73 Coagulation Laboratory: Methods, Standards and Cost Effective Testing (Part 1)

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This session features a case study approach to examine issues that impact coagulation results: sources of errors, methods of standardization, and new and cost effective testing. Coagulation testing is complex and there can be a disconnect in what the clinician expects to come forth from the laboratory and what can actually be provided by the laboratory.

- Identify solutions to areas of coagulation testing that can be enhanced by implementing good laboratory practices and standard operating procedures.
- Analyze real case studies and how to troubleshoot testing to determine the root cause and what steps to take to prevent reoccurrence.
- Enhance general knowledge of coagulation, standards and methods.

FACULTY:

Donna Castellone MS, MT(ASCP)SH
Entire Pathology Team
Hematopathology
Hematopathology
1.0 CME/CMLE Credit

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Coagulation Laboratory: Methods, Standards & Cost Effective Testing Part 1

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Disclosures

• Employee of Siemens Healthcare Diagnostics

Map of the United States
Objectives:

- Identify solutions in areas of coagulation that can be enhanced by implementing good laboratory practices and standard operating procedures
- Analyze real case studies and how to troubleshoot testing to determine root cause and what steps to prevent reoccurrence.
- Enhance general knowledge of coagulation, standards and methods.

Standardization

- Standard: consistently uniform and obtainable results from different laboratories utilizing dissimilar measurement procedures
- Results are traceable to a higher order reference measurement, which in turn is calibrated with accepted reference standards

Harmonization

- Results are traceable to a reference material
- However, neither the reference measurement procedure nor primary reference standard exist
Why do we need this?

• Enhance diagnostic accuracy
• Improve patient care and safety
• Commutability of healthcare information
• Challenge is to isolate a pure substance to which an individual reference method can link back to
• Coagulation is comprised of enzymes and unstable proteins, a unique challenge

NIBSC: National Institute for Biological Standards and Controls

WHO: World Health Organization

• Products are calibrated in units of biological activity established by consensus following extensive international studies involving many laboratories.
• Hierarchy of standards; WHO and NIBSC are the primary standards against which secondary standards are calibrated.
• Secondary standards may be national standards, regional standards or working reference materials used routinely in the laboratories of manufacturers, regulatory authorities or others.
• In this way the potency of biological medicinal products is calibrated traceable to the WHO primary standard.

Reference materials

• Protein C
• Protein S
• Antithrombin
• Factors II, V, VII, X, VIII, IX, XI, XIII
• Von Willebrand
• Lupus Negative Controls
Question:
What is a primary standard:

1. Value assigned by your laboratory
2. Obtained from WHO/NIBSC
3. Traceable to a WHO standard
4. Determined by the manufacturer

Answer

1. Value assigned by your laboratory: if this is done you are on your own
2. Obtained from WHO/NIBSC: primary standard calibrated in units of biological activity established by consensus
3. Traceable to a WHO standard Secondary standards may be national standards, regional standards or working reference materials used routinely in the laboratories of manufacturers
4. Determined by the manufacturer

What do you want from your coagulation assays?
• Precise results
• Robust assays
• Accurate results that can be used as an aid in diagnosis and treatment
• Reproducible results
How do you do this?

• Good SOP’s
• Effective QC practices
• Enroll in proficiency testing programs
• Good Laboratory Practices
• Understand coagulation results and their impact on patient care

Standard Operating Procedures:

• Should be reviewed by technologists performing the tests, better understanding of the process
• Include interfering substances and limitations
• Unusual results and what to do, flow charts
• CV’s for test results in both pathological and normal ranges- understanding the outcome of the CV
• Reference intervals: your analyzer, your population
• Assess competency: direct observation, tests, blind samples

Quality Control:

• Purpose is to detect errors in the laboratory that may lead to the presence of a clinical error
• This error forces a change in diagnosis or treatment in a patient unnecessarily
• Ensures consistency, accuracy and reliability of patient test results & reports
**QC material**

- Levels should reflect the testing population
- Ranges should be validated by running prior to being put into use
- Standards, run as QC to determine recovery of assigned value
- Don’t forget if you run low factor assays to run controls in that range

**What should everyone understand**

- Intra lab QC - looks at precision & accuracy
- Inter Lab QC - independent assessment of laboratories performance & compares analytical accuracy from data from all over
- Precision testing should be done in both the low, normal and high ranges
- Determine CV’s of the assay, is there a change in results, or is that the CV of the assay

**When do I recalibrate?**

- 1 level of control is out: re-run
- 2 levels of controls are out- recalibrate
- After recalibration- QC still out discard all reagents
- Check calibration curve to see if a point is very different, or curve is very different- may need to re-run either a point, or the curve
- Before calling service-
What to do? Go to the gold!

- Save all of your proficiency testing samples, even reconstituted
- Re-run the proficiency test samples, these are peer evaluated samples with known values
- If the results are not within range, and you have eliminated and or isolated analytical variables (reagents, buffers, standards, factor deficient plasma)
- Most likely you have an analyzer issue, call service

What about Proficiency Testing versus QC?

QC: Internal
- Not perfectly sensitive/specific
- Provides a range of results
- Doesn’t detect all instances of variations

PT: External
- Looks at accuracy & bias
- Compares a specific result
- Compares to other labs, using similar reagents, methods, & instruments

External Quality Assessment (EQA) or Proficiency Testing (PT)

- First results of assessment was in 1947
- Difference between EQA & PT testing is that EQA doesn’t have any effect on the status of the laboratory license
- Using it as a performance tool may identify potential problems
- Corrective actions for errors demonstrates quality improvement

Results

• Look to see if you are an outlier....(you know you do that first)
• Where are you in relation to other laboratories
• Review all the data
• What does this really tell you?
• Shifts, bias, trends...

Review report/ performance

• Read the entire report, great learning tool
• Look to see where you are within your reagent or analyzer peer group
• Huge amount of information
• Some new methodologies now "run" peer groups, may not be what you are using in your laboratory

Corrective Action

• Identify the source; clerical, technical, personnel
• Corrective Action – repeat testing is not corrective, you don’t identify the error.
  review QC and standard curves for that day
  if possible also check patients that were run that day
  reagents; were they fresh, end of a lot number
• Monitor corrective action
Does the laboratory have an action protocol for statistics……

- You must have an action protocol that DEFINES what you do when the statistics fall outside of the tolerance limits
- Do you change the ranges
- Do you re-calibrate
- Call for service
- Check precision on the instrument
- Make sure this is SOP
- Who should be notified and the corrective action
- Document the action, date and signed

Question:

Proficiency testing aids in the evaluation of

1. demonstrating precision
2. quality control methods
3. Intra-laboratory CV’s
4. Inter-laboratory accuracy

Answer:

1. demonstrating precision: precision is demonstrated by repeated measurements
2. quality control methods: evaluated by a QAP program, looks at a range of values
3. Intra-laboratory CV’s: within laboratory evaluation
4. Inter-laboratory accuracy: PT testing aids in the laboratory’s ability to demonstrate bias, trends, and variability among peer groups
Good Laboratory Practices

- Lot to lot validation
- Reference Interval Studies
- Instrument comparisons
- Linearity Studies
- Precision Studies

Consensus Process:

- Standard: identifies specific, essential requirements for materials, methods or practices.
- Guideline: criteria for a general operating practice, procedure, or material for voluntary use. May be used as written or modified to fit specific needs.
- Report: document that has not been subjected to consensus review

EP documents- Verification of performance:

- EP12-A: User protocol for evaluation of Qualitative test performance
  Test meets end user clinical & analytical goals
- EP10-A2: Preliminary Evaluation of Quantitative Clinical Laboratory Methods
  New instrument eval or after major maintenance
- EP9-A2: Method comparison & bias estimation
  Aligning 2 devices or method comparisons
Guidelines: Clinical Laboratory Standards Institute

- List of reference documents to promote best practices
- Uses consensus driven process combining industry, government and health care professionals
- Used to ensure scientific integrity, practicality and proper regard for public health and safety
- Range from guidelines on Veterinary Medicine, Molecular (MM), Hemostasis, Hematology, Flow Cytometry (H) to Automation (Auto)
- Guidelines are reviewed every 3 years to account for improvements and to remain current.

Tholen, D., MLD; August 2006

Hemostasis documents:

Wayne, Pennsylvania
Collection and Transport of Blood Specimens for Testing Plasma Based Coagulation Assays H21-A5

Remember:

Quality is how your department works when no one is looking!

Henry Ford
Understanding coagulation results

Case Studies

Case Study

- 16 year old male for a hernia operation
- Family has a positive history of bleeding; Jewish decent
- Results: PT=12.9 (10.2-13.5)
  APTT=33.0 (29.9-33.5)

Will this patient bleed?
Do we check for a factor deficiency?

The Coagulation Cascade
In Vitro Cascade

• Allows logical effective lab based screening
• Can be evaluated through the PT & APTT
• Doesn’t reflect clotting physiologically
• Does play a role in laboratory evaluation of a potential clotting disorder

Results:

• Look at APTT factors: VIII, IX and XI
• VIII = 102% (50-150%)
• IX= 84%
• XI=21%
• Abnormal level of factor XI despite the normal APTT
• Patient is deficient in factor XI
• Shouldn’t the APTT have been abnormal

How are your reagents?

• Do your reagents truly reflect normal factor levels
• Normal PT & APTT levels indicate patient have a minimum of ~ 30-35% of factor levels present
• If your reagent is insensitive to a factor, you may get a normal PT or APTT
• The reagent may not be able to pick up a factor level below 30%
Test reagent sensitivity for factors

- Dilute normal plasma with factor deficient plasma at different levels
- Run either a PT or APTT on the sample
- Compare the results to the upper limit of the normal range
- You may get a normal PT or APTT with an abnormal % factor level

What to do?

- Factor XI Sensitivity: APTT = (29.5-33.5)

<table>
<thead>
<tr>
<th>Normal plasma</th>
<th>Deficient = % Activity</th>
<th>APTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>500ul</td>
<td>0ul</td>
<td>100%</td>
</tr>
<tr>
<td>250ul</td>
<td>250ul</td>
<td>50%</td>
</tr>
<tr>
<td>125ul</td>
<td>375ul</td>
<td>25%</td>
</tr>
<tr>
<td>62.5ul</td>
<td>437.5</td>
<td>12.5%</td>
</tr>
</tbody>
</table>

This reagent does not reflect an abnormality until 12.5%

Reagent sensitivity: point which APTT is outside normal range:

<table>
<thead>
<tr>
<th>Reagent source</th>
<th>Contact</th>
<th>% F VIII</th>
<th>% F IX</th>
<th>% F XI</th>
<th>% F XII</th>
</tr>
</thead>
<tbody>
<tr>
<td>RB Silica</td>
<td>50</td>
<td>20</td>
<td>50</td>
<td>40</td>
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<tr>
<td>BB Silica</td>
<td>60</td>
<td>20</td>
<td>60</td>
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<td>40</td>
<td>30</td>
<td>50</td>
<td>40</td>
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<tr>
<td>Soy Ellagic</td>
<td>60</td>
<td>50</td>
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</tr>
<tr>
<td>RB/Soy Ellagic</td>
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<td>40</td>
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<tr>
<td>BB EA/Kao</td>
<td>50</td>
<td>10</td>
<td>60</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

Factor Sensitivity

• It is important to understand how your reagents perform
• Small investment for a lot of information
• Should be performed even if you do not run factor assays

Case Study:

• Pre-operative patient APTT 49.1 (25-36 seconds)
• No history of bleeding
• No medications
• What can prolong an APTT
• Pre-analytical variables- short draw
• Presence of heparin
• What factors deficiencies may prolong the APTT?
• Those in the Intrinsic pathway: VIII, IX, XI, XII
• An APTT may also be prolonged due to an inhibitor

Prolonged screening test:

• Next step is to perform a mixing study
• Correction: factor deficiency (patient may bleed, unless FXII)
• No correction: inhibitor (more likely a risk for thrombosis, unless specific factor inhibitor, then they can bleed)
Classical 1:1 Mixing Study

Step 1: Immediate Mix

- A
- B
- C

Patient
PNP
1:1 Mix

1. Test all.
2. Compare C to A & B. Did C correct?
3. Incubate all.

Step 2: Incubated Mix

- A
- B
- C
- D

Patient
PNP
Mix
Incubated Tubes
Control

1. Test all.
2. Compare incubated C to D. Is it prolonged? Yes, possible time dependent inhibitor.
3. Interpret final results

Results:

- APTT = 42.1 seconds (25-36 seconds)
- Pooled Normal Plasma = 31.5 seconds
- Mixing study 1:1 = 36.5

- Is this a correction?

Interpretation of a Mixing Study

- Based on PT or aPTT normal range
  - Within limits @ 2SD or 3SD
  - Within 5 seconds of the 25D upper limit
- Rosner Index
  - 1:1 mix
  - Index = \[ \frac{\text{CT of 1:1 mix} - \text{CT of NPP}}{\text{CT of NPP}} \times 100 \]
  - \(<15 = \text{FD} >15 = \text{Inhibitor}\)
- NPP tested with Mixing Study
  - Within 5 seconds of NPP value
  - >10% of NPP value
  - Lack of correction @ >15% of NPP
- No recommendations or guidelines from ISTH Scientific & Standardization Committee CAP Coagulation Resource Committee
Variables affecting mixing studies

- Heparin, OAC, DTI........ideally do not perform
- Pre-analytical variables the same as PT & APTT
  - PPP critical for proper id of LA
- Reagent Sensitivity
  - Level where factor deficiency prolong assay
  - LA sensitivity depends on concentration & type of phospholipid in APTT reagent
- Normal Pool Plasma
  - Fresh/frozen human plasma
  - No lyophilized products
  - Minimum 20 normal individuals (not normal patients)
  - Must by PPP (<5 x 10^9/L)
  - Normal value within the normal range of PT or APTT

What do you do to standardize this test?

- Adhere to consistent policies in your laboratory- define your criteria and stick to it
- Eliminate the possibility of heparin being on board, perform a thrombin time
- Eliminate the test, many laboratories feel it is too confusing, and just proceed with additional testing

What do we have?

- A repeat APTT that is still prolonged 42.1 seconds (25-36 seconds)
- PNP =31.0 seconds, mixing study is 36.4 seconds 5.5 seconds from PNP
- > 5 seconds from PNP
- > normal range
- Not a correction
- Proceed with inhibitor testing
Question:

Pre-op patient presents with a PT 10.5 sec with an APTT of 33 sec., cleared for surgery, has a major bleed. Possible causes:

1. Insensitive reagent to APTT factors
2. Presence of a lupus anticoagulant
3. Short draw sample
4. Factor VII deficiency

Answer:

1. Insensitive reagent to APTT factors: Normal APTT, patient bleeds, reagent doesn’t prolong APTT when levels fall to 30%
2. Presence of a lupus anticoagulant: APTT should be prolonged, patient more at a risk for thrombosis
3. Short draw sample: 9:1 ratio, short draw, too much anticoagulant, APTT should be prolonged
4. Factor VII deficiency: normal PT

Monitoring UFH

- Important responsibility of the clinical laboratory
- Global Assays (non-specific)
  - APTT
    - Described in 1953
    - Most widely used test
    - Adapted to monitor heparin therapy
    - Inexpensive and easy to perform
  - Activated clotting time (ACT)
    - Limited to near patient use—cardiopulmonary bypass procedures
    - Best suited for high levels of heparin
  - Thrombin clotting time (TCT)
    - Not very useful—rapidly prolonged with low doses of heparin
- Specific Assay
  - Chromogenic anti-factor Xa
Case Study

• Patient presents with a DVT, placed on unfractionated heparin
• Given a bolus dose of heparin - monitored by the APTT
• First test taken 4 hours post dose
• APTT= 67.5 sec (25-35 sec)
• Develops a PE
• Was the patient properly anticoagulated?

Laboratory Monitoring of UFH

• aPTT
  – 4-6 hours after bolus dosage and every 24 hours thereafter
  • A dose adjustment requires monitoring 6 hours after the dose adjustment
  – 1.5-2.5 x “normal”
  – Therapeutic target—0.3-0.7 anti-Xa U/mL
  – Monitor platelet count daily

Therapeutic Range for UFH

• Traditionally based on a therapeutic range of 1.5-2.5 x “normal”
  – Designed to reduce the risk of recurrent of venous thrombosis
  – Based on observations by Basu, 1972 on a specific manufacturer’s reagent
  – Rabbit thrombosis model by Chiu, 1977 using the same reagents actually supported the 1.5-2.5 therapeutic range
  – No other studies had been performed to differentiate the use of a threshold aPTT value versus a bolus dose of heparin to prevent thrombosis
  – Eventually a protamine sulfate titration range was established
    • 0.2-0.4 U/mL corresponding to a range of 1.5-2.5
  – Protamine titration range later equated to anti-Xa range by Levine, 1994
    • 0.35-0.67 U/mL based on chromogenic assay of factor Xa inhibition
    • Later modified to 0.3-0.7 U/mL by ACCP
UFH Therapeutic Range

- Problems with the 1.5-2.5 range
  - Could lead to inadequate heparinization result in thrombosis
  - aPTT response varies with different manufacturer’s reagents
  - aPTT response varies with different instrumentation
  - A patient’s baseline aPTT often is not a reliable measure for comparison
    - Patients with recent thrombotic episode → shortened aPTT
    - Patients with undiagnosed LA → high base-line aPTT
    - Patients with factor deficiency → high base-line aPTT
- ACCP and CAP suggested establishing a therapeutic range
  - Based on the relationship of the local aPTT versus heparin levels in specimens collected from heparinized patients

CAP

- HEM.23453 Phase I
  - Is there documentation that the aPTT-based heparin therapeutic range is established and subsequently validated when appropriate?
  - NOTE: The heparin-responsiveness of aPTT reagents may change from lot to lot and among different reagents used on different instrument platforms. For this reason, it is necessary to establish the heparin therapeutic range for the aPTT assay with each change of coagulation instrument and/or reagent type. The therapeutic range must be validated with each new lot of a given aPTT reagent
- HEM.23476
  - Is there documentation that the aPTT based heparin therapeutic range is established and validated using an appropriate technique?

CAP

- It is recommended that the first method be used initially to establish the therapeutic range before starting patient testing with a new instrument or new reagent, while the second method can be used for validation of the therapeutic range with subsequent reagent lot changes.
- It is not best practice to use plasma samples spiked with heparin in vitro to calculate the therapeutic range, as differences in heparin binding proteins in vitro may lead to overestimation of the therapeutic range.
Heparin Therapeutic Curve

- CAP recommends that each laboratory establishes its own heparin therapeutic range for each new lot of aPTT reagent based on reagent:instrument combination
- Heparin Anti-Xa Method
  - 50-60 plasma samples collected from patients treated with UFH
  - Mix of samples should span the therapeutic range
  - No more than two samples on the same patient
  - The PT/INR should normal (INR <1.3)
  - Assay aPTT, anti-factor Xa (UFH), and PT/INR
  - Plot the aPTT on the y-axis and the anti-Xa units on the X-axis
  - Draw a line through the middle of the points
  - The UFH therapeutic range is equivalent to
    - 0.3-0.7 units/mL Anti-Xa Heparin assay

Brill-Edwards Technique

Therapeutic Range= 0.3-0.7U/ml

HEPARIN THERAPEUTIC RANGE

Potential Problems with the aPTT

- Type of instrumentation can influence the results
  - Electromechanical versus photo-optical detection
- aPTT reagents vary in their sensitivity to heparin and to clotting factors
  - > 300 commercial assays to measure the aPTT
  - No universal standard like the INR
- Spontaneous aPTT prolongation
  - Lupus anticoagulants and other antiphospholipid antibody inhibitors
  - Congenital and acquired factor deficiencies
  - Liver disease
  - Concurrent oral anticoagulant therapy
  - DIC
  - Or can have: AT deficiency, increased I or VIII,
Potential Problems with the aPTT

- Renal Disease
- Decreased levels of AT may lead to “shortened” aPTT values
  - Congenital AT deficiency
  - Acquired AT deficiency
    - Excess/prolonged heparin administration
    - Liver disease, DIC, etc
- PF4 release may neutralize anticoagulant activity of heparin
- aPTT is a non-specific assay—does not directly measure heparin
- Not responsive in monitoring LMWH or heparinoids

Alternative Method: Subsequent years

- Cumulative summation of reagent mean differences
  - Initial therapeutic range established using the anti-Xa method
  - Run aPTT on samples with both the old and new lot of reagent
  - Plot the old lot on the X-axis and the new lot on the Y-axis
  - Determine the sum, mean and difference of the results with each new lot
  - Record the difference in the means to compare with past studies
  - A change of <7 seconds between the differences in the means is acceptable
  - A change of >7 seconds between the differences in the means requires action

<table>
<thead>
<tr>
<th>Year</th>
<th>Old Lot Mean</th>
<th>New Lot Mean</th>
<th>Difference</th>
<th>Action</th>
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</thead>
<tbody>
<tr>
<td>2006</td>
<td>28.0</td>
<td>31.0</td>
<td>3.2</td>
<td>Accept</td>
</tr>
<tr>
<td>2007</td>
<td>31.0</td>
<td>27.0</td>
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</tr>
<tr>
<td>2008</td>
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<td>43.0</td>
<td>10.0</td>
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<tr>
<td>2008-B</td>
<td>33.0</td>
<td>36.0</td>
<td>3.0</td>
<td>Accept</td>
</tr>
</tbody>
</table>

Chromogenic Anti-Factor Xa to Monitor UFH

- When Xa is present in excess along with AT \( \Rightarrow \) the inactivation of Xa will be a function of the concentration of heparin
- The amount of Xa that remains after inactivation can be measured with a chromogenic substrate
- Chromogenic substrates are short amino acid sequences that contain PNA group
- Proteolysis of the chain occurs by the residual factor Xa liberating the PNA
- This liberation is measured as a change in OD/unit of time

\[
\text{AT (excess)} + \text{Heparin} \Rightarrow [\text{Heparin-AT}] + \text{AT}
\]
\[
[\text{Heparin-AT}] + \text{Xa (excess)} \Rightarrow [\text{Heparin-AT-Xa}] + \text{Xa}
\]
\[
\text{Xa that remains can be measured with a chromogenic substrate}
\]
\[
\text{Chromogenic Substrate} + \text{Xa} \Rightarrow \text{peptide} + \text{pNA}
\]
- Short amino acid sequences that contain PNA group
- Proteolysis of the chain occurs by the residual factor Xa liberating the PNA
- Measure the released pNA
Chromogenic Anti-Factor Xa

- Advantages
  - Not affected by preanalytical variables
  - Assess the true level of heparin present in the patient’s plasma
  - Can be used to monitor UFH therapy in the following conditions
    - Patients with a LA who present with prolonged aPTTs
    - Patients with an underlying defect in the contact factors that manifests as a prolonged aPTT
    - Patients recently on Warfarin therapy with perhaps an unreliable aPTT
    - The only assay available to measure the activity of LMWH
    - Available on most automated analyzers today
    - Not affected by short sample draws
    - No need to establish a aPTT therapeutic range

Quality in the Coagulation Laboratory

- Important to implement good processes
- Adhere to these processes
- Enhance Quality
- Better Patient Results