Anticoagulation in Thrombophilias

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Objectives

- Define hypercoagulability and list common types of related disorders
- List the pathophysiology, prevalence and genetics of hypercoagulable states
- Discuss the diagnosis and testing of various hypercoagulable states
- Review the current recommendations for anticoagulation in hypercoagulable states

Introduction

- Procoagulant and anticoagulant factors in the blood are normally in balance
- Hypercoagulability
  - Increased risk of developing clots in arteries or veins
- Genetic
  - Individual is born with certain factors that increases risk
- Acquired
  - Result of surgery, trauma or a medical condition
- May also be referred to as thrombophilia

Hypercoagulable States. 2014. Available at: http://my.clevelandclinic.org/services/heart/disorders/hypercoagstate. Accessed September 21, 2014.

Assessment

- Personal and family medical history is essential
- May qualify for screening if :
  - Family history of abnormal blood clotting
  - Abnormal blood clotting at a young age (<50 years of age)
  - Thrombosis in unusual locations, such as veins in the arms, liver, intestines, kidney, or brain
  - Idiopathic blood clots
  - Blood clots that recur
  - Stroke at a young age

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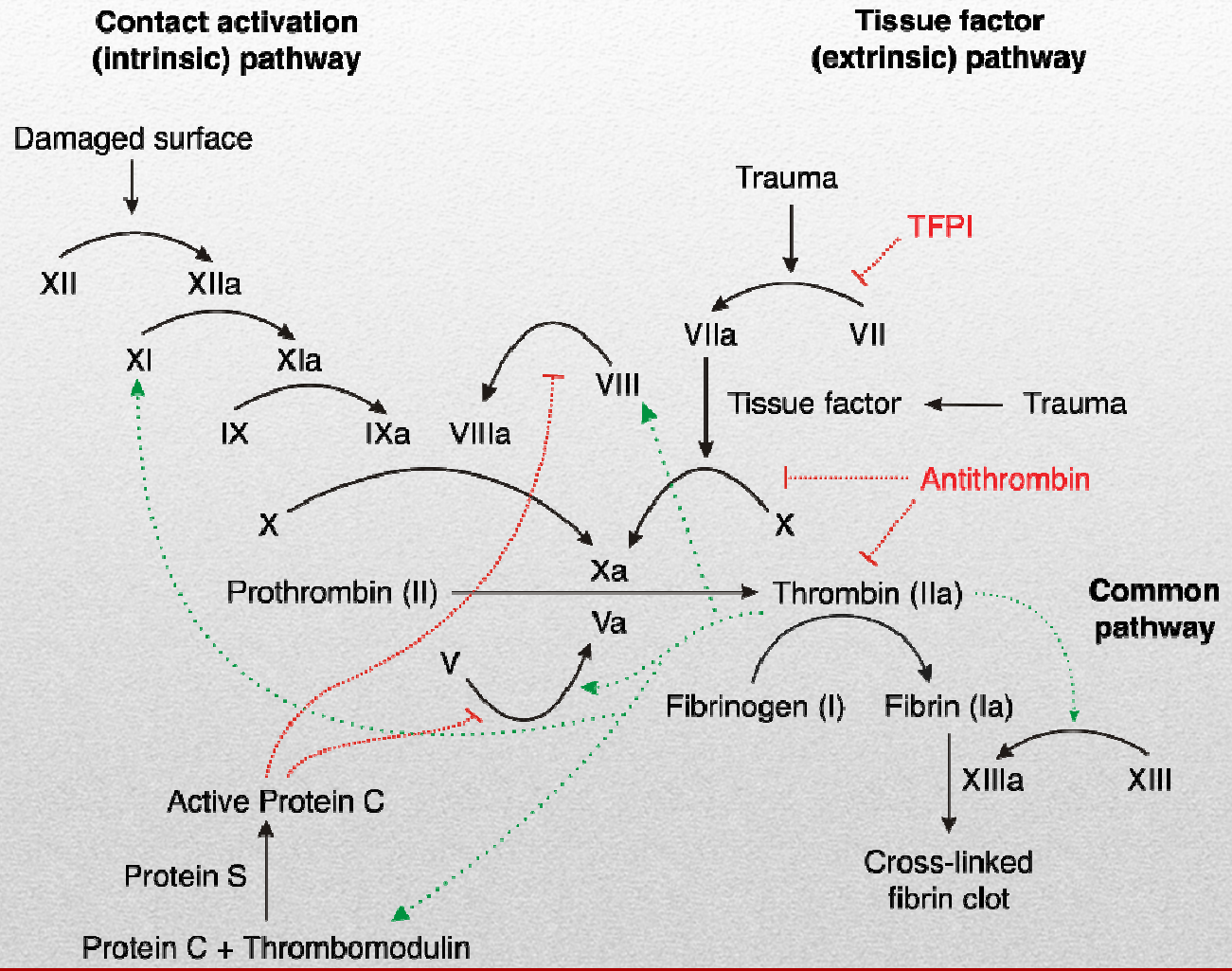
Hypercoagulable States

- Genetic
  - Factor V Leiden
  - Protein C and Protein S deficiency
  - Prothrombin gene mutation
- Acquired
  - Antiphospholipid syndrome

Hypercoagulable States. 2014. Available at: http://my.clevelandclinic.org/services/heart/disorders/hypercoagstate. Accessed September 21, 2014.

Background Information



Wikipedia, the free encyclopedia. Coagulation Full. Available at: http://en.wikipedia.org/wiki/Thrombin#mediaviewer/File:Coagulation_full.svg.

Factor V Leiden

- Most common inherited form of thrombophilia

Mutation in the F5 gene

↓

Slows the rate at which APC can inactivate factor V

↓

Activated factor V remains in circulation longer

↓

Conversion of prothrombin to **thrombin**

APC: Activated Protein C

Factor V Leiden Thrombophilia. 2014. Available at: http://ghr.nlm.nih.gov/condition/factor-v-leiden-thrombophilia. Accessed September 22, 2014.

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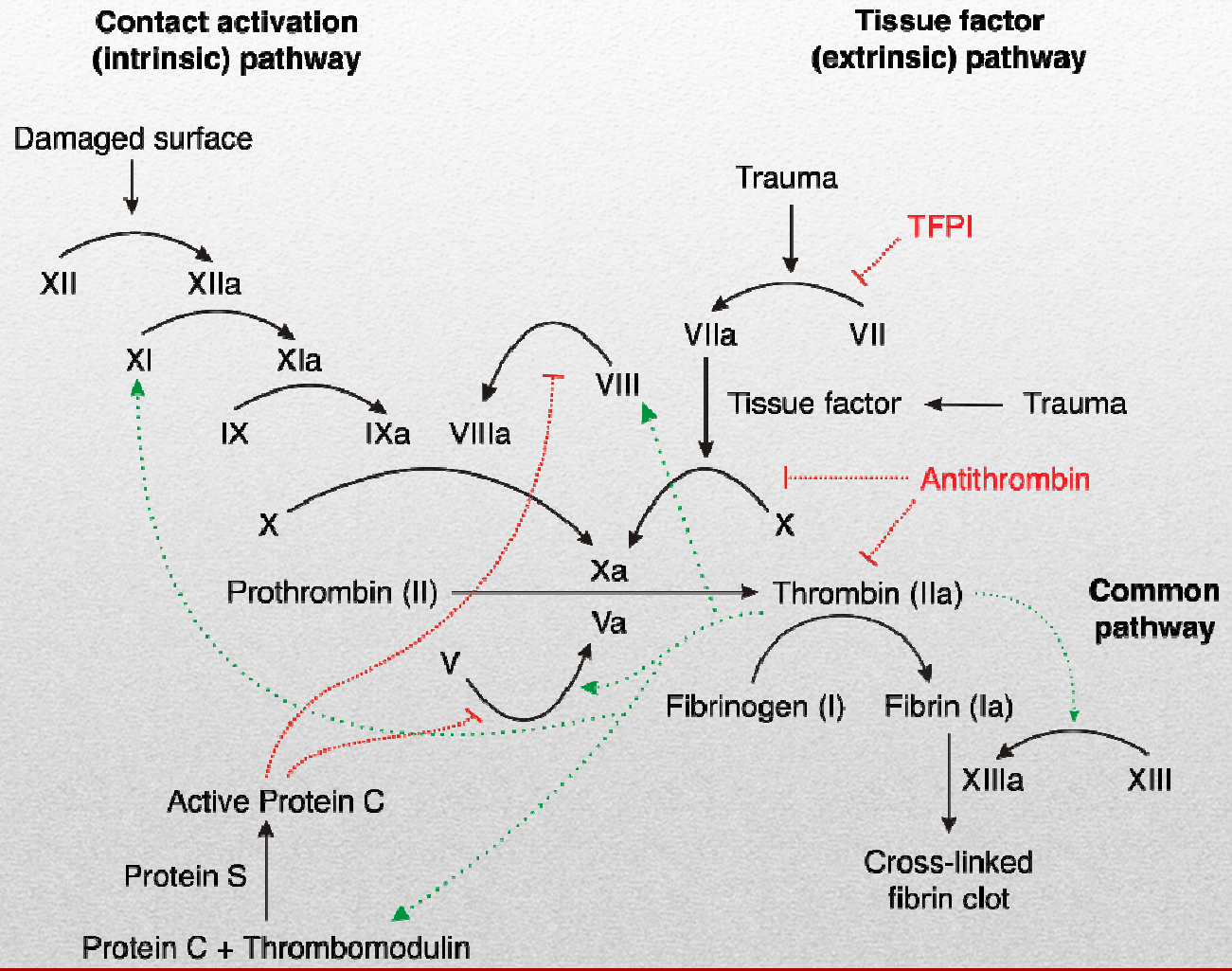

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Factor V Leiden

- Clot risk depends on how many copies of the mutation have been inherited
- Heterozygous vs Homozygous
  - Heterozygous inherit one copy
    - Risk is 3-8 in 1,000
    - Most common type
    - 95 percent of cases of hereditary APC resistance
  - Homozygous inherit two copies (one from each parent)
    - Risk increases to 80 in 1,000
    - Rare
    - 1 percent of patients with the factor V Leiden mutation

APC: Activated Protein C

Factor V Leiden Thrombophilia. 2014. Available at: http://ghr.nlm.nih.gov/condition/factor-v-leiden-thrombophilia. Accessed September 22, 2014.

Factor V Leiden

- Diagnosis
- APC resistance assay
  - Precursor to DNA analysis
  - Shows minimal increase in activated partial thromboplastin time (aPTT) when APC is added to patient's plasma
- DNA analysis
  - Confirms the actual amino acid substitution on the *F5* gene

APC: Activated Protein C

Grody WW et al. American College of Medical Genetics consensus statement on factor V Leiden mutation testing. *Genet Med.* 2001;3(2): 139-48.

Protein C & S Deficiency

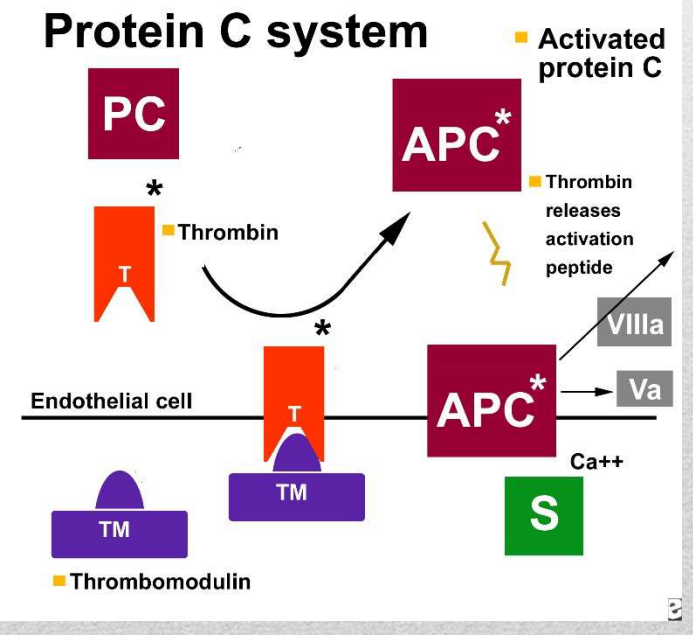
- Deficiencies in protein C & S disrupts the balance between procoagulant and anticoagulant proteins
- Protein C is found on the long arm of chromosome 2
- Protein S is a vitamin K-dependent glycoprotein
  - Cofactor of the protein C system
- APC inactivates factor Va and factor VIIIa at an increased rate in the presence of protein S

APC: Activated Protein C

Culer A, et al. Protein C Deficiency. Medscape. 2013. Available at: http://emedicine.medscape.com/article/205470-overview#a0104.

Protein C & S Deficiency

- APC inactivates coagulation factors Va and VIIIa
  - Required for thrombin generation
- Protein S enhances the catalytic activity of APC



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Protein C & S Deficiency

- Heterozygous
  - Autosomal dominant
  - Activity levels of protein C are about half of a normal patient
- Type I deficiency (quantitative)
  - Concentration of plasma protein C is decreased
  - Varies from severe thrombotic tendencies to asymptomatic
- Type II deficiency (functional)
  - Less common than type I
  - Decreased activity with normal levels of protein C

Culer A, et al. Protein C Deficiency. Medscape. 2013. Available at: http://emedicine.medscape.com/article/205470-overview#a0104.

Protein C & S Deficiency

- Screening
  - Decreased activity of protein C
  - True hereditary deficiency is defined as <50% activity level
  - Heterozygous deficiency or low end of the normal distribution
    - 65%-55% activity level
  - Functional protein C assay
  - Reflexive immunologic assay

Culer A, et al. Protein C Deficiency. Medscape. 2013. Available at: http://emedicine.medscape.com/article/205470-overview#a0104.

Protein C & S Deficiency

- Functional assays
  - Uses the venom of the southern copperhead snake
  - Activates the protein C zymogen to APC
  - APC activity can be measured by clotting assay
- Immunologic assays
  - Enzyme-linked immunosorbent assays (ELISA's)
  - Radioimmunoassays (RIA's)
  - Electroimmunoassays

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Prothrombin Gene Mutation

- Prothrombin is the precursor of thrombin
- It is a vitamin K-dependent protein
  - Synthesized in the liver
- The mutation occurs at the G20210A nucleotide
  - Efficiency of mRNA processing is altered
  - Disruption in the decay rate of prothrombin mRNA

Bauer KA, et al. Prothrombin gene mutation: Thrombotic risk and diagnosis. UptoDate. 2014. Accessed September 29, 2014.

Prothrombin Gene Mutation

- Genetics
- Heterozygous carriers
  - 30 percent higher plasma prothrombin levels than normal
- Homozygous carriers
  - Substantially higher than that in heterozygotes
- Most common in Caucasian population
- Many symptomatic patients will also have factor V Leiden

Bauer KA, et al. Prothrombin gene mutation: Thrombotic risk and diagnosis. UptoDate. 2014. Accessed September 29, 2014.

Prothrombin Gene Mutation

- Pooled analysis of 8 case-control studies
- Odds ratio of developing VTE
  - Prothrombin gene mutation heterozygotes — 3.8
  - Factor V Leiden heterozygotes — 4.9
  - Both mutations (double heterozygotes) — **20.0**

Bauer KA, et al. Prothrombin gene mutation: Thrombotic risk and diagnosis. UptoDate. 2014. Accessed September 29, 2014.

Prothrombin Gene Mutation

- Diagnosis
- Polymerase chain reaction (PCR)
  - Detect the G20210A prothrombin gene mutation in DNA
- Multiplex PCR amplification
  - Used to detect both prothrombin mutation and Factor V Leiden
  - Region of both genes using whole blood as the DNA source

Bauer KA, et al. Prothrombin gene mutation: Thrombotic risk and diagnosis. UptoDate. 2014. Accessed September 29, 2014.

Treatment

- Treatment is recommended if acute VTE develops
- Anticoagulant medications include
  - Warfarin
  - Unfractionated heparin
  - Low-molecular weight heparin
  - Fondaparinux
  - Dabigatran
- Prophylaxis should be used after surgery or extended hospital stay

Hypercoagulable States. 2014. Available at: http://my.clevelandclinic.org/services/heart/disorders/hypercoagstate. Accessed September 21, 2014.

Antiphospholipid Syndrome

- Autoimmune disorder
- Characterized by an increased tendency to form clots
  - Clots can develop in any vessel in the body
    - Most commonly occurs in lower limbs
- Other signs and symptoms
  - Thrombocytopenia
  - Anemia due to hemolysis
  - Livedo reticularis

Antiphospholipid Syndrome. 2013. Available at: http://ghr.nlm.nih.gov/condition/antiphospholipid-syndrome. Accessed October 1, 2014.

Antiphospholipid Syndrome

- APS in pregnancy
  - 10-15% of women with miscarriages have this condition
  - Complications
    - Preeclampsia
    - Placental insufficiency
    - Early delivery or miscarriage
- Catastrophic antiphospholipid syndrome (CAPS)
  - Multiple clots in various blood vessels throughout the body
  - Blocks blood flow and causes organ failure

APS: Antiphospholipid Syndrome

Antiphospholipid Syndrome. 2013. Available at: http://ghr.nlm.nih.gov/condition/antiphospholipid-syndrome. Accessed October 1, 2014.

Antiphospholipid Antibodies

- Antibodies against phospholipids in the lining of cells
  - Bind to proteins and causes them to bind to other molecules
  - Binding to molecules activates clotting pathway
- Diagnosis
  - Presence of ≥1 type of antiphospholipid antibody (aPL) on 2 different times at least 12 weeks apart
- Associated with the presence of autoimmune diseases
  - Occurs most commonly in people with SLE
    - 10-15% of people with SLE have antiphospholipid syndrome

aPL: Antiphospholipid antibody
SLE: Systemic Lupus Erythmatosus

Antiphospholipid Syndrome. 2013. Available at: http://ghr.nlm.nih.gov/condition/antiphospholipid-syndrome. Accessed October 1, 2014.

Antiphospholipid Antibodies

- Three major aPLs
  - Anticardiolipin antibodies (aCL)
  - Antibodies to beta-2-glycoprotein-I (beta-2-GP-I)
  - Lupus anticoagulant (LA)
- Beta-2-GP-I is the main antigenic target of aPL
- aPLs are autoantibodies

Harris ED, et al. *Kelley's Textbook of Rheumatology*. 7th ed. St. Louis, Mo: WB Saunders; 2005.

aPL: Antiphospholipid antibody

Antiphospholipid Antibodies

- Odds ratio of developing VTE or arterial thromboembolism
  - Lupus anticoagulant — 11
  - Medium or high levels of aCL — 1.6
- Risk is even higher with positivity to 3 aPL activities
  - LA, aCL, and beta-2-glycoprotein-I

Bermas BL, et al. Clinical manifestations of the antiphospholipid syndrome. UpToDate. 2013.

LA: Lupus Anticoagulant
aCL: Anticardiolipin antibodies
aPL: Antiphopholipid antibodies

Antiphospholipid Antibodies

- Lupus Anticoagulant (LA) causes prolongation in:
  - Activated partial thromboplastin time (aPTT)
  - Dilute Russell viper venom time (dRVVT)
  - Kaolin clotting time
  - Prothrombin time
- Prolongation is not reversed when the patient's plasma is diluted 1:1 with normal platelet-free plasma

Bermas BL, et al. Clinical manifestations of the antiphospholipid syndrome. UpToDate. 2013.

LA: Lupus Anticoagulant

Antiphospholipid Antibodies

- aPL bound to phospholipids may be detected by:
  - Lupus anticoagulant tests
  - Anticardiolipin antibody ELISA
  - Anti-beta-2 glycoprotein-I ELISA
- Other tests include:
  - Partial thromboplasin time (PTT)
  - Russell viper venom time
  - Thromboplastin inhibition test

Bermas BL, et al. Clinical manifestations of the antiphospholipid syndrome. UpToDate. 2013.

aPL: Antiphospholipid antibody

APS Treatment

- Asymptomatic patients with positive blood tests do not require treatment
- Prophylaxis
  - Avoid oral contraceptives and smoking
  - Prophylactic anticoagulation for surgery or hospital stay
  - Statins for patients with hyperlipidemia
  - Hydroxychloroquine for SLE patients
  - Stay active during long periods of inactivity

APS: Antiphospholipid Syndrome

Movva S, et al. Antiphospholipid Syndrome Treatment. Medscape. 2014. Available at: http://emedicine.medscape.com/article/333221-treatment.

APS Treatment

- Full anticoagulation warranted if patient presents with a clot
  - IV or subcutaneous heparin followed by warfarin
- INR targets
  - 2.0-3.0 for venous thrombosis
  - 3.0 for arterial thrombosis
  - 3.0-4.0 for patients with recurrent thrombosis while therapeutic
- Treatment is generally lifelong

APS: Antiphospholipid Syndrome

Movva S, et al. Antiphospholipid Syndrome Treatment. Medscape. 2014. Available at: http://emedicine.medscape.com/article/333221-treatment.

APS Treatment

- Other options
  - Combination of warfarin and aspirin for refractory cases
  - New oral anticoagulants have not been studied
    - RAPS (Rivaroxaban in antiphospholipid syndrome) trial currently ongoing
  - May be considered if patient is allergic/intolerant to warfarin
  - Rituximab for recurrent thrombosis with therapeutic INR
    - May be effective for other clinical manifestations

APS: Antiphospholipid Syndrome

Movva S, et al. Antiphospholipid Syndrome Treatment. Medscape. 2014. Available at: http://emedicine.medscape.com/article/333221-treatment.

APS Treatment: Pregnancy

- Treatment during pregnancy
  - History of pregnancy loss
    - Prophylactic subcutaneous heparin and low-dose aspirin
    - Therapy is withheld at the time of delivery
    - Restarted after delivery for 6-12 weeks postpartum
  - History of thrombosis
    - Therapeutic doses of heparin
  - Prenatal and post-partum
    - Prophylactic dose for no history of thrombosis
    - Long term full anticoagulation for history of thrombosis

APS: Antiphospholipid Syndrome

Movva S, et al. Antiphospholipid Syndrome Treatment. Medscape. 2014. Available at: http://emedicine.medscape.com/article/333221-treatment.

Take Home Points

- There are various types of genetic and acquired disorders that may put a person at a higher risk for developing clots
- Anticoagulant therapy is not warranted in genetic thrombophilias unless there is an active clot or high risk for one (ie surgery, etc)
- Antiphospholipid syndrome has specific INR requirements depending on clinical situation

References

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10. Movva S, et al. Antiphospholipid Syndrome Treatment and Management. Medscape. 2014. Available at: http://emedicine.medscape.com/article/333221-treatment. Accessed October 1, 2014.

Questions

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