APTT vs Anti-Xa for Unfractionated Heparin Anticoagulation Monitoring

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Objectives

- Review clinical indications and considerations for unfractionated heparin (UFH) anticoagulation
- Understand the current laboratory methods and practices used to guide UFH anticoagulation
- Discuss the limitations of these assays and discuss implementation of alternative strategies and hurdles associated with same.
UFH citations


• Laboratory:
UFH: What does it do

Sulfated glycosaminoglycan which complexes with antithrombin (AT)

- Kinetically enhances AT activity
- AT is a serine protease inhibitor
  - Serine proteases:
    - XIIa, XIa, Xa, IXa, Thrombin
- Non-specific UFH binding
  - monocytes, endothelium, circulating proteins
UFH Anticoagulation - Clinical

- **Indications**
  - Treatment (e.g. VTE, ACS)
  - Prophylaxis (e.g. trauma)
  - Other (e.g. ECLS)

- **Infusion dose**
  - Weight based (total vs ideal vs adjusted)
  - To bolus or not
  - Maximum infusion rate
UFH Anticoagulation - Clinical

- Weight
- Laboratory Testing – baseline
  - CBC
  - PT and APTT
- Monitoring
  - Infusions vs subcutaneous
  - Guideline driven (e.g. CHEST)
  - Institution specific
  - Others (e.g. JCAHO)
UFH Anticoagulation – Clinical

• Although in place for ~60 years, the supporting evidence for current practices:
  • Weight based: weak
  • Monitoring frequency: weak
  • Monitoring methods (APTT vs anti-Xa): weak
  • Therapeutic targets:
    • APTT: very weak
    • Anti-Xa: very weak

UFH Anticoagulation – Laboratory

- Majority clinical laboratories use APTT
  - Reporting methods
    - Seconds
    - Ratios – historical, not recommended
  - Heparin Therapeutic Range (HTR)

- Alternatives:
  - When baseline APTT is elevated
  - When there is UFH “resistance”
UFH Anticoagulation – Laboratory

• Guidance
  • College of American Pathologists (CAP)
    • Checklist requirements
  • Publications
    • CLSI H47-A2 Approved Guideline 2008
    • Described Anti-Xa (protamine) vs APTT HTR (ratios 1.5-2.5)
CAP Recommendations for UFH monitoring

• Adjusted and therapeutic doses requires monitoring
• Monitoring to occur at 6 hour intervals until desired response reached.
  • For IV: daily monitoring thereafter, pref. before 1000
• Phlebotomy opposite extremity of infusion site
• Provide method and therapeutic range
CAP Recommendations for UFH monitoring

• Baseline aPTT and platelet count
• Therapeutic range for each lot aPTT reagent assessed by ex-vivo samples using:
  • Comparisons with heparin level
    • Anti-Xa or protamine titration
  • Comparisons with previously validated reagents
• Does not advocate in-vitro spiking for determining HTR
Reminders...
“Waterfall” Coagulation Cascade:

- FXII
- FXI
- FIX
- FVIII
- FV
- FX
- FII
- Fibrinogen
- Thrombin
- Fibrin

**APTT**

**PT**

- Heparin
- Anti-Xa DOAC
- Anti-IIa DOAC
Anti-Xa activity

plasma [heparin] + (exogenous antithrombin)

Excess fXa

AT-heparin-Xa complex + residual fXa

Chromogenic substrate

yellow color
APTT vs Anti-Xa

**APTT**
- Diagnostic test
  - Factor deficiency
  - Inhibitor assessment
    - Factor
    - Lupus anticoagulant
- Monitoring test
  - UFH
  - DOAC assessment
  - Measure of Rx efficacy
    - FFP/Cryo therapy
    - Factor replacement

**Anti-Xa**
- Monitoring test only
  - UFH
  - LMWH
  - Pentasaccharide
  - DOAC
    - Xarelto (rivaroxaban)
    - Eliquis (apixaban)
    - Saveysa (edoxaban)
    - Bevyxxa (betrixaban)
Limitations of Testing

APTT

- Pre-analytical:
  - Sample stability, temperature, tourniquet time, site selection, citrate:blood ratio, etc.
- Analytical:
  - factor levels (high or low), inhibitors, anticoagulants, antibiotics, physiology, different lot sensitivity to factors and anticoagulants

Anti – Xa

- Pre-analytical:
  - Timing of sample
  - Sample stability
  - Site selection
  - Processing
- Analytical:
  - Cannot differentiate between anti-Xa drugs
  - Possible challenges with icterus and lipemia
  - Calibration
CAP Recommendations for UFH monitoring

• Therapeutic range for each lot aPTT reagent assessed by ex-vivo samples using:
  • Comparisons with heparin level
    • Anti-Xa or protamine titration really?
  • Comparisons with previously validated reagents
• Does not advocate in-vitro spiking for determining HTR
UFH Therapeutic range (HTR)

Anti-Xa activity, U/ml

R²: 0.47

70-95 seconds

2018 CAMLT Annual Meeting Sep 30, 2018
Modified Brill-Edwards method

- VTE Rx patients only
- Comparison between APTT and Anti-Xa
- APTT HTR corresponding to 0.3 – 0.7 in treated patients
- \( R^2 \) ranges between 0.35-0.70 (never come close to 0.70)
- Recheck with every APTT reagent lot change
**CAP Recommendations for UFH monitoring**

- Therapeutic range for each lot aPTT reagent assessed by ex-vivo samples using:
  - Comparisons with heparin level
    - Anti-Xa or protamine titration
    - Comparisons with previously validated reagents
- **Does not advocate in-vitro spiking for determining HTR**
In-vitro addition vs Brill-Edwards HTR

In-vitro UFH range: 60-119s

BE UFH range: 70-95s

Anti-Xa activity, U/ml vs BCS aPTT, s
Proposed Alternative HTR Assessment for New lot APTT reagents

* Comparing of commercial or UFH enriched NPP on current and new lot reagents
* Limits: slope? or intercept? or $R^2$? of combination thereof…

Lot 2 = 1.0733x - 4.6963
$R^2 = 0.9965$

Lot 1 = 1.0361x - 0.5173
$R^2 = 0.9984$

Lot 2 = 0.9107x + 4.3218
$R^2 = 0.99998$

Lot 1 = 1.1709x - 6.0628
$R^2 = 0.9997$

2018 CAMLT Annual Meeting Sep 30, 2018
CAP Recommendations for UFH monitoring

• Therapeutic range for each lot aPTT reagent assessed by ex-vivo samples using:
  • Comparisons with heparin level
    • Anti-Xa or protamine titration
  • Comparisons with previously validated reagents
• Does not advocate in-vitro spiking for determining HTR
• Validation of UF heparin sensitivity of aPTT: Comparison with existing, validated reagent
  • Accumulating samples and freezing
    • NO minimum number detailed (Brill-Edwards: N=30)
    • Platelet-poor
    • No 2 samples on a given patient
  • Select reagent with comparable sensitivity
  • Comparison testing
    • old “x” axis vs new “y” axis
  • Cumulative summation of differences
    • Mean of new and old reagents
    • Difference between new – old
    • Cumulative difference over lots
      • <5sec: NS; 5-7sec: concern; >7sec: action
Evidence supporting CAP summation of differences recommendations for UFH HTR assessment

Concept from S Moll, UNC
Heparin Therapeutic Range (HTR)

- Problems for new lot HTR assessment:
  - No recommended sample size
  - No more than 2 samples per patient
  - CAP recommendations (vague)
  - Not reproducible (beginning vs end)
  - Poor sample handling for Anti-Xa testing
  - Occurs every 12-14 mos
  - HTR changes to dosing order sets
UFH Monitoring: Recommendations

Acceptable HTR methods:
• >20 samples (preferred N=30-50)
• <10% from same patient
• Samples with INR <1.3
• Frozen samples acceptable if demonstrated equivalence between fresh and frozen results
• Must be determined on all instruments in use
• Cannot use single instrument for multiple labs/sites/instruments

UFH Monitoring: Recommendations

Linearity between APTT and Anti-Xa measurements

UFH Monitoring: Why not ratios

APTT ratios are not optimal

Heparin “resistance”

Failure to achieve a therapeutic aPTT despite adequate or maximal dosing:

- Elevated fibrinogen
- Elevated factor VIII
  - Depressed antithrombin
  - Drug not given
  - Wrong patient
Heparin “resistance”

Alternative strategies:
Most likely available, but not often utilized:
Thrombin time
  Linear
  TR can be created using UFH enriched normal pooled plasma

May be available:
  Anti-Xa
Anti-Xa measurements

Two types chromogenic methods:
- With or without Antithrombin (AT)
- Without AT supplementing
  \(<50\% \text{ AT} = \downarrow \text{Anti-Xa}\)
  Sample mixing with NPP

Calibration – variable
- UFH, LMWH, Hybrid
- Commercial vs In-house preparation
Anti-Xa activity: AT influence
UFH via HTR monitoring

We know the APTT is dismal
Challenges with determining HTR
Guidelines - CAP
Feasibility – smaller labs
Analytical – Pre-analytical variables
Quality of sample, time delays, other existing conditions, etc

Some labs opting for Anti- Xa testing
UCDHS UFH-HTR Challenges

- Historical:
  - Poor communication between laboratory and end-users
  - Implementing embedded comments within APTT result
  - HTR at beginning of lot does not reproduce at end of lot use
  - Timing and dosing order set changes
    - Easy for the lab, more challenging for the pharmacy
  - The straw…
2016: New lot APTT evaluation

This is more awful than usual
2016: New lot APTT evaluation

- APTT run on fresh samples
  - Auto-program run any elevated APTT with INR <1.19
  - Samples meeting criteria were saved:
    - Allegedly within 2 hours of collection
    - Allegedly after double centrifugation
    - Frozen at -70°C
- Recommendation to run concurrent fresh APTT and anti-Xa activity
2016: New lot APTT evaluation

Current APTT = 45.823x + 45.516
R² = 0.3615

New APTT = 51.186x + 48.188
R² = 0.3676

Estimate: 65-85s
2016 UCDHS UFH Monitoring

- Presented data to Thrombosis Subcommittee
  - Concerns about initial data and subsequent data
    - Most likely poor processing before freezing
  - Concerns about lot changes and failure to reproduce HTR
- Recommendations made by laboratory to consider switching to anti-Xa measurements
  - Paradigm shift in practice
  - Similar shift to when we implemented INR reporting
UFH Anti-Xa monitoring: Education

- Rationale for monitoring change
- Identify potential cost and labor savings
- Identify potential putative benefits of 24/7 anti-Xa testing
  - Current practice is once daily anti-Xa testing
## Education: APTT vs Anti-Xa

### Rationale for change

<table>
<thead>
<tr>
<th>APTT</th>
<th>Anti-Xa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenced by 8 Fx levels</td>
<td>Monitoring test only</td>
</tr>
<tr>
<td>Poor specificity</td>
<td>• UFH, Anti-Xa DOAC</td>
</tr>
<tr>
<td>Diagnostic test</td>
<td></td>
</tr>
<tr>
<td>• Screen for Fx deficiency</td>
<td></td>
</tr>
<tr>
<td>• Screen for Inhibitor</td>
<td></td>
</tr>
<tr>
<td>Monitoring test</td>
<td></td>
</tr>
<tr>
<td>• UFH, DTI, DOAC</td>
<td></td>
</tr>
<tr>
<td>• Post Fx Rx</td>
<td></td>
</tr>
</tbody>
</table>
Monitoring UFH with Anti-Xa
Rationale for change – Cost?

- Shorter time to therapeutic target (TTT)
  - Within 6 hours (54% Anti-Xa vs 27% APTT)
  - Within 24 hours (74% Anti-Xa vs 63% APTT)
- Less dosing changes with 24 hours
  - Average 1.7 for APTT
  - Average 1.0 for Anti-Xa

Monitoring UFH with Anti-Xa
Rationale for change – Cost vs Savings?

- TTT
  - Ave 28 Hrs with Anti-Xa vs 48 Hrs with APTT
- More test results within TT goal:
  - 66% for Anti-Xa vs 42% for APTT
- Less rate changes within 24 hours:
  - 0.8 for Anti-Xa vs 1.6 for APTT

## Monitoring UFH with Anti-Xa

### Rationale for change – Savings?

Less RBC transfusions associated with Anti-Xa UFH monitoring

<table>
<thead>
<tr>
<th>UFH Indication</th>
<th>Odds ratio (95% CI)</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS</td>
<td>0.16 (0.14 – 0.18)</td>
<td>14822</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.41 (0.29 – 0.57)</td>
<td>1568</td>
</tr>
<tr>
<td>VTE</td>
<td>0.35 (0.26 – 0.48)</td>
<td>4414</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>UFH Indication</th>
<th>Bleed % Anti-Xa</th>
<th>Bleed % APTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS</td>
<td>7.0%</td>
<td>24.6%</td>
</tr>
<tr>
<td>Stroke</td>
<td>13.8%</td>
<td>21.9%</td>
</tr>
<tr>
<td>VTE</td>
<td>3.9%</td>
<td>8.6%</td>
</tr>
</tbody>
</table>

Monitoring UFH with Anti-Xa
Rationale for change – ?

- Stanford University hospital
- For ~ 9 years
- Discordant APTT vs Anti-Xa (higher APTT)
  - High 1-2 samples
  - Constant high >2 samples
  - Increased bleeding
  - Increased mortality
- Their practice: first 3 samples APTT + Anti-Xa

### 2016 UCDHS UFH Monitoring

Analyzing the data from UFH treated patients (N=243):

<table>
<thead>
<tr>
<th>Rate Change</th>
<th>Current APTT</th>
<th>Anti-Xa (0.3-0.7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Rate Change</td>
<td>78</td>
<td>143</td>
</tr>
<tr>
<td>Rate reduced</td>
<td>61</td>
<td>53</td>
</tr>
<tr>
<td>Rate increased</td>
<td>78</td>
<td>47*</td>
</tr>
</tbody>
</table>

* Included 15 liver failure patient samples
Reasons (and benefits) to transition for Anti-Xa UFH monitoring

- TTT reached sooner
- Less dose changes
- Less testing
- 24/7 Anti-Xa testing
  - Putative benefit – Anti-Xa DOAC measurements
- No need for annual APTT reagent lot evaluation
  - Never change UFH dosing order sets again (?)
- Dwindling and exiting expertise in the field
UCDHS transition to Anti-Xa

1. What are the issues?
2. Did the transition happen?
UCDHS UFH Anti-Xa implementation

Identifying stakeholders
- Pharmacy, Surgery, ICU, GenMed, HemeOnc, ECLS
  - CMO meeting – on board
  - P&T committee – on board

Education
- Ownership
- Who takes lead and calls
- Lab logistical issues
  - Changing practice in laboratory
    - Staff?
    - Reagents?
  - Cost differential

Putative benefits for 24/7 Anti-Xa operation?
UCDHS transition to Anti-Xa

Transition to anti-Xa monitoring occurred

Difficulties associated with transition:

Education process

Dosing nomograms

Concurrent therapy (e.g. apixaban when admitted)

Interferences with testing (APTT or Anti-Xa)
Special recognition

- Faculty:
  - Richard White, MD
  - Adam Giermasz, MD

- Pharmacists:
  - William Dager, PharmD
  - Aaron “Josh” Roberts, PharmD

- Clinical laboratory scientists:
  - Leslie Freeman, CLS
  - Lisa Gandy, CLS
Thank you...

Any Questions?