HAEMATOLOGY
H.A009 - THROMBOPHILIA ADVICE Trust Doc ref 4648

Role of thrombophilia screening:

Venous thromboembolism (VTE) is a multifactorial disease. There is a thrombotic threshold for everyone, which if exceeded will cause thrombosis. The threshold is altered throughout life by environmental and lifestyle factors. Detectable thrombophilic defects are only **one** of the known risk factors for thrombosis and should not be acted upon in isolation. Every patient with VTE should be assessed for clinical risk factors first - e.g. obesity, recent surgery, immobility, increasing age, malignancy – as some may be modifiable. In most instances thrombophilia screening contributes little to future management.

General points about thrombophilia screens:

- For the vast majority of patients presenting with VTE, thrombophilia testing is of limited benefit.
- The finding of heritable thrombophilia should not influence decisions regarding the intensity of anticoagulation.
- Duration of anticoagulation after VTE is mainly determined by clinical factors estimating the risk of recurrent VTE, and the risk of bleeding associated with anticoagulation.
- The advice regarding thromboprophylaxis to prevent future thrombosis remains unchanged.
- Thrombophilia results should not be used in isolation to determine if it is safe to prescribe oestrogen containing contraceptives, HRT or other medications known to carry a thrombotic risk (see specific Gynaecology department guidance in these situations).

Who to consider for screening?

- Selected individuals from thrombosis prone families can be considered for testing. Care should be taken before testing to consider how the results will be of benefit. In almost all patients, the results do not influence current or subsequent management. People with a strong family history of thrombosis should be considered at increased risk, irrespective of the results of a thrombophilia screen.
- Pregnant women with a history of VTE, or who have a family history of VTE in a first degree relative. This may help make decisions about thromboprophylaxis in pregnancy.
- As part of investigations for pregnancy loss.
- Individuals who require investigation for suspected antiphospholipid syndrome (request lupus anticoagulant/anticardiolipin antibodies only).
- Selected patients after unprovoked VTE who are planning to stop anticoagulation if the results would change management. Testing for antiphospholipid syndrome (APS) and testing for hereditable thrombophilia in patients who also have a first degree relative with a history of VTE could be considered.

- Selected patients with unprovoked VTE and risk factors for APS. Testing for APS can be considered if the result would change choice of anticoagulant. Features in VTE patients which can be suggestive of APS are: history of SLE or autoimmune disease, livedo reticularis, prolonged APTT prior to anticoagulation, recurrent VTE, VTE at unusual sites, history of arterial thrombosis without risk factors, thrombocytopenia, recurrent miscarriage/still birth/severe pre-eclampsia).

When is screening not advised?

- Patients with VTE where anticoagulation is being continued indefinitely should not be tested for hereditary thrombophilia. The result of a hereditary thrombophilia test will not change management (see above for suspected APS).

- Patients with provoked VTE.

- Asymptomatic patients with no personal or family history of VTE.

- Children under 16. Genetic screening of children under 16 is not advised without good clinical indication and genetic counselling.

- Results of previous inherited thrombophilia screen available. The genetic tests should not be repeated; clotting based assays are as accurate as methodology allows and should only be repeated if advised to do so by the laboratory or haematology.

- Arterial thrombosis. Patients with arterial thrombosis should not be tested for heritable thrombophilia. Where the cause of arterial thrombosis is not known, consideration can be given to testing for antiphospholipid syndrome.

Types and timing of thrombophilia screens:

There are 2 types of screen:

Heritable thrombophilia screen
- Protein C (clotting based)
- Protein S (clotting based)
- Antithrombin (clotting based)
- Factor V Leiden (genetic test)
- Prothrombin gene mutation (genetic test)

Acquired (not hereditary) thrombophilia Screen
- Lupus anticoagulant (clotting based)
- Anticardiolipin antibodies (ELISA based)

For a full thrombophilia screen send 3 x blue, 1 yellow and 1 purple vacutainer if all tests required. Otherwise select specific tube for test (clotting based = blue; genetic = purple; ELISA = yellow)

Clotting based assays are affected by anticoagulants (heparin, warfarin, DOACs - apixaban, edoxaban, dabigatran and rivaroxaban) and by acute thrombosis, and therefore should not be performed at the time of an acute clot, or whilst a patient is anticoagulated. The clotting based tests should be performed 4-6 weeks after anticoagulation stops. Genetic tests are **not** affected by

the above and can be performed at any time. If testing on anticoagulants (excluding warfarin) is deemed beneficial, discuss with the laboratory regarding options for anticoagulant removal from the sample to permit testing.

Interpretation of results

Acquired causes of reduced Protein C, Protein S and antithrombin levels occur more frequently than hereditary deficiency. Hereditary deficiency should only be diagnosed after exclusion of acquired causes and confirmed on repeat testing by a haematologist.

Acquired causes of low Protein C, Protein S and antithrombin levels are listed below:

Protein C: Vitamin K antagonists (warfarin), liver disease, DIC
Protein S: Pregnancy, combined oral contraceptive, vitamin K antagonists (warfarin), vitamin K deficiency, liver disease, sickle cell disease, acute chickenpox infection
Antithrombin: Acute thrombosis, heparin therapy, liver disease, nephrotic syndrome, asparaginase therapy

Lupus anticoagulant and anticardiolipin antibodies
Positive results can be found in normal healthy individuals. A diagnosis of antiphospholipid syndrome should only be made in patients fulfilling the specific clinical diagnostic criteria (thrombotic or obstetric) and persistently positive tests (2 positive results at least 12 weeks apart).

Estimate of risks of venous thromboembolism:

• lifetime overall risk of VTE	5%
• Incidence of VTE (increases with age)	1:1000 person years
• Incidence of VTE in women age < 40 yrs not on combined OCP	1 :10,000 person years
• Incidence of VTE in women age <40yrs on combined OCP	4 :10,000 person years
• Incidence of VTE in pregnancy	1-2:1000 pregnancies
• Incidence of VTE in women aged 50-59 yrs not on HRT	7-9:10,000 person years
• Incidence of VTE in women aged 50-59 yrs taking HRT	18-23:10,000 person years

Estimates of prevalence of thrombophilic abnormalities and relative risks of thrombosis:

thrombophilic abnormality	prevalence in population	relative risk for first VTE	relative risk for recurrent VTE
antithrombin deficiency	0.02%	5-10	1.9-2.6
protein C deficiency	0.2%	4-6.5	1.4-1.8
protein S deficiency	0.03% - 0.13%	1-10	1.0-1.4
factor V Leiden mutation (heterozygous)	3% - 7%	3-5	1.4
prothrombin gene mutation	0.7% – 4%	2-3	1.4

NB. The absolute risk of thrombosis for any given patient will depend on age and other thrombotic risk factors. Absolute risks can be more informative when counselling patients regarding their individual risk of thrombosis.

Testing for acquired genetic traits

Acquired genetic traits such as paroxysmal nocturnal haemoglobinuria (PNH) and the myeloproliferative neoplasm (MPN) mutations can - rarely - predispose to thrombosis. Thromboses associated with PNH and MPN can occur anywhere in the venous or arterial systems but are particularly seen in unusual sites such as splanchnic vein thrombosis (including portal vein, mesenteric vein and splenic vein thrombosis, and the Budd–Chiari syndrome) and cerebral venous sinus thrombosis (CVST).

When should acquired genetic traits be screened for?

- Send PNH testing in patients with thrombosis at unusual sites and abnormal haematological parameters (unexplained cytopenias and abnormal red cell indices) or evidence of haemolysis (i.e., raised lactate dehydrogenase, bilirubin and reticulocyte count)

- Send testing for JAK2 mutation panel in patients with thrombosis at unusual sites and with full blood count abnormalities suggestive of a myeloproliferative neoplasm – select ‘thrombocytosis’ or ‘erythrocytosis’ to attain the correct genetic panel on WebICE

- Send testing for the JAK2 mutation in patients with splanchnic vein thrombosis or CVST in the absence of clear provoking factors and a normal FBC

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