3. Guidelines for Investigating Thrombophilia

Compilation and editing of this volume:

Consultant Haematologists

Dr. Sudharma Vidyathilake
Dr. Mala Tudawe
Dr. Nishadya Ranasinghe
Dr. Baddika Jayarathne
Dr. Mala Mangalika Jayathilake
Dr. Senani Williams
Dr. Visaka Rathnamalala
Dr. Sashikala Suresh

List of contributors

Consultant Physicians

Dr. Bandula Wijesiriwardane
Dr. Anuja Premawardene

Consultant Surgeon

Dr. Ishan De Zoysa

Coordinators

Consultant Histopathologists

Dr. Siromi Perera
Dr. Kamani Samarasinghe
Dr. Modini Jayawickrama

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3.1 Definition of thrombophilia

This term is used to describe disorders of haemostatic mechanisms which are likely to predispose to thrombosis. It could be hereditary, acquired or mixed.

The following patients should be investigated for thrombophilia

- **Less than □0 years** with **unprovoked thrombotic episodes** – arterial or venous including pulmonary embolism, proven by CT scan, USS, Duplex scanning or venogram.
- Second and third trimester foetal loss or intra uterine growth retardation in the absence of obvious fetal or maternal abnormalities.
- Recurrent consecutive first trimester abortions – 2 or more.
- Severe pregnancy induced hypertension.
- Thrombotic events associated with Oral Contraceptive Preparations and Hormone Replacement Therapy without any obvious cause.
- Thrombosis at an unusual site
- Unexplained neonatal thrombosis including purpura fulminans.

- Warfarin induced skin necrosis.
- Screening of family members of patients with heritable causes of thrombosis.

3.2 Investigations in a suspected thrombophilic patient

3.2.1 When to investigate

- These should not be done during an acute episode or while the patient is on anticoagulants.
- Should be done at least one month after completion of a course of anticoagulation.
- Should not be done in the presence of viral infection while on Oral contraceptives, Hormone replacement therapy or during pregnancy.
- PCR based genetic tests may be done during anticoagulation
  e.g. Factor V Leiden, Prothrombin gene mutation.

3.2.2 Initial assessment

Initial assessment should be directed at determining whether there are any overt risk factors for thrombosis.

- Personal history and clinical examination may give a clue regarding the presence of

- malignancy
- autoimmune diseases
- nephritic syndrome
- myeloproliferative disorders

- Family history
- Acquired causes can be ruled out by doing;

  - Full blood count and blood picture **
  - Liver function tests
  - Renal function tests

**Full blood count
- increased PCV in polycythaemia
- increased platelets in essential thrombocythemia
- anaemia and polychromasia in Paroxysmal nocturnal haemoglobinuria
- rouleaux formation in multiple myeloma

All the tests fall into Grade X unless specified.

3.2.3 First line screening tests for thrombophilia

Coagulation screen –

- Prothrombin time
- Activated partial thromboplastin time
- Activated partial thromboplastin time with mixing tests

- Thrombin time
- Fibrinogen
- Reptilase time
- Clot observation

3.2.4 Second line tests –

- Anti phospholipid syndrome – should be tested twice, 12 weeks apart for confirmation. More than one test should be positive for confirmation.
- Anti cardiolipin antibodies
- Anti-β2 glycoprotein I antibodies
- Kaolin clotting time
- Dilute Russle's Viper venom test
- Anti-thrombin level
- Protein C level
- Protein S level
- Factor V Leiden mutation (Grade Y)
- Activated Protein C resistance (Grade Y)
- Prothrombin gene mutation (Grade Y)
- Homocystein levels (Grade Y)
- Ham's test /urine for haemosiderin/ CD 55/CD59 by flow cytometry - if relevant (Grade Y)
- Factor VIII levels – if relevant

If a test is positive ideally the test must be repeated at least once before the diagnosis is confirmed.

Failure to detect a positive result does not mean that thrombophilia does not exist.

3.3 Management of an acute thrombotic event

Baseline full blood count, PT and APTT

- Therapeutic range - Unfractionated Heparin – loading dose 75 u/kg i.v. stat followed by 18 units /kg /hr i.v. infusion
- Please refer manufacturer's leaflets for further dose modifications
- Monitor with APTT until APTT is over 1.5 – 2.0 times the baseline APTT.

APTT should be done 6h after starting heparin therapy. If not in the therapeutic range (1.5 – 2 times that of baseline APTT) adjust the dose. Monitor 6 hourly till it reaches the therapeutic level. Then review with APTT daily.

- Full blood count on Day 1, 3 and 5 to check platelet count to detect heparin induced thrombocytopenia

- For those with a history of exposure to Heparin within the past 100 days to have full blood count on day 1 and 24 hours after commencing heparin

- LMWH – b.d./ daily. Please refer manufacturer's leaflets for further dose modifications. Activated Xa activity can be used to monitor therapy.

- Known patients with protein C and S deficiency should be treated with Warfarin only when adequate heparinization is achieved.

For others commence Warfarin on

Day 1 - 5 mg at 6.p.m.

Day 2 – 5 mg at 6.p.m.

Day 3 – Check INR in the morning and adjust dose accordingly to maintain INR within therapeutic range. Check daily till the INR is within therapeutic range.

Stop heparin when INR is within therapeutic range for 2 consecutive days.

3.4 References

These guidelines are based on the guidelines published by the British Committee for Standards in Haematology.

1. Guidelines on the use and monitoring of heparin *British Journal of Haematologyl. 2006; 133, 19-34.*

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3. Guidelines for the investigation and management of antiphospholipid syndrome *British Journal of Haematology 2000; 109, 704-715.*

4. Investigation and management of heritable thrombophilia *British Journal of Haematology 2001; 114(3), 512-528.*

5. Goodnight S, Hathaway W.*Disorders in Haemostasis and Thrombosis, A Clinical Guide.*USA:Mc Graw-Hill, 2001.