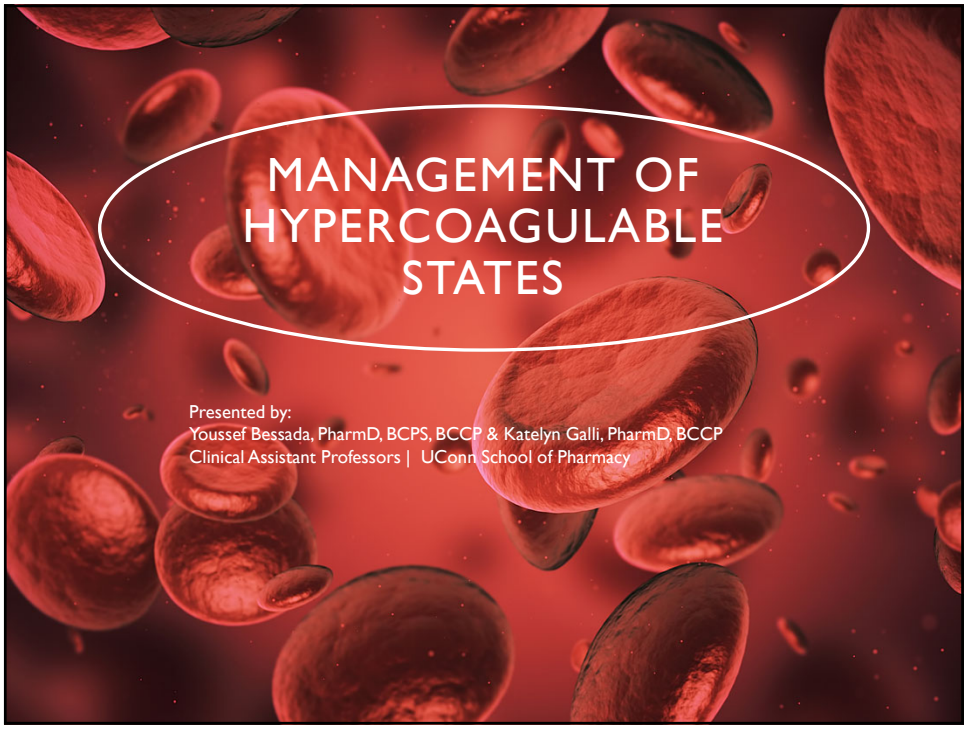


1

Dr. Bessada and Dr. Galli have no conflict of interest associated with this presentation

FACULTY DISCLOSURE

2

LEARNING OBJECTIVES

At the conclusion of this activity, pharmacists will be able to:

1. Describe inherited hypercoagulable states
2. Describe acquired hypercoagulable states
3. Apply management strategies for various hypercoagulable states including:
   - Anithrombin III Deficiency
   - Protein C or S Deficiency
   - Factor V Leiden
   - Prothrombin gene mutation
   - Hyperhomocysteinemia
   - Antiphospholipid Antibody Syndrome

3

CASE STUDY

GV is a 35 year-old female recovering from a new PE.

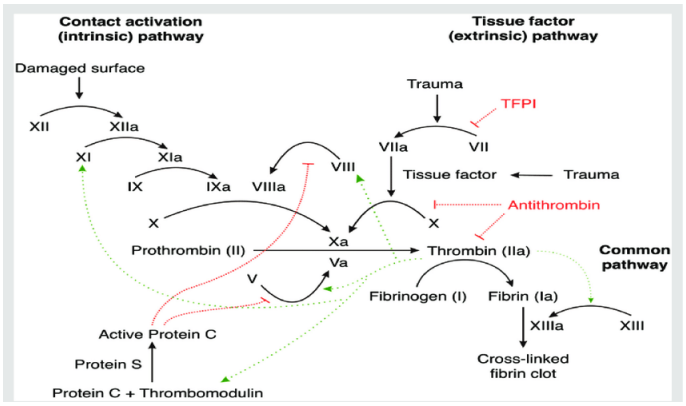
She is currently being treated with apixaban 5 mg PO BID after completing 7 days of 10 mg PO BID.

PMH: Not pertinent

SH: Full time accountant, social alcohol use, negative tobacco

FH: Mother and father healthy

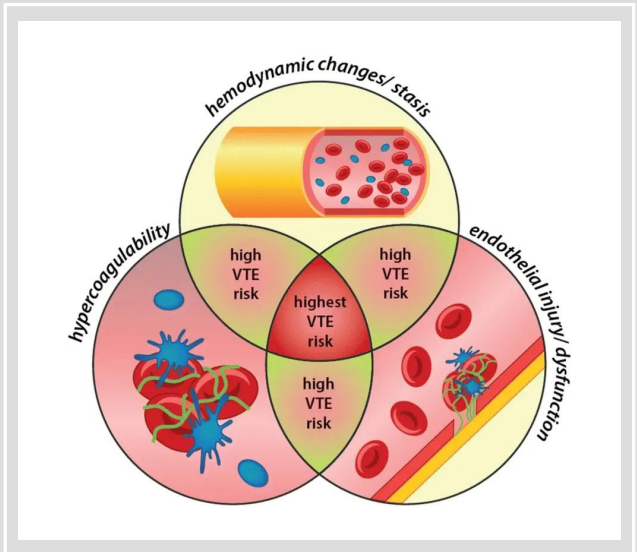
4



COAGULATION CASCADE

https://www.researchgate.net/publication/334593905/figure/fig2/AS:782905202720768@1563670554849/Coagulation-cascade-showing-Intrinsic-Extrinsic-and-Common-Pathways-Image-from.png

5



PATHOPHYSIOLOGY

https://0.wp.com/pathosomes.com/wp-content/uploads/2022/03/Virchows-Triad.png

6

HEREDITARY THROMBOPHILIA

- Genetic tendency to develop venous thromboembolism (VTE)
- 24-37% patients with VTE
- Most common causes
  - Factor V Leiden mutation
  - Prothrombin G20210A mutation
- Other:
  - Antithrombin III (ATIII) deficiency
  - Protein C/S deficiency
  - Hyperhomocysteinemia

7

WHICH OF THE FOLLOWING FACTORS WOULD MORE LIKELY INDICATE AN INHERITED THROMBOPHILIA IN GV? (OBJECTIVE #1)

A. A relative with a known clotting disorder
B. Active combination oral contraception use
C. Recent travel overseas on a long flight

8

WHICH OF THE FOLLOWING FACTORS WOULD MORE LIKELY INDICATE AN INHERITED THROMBOPHILIA IN GV? (OBJECTIVE #1)

A. **A relative with a known clotting disorder**
B. Active combination oral contraception use
C. Recent travel overseas on a long flight

9

ACQUIRED (SECONDARY) HYPERCOAGULABLE STATES

- Antiphospholipid antibody syndrome (APS)
- Cancer and myeloproliferative disorders
- Medications (e.g. antineoplastics, oral contraception, hormone replacement therapy)
- Recent trauma or surgery
- Prolonged immobility
- Smoking
- Pregnancy
- Autoimmune and inflammatory disorders

10

WHICH OF THE FOLLOWING CONDITIONS IS MORE LIKELY TO BE AN ACQUIRED FORM OF THROMBOPHILIA? (OBJECTIVE #2)

A. Antiphospholipid antibody
B. Factor V Leiden
C. Prothrombin gene mutation

11

WHICH OF THE FOLLOWING CONDITIONS IS MORE LIKELY TO BE AN ACQUIRED FORM OF THROMBOPHILIA? (OBJECTIVE #2)

A. Antiphospholipid antibody
B. Factor V Leiden
C. Prothrombin gene mutation

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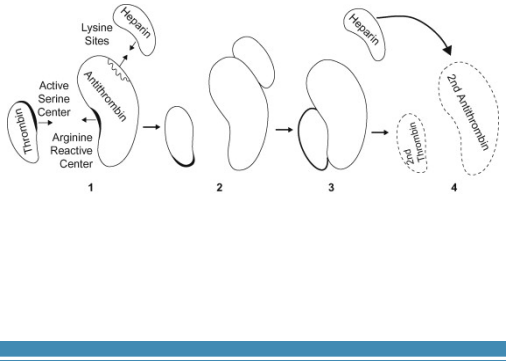
ANTITHROMBIN III (ATIII)

- Glycoprotein produced in the liver
- Half life: 2.8-4.8 days
- Inactivates clotting factors
- Action enhanced by heparin



https://www-sciencedirect-com.ezproxy-lib.uconn.edu/topics/neuroscience/antithrombin-iii

13

INHERITED AT III DEFICIENCY

- Prevalence in VTE population: 2.2%
- Autosomal dominant mutation
  - Homozygous = incompatible with life
  - Heretozygous = RR for VTE recurrence: 2.01
- Age at presentation varies

Middeldorp S, et al. Blood Adv. 2023;7(22):7101-7138.

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ACQUIRED AT III DEFICIENCY

Impaired production	• Liver disease • Vitamin K antagonism • Pregnancy • ECMO
Increased excretion	• Nephrotic syndrome • Heparin therapy • Hemodialysis • ECMO
Accelerated consumption	• Disseminated intravascular coagulation • Pregnancy • ECMO

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CONSEQUENCES OF AT III DEFICIENCY

- Increased risk of VTE
  - Common Sites: DVT of leg, iliofemoral and mesenteric veins
  - Arterial thrombosis not characteristic
  - Pregnancy complications
- Heparin insensitivity
  - AT III required to inactive FXA

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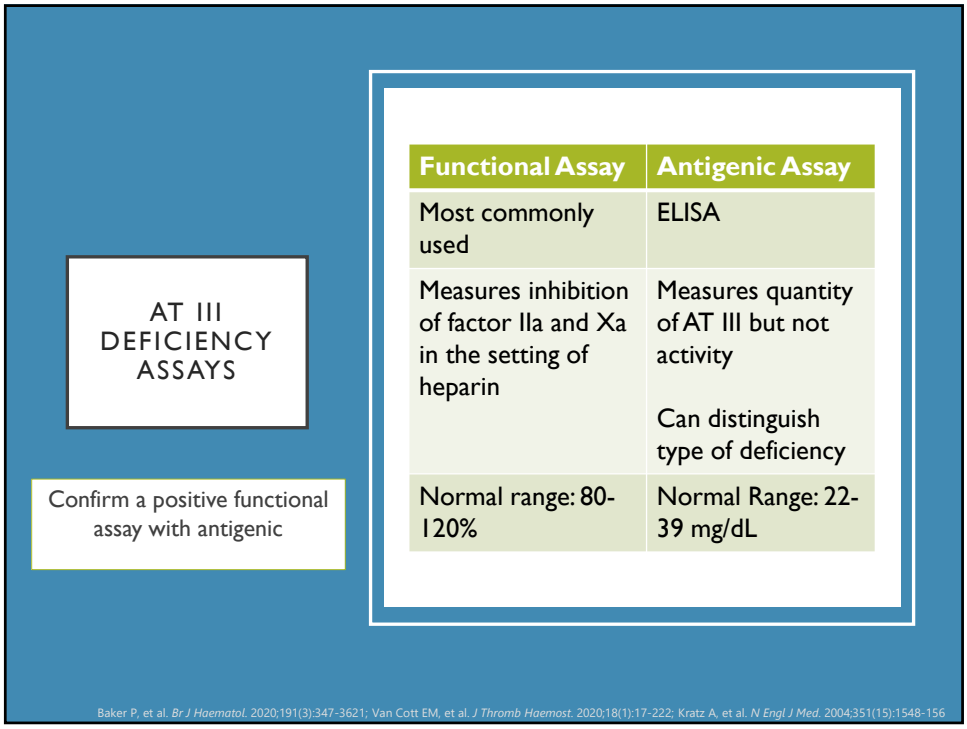
DIAGNOSIS OF AT III DEFICIENCY
Differential diagnosis
Laboratory testing
Suspected inherited thrombophilia based on family history or atypical presentation
Women with a family history of VTE and thrombophilia considering oral contraception or HRT and ante-or post-partum
Suspected heparin resistance
Asparaginase therapy or extracorporeal membrane oxygenation
Do not perform:
During acute thrombosis/illness
Active heparin therapy
Active warfarin therapy
Middeldorp S, et al. Blood Adv. 2023;7(22):7101-7138.

17


AT III DEFICIENCY ASSAYS
Confirm a positive functional assay with antigenic
Functional Assay
Antigenic Assay
Most commonly used
ELISA
Measures inhibition of factor IIa and Xa in the setting of heparin
Measures quantity of AT III but not activity
Can distinguish type of deficiency
Normal range: 80-120%
Normal Range: 22-39 mg/dL
Baker P, et al. Br J Haematol. 2020;191(3):347-3621; Van Cott EM, et al. J Thromb Haemost. 2020;18(1):17-222; Kratz A, et al. N Engl J Med. 2004;351(15):1548-156

18

CASE STUDY

- GV undergoes thorough thrombophilia testing, including a functional assay for antithrombin III deficiency. Her results are 93%.

19

WHICH OF THE FOLLOWING ARE THE MOST APPROPRIATE NEXT STEPS FOLLOWING A 'NORMAL' FUNCTIONAL ASSAY FOR ATIII DEFICIENCY? (OBJECTIVE #3)

A. Administer vitamin K PO 5mg once and discontinue anticoagulation
B. Confirm functional assay results with an antigenic assay
C. Continue anticoagulation and consider alternative diagnosis

20

WHICH OF THE FOLLOWING ARE THE MOST APPROPRIATE NEXT STEPS FOLLOWING A 'NORMAL' FUNCTIONAL ASSAY FOR ATIII DEFICIENCY? (OBJECTIVE #3)

A. Administer vitamin K PO 5mg once and discontinue anticoagulation

B. Confirm functional assay results with an antigenic assay

C. **Continue anticoagulation and consider alternative diagnosis**

21

AT III DEFICIENCY MANAGEMENT

Avoidance of potentially reversible risk factors (e.g. hormonal therapies)

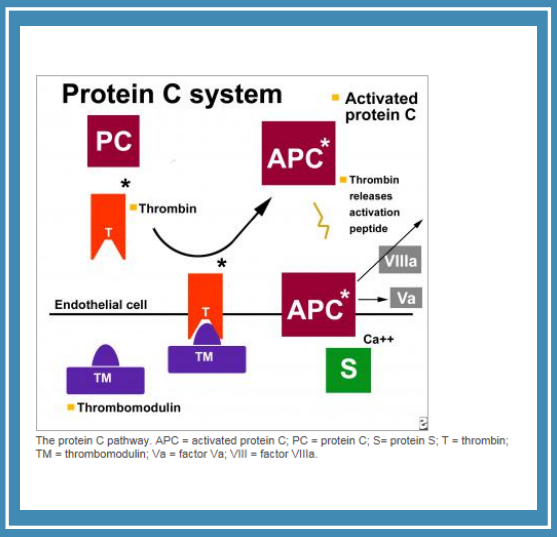
Thromboprophylaxis in high-risk situations

Patients with thrombosis

- Anticoagulation with either warfarin or direct oral anticoagulants (DOACs)
- AT replacement ***may*** be warranted in the acute setting for patients hospitalized with acute thrombosis and nonresponsive to heparin
  - Dosing dependent on product
  - Baseline AT level and body weight dependent

Bauer KA, Nguyen-Cao TM, Spears JB. Ann Pharmacother. 2016 Sep;50(9):758-67; Bravo-Pérez C, Vicente V, Corral J. Expert Rev Hematol. 2019 Jun;12(6):397-405.

22



The protein C pathway. APC = activated protein C; PC = protein C; S= protein S; T = thrombin; TM = thrombomodulin; Va = factor Va; VIII = factor VIIIa.

PROTEIN C & S PHYSIOLOGY

- Activated by thrombin bound to endothelial thrombomodulin to activated protein C (aPC)
- aPC inactivates factors Va & VIIIa
- The inhibitory effect enhanced by protein S

https://img.medscapestatic.com/pi/meds/ckb/69/36669tn.jpg

23

Inherited	Acquired

• Due to protein C gene mutations
• Type I - Quantitative deficiency
  • protein C concentration 50% of normal in antigen and activity levels
  • More common
• Type II deficiency- Functional deficiency
  • normal plasma protein C antigen levels with decreased functional activity due to point mutations
	• Liver disease
	• Severe infection
	• Septic shock
	• Disseminated intravascular coagulation
	• Acute respiratory distress syndrome
	• Surgery
	• Pharmacotherapy (e.g. chemotherapy, L-asparaginase)

PROTEIN C DEFICIENCY ETIOLOGY

Goldenberg NA, Manco-Johnson MJ. *Haemophilia.* 2008;14(6):1214-21.

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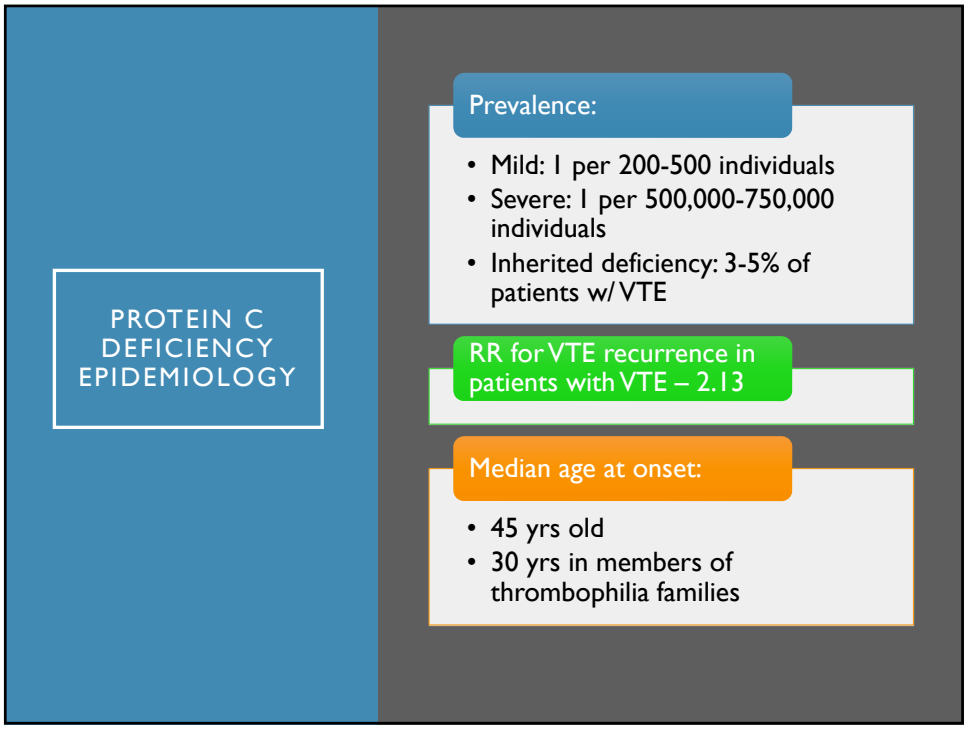

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PROTEIN S DEFICIENCY ETIOLOGY

Inherited	Acquired

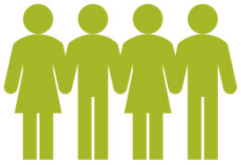
• Caused by mutations in the PROS1 gene
• 3 phenotypes
• Type I-Quantitative defect
  • 50% of normal S antigen level
  • Reductions in free protein S antigen and functional activity
• Type II-Qualitative defect
  • Normal total and free levels
  • Diminished functional activity
• Type III
  • Normal antigen levels
  • Selectively reduced levels of free protein S and functional activity to <40% of normal
	• Pregnancy
	• Pharmacotherapy (Oral contraceptives, L-asparaginase chemotherapy)
	• Disseminated intravascular coagulation
	• Acute thromboembolic disease
	• Liver disease
	• Nephrotic syndrome
	• HIV infection

Goldenberg NA, Manco-Johnson MJ. *Haemophilia*. 2008;14(6):1214-21.

26

PROTEIN S DEFICIENCY EPIDEMIOLOGY

- Incidence
  - 10% families with inherited thrombophilia
  - Prevalence 2.3% among consecutive patients with 1st VTE
  - 0.03 - 0.13% general population
- Inheritance of protein S is autosomal dominant
  - Homozygous = incompatible with life
  - Heterozygous = RR for VTE recurrence: 1.3
- Mean age at presentation 28 yrs old



Middeldorp S, et al. Blood Adv. 2023;7(22):7101-7138

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WHICH OF THE FOLLOWING PHARMACOTHERAPY IS ASSOCIATED WITH ACQUIRED PROTEIN S DEFICIENCY? (OBJECTIVE #2)

A. Oral contraceptives
B. Unfractionated heparin
C. Vitamin K

28

WHICH OF THE FOLLOWING PHARMACOTHERAPY IS ASSOCIATED WITH ACQUIRED PROTEIN S DEFICIENCY? (OBJECTIVE #2)

A. **Oral contraceptives**
B. Unfractionated heparin
C. Vitamin K

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PROTEIN C AND S DEFICIENCY PRESENTATION

- Venous thromboembolism (VTE)
- Neonatal purpura fulminans or fetal loss
- Warfarin-induced skin necrosis in adults

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PROTEIN C & S DEFICIENCY: VTE

7-8.5x increased risk

Initial episode

- 70% spontaneous
- 30% concomitant risk factors (eg, pregnancy, oral contraceptives, surgery, or trauma)

Most common presentation

- Axillary
- Mesenteric
- Cerebral venous thrombosis
- Arterial thrombosis not common

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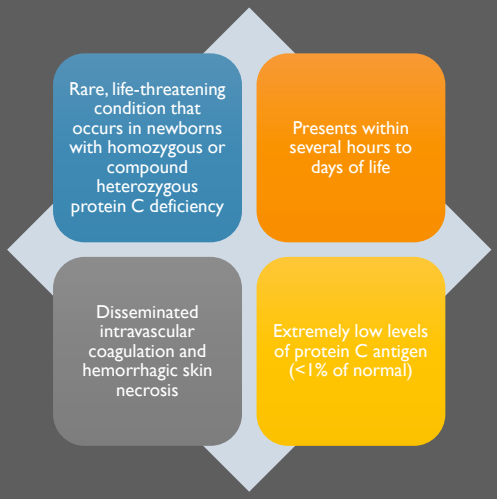
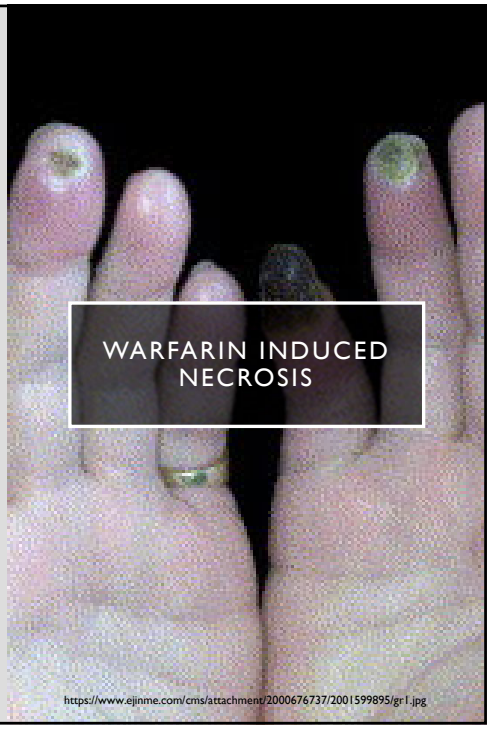
NEONATAL PURPURA FULMINANS



32

- Associated with large loading doses of warfarin
- Occurs within first several days of warfarin therapy]
  - Protein C activity decreases ~50% within 1 day
  - Increased thrombin generation at initiation
- Diffuse microthrombi within dermal and subcutaneous capillaries, venules, and deep veins
- Endothelial cell damage results in ischemic skin necrosis and extravasation
- Skin lesions occur on extremities, breasts, trunk, and male genitalia
- Rapid reversal necessary



33

DIAGNOSIS OF PROTEIN C DEFICIENCY

- Differential diagnosis
- Methodologies for measurement of protein C differ among laboratories
  - Protein C antigen levels in adults range from 70-140%
    - < 55%: Genetic abnormality
    - 55-65%: Indeterminate
  - Full term infants: 20-40% adult levels
  - Use age-based norms for the specific laboratory performing the test in neonates
- Timing
  - Avoid during acute thrombosis/illness
  - Wait 2 weeks after discontinuing warfarin
  - Heparin does not alter Protein C levels

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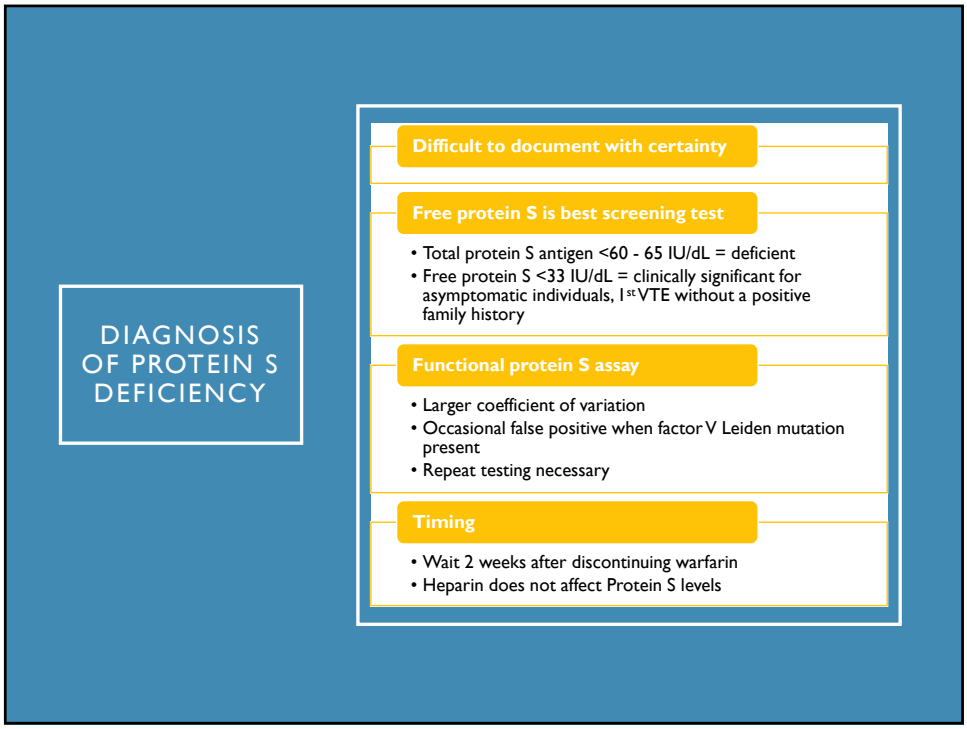
DIAGNOSIS OF PROTEIN S DEFICIENCY
Difficult to document with certainty
Free protein S is best screening test
• Total protein S antigen <60 - 65 IU/dL = deficient
• Free protein S <33 IU/dL = clinically significant for asymptomatic individuals, 1st VTE without a positive family history
Functional protein S assay
• Larger coefficient of variation
• Occasional false positive when factor V Leiden mutation present
• Repeat testing necessary
Timing
• Wait 2 weeks after discontinuing warfarin
• Heparin does not affect Protein S levels

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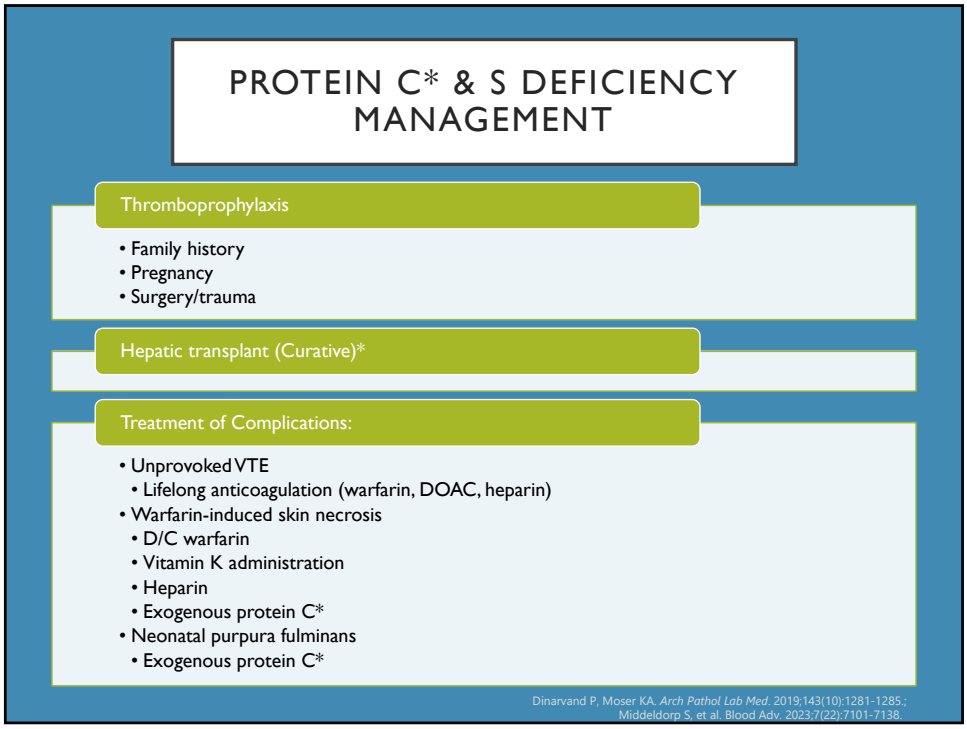
PROTEIN C* & S DEFICIENCY MANAGEMENT
Thromboprophylaxis
• Family history
• Pregnancy
• Surgery/trauma
Hepatic transplant (Curative)*
Treatment of Complications:
• Unprovoked VTE
• Lifelong anticoagulation (warfarin, DOAC, heparin)
• Warfarin-induced skin necrosis
• D/C warfarin
• Vitamin K administration
• Heparin
• Exogenous protein C*
• Neonatal purpura fulminans
• Exogenous protein C*
Dinarvand P, Moser KA. Arch Pathol Lab Med. 2019;143(10):1281-1285.; Middeldorp S, et al. Blood Adv. 2023;7(22):7101-7138.

36

A PATIENT DEVELOPS MICROTHROMBI IN EXTREMITIES TWO DAYS AFTER STARTING WARFARIN 10 MG FOR 2 DOSES. HIS INR IS 1.8. WHICH OF THE FOLLOWING IS THE MOST APPROPRIATE INITIAL MANAGEMENT? (OBJECTIVE #3)

A. Bridge warfarin with apixaban 5 mg
B. Vitamin K administration
C. Warfarin10 mg again to hit goal INR

37

A PATIENT DEVELOPS MICROTHROMBI IN EXTREMITIES TWO DAYS AFTER STARTING WARFARIN 10 MG FOR 2 DOSES. HIS INR IS 1.8. WHICH OF THE FOLLOWING IS THE MOST APPROPRIATE INITIAL MANAGEMENT? (OBJECTIVE #3)

A. Bridge warfarin with apixaban 5 mg
B. Vitamin K administration
C. Warfarin10 mg again to hit goal INR

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PROTHROMBIN GENE MUTATION

- Prothrombin (Factor II) = precursor of thrombin
- Vitamin K-dependent protein synthesized in liver
- Half-life ~3-5 days
- Prothrombin G20210A - human prothrombin gene
  - Guanine to adenine substitution at nucleotide 20210
  - Heterozygous carriers have 30% higher plasma prothrombin levels

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PROTHROMBIN GENE MUTATION EPIDEMIOLOGY

- 2nd most common hereditary thrombophilia
- 2-4% Caucasian population
  - More common in European ancestry
  - 0.7-6.5% of Caucasians heterozygous for the allele
  - RR for first VTE in individuals with family history: 2.35
- 0.4% African American population

https://www.stoptheclot.org/learn_more/prothrombin-g20210a-factor-ii-mutation/lots; Middeldorp S, et al. Blood Adv. 2023;7(22):7101-7138

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PROTHROMBIN GENE MUTATION CONSEQUENCES

VTE

- Increased risk of cerebral vein thrombosis in patients using oral contraceptives
- 2.8-fold increased risk for first episode DVT in both sexes and all age groups
- Unclear risk of recurrence
- Increased risk of VTE in pregnancy

Arterial thrombosis

- Not a risk factor for ischemic disease in older patients
- Possible increased risk in younger patients

https://my.clevelandclinic.org/health/diseases/21810-prothrombin-gene-mutation#)

41

PROTHROMBIN GENE MUTATION DIAGNOSIS & MANAGEMENT

Diagnosis

- Polymerase chain reaction

Treatment

- Thromboprophylaxis
  - Pregnancy
  - Surgery
  - Trauma
- Chronic anticoagulation
  - Vitamin K antagonists
  - DOACs

https://www.healthline.com/health/prothrombin-gene-mutation#takeaway;
Arora P, Palkimas S, Talamo L, Maitland HS. *Blood*. 2017;130(Suppl 1):3724.

42

A PATIENT SCREENS POSITIVE FOR PROTHROMBIN GENE MUTATION, BUT HAS NO SIGNS OF ACTIVE THROMBOSIS. WHAT IS THE BEST TREATMENT PLAN? (OBJECTIVE #3)

A. Begin chronic oral anticoagulation with a DOAC to prevent future thrombotic events

B. Consider prophylactic doses of anticoagulation should the patient ever have surgery

C. Start warfarin therapy with a goal INR of 2.5-3.5 given increased risk of VTE

43

A PATIENT SCREENS POSITIVE FOR PROTHROMBIN GENE MUTATION, THOUGH HAS NO SIGNS OF ACTIVE THROMBOSIS. WHAT IS THE BEST TREATMENT PLAN? (OBJECTIVE #3)

A. Begin chronic oral anticoagulation with a DOAC to prevent future thrombotic events

B. Consider prophylactic doses of anticoagulation should the patient ever have surgery

C. Start warfarin therapy with a goal INR of 2.5-3.5 given increased risk of VTE

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FACTOR V LEIDEN

- Circulates in plasma in inactive form
- Thrombin activates factor V by proteolysis
- Factor Va serves as a cofactor in the prothrombinase complex → cleaves prothrombin to generate more thrombin
- Single point mutation in factor V of arginine at position 506 to glutamine
  - Abolishes cleavage site of activated protein C (APC)
  - Factor V resistant to APC inactivation
    - Accounts for >95% of cases of protein C resistance

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ACQUIRED CAUSES OF APC RESISTANCE

- Elevated factor VIII levels
- Estrogen
  - Oral contraceptives
  - Hormone Replacement Therapy
  - Pregnancy
- Cancer
- Antiphospholipid antibodies
- Protein S deficiency
- Proteinuria
- High BMI
- Smoking

46

FACTOR V LEIDEN EPIDEMIOLOGY

- Most common hereditary defect in Caucasians
  - Accounts for 40-50% of cases
  - Occurs in 5% of general population
  - Occurs in 19% of patients with 1st DVT
- 3.5-fold increased risk of VTE
- RR for first VTE in individuals with a family history: 2.71
- Increased risk of thrombosis
  - Homozygous (~1.5%)
  - Pseudohomozygote state
  - Presence of a 2nd hererditary defect
- Heterozygotes account for approximately 17.5% of patients with factor V Leiden mutation

Middeldorp S, et al. Blood Adv. 2023;7(22):7101-7138; Favaloro EJ, Lippi G. *Hemostasis and Thrombosis: Methods and Protocols*. New York, NY: Humana Press: Springer Nature; 2017.

47

FACTOR V LEIDEN CONSEQUENCES

~ 5% heterozygotes will experience VTE in lifetime

- Risk increases with age
- Major manifestation DVT±, PE (large proximal iliofemoral vein)
- Also risk factor for: isolated PE, cerebral, mesenteric, portal vein thrombosis and superficial vein thrombosis
- Risk of recurrent DVT

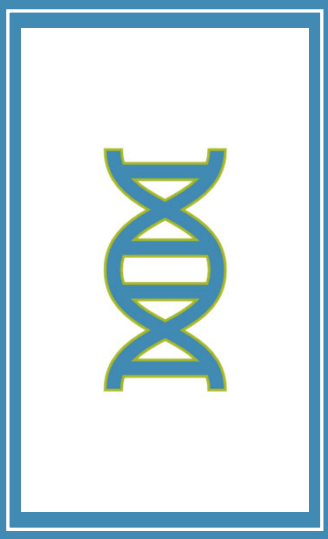
Does not increase overall mortality

Arterial thrombosis-weak or no association

Unexplained recurrent late pregnancy loss

- Possibly due to thrombosis of placental vessels

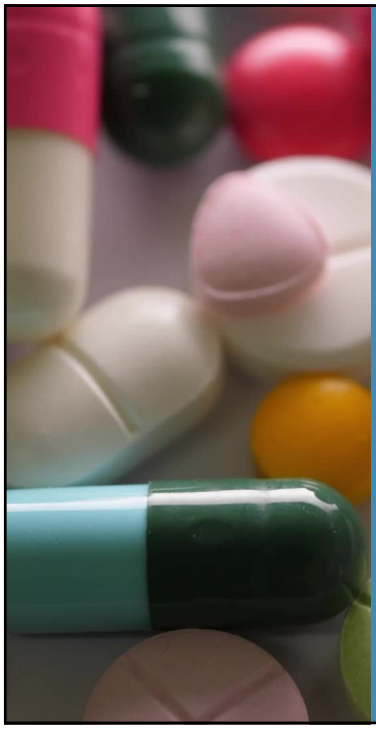
48



FACTOR V LEIDEN DIAGNOSIS

- Not routinely recommended to guide thromboprophylaxis in patients with a family history
- Genetic testing: assay DNA sequence to determine heterozygous vs homozygous mutation
- Functional APC resistance assay
  - 1st generation: not sensitive/specific for factor V leiden mutation
  - 2nd generation: correlate well with presence of mutation
    - Less costly than genetic test
    - False normal results
      - Presence of Lupus anticoagulant
      - Therapy with DTI or FXA inhibitor
  - Abnormal results confirmed by genotyping

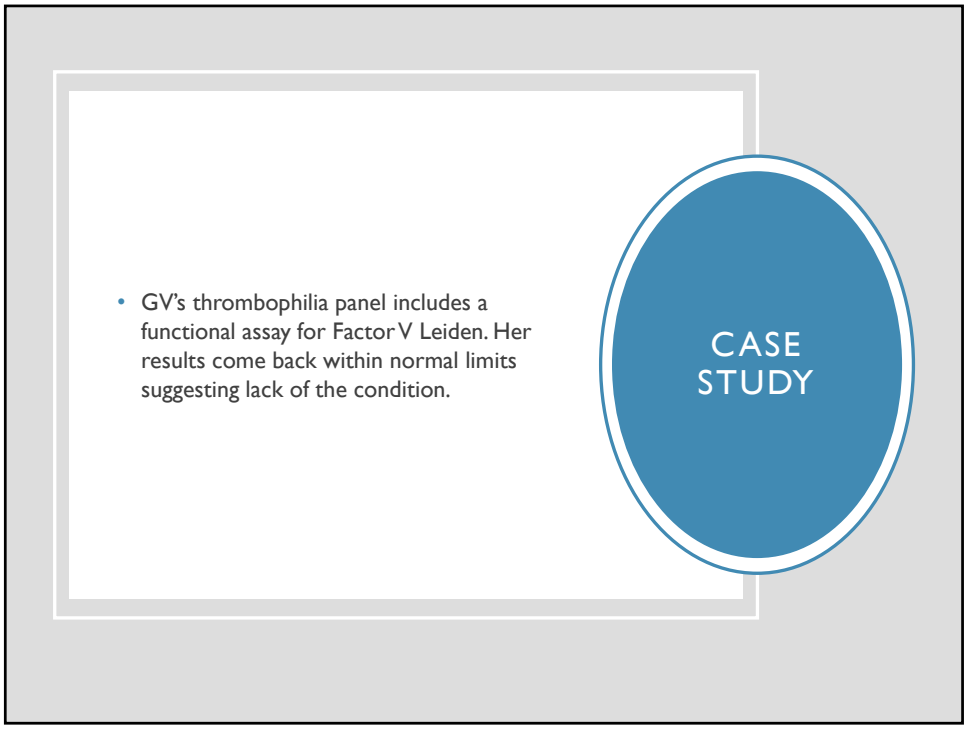
49



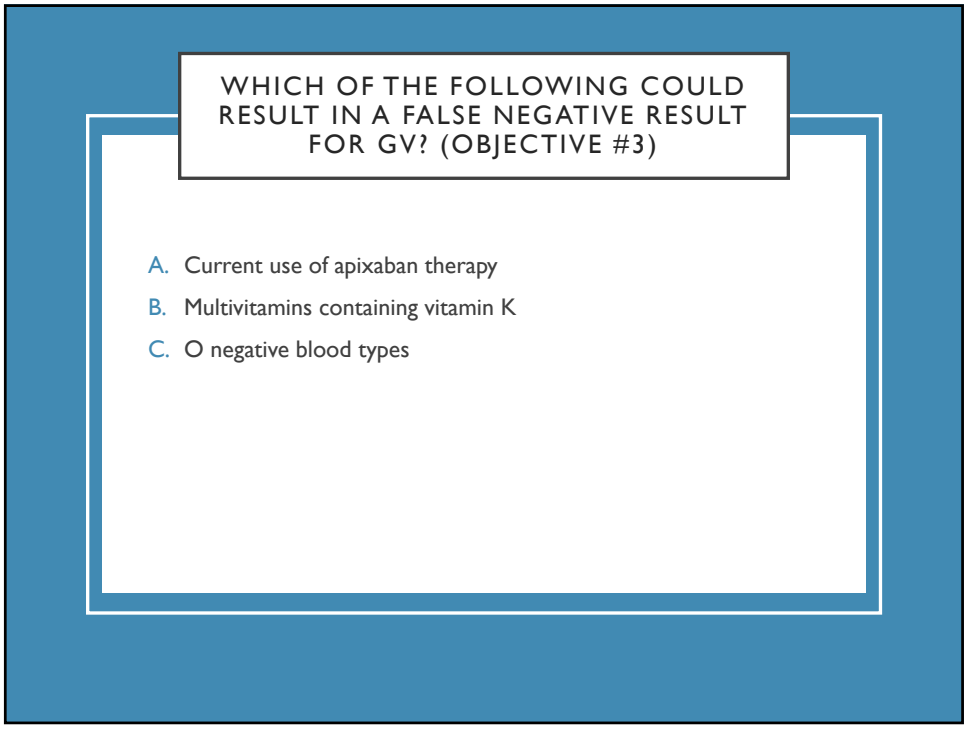
FACTOR V LEIDEN MANAGEMENT

- Thromboprophylaxis
  - Pregnancy
  - Surgery
  - Trauma
- Chronic anticoagulation
  - Vitamin K antagonists
  - DOACs

50


CASE STUDY
• GV's thrombophilia panel includes a functional assay for Factor V Leiden. Her results come back within normal limits suggesting lack of the condition.

51


WHICH OF THE FOLLOWING COULD RESULT IN A FALSE NEGATIVE RESULT FOR GV? (OBJECTIVE #3)
A. Current use of apixaban therapy
B. Multivitamins containing vitamin K
C. O negative blood types

52

WHICH OF THE FOLLOWING COULD RESULT IN A FALSE NEGATIVE RESULT FOR GV? (OBJECTIVE #3)

A. **Current use of apixaban therapy**
B. Multivitamins containing vitamin K
C. O negative blood types

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HYPERHOMOCYSTEINEMIA

- Homocysteine is a sulfur-containing amino acid involved in metabolic pathways leading to the formation of other amino acids
- Deficiency in the cystathionine B-synthase (CBS) enzyme, defective methylcobalamin synthesis, or abnormality in methylene tetrahydrofolate reductase (MTHFR) → increased levels of homocysteine
- Elevated homocysteine → free radicals, vascular cell damage → increased risk of venous and arterial thrombosis
- Prevalence: Occurs in 5-7% of population

https://www.merckmanuals.com/professional/hematology-and-oncology/thrombotic-disorders/hyperhomocysteinemia; https://www-ncbi-nlm-nih-gov.ezproxy.lib.uconn.edu/sites/books/NBK554408/

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HYPERHOMOCYSTEINEMIA ETIOLOGY

- Genetic defects in the enzymes involved in homocysteine metabolism
- Nutritional deficiencies in vitamin cofactors
  - Folate
  - Vitamin B12
  - Vitamin B6
- Cigarette smoking
- Chronic kidney failure
- Medications
  - Fibrates
  - Metformin
  - Methotrexate
  - Cholestyramine

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HYPERHOMOCYSTEINEMIA CONSEQUENCES

- Increased risk of cardiovascular and cerebrovascular disease
  - ACS
  - Coronary heart disease
  - Atherosclerosis
  - Heart failure
  - Cardiovascular and all-cause mortality
  - Carotid artery stenosis
  - Stroke
- PE/VTE
- Obstetric complications
  - Birth defects

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HYPERHOMOCYSTEINEMIA DIAGNOSIS

- Laboratory assays measure total plasma homocysteine concentrations
  - Normal
    - 5-15 mcmol/L
  - Hyperhomocysteinemia:
    - Moderate: 15-30 mcmol/L
    - Intermediate: 30-100 mcmol/L
    - Severe: >100 mcmol/L

https://www.healthline.com/health/homocysteine-levels

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HYPERHOMOCYSTEINEMIA TREATMENT

- Patients with concomitant homocystinuria and severe hyperhomocysteinemia
  - Pyridoxine
  - Folic acid
  - Hydroxocobalamin
- Hyperhomocysteinemia without homocystinuria
  - Folic acid supplementation could lower homocysteine levels
  - May not reduce CV risk unless concomitant homocystinuria
  - May potentially reduce carotid atherosclerosis progression
  - Mild primary stroke prevention
  - Delay brain atrophy in mild cognitive impairment

https://www-ncbi-nlm-nih-gov.ezproxy.lib.uconn.edu/sites/books/NBK554408/

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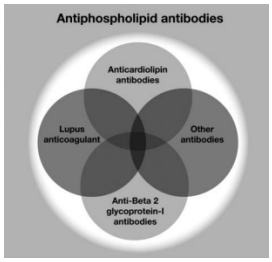
ANTIPHOSPHOLIPID ANTIBODY SYNDROME PATHOPHYSIOLOGY

- Coagulation reactions take place on a phospholipid surface
- Cell membrane damage allows negatively charged phospholipids to come into contact with the blood → bind to several clotting factors
- Antibody production attacks phospholipids → clot formation
  - Susceptible patients with exposure to infectious agents or rheumatic disease
  - Additional cause required for development of syndrome



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https://www-ncbi-nlm-nih-gov.ezproxy.lib.uconn.edu/sites/books/NBK554408/

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ANTIPHOSPHOLIPID ANTIBODY SYNDROME EPIDEMIOLOGY

- 1-5% of population
- Twice as common in women than in men
- Antiphospholipid antibody syndrome is the cause:
  - 14% strokes
  - 11% MI
  - 10% DVT
  - 6% pregnancy morbidity
  - 9% pregnancy losses
- Recurrent events likely if anticoagulation is discontinued after 3 months

Durante A, Bronzato S. JAMA Netw Open. 2023;6(10):e2336530; Gaspar P, Sciascia S, Tektonidou MG. Rheumatology (Oxford). 2024;63(SI):SI24-SI36.

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ANTIPHOSPHOLIPID ANTIBODY SYNDROME CONSEQUENCES

- 30-fold increased risk for thrombosis
- Venous thrombosis
  - DVT (including renal, hepatic, subclavian, cerebral sinuses, vena cava)
  - PE
  - Superficial thrombophlebitis
- Arterial thrombosis
  - Stroke
  - Heart attack
- Pregnancy complications
  - High risk of pregnancy loss ≥ 10 weeks of pregnancy
  - Eclampsia
  - Preeclampsia
  - Placental insufficiency
    - Recurrent miscarriage

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APS DIAGNOSIS

Clinical Criteria	Laboratory Criteria
Vascular thrombosis	**Lupus anticoagulant**
≥ 1 unexplained death of fetus (≥ 10 wks)	IgG and/or IgM **anticardiolipin** antibody
≥ 1 premature births (< 34 wks) due to eclampsia, preeclampsia, placental insufficiency	IgG or Igm anti-**beta2 glycoprotein-1** antibody

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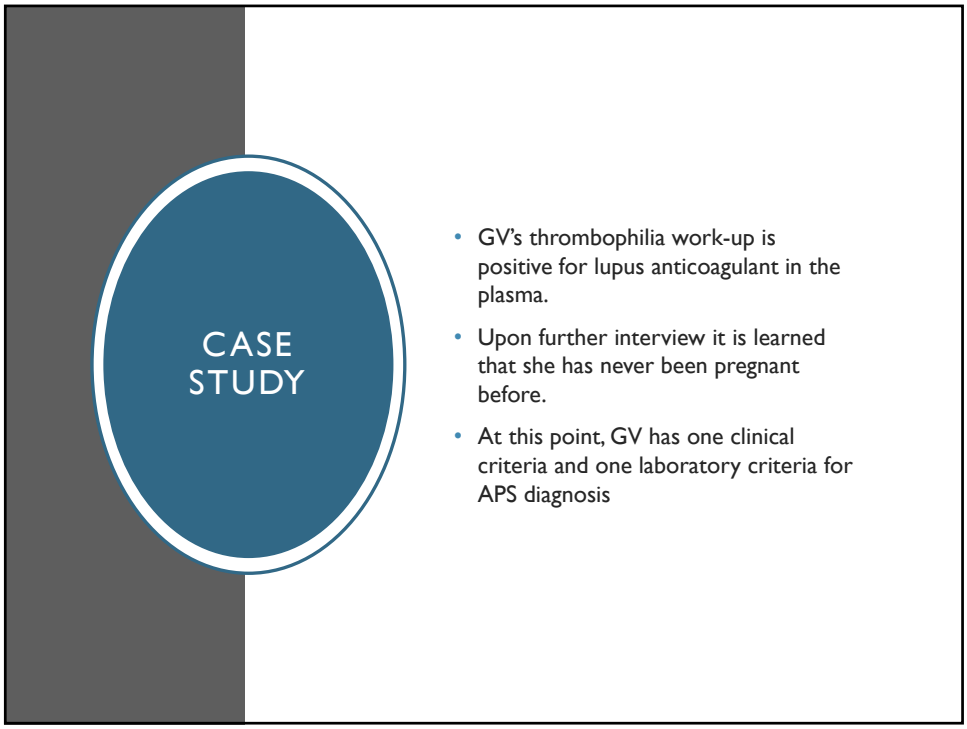
CASE STUDY
• GV's thrombophilia work-up is positive for lupus anticoagulant in the plasma.
• Upon further interview it is learned that she has never been pregnant before.
• At this point, GV has one clinical criteria and one laboratory criteria for APS diagnosis

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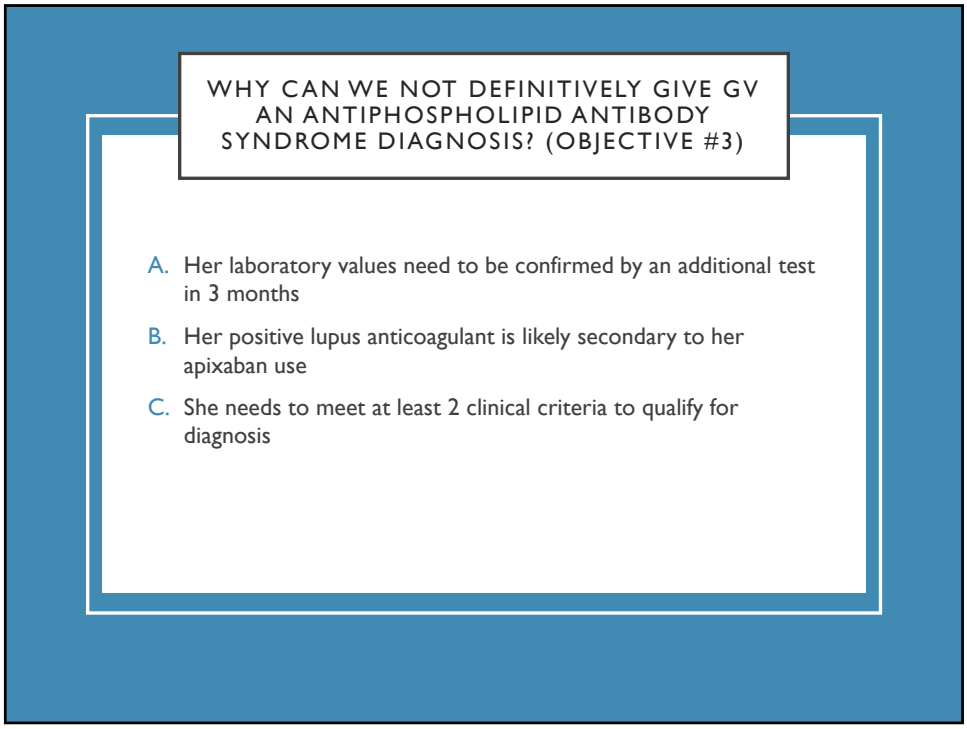
WHY CAN WE NOT DEFINITIVELY GIVE GV AN ANTIPHOSPHOLIPID ANTIBODY SYNDROME DIAGNOSIS? (OBJECTIVE #3)
A. Her laboratory values need to be confirmed by an additional test in 3 months
B. Her positive lupus anticoagulant is likely secondary to her apixaban use
C. She needs to meet at least 2 clinical criteria to qualify for diagnosis

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WHY CAN WE NOT DEFINITIVELY GIVE GV AN ANTIPHOSPHOLIPID ANTIBODY SYNDROME DIAGNOSIS? (OBJECTIVE #3)

A. **Her laboratory values need to be confirmed by an additional test in 3 months**

B. Her positive lupus anticoagulant is likely secondary to her apixaban use

C. She needs to meet at least 2 clinical criteria to qualify for diagnosis

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ANTIPHOSPHOLIPID ANTIBODY SYNDROME MANAGEMENT

- First Line Therapy: Vitamin K-antagonists with INR goal 2.0-3.0
  - Venous blood draws required
- DOACs should not be routinely used in APS patients, especially in those with a high-risk profile
  - Increased odds (OR 4.46) of composite of arterial or venouse thrombosis compared to VKAs
  - increased odds (OR 5.43) of subsequent ATE, especially stroke

Khairani CD, et al. *J Am Coll Cardiol.* 2022;79(20):2058-2068;
Arachchillage DJ, et al. *Br J Haematol.* 2024;196(35):1281-1295;

https://apsfa.org/inr-finger-stick-machines

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CASE STUDY

- Upon further testing, GV is confirmed to have Antiphospholipid Syndrome (triple-positive).
- She has come to your clinic to discuss ongoing treatment options.
- Her preference is to stay on the apixaban.

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WHICH OF THE FOLLOWING OPTIONS IS MOST APPROPRIATE MANAGEMENT STRATEGY FOR GV? (OBJECTIVE #3)

A. Continue apixaban
B. Switch to dabigatran
C. Switch to warfarin

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WHICH OF THE FOLLOWING OPTIONS IS MOST APPROPRIATE MANAGEMENT STRATEGY FOR GV? (OBJECTIVE #3)

A. Continue apixaban
B. Switch to dabigatran
C. **Switch to warfarin**

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TAKE HOME POINTS

- Hypercoagulable states are associated with significant morbidity and mortality
- Various diagnostic tools are available for assessing inherited versus acquired conditions
- Therapeutic anticoagulation is not always indicated without a thrombotic event, but prophylaxis should be utilized in high-risk situations

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