Table of Contents

**Introduction** .......................... 2

**Overview** ............................. 2

**Indications for Thrombophilia Testing** 4

**Inherited** .............................. 4
  Factor V Leiden .......................... 5
  Prothrombin Mutation (PGM) ............... 5
  Antithrombin Deficiency (ATD) ............. 5
  Protein C & S ................................ 5
  Dysfibrinogenemia .......................... 6

**Acquired** ............................... 6
  Increased Risk States ......................... 6
  Antiphospholipid Syndrome ....................... 6
Introduction

- Thrombosis occurs when delicate balance between prothrombotic and anticoagulant forces disturbed.
- Classic Triad: (Virchow's triad)
  1. **Stasis** (Accumulated coagulation proteins)
  2. **Hypercoagulability** (Synergizes with stasis/vascular damage to tip balance)
  3. **Vascular Damage** (Exposes tissue factor TF and collagen, reduces conc of antithrombotics)

Overview

- **Inherited Thrombophilia**

<table>
<thead>
<tr>
<th>Type</th>
<th>Risk of VTE</th>
<th>Recurrent VTE?</th>
<th>How Common</th>
<th>Diagnosis / Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden (FVL)</td>
<td>LOW (homo- 1.8%/year)</td>
<td>NO!</td>
<td>MOST COMMON</td>
<td>- Activated Protein C resistance assay</td>
</tr>
<tr>
<td></td>
<td>(hetero- 0.5%/year)</td>
<td></td>
<td></td>
<td>- Confirmed by: PCR-based DNA testing</td>
</tr>
<tr>
<td>Prothrombin Mutation (PGM) [G20210A mutation]</td>
<td>LOW (hetero --&gt; 2.5x) (Recurrence unlikely)</td>
<td>NO!</td>
<td>COMMON</td>
<td></td>
</tr>
<tr>
<td>Antithrombin Deficiency (ATD)</td>
<td>HIGHER (Initial: 1.8%/y Recurrence: Rate 55%)</td>
<td>YES</td>
<td>RARE</td>
<td>- Antithrombin Activity Assay</td>
</tr>
<tr>
<td>Protein C &amp; S Deficiency</td>
<td>MODERATE (Initial: 1.5% Recurrence: 6.2%/y)</td>
<td>YES</td>
<td>RARE</td>
<td></td>
</tr>
<tr>
<td>Dysfibrinogenemia</td>
<td>RARE (Primary)</td>
<td></td>
<td>RARE</td>
<td>- Disproportionate reduction in fibrinogen activity compared with antigen levels.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- OR: Reptilase Time (from snake)</td>
</tr>
<tr>
<td>Type</td>
<td>Risk of VTE</td>
<td>Recurrent VTE?</td>
<td>How Common</td>
<td>Diagnosis / Notes</td>
</tr>
<tr>
<td>-------------------------------</td>
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<td>-------------------------------------------------------</td>
</tr>
<tr>
<td>Acquired Thrombophilias</td>
<td></td>
<td></td>
<td></td>
<td>- Can bleed or clot.</td>
</tr>
<tr>
<td>• <strong>Antiphospholipid Syndrome</strong></td>
<td>VERY HIGH (Highest!)</td>
<td></td>
<td></td>
<td>- Clinical + Lab evidence</td>
</tr>
<tr>
<td></td>
<td>(Venous and Arterial)</td>
<td></td>
<td></td>
<td>(Lab Evidence: Anticardiolipin,</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Anti-β2-Glycoprotein, Lupus Anticoagulant)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>- Use Anti-Xa to monitor UFH (or LMWH), PTT unreliable</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>in lupus anticoagulant. <strong>Long-term anticoag w/ warfarin.</strong></td>
</tr>
<tr>
<td>Catastrophic Antiphospholipid Syndrome</td>
<td>VERY RARE</td>
<td></td>
<td></td>
<td>- Anticoagulation</td>
</tr>
<tr>
<td></td>
<td>LIFE Threatening (48% mort.)</td>
<td></td>
<td></td>
<td>- High dose corticosteroids, IVIG, plasma exchange.</td>
</tr>
<tr>
<td></td>
<td>Disseminated microvascular thrombosis, multi-organ failure.</td>
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<tr>
<td>Cancer</td>
<td>High: Pancreatic, Brain Me...</td>
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<tr>
<td></td>
<td>Med: Lung, Lymphoma</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Low: Prostate, Breast</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td>- Inpatient surgery (70 fold incr)</td>
<td></td>
<td>- Hip, Knee arthroplasty, and cancer surgery = highest risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Outpatient surgery (10-fold)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other:</td>
<td>Variable</td>
<td></td>
<td></td>
<td>- In acute thrombosis, liver disease, anticoagulant therapy</td>
</tr>
<tr>
<td>- Acquired Protein C/S deficiency</td>
<td></td>
<td></td>
<td></td>
<td>- Antithrombin deficiency (Nephrotic Syndrome)</td>
</tr>
<tr>
<td>- Antithrombin deficiency</td>
<td></td>
<td></td>
<td></td>
<td>- Protein S deficiency (estrogen therapy, incr C4b)</td>
</tr>
</tbody>
</table>
### Indications for Thrombophilia Testing

- **Big debate around whether it’s valuable.**
- More common disorders are not associated with recurrent thrombosis (in heterozygotes), such as Factor V Leiden and Prothrombin mutation.
  - and most higher-risk syndromes (like AT3 deficiency) are RARE.
- **Thrombophilia testing often does not change management**
- **Provoked vs. Unprovoked is a better indicator of recurrence.**
- Testing "higher risk" groups may increase yield:
  - Younger patients ≤ 40yo
  - Patients with positive family hx (1st deg. relative with VTE)
  - Patients with idiopathic VTE
  - VTE in unusual sites
  - Recurrent VTE
  - Warfarin skin necrosis
  - Pediatric patients with purpura fulminans
  - Patients planning future pregnancies.
- **When to screen?**
  - **Affected by Acute Thrombosis**
    - Antithrombin
    - Protein C
    - Protein S
    - Dysfibronogenemia
  - **Unaffected by Acute Thrombosis**
    - Factor V Leiden
    - Prothrombin G20210A
  (Must wait until after off of anticoagulants x2-4weeks)

- **Bottom Line:**
  - DO NOT test for inherited thrombophilia disorders in the setting of an acute thrombus!
    - One you can test for (genetic) have no increased recurrence rate, and others are inaccurate.
    - If you must test, test only >2weeks after anticoagulation is finished
  - **Generally does not change the management.**
  - Best predictor of recurrent thromboembolism is "unprovoked" vs. "provoked".
    - Many unprovoked VTE patients are on lifetime of anticoagulation, but a discussion of risks/benefits needs to be done with the patient.

- Some clinicians do D-Dimer 2 weeks before stopping anticoagulation as an indicator for recurrence risk (if high, continue anticoagulation), and also repeat 2 weeks after stopping to re-check risk.

### Inherited
• Least potency, more common
  • Factor V Leiden
    ◦ (MOST COMMON 5% of Caucasians, 2% of Latinos, 1% of African-Americans, 0.5% Asian)
  ◦ Prothrombin G20210A mutation
• Most potent and most rare: (1 in 4000 -6000)
  ◦ Antithrombin Deficiency
  ◦ Protein C & Protein S Deficiencies

**Factor V Leiden**
- MOST COMMON inherited thrombophilic disorder
  - 5% of Caucasians, 2% of Latinos, 1% of African-Americans, 0.5% Asian
- **Pathophysiology:**
  - Thrombin binds endothelial receptor thrombomodulin --> Protein C is activated to "Activated Protein C"
  - When Protein S is a cofactor, activated protein C inhibits Factor V and Factor VIII.
  - Factor V Leiden is a mutation making it resistant to activated protein C --> cause persistently active Factor V.
  - Factor V heterozygocity and homozygocity both increase risk of VTE (between 2-5 fold)
    - DO NOT increase risk of arterial thrombosis.
    - Heterozygocity (2-5x VTE incidence, absolute annual risk 0.5%)
    - Homozygous (up to 50x VTE incidence, absolute annual risk 1.8%)
- Pts with OCP, immobility, pregnancy synergize with Factor V Leiden to increase VTE risk.
- **Diagnosis:**
  - Activated Protein C Resistance Assay --> Abnormal
  - DNA Testing (PCR-based) to check for mutation.
- NOTE: Does not appear to be a risk factor for recurrent thrombosis

**Prothrombin Mutation (PGM)**
- Prothrombin G20210A mutation (PGM) --> 1-2% of non-Hispanic Whites, Mexican Americans.
- Most common inherited cause of thrombosis (although risk is low, and it's not common)
- Mutation stabilizes non-translated region of prothrombin mRNA --> increases prothrombin protein levels.
  - Heterozygous --> 30% more prothrombin --> 2.5x risk of VTE
  - Homozygous --> 70% more
  - Double-heterozygous Factor V Leiden + Prothrombin = 7x increased risk of VTE (5x recurrence risk)
- **Diagnosis:**
  - PGM DNA testing
- NOTE: This does not appear to be a risk factor for recurrent thrombosis.

**Antithrombin Deficiency (ATD)**
- RARE, but reasonably high risk of thrombosis
- Pathophysiology:
  - Antithrombin (used to be AT3, but no 1 or 2, so removed number) endogenous antithrombotic protein that inhibits serine proteases (thrombin and factor Xa).
  - Heparin/LMWH/fondaparinux usually accelerates Antithrombin activity several thousand-fold.
- 1.8%/year additional risk of thrombosis (recurrence rate of 55%)
- Venous + Arterial (under FVL and PGM)
- Rarely causes heparin resistance
- Various types:
  - Type I - impair protein synthesis (high risk of VTE)
  - Type II - Mutations affecting thrombin (type IIa) and heparin (IIb) binding sites.
- **Diagnosis:**
  - Antithrombin activity assay (detects all 3 types).

**Protein C & S**
- Protein C (anticoagulant)
When thrombin binds to endothelial receptor (thrombomodulin) activates protein C. Protein C (cofactor protein S) binds to inactivate Factors V and VIII.

- Deficiency = hypercoagulability
- 1.5%/year risk of initial thrombosis + recurrent VTE (6.2%/year) --> present 10-15yo.

- **Protein S**
  - Cofactor for Protein C to degrade Factor V and VIII
  - Vitamin K-dependent factor
  - Facilitates inactivation of FXa by tissue factor inhibitor
  - Circulates in free form (40%) and bound to C4b binding protein.
    - Can be Type I (quantitative abnormality) and Type II (qualitative)
    - Type III - increase in C4b bound fraction
  - Half of VTE events are unprovoked. (50% symptomatic before 55yo).

### Dysfibrinogenemia
- Fibrinogen converted to fibrin, fibrin cross-linked.
- Mutation in $\alpha$, $\beta$, or $\gamma$ fibrinogen genes
- Can bleed or clot!

### Acquired

- **Much more common, and often greater thrombotic risk than inherited thrombophilia**

#### Increased Risk States
- Increased risk of thrombosis:
  - Age
  - Surgery
    - Found that thromboembolic risk is high 1 year post surgery.
    - Major inpatient surgery = 70-fold increased risk of VTE (Ambulatory surgery = 10-fold)
  - Cancer (increases risk by 4-20-fold)
    - Called **Trousseau Syndrome**
      - (described in pancreatic cancer, and described in himself as he was dying of gastric cancer)
      - (Cancer expresses tissue factor, platelet disorders, chemo, etc.)
    - **High Risk**: Pancreatic, Brain
    - **Intermediate Risk**: Lung Cancer, Lymphoma
    - **Low Risk**: Breast & Prostate Ca.
  - Hence: if active VTE, must anticoagulate with LMWH.

### Antiphospholipid Syndrome
- Acquired autoimmune disorder associated with venous or arterial thromboembolism.

- **Pathophysiology:**
  - Antibodies to phospholipids such as cardiolipin or phospholipin-binding proteins such as Beta-2-glycoprotein 1.
  - Why they clot is not understood.

- **Presentation:**
  - Pregnancy loss
  - Thrombocytopenia
  - Renal insufficiency, Vasculitis, Cardiac Valvular abnormalities

- **Manifestations:**
  - VTE (59%)
  - Arterial Thrombosis (28%)
  - Aterial Thromboembolism (13%)

- Primary or Associated with other autoimmune diseases (i.e. Lupus)

- **Diagnosis:**
  - IgG, IgM,[sometimes IgA] --> **Anti-cardiolipin, Anti-$\gamma$-2-glycoprotein 1** (ELISA's)
    - Can cause increased clotting times (PTT, Dilute Russel's Viper Venom time)
  - Lupus Anticoagulant --> When anti-phospholipid antibodies cause a prolongation of the PTT
• MUST have clinical symptoms (1-5% will have positive tests)
  • Clinical Criteria (one of) | Laboratory Criteria (one of)

1. **Vascular Events** (Arterial, Venous, or microvascular thrombosis).
   - Histopathology cannot demonstrate vessel wall inflammation
2. **Pregnancy Morbidity**
   - ≥1 unexplained fetal deaths ≥10w
   - ≥1 premature births <34w due to eclampsia, pre-eclampsia, placental

1. **Lupus Anticoagulant**
   - must be positive using a phospholipid-dependent clotting assay (aPTT, Russell viper venom assay, kaolin clotting time, dilute PT) with phospholipid dependence ≥2 times at least 12w apart
2. **Anticardiolipin Antibody**
   - By ELISA (IgG or IgM) ≥2 occasions >12w apart.
3. **β₂-Glycoprotein I antibody**
   - By ELISA (IgG or IgM by ELISA) on ≥2 occasions >12w apart

**Management:**

• If positive APS and prolonged PTT, must has anti-Xa assays for UHF monitoring (or use LMWH).
• Long-term anticoagulation with warfarin (INR 2-3) [Recurrence Risk is HIGH]
  (IN the past targeted higher INRs, but now studies show no need)
  • If recurrent thromboembolism despite warfarin --> target INR 3-4. (or consider LMWH or fondaparinux)
  • If INR elevated, may need to use chromogenic Factor X to monitor warfarin.
• Reducing miscarriage risk: UNFH or LMWH + ASA.