Guidelines for Screening for Thrombophilia

Compiled by Dr Emma Wypkema

Introduction:

Thrombophilia indicates the presence of a hypercoaguable state leading to a thrombotic tendency. When a person with an underlying predisposition to thrombosis is exposed to clinical risk factors, venous thromboembolic disease may occur. This tendency may be inherited (Table I) or acquired (Table II).

Table I: Hereditary Thrombophilia
Antithrombin III deficiency
Protein C deficiency
Protein S deficiency
Activated Protein C resistance
Factor V Leiden
Prothrombin G20210A
Homocysteinaemia (MTHFR mutation) and Homocystinuria
Increased Plasma factors (Fibrinogen, Prothrombin, Factor VIII, IX and XI)
Dysfibrinogenaemia
Reduced Tissue Factor pathway inhibitor

Table II: Acquired or secondary thrombophilia
Advanced age
Immobility
Air travel
Trauma and Post-operative states
Dehydration
HIV infection and TB therapy
Antiphospholipid Syndrome and other Autoimmune diseases
Disseminated Intravascular Coagulation (DIC)
Thrombotic Thrombocytopenic Purpura (TTP)
Heparin induced thrombocytopenia (HITT)
Hyperhomocysteinaemia
Oral Contraceptives and Hormone replacement therapy
Pregnancy/Postpartum state
Selective oestrogen receptor modulatory therapy (e.g. tamoxifen, raloxifene)
Active malignancy
Chemotherapy (e.g. L-asparaginase, thalidomide, anti-angiogenesis therapy)
Myeloproliferative Disorders
Nephrotic Syndrome
Paroxysmal Nocturnal Haemoglobinuria (PNH)
Wegener granulomatosis
Inflammatory bowel disease
Thromboangiitis obliterans (Buerger's disease)
Behçet syndrome
Venous vascular abnormalities
Sickle Cell Disease

INVESTIGATING HYPERCOAGUABLE STATES:

The susceptibility to thrombosis does not imply an absolute requirement for primary or secondary prevention, or for treatment. Thrombophilia should therefore be considered in the context of other risk factors. Currently there is no single laboratory assay or simple set of assays that will identify all thrombophilias, and therefore a detailed history, including family and past history of thrombosis, and a thorough clinical assessment is important to guide the investigations required.

Initial General Diagnostic and special Coagulation Laboratory (Level I) testing:

FBC with peripheral blood smear
INR and PTT
Thrombin time
Lupus Anticoagulant and Antiphospholipid Antibodies
Activated Protein C Resistance
Factor V Leiden
Prothrombin G20210A
Antithrombin III
Protein C
Protein S
Plasma Homocysteine/PCR for MTHFR mutation
Prothrombin, Fibrinogen, Factor VIII
Lipoprotein (a)

Additional Selective Laboratory (Level II) testing (should be considered if thrombophilia is strongly suspected and level I testing is normal):

Flow cytometry (for Paroxysmal Nocturnal Haemoglobinuria)
Plasma ADAMTS-13 activity (for inherited or acquired TTP)
Plasminogen activity (for ligneous conjunctivitis/gingivitis)
Heparin induced thrombocytopenia testing (plasma anti-PF4, etc.)
PCR for the JAK-2 mutation
Factor IX, XI, XII, Prekallikrein, High Molecular Weight Kininogen

Additional Selective General Diagnostic testing:

ESR, chemistries, PSA, B-HCG, Ca-125, ANF
CXR, urinalysis, mammogram
Upper and lower GIT imaging
ENT consultation, especially for smokers
Abdominal imaging
Endometrial biopsy
Angiography

Important Practical Pitfalls in Coagulation screening for Thrombophilias:

- Thrombophilia screening should be delayed until 2 weeks after discontinuation of anticoagulation therapy because the results are altered by the acute event (Low Protein C, S and ATIII) and by anticoagulant therapy (Low Protein C and S in Warfarin therapy, low ATIII in Heparin therapy and low Protein C, S, Lupus Anticoagulant and other factors performed with clotting techniques are affected by the DOACs).
- Normal ranges for ATIII, Protein C and Protein S are wide, and deficient patients may have levels that are only slightly below normal. Repeat testing is often required for diagnostic confidence.
- Pregnancy induces a state of resistance to the anticoagulant effect of Protein C, which can mimic Factor V Leiden if APC resistance is used as the only screening test.
- Pregnancy and oral contraceptives can lead to the fall in plasma Protein S concentration.
- Infection and inflammation may give rise to false positive Antiphospholipid antibodies, elevated Factor VIII levels, low free Protein S and elevated Lipoprotein (a).
- Liver disease may give rise to low Protein C, S and ATIII levels.

RECOMMENDATIONS FOR SCREENING OF HYPERCOAGUABLE STATES:

The decision to test selected patients should be based on whether or not test results are likely to influence treatment and/or the duration and intensity of prophylaxis. Initiation and intensity of anticoagulation therapy following the diagnosis of acute venous thrombosis should be the same in patients with and without heritable thrombophilia.

Recommendations for screening prior to surgery:

- Screening for thrombophilia in unselected patients prior to surgery is not indicated.
- Screening for thrombophilia in selected asymptomatic patients prior to surgery with a strong family history of unprovoked/recurrent VTE (high risk thrombophilia) is recommended, and a positive result may be of value in determining the duration and intensity of prophylaxis required.
- Screening for thrombophilia in asymptomatic patients with a family history of low risk thrombophilia (e.g. Heterozygous Factor V Leiden, Heterozygous Prothrombin 20210A) prior to surgery is not cost effective.
- Screening for thrombophilia in patients who have had a previous VTE would be of value if the event was unprovoked, if the patient is young, if the event occurred at an unusual site or if the patient had a history of recurrent VTE.

Recommendations for screening of hospitalized patients:

- All hospitalized patients should be assessed for risk of VTE regardless of heritable thrombophilia based on a clinical risk assessment. The presence of a known heritable thrombophilia may influence risk assessment.

Recommendations for screening of relatives:

- Screening asymptomatic relatives with low-risk thrombophilia (e.g. heterozygous Factor V Leiden and Prothrombin G20210A) is not cost effective.
- Screening asymptomatic relatives with high-risk thrombophilia (ATIII, Protein C and Protein S) is recommended in selected thrombosis prone families.

Recommendations for screening of women considering Hormone therapy:

- Women considering oral contraception or hormone replacement therapy may benefit from screening if they have a first-degree relative with venous thrombosis who has a known heritable thrombophilia. This may assist counseling of selected women, particularly if a high-risk thrombophilia has been identified.
- Alternative contraception or transdermal HRT should be considered if screening of a first-degree relative with thrombosis was negative, as a negative result does not exclude an increased risk of venous thrombosis.

Recommendations for screening of pregnant women:

- Women should be assessed for risk of pregnancy associated venous thrombosis in relation to clinical risk factors.
- Pregnant women with a previous unprovoked venous thrombosis during pregnancy or while on oral contraceptive therapy, or associated with a minor provoking factor (e.g. travel) should be screened and considered for prophylaxis if a thrombophilia is found.
- Pregnant women with a previous event due to a major provoking factor e.g. surgery or major trauma, would not usually require prophylaxis or screening.
- In asymptomatic pregnant women with a family history of venous thrombosis should be screened if an event in a first-degree relative was unprovoked, or provoked by pregnancy, hormone therapy or a minor risk factor. The result would be more informative if the first-degree relative has a known thrombophilia.

Recommendations for screening Paediatric patients:

- Neonates/children with Purpura fulminans should be tested urgently for Protein C and S deficiency.
- Neonates/children with non-catheter related thrombosis or stroke should be screened for Thrombophilia.
- There is not enough data available to make a recommendation for screening in Neonates/children with symptomatic catheter-related thrombosis.
- Testing is not recommended in neonates/children with asymptomatic catheter related thrombosis.
- Screening of adolescents with spontaneous thrombosis is recommended.
- The decision to screen asymptomatic children with a strong positive family history should be made on an individual basis after counseling.

Important considerations when screening for Hypercoaguable States:

- VTE in one or more first-degree relatives increases the risk of VTE by approximately 2-fold.
- A potential advantage of screening these patients is to identify asymptomatic individuals who test positive so that preventative measures can be taken.
- ATIII, Protein C and Protein S deficiency are associated with a significantly higher risk for VTE compared to heterozygous Factor V Leiden and Prothrombin G20210A mutations. Homozygous or double heterozygous carriers of Factor V Leiden and/or Prothrombin 20210A mutations are associated with a high risk for VTE.
- It should be noted that a negative thrombophilia screen might lead to false reassurance, because of the presence of as-yet-unknown thrombophilia defects in families with a strong thrombotic tendency.

These guidelines have been compiled by Dr. Emma Wypkema, Consultant Haematologist and Head of the Lancet Thrombosis and Haemostasis Unit.

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The 13th of October is the birthday of Virchow, an eminent German physician Rudolf Virchow (1821-1902). Virchow's triad or the triad of Virchow (/ˈfɪrkoʊ/) describes the three broad categories of factors that are thought to contribute to thrombosis. Hypercoagulability, Hemodynamic changes (stasis, turbulence) and Endothelial injury/dysfunction.

Lancet has partnered with the ISTH (International Soceity of Thrombosis and Haemostasis) in creating awareness of Thrombotic Disorders for World Thrombosis Day - 13th of October 2015.

www.WorldThrombosisDay.Org

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