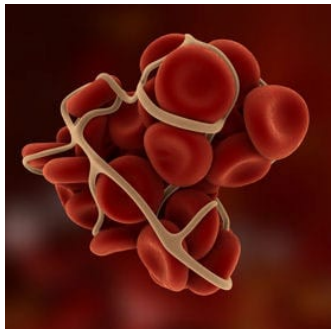
Quality in the Coagulation Laboratory

Donna D. Castellone, MS,MT(ASCP)SH
New York Presbyterian Hospital-Columbia
QA Manager, Specialty Testing
Supervisor, Special Coagulation & Hematology

8/28/2019

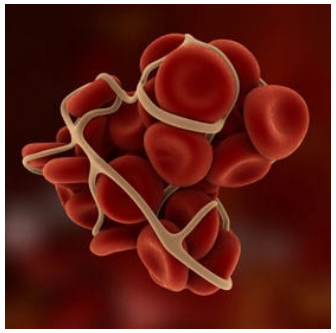
Quality in the Coagulation Laboratory



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.

Quality in the Coagulation Laboratory



WHY do we need this?

- Enhance diagnostic accuracy
- Improve patient care and safety
- Commutability of healthcare information
- Coagulation is comprised of enzymes and unstable proteins – a unique challenge

CardinalHealth

What do you want from your Coagulation assays? How do you do this?

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

Healthcare quality is getting the right care to the right patient at the right time – every time!

Quality in the Coagulation Laboratory

Quality Management System

- Quality Management Plan - There must be a document that describes the overall QM program
- It can be a broad-range plan can cover all of the CLIA Quality System requirements
- Should contain monitors of key indicators of quality
- These indicators should be during the pre-analytical, analytical and post analytical stage

What Key Indicators can be Monitored in Coagulation?

THRESHOLDS SHOULD BE MEANINGFUL AND ACHIEVABLE:

Pre-analytical: ~64% errors in this phase

- Short draw samples, hemolysis, time to be processed
- Who are your repeat offender-ed, pediatrics

Analytical: Test Order Accuracy

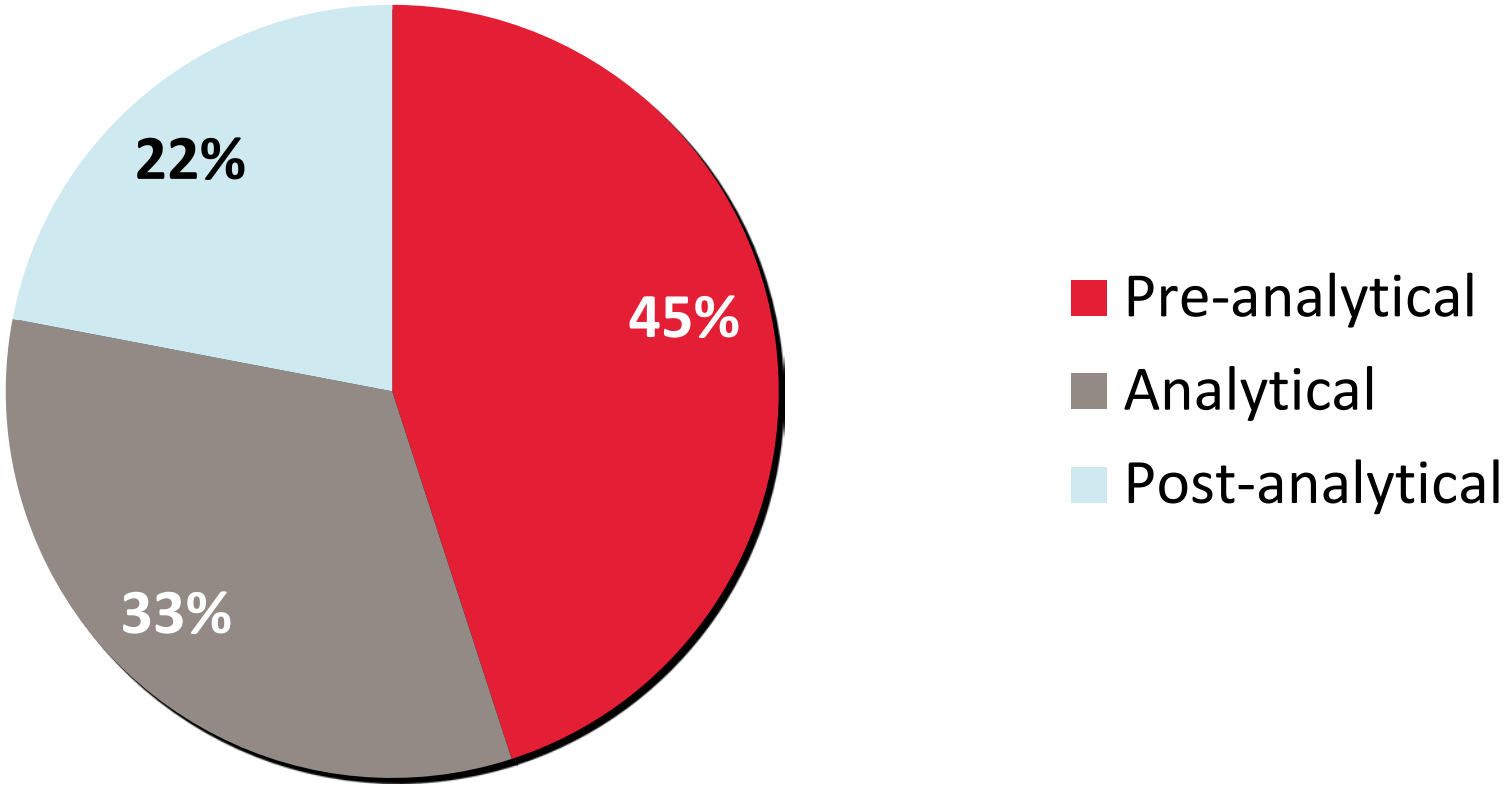
- ***Why*** are certain test being ordered? Excess amount of Factor X testing being performed. Investigate, contact physicians
- ***Rejection logs***; data mining- found wrong tubes being processed for testing, platelet testing without scheduling, testing getting cancelled
- ***Turnaround Time***: poor turn around time, may be due to add on testing; how do you set your benchmarks- look to guidelines or clinician expectations - in particular for factor assays

Post-analytical:

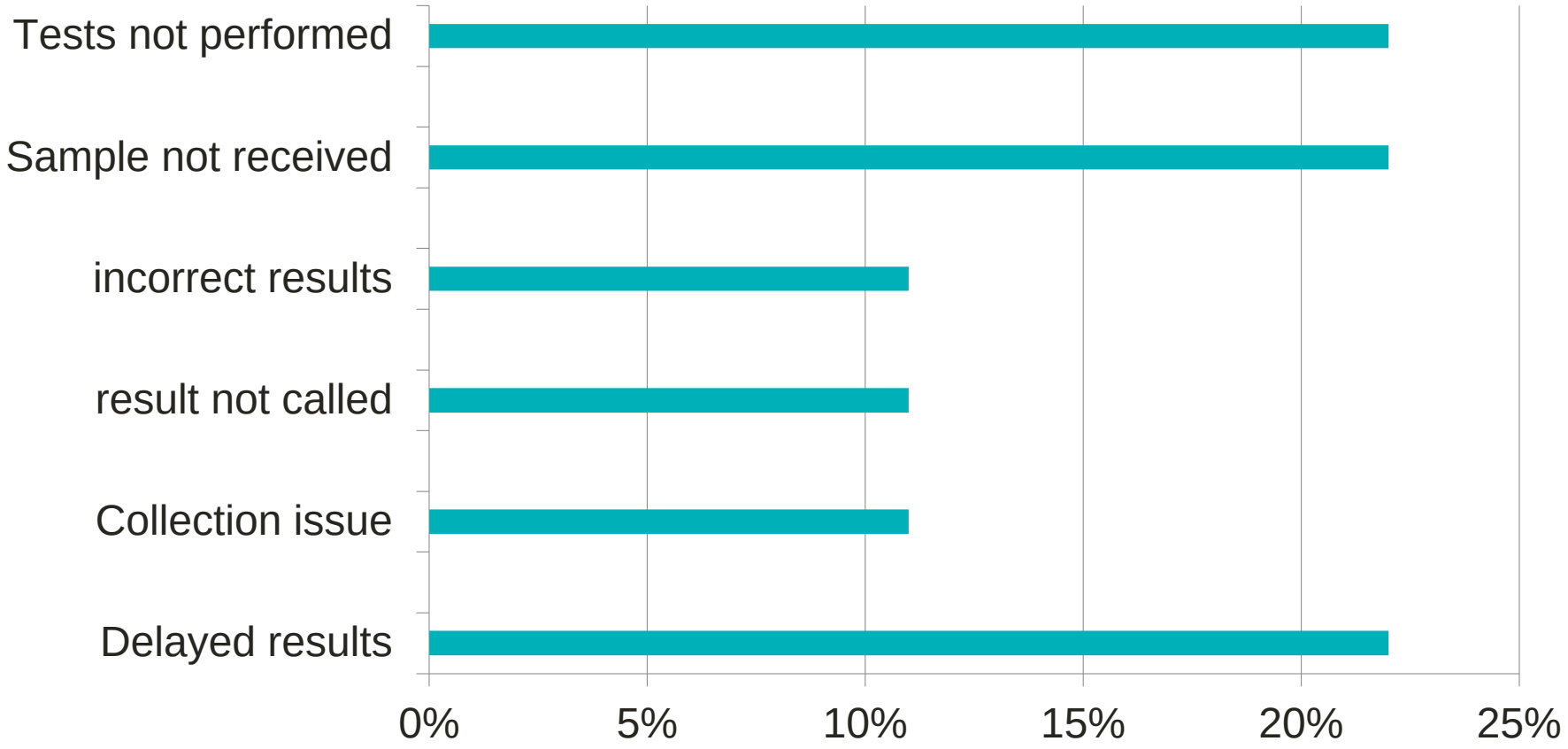
- Reports – flagging values

Quality Assessment Formal Event Recording

JANUARY – JUNE 2019



Quality Assessment Recorded Issues

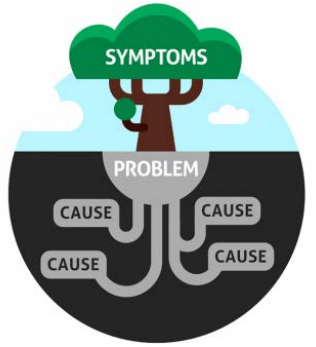


TAT for Coagulation Scoreboard

Factor VIII	Jan	Feb	March	April	May
< 24 hours	90%	96%	98%	85%	88%
> 24 hours	10%	4%	2%	15%	12%
TAT	0.5	0.4	0.4	0.9	1.1
% compliance	100%	100%	100%	100%	100%

BENCHMARK: 2 DAYS

Evaluate Errors



Root Cause Analysis

- Want to identify and evaluate errors, incidents and other problems that may interfere with patient care services. Can no longer say, “I can’t control that”
- Need a mechanism to capture internal and external sources such as complaints, including mistakes and near misses
- Conduct root cause analysis of occurrences, issues, errors and gaps in quality
- Outcome is to demonstrate risk reduction activities based on such root cause analyses – do not band-aid situations

Plan. Do. Check. Act

- PDCA model of continuous improvement
- Deming cycle or wheel of improvement
- When starting a new improvement project
- When developing a new or improved design of a process, product or service.
- When defining a repetitive work process
- When planning data collection and analysis in order to verify and prioritize problems or root causes
- When implementing any change

HTTP://ASQ.ORG/LEARN-ABOUT-QUALITY/PROJECT-PLANNING-TOOLS/OVERVIEW/PDCA-CYCLE.HTML

Continuous Improvement

- **PLAN**: Specimen rejection log for Special coagulation P2Y12 and Aspirin. 40% of the samples rejected are due to improper tube being collected.
- **DO**: Track where the frequent offenders are, and follow up for re-training, posted reminders of what tubes to use.
- **CHECK**: Monitor the amount of samples that continue to be collected improperly.
- **ACT**: After 1 month, 50% reduction in the number of rejected tubes, of those, 28% were due to improper tube collection. Continue to evaluate where the issues are coming from, and retrain. Most amount occurred in 1 day and were from phlebotomy, they were alerted and retrained.

CardinalHealth

QI-11 Continuous Improvement

- **PLAN**: Implement less order entry errors in particular for factor X
- **DO**: monitor the number of factor X assays and patients also on heparin
- **CHECK**: appeared most of the factor X were in reality anti-xa assays. Caused patient treatment delays, possible under or over anticoagulated
- **ACT**: **Our LIS has a pop-up window when ordering this test: Factor X assay looks at the activity levels of factor X and does not monitor heparin levels**

Internal Audit – Tracer Method

LOOK AT THE ENTIRE SYSTEM FOR A SPECIFIC ANALYTE FROM START TO FINISH

Must have a purposeful document that follows the pre-analytic, analytic, and post-analytical process

Any deficiencies must have a corrective action and date by which this should be completed. For more critical findings, TAT for correction should be ASAP –

Looks at:

- Are we adhering to our own quality system?
- Is this process effective?
- Is the system as a whole effective?
- Look for opportunities to improve

Findings of a Tracer Audit: Bethesda VIII – Questionable Patient Results

DISCOVERY:

Pre-analytical:

Inhibitors were being performed on all requests, high FVIII's

Analytical:

1. Using the same material for calibration as control
2. Patient dilutions were not clear
3. Protocol did not follow process
4. Analyzer settings did not allow proper identification of test being ordered

Post-analytical:

Test is linear between 25-75%, results were being extrapolated; needed to change our dilutions results within the curve

Corrective Actions:

METHODICALLY GOING THROUGH THE ENTIRE PROCESS UNCOVERED SEVERAL PRACTICES THAT NEED TO BE CLARIFIED

- Flow chart posted to understand inhibitor process
- Protocol re-written – everyone re-trained
- Implemented different material for controls and calibrators
- Set up clear testing parameters on the analyzer
- Updated dilutions and method of calculations

Inspection Readiness

- ❑ Reduce number of inspection deficiencies
- ❑ Need a process to keep up with changing requirements and regulations
- ❑ Engage staff in the quality process

Top 10 CAP Deficiencies

Directive	Requirement	# of deficiencies
GEN.55500	Competency	1979
COM.01200	Activity Menu	1810
COM. 10000	Procedures	1345
COM. 01700	PT evaluation	1178
COM.10100	Procedure review	1137
GEN. 20375	Document control	1036
COM.30300	Reagent Labeling	1032
COM. 01400	PT Attestation	968
COM. 04200	Monthly Review	919
COM. 30450	New Lot Confirmation	897

2016 COLLEGE OF AMERICAN PATHOLOGISTS

Main Issues in Coagulation:

1. Platelet poor plasma
2. INR verification
3. Correct reporting/use of your D-dimer
4. Linearity studies, standard curves
5. Evaluation of educational challenges – must be purposeful
6. Heparin therapeutic range
7. Providing information to clinicians regarding impact of anticoagulant

PT: FVIII Assay

Result: 151 : Mean =123 SD= 15.1 SDI = 1.8 Limits: 98-148

- No PT material left
- Checked curves, checked QC, brand new lot of reagents- not a lot of historical QC
- QC was in, but on the higher side
- Calibrate assay daily- compared the curves- the highest point was most different
- Re-ran some patients from that day
- Slightly lower results, but not moving from normal to abnormal even on borderline results (Reference range is 56-191)
- Sometimes the result may be statistically significant, but NOT clinically significant- e.g. investigate YES- impact on patient care – minimal
- A report should be written up with all of your findings, possible reason and action. Signed by the director or designee

Quality Control

Purpose: detect errors in laboratory that may lead to presence of 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
- 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

When to Recalibrate?

1 Level of Control is Out: Re-Run

2 Levels of Control are out: Recalibrate

- 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
- After recalibration- QC still out discard all reagents
- Before calling service-
- Try running PT material- peer evaluated material a lot of information
- Look at independent controls

CardinalHealth

Action Protocol for Changes in Monthly Statistics

LABORATORY **MUST** HAVE AN ACTION PROTOCOL THAT DEFINES WHAT TO DO WHEN STATISTICS FALL OUTSIDE OF TOLERANCE LIMITS

- What are those limits- can use published CV's, or manufacturer's recommendation
- When do you change range? Procedure and actions must match.
- State a level in your procedure that can prompt a change: e.g. a deviation in monthly QC >10%
- For factor assays, was their a change in the lot of deficient plasma
- When you have reviewed all documentation and there are no outside sources of error, and a shift has occurred- change the range
- Document what and why it was done

Case Study: New Lot of Quality Control

Laboratory Regulations: run control 20x to demonstrate the ranges

- Do I have to use these ranges?
- How do I run my 20 points?
- Over 20 days- or 5 times over 4 days
- Can I use the manufacturers range?

Results for FX Normal Control:

MANUFACTURERS RANGE: 80 – 120 SEC

FVIII	Day 1	Day 2	Day 3	Day 4
	95	93	95	96
	94	94	96	95
	95	95	95	95
	94	93	96	96
	94	94	95	96

MEAN 95% RANGE 85-105

Case Study

Review of the 1st Month

- Mean 102%
- Out of 30 days- 10 days spent, re-running controls-
- Wasting time and reagents to get controls within range
- This was happening throughout all of the laboratories
- If you review the 20 control runs, looks like a precision run
- Not unique to coagulation- all disciplines
- If we would enter these ranges, we would spend a lot of time and money and effort in having techs re-run, re-calibrate and hold up the runs.
- Running 20 controls was not working

Case Study

Solution

- We still run the 20 points; however we use this as a verification of the manufacturer’s ranges.
- The first month, we enter the manufacturers ranges.
- After a month of running in a real-world setting, we re-evaluate the “true” ranges.
- Much less time wasted on trying to hit a “perfect target” which did not really reflect the testing environment- your analyzer, your reagents in your lab, with different operators

Case Study: New Shipment for Lot of FVIII Deficient Plasma

- New lot of aPTT reagents had already been validated with this lot of FVIII deficient plasma
- However, a new shipment of factor VIII was being put in use
- New shipment is evaluated:

FVIII	Old lot	New Lot	% difference	Acceptable
Abnormal control	42%	41%	1%	y
Normal control	98%	100%	2%	y
Abnormal patient	35%	22%	37%	**n**
Normal patient	123%	97%	21%	**n**

CardinalHealth

Can I use these Reagents?

- Controls are within range- patient samples are not within range-
- FVIII is heat labile, maybe the samples are bad?
- Tested another normal and abnormal patient sample, still out of range
- Check independent controls matrix mimics FFP

FVIII	Control result OLD	Control result NEW	% difference	Acceptable
Abnormal control	34	21	38%	N
Normal control	98	77	21%	N

New Lot of Reagents, Minimal Historical Data

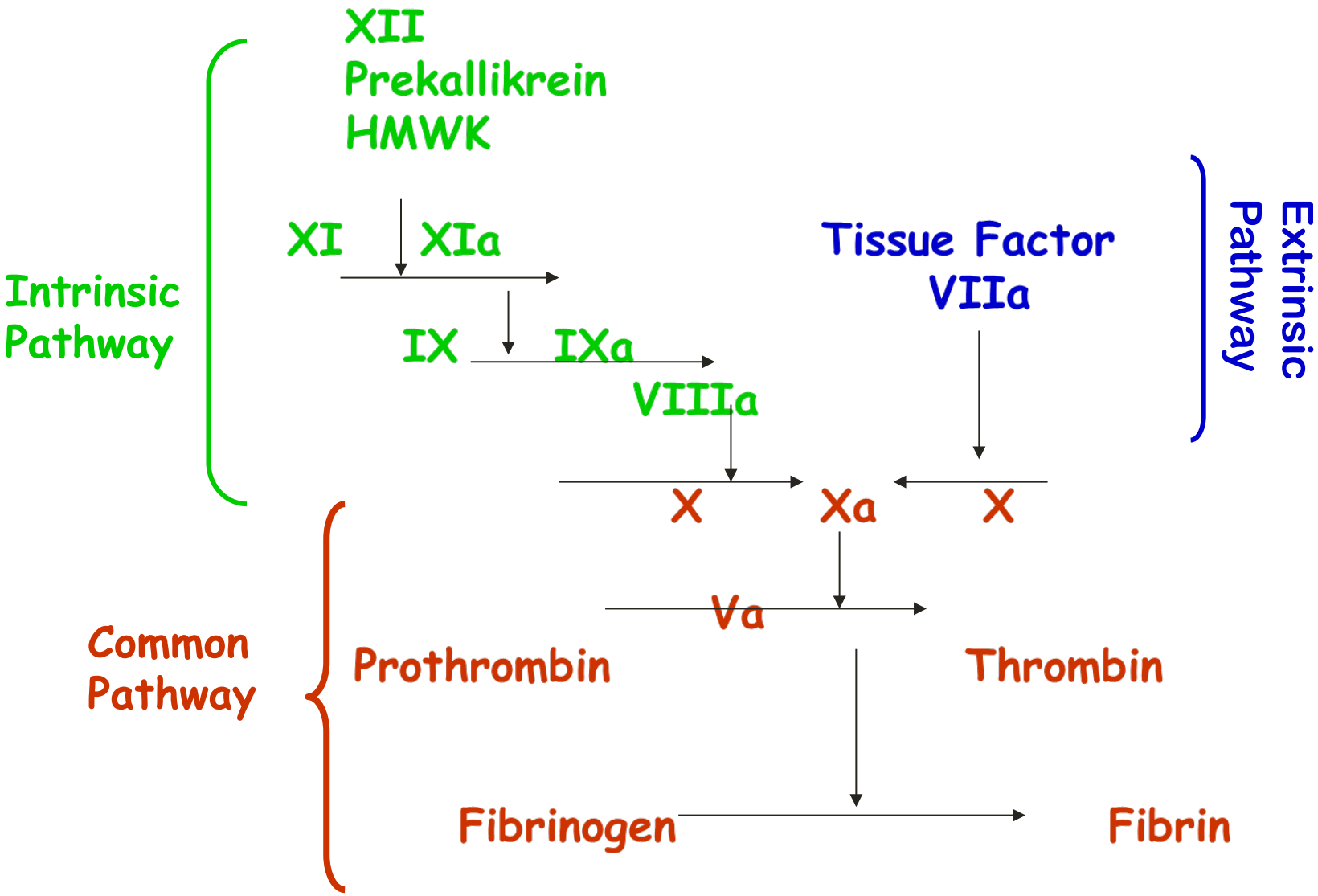
- Recalibrated, no change
- Could it be the reagents? All other aPTT based assays were working fine.
- However, did reconstitute new reagents, still no change
- **Bad lot of deficient plasma- even though we have been using the lot same as previously used-Possible shipment issue- got a new lot/shipment-**
- All results were within acceptable levels
- MUST test both patient and controls-
- Helps to have independent controls on hand
- Also can test PT material- can be very helpful in troubleshooting

Case Study: Understanding your Reagents

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

I. Will this patient bleed?
II. Do we check for a factor deficiency?
III. What is the most important information when evaluating if a patient will bleed?

The Coagulation Cascade



Results:

- Look at APTT factors: VIII, IX and XI (nr 50-150%)
- VIII = 102%
- 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% 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

FACTOR XI SENSITIVITY: APTT= (29.5 – 33.5)

NORMAL +	DEFICIENT =	% ACTIVITY	APTT
PLASMA	**PLASMA**		
500UL	0UL	100%	29.0
250UL	250UL	50%	31.0
125UL	375UL	25%	32.0
62.5UL	437.5	12.5%	36.0

This reagent does not reflect an abnormality until 12.5%

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 to understand what the approximate levels of factor activity will prolong screening tests
- In this case the family history is positive:
  - FXI deficiency occurs in up to 8% of Ashkenazi Jews
  - Incidence is estimated at 1 in 100,000 in the general population
  - FXI deficiency is inherited in an autosomal recessive pattern
  - Men and women are affected equally
  - The level of FXI doesn't correlate to bleeding

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 or DOACs- can perform a thrombin time for detection
- 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)

I. Do you use FFP for the mixing study, can I use a lyophilized standard human plasma?

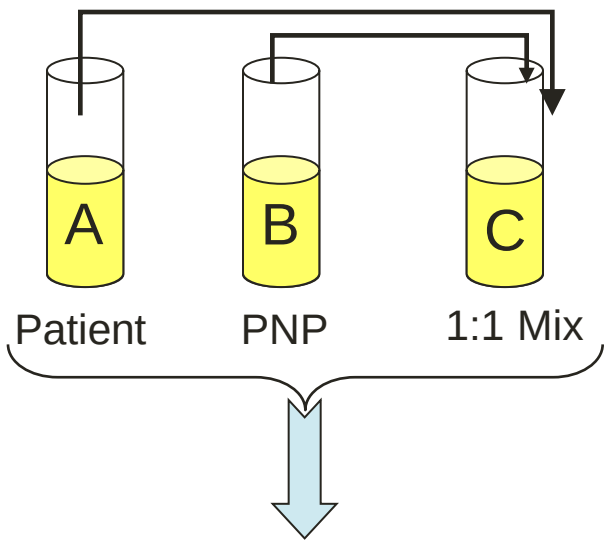
II. Do I incubate? How long?

III. Do I incubate separately? Together? Both?

IV. Is this test cost effective? What information do I get from it?

Classical 1:1 Mixing Study

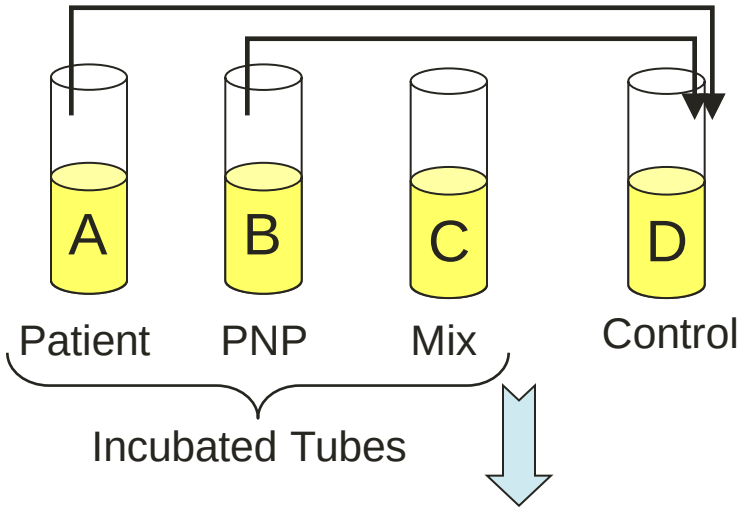
Step 1: Immediate Mix



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

1-2 hrs., 37C

Step 2: Incubated Mix



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? What are the variables that can impact a mixing study?

1. PPP critical for proper id of AN INHIBITOR; platelets are phospholipids and will falsely shorten your results, when reacting with reagents
2. Reagent Sensitivity: at what level of factor deficiency will prolong your aPTT
3. Normal Pool plasma: must be ppp, have adequate levels of factors

COMPRISED OF A MINIMUM OF NORMAL INDIVIDUALS, NOT NORMAL PATIENTS

Interpretation of a Mixing Study

- **Based on PT or aPTT normal range**
  - **Within limits @ 2SD or 3SD**
  - **Within 5 seconds of the 2SD upper limit**
- **Rosner Index**
  - **1:1 mix**
  - **Index = $\frac{\text{CT of 1:1 mix – CT of NPP}}{\text{CT of patient}}$ x 100**
    <15 = FD >15 = 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

What do we have? (In my Lab)

- 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/partial correction
- Proceed with inhibitor testing

How 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, best test for residual heparin
- Can report just numbers and let the clinicians interpret
- Can report with an interpretation
- Eliminate the test, many laboratories feel it is too confusing, and just proceed with additional testing

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?**

Based on APTT Result

- Prolonged aPTT
- What is the sensitivity of the aPTT reagent to heparin
- Not good enough to use 1.5-2.5 times the mean of the normal range
- Performed an anti-Xa assay = 0.25U/ml anti-Xa (0.3-0.7u/Ml)
- Patient is under anticoagulated
- If results are inaccurate and anticoagulation is excessive there could be a bleed
- If results are inadequate patients could clot

APTT Monitoring - Disadvantages

- Numerous factors elevate APTT:
  - Warfarin therapy
  - Lupus anticoagulants
  - Factor deficiency, liver disease
- APTT response to heparin exaggerated
- *Potential to under-anticoagulate patients*
- *Elevated factor VIII and I, shorten APTT*
- *Potential to over-anticoagulate patients*
- *No standard to cross reference APTT among laboratories*
- *No dose response relationship with heparin and APTT*

Winter, W and Harris, WE, (2008), Anti-coagulant Monitoring in the Core Lab, Advance for Laboratory Professionals, pg.54-61.

CAP Requirement

- 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

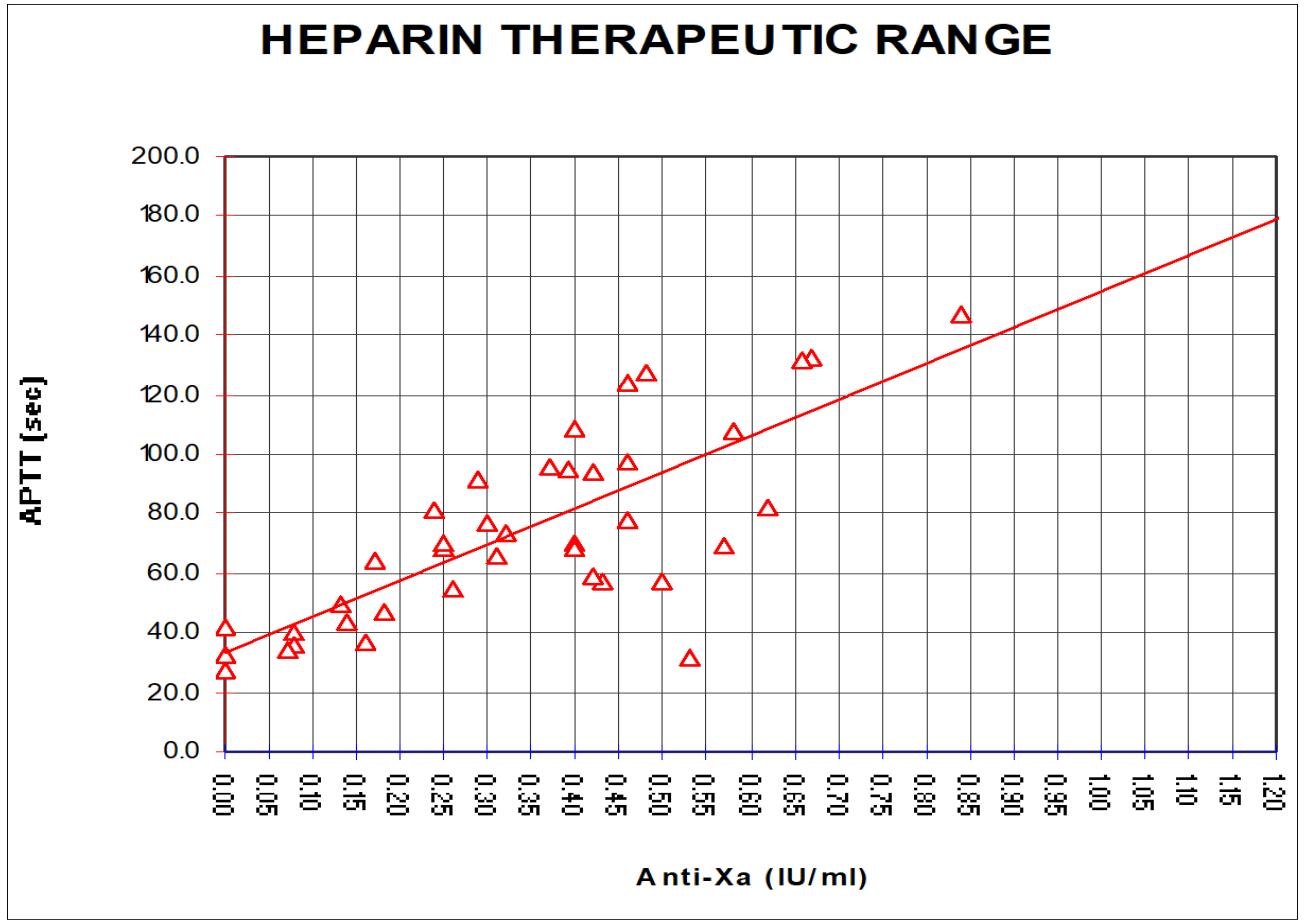
Heparin Therapeutic Range

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 70-120 SECONDS



CardinalHealth

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 <5 seconds between the differences in the means is acceptable
- A change of >5 seconds between the differences in the means requires action

Year	Mean Old Lot	Mean New Lot	Difference New-Old	Cum Sum	Action
2006	34.0	37.2	3.2	3.2	
2007	37.2	33.0	-4.2	-1.2	Accept
2008	33.0	43.0	10.0	8.8	Reject
2008-B	33.0	36.0	3.0	1.8	Accept

The “Do’s" and “Don’ts” to Enhance Quality in the Coagulation Laboratory

DO

- DO ask questions: use the five whys to perform a root cause analysis
- DO Listen to the issues from your front-line staff, have everyone work on problem solving

DON’T

- DON’T blame people: Focus on systems, not individuals- 99% of people want to do the right thing!
- DON’T say this can’t be solved, get someone who doesn’t know the process, a new set of eyes, they may see things you are missing

Thank you for your time!

“QUALITY IS NOT A GIVEN BUT NEEDS TO BE A PRACTICE; PATIENT CARE AND TEST OUTCOMES DEPEND ON IT.”