Thrombophilia Work-up Recommendations
Introduction:
The most common presentations of venous thromboembolism (VTE) are lower extremity deep vein thrombosis (DVT) and/or pulmonary embolism (PE). Arterial thromboembolic events (ATE) are less common but can lead to more serious outcome. The etiologies for thromboembolism can be divided into two main groups: hereditary and acquired, and some events can be triggered by both. Detailed medical, social and family history are critically important to help identify the underlying etiology. Inherited thrombophilic conditions including gene mutations and or protein deficiencies are less frequent. Making decisions regarding indication, timing and or appropriate laboratory testing for thrombophilia can be challenging, especially in the acute event. This document reviews hereditary and acquired etiologies for thromboembolism, and provides appropriate work up recommendations based on the current evidence.

Evidence:
A very careful patient and family history may help identify different etiologies for thromboembolism and can help make decisions regarding appropriate work up plan. Differentiating between provoked and unprovoked event is crucially important since the work up and management plans are different. Risks factors that should be questioned include history of immobility, pregnancy, trauma, surgery, or recent hospitalization. Other risks that should be investigated include past history of thromboembolism, presence of prothrombotic disorders, medications and drug use, obstetric history, constitutional symptoms, and family history of thromboembolism.

Physical exam may reveal signs of malignancy, hepatic vein thrombosis, polycythemia vera, and nephrotic syndrome. Initial work up including a CBC, hepatic and renal function tests, basic coagulation tests, venous duplex ultrasound and or chest CT, may help identify the underlying etiology. Testing patients with VTE for hypercoagulable disorders (especially inherited thrombophilias) and malignancy is controversial. Several trials report no difference in recurrence rates in patients with or without inherited thrombophilia, on or off anticoagulation. Further testing should only be considered if testing results would affect management plan for patients and/or their family members, especially if hormonal therapy is considered. This should be weighed against the harms of testing including a lack of improved survival, inappropriate anticoagulation and undue anxiety in the patient (and/or asymptomatic relatives). In general, other than age-appropriate cancer screening, routine evaluation for occult malignancy in patients with thromboembolism is not warranted. For all patients in whom testing is being considered, it is critical to consider patients’ values and preferences.

Here we discuss our work-up recommendations for patients with thromboembolism.
Recommendations:

1- All patients with diagnosed VTE should have thorough history and physical exam to determine if the VTE is provoked versus unprovoked.

2- Risks that should be investigated include:
   A- Immobility, pregnancy, trauma, surgery, or recent hospitalization.
   B- Past personal or family history of thromboembolism.
   C- Presence of prothrombotic disorders (eg, autoimmune disorders, malignancy, myeloproliferative disorders, nephrotic syndrome, inflammatory bowel disease).
   D- Hormonal medications (eg, hormonal contraceptives, hormonal replacement), or drugs that can induce the development of lupus anticoagulants or antiphospholipid antibodies (eg, hydralazine, procainamide, phenothiazines).
   E- Illicit drug use (eg, amphetamines, cocaine).
   F- Obstetric history: recurrent fetal loss may suggest underlying thrombophilia such as antiphospholipid syndrome.
   G- Constitutional symptoms: weight loss, loss of appetite and night sweats may indicate underlying malignancy.

3- Appropriate systemic physical exam may reveal the underlying etiology:
   A- Breast cancer: lymphadenopathy or breast masses
   B- Hepatic vein thrombosis: ascites and hepatomegaly
   C- Polycythemia Vera: unexplained splenomegaly
   D- Nephrotic syndrome: edema

4- For all patients with VTE, we recommend the following work up:
   A- CBC with blood smear:
      - Thrombocytosis and or high red blood cell count may indicate myeloproliferative disorder
      - Pancytopenia may indicate paroxysmal nocturnal hemoglobinuria (PNH)
      - Thrombocytopenia with history of heparin use may indicate heparin induced thrombocytopenia (HIT)
      - Schistocytes with cell fragmentation may indicate DIC
   B- Renal and hepatic function tests
   C- Basic coagulation labs including aPTT and PT/INR
   D- ESR and CRP in selected patients with possible underlying malignancy and or autoimmune disorder

5- For most patients, extensive imaging other than that required for the diagnosis of VTE (eg, lower extremity ultrasound, CT pulmonary angiogram) is not necessary.

6- Additional testing for thrombophilia (Figure 1):
   A- Patients with provoked VTE or first unprovoked VTE should not be tested since management and outcome are not necessarily altered by results.
   B- Patients with recurrent unprovoked event and documented family history of unprovoked VTE in a first degree relative younger than 45 years:
      i) Consider testing for inherited thrombophilia (levels of protein S, protein C, and antithrombin, factor V Leiden and prothrombin gene mutations) in a patient who is not interested in long-term anticoagulation and is considering hormonal therapy.
      ii) Consider testing for inherited thrombophilia in a patient who is not interested in long-term anticoagulation as long as patient
is willing to accept aggressive risk lowering recommendations (eg, smoke cessation, life style modifications, more aggressive thromboprophylaxis when at risk) in case testing is positive.

iii) Consider testing for inherited thrombophilia in a first degree relative who is considered for hormonal therapy.

iv) Consider testing for inherited thrombophilia in a first degree relative as long as he or she is willing to accept aggressive risk lowering recommendations in case testing is positive.

C- Patients with unprovoked event and no family history of VTE

i) Consider testing young patients (< 45 years) for inherited thrombophilia and antiphospholipid syndrome (lupus anticoagulants, anticardiolipin and B2 glycoprotein antibodies) if results would alter management plan (avoiding hormonal exposure, aggressive risk lowering recommendations).

ii) Consider testing patients with recurrent VTE for inherited thrombophilia and antiphospholipid syndrome if results would alter management plan (avoiding hormonal exposure, aggressive risk lowering recommendations).

iii) Consider testing patients with unusual locations of VTE (portal hepatic, mesenteric, or cerebral veins) for inherited thrombophilia and antiphospholipid syndrome. Consider evaluation for JAK2 mutations and paroxysmal nocturnal hemoglobinuria (PNH) in patients with portal or hepatic vein thrombosis.

iv) Consider testing patients with warfarin induced skin necrosis for protein C and protein S levels and factor V Leiden mutation.

D- Patients with arterial thrombosis

i) Consider testing for antiphospholipid syndrome

ii) Consider testing for PNH in patients with anemia

iii) Consider testing JAK2 mutations in patients with possible underlying myeloproliferative disorders

iv) Consider testing for heparin induced thrombosis (HIT) by ordering heparin antibodies in patients with heparin exposure and ≥ 50% reduction of platelet count.

v) Consider testing for lipoprotein a level in patients with family history of premature cardiovascular disease.

E- Patients that should not be tested for thrombophilia

i) Provoked VTE

ii) First unprovoked VTE

iii) Upper extremity DVT

iv) Active malignancy

v) Inflammatory bowel disease

vi) Confirmed myeloproliferative disorders

vii) HIT

viii) Retinal vein thrombosis

7- Timing of tests:

A- Acute thrombosis and anticoagulants (heparin, warfarin, DOACs) affect levels and/or functional activity of many thrombophilia testing (Table 2).

B- If testing is considered, recommend testing at least two weeks following discontinuation of anticoagulation, when feasible.

C- Factor V and prothrombin gene mutations can be tested at any time if considered.

8- Other testing

A- Homocysteine levels and mutational analysis for methylene tetrahydrofolate reductase (MTHFR), should not be performed since
causal role of hyperhomocysteinemia in thrombosis is unclear. Furthermore, lowering homocysteine levels with folic acid, pyridoxine, and vitamin B12 does not appear to reduce the rate of VTE in patients with hyperhomocysteinemia.

9- Evaluation for occult malignancy
   A- Recommend regular malignancy testing (Pap smear, mammography, colonoscopy, prostatic exam, PSA) based on patient’s gender and age.
   B- Consider further testing for malignancy only if there is clinical suspicion for one.

References
### APPENDIX

#### Table 1: Risk factors (causes) for the development of venous thrombosis

<table>
<thead>
<tr>
<th>Inherited thrombophilia</th>
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<tbody>
<tr>
<td>Factor V Leiden mutation</td>
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<tr>
<td>Prothrombin G20210A mutation</td>
</tr>
<tr>
<td>Protein S deficiency</td>
</tr>
<tr>
<td>Protein C deficiency</td>
</tr>
<tr>
<td>Antithrombin (AT) deficiency</td>
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<table>
<thead>
<tr>
<th>Other disorders and risk factors</th>
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</thead>
<tbody>
<tr>
<td>Malignancy</td>
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<tr>
<td>Presence of a central venous catheter</td>
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<tr>
<td>Surgery, especially orthopedic</td>
</tr>
<tr>
<td>Trauma</td>
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<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
</tr>
<tr>
<td>Certain cancer therapies (eg, tamoxifen, thalidomide, lenalidomide)</td>
</tr>
<tr>
<td>Immobilization</td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>Congenital heart disease</td>
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<tr>
<td>Antiphospholipid syndrome</td>
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<tr>
<td>---------------------------</td>
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<tr>
<td><strong>Myeloproliferative neoplasms</strong></td>
</tr>
<tr>
<td>Polycythemia vera</td>
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<tr>
<td>Essential thrombocytthemia</td>
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<tr>
<td>Paroxysmal nocturnal hemoglobinuria</td>
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<td>Inflammatory bowel disease</td>
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<tr>
<td>Nephrotic syndrome</td>
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### Table 2: Clinical settings that may interfere with testing for thrombophilia

<table>
<thead>
<tr>
<th>Hypercoagulable disorder for testing</th>
<th>Confounding factors</th>
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<tbody>
<tr>
<td></td>
<td>Acute thrombosis</td>
<td>Heparin therapy</td>
</tr>
<tr>
<td>Antithrombin (deficiency)</td>
<td>Can be lowered*</td>
<td>Lowered</td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Factor VIII level</td>
<td>Acute phase reactant. Do not test while inflammation is still present.</td>
<td></td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>NC</td>
<td>Cannot measure*</td>
</tr>
<tr>
<td>Protein C (deficiency)</td>
<td>Can be lowered*</td>
<td>NC</td>
</tr>
<tr>
<td>Protein S (deficiency)</td>
<td>Can be lowered*</td>
<td>NC</td>
</tr>
<tr>
<td>Prothrombin gene mutation</td>
<td>NC</td>
<td>NC</td>
</tr>
</tbody>
</table>

**Acquired AT deficiency:**

Neonatal period, pregnancy, liver disease, DIC, nephrotic syndrome, major surgery, acute thrombosis, treatment with L-asparaginase, heparin, or estrogens

**Acquired protein C deficiency:**

Neonatal period, liver disease, DIC, chemotherapy (CMF), inflammation, acute thrombosis, treatment with warfarin or L-asparaginase

**Acquired protein S deficiency:**

Neonatal period, pregnancy, liver disease, DIC, acute thrombosis, treatment with warfarin, L-asparaginase, or estrogens
NC: not changed; LMW heparin: low molecular weight heparin; AT: antithrombin; DIC: disseminated intravascular coagulation; CMF: cyclophosphamide, methotrexate, 5-fluorouracil.

* Results can be affected by acute thrombosis; it is most cost effective to avoid testing for these deficiencies during the initial presentation. However, if plasma levels are well within the normal range at presentation, deficiency of these proteins is essentially excluded. Common causes for an acquired deficiency of AT, protein C, or protein S are listed.

¶ Some laboratories can test for a lupus anticoagulant in the presence of heparin, but many cannot.

Δ If it is important to measure for these deficiencies while the patient is still anticoagulated, switch the treatment to full-dose heparin or LMW heparin and discontinue Coumadin for at least two weeks before measurement. Comparing protein S or C levels with prothrombin antigen in stable anticoagulated patients is not reliable, as accurate measurement of prothrombin antigen levels is a research assay which is not generally available.

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**Figure 1: THROMBOPHILIA WORK UP RECOMMENDATION ALGORITHM**

- **Provoked or first unprovoked VTE**: No further work up needed.
- **Recurrent unprovoked VTE with documented family history**: Patients: Consider inherited thrombophilia testing.*
- **Unprovoked VTE with no family history**: Patient: Consider inherited thrombophilia and APS testing¶
- **Arterial Thromboembolism**: Consider testing for: APS, HIT, Myeloproliferative disorders, PNH and lipoprotein a.

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**APS**: Antiphospholipid syndrome, **HIT**: Heparin-induced thrombocytopenia, **PNH**: Paroxysmal nocturnal hemoglobinuria, **VTE**: Venous thromboembolism

* In patient who is not interested in long-term anticoagulation and is considering hormonal therapy, and/or in patient who is not interested in long-term anticoagulation and is agreeable to aggressive risk lowering recommendations.

# Relatives who are considered for hormonal therapy and/or are agreeable for aggressive risk lowering recommendations.

¶ Young patients (<45 years old), recurrent VTE, unusual location for deep vein thrombosis, or warfarin-induced skin necrosis.