However, levels are higher in individuals who are elderly, pregnant, or have a variety of pathological states (e.g. cancer). This reflects increased levels of fibrinolysis, which, in some cases, results in an elevated D-dimer result. As an elevated D-dimer can occur in many pathological states, it is important to consider the clinical context and whether the findings are being used within a validated scoring system.
The Assay

D-dimer assays use commercial antibodies that recognize unique epitopes on the D-dimer fragments of fibrin. The specific epitopes recognized vary between assays, which can affect the sensitivity and specificity of the test.\(^1\) D-dimer assays can be qualitative (e.g. positive or negative) or quantitative, and the latter results are reported in fibrinogen equivalent units (FEU) or D-dimer units (DDU).

The HRLMP offers a quantitative D-dimer assay that is an automated, latex immuno-agglutination test (LIA test). This assay uses latex microparticles that are coated with two murine monoclonal, anti-human D-dimer antibodies. When these microparticles are mixed with patient plasma, the D-dimers in the test plasma alter the turbidity of the solution due to agglutination, and the extent of this agglutination is quantified to obtain the D-dimer result.\(^2\) The D-dimer assay used in the HRLMP has a lower limit of detection of 270 μg/L FEU and an upper limit of 4000 μg/L FEU. Quantification of levels up to 20,000 μg/L FEU is technically possible but this is rarely indicated and it significantly increases the cost of testing, as measuring levels >4000 μg/L FEU requires repeating the test with multiple dilutions of the plasma sample. The D-dimer assay offered by the HRLMP may be falsely elevated by high levels of rheumatoid factor (>50 IU/mL) or by anti-mouse antibodies.\(^3\)

Clinical Uses

D-dimer assay uses have been explored in many research studies. At present, international guidelines recommend testing of D-dimer for two clinical situations: VTE and DIC, as outlined below.

D-Dimer in Venous Thromboembolic Disease

D-dimer is most widely used for ruling out VTE in patients with a low/moderate pre-test probability. Wells et al. described a clinical prediction rule in 2003 to aid in the evaluation of suspected VTE.\(^4\) In 2009, Bates et al assessed the D-dimer assay currently used by the HRLMP (Diagnostica Stago LIA Dimer) and identified that a cut point of 500 μg/L FEU provided excellent sensitivity for VTE and an acceptable negative predictive value in a validation patient cohort.\(^5\) The 2012 American College of Chest Physicians Guidelines\(^6\) and the 2015 Thrombosis Canada guidelines suggest that for patients with a low/moderate or an “unlikely” pre-test probability of VTE (based on a validated scoring system), a negative high sensitivity D-dimer rules out VTE without further testing.\(^7,8\) Other uses of D-dimer in VTE assessment such as predicting risk of recurrence have been investigated and may be helpful in carefully selected patients.\(^9\)

D-Dimer in Disseminated Intravascular Coagulation

The second recommended use for the D-dimer assay is in the diagnosis of DIC. The diagnosis of DIC can be difficult because the complex clinical situations in which DIC often develops can also increase D-dimer levels (e.g., trauma, sepsis, etc.). A number of scoring systems have been developed to aid making a diagnosis of DIC. In 2013, the International Society of Thrombosis and Hemostasis (ISTH) Scientific and Standardization Committee published recommendations on the diagnosis of treatment of DIC,\(^10\) that include the use of a scoring system for diagnosing overt DIC, with consideration of monitoring the score to document deterioration or improvement. The ISTH recommendations, like all DIC scoring systems, include a measurement of fibrin degradation, which can be a D-dimer level or an estimate of other fibrin degradation products, that are to be used in combination with a validated clinical scoring tool for the diagnosis of DIC.\(^11\)
Research Uses

The utility of the D-dimer has also been investigated in many settings including the diagnosis of aortic aneurysm, the exclusion of VTE in non-standard groups (e.g., the elderly, pregnant individuals), predicting prognosis in cancer patients, predicting prognosis in pancreatitis, as well as other clinical areas. Some studies have explored measurement of D-dimer using point of care devices. The use of the D-dimer in these other clinical situations has not been incorporated into national or international guidelines, so such testing is best restricted to research settings.

Conclusion and Recommendations

As a measure of fibrinolysis, the D-dimer assay is useful for excluding VTE in low/moderate risk patients and for diagnosing DIC. The D-dimer may also be useful in predicting VTE recurrence risk in carefully selected patients. Currently, there is limited evidence to support the use of this assay for other purposes, although other uses are being researched.

Ordering any laboratory investigation requires careful assessment of the patient and consideration of the impact of the potential results of the assay. At the current time the D-dimer test is recommended in two settings:

1. **VTE**: a D-dimer should be performed in the setting of patients with a low/moderate or unlikely pre-test probability of VTE based on a validated clinical score: a negative high sensitivity D-dimer in these patients excludes VTE. A D-dimer may be considered to predict risk of recurrence in carefully selected patients.

2. **DIC**: if D-dimer testing is performed, a validated DIC score tool should be used to help evaluate the findings.

Dr. Clinton Lewis, PGY4, Adult Hematology Program, McMaster University
Karen Moffat, Technical Specialist, Coagulation, HRLMP
Dr. Cathy Hayward, Head, Coagulation, HRLMP

References
News from HRLMP

Congratulations to everyone as we celebrate National Medical Laboratory Week!

As we conclude a very successful IQMH accreditation visit, it is very fitting that we take this opportunity to thank each one of you for the work that you do each day for our patients. Each day we see your commitment to patient care and patient safety, as well as your commitment to the profession and to each other.

As part of the IQMH assessment, the assessors conducted interviews with clinicians at every site including physicians, nurse managers, and other health professionals. The feedback was consistent: the HRLMP laboratories provide excellent service and contribute to excellent patient care at HHS and SJHH. This is truly a testament to your professionalism and the quality of your work.

The week of April 24th, is a chance for us to celebrate our entire team: Medical Laboratory Technologists, Medical Laboratory Assistants, Pathologist Assistants, Morgue Technicians, Technical Specialists, Managers/Supervisors, Medical /Scientific and Clerical staff.

Thank you for all that you do, and for making the HRLMP a leader in laboratory medicine.

Sincerely,
Dr. John Fernandes
Duane Boychuk
Rebecca Repa

News from HRLMP Administration

April 24, 2016

It is with heavy hearts that we announce the passing of Thelma MacDonald.

We are deeply saddened at the loss of our wonderful friend and colleague Thelma MacDonald at the young age of only 51. Thelma worked in the department of Pathology for more than 30 years and had many friends both old and new at JHCC. The staff has many fond (and funny) memories of her long years of friendship with us. She leaves behind two wonderful children Tamia (17) and Alexia (11).

News from Chemistry

We want to share some great news regarding receiving the CSCC Award for Innovation in Laboratory Medicine for 2016. The innovation stems from the important findings of the VISION Study [Dr. Devereaux, PI] and the work of a number of HRLMP biochemists in getting this study going on the lab front.

I also want to thank the HRLMP for supporting research that involves the clinical laboratory and want to acknowledge the hard work of the laboratory staff and their commitment to improving patient care through research.

Dr. P. Kavsak
(excerpt from award letter below)
Education News

A great celebration for **National Medical Laboratory Science week** was held on Wednesday April 27th, 2016 in the Ewart Angus Center, McMaster University with pizza and refreshments.

The theme for this years celebration was **Medical Laboratory Science - We’ve Come a Long Way, Baby!**

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**Click on the link below and watch a fun tribute to Medical Laboratory Science – In da lab by ZDOGGMD**

[https://www.youtube.com/watch?v=KqAVacVpbQk](https://www.youtube.com/watch?v=KqAVacVpbQk)

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**News from Genetics**

As we celebrate Medical Laboratory Science, we’re thrilled to share that **Meredith Hanna**, from our Molecular Genetics Laboratory, was randomly selected as the grand prize winner in the **HHS Share Story Submission**.

Read the full story below and see why 2015 was the best Christmas ever for one family …

We work in the Molecular Genetics Laboratory at MUMC, where we test for hemoglobinopathies and a variety of other
We received a prenatal sample from Mount Sinai hospital in Toronto, on Dec 22 2015, three days before Christmas, for Beta Thalassemia testing. Both parents are carriers of Beta Thalassemia mutations and thus their baby had a 25% risk of inheriting both mutations and being affected with Beta Thalassemia, a very serious illness. Our turnaround time for prenatal samples is 2 weeks, but since Christmas was so close, we really wanted to expedite testing so that the family would have an answer before Christmas. And luckily, fate was on our side, all the testing worked beautifully and we were able to complete testing in just 2 days, on Christmas Eve. It was also happy news, since the baby was only a carrier of one parental mutation and was thus not affected with Beta Thalassemia. The report was faxed to the referring centre on Christmas Eve, and a couple of hours later we received a phone call from the genetic counsellor from Mount Sinai who was working on the case. She told us she had just called the family to share the happy news. The mom was home getting things ready for the holidays and she answered the phone and was SO happy to hear the news – she said she was going to wrap up a copy of the report and put it under the tree for her husband to open for Christmas!!!! The counsellor wanted to share that story with us since, as lab technologists, we are more “behind the scenes” in our patients’ care, and we rarely get to find out what happens after we finish testing. She expressed her sincere appreciation for all of our hard work, and to tell us that we are a wonderful lab to deal with. She wanted to thank us on behalf of all the counsellors at Mount Sinai for the great work that we do. It was the nicest, most thoughtful phone call, especially on Christmas Eve. It is moments like that which make our jobs so worthwhile, and proud of the care we provide to our patients. It left us all in tears!
Last but not least, we would like to congratulate Jean Brookings on her retirement. Jean has worked within the laboratory since 1982 starting first as a research technologist with Dr. Uchida before joining the Regional Cytogenetics Laboratory. She has made important contributions to the Cytogenetic Laboratory since and brought with her a wealth of experience in chromosome analysis, peripheral blood and bone marrow culturing, and slide making. Her colleagues affectionately describe her as a meticulous technologist who likes to test her limits and loves to volunteer. While we will miss her smiling face, we wish her all the best in her retirement.

News from Hematology

Congratulations to Dr. Irwin Walker who has been appointed the new Joseph E. DesRoches Chair in Bone Marrow Transplantation, effective November 1, 2015.

The Chair is being endowed through funds from a former patient, Joe DesRoches and others, including the Department of Medicine. An event to celebrate the appointment was held with the donor family.

Dr. Walker is currently a professor in the Division of Hematology and Thromboembolism in the Department of Medicine and an associate member of the Department of Oncology. He is also director of the Hamilton Bone Marrow Transplant Program.

Please note that the implementation of the new Sysmex CBC analyzer across the HRLMP has been delayed to the week of June 14 – 17, 2016.

Time to Shine!

The most recent Shine Wellness newsletter ‘spotlighted’ our own medical lab assistant Diana Alampi from the HRLMP Malignant Hematology laboratory at the Juravinski site. This article summarizes how she overcame her difficulties. We are proud of her success and her willingness to share the story of her struggle with narcolepsy.

Please click on the link below to learn more about Diana and the challenges that she does not allow to stop her!

http://www.shinehhs.ca/cool-stuff/shine-spotlight/
Lab Connections

Molecular Hematology and Red Cell Disorders laboratory goes international!

Read about this phenomenal laboratory experience as summarized by Sarah Tebasulwa, a laboratory technologist from Makerere University Hospital, Uganda.

Visiting Training Program (VTP) Experience
Learning Isoelectric Focusing (IEF) at McMaster University, Hamilton, Ontario, Canada

Acknowledgement and Benefits:

I thank the American Society of Hematology (ASH) for their sponsorship and acknowledge Dr. Madeleine Verhovsek, hematologist at McMaster University and Medical Director of the McMaster Red Cell Disorders Laboratory and the tutorship working team which made my training a success.

I took a 2 month VTP on using isoelectric focusing (IEF) in the Red Cell Disorders Laboratory located at McMaster University, Hamilton, Ontario, Canada, 10th May 2013 - 24th June 2013.

• A donation of 3 piece equipment IEF power pack, cooling unit and chamber as seen below (photo 1 of equip) from Hamilton Regional Laboratory Medicine Program, Ontario, Canada
• After that training, I am now able to perform IEF reliably and independently.
• The training permits us to offer the sensitive and accurate results of SCD patients diagnosis.
• I am able to train laboratory technologists to perform IEF electrophoresis technique in testing infants for hemoglobinopathies.
• We have acquired strength and improvement in offering free services of IEF to our patients who cannot afford to meet the expense of the IEF elsewhere in our country.

Sarah Tebasulwa

Lesia Sniouolis came to the McMaster Hematology/Coagulation and Transfusion Medicine Labs in February 1981. She and her husband, Ray, had purchased a home in the Hamilton area to be close to family, and the commute to Toronto General Hospital was becoming arduous. Soon, it became apparent that Lesia had a natural talent for morphology and she focused on Hematology. She quickly became the resource for identifying cells within the lab. She shared her talents by teaching morphology and mentoring Mohawk College
and St. Clair College students, McMaster medical students, new staff, as well as her co-workers.

In addition to Lesia’s technical skills, she is known as a kind, humble, approachable person. She is highly respected for her integrity in her work.

Retirement will give Lesia the freedom to spend time with her new grandson, bake wonderful creations, attend film festival movies, travel and take up photography.

We wish Lesia well in retirement. She will be dearly missed by all.

News from Microbiology

The HRLMP Microbiology staff and residents were well represented at the annual AMMI-CACMID meeting in Vancouver recently.

Mark Gaskin, Technical Specialist, Microbiology presented on automated blood culture processing.

Lawrence Dalle Vedove, microbiology’s Senior Technologist, presented data on improved cryptococcal antigen tests.

Drs. Fatimah Al Mutawa and Diana Whellams presented posters on lab and clinical aspects of Group B streptococcal infections.

In addition, Dr. Mark Loeb is leading a WHO group on essential antibiotics for the WHO Essential List of Medicines, and attended a meeting in Switzerland.

News from Pathology

New Pathologists to Join the HRLMP

Four new pathologists will be joining us soon! This is great news for our Anatomical Pathology Program.

Please welcome …

Dr. Hamid Kazerouni from Memorial University of Newfoundland will start at the Juravinski Hospital on April 18, 2016.

Dr. Martin Hyrcza from the University of Toronto will start at St. Joseph’s Healthcare on June 1, 2016.

Dr. Phillip Williams from the University of Toronto has accepted our offer and will fill the vacancy created by the retirement of Dr. Elavathil at the Juravinski Hospital on July 4, 2016.

Dr. Jane Turner, senior pathologist from St. Louis, Missouri, will join our forensics team at the General Hospital in mid-July 2016.
Heli Stephenson, the Senior Technologist in Histology at St. Joseph’s Healthcare is retiring after a distinguished 47 year career. Heli started working at St. Joes in 1969. She obtained her Subject RT in Histology from the CSLT in 1970. Heli has seen a lot of changes in her career. From working in a tiny basement lab, sharing a room with a tissue processor, another MLT and the Manager’s desk, to the current large lab full of windows and light.

The entire lab community has benefitted from Heli’s leadership and dedication to patient care at St. Joes. She has set a high work standard for the next generation of MLT’s to continue, many of whom she has trained over the years. While she will be sorely missed, we wish her all the best in the start of this new chapter in her life.

The HRLMP Pathology Department announces the retirement of Dr. Leela Elavathil.

Dr. Elavathil has been an integral member of our department for 27 years. She began her career at the Hamilton General Hospital and moved to the Juravinski Hospital and Cancer Center (after laboratory amalgamation) and after fellowship training in breast cancer pathology, took on a lead role in the breast cancer pathology program.

We have been fortunate to have Dr. Elavathil as a strong leader in this area. With her expertise and leadership, Hamilton has become a major centre for women with breast cancer and there is a strong quality program in this region. She was instrumental in several initiatives including the new CIBC Breast Cancer Assessment Center, breast biomarker validation, and is generally known as a leading expert in breast cancer diagnosis in the LHIN.

Additionally, Dr. Elavathil is a warm, caring individual, one of the 'anchors' of the department and the staff at the JHCC will miss her greatly, although we know that her husband Jacob will be grateful to see her working less than her usual 100 hours per week!
Dear Colleagues:

RE: IQMH Accreditation Completion

As you are all aware, we have recently completed, with success, our 2016 IQMH Accreditation! Our sincerest thanks to all staff for this remarkable achievement! This success is a marker of the enthusiasm and true professionalism within our laboratory program.

Due to the size and complexity of our program, our review resulted in the largest number of assessors and the longest visit ever by IQMH to a healthcare facility – a seven-day visit by 13 assessors with a review of approximately 500 requirements per site. Despite the magnitude, we were cited for only one program-wide and four site-specific major non-conformances, as well as 119 minor non-conformances with approximately half of these representing single non-conformances flagged across all five sites. We will need to address these in the coming weeks.

Assessors were particularly impressed with our revolutionary instrumentation – the WASP™ in Microbiology, Sysmex in the Core Laboratories, and next-generation-sequencing in Genetics. The adoption of order-of-draw beads to improve pre-analytical processes was recognized as a fantastic idea, the progress made in the management of POCT was applauded, and the zero non-conformances in LIS was praised! The assessors reported that although they came to assess us, they left learning A LOT from us!

Although many people worked very hard in contributing to this success, we would like to highlight in particular the efforts of Cathie McCallum and Andrea Tjahja, who worked tirelessly over the past several months to ensure our portrayal in the best possible light to IQMH assessors.

Our specialists, Susie Maia-Castellan, Teri Johnson, Spencer Brown, and Allahna Elahie, and many members of our professional staff also contributed to our success. I cannot identify everyone, but I would like to identify Dr. Cheryl Main and Dr. Vina Alexopoulou as having made significant contributions to a successful IQMH Accreditation.

Thanks again to everyone for this remarkable achievement.

Sincerely,

Dr. J. Fernandes
Mr. D. Boychuk
Ms. R. Repa
Dr. M. Crowther
Mr. D. Langstaff

Read more about Josephine Baldwin, the HRLMP Research Coordinator.

Research News

**Why you should know Josephine Baldwin ...**

As introduced in our February 2016 edition of our newsletter, Josephine Baldwin is the HRLMP Research Coordinator.

In this edition, we summarize the required information to move the laboratory testing for research projects forward in all of our HRLMP departments.

Information required to be sent to Josephine includes:

- The name of the primary investigator and study coordinator, if applicable
Lab Connections

- Copy of the study protocol, if applicable
- Copy of the Hamilton Integrated Research Ethics Board (HiREB) approval, if applicable
- Laboratory testing required
- Volume of samples
- Study duration

Based on the provided information, Josephine’s office will then be able to provide an accurate quote for the requested laboratory testing.

Once the laboratory testing is completed or at prearranged specific times, Josephine’s office will provide a laboratory invoice to the investigator.

Research is an important and essential component of the HRLMP Mission of “Service, Education and Research” and we welcome the opportunity to provide the laboratory services needed for your current and/or upcoming research projects.