Thrombotic Disorders

(See also *Harrison's Principles of Internal Medicine*, 17th Edition, Chapters 111 and 112)

Definition

- Thrombosis
  - Formation of a blood clot within the vascular system
  - Occurs normally in response to hemorrhage
  - When it occurs at the wrong place or at the wrong time, thrombosis can lead to reduced blood flow to critical organs such as the brain, lungs, and myocardium.
- Thrombotic disorders
  - Group of inherited and acquired disorders that cause abnormal activation of the hemostatic system
  - Lead to increased risk of thrombosis
  - Also known as hypercoagulable state
  - Play a major role in the pathogenesis of venous thromboembolism
  - Play a less clearly defined role in the pathogenesis of arterial thrombosis
- Thrombophilia: term used to describe primary thrombotic disorders
  - Inherited disorders
    - Factor V Leiden (resistant to inhibition by activated protein C)
      - 5–8-fold increased risk of thrombosis in heterozygotes
      - 50–80-fold increased risk in homozygotes
    - Antithrombin III deficiency
    - Protein C deficiency
    - Protein S deficiency
    - Prothrombin gene mutation (*G20210A*)
      - 2–4-fold increased risk in heterozygotes
      - 10-fold increased risk in homozygotes
  - Acquired disorders
    - Antiphospholipid antibody syndromes; 10-fold increased risk
      - Anticardiolipin antibody (ACLA) thrombosis syndrome
      - Lupus anticoagulant (LA) syndrome
    - Malignancy; 10–20-fold increased risk
    - Major surgery; 6-fold increased risk
    - Immobilization; 11-fold increased risk
    - Oral contraceptive use; 4-fold increased risk
    - Thalidomide use (or its congeners) especially in combination with dexamethasone; 10–20% incidence
    - Heparin-induced thrombocytopenia; 50-fold increased risk
    - Pregnancy; 5-fold increased risk
    - Myeloproliferative disorders
    - Inflammatory bowel disease
    - Nephrotic syndrome
    - Paroxysmal nocturnal hemoglobinuria: 40% incidence

        - Hyperviscosity syndrome; Waldenstrom's macroglobulinemia, multiple myeloma
        - Trauma
    - Combined disorders
        - Oral contraceptive use in a Factor V Leiden heterozygote; 35-fold increased risk
    - See Antiphospholipid Antibodies and Inherited Prothrombotic Disorders for details of these disorders.

Epidemiology

- Incidence
    - Deep venous thrombosis (DVT): 1% of persons annually in the general population >60 years of age
    - Pulmonary embolism (PE): 69 cases per 100,000 persons annually
    - Factor V Leiden
        - Particularly common heritable defect associated with a hypercoagulable state
        - Present in 20% of cases of unexplained venous thromboembolism
        - May account for 25% of recurrent DVT or PE
    - Deficiencies of antithrombin, protein C, and protein S
        - Account for <10% of all recurrent venous thrombosis
        - Mild (heterozygous) antithrombin deficiency the most common defect (1 in 2000 population; 1% of DVT)
    - Prothrombin gene mutation (*G20210A*)
        - Heterozygotes account for ~18% of cases with family history of venous thrombosis and 6% of first episode of DVT.
    - Antiphospholipid antibodies
        - Present in 10–20% with venous thrombosis
        - ACLA thrombosis syndrome >5 times more common than LA thrombosis syndrome
        - Present in 1–5% of young, healthy population
        - Present in 12–30% of patients with systemic lupus erythematosus (SLE)
        - Increases with age and coexistent diseases
    - Hyperhomocystinemia
        - 10–20% prevalence in venous thrombosis
    - Most cases of DVT occur in people with multiple risk factors that may include:
        - Smoking; 2–3-fold increased risk
        - Obesity; 2–3-fold increased risk
        - Immobilization; 11-fold increased risk
        - Surgery; 6-fold increased risk
        - Oral contraceptive use; 4-fold increased risk
        - Malignancy; 10–20-fold increased risk
- Age
    - More common with advanced age
    - Hazard ratio 1.7 for every decade of life after age 55
    - DVT incidence 17/100,000 for age 40–49 years; 232/100,000 for age 70–79 years
- Sex
    - More common in women than men

Mechanism

- Thrombi are composed of insoluble fibrin, platelets, and trapped red and white cells and are typically formed on disrupted endovascular surfaces.
- A wide variety of mechanisms can lead to increased thrombus formation, including:
  - Endothelial damage
  - Sluggish blood flow
  - Defective inhibition of coagulation factors
  - Impaired clot lysis
  - Antiphospholipid antibodies
  - See Differential Diagnosis for specific disorders.
- Venous thromboembolism is thought to be caused by underlying genetic predisposition and acquired precipitating events.
- Primary hypercoagulable states are due to:
  - Decreased antithrombotic proteins
    - Antithrombin deficiency
    - Protein C deficiency
    - Protein S deficiency
  - Increased prothrombotic proteins
    - Factor V Leiden
    - Prothrombin gene mutation (*G20210A)*
    - Increased levels of factors VII, XI, IX, VIII, von Willebrand factor

Symptoms & Signs

- May be asymptomatic or can manifest as a thromboembolic event such as:
  - Venous thrombosis
    - DVT
    - PE
    - Budd-Chiari syndrome
  - Arterial thrombosis
    - Coronary artery thrombosis
    - Cerebrovascular thrombosis
    - Transient ischemic attacks
    - Mesenteric vascular insufficiency
    - Occlusion of blood flow to extremities
  - Retinal vascular thrombosis
  - Recurrent second trimester miscarriage
  - Placental infarction

Differential Diagnosis

Inherited

- Defective inhibition of coagulation factors
  - Factor V Leiden (resistant to inhibition by activated protein C)
  - Antithrombin III deficiency
  - Protein C deficiency
  - Protein S deficiency
  - Prothrombin gene mutation (*G20210A*)
  - Heparin cofactor II deficiency

- Impaired clot lysis
  - Dysfibrinogenemia
  - Plasminogen deficiency
  - Tissue plasminogen activator (tPA) deficiency
  - PAI-1 excess
  - Factor XII deficiency
- Elevated levels of clotting factors and chemokines
  - Factor VIII
  - Factor IX
  - Factor XI
  - Thrombin-activatable fibrinolysis inhibitor
  - Interleukin-8
- Uncertain mechanism
  - Homocystinuria: thought due to endothelial damage
- For details of these disorders, see Antiphospholipid Antibodies and Inherited Prothrombotic Disorders.

Acquired

- Diseases or syndromes
  - LA/ACLA syndrome
  - Malignancy
  - Myeloproliferative disorder
  - Thrombotic thrombocytopenic purpura
  - Estrogen treatment
  - Tamoxifen treatment
  - Hyperlipidemia
  - Diabetes mellitus
  - Hyperviscosity
  - Nephrotic syndrome
  - Congestive heart failure
  - Atrial fibrillation
  - Paroxysmal nocturnal hemoglobinuria
  - Heparin-induced thrombocytopenia
  - Inflammatory bowel disease
- Physiologic states
  - Pregnancy (especially postpartum)
    - HELLP syndrome (*h*emolysis, *e*levated *l*iver enzymes, *l*ow *p*latelets)
  - Obesity
  - Postoperative state
  - Trauma
  - Immobilization
  - Intravenous drug use
  - Previous thromboembolism
- Old age

Diagnostic Approach

- Complete history, including careful family history, and physical examination aimed at assessing the presence of risk factors
- Thrombotic disorders should be considered in patients with recurrent episodes of venous thromboembolism (DVT or PE)

- Primary thrombotic disorders can often be identified by a careful history.
  - Three important diagnostic clues are:
    - Repeated episodes of thromboembolism without an obvious predisposing condition
    - Family history of thrombosis
    - Well-documented thromboembolism in adolescents and young adults
- Patients who develop DVT or PE without a clear predisposing factor and who have a strong family history, present under age 30, or have 1 or more episodes should have assays for:
  - Antithrombin III
  - Proteins C and S
  - Factor V Leiden
  - Kaolin clotting time (KCT) or dilute Russell viper venom time (dRVVT) if partial thromboplastin time (aPTT) is prolonged

Laboratory Tests

Inherited prothrombotic disorders

- Antithrombin III
  - Normal plasma value is 5–15 mg/L (50–150%).
  - Values only slightly below normal increase the risk of thrombosis.
  - For optimal screening, the antithrombin III concentration is measured by immunoassay, and the plasma antithrombin and heparin cofactor activity are assessed with functional assays.
- Protein C and S
  - Both free and total protein S levels or C4b-binding protein levels should be assessed for maximum accuracy.
  - The correlation between levels of proteins C and S and the risk of thrombosis is not as precise as for antithrombin III deficiency.
- Factor V Leiden
  - Leiden mutation analysis is usually performed by polymerase chain reaction or dot blot assay.
  - Specificity is ~ 100%.

Acquired prothrombotic disorders

- There are 2 basic groups of testing for acquired prothrombotic disorders.
  - Antiphospholipid antibodies (e.g., to cardiolipin, phosphatidylserine, and β_2-GpI)
    - Nonspecific (lupus-like) inhibitors prolong coagulation tests by binding to phospholipids.
    - Assayed by anticoagulant effect (LA activity) or ability to bind to the complex phospholipid cardiolipin (ACLA activity)
    - High titers of immunoglobulin G anticardiolipin (>50 IU) indicate high risk for clotting.
    - Tests for LA or ACLA activity not well standardized; results may vary among and within patients.
  - Coagulation tests
    - Partial thromboplastin time (aPTT): prolonged in the presence of antiphospholipid antibodies
    - KCT and dRVVT: more specific tests for antiphospholipid antibodies
- The best predictor of thrombosis risk is a consistent prolongation of more than 1 coagulation test coupled with a high titer of ACLA activity.

- Repeat testing may be justified if clinical manifestations of the antiphospholipid antibody syndrome (APS) appear.
    - To diagnose APS with or without SLE requires the presence of clotting and/or repeated fetal losses plus
    - At least 2 positive tests for antiphospholipid antibodies, at least 6 weeks apart

Imaging

- Duplex venous ultrasonography
    - Noninvasive test used most often to diagnose DVT
- MRI
    - Noninvasive method to detect DVT and PE
    - Useful in suspected thrombosis in pelvic veins or superior and inferior vena cava
    - Used to establish cause of stroke
- CT of chest with contrast
    - Superseding lung scan as principle imaging test for diagnosis of PE
- CT of head
    - To establish cause of stoke
- Ventilation/perfusion lung scanning
    - To diagnose PE
- Pulmonary angiography
    - Most specific examination for definitive diagnosis of PE
- Arteriography
    - To confirm diagnosis and extent of arterial occlusion

Treatment Approach

- General
    - Initial treatment depends on the type of thrombosis.
        - See Deep Venous Thrombosis, Pulmonary Thromboembolism, Approach to Stroke.
    - Long-term treatment depends on the underlying disorder.
- Inherited prothrombotic disorders
    - Treatment recommendations are still evolving.
    - All patients who present with thrombosis should receive standard initial therapy with conventional or low-dose heparin followed by 3 months of oral warfarin.
    - It is unclear which patients should go on to receive long-term (possibly lifelong) anticoagulation.
    - See Antiphospholipid Antibodies and Inherited Prothrombotic Disorders for details.
- Acquired prothrombotic disorders
    - Risk factor modification (e.g., discontinuation of prothrombotic medications) or treatment of the underlying disease may reduce risk of thrombosis.
    - Antiphospholipid syndrome due to lupus-related APS
        - Anticoagulation to maintain the internalized normal ratio (INR) at 3.0 may be beneficial in reducing the incidence of recurrent thromboses.

Specific Treatments

General

- Treatment of thrombotic event varies depending on the type of thrombosis; see:
    - Deep Venous Thrombosis

    - Pulmonary Thromboembolism
    - Approach to Stroke
    - See below for discussion of common antithrombotic agents.
- Treatment or prevention of the underlying thrombotic disorder
    - Discontinue prothrombotic medications.
    - Treat underlying disease, if possible.
    - For treatment of patients with inherited disorders or antiphospholipid antibodies, see Antiphospholipid Antibodies and Inherited Prothrombotic Disorders.
    - In other acquired disorders, continuation of antithrombotic treatment beyond initial treatment period should be considered based the underlying disorder, number of prior episodes of thrombosis, and the patient's risk of bleeding.

Anticoagulant agents

- See Anticoagulant Therapy for details.
- Heparins
    - Mechanism of action: enhances activity of antithrombin III
    - Unfractionated heparin (UFH):
        - Should be given only if low-molecular-weight heparin (LMWH) is unavailable or parenteral therapy is required
        - Monitor by following aPTT; should be maintained between 1.5 and 2 times upper normal limit.
        - Major complication of UFH therapy is hemorrhage—manage by discontinuing heparin; for severe bleeding, administer protamine (1 mg/100 U heparin); results in rapid neutralization.
    - LMWH
        - Agent of choice for outpatient
        - Can be administered subcutaneously (SC)
        - Monitoring of the aPTT is unnecessary.
        - Less likely to induce antibodies and thrombocytopenia
        - Agents: enoxaparin, dalteparin, tinzaparin
- Warfarin (Coumadin)
    - Mechanism of action
        - Vitamin K antagonist; decreases levels of factors II, VII, IX, X, and anticoagulant proteins C and S
    - Dosing
        - Initial load of 5–10 mg PO qd administered over 2–3 days
        - Followed by titration of daily dose to keep the prothrombin time (PT) 1.5–2 times control or 2–3 times if the INR method is used
    - Complications
        - Hemorrhage, warfarin-induced skin necrosis (rare, occurs in persons deficient in protein C), teratogenic effects
        - Warfarin effect reversed by administration of vitamin K; fresh frozen plasma infused if urgent reversal necessary
    - Interactions
        - Agents that potentiate warfarin effect: chlorpromazine, chloral hydrate, sulfonamides, chloramphenicol, other broad-spectrum antibiotics, allopurinol, cimetidine, tricyclic antidepressants, disulfiram, laxatives, high-dose salicylates, thyroxine, clofibrate
        - Agents that antagonize warfarin effect: vitamin K, barbiturates, rifampin, cholestyramine, oral contraceptives, thiazides
- Pentasaccharides
    - Directly inhibits factor Xa

    - May result in less heparin-induced thrombocytopenia than UFH and LMWH
    - Fondaparinux
        - Given SC
        - Does not require monitoring
    - Idraparinux
        - Has a half-life of 130 hours, which may facilitate once-weekly dosing for primary and/or secondary prevention of thromboembolic events
- Direct thrombin inhibitors
    - New class of anticoagulants
    - Commonly used in patients with heparin-induced thrombocytopenia
    - Also being compared with LMWHs
    - Agents: lepirudin, argatroban, bivalirudin, ximelagatran
- In-hospital anticoagulation
    - Usually initiated with heparin, with subsequent maintenance on warfarin after an overlap of 3 days
- Duration of therapy depends on underlying condition.
    - Calf DVT with clear precipitating cause: 3 months
    - Proximal or idiopathic DVT: 6–12 months
    - First DVT with documented thrombophilic abnormality: 6–12 months
    - First DVT with antiphospholipid antibodies or 2 or more thrombophilic abnormalities: 12 months
    - Recurrent idiopathic DVT: 12 months minimum
    - PE: 6 months minimum
    - Embolic disease with ongoing risk factor: long term or indefinite

Fibrinolytic agents

- See Fibrinolytic Therapy for details.
- Mechanism of action: clot lysis by activating plasmin, which degrades fibrin
- Indications include:
    - Acute ST-elevation myocardial infarction within 6 hours of symptom onset
    - Hemodynamically unstable PE
    - Arterial embolic occlusion of extremity
    - Central venous line–associated thrombosis
    - Thrombolysis for DVT
        - Lower incidence of postphlebitic syndrome (chronic venous stasis, skin ulceration) than with heparin therapy
        - Also associated with significant risk of bleeding complications
        - Risks may not outweigh the benefits.
- Tissue plasminogen activator (tPA, alteplase),
    - For acute myocardial infarction (MI) and massive PE (adult > 65 kg), 10-mg IV bolus over 1–2 min, then 50 mg IV over 1 h and 40 mg IV over next 2 h (total dose = 100 mg)
    - tPA is slightly more effective but more expensive than streptokinase for treatment of acute MI.
- Streptokinase
    - For acute MI, 1.5 million IU IV over 60 min; or 20,000 IU as a bolus intracoronary (IC) infusion, followed by 2000 IU/min for 60 min IC
    - For PE or arterial or DVT, 250,000 IU over 30 min, then 100,000 IU/h for 24 hours (PE) or 72 hours (arterial or DVT)
- Urokinase
    - For PE, 4400 IU/kg IV over 10 minutes, then 4400 (IU/kg)/h IV for 12 hours.
- Fibrinolytic therapy is usually followed by period of anticoagulant therapy with heparin.

- Fibrinolytic agents are contraindicated in patients with:
  - Active internal bleeding
  - Recent (<2–3 months) cerebrovascular accident
  - Intracranial neoplasm, aneurysm, or recent head trauma

Antiplatelet agents

- See Antiplatelet therapy for details.
- Aspirin
  - Effective in treatment of stable and unstable angina, acute MI, transient ischemic attack and incomplete stroke, stroke following carotid artery surgery, and atrial fibrillation
  - Reduces mortality after coronary artery bypass surgery
  - Advisable following peripheral arterial bypass surgery and carotid endarterectomy and in patients with intermittent claudication
  - Minimum effective dose: 75–325 mg/d
- Thienopyridines
  - Clopidogrel (400-mg loading dose then 75 mg/d) together with aspirin may be beneficial in lowering incidence of arterial thrombotic events (stroke, MI) in high-risk patients.

Interruption of the inferior vena cava

- Patients with recurrent PE despite adequate anticoagulation or those who have a contraindication to anticoagulation are candidates for inferior vena cava interruption, preferably with a removable filter.

Monitoring

- UFH therapy
  - Monitor aPTT to achieve target of at 2X normal.
  - Monitor platelet count for possible development of heparin-induced thrombocytopenia.
- Warfarin therapy
  - Monitor PT to maintain a target INR of 2.0–3.0 with high-intensity therapy and 1.5–2.0 with low-intensity therapy

Complications

- General
  - Recurrent thromboembolism
- Antiphospholipid syndrome:
  - Arterial thrombosis
    - Coronary artery thrombosis
    - Cerebrovascular thrombosis
    - Transient ischemic attacks
  - Venous thrombosis
  - Retinal vascular thrombosis
  - Recurrent second trimester miscarriage
  - Placental infarction
  - Thrombocytopenia

- Anticardiolipin antibodies can also be associated with:
  - Livedo reticularis
  - Necrotizing purpura
  - Stasis ulcers of ankles
- Rarely, catastrophic antiphospholipid syndrome
  - Massive venous thrombosis
  - Respiratory failure
  - Cerebrovascular accident
  - Renal impairment
  - Liver function abnormalities
  - Adrenal insufficiency
  - Areas of cutaneous infarction

Prognosis

- Prognosis depends on the type of thrombosis and the underlying disorder; see
  - Approach to Stroke
  - Deep Venous Thrombosis
  - Pulmonary Thromboembolism
  - Antiphospholipid Antibodies and Inherited Prothrombotic Disorders
- Risk of thromboembolic event
  - Antithrombin deficiency
    - Greater risk of thromboembolic event than other prothrombotic disorders
    - Up to 85% have thromboembolic event by age 50.
  - Correlation between levels of proteins C and S and the risk of thrombosis is not as precise as for antithrombin III deficiency.
  - Factor V Leiden
    - Heterozygosity increases lifetime risk 7-fold.
    - Risk rises steadily with age.
    - Homozygote has 20-fold risk.
    - Heterozygosity coupled with oral contraceptives or pregnancy increases risk at least 15-fold.
    - Additive risk with other inherited defects
  - Inheritance of multiple mutations increases the risk of thrombosis.

Prevention

- There is no means of prevention for inherited prothrombotic disorders.
- Avoidance of certain drugs that may cause a hypercoagulable state
  - Oral contraceptives
  - L-asparaginase
  - Granulocyte-macrophage colony-stimulating factor
  - Tamoxifen

ICD-9-CM

- 453.9 Other venous embolism and thrombosis of unspecified site
- 453.__ Other venous embolism and thrombosis, (Use fourth and fifth digits for specificity)

See Also

- Anticoagulant Therapy

- Antiphospholipid Antibodies and Inherited Prothrombotic Disorders
- Antiplatelet Therapy
- Approach to Stroke
- Deep Venous Thrombosis
- Fibrinolytic Therapy
- Pulmonary Thromboembolism
- Superficial Thrombophlebitis
- Thrombotic Thrombocytopenic Purpura

Internet Sites

- Professionals
  - Venous Thrombosis clinical trials
    ClinicalTrials.gov
- Patients
  - What are Anticoagulants and Antiplatelet Agents?
    American Heart Association

General Bibliography

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PEARLS

- In 1865, Professor Armand Trousseau first reported the association between cancer and thrombosis.
- 95% of venous thromboses are in the veins of the legs.
- A precipitating event can be identified in about 80% of people with their initial venous thromboembolism.
- Venous thromboembolism is actually present in only 20–30% of people suspected of having the problem on clinical grounds.
- In many patients, venous clots are clinically silent and only manifest themselves when PE occurs.

- An exhaustive and expensive search for an occult cancer is not warranted in a patient presenting with their first venous thromboembolism.
    - Occult cancer is detected in 4% or fewer of such patients, and no data suggest that the outcome of the cancer is improved by treatment begun before other symptoms bring the tumor to clinical attention.
- In the setting of migratory or recurrent venous thromboembolism, a complete history and physical examination including rectal and pelvic examinations, complete blood count, routine chemistries (including serum protein levels), prostate-specific antigen and CA-125 levels, chest x-ray, and abdominopelvic ultrasonography is a reasonable approach to detecting an underlying malignancy.
- The greatest risk factor for venous thromboembolism is prior venous thromboembolism; in idiopathic venous thromboembolism, the recurrence rate without anticoagulation is 7–8%/year over the next 2 years.