Hypercoagulable States

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Faculty Disclosure

- Dr. Rizal has no actual or potential conflict of interest associated with this presentation

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Learning Objectives

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

- Describe inherited hypercoagulable states
- Describe acquired hypercoagulable states
- Discuss management strategies for various hypercoagulable states including Anithrombin III Deficiency, Protein C or S Deficiency, Factor V Leiden, Prothrombin gene mutation, Hyperhomocysteinemia and Antiphospholipid Antibody Syndrome

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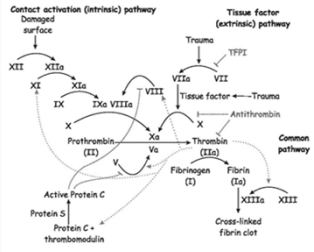
Normal Physiology: Coagulation Cascade



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Hereditary Thombophilia

- Genetic tendency to develop venous thromboembolism
- Total incidence of inherited thrombophilia: 24-37% in patients w/ DVT vs. 10%
- Most Common >50% of cases
  - Factor V Leiden mutation
  - Prothrombin G20210A mutation
- Remainder
  - Deficiencies of antithrombin III, protein C or protein S
  - Hyperhomocysteinemia

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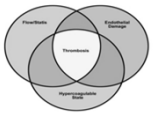
Acquired Hypercoagulable States

- Antiphospholipid antibody syndrome
- Cancer
- Some medications used to treat cancer, such as tamoxifen, bevacizumab, thalidomide and lenalidomide
- Recent trauma or surgery
- Central venous catheter placement
- Obesity
- Prolonged bed rest or immobility
- Extended travel
- Hyperviscosity
- Smoking
- Pregnancy
- Estrogen use eg. Oral contraceptives
- Hormone replacement therapy
- Glucocorticoids
- Heparin-induced thrombocytopenia
- Thrombotic thrombocytopenic purpura
- Congestive failure
- Diabetes Mellitus
- Hyperlipidemia
- Previous history of deep vein thrombosis or pulmonary embolism
- Myeloproliferative disorders such as polycythemia vera or essential thrombocytosis
- Inflammatory bowel syndrome
- Nephrotic syndrome (too much protein in the urine)

VIRCHOW'S TRIAD



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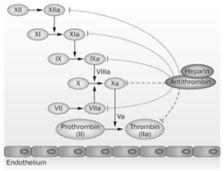
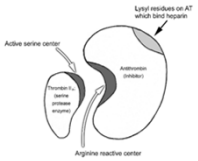
Antithrombin III Deficiency

- Physiology
  - Serine protease inhibitor produced in the liver
  - Half life: 2.8-4.8 days
  - Inactivates several clotting factors including Factor Xa, Factor IXa, Factor XIa, Factor XIIa, Factor VIIa and Factor IIa
  - Heparin enhances binding of Antithrombin to Factor II and Factor X





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Antithrombin III Deficiency

- 2 Forms:
  - Inherited
    - Inherited deficiencies are due to AT gene mutations
      - Type I deficiency-reduced AT level
      - Type II deficiency-functionally defective AT
  - Acquired
    - Impaired production of functional AT
      - eg, due to liver disease, warfarin therapy, asparaginase therapy
    - Increased excretion
      - eg, in nephrotic syndrome, heparin
    - Accelerated consumption
      - as occurs in acute thrombosis or disseminated intravascular coagulation

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Acquired Antithrombin III Deficiency

- Reduced plasma AT levels
  - Extracorporeal membrane oxygenation (ECMO)
  - Hemodialysis
  - Major surgery
  - Estrogen therapy
  - Pregnancy
    - AT level reduced during pregnancy induced hypertension, preeclampsia, eclampsia

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Antithrombin III Deficiency

- Incidence
  - Prevalence in general population: 0.2-0.02% (1 in 500-5,000 individuals)
- Autosomal dominant
- Homozygous antithrombin deficiency incompatible with life
- Heretozygous antithrombin deficiency
  - 4% of families with inherited thrombophilia
  - 1% of consecutive patients with first episode DVT
- Age at presentation
  - Varies widely, some individuals never have a thromboembolic event in their lifetime

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Antithrombin III Deficiency

- Consequences:
  - Increased risk of VTE
    - Risk varies among populations
    - 40-60% of normal AT allows thrombin generation and fibrin deposition to veins
    - Common Sites: DVT of leg, iliofemoral and mesenteric veins
    - Less common sites: Vena cava, renal, retinal, cerebral, or hepatic veins
    - Arterial thrombosis has been reported but is not characteristic
    - High risk of thrombosis during pregnancy
  - Heparin insensitivity
    - Heparin and LMWH require AT to inactivate factor Xa

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Antithrombin III Deficiency

- Diagnosis
  - Differential diagnosis of AT deficiency includes other causes of thromboembolism and other causes of heparin resistance
  - Perform laboratory testing only on:
    - Patients with suspected inherited thrombophilia based on family history or atypical presentation
    - Suspected heparin resistance
    - Asparaginase therapy or extracorporeal membrane oxygenation
  - Normal antithrombin level sufficient to exclude the disorder
  - Low levels should be confirmed at a later date

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Antithrombin III Deficiency

- Choice of assay
  - AT-heparin cofactor assay
    - A functional assay for plasma AT activity
    - Measures ability of heparin to inhibit coagulation factor IIa or Xa which requires AT activity
    - Factor Xa inhibition generally preferred due to improved specificity
    - Normal AT activity range: 80-120% at most laboratories
    - Laboratory-specific values should be used to take into account instrument and assay variability
  - AT-Protein level assay
    - Enzyme-linked immunosorbent assay (ELISA)
    - Unable to identify individuals with Type II AT deficiency
    - Can be used to distinguish between type I and type II defects in individuals with deficient AT activity
- Timing of testing
  - Do not perform test:
    - During acute thrombosis or comorbid illness (transient low levels)
    - Patients on heparin therapy (increased clearance of AT thus false low reading)
    - Warfarin therapy (plasma antithrombin levels elevated to normal range)
      - Wait >2 weeks after discontinuation

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Antithrombin III Deficiency

- Management
  - Anticoagulation
    - Thrombin Inhibitors eg. Argatroban
    - Prophylaxis for high-risk patients with AT deficiency eg: pregnancy, surgery
    - Lifelong anticoagulation for patients with unprovoked VTE
  - AT replacement
    - Recombinant human antithrombin produced from the milk of transgenic goats (rhAT, ATryn)
    - Antithrombin concentrate derived from pooled human plasma (Thrombate III)
    - Dose and schedule depend on the product used
      - once daily dosing for plasma-derived AT
      - continuous infusion for recombinant AT
      - AT is dosed in units of activity
        - » one unit is defined as the amount of AT in one milliliter of pooled normal human plasma
      - Patient's baseline AT activity level and body weight (used for initial dose calculation), and the clinical setting (dosing of the concentrate differs in pregnancy versus surgery)

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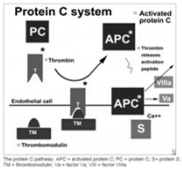
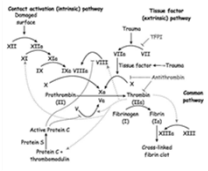
Protein C Deficiency

- Physiology
  - Vitamin K-dependent protein synthesized in the liver
  - Activated by thrombin (bound to endothedial thrombomodulin) to the serine protease activated protein C (aPC)
  - aPC inactivates factors Va and VIIIa
  - The inhibitory effect of aPC is markedly enhanced by protein S





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Protein C Deficiency

- 2 Forms:
  - Inherited
    - Due to protein C gene mutations
      - Type I deficiency-Quantitative deficiency
        - » Heterozygous patients have plasma protein C concentration which is 50% of normal in antigen and activity levels
        - » More common
        - » Marked phenotypic variability
      - Type II deficiency-Functional deficiency
        - » normal plasma protein C antigen levels with decreased functional activity due to point mutations
  - Acquired
    - Liver disease
    - Severe infection
    - Septic shock
    - Disseminated intravascular coagulation
    - Acute respiratory distress syndrome
    - Postoperative state
    - Breast cancer patients receiving cyclophosphamide, methotrexate, and 5-fluorouracil
    - L-asparaginase therapy
    - Acute viral or bacterial infections, including meningococcemia

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Protein C Deficiency

- Incidence
  - Prevalence:
    - 1 in 200-500 individuals in healthy population
    - Congenital deficiency present in 3-5% of patients w/ thromboembolism
- Inheritance is autosomal dominant
- Age at presentation
  - 20-50 yrs old
  - Median age at onset:
    - 45 yrs in unselected patients
    - 30 yrs in members of thrombophilia families

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Protein C Deficiency

- Individuals with hereditary protein C deficiency can present with:
  - Venous thromboembolism (VTE)
  - Neonatal purpura fulminans in newborns
  - Warfarin-induced skin necrosis in adults

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Protein C Deficiency

- Venous thromboembolism
  - 7 fold increased risk of developing VTE
  - Risk of developing VTE varies among families
  - Presence of 2nd thrombotic defect eg. factor V leiden increases risk of VTE
  - 60% of patients develop recurrent venous thrombosis
  - 40% of patients have signs of PE
  - Risk of VTE increases with age
  - Initial episode
    - 70% of cases-Spontaneous
    - 30% of cases-Risk factors (eg, pregnancy, oral contraceptives, surgery, or trauma)
  - DVT of legs, iliofemoral and mesenteric veins most common
  - Cerebral venous thrombosis
  - Arterial thrombosis reported but not common

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Protein C Deficiency

- Neonatal purpura fulminans
  - Rare, life-threatening condition that occurs in newborns with homozygous or compound heterozygous protein C deficiency
  - Presents within several hours to days of life
  - Disseminated intravascular coagulation and hemorrhagic skin necrosis
  - Extremely low levels of protein C antigen (<1% of normal)
- Fetal loss
  - Increased odds ratio for fetal loss

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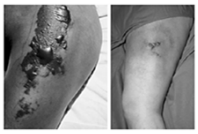
Protein C Deficiency

- Warfarin-induced skin necrosis
  - Associated with large loading doses of warfarin
  - Occurs within 1st several days of warfarin therapy due to transient hypercoagulable state
  - Warfarin initiation decreases protein C activity to approximately 50% of normal within 1 day
  - Increased thrombin generation at warfarin initiation
  - Diffuse microthrombi within dermal and subcutaneous capillaries, venules, and deep veins, with endothelial cell damage, resulting in ischemic skin necrosis and marked red blood cell extravasation
  - The skin lesions occur on the extremities, breasts, trunk, and penis (in males)
  - Rapid reversal important to avoid necrosis



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Protein C Deficiency

- Diagnosis
  - Differential diagnosis of protein C deficiency includes other causes of thromboembolism
  - Mean protein C concentrations increase by approximately 4% per decade
  - Average concentration of protein C in human plasma = 4mcg/ml
  - Protein C antigen levels in adults range from 70-140% of normal
    - Protein C levels <55% of normal: Genetic abnormality
    - Protein C levels 55-65% of normal: Indeterminate and require re-testing
  - Full term infants: protein C levels 20-40% of normal adult levels, preterm infants have even lower levels
    - Use age-based norms for the specific laboratory performing the test in neonates
  - Methodologies for measurement of protein C differ among laboratories

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Protein C Deficiency

- Assays
  - Functional Assay
    - Preferred for screening
    - Detect both type I and II defects
    - Activate protein C using either thrombin, thrombin-thrombomodulin complex or venom of southern copperhead snake (Agkistrodon contortrix)
    - Assess enzyme activity using either a chromogenic substrate or by measuring activated protein C anticoagulant activity in a factor Xa one-stage clotting assay or partial thromboplastin time
  - Immunologic Assay
    - Useful in characterizing patients as having a type I or II defect
    - Types
      - Electroimmunoassay
      - Enzyme-linked immunosorbent assay
      - Radioimmunoassay
- Timing of testing:
  - Wait 2 weeks after discontinuing oral vitamin K antagonist
  - Warfarin therapy reduces functional and immunologic measurement of protein C
  - Heparin therapy does not alter plasma protein C levels
  - Testing should not be performed during acute thrombosis or comorbid illness
  - Normal plasma protein C levels at presentation exclude deficiency
  - Low plasma protein C levels at presentation must be confirmed by repeat testing after anticoagulation is discontinued

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Protein C Deficiency

- Management
  - Thromboprophylaxis
    - Strong family history of thrombosis
    - Pregnancy and the postpartum state
    - Surgery
    - Trauma
  - VTE
    - Lifelong anticoagulation following a spontaneous thromboembolic event
    - Preference of DOACs because of availability and familiarity
    - Ensure therapeutic aPTT or Xa levels before starting warfarin
    - Start low dose warfarin to avoid warfarin induced skin necrosis
  - Warfarin-induced skin necrosis
    - Immediate discontinuation of warfarin
    - Vitamin K administration
    - Heparin therapy
    - Exogenous protein C administration for patients with protein C deficiency
      - FFP
      - Purified protein C concentrate (Ceprotin)
  - Neonatal purpura fulminans
    - Immediate exogenous protein C administration for patients with protein C deficiency
    - Lifelong anticoagulation

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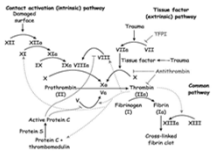
Protein S Deficiency

- Vitamin K-dependent glycoprotein
- Enables activated protein C to inactivate factor Va and VIIIa at an increased rate
- Serves as a cofactor for protein C enhancement of fibrinolysis
- Directly inhibits prothrombin activation via interactions with other coagulation factors
- Synthesized by hepatocytes, endothelial cells, and megakaryocytes
- Circulates in two forms:
  - Free Form (40-50%)
    - Has activated protein C cofactor activity
  - Bound to the complement component, C4b-binding protein
- Average plasma concentration of total PS antigen in normal adults: 23 mcg/ml
- Total protein S levels increase with age
- Levels significantly lower and more variable in females than males



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Protein S Deficiency

- Incidence
  - Occurs in 10% of families with inherited thrombophilia
  - Prevalence 1% among consecutive patients with 1st episode DVT
  - Prevalence 0.03 - 0.13% general population
- Homozygous protein S deficiency incompatible with life
- Inheritance of protein S is autosomal dominant
- Heterozygous individuals in these families frequently had recurrent thromboembolism
- Age at presentation
  - First thrombotic event occurs between 15-68 years (Mean age-28yrs)
    - 56% spontaneous
    - Remainder precipitated by an identifiable factor eg. age, surgery, immobility, pregnancy

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Protein S Deficiency

- 2 Forms
  - Inherited
    - Caused by mutations in the PROS1 gene
    - 3 phenotypes of protein S deficiency
      - Type I-Quantitative defect
        - » 50% of normal total S antigen level
        - » Marked reductions in free protein S antigen and protein S functional activity
      - Type II-Qualitative defect
        - » Normal total and free protein S levels
        - » Diminished protein S functional activity
      - Type III
        - » Normal total protein S antigen measurements
        - » Selectively reduced levels of free protein S and protein S functional activity to <40% of normal
  - Acquired
    - Pregnancy
    - Oral Contraceptive use
    - Disseminated intravascular coagulation
    - Acute thromboembolic disease
    - L-asparaginase chemotherapy
    - Liver disease
      - Total and free protein S levels moderately decreased
    - Nephrotic syndrome
      - Increased total protein S antigen but reduced protein S functional assays
      - Loss of free protein S in the urine and elevation in plasma C4b-binding protein concentrations
    - HIV infection
      - Significantly reduced total and free protein S levels

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Protein S Deficiency

- Clinical Presentation
  - Similar to patients with antithrombin and protein C deficiency
    - VTE
      - 8.5x higher lifetime probability of developing thrombosis
      - Presence of 2nd thrombotic defect increases risk of VTE
      - Risk of VTE is not increased in the absence of a family history of VTE
      - Axillary, mesenteric, and cerebral vein thrombosis
      - Arterial thrombosis reported but not common
    - Warfarin-induced skin necrosis
    - Thrombophlebitis
    - PE
    - Fetal loss

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Protein S Deficiency

- Diagnosis
  - Difficult to document with certainty
  - Free protein S is the best screening test
  - Genetic testing not readily available
  - Testing restricted to VTE patients with strong family history
  - Total protein S antigen <60 - 65 international units/dL are considered to be in the deficient range
  - Free protein S levels <33 units/dl clinically significant for asymptomatic individuals and those with 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

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Protein S Deficiency

- Assays:
  - Protein S antigen
    - Both free and total protein S are measured by ELISA methods in the laboratory
      - Total protein S antigen is measured by various types of immunoassay techniques
        - » Dilution of plasma samples favors dissociation of the PS-C4b-binding protein complexes
      - Free protein S is measured using monoclonal antibody-based assay and ligand sorbent assays
  - Functional protein S assays
    - Based upon the ability of protein S to serve as a cofactor for the anticoagulant effect of activated protein C
    - Lack specificity for protein S thus can lead to erroneous diagnosis
- Timing of testing:
  - Wait 2 weeks after discontinuing oral vitamin K antagonist
  - Warfarin therapy substantially reduces antigenic and functional levels of protein S
  - Heparin therapy does not alter plasma protein S levels
  - Normal plasma protein S levels at presentation exclude deficiency
  - Low plasma protein S levels at presentation must be confirmed by repeat testing after anticoagulation is discontinued
  - Testing should not be performed during acute thrombosis or comorbid illness

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Protein S Deficiency

- Management of VTE
  - Heparin
    - IV heparin or SC LMWH for 1st 5 days
  - Warfarin
    - Initiate after 2 days and overlap with heparin for 5 days
    - Decision for lifelong anticoagulation made based on patient specific factors
  - DOAC
  - Dabigatran
- Prophylaxis
  - Administer heparin to asymptomatic carriers:
    - Pregnant
    - Undergoing surgery
    - Orthopedic surgery
  - Avoid medications that can cause clots eg. oral contraceptives

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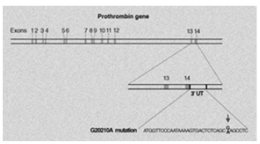
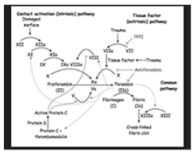
Prothrombin Gene Mutation

- Physiology
  - Prothrombin (factor II) is the precursor of thrombin, the end-product of the coagulation cascade
  - Vitamin k-dependent protein which is synthesized in the liver and circulates with a half-life of approximately 3-5 days
  - Prothrombin G20210A - human prothrombin gene
  - Guanine to adenine substitution at nucleotide 20210 of the prothrombin gene
  - Heterozygous carriers have 30 percent higher plasma prothrombin levels than normal





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Prothrombin Gene Mutation

- Incidence
  - 2nd most common hereditary defect
  - Overall prevalence 2% in general Caucasian population
  - 0.7-6.5% of Caucasians heterozygous for the allele
  - Infrequent among individuals of Asian or African descent
  - Variability in geographic distribution
    - Spain (highest)
    - Europe (Southern higher than northern)

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Prothrombin Gene Mutation

- Consequences
  - VTE
    - Increased risk for deep vein and cerebral vein thrombosis
    - Increased risk of cerebral vein thrombosis in patients using oral contraceptives
    - 2.8 fold increased risk for 1st episode DVT in both sexes and all age groups
    - Presence 2nd thrombotic defect (eg. factor V Leiden) increases the thrombotic risk 3-5 times over a single defect
    - Unclear increased risk of recurrent VTE
    - Increased risk of VTE in pregnancy
  - Arterial thrombosis
    - Not a risk factor for cerebrovascular ischemic disease in older patients
    - Possible increased risk in younger patients

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Prothrombin Gene Mutation

- Diagnosis
  - Polymerase chain reaction
    - Used to detect mutation
  - Plasma prothrombin activity & antigen levels
    - Cannot be used to screen patients due to significant overlap with the normal population

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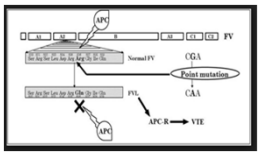
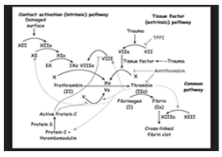
Factor V Leiden

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





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Factor V Leiden

- Acquired causes of activated protein C resistance
  - Elevated factor VIII levels
    - Levels increased in inflammatory disorders and pregnancy
  - Increased estrogen
    - Mechanism
      - Reduced protein S
      - Increased prothrombin
      - Increased factors VIII, IX , X and others
    - Oral contraceptives
      - 3rd generation oc associated with acquired protein c resistance and increased thrombotic risk
      - Risk of thrombosis 1in 345 (10x that of oc use in pt's w/o factor v leiden mutation)
    - Hormone Replacement Therapy
      - Hazard ratio of 2 for acquired protein C resistance
    - Pregnancy
  - Cancer
  - Antiphospholipid antibodies
  - Protein S deficiency
    - Can cause appearance of activated protein C resistance in some functional assays
    - Not an independent cause of activated protein C resistance
  - Other factors
    - Proteinuria, elevated body mass index, and smoking

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Factor V Leiden

- Prevalence
  - Most common hereditary defect in Caucasians
    - Found in 1-8% of Caucasians (European, Jewish, Israeli, Arab, Canadian and Indian)
    - Accounts for 40-50% of cases
    - Not found in African Americans, Chinese, Japanese
  - Occurs in 5% of general population
  - Occurs in 20% of patients with 1st DVT
- 3.5 fold increased risk of VTE
- Risk of thrombosis increases dramatically in the homozygous, pseudohomozygote state or in the presence of a 2nd hereditary defect
- Homozygotes account for approximately 1% of patients with factor V leiden mutation

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Factor V Leiden

- Clinical Significance
  - Approximately 5% of factor V Leiden heterozygotes will experience venous thromboembolism during their lifetime
  - VTE
    - 10-26% of pt's with VTE have factor V Leiden mutation
    - Risk of VTE increases with advancing age
      - Major manifestation DVT±, PE (large proximal iliofemoral vein)
      - Isolated PE
      - Risk factor for cerebral, mesenteric, portal vein thrombosis and superficial vein thrombosis
    - Risk of recurrent DVT
      - Though conflicting data exists, presence of factor V Leiden mutation is likely not associated with increased 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

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Factor V Leiden

- Diagnosis
  - Genetic Testing
    - Detect directly by analyzing genomic DNA from peripheral blood mononuclear cells
    - Genetic testing which assays DNA sequence unaffected by anticoagulants and other drugs
    - Can determine if patient is homozygous or heterozygous for the mutation
    - Use in patients suspected of having inherited factor V leiden mutation based on family history
  - Functional activated protein C resistance assays
    - 1st Generaton
      - Measure aPTT level using unaltered plasma
      - Not sensitive or specific for factor V leiden mutation
    - 2nd Generation-Preferred
      - Measure aPTT level after pt's plasma diluted with factor V deficient plasma
      - Limits influence of other coagulation factor levels on clotting time determinations
      - Correlate very well with the presence of factor V leiden mutation
      - Cost less than genetic tests
      - False normal results possible with:
        - » Presence of lupus anticoagulant
        - » Therapy with direct thrombin inhibitors eg. Argatroban, Dabigatran
        - » Therapy with factor Xa inhibitor eg. Rivaroxaban
      - Abnormal results should be confirmed by genotyping for the factor V leiden mutation

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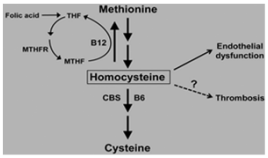
Hyperhomocysteinemia

- Physiology
  - 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)
- Prevalence
  - Occurs in 5-7% of population



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Hyperhomocysteinemia

- Causes
  - Genetic defects in the enzymes involved in homocysteine metabolism
    - Thermolabile variant of methylene tetrahydrofolate reductase (MTHFR)
    - Occurs in 5-14% of population
  - Nutritional deficiencies in vitamin cofactors
    - Folate
    - Vitamin B12
    - Vitamin B6
  - Cigarette smoking
  - Chronic kidney failure
    - Decreased renal removal and impaired metabolism
  - Medications
    - Fibrates and nicotinic acid, can raise homocysteine levels by approximately 30%
    - Metformin
    - Methotrexate
    - Cholestyramine

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Hyperhomocysteinemia

- Prothrombotic effects
  - Attenuation of endothelial cell tissue plasminogen activator binding sites
  - Activation of factor VIIa and V
  - Inhibition of protein C and heparin sulfate
  - Increased fibrinopeptide A and prothrombin fragments 1 and 2
  - Increased blood viscosity
  - Decreased endothelial antithrombotic activity due to changes in thrombomodulin function

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Hyperhomocysteinemia

- Clinical Significance
  - Increased risk of cardiovascular and cerebrovascular disease
    - Myocardial infarction, other acute coronary syndromes, and recurrent coronary events
    - Premature coronary heart disease
    - Atherosclerosis
    - Heart failure
    - Cardiovascular and total mortality
    - Adverse outcomes after angioplasty
    - Carotid artery stenosis
    - Stroke, recurrent stroke, and silent brain infarct
  - Venous thromboembolism
    - PE/DVT
    - Moderate hyperhomocysteinemia may be risk factor for recurrent VTE
  - Others
    - Obstetric complications
    - Birth defects
    - Osteoporosis
    - Dementia

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Hyperhomocysteinemia

- Diagnosis
  - Laboratory assays measure total plasma homocysteine concentrations
  - Levels:
    - Normal
      - 5-15 µmol/L
    - Hyperhomocysteinemia:
      - Moderate: 15-30 µmol/L
      - Intermediate: 30-100 µmol/L
      - Severe: >100 µmol/L
- Treatment
  - Direct vitamin supplementation
  - Do not treat patients w/ cardiovascular disease/VTE with vitamin supplementation aimed at decreasing homocysteine levels

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Antiphospholipid Antibody Syndrome

- Physiology
  - Coagulation reactions must take place on a phospholipid surface
  - Tissue injury damages cell membranes which allows negatively charged phospholipids (normally present on the underside of cell membranes) to come into contact with the blood
  - Phospholipids also appear on activated platelet surfaces
  - Several clotting factors bind directly to negatively charged phospholipids

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Antiphospholipid Antibody Syndrome

- Pathophysiology
  - Immune system produce antibodies which attacks the phospholipids or proteins bound to phospholipids leading to increased clot formation
  - Occurs in susceptible patients following incidental exposure to infectious agents or in patients with rheumatic disease eg. SLE
  - Once antiphospholipid antibodies are present, a 2nd cause is required for the development of antiphospholipid antibody syndrome eg. Smoking, prolonged immobility, pregnancy, postpartum period, oral contraceptive use, hormone replacement therapy, malignancy, nephrotic syndrome etc.
  - Antibodies have procoagulant effect on:
    - Protein C
    - Annexin V
    - Platelets
    - Serum proteases
    - Toll-like receptors
    - Tissue factor
    - Impaired fibrinolysis
  - Antiphospholipid antibodies increase vascular tone
    - Atherosclerosis
    - Fetal loss
    - Neurological damage

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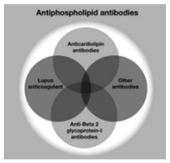
Antiphospholipid Antibody Syndrome

- Antiphospholipid antibodies
  - Anti-Beta 2 glycoprotein 1 antibody
    - B2 glycoprotein
      - Phospholipid binding protein
      - Apolipoprotein H
  - Lupus anticoagulant
  - Anticardiolipin antibodies



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Antiphospholipid Antibody Syndrome

- Prevalence
  - Occurs in 1-5% of population
  - Incidence: 5 cases per 100,000 persons per year
  - Twice as common in women than in men
  - Antiphospholipid antibody syndrome is the cause:
    - 14% of all strokes
    - 11% of MI
    - 10% of DVT
    - 6% of pregnancy morbidity
    - 9% of pregnancy losses
- Recurrent events likely
    - High rate of recurrence if anticoagulation is discontinued 3 months after initiation of anticoagulation
    - Lifelong anticoagulation recommended

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Antiphospholipid Antibody Syndrome

- Clinical Significance
  - 30 fold increased risk for thrombosis
  - Venous thrombosis
    - DVT
      - Calf
      - Renal veins
      - Hepatic
      - Axillary
      - Subclavian
      - Retinal
      - Cerebral sinuses
      - Venae cavae
    - PE
    - Superficial thrombophlebitis
  - Arterial thrombosis
    - Stroke
    - Heart attack
    - Clots in the arteries of the arm, leg, eye, kidney, or abdomen
  - Pregnancy complications
    - High risk of pregnancy loss ≥ 10 weeks of pregnancy
    - Eclampsia
    - Preeclampsia
    - Placental insufficiency
    - Recurrent miscarriage

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Antiphospholipid Antibody Syndrome

- Diagnosis
  - The occurrence of at least one clinical feature: either venous or arterial thromboses, or pregnancy morbidity
    - Unequivocal imaging or histologic evidence of thrombus in any tissue or organ
    - Pregnancy morbidity
      - Otherwise unexplained death at ≥10 weeks gestation of a morphologically normal fetus
      - ≥1 premature births before 34 weeks of gestation because of eclampsia, preeclampsia, or placental insufficiency
      - ≥3 embryonic (<10 weeks gestation) pregnancy losses unexplained by maternal or paternal chromosomal abnormalities or by maternal anatomic or hormonal causes
  - Presence of antiphospholipid antibody in the plasma on 2 separate occasions at least 12 weeks apart and no more than 5 yrs prior to clinical manifestation

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Antiphospholipid Antibody Syndrome

- Laboratory Diagnosis
  - Clotting assay
    - Lupus anticoagulant activity detection
    - Antiphospholipid antibody syndrome causes prolongation of aPTT, dRVVT, kaolin clotting time which is not reversed when patient's plasma is diluted 1:1 with normal platelet-free plasma
    - Lab errors very common
  - ELISA
    - Anti-beta-2 glycoprotein 1
      - Antibodies to beta-2-GP-I of IgG or IgM isotype at a titer >99^{th} percentile for the testing laboratory
    - Anticardiolipin antibody
      - IgG and/or IgM anticardiolipin antibodies (aCL) in moderate or high titer (>40 units GPL or MPL or >99^{th} percentile for the testing laboratory)
- INR Monitoring
  - False elevation in INR
  - Correlation with Factor II (15-25) or Factor X levels (20-40)

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Antiphospholipid Antibody Syndrome

- Treatment
  - Vitamin K-antagonists (VKA) with INR 2.0-3.0 is first-line treatment for a first or recurrent APS-related venous thrombotic event
  - DOACs should not be routinely used in APS patients, especially in those with a high-risk profile (triple positivity to aPL, arterial thrombosis, and recurrent thrombotic events)

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