Evaluation of Unexplained Prolonged APTT &/or PT
Review & Update 12-2016

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Special Coagulation Lab, Coagulation Clinic & Hemophilia Center
Prolonged APTT &/or PT (Nichols WL)

Disclosures + Outline-Objectives

• Disclosures
  – NO Financial Relationships or Conflicts nor Off-label Therapeutic Products
  – Laboratory Diagnostic Products / Procedures: may or may not be FDA-approved and/or routinely available

• Outline - Objectives
  – Revisit the plasmatic procoagulant pathways
  – Recollect test procedures (APTT, PT, TT, DRVVT, Mix study)
  – Recount pathophysiologic categories of plasmatic coagulopathies
  – Discuss differing mechanisms and differential diagnostic features
  – Identify effective laboratory testing strategies: ALGORITHM(s)
  – Case
PROCT / Prolonged Clot Time Profile (Mayo/MML #83097)

Activated Partial Thromboplastin Time (APTT)
Is result within normal range?

STOP
No additional APTT testing

YES
APTT Mixing Test (1:1 mix with normal plasma)

NO

Prothrombin Time (PT)
Is result within normal range?

STOP
No additional PT testing

YES
PT Mixing Test (1:1 mix with normal plasma)

NO

Thrombin Time (TT)
Is result within normal range?

STOP
Reptilase Time (RT)

YES

NO

STOP
No additional DRVVT testing

YES

NO

Dilute Russell Viper Venom Time (DRVVT)
Is result within normal range?

STOP
DRVVT Mixing Test (1:1 mix with normal plasma)

YES

NO

Does result correct sufficiently?

YES

If indicated:
Factor Assays: VIII, IX, XI, XII

NO

If TT is normal:
Perform platelet neutralization procedure (PNP)

Does result correct sufficiently?

YES

If indicated:
Factor Assays: II, V, VII, X

NO

STOP
No additional DRVVT testing

Does result correct sufficiently?

YES

DRVVT Confirmatory Testing

NO

Review all results. Additional clarification or testing needed?

YES

Perform one or more as needed:
• Factor inhibitor screen and titer
• Factor assays
• Staclot LA and/or DPT
• Clinical information review

NO

Interpretation of all results is performed

Also performed:
• Fibrinogen
• D-dimer
• Soluble fibrin monomer
Case - 1

- **PT/INR**: 12.1s/1.1 (<12.8s/<1.2)
- **APTT**: 48s (26-36s)
  - APTT 1:1 mix: 43s (26-36s)
  - PNP-APTT*: 52s (neg. for LA)
  - PNP buffer control APTT: 58s
- **Thrombin Time (TT)**: 22s (15-23s)
- **DRVVT (Screen Ratio)**: 1.1 (<1.2)
- **StaClot APTT**: 71s (<60-70s)
- **Staclot Delta (Hex)**: 4s (<8-13s)
- **Fibrinogen**: 445 mg/dL (200-430)
- **D-dimer**: 610 ng/mL (<250)
- **Reflexive/Supplemental Tests?? (Which?)**
- **Clinical Information??**

*PNP = Pltlt. Neutraliz. Procedure
Prolonged Clotting Times - Mechanisms

- Coagulation factor deficiency(ies)
- Coagulation inhibition
- Both
- Neither (spurious)

"Mixing Test" for initial evaluation --> Interpretation
Inhibition vs Factor Deficiency
Mixing Patterns → Interpretation

APTT (sec)

Normal (%) 100 80 50 20 10 0
Patient (%) 0 20 50 80 90 100

Inhibitor Deficiency

upper normal
Prolonged APTT &/or PT
MIXING STUDIES & ISSUES

• Mixing studies performed / interpretable only if baseline (screening) clotting time "significantly" prolonged = > upper normal (> +2SD or >97.5%ile vs. > +3SD or >99%ile cutoff)
  – 1 sec prolonged? • 2-5 sec prolonged? • >5 sec prolonged?

• 1:1 Mix (Pt:NPP) should normalize the prolonged clotting time (provides ≥50% of all factors) into the reference range if no inhibitor (but, weak inhibitor may "correct" - significance?)

• Incubated mixing studies (1-2 hrs): essential for detecting time-dependent inhibition (especially VIII inhibitors; rarely LA)
  – Compare w. incubated controls (Pt, NPP) mixed just before testing
  – Positive = incubated mix APTT ≥10-20% ↑ vs. control mix APTT

• Relatively few or limited studies - and evidence or guidelines - for performing & interpreting mixing studies (see CLSI LA testing guidelines 2014 = CLSI H60A document)

• Ratio reporting may be useful (ie, Pt:NPP ratio or normalized ratio)

• Laboratories should define reference ranges and “cut-offs” for mixing studies
Plasmatic Coagulopathies
Pathophysiologic Classification: SICKFAIL

• **S** = Spurious
• **I** = Inhibitors
• **C** = Congenital/Hereditary factor deficiencies
• **K** = Vitamin *K* deficiency
• **F** = Factor deficiencies (acquired) - single or multiple
• **A** = Anticoagulants
• **I** = ICF (intravascular coagulation & fibrinolysis) or DIC (disseminated intravascular coagulation)
• **L** = Liver disease
Spurious Coagulopathies
Mainly Pre-Analytical = Sample or Patient Issues

- Hematocrit abnormal
  >55 or <25: ↑ PT, APTT
- Incomplete tube fill
- Wrong/No anticoagulant
  EDTA, heparin, serum
- Heparin contamination
  “Line draw”
- Anticoagulant Rx effects
  heparin, warfarin, DTI, Xa inhibitor, etc.
- Other Rx effects
  Fibrinolytic Rx, DDAVP, etc.

- Transfusion effects
  FFP, Cryo, Factor concentrate
- Difficult venipuncture
  → clotting in vitro
- Lipemia, hemolysis, icterus
- Warm proteolysis
  loss of VIII & V: ↑ PT/APTT
- Cold activation
  VII → VIIa (short PT)
- Residual platelets
  ↓ LA sensitivity; ↓ thrombin time

Be Aware! These are not rare!
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Vitamin K Deficiency

• **Common:** Neonates; Hospitalized patients

• **Limited body stores of fat-soluble Vitamin K**
  - 1-2 mg total stores in adults; metabolic requirement ~0.1 mg/day

• **Function:** gamma carboxylation of glutamic acid --> “Gla”: binds Ca$^{++}$ & phospholipids (PS, PE)

• **Vitamin K-dependent factors:** II, VII, IX, X, C, S, (Z)

• **Diagnosis:**
  - $\uparrow$ PT > $\uparrow$ APTT
  - K-dependent factors low; others NL (I, V, VIII, XI, XII, etc.)
  - Response of PT (+/- factors) to Vitamin K Rx
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Anticoagulants

- **Coumarins**: Vitamin K antagonists (II, VII, IX, X, C, S)
  - Dicumarol
  - Warfarin (Coumadin®, generics)
  - Indanediones (Miradon®)
  - Superwarfarins (Brodifacoum®, others)

- **Heparins**: Antithrombin-thrombin (&/or AT-Xa) complex catalysis
  - Unfractionated heparins (UFH)
  - Low molecular weight heparins (LMWH) + fondaparinux (Arixtra®)
  - Endogenous heparinoids (rare)

- **Direct Thrombin Inhibitors**: Antithrombin - independent
  - Hirudins - Refludan®; Bivalirudin®; etc.
  - Others - Acova® (argatroban); Pradaxa® (dabigatran); etc.

- **Direct Factor Xa Inhibitors**: Antithrombin - independent
  - Xaralto® (rivaroxaban); Eliquis® (apixiban); Savaysa® (edoxaban)
Anticoagulants (Coumarins)

- **Coumarins**: Vitamin K antagonists (II, VII, IX, X, C, S)
  - Typical test results:
    - PT>APTT prolongation; TT Normal; DRVVT prolonged
    - Mixing studies: no or minimal inhibition (PIVKAs)
    - K-dependent factors low; others normal (eg, F V)

- **Unusual Coumarin Effects**:
  - **Anticoagulant malingerers** (“Dicumarol eaters”)
    - Warfarin toxicologic assay
  - **Superwarfarin poisoning** (“Rat poison”)
    - Prolonged effect [weeks]; Vitamin K-resistance: 50-100 mg/day to Rx
    - Brodifacoum toxicologic assay
Anticoagulants - Heparin

Coagulation Test Effects (Typical)

Unfractionated Heparin (UFH)

• APTT -- Prolonged (variably)
• PT -- Normal (heparin neutralizer in PT reagent)
• TT -- Markedly prolonged (bovine thrombin)
• RT -- Normal
# Thrombin Time (TT) & Reptilase Time (RT) Diagnostic Patterns*

<table>
<thead>
<tr>
<th>TT</th>
<th>RT</th>
<th>CAUSES</th>
<th>OTHER TESTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged</td>
<td>Normal</td>
<td>Heparin or inhibitor of bovine thrombin</td>
<td>Human TT &amp;/or heparin assays</td>
</tr>
<tr>
<td>Prolonged</td>
<td>Prolonged</td>
<td>Hypo- or afibrinogenemia</td>
<td>Fibrinogen (endpoint assay) +/- kinetic</td>
</tr>
<tr>
<td>Prolonged</td>
<td>Prolonged</td>
<td>Dysfibrinogenemia</td>
<td>Kinetic fibrinogen vs. antigen or endpoint assay</td>
</tr>
<tr>
<td>Prolonged</td>
<td>Prolonged</td>
<td>Fibrin- split products</td>
<td>FSP or D-dimer assay (+ Fibrinogen)</td>
</tr>
</tbody>
</table>

*Typical patterns (exceptions exist); extent of abnormalities varies.
Other Anticoagulants
Impacts on Coagulation Testing

- **Low Molecular Weight Heparins (LMWHs)**
  - Minimal (usually) but variable effects on APTT, TT
  - Rx monitoring - chromogenic heparin (anti-Xa) assay

- **Direct Thrombin Inhibitors (DTIs)**
  - Hirudins or Small molecules (argatroban, dabigatran)
  - Prolonged TT ± PT, APTT, DRVVT (not the RT)

- **Direct Coagulation Factor Xa Inhibitors**
  - Variably prolonged PT ± APTT, DRVVT (not TT, RT)
  - Chromogenic anti-Xa assay may detect... Calibrated assays limited available

LMWHs or Direct Inhibitors can interfere w. diagnostic coag testing (false results) - especially if Rx unknown to laboratory!!
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Liver Disease: Hemostatic & Coagulation Effects (typical)

- Thrombocytopenia
- Prolonged clotting time tests; “no inhibition”
  - ↑PT, DRVVT > ↑APTT, (TT)
- Multiple coagulation factor / protein deficiencies
  - K-independent factors: ↓I, V, XI, XII, AT
  - ↑VIII
- Intravascular coagulation & fibrinolysis increased
  - Fibrin degradation products (D-dimer) ↑
  - Soluble fibrin monomer complex (SFMC) ↑
- Bleeding >> Thrombosis
Plasmatic Coagulopathies
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• $S =$ Spurious
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• $C =$ Congenital factor deficiencies
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• $I =$ ICF (intravascular coagulation & fibrinolysis) or DIC (disseminated intravascular coagulation)
• $L =$ Liver disease
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Deficient factor</th>
<th>PT*</th>
<th>APTT*</th>
<th>Prevalence</th>
<th>Mode of inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemophilia A</td>
<td>Factor VIII</td>
<td>Normal</td>
<td>Prolonged</td>
<td>1:5000†</td>
<td>X-linked recessive</td>
</tr>
<tr>
<td>Hemophilia B</td>
<td>Factor IX</td>
<td>Normal</td>
<td>Prolonged</td>
<td>1:30,000†</td>
<td>X-linked recessive</td>
</tr>
<tr>
<td>Hemophilia C</td>
<td>Factor XI</td>
<td>Normal</td>
<td>Prolonged</td>
<td>Up to 4%‡</td>
<td>Autosomal</td>
</tr>
<tr>
<td>von Willebrand disease (VWD)</td>
<td>VWF +/- F-VIII</td>
<td>Normal</td>
<td>Normal/prolonged</td>
<td>Up to 1%</td>
<td>Autosomal</td>
</tr>
<tr>
<td>Hageman factor deficiency**</td>
<td>Factor XII</td>
<td>Normal</td>
<td>Prolonged</td>
<td>Up to ~1%</td>
<td>Autosomal</td>
</tr>
<tr>
<td>Fletcher or Fitzgerald factors**</td>
<td>PK or HMWK</td>
<td>Normal</td>
<td>Prolonged</td>
<td>Rare§</td>
<td>Autosomal</td>
</tr>
<tr>
<td>Factor VII (Stable factor)</td>
<td></td>
<td>Prolonged</td>
<td>Normal</td>
<td>1:500,000</td>
<td>Autosomal</td>
</tr>
</tbody>
</table>

Rarer coagulation factor deficiencies

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Deficient factor</th>
<th>PT*</th>
<th>APTT*</th>
<th>Prevalence</th>
<th>Mode of inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V (Labile factor)</td>
<td></td>
<td>Prolonged</td>
<td>Prolonged</td>
<td>1:1 million</td>
<td>Autosomal</td>
</tr>
<tr>
<td>Factor II (Prothrombin)</td>
<td></td>
<td>Prolonged</td>
<td>Normal/prolonged</td>
<td>Rare§</td>
<td>Autosomal</td>
</tr>
<tr>
<td>Factor X (Stuart-Prower)</td>
<td></td>
<td>Prolonged</td>
<td>Normal/prolonged</td>
<td>1:500,000</td>
<td>Autosomal</td>
</tr>
<tr>
<td>Factor XIII (FSF)</td>
<td></td>
<td>Normal</td>
<td>Normal</td>
<td>Rare§</td>
<td>Autosomal</td>
</tr>
<tr>
<td>Factor I (Fibrinogen)</td>
<td>(Afib; Hypofib; Dysfib)</td>
<td>Prolonged/NI</td>
<td>Prolonged/Normal</td>
<td>Rare§</td>
<td>Autosomal</td>
</tr>
<tr>
<td>Combined: V+VIII; II+VII+IX+X</td>
<td></td>
<td>Prolonged</td>
<td>Prolonged</td>
<td>Rare§</td>
<td>Autosomal</td>
</tr>
</tbody>
</table>

*APTT = activated partial thromboplastin time; PT = prothrombin time.
† Male births. ‡ Among Ashkenazi Jews. § Case reports. ** No bleeding.

Plasmatic Coagulopathies

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Factor Deficiencies - **Multiple**

Acquired (Patterns)

- Vitamin K Deficiency -- ↓ II, VII, IX, X, C, S
- Liver Disease -- ↓ Vit. K factors, I, V, XI (↑ VIII)
- ICF/DIC -- ↓ I, V, VII, AT, Plasminogen, Antiplasmin, etc.
- Inflammation -- ↓ XI, XII (↑ VIII & Fibrinogen)
- T-cell (peripheral) Lymphomas - ↓ I (± II, V, VII, AT, etc.)
- L-Asparaginase Rx -- ↓ Fibrinogen [I], AT (±C, S, etc.)
Factor Deficiencies - Single Acquired (Non-immune or Immune: but no activity inhibition)

• **Factor II** (Prothrombin)
  • Lupus anticoagulant (non-neutralizing antibodies)

• **Factor V**
  • *Myeloproliferative disorders* (cell absorption, proteolysis?)

• **Factor X**
  • *Systemic amyloidosis* (perivascular amyloid absorption)
  • Lupus anticoagulant (non-neutralizing antibodies)

• **Factor VIII (+ Von Willebrand Factor: VWF)**
  • Acquired von Willebrand syndrome (AVWS)
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**I** = ICF (intravascular coagulation & fibrinolysis) or **DIC** (disseminated intravascular coagulation)

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Fibrin enhances plasmin generation (binds plasminogen and t-PA)
Intravascular Coagulation & Fibrinolysis ("ICF")

- **ICF** -- a spectrum of increased responses of the coagulation system to stimuli

- **Stimuli:** "Physiological" ---> Pathological
  - Bleeding
  - Surgery, Trauma
  - Thromboembolism
  - Sepsis, Malignancy
  - Vascular or Obstetric Disorders
  - Liver failure, Snake bites, Etc.

- **Clinical/Laboratory Scenarios:**
  - Acute, Subacute, Chronic
  - Mild --> Severe
  - Compensated --> Decompensated
  - Bleeding, Tissue Ischemia, Thromboembolism & A[pre]symptomatic
ICF / DIC Laboratory Testing
Typical Results - Extent, Severity Vary

- Platelet count ↓
- PT ↑ ± APTT ↑
- Fibrinogen ↓
- D-dimer ↑ (increased thrombin & plasmin)
- SFMC ↑ (increased thrombin)

Supplemental DIC/ICF coag tests:

- Factor levels ↓ (II, V, VII, X, XI, etc.)
- Antithrombin, Plasminogen, Antiplasmin
- Thrombin-Antithrombin (TAT complex)

ICF/DIC coagulation tests are **not specific** for diagnosis of clinical DIC

- “Positive” tests (e.g., D-Dimer & SFMC elevations) associated with:
  - Bleeding; Surgery; Trauma; Liver disease; Thromboembolism;
  - Hypercoagulable states, Etc.

Correlate lab data & clinical information!
Intravascular Coagulation & Fibrinolysis

“Primary” Fibrinolysis

• Activation of excessive Fibrinolysis -- without activation of coagulation (Thrombin generation)

• Bleeding

• Laboratory:
  – D-dimer & FDP elevation (increased Fibrinolysis)
  – SFMC typically negative (reflects Thrombin)
  – Fibrinogen may be low (Fibrinogenolysis)
  – Plasminogen & Antiplasmin low (also in DIC/ICF)
  – Antithrombin usually not low

• Associated diseases: Amyloidosis, Prostatic carcinoma, Cirrhosis, Thrombolytic therapy
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Coagulation Inhibitors

- **Specific Factor Inhibitors** (antibodies)
  - VIII, V, IX, II, X, XIII, VWF, etc. (neutralizing vs. non-neutralizing)

- **“Non-specific” Coagulation Inhibitors**
  - Lupus anticoagulants
    (“antiphospholipid” antibodies)
  - Dysproteinemias
    (MGUS, myeloma, Waldenström’s, amyloidosis-AL)
  - Other: Fibrin degradation products, etc.

- **“Global” Inhibitors** (thrombin &/or Xa inhibition)
  - Heparins, DTIs, Direct-acting Factor Xa inhibitors
Specific Factor Inhibitors
(Approximate Prevalence / Incidence Ranking)

1. Factor VIII (human, porcine)
2. Factor V (human, bovine)
3. Thrombin (bovine)
4. Factor IX (severe Hemophilia B)
5. Von Willebrand factor (VWF)
6. Other Factors (rare):
   I, II, VII, X, XI, XII, XIII, etc.
Factor VIII Inhibitors (Prolonged APTT)

• Hemophilia A (severe) (alloantibodies)
  • Prevalence: up to 20-25%

• “Acquired Hemophilia” (autoantibodies)
  • Autoimmune disorders (5-10%)
  • Postpartum (5-10%)
  • Malignancies (?5%)
  • “Old healthy people” (70-85%)

• Allo- vs. Auto-antibody inhibitors differ:
  • lab features (kinetics of neutralization)
  • clinical features (pattern of bleeding syx)
Factor (VIII) inhibitor screen: incubated mixing test (APTT)

<table>
<thead>
<tr>
<th>Pool</th>
<th>Immediate</th>
<th>1 Hour</th>
<th>Result</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>109</td>
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<table>
<thead>
<tr>
<th>Mixtures</th>
<th>(1 part pool + 4 parts patient)</th>
<th>Immediate</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>100%</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50%</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25%</td>
<td>18</td>
</tr>
</tbody>
</table>

Expected: 21.8 + 0.8 = 22.6

Result: 22

<table>
<thead>
<tr>
<th>Patient</th>
<th>Immediate</th>
<th>1 Hour</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100%</td>
<td>-</td>
<td>&lt;1</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>-</td>
<td>&lt;1</td>
</tr>
<tr>
<td></td>
<td>25%</td>
<td>-</td>
<td>&lt;1</td>
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</tbody>
</table>

Result: <1

<table>
<thead>
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<th>Mixtures</th>
<th>1 Hour</th>
<th>Result</th>
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<tr>
<td></td>
<td>Together</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25%</td>
</tr>
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</table>

Expected: 19

Result: 4

<table>
<thead>
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<th>Mixtures</th>
<th>1 Hour</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Separate</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25%</td>
</tr>
</tbody>
</table>

Result: 20

No immediate, but progressive incomplete inhibition of FVIII activity (type II kinetics): POSITIVE SCREEN
### Bethesda FVIII Inhibitor Titering Assay

**After 2 hours at 37°C**

<table>
<thead>
<tr>
<th></th>
<th>% Factor</th>
<th>% Residual</th>
<th>&quot;Factor&quot; from chart</th>
<th>X Dilution</th>
<th>= Bethesda Units</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pool</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>47</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>% factor in mixture</td>
<td>% factor in pool</td>
<td>x 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dilution + equal volume pool</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>undiluted</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>5</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1:2</td>
<td>44</td>
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<tr>
<td>1:4</td>
<td>26</td>
<td>55</td>
<td>0.85</td>
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Lupus Anticoagulants (LA) (Antiphospholipid Antibodies) Diagnostic Laboratory Criteria/Recommendations*

1. **Prolonged** phospholipid-dependent clot time(s)
   - APTT, DRVVT, PCT, KCT/SCT, (D)PT, etc. (≥2 tests - Δ principles)

2. **Inhibition** demonstrated -- mixing tests

3. **Phospholipid dependence** demonstrated
   - PNP (APTT); DRVVT “Confirm”; Staclot LA Hex PL; etc.

4. Evaluate for / Exclude **confounding coagulopathies** --
   - Factor defic./inhib., Heparin, Warfarin, DTI, etc.

5. For full APL eval. include supplemental testing (ELISA) for serum IgG/M anti-Cardiolipin/β-2 Glycoprotein I antibodies**


Dysproteininemic Coagulopathies
(Paraproteinemias inhibiting clot times)

- **Dysproteinemias**: MGUS, Myeloma, Waldenström’s macroglobulinemia
- **Monoclonal immunoglobulins (G, M, A)**
  - "Interfere" with coag protein assembly & function
    - Thrombin generation
    - Fibrin assembly
  - Specific inhibition of coag factor(s) - less common
- Prolonged, inhibited PT, APTT or both
- Asymptomatic > Bleeding
Coagulation Inhibitors - Differential Dx
(Listed by Descending Prevalence - approximate)

1. Anticoagulant Inhibitor Compounds and Substances
   - Heparin (unfractionated) & LMWHs
   - Direct thrombin inhibitors (DTIs) & Xa inhibitors
   - EDTA (ethylenediaminetetra-acetic acid) - instead of citrate plasma

2. Lupus Anticoagulant (LA) - “Antiphospholipid Abs”

3. Specific Coagulation Factor Inhibitors (Antibodies)
   - Factor VIII inhibitors (allo- and auto-antibodies)
   - Inhibitors of other coagulation factors (V, IX, II, X, XI, XIII)

4. Monoclonal Immunoglobulinopathies (Antibodies)
   - Monoclonal gammopathy of undermined significance (MGUS)
   - Macroglobulinemia, Multiple myeloma, Systemic amyloidosis (AL)

5. Fibrin Degradation Products (FDPs) & Other Non-specific Coagulation Inhibitors
Plasmatic Coagulopathies
Pathophysiologic Classification: SICKFAIL*

- **S** = Spurious
- **I** = Inhibitors
- **C** = Congenital/Hereditary factor deficiencies
- **K** = Vitamin K deficiency
- **F** = Factor deficiencies (acquired) - single or multiple
- **A** = Anticoagulants
- **I** = ICF (intravascular coagulation & fibrinolysis) or DIC (disseminated intravascular coagulation)
- **L** = Liver disease

*Thanks to Dr. Gerald Holcomb (Mayo Hem Emeritus) for the mnemonic idea, and to Dr. Paul Monahan (UNC Chapel Hill) for updating this one: SICKFAIL/SIKFAIL
Coagulation Test Panels
Reflexive Testing & Interpretive Reporting
“Consultative” Test Panels

• Mayo Medical Laboratories (MML) Testing Panels/Profiles
  – Lupus Anticoagulant (LA) (MML 83092 profile = LUPPR)
  – Prolonged Clotting Times (unexplained) (MML 83097 profile = PROCT)
  – Other panels: Bleeding, Thrombosis, VWD, Factor Inhibitor (+ DIC, PltFl Fn – not MML; Mayo in-house only)

• Testing from Other Reference or Hospital Coagulation Laboratories
  – Lupus Anticoagulant (LA) test panel
    • Many specialized coag labs offer LA tests +/- panel: vary in panel content, reflexes & interpretive reporting
  – Prolonged/Abnormal PT/APTT test panel
    • Few labs offer -- varies in test content, reflexes, reporting
  – Mixing study (APTT, PT) +/- incubation → interpretation: available in many coag labs
PROCT / Prolonged Clot Time Profile (Mayo/MML #83097)

- **Activated Partial Thromboplastin Time (APTT)**
  - Is result within normal range?
    - **YES**
      - Stop; No additional APTT testing
    - **NO**
      - APTT Mixing Test (1:1 mix with normal plasma)

- **Prothrombin Time (PT)**
  - Is result within normal range?
    - **YES**
      - Stop; No additional PT testing
    - **NO**
      - PT Mixing Test (1:1 mix with normal plasma)

- **Thrombin Time (TT)**
  - Is result within normal range?
    - **YES**
      - Stop; No additional TT testing
    - **NO**
      - Reptilase Time (RT)

- **Dilute Russell Viper Venom Time (DRVVT)**
  - Is result within normal range?
    - **YES**
      - Stop; No additional DRVVT testing
    - **NO**
      - DRVVT Mixing Test (1:1 mix with normal plasma)

- **Does result correct sufficiently?**
  - **YES**
    - If indicated: Factor Assays: VIII, IX, XI, XII
  - **NO**
    - If TT is normal: Perform platelet neutralization procedure (PNP)

- **Review all results. Additional clarification or testing needed?**
  - **YES**
    - Perform one or more as needed:
      - Factor inhibitor screen and titer
      - Factor assays
      - Staclot LA and/or DPT
      - Clinical information review
  - **NO**

- **Interpretation of all results is performed**

**Also performed:**
- Fibrinogen
- D-dimer
- Soluble fibrin monomer
Case - 1

- PT/INR: 12.1s/1.1 (<12.8s/<1.2)
- APTT: 48s (26-36s)
  - APTT 1:1 mix: 43s (26-36s)
  - PNP-APTT*: 52s (neg. for LA)
  - PNP buffer control APTT: 58s
- Thrombin Time (TT): 22s (15-23s)
- DRVVT (Screen Ratio): 1.1 (<1.2)
- StaClot APTT: 71s (<60-70s)
- Staclot Delta (Hex): 4s (<8-13s)

- Fibrinogen: 445 mg/dL (300-430)
- D-dimer: 610 ng/mL (<250)
- Reflexive/Supplemental Tests?
- Clinical Information?

*PNP = Pltlt. Neutraliz. Procedure
Case - 2

- **PT/INR:** 12.1s/1.1 (<12.8s/<1.2)
- **APTT:** 48s (26-36s)
  - APTT 1:1 mix: 43s (26-36s)
  - PNP-APTT*: 52s (neg. for LA)
  - PNP buffer control APTT: 58s
- **Thrombin Time (TT):** 22s (15-23s)
- **DRVVT (Screen Ratio):** 1.1 (<1.2)
- **StaClot APTT:** 71s (<60-70s)
- **Staclot Delta (Hex):** 4s (<8-13s)

**Reflexive/Supplemental Tests**

- **Factor VIII:** ≥191% (55-200%)
- **Factor IX:** 94% (65-140%)
- **Factor XI:** ≥115% (55-150%)
- **Factor XII:** 123% (55-180%)

What is the likely diagnosis (causing APTT prolongation)?
Coagulation Inhibitors - Differential Dx
(Listed by Descending Prevalence - approximate)

1. Anticoagulant Inhibitor Compounds and Substances
   - Heparin (unfractionated) & LMWHs
   - Direct thrombin inhibitors (DTIs) & Xa inhibitors
   - EDTA (ethylenediaminetetra-acetic acid) - instead of citrate plasma

2. Lupus Anticoagulant (LA) - “Antiphospholipid Abs”

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4. Monoclonal Immunoglobulinopathies (Antibodies)
   - Monoclonal gammopathy of undermined significance (MGUS)
   - Macroglobulinemia, Multiple myeloma, Systemic amyloidosis (AL)

5. Fibrin Degradation Products (FDPs) & Other Non-specific Coagulation Inhibitors
Case - 3

• **PT/INR: 12.1s/1.1** ($\leq 12.8s/<1.2$)
• **APTT: 48s** (26-36s)
  - APTT 1:1 mix: **43s** (26-36s)
  - PNP-APTT*: **52s** (neg. for LA)
  - PNP buffer control APTT: **58s**
• **Thrombin Time (TT): 22s** (15-23s)
• **DRVVT (Screen Ratio): 1.1** (<1.2)
• **StaClot APTT: 71s** (<60-70s)
• **Staclot Delta (Hex): 4s** (<8-13s)

**Relevant Clinical Information**

• No significant bleeding
• No anticoagulant Rx
• Serum protein electrophoresis & immuno-electrophoresis:
  - **0.2 g/dL IgGλ** M-protein
• MGUS (monoclonal gammopathy of unknown significance)

**What is the likely diagnosis (cause of APTT prolongation)?**
Questions & Discussion
PREPARE TO DETOUR
FROM NORMAL PATH