# GUIDANCE ON THROMBOPHILIA TESTING- Full Clinical Guideline

Reference no.: CG-CLIN/4500/24

## 1. Introduction

The incidence of venous thromboembolism (VTE) in the general population increases with age. The term thrombophilia describes the tendency of an individual to get venous thromboembolism. It can either be heritable or acquired. **Heritable thrombophilia** includes Antithrombin, Protein C, Protein S, Factor V Leiden and Prothrombin Gene variant. **Acquired thrombophilia** may include Antiphospholipid syndrome and Myeloproliferative neoplasms.

## 2. Aim and Purpose

The purpose of this guideline is to aid clinicians in UHDB and GP's working in Derbyshire when requesting for Thrombophilia testing.

## 3. Definitions, Keywords

Acquired Thrombophilia

Heritable Thrombophilia

VTE

## 4. Thrombophilia Testing

The thrombophilia testing panel in UHDB includes testing for Antithrombin, Protein C, Protein S, APCr screen, Prothrombin Gene variant and Lupus anticoagulant. Factor V Leiden will be added by the laboratory to confirm an abnormal APCr screen.

Thrombophilia testing is expensive and time consuming. <u>It should not be carried out unless the results may influence the clinical management.</u>

The request form must contain all the relevant clinical details:

- Any incomplete or inappropriate requests will not be processed.
- Do not forget to mention any known thrombophilia in the family.
- Kindly record the patient's anticoagulant medication.

All requests will be screened by either Haematology Clinicians or Specialist Biomedical Scientists and if there is no evidence in the clinical details that the requests meet the

indications in these guidelines, these requests will not be processed. The samples from these unprocessed requests will be stored by the laboratory for 28 days. During this time any additional information may be provided by the clinician to the laboratory by E-mailing uhdb.coagulation@nhs.net.

After 28 days the samples will be discarded.

## 5. Timing of the Test

The timing of thrombophilia testing is very important. **Do not perform testing in the setting of Acute thrombosis.**

## 6. Sampling

6 x Blue top (Citrate) – appropriately filled blood bottles should be provided for thrombophilia screening
1 x Gold top (Clotted) sample should be sent to test Anticardiolipin and Beta 2 Glycoprotein.

## 7. Indications

Definitive Indications:

- Venous thrombosis at unusual sites e.g Cerebral or Abdominal. Suggest discussion with Haematology for such cases.
- Neonatal Purpura Fulminans
- Warfarin Induced skin necrosis
- Patients with known Thrombophilia in first degree relative, where this is going to have a clinical impact, for example female descendants of reproductive age.

Possible Indications- Discuss first with Haematology:

- 1st unprovoked VTE (DVT/PE) in patients, with no family history of VTE but wishing to discontinue anticoagulation.
- 1st provoked VTE (DVT/PE) in very young (<25 years old) patients.

NB: In all of these relevant indications, thrombophilia testing may not be useful as this is unlikely to alter the management of the patient.

## 8. Limitations of Thrombophilia Screen

Thrombophilia screen is only able to pick up the heritable thrombophilia that is known to us. Be aware that 50% of unprovoked VTE patients will have a negative thrombophilia screen. Therefore, a negative result should not provide false reassurance. Patient's personal and family history is of the utmost importance.

**Thrombophilia testing does not predict the risk of recurrence of VTE in most of the cases.**

Decision regarding long term anticoagulation should be made in the context of the clinical situation (i.e. whether the VTE was provoked or unprovoked and bleeding risk etc), regardless of whether heritable thrombophilia is known or not.

In many families, there is a low risk of thrombosis in asymptomatic relatives. The results of thrombophilia testing may be misinterpreted and lead to anxiety and distress otherwise healthy individuals.

## 9. Other situations

### Pregnancy:

- The risk of VTE increases by 5-10 times in pregnancy and this increases many folds in women with previous history of VTE.
- Almost all women with previous history of VTE would qualify for thromboprophylaxis during pregnancy on clinical grounds anyway. Hence, thrombophilia testing is not required.
- All women with unprovoked VTE should be tested for Antiphospholipid antibodies.
- Consider thrombophilia screen in women with no personal history of VTE but family history of unprovoked VTE or oestrogen related VTE when aged <50 years.

**NB: Protein S levels drop in pregnancy, therefore should not be tested.**

### Contraceptive Pill/ Hormone Replacement Therapy (HRT):

- Thrombophilia testing should not be performed to guide clinical decisions.

### Children:

- Thrombophilia testing in children is rarely indicated and should only be performed after discussion with the Paediatric Haematologist.
- Testing for Protein C and Protein S can be considered in the context of neonatal fulminans purpura. Children with early onset spontaneous thrombosis and unprovoked VTE should be investigated for Antithrombin III and Antiphospholipid antibodies.

### Arterial Thrombosis:

- Only antiphospholipid antibodies and Jak2/CALR (myeloproliferative mutations screen) should be tested as they are known to cause arterial thrombosis

**Screening Asymptomatic Relatives:**

- **Do not screen asymptomatic relatives without previous discussion with haematology**
- Thrombophilia testing in asymptomatic relatives of people with low-risk thrombophilia i.e. Factor V Leiden and Prothrombin gene mutations, is not recommended, as the annual risk of unprovoked VTE in affected family members is low.
- Testing for high-risk heritable thrombophilia i.e. Antithrombin III, Protein C and Protein S, might be appropriate but these individuals should be carefully assessed and counselled prior to testing.

## 10. Summary Table

| **THROMBOPHILIA TESTING RECOMMENDED** |
|---|
| Neonatal purpura fulminans – Limited screening (Protein C & Protein S ONLY) |
| Warfarin induced skin necrosis – Limited screening (Protein C & Protein S ONLY) |
| VTE at unusual site – Abdominal or Cerebral – Full thrombophilia screen + JAK2/CALR screen |
| Arterial thrombosis where Antiphospholipid Syndrome is suspected – Limited screening (Lupus Anticoagulant, Beta 2 Glycoprotein and Anti Cardiolipin antibodies, Jak2/CALR screenONLY) |
| 1st “Unprovoked” VTE in patients but no family history of VTE in first degree relative, where considering to stop anticoagulation – Limited screening (Lupus Anticoagulant, Beta 2 Glycoprotein and Anti Cardiolipin antibodies ONLY) |
| 1st “Unprovoked” VTE in patients who have first degree relative with a history of VTE and where considering to stop anticoagulation – Full thrombophilia screen |
| Patients with “Provoked” VTE at a very young age only in exceptional circumstances, after discussion with Haematologist |
| Asymptomatic relatives of patient with known high-risk thrombophilia |

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| (Antithrombin III, Protein C and Protein S deficiency), especially if considering Oestrogen based contraception or HRT – Test ONLY for the known deficiency |
| **THROMBOPHILIA TESTING NOT INDICATED & SHOULD NOT BE PERFORMED** |
| • Acute thrombosis (VTE)<br>• Patients on anticoagulation, when the decision to carry on anticoagulation indefinitely has already been made<br>• Arterial thrombosis, where Antiphospholipid Syndrome is not suspected or ruled out<br>• Central Venous Catheter related thrombosis<br>• Children other than Neonatal purpura fulminans – without discussion with Paediatric Haematologist<br>• Decisions about starting Oestrogen containing contraceptives/HRT other than the exceptions mentioned above |

**11. References (including any links to NICE Guidance etc.)**

1. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing
https://www.nice.org.uk/guidance/ng158/chapter/Recommendations#thrombophilia-testing

2. Clinical guidelines for testing for heritable thrombophilia
https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-2141.2009.08022.x

3. The psychological impact of testing for thrombophilia: a systematic review
D M Cohn[1], F Vansenne, A A Kaptein, C A J M De Borgie, S Middeldorp
https://pubmed.ncbi.nlm.nih.gov/18466313/

4. Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium Green-top Guideline No. 37a April 2015
https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-37a.pdf

5. Investigation and management of heritable thrombophilia,

Isobel D Walker, M Greaves, F. E Preston
https://onlinelibrary.wiley.com/doi/10.1046/j.1365-2141.2001.02981.x

6.Guideline on the investigation, management and prevention of venous thrombosis in children

Elizabeth Chalmers[1], Vijeya Ganesen, Ri Liesner, Sanjay Maroo, Timothy Nokes, D Saunders, Michael Williams, British Committee for Standards in Haematology
https://pubmed.ncbi.nlm.nih.gov/21595646/

## Documentation Controls

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| **Reference Number**<br><br>CG-CLIN/4500/24 | **Version: 1** | | **Status**<br><br>Final | Author:<br>Dr Charalampos Kartsios<br>Job Title:<br>Consultant Haematologist |
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| | 1 | Oct 2024 | Dr Kartsios | New guideline |
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| **Training and Dissemination:** There will be a communication launch via Net-i as part of a communication plan and via the attendees of the Thrombosis group meeting. | | | | |
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