

Hypercoagulability

Synonym: Thrombophilia

Venous thrombotic events have different risk factors than arterial events. The following discussion pertains to only **venous** thrombotic events, most commonly deep venous thrombosis and pulmonary embolism.

Patients can simplistically be divided into moderate risk and high-risk categories in terms of their likelihood of having laboratory evidence of hypercoagulability:

Moderate Risk

Patients 50 years of age and older with venous thrombosis without a positive family history (first degree relative with venous thrombosis) and without thrombosis at an unusual site (e.g. cerebral vein, upper extremity vein, or mesenteric vein):

A more abbreviated panel is suggested:

- Factor V Leiden
- Prothrombin 20210 Mutation
- DRVVT*
- PTT-LA*
- Anti-Cardiolipin Antibodies + Anti-Beta 2 Glycoprotein 1 Antibodies*
- Homocysteine Level

*A positive test result should be confirmed after 12 weeks before diagnosing an antiphospholipid antibody syndrome.

High Risk

Patients with venous thrombosis under 50 years old, a positive family history, or thrombosis at an unusual site.

In this situation a more comprehensive panel is reasonable adding the following to the above panel:

- Protein C (PC) Activity*
- Protein S (PS) Activity*
- Anti-thrombin (AT) Activity

*If positive, consider testing for protein C or protein S antigens.

Important

Anticoagulation therapy and other medical conditions can confound laboratory testing for hypercoagulability.

Testing of patients on anticoagulation

- DNA-based tests (Factor V Leiden and Prothrombin 20210 mutation) can be done anytime.
- Anti-cardiolipin antibodies and PTT-LA are also relatively unaffected.
- DRVVT is not reliable on warfarin.
- Protein C and S are suppressed by warfarin; less affected by heparin.
- Theoretically, for patients on a stable dose of warfarin for at least one month, can ratio protein C and protein S antigens levels to Factor X (or another vitamin K dependent factor with a long half-life).

However, this is not well standardized. It is preferable to wait until the patient is off warfarin for 2 weeks.

- Anti-thrombin tends to be decreased with heparin.
- The effects of the various low-molecular weight preparations upon lab tests for hypercoagulability are not well established; in general, they seem to be less than those of unfractionated heparin.
- Direct thrombin inhibitors (argatroban, lepirudin) are not well studied in this regard; they appear to significantly increase PS and PC activity assay levels. Lepirudin, but perhaps not argatroban, can often yield false positive DRVVT results.

Common medical conditions that affect AT, PC, and PS

- Pregnancy, estrogen, and oral contraceptives: lower AT and especially PS, but can increase PC.
- Acute thrombosis, postoperative state, DIC, and severe liver disease: lower all three assays.

General Comments

- The results of hypercoagulability testing generally do not affect the acute management of a patient with venous thrombosis. However, it is advisable to check baseline aPTT and INR values before initiating anticoagulation. Lupus anticoagulants can prolong aPTT and/or INR and complicate therapeutic monitoring. If at all possible, it is recommended that more extensive testing for hypercoagulability be deferred until the patient is remote from a thrombotic event and off all anticoagulation medications and hormonal therapies to allow a more straightforward interpretation of the results.
- If the patient has already “declared” him/herself as high-risk; e.g. recurrent unprovoked thrombotic events, lab testing is somewhat superfluous. The practical question is often: Does this patient need to be on lifelong anticoagulation (generally warfarin)? If the answer is already “yes” from the clinical history, no degree of laboratory testing will remove that risk. Lab testing is useful for patients in the “gray zone” where the role and duration of anticoagulation is uncertain.
- Testing asymptomatic individuals, even if they have an affected family member, is not widely advocated since it has minimal effect of patient management; the best data in this regard comes from large epidemiologic studies from the Netherlands. However, it may be reasonable to test family members who desire to be proactive in their health care and know their risk status.
- Testing women prior to going on oral contraceptives is also not generally advocated in the absence of a family history of thrombotic disease.
- Testing for methylene-tetrahydrofolate reductase (MTHFR) mutations and homocysteine is controversial. Recent studies suggest that homocysteine is a relatively weak predictor of venous thrombotic events. Although folate supplementation can slightly lower homocysteine levels, studies to date have not shown that this translates into reduced thrombotic risk.
- Factor VIII levels may be associated with thrombotic risk, but as an acute phase reactant this test should be avoided in hospitalized patients.
- Patients being tested for antiphospholipid syndrome with normal anti-cardiolipin, beta 2 glycoprotein, and hyper anticoag should be tested for anti-phosphatidylserine prothrombin antibody.

Contact Information

Marshfield Labs Customer Service 800-222-8535

Questions of Comments

If a patient has an unusual situation, the results of the above work-ups are confusing, or have unclear clinical implications, please refer questions or comments to:

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The following hematologist can give a more in-depth consultation for patients in the Marshfield Clinic system:

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