Antiphospholipid Syndrome

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Antiphospholipid Syndrome (APS)

- 1983 - Dr. Graham Hughes and his team in London described “sticky blood”
  - Lupus patients had a tendency to blood clots, headaches, strokes and, in pregnancy, clotting of the placenta and miscarriage
  - These patients had “antiphospholipid antibody”
  - Recognized syndrome also occurred without lupus
- Mid 1990s – renamed “Hughes Syndrome”

Entity plagued by Misnomers

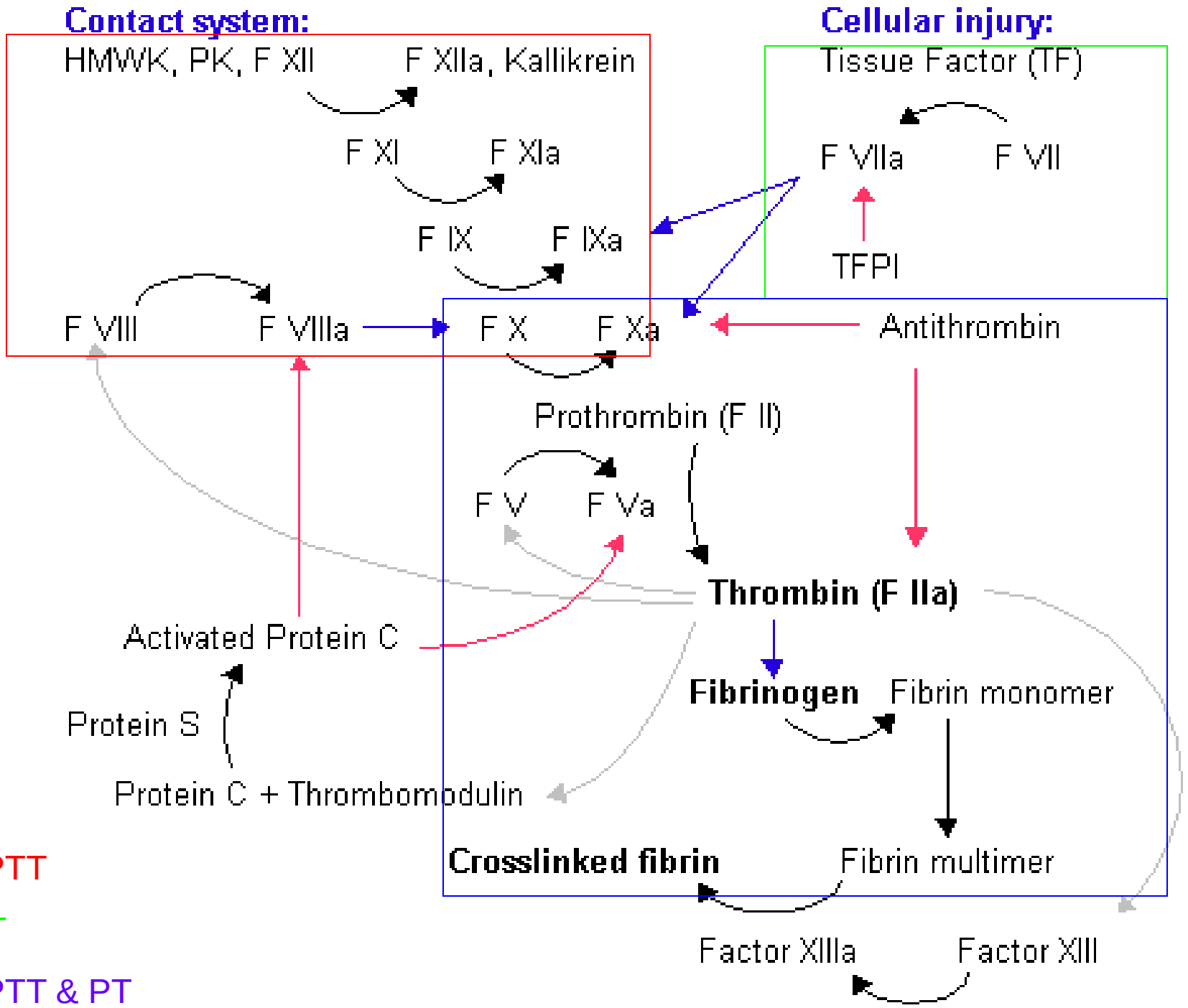
- Antiphospholipid antibodies – antigen is a protein that binds phospholipid
- Lupus anticoagulant
  - Frequently found outside the clinical spectrum of SLE
  - Prolong aPTT *in vitro,* but associated with a hypercoagulable state *in vivo*

Antiphospholipid Syndrome

- Primary APS
  - Occurs without underlying disease
- Secondary APS
  - Occurs in the setting of underlying disease
    - SLE
    - Sjögren's
    - Malignancy

Pathophysiology

- “2-hit” hypothesis
  - Preexisting or coincident vascular damage
  - Antiphospholipid antibody
    - May bind platelet phospholipids and promote coagulation
    - May bind endothelial cell phospholipids and induce cell damage
    - May interfere with protein C, protein S and/or thrombomodulin function


Contact system:
HMWK, PK, F XII
F XIIa, Kallikrein
F XI
F XIa
F IX
F IXa
F VIII
F VIIIa
F X
F Xa
Cellular injury:
Tissue Factor (TF)
F VIIa
F VII
TFPI
Antithrombin
Prothrombin (F II)
F V
F Va
Thrombin (F IIa)
Activated Protein C
Protein S
Protein C + Thrombomodulin
Fibrinogen
Fibrin monomer
Crosslinked fibrin
Fibrin multimer
Factor XIIIa
Factor XIII
aPTT
PT
aPTT & PT

Diagnostic Criteria for APS

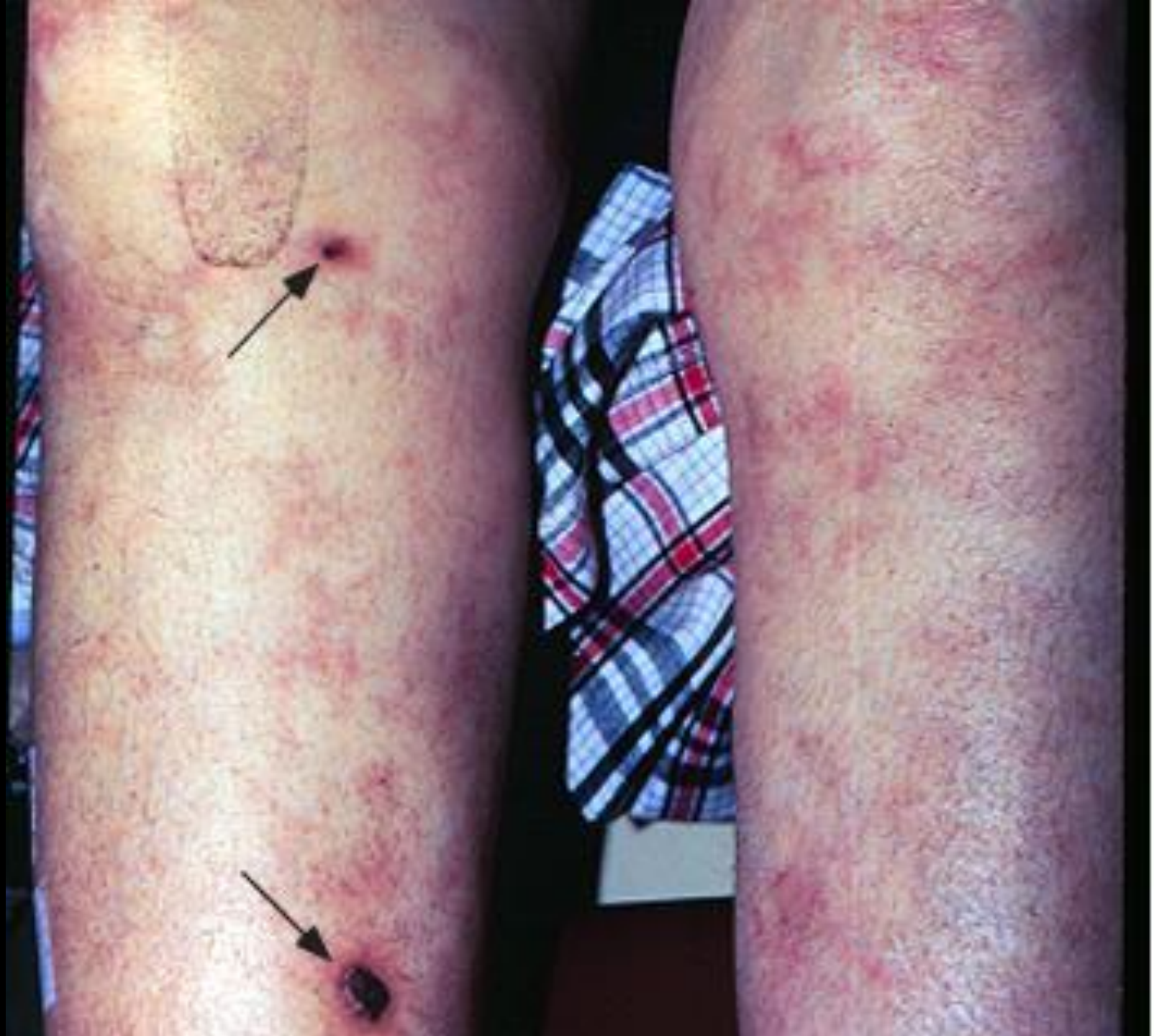
- One or more clinical criteria
- One or more laboratory criteria

Clinical Criteria

- ≥ 1 episodes of venous, arterial or small vessel thrombosis
  - Deep vein thrombosis
  - Stroke/TIA
  - Pulmonary embolism
  - Superficial thrombophlebitis
- Pregnancy morbidity
  - Unexplained death at ≥ 10 weeks gestation of morphologically normal fetus
  - ≥ 1 premature births (< 34 weeks gestation) secondary to eclampsia, preeclampsia or placental insufficiency
  - ≥ 3 pregnancy losses (<10 weeks gestation) unexplained by chromosomal, maternal anatomic or hormonal causes

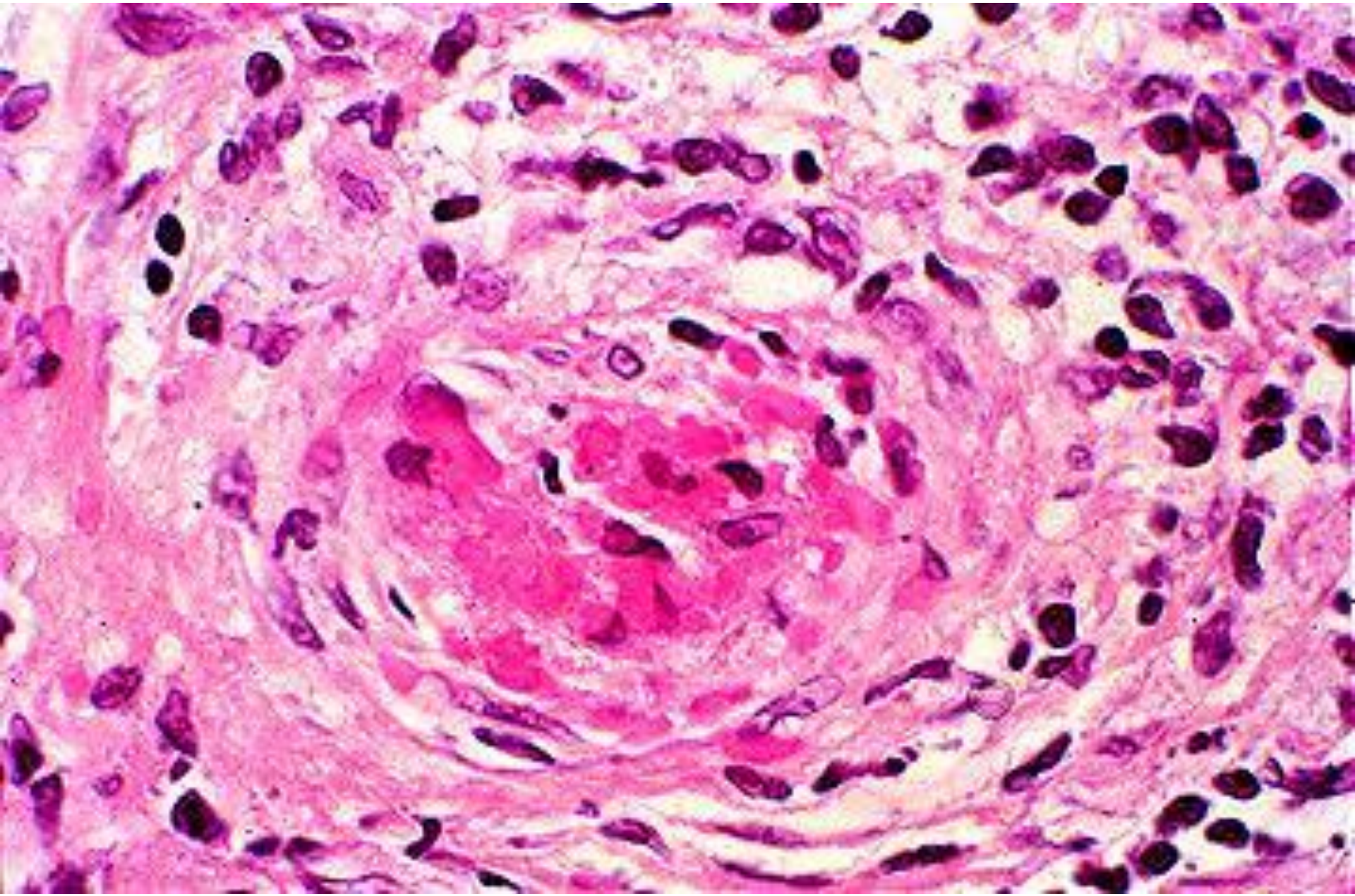
Related clinical & laboratory findings

- Migraine headache
- Raynaud phenomenon
- Thrombocytopenia (50-140K)
- Microangiopathic hemolytic anemia
- Cutaneous ulcers
- Livedo reticularis
- Adrenal insufficiency
- Pulmonary hypertension
- Avascular necrosis
- White matter lesions on MRI
- Valvular heart disease – fibrin and platelet deposits



Thromboses

- Venous > arterial
- DVT & PE
  - More frequent with lupus anticoagulant
  - Antiphospholipid antibody in 5-21% of patients
- Coronary, cerebrovascular and peripheral arterial events
  - More frequent with anticardiolipin antibodies



Catastrophic Antiphospholipid Syndrome

- Rare
- Multiorgan failure
  - Due to widespread thrombotic disease
- + DIC panel
- Frequently fatal (50% mortality)

Antiphospholipid Antibodies

- 1-15% of the general population
- 50-70% of patients with SLE
  - Frequency of APS much lower!
- Transient antibodies

Laboratory Criteria

- Antiphospholipid antibodies
  - Lupus anticoagulant
  - Anticardiolipin antibodies
  - Anti-β2 glycoprotein I antibodies
  - Two or more occasions at least 12 weeks apart
  - No more than five years prior to clinical manifestations

Lupus Anticoagulant (LA)

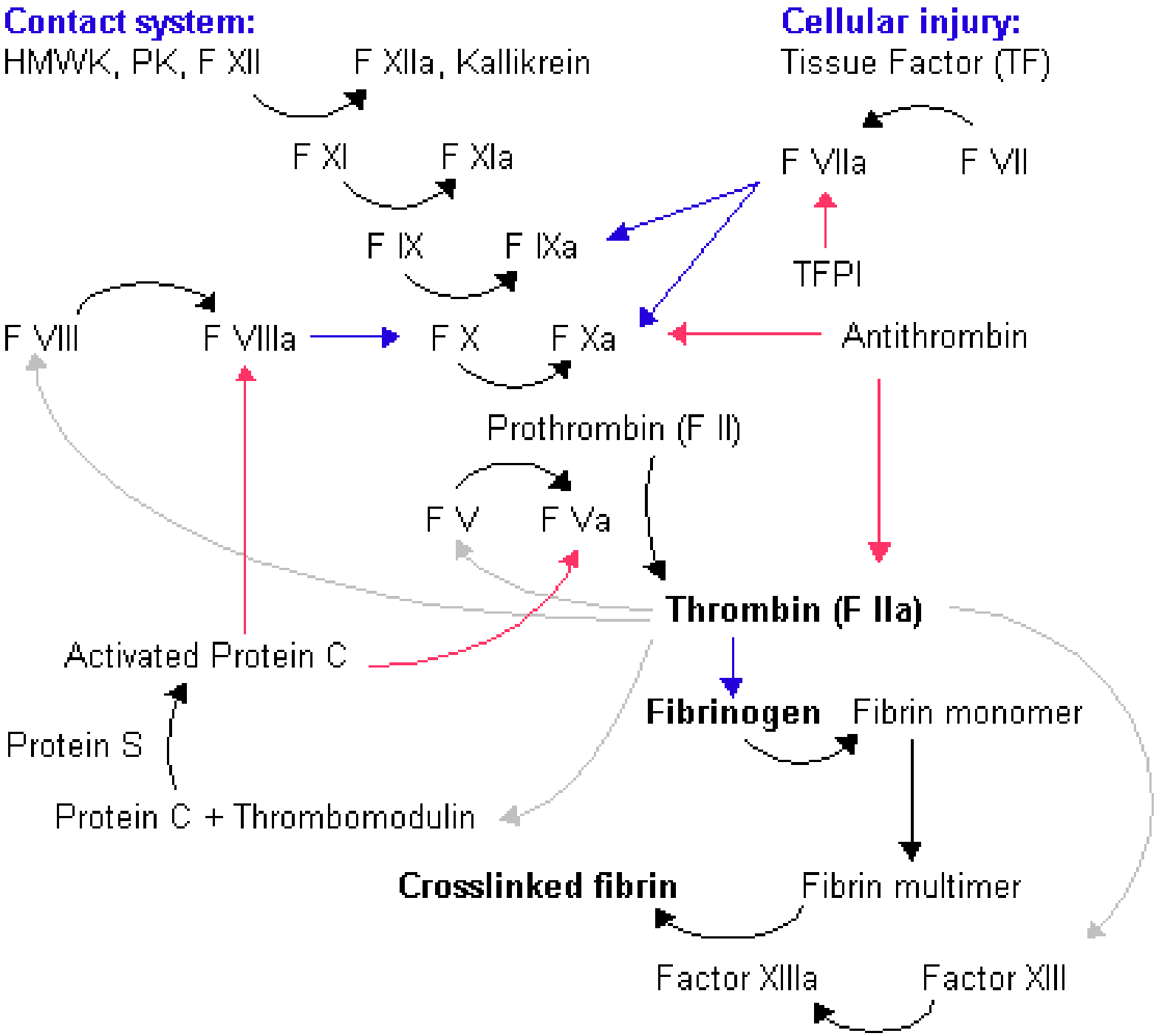
- Prolongs phospholipid dependent coagulation tests
  - Activated partial thromboplastin time (aPTT)
  - PT rarely affected – reagent contains high concentration of phospholipid
- Undefined epitopes
- 50% of patients with LA meet criteria for SLE
- Can be associated with medications – quinidine, procainamide, chlorpromazine
- With LA ~30% risk of developing APS symptoms
- Clotting assays
  - All testing performed with platelet poor plasma

Evaluation of lupus anticoagulant

- Step 1: Test for prolongation of coagulation in ≥ 1 phospholipid dependent *in vitro* coagulation assay

Laboratory Evaluation of LA

- PTT-LA
  - Reduced amount of phospholipid present
- Dilute Russell Viper Venom Time (dRVVT)
  - Russell Viper Venom directly activates factor X (common pathway)
    - Phospholipid dependent
  - More sensitive than the aPTT test
    - Not influenced by deficiencies or inhibitors of clotting factors VIII, IX or XI
    - dRVVT reagent is diluted to ensure that it has a low phospholipid concentration, increasing the sensitivity for LA
      - Patient without LA will clot in 36-42 seconds
      - Patient with LA will have prolonged clotting
  - Must use platelet poor plasma
  - Contains heparin inhibitor (Hepzyme)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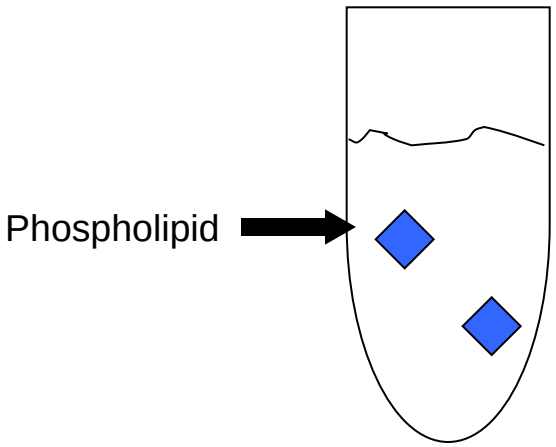
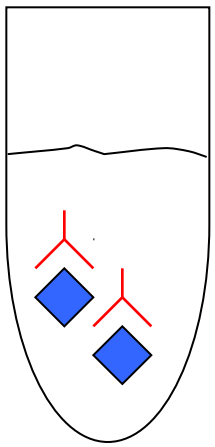
Factor XIII

Dilute Russell Viper Venom Time



Normal plasma
dRVVT 36-42 sec



Plasma with lupus anticoagulant
dRVVT > 43 sec

Evaluation of lupus anticoagulant

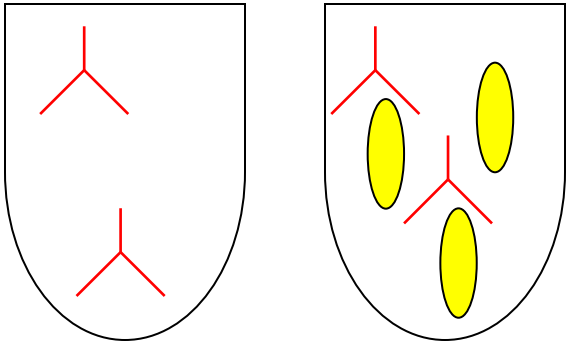
- Step 2: Mixing studies
  - Mix equal parts patient and control plasma
  - aPTT will correct if prolongation due to factor deficiencies
  - If LA present will fail to correct aPTT
    - Clotting time > 5 seconds longer than control plasma alone
    - Usually immediate acting

Evaluation of lupus anticoagulant

- Step 3: Neutralization study
  - Addition of phospholipid will neutralize lupus anticoagulant
  - Measured aPTT will become shortened
  - Platelet neutralization
    - Lysates of frozen, thawed and washed platelets
  - Hexagonal phase phospholipid neutralization

LA Confirmatory Tests

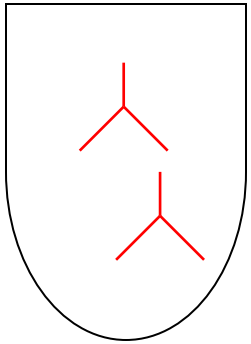
Platelet Neutralization



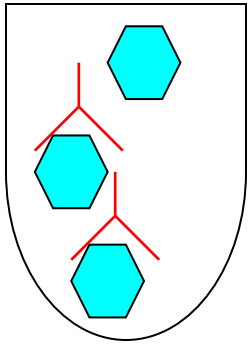
Prolonged aPTT

Shortened aPTT

Sta Clot-LA



Prolonged aPTT



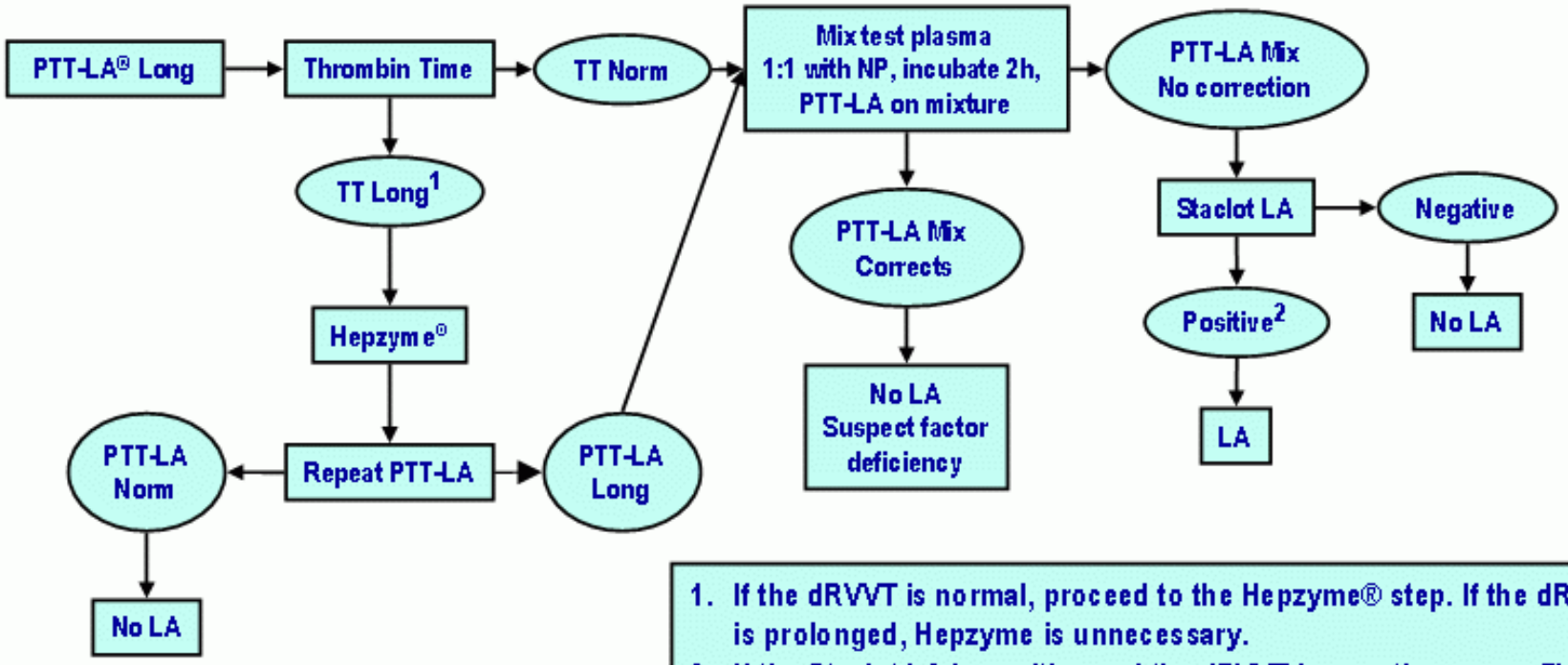
Shortened aPTT

Clotting time >8 seconds shorter after addition of PL = + for LA

Evaluation of lupus anticoagulant

- Step 4: Rule out other coagulopathies
  - Specific factor assays
    - With LA, factor activity appears to increase with increasing dilutions of plasma
      - Diluting lupus anticoagulant

Lupus Anticoagulant Flow Chart
Lupus Anticoagulant-Sensitive Partial Thromboplastin Time (PTT-LA®) and StaClot LA®



1. If the dRVVT is normal, proceed to the Hepzyme® step. If the dRVVT is prolonged, Hepzyme is unnecessary.
2. If the Staclot LA is positive and the dRVVT is negative, assay FVIII to determine if the positive Staclot LA is due to a FVIII inhibitor.

Anticardiolipin antibodies

- May occur with infections or medications
  - These are rarely of clinical significance
- May be B2-glycoprotein I dependent
  - Usually those found in autoimmune disease
  - Not those antibodies formed secondary to infection
- May behave like a lupus anticoagulant in *in vitro* testing
- Alone, may not be a risk factor for thrombosis
- Presence is a risk factor for recurrence of thromboembolic events
- Measure via ELISA
  - IgG, IgM or IgA
  - + if medium/high titer
    - >40 GPL or MPL or >99th percentile

B2-Glycoprotein I Antibodies

- Most common target of APA
- Found in patients with APS and positive anticardiolipin antibodies
  - Without anti-β2-GP-I may not have increased clotting risk
  - Not present with antibodies formed secondary to infection

Other Antibodies

- Anti-prothrombin
- Anti-annexin V
- Anti-phosphatidylserine
- Anti-phosphatidylinositol
- Associated with APS
  - Clinical role poorly understood

Thrombotic Risk

- In patients with APS:
  - Thrombosis rate ~2.4%/year
  - Thrombosis risk ↑ 6-10X
  - 10-15%/year recurrence rate without anticoagulation therapy
  - In secondary APS, ongoing vasculitis = continual risk for thrombosis

Venereal Disease Research Laboratory (VDRL)

- Serologic test for syphilis
- Measures agglutination of lipid particles containing cholesterol and cardiolipin
  - Antiphospholipid antibodies may bind and cause agglutination → False + VDRL
  - Occurs in ½ of patients with APS

Treatment

- After venous thrombosis:
  - Heparin followed by Coumadin
    - Highest risk of recurrence in first 6-12 months
- After arterial thrombosis:
  - Aspirin +/- coumadin
- Secondary APS:
  - Aspirin, hydroxychloroquine, pentoxifylline, coumadin or LMW Heparin
- Catastrophic APS:
  - Aspirin, coumadin, corticosteroids, plasmapheresis, IVIG
- Pregnancy
  - Aspirin +/- prednisone

References

- Henry's Clinical Diagnosis and Management by Laboratory Methods
- Uptodate.com
- Garcia DA, et al. How we diagnose and treat thrombotic manifestations of the antiphospholipid syndrome: A case-based review. Blood. Online July 20, 2007
- Giannakopoulos B, et al. Current concepts on the pathogenesis of the antiphospholipid syndrome. Blood; 15 Jan 2007 (109)2; 422-30.
- Galli M, et al. Lupus anticoagulants are stronger risk factors for thrombosis than anticardiolipin antibodies in the antiphospholipid syndrome: a systematic review of the literature. Blood; 1 March 2003 (101)5; 1827-32.