Thrombophilia Testing: What, When, and Whom to Test

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Full disclosures

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Research funding: FDA, NIH, Stago, T2 Biosystems

Patents: Novel assays for HIT laboratory testing
Objectives

What: Define the components of a typical thrombophilia panel

Who: Identify which patients are appropriate for thrombophilia testing

When: Determine when and when not to request thrombophilia testing

Hemostasis is a balance
Thrombophilia is an imbalance

**Procoagulants:**
1. Factor V Leiden
2. Prothrombin mutation

**Anticoagulants:**
1. Protein C deficiency
2. Protein S deficiency
3. Antithrombin deficiency

The coagulation cascade

- **Intrinsic pathway**
  - Xa
  - **Prothrombin** (II) → **Thrombin** (IIa)
  - Fibrinogen → Fibrin (monomer) → Fibrin (polymer) → Fibrin (X-linked)

- **Extrinsic pathway**
  - Xa
  - **Prothrombin** (II) → **Thrombin** (IIa)
  - Fibrinogen → Fibrin (monomer) → Fibrin (polymer) → Fibrin (X-linked)

- **Common pathway**
  - Va
  - Thromboplastin
  - Ca++
The coagulation hemostasis cascade

Intrinsic pathway
Extrinsic pathway
Common pathway

Prothrombin (II) → Thrombin (IIa) → XIIIa

Fibrinogen → Fibrin (monomer) → Fibrin (polymer) → Fibrin (X-linked)

Clinical manifestations: ↑ Risk of VTE

Venous thromboembolism (VTE)

But no or negligible ↑ risk of arterial thrombosis

## Putting the VTE risk in perspective

<table>
<thead>
<tr>
<th>Thrombophilia</th>
<th>Prevalence</th>
<th>RR of VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT G20210A (heterozygous)</td>
<td>1-5% in Caucasians</td>
<td>2.8</td>
</tr>
<tr>
<td>FVL (heterozygous)</td>
<td>5-8% in Caucasians</td>
<td>4.9</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>0.2-0.5%</td>
<td>7.3</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>0.2-0.5%</td>
<td>8.1</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>0.03-0.13%</td>
<td>8.5</td>
</tr>
<tr>
<td>PT/FVL compound heterozygosity</td>
<td>0.1%</td>
<td>20.0</td>
</tr>
<tr>
<td>FVL homozygosity</td>
<td>0.06-0.25%</td>
<td>80</td>
</tr>
<tr>
<td>OCP use + FVL heterozygosity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT/FVL compound heterozygosity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>THR/TKR (w/o anticoagulation)</td>
<td></td>
<td>~1000</td>
</tr>
</tbody>
</table>
Thrombophilia testing

Seek and ye shall find… The tip of the iceberg…

<table>
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<tr>
<th></th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy controls</td>
<td>10%</td>
</tr>
<tr>
<td>Patients with VTE</td>
<td>24-37%</td>
</tr>
</tbody>
</table>

Thrombophilia: to test or not to test?

1. Guide patient management
2. Facilitate testing of family members
3. Comfort of knowing

Duration of treatment?

- 1. Undue patient anxiety
- 2. Cost
- 3. Negative testing does not rule out presence of an unknown thrombophilia

PRO

CON
Thrombophilia and the risk of VTE recurrence

No difference in recurrence rate among FVL carriers and non-carriers
Similar findings for carriers of prothrombin mutation
Conclusion: Common thrombophilias do not influence recurrence risk or management

So what is the best predictor of recurrence?
Answer: the cause of the first VTE
Hereditary thrombophilias: to test or not to test?

Consider testing:
- Young patients (< 50 years-old) with unprovoked VTE
- Patients with a positive family history of VTE
- Patients who “need” to know

Do not test:
- Older patients
- Patients with a provoked VTE
When (not) to test

<table>
<thead>
<tr>
<th>Defect</th>
<th>Common causes of acquired deficiency</th>
</tr>
</thead>
</table>
| Protein C deficiency | 1. Acute thrombosis  
|                  | 2. Warfarin/vitamin K deficiency  
|                  | 3. Liver disease  
|                  | 4. Sepsis |
| Protein S deficiency | 1. Acute thrombosis  
|                  | 2. Warfarin/vitamin K deficiency  
|                  | 3. Liver disease  
|                  | 4. Pregnancy/OCP use |
| AT deficiency   | 1. Acute thrombosis  
|                 | 2. Heparin  
|                 | 3. Liver disease |

A brief word about acquired thrombophilia testing

**Antiphospholipid Ab’s**
- Lupus anticoagulant
- Anticardiolipin
- Anti-B2GP1
- APS = clinical + laboratory criteria
- Associated with ↑ risk of venous and arterial thromboembolism
- Indefinite AC is standard but not supported by high quality evidence

**HIT**
- ↑ risk of venous and arterial thromboembolism
- Assess clinical probability of HIT using 4T score
- Low probability 4T score: 99.8% NPV
- Do not order HIT lab testing or treat for HIT in patients with a low probability 4T score

**Malignancy**
- ↑ risk of venous and arterial TE
- ~10% of patients with unprovoked VTE will be diagnosed with cancer in the next year
- No evidence of benefit of screening asymptomatic patients
- Expert recommendation is age-appropriate cancer screening only
Take-home points

Thrombophilias include hereditary and acquired conditions.

Hereditary thrombophilias predispose to VTE. Acquired thrombophilias predispose to venous and arterial TE.

For most patients, thrombophilia testing is not indicated.

Always consider the potential benefits and harms before testing.