The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Improving Acute Care Using Coagulation Mixing Studies

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Surgeons and physicians order PT and PTT assays to predict bleeding risk, often generating isolated, unexplained prolonged PTs or PTTs. In follow-up, the laboratory practitioner mixes patient plasma with normal plasma and repeats the assay. Mixing studies may be provided at community hospitals and acute care facilities. The information gained from mixing studies is an essential first step in the diagnosis of many hemostatic abnormalities. During this presentation, we discuss the importance of mixing studies, describe how they are performed, and show how their results contribute to the diagnosis.

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Bottom Line at the Start (BLAST)

The participant…

- Lists the clinical applications for a PTT mixing study.
- Lists the steps to perform a PTT mixing study.
- Explains why the mixing study is an acute care assay.
- Correlates mixing study results with lupus anticoagulant and specific inhibitor testing.

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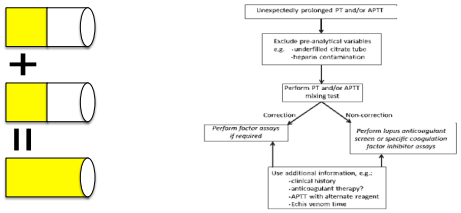
Mixing Study: An Acute Care Assay

Differentiates a coagulopathy from a specific inhibitor or from a lupus anticoagulant



Kershaw GK, Orellana D. Mixing tests: diagnostic aides in the investigation of prolonged prothrombin times and activated partial thromboplastin times. Semin Thrombos Hemost 2013;39:283–90.

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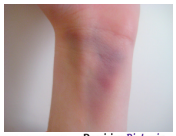
Case: 32-yo Female Pre-op Screen

- Six weeks post-partum
- Easy bruising, frequent nosebleeds, vaginal bleeding



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Pre-op Screen 32-yo Female, 6 Weeks Post-partum

Assay	Patient	RI
HGB	11.8 g/dL	12–15 g/dL
PT	12.4 s	9.8–12.6 s
PTT (APTT)	42.5 s	25–35 s
PLT count	310,000/µL	250–450,000/µL
Fibrinogen	320 mg/dL	220–498 mg/dL
Isolated, prolonged PTT—response? Go to 1:1 PTT mix		

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Rule Out Heparin, DOACs

Assay	Patient	RI
Thrombin time (TT)	14 s	<21 s
Anti-Xa	0.0 U/mL	0.4–0.7 U/mL

- Inpatient—unrecorded UFH flush of vascular access device
  - neutralize w/ Hepsorb (polybrene) or Hepzyme, proceed if TT normal
- Outpatient: direct oral anticoagulant (DOAC): discontinue
  - Dabigatran, direct thrombin inhibitor, TT markedly prolonged
  - Direct anti-Xa like rivaroxaban elevates anti-Xa, may prolong PTT

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Direct Oral Anticoagulants (DOACs)

- Oral direct anti-Xa anticoagulants
  - Rivaroxaban; Xarelto
  - Apixaban: Eliquis
  - Edoxaban; Savaysa
  - Betrixaban; now at the FDA
- Oral direct thrombin inhibitor (DTI)
  - Dabigatran; Pradaxa
- If no A/C, perform 1:1 PTT mix to differentiate factor deficiency from factor-specific inhibitor or the "non-specific inhibitor," lupus anticoagulant (LA, LAC)

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PTT Mixing Study: Cheap and Simple

- Start within 2 hours of collection to avoid specimen degradation
  - Factors V (FV) and VIII (FVIII) deteriorate
- Ensure patient plasma is platelet-poor, < 10,000/uL
  - If not, platelets release platelet factor 4, coagulation factor V
- Mix patient plasma 1:1 with pooled normal plasma (NP) and perform immediate PTT on mixture
- Correction: If PTT of 1:1 mix is ≤10% longer than NP PTT
  - Factor deficiency? (But first you must incubate and repeat)
- No correction: 1:1 mix is >10% longer than NP PTT
  - Non-specific inhibitor, usually LA
  - Specific inhibitor (anti-FVIII), usually requires 37°C incubation

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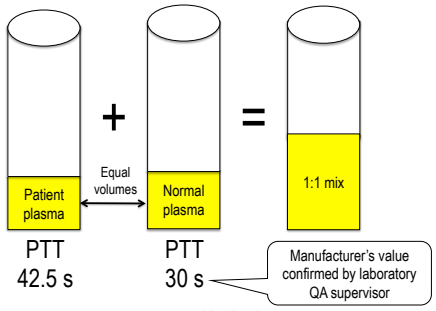
PTT Mixing Study



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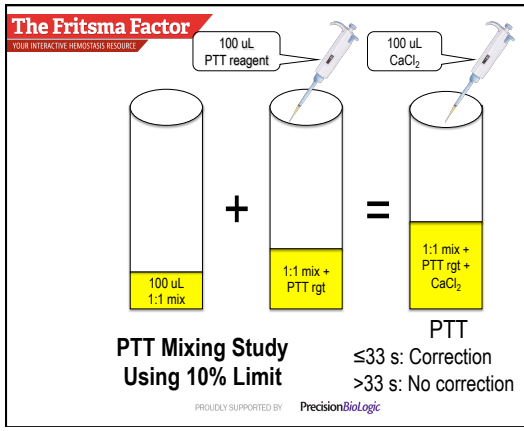

PTT Mixing Study Using 10% Limit

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1:1 PTT Mix with Incubation

- PTT of immediate mix ≤10% longer than NP
  - Correction: factor deficiency? But first…
  - Incubate 1:1 mix 1–2 hours and repeat
- Correction after incubated mix = factor deficiency
- No correction: PTT remains >10% above NP
  - Specific inhibitor such as anti-FVIII
    - IgG_4: Temp dependent, usually requires incubation
    - However, some inhibitors neutralize FVIII within 10 min
    - May detect in immediate mix

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1:1 PTT Mix with Incubation

- Reflex to incubation if unincubated mix corrects
- Must also incubate NP
- Compare mix PTT to incubated NP PTT
- May also detect temperature-dependent LA
  - ~15% of LAs are temperature-dependent

Thom J, Ivey L, Eikelboom J. Normal plasma mixing studies in the laboratory diagnosis of lupus anticoagulant. J Thromb Haemost 2003;1:2689–91

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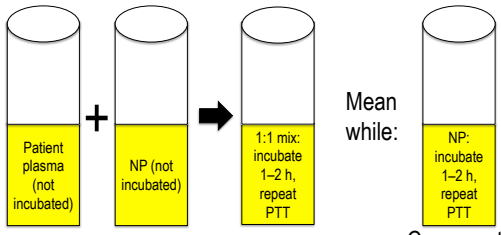
37°C Incubated 1:1 PTT Mix



PTT 42.5 s

PTT of Mix
≤38.5 s: Correction
>38.5 s: No correction

Compare to incubated PTT: 35 s

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Mixing Study Result
32-yo Female, 6 Weeks Post-partum

Assay	Result	RI	Comment
PTT	42.5 s	25–35 s	Confirms previous PTT
PTT/control 1:1 mix immediate	32.1 s		NP: 30s
PTT/control 1:1 mix 1–2 h at 37°C	37.3 s	Incubate NP: 35s	
Conclusion: both immediate *and* incubated mix PTTs correct, suspect factor deficiency, arrange for factor assays and von Willebrand disease profile			

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Factor Assay Results
32-yo Female, 6 Weeks Post-partum

Factor	Result	RI	Comment
VIII	32%	50–150%	 ?
IX	92%		
XI	131%		
XII	113%		XII, HMWK & PK deficiency not associated with bleeding
HMWK	ND	65–135%	
PK			

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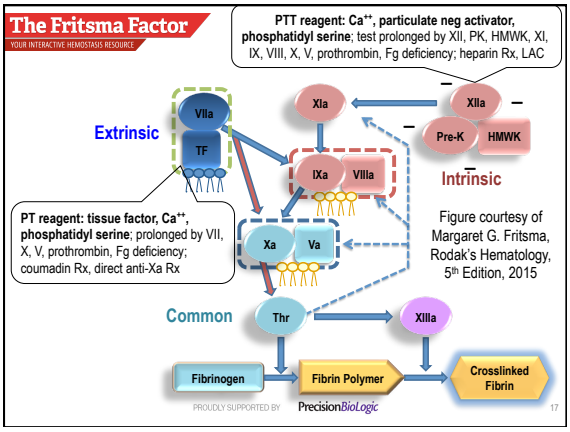

Figure courtesy of Margaret G. Fritsma, Rodak's Hematology, 5th Edition, 2015

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PT and PTT Results in Inherited Single-factor Coagulopathies

PT	PTT	Single Factor Deficiency
Long	Normal	VII
Long	Long	X, V, II, and fibrinogen[1]
Normal	Long	VIII, IX, XI[2]

[1]PT & PTT prolonged only when fibrinogen is <100 mg/dL, perform fibrinogen assay (fibrinogen assay often added to initial screen)
[2]Contact factor deficiencies XII (1–3% prevalence), prekallikrein (PK, Fletcher), or high molecular weight kininogen (HMWK, Fitzgerald) also prolong PTT results, but not associated with bleeding

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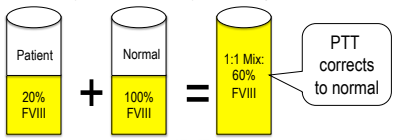
PTT Mix: Why Does This Work?

- Hypothetical 20% F VIII level prolongs PTT
  - PTT rgts are calibrated to prolong at 30–40% FVIII, IX, XI
- Add NP with established 100% factor level
  - 1:1 mix, average of 100% and 20% = 60%, PTT corrects
- Hypothetical anti-FVIII or lupus anticoagulant
  - With typical avidity, retains its ability to prolong the mix



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52-yo Athletic Female

Pre-op screen for total hip replacement

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52-yo Athletic Female
Screen Prior to Hip Replacement Surgery

Test	Result	RI
HGB	14.1 g/dL	12–15 g/dL
PT	11.2 s	9.8–12.6 s
PTT	58 s	25–35 s
PLT	170,000/μL	150–400,000/μL
Fibrinogen	410 mg/dL	220–498 mg/dL
Patient reports no bleeding or bruising, no thrombosis		

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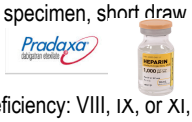
Isolated Prolonged PTT: Differential

- Could be nothing: 5% of normals exceed limit
- Preanalytical variable: green or lavender-closure tube, hemolysis, lipemia, clotted specimen, short draw
- Outpatient: dabigatran
- Inpatient: unreported UFH



- Congenital single factor deficiency: VIII, IX, or XI, hemophilia A, B, or C with bleeding; VWD
- Congenital FXII, PK, or HMWK without bleeding
- Acquired FVIII inhibitor with severe bleeding
  - Anti-factor VIII, "Acquired hemophilia"
- Lupus anticoagulant (LA)

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52-yo Female PTT Mixing Study

Test	Result	Comment
TT	17 s	RI: < 21 s, rules out dabigatran
PTT	58 s	RI: 25–35 s
PTT NP	28 s	Correction if < 30.8 s (10%)
1:1 mix	35 s	25% longer than NP = no correction
What is the next step?		

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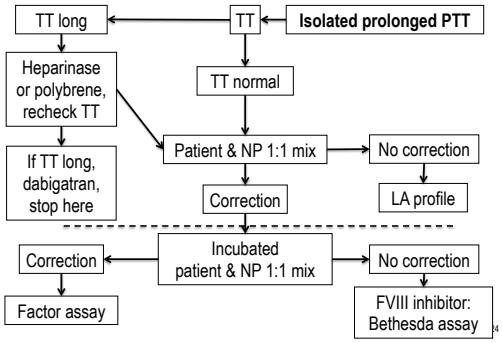
Acute Care PTT Mixing Study Algorithm



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Mixing Study Considerations

- Preanalytical variables
  - Anti-Xa rivaroxaban, apixaban, edoxaban prolong PT, PTT
  - Dabigatran and UFH prolong PT, PTT
  - Clotted, hemolyzed, lipemic specimen
  - Underfilled tube, wrong anticoagulant
  - Must be platelet-poor, <10,000/uL patient and NP
- Heparinase neutralizes ≤1 unit/mL UFH
- 15% of anti-FVIII inhibitors are detected in immediate mix
- 15% of LAs require incubation
- Weak LAs may be missed in 1:1 mix
  - Select a more LA-sensitive PTT reagent or prepare a 4:1 mix

Mostly

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The "LA Cofactor" Effect

- Initial PTT = 48 s, RI 25–35; 1:1 mix *prolongs* to 54 s
- LA binds IIa, slows clot formation, NP in mix adds IIa?
  - Or placental annexin V?

- Magrath M. Lupus cofactor phenomenon. Letter J Clin Pathol 1990,42:264.
- Rand JH, Wu XX, Andree HA, et al. Antiphospholipid antibodies accelerate plasma coagulation by inhibiting annexin-V binding to phospholipids: a "lupus procoagulant" phenomenon. Blood. 1998;92:1652–60.
- Clyne LP. Plasma requirement for expression of lupus-like anticoagulant. Folia Haematologica int Ma Klin Morphol Blutforsch 1986;113:841

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Normal Plasma Source?

- Home brew: ~pool 20 normal plasmas, male ≅ female
  - Ensure plasma is platelet-poor; < 10,000/uL; PTT ≅ mean of RI
  - Ensure NP has ~100% of all factors, especially VIII, IX, and XI
  - Elevated FVIII causes false negative results
  - Screen each for LA, specific factor inhibitors. HBV, HCV, HIV
  - Aliquot and freeze
- Or purchase commercial plasma
  - GMP & frozen meets all criteria
  - Lyophilized plasma acceptable when validated
    - Processed with stabilizers

Clinical and Laboratory Standards Institute. One-stage prothrombin time (PT) test and activated partial thromboplastin time test (APTT) approved guideline—second edition. CLSI Document H47-A2. CLSI, Wayne PA. 2008.

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What Limit Defines Correction?

No Consensus; Fritsma Factor 2015 Quick Question Answers

- Limits based on a fixed PTT value such as reference interval
  - 1:1 mix within RI upper limit (95% or 99% confidence interval, 39%)
  - 1:1 mix within RI upper limit + 5 seconds (8%)
- Limits based on the pooled normal plasma PTT value
  - 1:1 mix within NP PTT value + 5 seconds (14%)
  - 1:1 mix within NP PTT + 10% (32%)
- Rosner or Chang limit formula using patient, NP, and 1:1 mix results
  - Rosner formula produces a ratio
  - Chang's formula produces % deviation, requires incubation of patient plasma
- Other (7%): combination of RI and Rosner
  - Dedicated RI for mix

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Chang Index: Limit Based on % Correction

$$\%\ \text{Correction} = \frac{\text{Patient PTT} - \text{1:1 mix PTT}}{\text{Patient PTT} - \text{NP PTT}} \times 100$$

$$\%\ \text{Correction} = \frac{42.5 - 32.1 = 10.4}{42.5 - 30 = 12.5} = 0.83 = 83\%$$

Incubate patient plasma, NP, and mix

Factor Deficiency	=	≥ 75%
Inhibitor	=	< 75%

% Correction verified by local laboratory

Chang SH, Tillema V, Scherr D. A "percent correction" formula for evaluation of mixing studies. Am J Clin Pathol 2002;117:62–73.

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Rosner Index

$$\text{Rosner Index} = \frac{\text{1:1 mix PTT} - \text{NP PTT}}{\text{Patient PTT}} \times 100$$

$$\text{Rosner Index} = \frac{32.1 - 30}{42.5} \times 100 = 4.9$$

Inhibitor	≥ 11
Correction	< 11

Slightly more conservative than 10%

Rosner index validated by local laboratory

Rosner E, Pauzner R, Lusky A, Modan M, Many A. Detection and quantitative evaluation of lupus circulating anticoagulant activity. Thromb Haemost 1987; 57: 144-147.

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59-yo Male
Former Hockey Player

Total knee replacement preop labs

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59-yo Male Former Hockey Player
Screen Prior to Knee Replacement Surgery

Test	Result	RI
HGB	14.8 g/dL	12–15 g/dL
PT	11.2 s	9.8–12.6 s
PTT	38 s	25–35 s
PLT	310,000/μL	150–400,000/μL
Fibrinogen	390 mg/dL	220–498 mg/dL
Patient reports no bleeding or bruising, no thrombosis		

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When to Perform Mixing Study

- Any PTT > RI upper limit
- Any PTT > RI upper limit + 5 seconds
- Any PTT > RI upper limit with consult
  - Is patient bleeding or clotting?
  - Possible "weak" LA: use 4:1 mix
  - Lupus sensitive PTT reagent
  - Factor sensitive PTT reagent

Pengo V, Tripodi A, Reber F, et al. Update of the guidelines for lupus anticoagulant detection. J Thrombos Haemost 2009;7:1737–40.

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59-yo Male Former Hockey Player

Test	Result	Comment
TT	17 s	RI: < 21 s, rules out dabigatran
Anti-Xa	0.0	0.4–0.7 U/mL, r/o direct anti-Xa
PTT	38 s	RI: 25–35 s
PTT NP	31 s	Correction if < 34.1 s (10%)
1:1 mix	35 s	Correction? No correction?
What is the next step?		

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59-yo Male Former Hockey Player
Clinical Consult

- Consult: if no medical conditions go on to TKR
- Prior thrombotic events (VTE)
  - Perform mix using 4:1 patient plasma to NP
  - Or choose PTT reagent that is LA-sensitive
- If anatomic bleeding, test for FVIII, FIX, FXI
  - Vitamin K deficiency: factor VII
  - Renal insufficiency
  - Liver disease (factor V), malignancy, VWD

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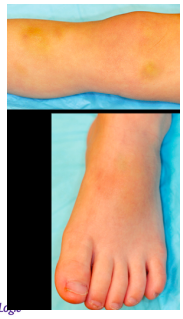
2 YO Hemophilic Boy

Bleed into knee and ankle



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2-yo Hemophilic Boy

Test	Result	RI
HGB	11.8 g/dL	9.6–15.6 g/dL
PT	11.2 s	9.8–12.6 s
PTT	65 s	25–35 s
PLT	310,000/μL	150–400,000/μL
Fibrinogen	390 mg/dL	220–498 mg/dL
Inflamed, swollen knee and ankle		

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Mixing Study Result 2-yo Hemophilic Boy

Assay	Result	RI	Comment
PTT	65 s	25–35 s	Confirms previous PTT
PTT/control 1:1 mix immediate	33.5 s	NP 30 s	Correction (ambiguous)
PTT/control 1:1 mix 1 h at 37°C	47.9 s	NP 35 s	Control is incubated alone and with mix
Conclusion: Anti-FVIII inhibitor			

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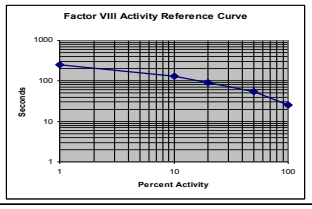
Factor VIII Assay

- Dilute plasma 1:10
- Add factor VIII-depleted reagent plasma 1:1
- Add PTT reagent, incubate 3 minutes
- Add $CaCl_2$, record interval to clot formation
- Compare result in seconds to calibration curve



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Factor VIII Assay Dilutions Parallelism Indicates No Inhibitor

Plasma Dilution	Seconds	Raw Factor VIII Activity	Computed Factor VIII Activity (× dilution)
1:10 "undiluted"	90 s	20%	20%
1:20	104 s	10%	20% (parallel)*
1:40	107 s	5%	20% (parallel)
1:80	110 s	2.5%	20% (parallel)
* <10% difference from undiluted indicates parallelism, no inhibitor			

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FVIII Assay Dilutions non-Parallelism Indicates Inhibitor

Plasma Dilution	Seconds	Raw Factor VIII Activity	Computed Factor VIII Activity (× dilution)*
1:10 "undiluted"	80 s	10%	10%
1:20	93 s	8%	16%
1:40	107 s	5%	20%
1:80	108 s	4%	32%
* >10% difference from undiluted, rising = non-parallel, implies inhibitor			

Kasper CK. Laboratory diagnosis of factor VIII inhibitors. In Kessler C, Garvey MB, Green D, Kasper C, Lusher J. Acquired Hemophilia 2nd Edition. Excerpta Medica 1995

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55-yo Male with Atrial Fibrillation

Test	Result	RI
HGB	13.8 g/dL	12–15 g/dL
PT	17.2 s	9.8–12.6 s
PTT	159 s	25–35 s
PLT	310,000/μL	150–400,000/μL
Fibrinogen	20 mg/dL	220–498 mg/dL

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55-yo Male with Atrial Fibrillation

Assay	Result	RI
PTT	159 s	25–35 s
TT	> 150 s	< 21 s
PTT/control 1:1 mix immediate	78 s	Control 30 s
PT/control 1:1 mix immediate	15.2 s	Control 12 s
What do you recommend?		

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If the PT is Prolonged

- Congenital deficiencies of II, V, VII, or X
  - PT and PTT long: II, V, X
  - PT only: VII, skip mixing and go to factor assay
  - Prevalence: 500,000–1:2,000,000
- Vitamin K deficiency: des-carboxy II, VII, and X
- Liver disease: PT prolongs before PTT due to des-carboxy II, VII, and X, reduced factor V
- Anti-Xa direct oral anticoagulants
  - Rivaroxaban, apixaban, edoxaban, betrixaban

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Isolated Prolonged PTT: Summary

- Random benign prolongation, 95% CI
- Lupus anticoagulant: prevalence of 1–3%
- Drug reaction producing transient LA
- Unrecorded heparin, dabigatran, oral anti-Xa
- Known hemophilic who fails FVIII concentrate Rx
- Hemorrhage or ecchymoses signal acquired coagulopathy; vitamin K deficiency, liver disease
- Specific inhibitor, anti-FVIII
  - Postpartum, malignancy
  - Autoimmune disorders, > 60-yo

Sahud MA. Factor VIII inhibitors. Laboratory diagnosis of inhibitors Semin Thromb Hemost 2000;26:195–203.

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Develop Mixing Study Reliability

- PTT reagent sensitivities to factors and to LA
  - Activator: ellagic acid, silica, kaolin, celite
  - 30–40% FVIII, FIX, FXI
  - Intermediate sensitivity to LA
- NP consistency: ~100% activity for all factors
- Consultation for equivocal patient results
- Employ consistent correction limit

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DIY Local Mixing Studies—Why?

- Unexpected isolated prolonged PTT or PT may require immediate therapy
- Local results may immediately direct therapy
- Delayed specimen may deteriorate
- Forward mixing study results to ref lab to direct follow-up, for instance, LA profile or Bethesda titer

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Bottom Line at the End (BLEAT)

The participant…

- Listed the clinical applications for a PTT mixing study.
- Listed the steps to perform a PTT mixing study.
- Explained why the mixing study is an acute care assay.
- Correlated mixing study results with lupus anticoagulant and specific inhibitor testing.

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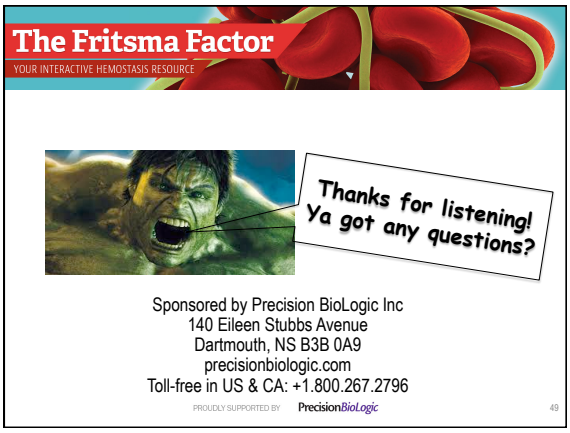
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