Thrombophilias and Causes of Hypercoagulability in the Hospital Setting

Thrombophilias and hypercoagulable states increase the risk of thrombosis (e.g., DVT, PE) in hospitalized patients, often due to genetic predispositions, acquired conditions, or hospital-specific factors. Understanding the causes, diagnosis, and management of hypercoagulability is critical to prevent life-threatening complications. This pamphlet provides students with a guide to diagnose, evaluate, and manage hypercoagulability in the hospital setting, with clinical scenarios to apply the knowledge.

Causes of Hypercoagulability

• Genetic Causes (Inherited Thrombophilias):

- Factor V Leiden Mutation:
  - Most common inherited thrombophilia (5% of Caucasians), autosomal dominant, mutation in factor V (resistant to activated protein C).
  - **Risk:** 5-10x increased risk of VTE, especially with other factors (e.g., pregnancy, OCP use).
- Prothrombin G20210A Mutation:
  - Second most common, autosomal dominant, increased prothrombin levels (factor II).
  - **Risk:** 2-3x increased risk of VTE, often with other triggers (e.g., surgery).
- Protein C Deficiency:
  - Autosomal dominant, reduced protein C activity (anticoagulant protein), risk of VTE and warfarin-induced skin necrosis.
  - **Risk:** 5-10x increased risk of VTE, neonatal purpura fulminans in homozygotes.
- Protein S Deficiency:
  - Autosomal dominant, reduced protein S (cofactor for protein C), increased risk of VTE.
  - **Risk:** 5-10x increased risk of VTE, similar presentation to protein C deficiency.
- Antithrombin Deficiency:
  - Autosomal dominant, reduced antithrombin (inhibits thrombin and factor Xa), high risk of VTE.

- **Risk:** 10-20x increased risk of VTE, heparin resistance (antithrombin needed for heparin efficacy).

- Rare Genetic Causes:
  - **Dysfibrinogenemia:** Abnormal fibrinogen, autosomal dominant, can cause thrombosis (or bleeding in some cases).
  - **Hyperhomocysteinemia:** MTHFR mutations (e.g., C677T), elevated homocysteine levels, 2-3x increased risk of VTE, stroke, often acquired (vitamin B12/folate deficiency).

Acquired Causes:

- Antiphospholipid Syndrome (APS):
  - Autoimmune disorder w/ antiphospholipid antibodies (lupus anticoagulant, anti-cardiolipin, anti-β2-glycoprotein I).
  - **Risk:** Recurrent VTE, arterial thrombosis, miscarriage, stroke; often associated with SLE.
- Malignancy:
  - Cancer increases risk via tumor procoagulants (e.g., tissue factor), chemotherapy, and immobility.
  - **Risk:** Pancreatic, lung, ovarian cancers have highest risk; 4-7x increased risk of VTE.
- Pregnancy and Postpartum:
  - Increased clotting factors (e.g., fibrinogen, factor VIII), decreased protein S, venous stasis.
  - **Risk:** 5-10x increased risk of VTE, highest in postpartum period (up to 6 weeks).
- Oral Contraceptives (OCPs)/Hormone Replacement Therapy (HRT):
  - Estrogen increases clotting factors (e.g., factor VIII, vWF), decreases protein S.
  - **Risk:** 3-4x increased risk of VTE, higher with combined OCPs, smoking, or genetic thrombophilias.
- Nephrotic Syndrome:
  - Loss of antithrombin in urine, increased clotting factors, hypoalbuminemia.
  - **Risk:** 2-5x increased risk of VTE, especially renal vein thrombosis.
- Inflammatory Conditions:
  - IBD, rheumatoid arthritis, vasculitis increase clotting factors via inflammation (e.g., IL-6 increases fibrinogen).
  - **Risk:** 2-3x increased risk of VTE, exacerbated by immobility.

• Hospital-Specific Causes:

- Immobility:
  - Prolonged bed rest (e.g., ICU, post-surgery) leads to venous stasis.
  - **Risk:** 2-5x increased risk of VTE, common in hospitalized patients.
- Surgery/Trauma:
  - Tissue injury releases tissue factor, activates coagulation; immobility adds risk.
  - **Risk:** 5-10x increased risk of VTE, highest in orthopedic, neurosurgery, trauma patients.
- Central Venous Catheters:
  - Indwelling catheters (e.g., PICC lines) cause endothelial injury, stasis.
  - **Risk:** 2-5x increased risk of upper extremity DVT, catheter-associated thrombosis.
- Sepsis:
  - Endotoxin-mediated activation of coagulation, decreased protein C/S, increased tissue factor.
  - **Risk:** 3-5x increased risk of VTE, DIC with thrombosis predominance.
- Obesity:
  - Increased clotting factors (e.g., fibrinogen, factor VIII), chronic inflammation, venous stasis.
  - **Risk:** 2-3x increased risk of VTE, common in hospitalized patients.
  - Dehydration:
  - Hemoconcentration increases clotting factor concentration, viscosity.
  - **Risk:** 2x increased risk of VTE, common in critically ill patients.

Causes of Hypercoagulability Table

Cause	Mechanism	Key Features	Risk of Thrombosis
Factor V Leiden	Resistance to activated protein C	Family history, recurrent DVT/PE	5-10x increased risk of VTE
APS	Antiphospholipid antibodies	Recurrent VTE, miscarriage, stroke	High risk (arterial/venous thrombosis)
Pregnancy	Increased clotting factors	Postpartum period, leg swelling	5-10x increased risk of VTE
Surgery/ Trauma	Tissue factor release, stasis	Post-orthopedic surgery, DVT risk	5-10x increased risk of VTE
Sepsis	Endotoxin-mediated coagulation	ICU setting, multiorgan failure	3-5x increased risk of VTE

Diagnosis and Labs

Initial Assessment:

- History:
  - Recent thrombosis (DVT, PE), family history of thrombosis, miscarriages (APS), recent surgery/trauma, OCP/HRT use, cancer history, immobility, ICU stay.
- Physical Exam:
  - Signs of thrombosis (leg swelling, tenderness, Homan's sign for DVT; dyspnea, tachycardia for PE), livedo reticularis (APS), obesity, post-surgical status.

Labs:

- **Inpatient Testing (Hospital Setting):**
- **Purpose:** Rapid assessment to identify hypercoagulability in the acute setting, guide immediate management (e.g., anticoagulation), and rule out active thrombosis.
  - **Tests Performed**:
    - **D-dimer:** Elevated in acute thrombosis (DVT/PE), DIC, sepsis; not specific for thrombophilia but useful to rule out VTE (normal <500 ng/mL).
    - **PT/INR/aPTT:** Often normal in thrombophilias; prolonged aPTT in APS (lupus anticoagulant).
    - **Platelet Count:** Normal in most thrombophilias; low in DIC, sepsis.
    - **Fibrinogen:** Elevated in inflammation (e.g., pregnancy, malignancy); low in DIC.
    - **CBC:** Polycythemia (e.g., cancer, dehydration), leukocytosis (sepsis, inflammation).
    - **CMP:** Elevated Cr (nephrotic syndrome), LFTs (liver disease, rare in hypercoagulability unless DIC).
  - **Imaging:** Duplex ultrasound (DVT), CT pulmonary angiogram (PE), CT/MRI for arterial thrombosis (e.g., stroke in APS).
  - **Rationale:** Inpatient testing focuses on immediate identification of thrombosis and reversible causes (e.g., immobility, sepsis). D-dimer and imaging are key for diagnosing acute events. Specific thrombophilia testing is often deferred unless urgent (e.g., APS with recurrent miscarriage in pregnancy).
- **Outpatient Testing (More Accurate, Diagnostic)**:

- **Purpose:** Detailed testing to confirm specific thrombophilias, assess long-term risk, and guide prophylaxis or family screening; performed in stable patients after acute thrombosis resolves.
    - Tests Performed:
        - **Thrombophilia Panel:** Factor V Leiden (PCR for R506Q mutation), prothrombin G20210A (PCR), protein C/S activity (functional assays), antithrombin activity.
        - **Antiphospholipid Antibodies:** Lupus anticoagulant (dilute Russell viper venom time), anti-cardiolipin antibodies, anti-β2-glycoprotein I (two positive tests, 12 weeks apart for APS).
        - **Homocysteine Levels:** Elevated in hyperhomocysteinemia (MTHFR mutations, B12/folate deficiency).
        - **Genetic Testing:** Confirms inherited thrombophilias (e.g., MTHFR mutations, rare deficiencies).
        - **Protein C/S and Antithrombin:** More accurate when patient is stable, off anticoagulation (warfarin/heparin interfere with assays).
        - **Rationale:** Outpatient testing is more specific for diagnosing thrombophilias but requires careful timing (e.g., 4-6 weeks post-thrombosis, off anticoagulation). Acute thrombosis, inflammation, or anticoagulation can falsely alter protein C/S or antithrombin levels, making inpatient results less reliable. These tests guide long-term management (e.g., extended anticoagulation, family screening).

Diagnostic Workup:

- Hospital Setting:
    - **Wells Score/Modified Geneva Score:** Risk stratify for DVT/PE, guide need for imaging.
    - **Mixing Studies:** If aPTT prolonged (e.g., APS with lupus anticoagulant), inpatient to differentiate from bleeding disorders.
    - **Imaging:** Urgent for suspected thrombosis (e.g., Duplex US for DVT, CT for PE).
- Outpatient Setting:
    - **Thrombophilia Testing:** As above, to confirm diagnosis and assess recurrence risk.
    - **Follow-Up Imaging:** If initial imaging negative but high suspicion (e.g., repeat US for DVT).

Diagnosis and Treatment Table

Cause	Diagnostic Approach	Treatment	Notes
Factor V Leiden	PCR for R506Q mutation (outpatient)	LMWH (enoxaparin 1 mg/kg SC BID)	Extended anticoagulation if recurrent.
APS	Lupus anticoagulant, anti-cardiolipin	Warfarin (INR 2-3), LMWH in pregnancy	Avoid DOACs, monitor for recurrence.
Pregnancy	D-dimer, Duplex US for DVT	LMWH (enoxaparin 1 mg/kg SC BID)	Continue 6 weeks postpartum.
Surgery/ Trauma	Wells score, Duplex US for DVT	Prophylaxis: enoxaparin 40 mg SC daily	Early mobilization, mechanical prophylaxis.
Sepsis	D-dimer, imaging for thrombosis	Treat sepsis, LMWH if stable	Monitor for DIC, avoid if bleeding risk.

Treatment and Overall Management

• General Principles:

- **Stabilize:** ABCs (airway, breathing, circulation), IV access, telemetry, monitor for thrombosis.
- **Treat Acute Thrombosis:** Anticoagulation, address reversible causes (e.g., immobility, sepsis).
- **Prevent Recurrence:** Prophylaxis, risk factor modification, long-term anticoagulation if indicated.

• Specific Treatments:

- Genetic Thrombophilias (Factor V Leiden, Prothrombin Mutation, Protein C/S Deficiency, Antithrombin Deficiency):
  - **Acute Thrombosis:** LMWH (enoxaparin 1 mg/kg SC BID) or UFH (80 units/kg IV bolus, then 18 units/kg/h, aPTT 60-80 sec), transition to DOAC (e.g., apixaban 5 mg PO BID) or warfarin (INR 2-3) for 3-6 months.
  - **Prophylaxis:** Enoxaparin 40 mg SC daily in high-risk settings (e.g., surgery, pregnancy).
  - **Duration:** Extended anticoagulation (lifelong) if unprovoked VTE, recurrent thrombosis, or homozygous mutation (e.g., factor V Leiden).
- Acquired Causes:
  - **APS:** Warfarin (INR 2-3) lifelong for unprovoked/recurrent thrombosis; LMWH in pregnancy (enoxaparin 1 mg/kg SC BID); avoid DOACs (higher thrombosis risk in APS).

- **Malignancy:** LMWH preferred (enoxaparin 1 mg/kg SC BID x 1 month, then 1.5 mg/kg daily); DOACs (e.g., apixaban) in stable patients; treat for ≥6 months or until cancer resolved.
- **Pregnancy/Postpartum:** LMWH (enoxaparin 1 mg/kg SC BID) until 6 weeks postpartum; avoid warfarin (teratogenic), DOACs (limited data).
- **OCPs/HRT:** Stop immediately; LMWH for acute thrombosis, counsel on alternative contraception (e.g., progesterone-only).
- **Nephrotic Syndrome:** LMWH (enoxaparin, dose-adjusted for CrCl), treat underlying cause (e.g., steroids for minimal change disease).
- **Inflammatory Conditions:** LMWH prophylaxis in hospitalized patients, treat underlying disease (e.g., anti-TNF for IBD).

- Hospital-Specific Causes:
  - **Immobility:** Prophylaxis with enoxaparin 40 mg SC daily, early mobilization, mechanical prophylaxis (e.g., compression stockings).
  - **Surgery/Trauma:** Enoxaparin 40 mg SC daily (or 30 mg BID for high-risk, e.g., orthopedic surgery), continue 10-35 days post-discharge; mechanical prophylaxis if bleeding risk.
  - **Central Venous Catheters:** Minimize catheter use, enoxaparin prophylaxis if high risk, treat catheter-associated thrombosis with LMWH (remove catheter if possible).
  - **Sepsis:** Treat infection (e.g., antibiotics, source control), LMWH prophylaxis if stable, monitor for DIC (heparin if thrombotic predominance).
  - **Obesity:** Enoxaparin 40 mg SC BID (higher dose due to increased risk), weight loss counseling.
  - **Dehydration:** IV fluids (NS 1-2 L bolus), enoxaparin prophylaxis, monitor for hemoconcentration.

- **Monitoring:**

- **Labs:** Q12-24h (D-dimer, platelets, fibrinogen) if DIC suspected; Cr for LMWH dosing.
- **Thrombosis:** Daily exam (leg swelling, dyspnea), repeat imaging if symptoms worsen (e.g., Duplex US for DVT progression).
- **Bleeding:** Q1-2h if on anticoagulation (vital signs, oozing, Hgb drop), imaging if internal bleed suspected (e.g., CT for retroperitoneal hematoma).

Key Pearls

- **Hypercoagulability:** Genetic (factor V Leiden, prothrombin mutation), acquired (APS, malignancy), hospital-specific (immobility, surgery).

- **Labs:** D-dimer, imaging for acute thrombosis (inpatient); thrombophilia panel (outpatient).
- **Genetic:** LMWH for acute thrombosis, extended anticoagulation if unprovoked/recurrent.
- **APS:** Warfarin (INR 2-3), avoid DOACs; LMWH in pregnancy.
- **Hospital-Specific:** Prophylaxis (enoxaparin 40 mg SC daily), early mobilization, treat reversible causes (sepsis, dehydration).
- **Testing:** Inpatient (D-dimer, imaging for acute thrombosis); outpatient (thrombophilia panel for specific diagnosis).
- **Monitor:** Labs q12-24h, daily exam for thrombosis, bleeding signs q1-2h if on anticoagulation.

References

- UpToDate: "Thrombophilia: Diagnosis and Management in the Hospitalized Patient" (2025).
- NEJM: "Hypercoagulable States: A Review" (2024).
- Blood: "Antiphospholipid Syndrome: Diagnosis and Treatment" (2023).
- J Thromb Haemost: "Management of VTE in Pregnancy" (2023).

Clinical Scenarios

Case 1: A 35-Year-Old Female with DVT

- **Presentation:** A 35-year-old female on OCPs presents with left leg swelling and pain for 2 days. Exam: BP 130/80 mmHg, HR 90 bpm, left leg edema, calf tenderness, BMI 32.
- **Labs:** D-dimer 1500 ng/mL, Cr 0.9 mg/dL (CrCl 80 mL/min), normal INR, platelets 200,000/µL.
- **Imaging:** Duplex US confirms left popliteal DVT.
- **Diagnosis:** Hypercoagulability Due to OCP Use and Obesity → DVT on US, OCP use, obesity.
- **Management:** Stop OCP. Start enoxaparin 1 mg/kg SC BID (80 mg BID, BMI 32). Transition to apixaban 10 mg PO BID x 7 days, then 5 mg BID (3-6 months). Counsel on weight loss, progesterone-only contraception. Monitor for bleeding q1-2h, repeat US in 1 week. Outpatient thrombophilia testing (factor V Leiden, prothrombin mutation) after anticoagulation completed.

Case 2: A 28-Year-Old Pregnant Female with PE

- **Presentation:** A 28-year-old female at 32 weeks gestation presents with dyspnea and chest pain for 1 day. Exam: BP 110/70 mmHg, HR 110 bpm, SpO2 90% on room air, no leg swelling.
- **Labs:** D-dimer 2000 ng/mL, Cr 0.8 mg/dL, platelets 180,000/µL.
- **Imaging:** CT pulmonary angiogram shows right segmental PE.
- **Diagnosis:** Hypercoagulability Due to Pregnancy → PE on CT, pregnant at 32 weeks.
- **Management:** Start enoxaparin 1 mg/kg SC BID (70 mg BID). Oxygen to maintain SpO2 >92%. Continue enoxaparin until 6 weeks postpartum. OB consult for delivery planning (stop enoxaparin 24h prior). Monitor for bleeding q1-2h, repeat CT if symptoms worsen. Outpatient thrombophilia testing post-pregnancy (e.g., protein S deficiency).

Case 3: A 50-Year-Old Male with Sepsis and Thrombosis

- **Presentation:** A 50-year-old male in the ICU with sepsis (pneumonia) develops right arm swelling around a PICC line. Exam: BP 90/60 mmHg, HR 120 bpm, Temp 39°C, right arm edema, sputum culture: S. pneumoniae.
- **Labs:** D-dimer 3000 ng/mL, platelets 90,000/µL, fibrinogen 150 mg/dL, Cr 1.5 mg/dL.
- **Imaging:** Duplex US confirms right subclavian DVT.
- **Diagnosis:** Hypercoagulability Due to Sepsis and Central Venous Catheter → DVT on US, sepsis, PICC line.
- **Management:** Remove PICC line. Start enoxaparin 1 mg/kg SC daily (80 mg daily, CrCl 40 mL/min). Ceftriaxone 1 g IV daily + azithromycin 500 mg IV daily (pneumonia). NS 2 L IV bolus, monitor for DIC (q12h labs: platelets, fibrinogen, D-dimer). ICU monitoring for sepsis, bleeding q1-2h. Outpatient follow-up for catheter use reduction, possible APS testing if recurrent thrombosis.