University Hospitals Coventry & Warwickshire NHS Trust

Clinical Guideline (full)

HEREDITARY THROMBOPHILIA SCREENING GUIDELINE

E-Library Reference	CG 1789

Version	V4
Approving forum (QIPS or equivalent):	QPS and haematology network meeting
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Expiry Date:	30/06/2020
Target Audience:	Requestors of hereditary thrombophilia screens

Superseded UHCW Clinical Guideline(s): (if applicable)	CG1789 (V4)
UHCW Associated Records:	none
Keywords:	Thrombophilia

Clinical Operating Procedures relating to this guidance (please list)	
Summary version available	☐

Guideline clinical content
Clinical Guidelines assist in decision-making; they do not replace clinical judgement. Regardless of the strength of evidence, it remains the responsibility of the clinician to interpret the application of the clinical guidance to local circumstances and the needs and wishes of the individual patient. Where variations of any kind do occur, it is important to document the variations and the reason for them in the patient's health record. If in doubt, seek senior advice.
Introduction
Coventry and Warwickshire Pathology Network, in line with national guidance [(1)], require certain clinical indications (see section 6.1) to be present **and clearly noted on the request form** prior to proceeding with testing for hereditary thrombophilia.
Summary
If the request does not satisfy the criteria a comment will be generated stating "Patient clinical details do not satisfy criteria for appropriate thrombophilia screening – refer to Hereditary Thrombophilia Screening Guidelines. Sample will be stored for 1 month. Please contact a haematologist if you wish to discuss further." An evidence-based approach will be required for requests outside these criteria.
Definitions
None
Guideline details

Common problems and pitfalls with hereditary thrombophilia screening

(1) Utility of testing

Thrombophilia tests have been historically requested for patients with venous thromboembolism. Increasing data over the last 15 years have demonstrated the limitations of these tests.

Thrombophilias have an uncertain role in predicting recurrence of thrombosis despite being highly associated with 1st VTE. Risk prediction models are currently the best evidence based modalities that may predict risk for further thrombosis (DASH, VIENNA, HERDOO 2) and do not include thrombophilia tests.

Thrombophilia tests are costly and time consuming and should only be used when there is an evidence base to justify the test and where they may impact on clinical management.

There is no evidence that hereditary thrombophilia should influence intensity of anticoagulation nor the duration of anticoagulation.

There is also limited evidence that testing asymptomatic affected relatives leads to better outcomes (9), although in certain high risk situations e.g. pregnancy, it may be considered; but the limitations of testing should be discussed fully with the patient.

(2) Antiphospholipid Syndrome

This is an **acquired** thrombotic tendency and as such is not covered in this guideline - requests for the individual tests should be requested separately; they are not included as a part of an hereditary thrombophilia screen.

(3) Timing of testing

Acute thrombosis (within 1 month) and anticoagulation (heparin/warfarin/DOACS) affect many of the thrombophilia tests making interpretation unreliable. **DO NOT** request screening during an acute episode and until off anticoagulation for at least 1 month[$]

(Please note excessive alcohol intake can result in low antithrombin levels, clinicians should bear this in mind when interpreting results)

Pregnancy, combined oral contraceptive pill (COCP) and hormone related therapy (HRT) can also affect results – testing should be avoided in these situations unless there is clinical urgency (discuss with haematologist / obstetrician).

[$] Urgent testing should only be performed to evaluate protein C and S levels in suspected purpura fulminans. Testing for antithrombin levels can be checked in the rare situation of patients failing heparin based treatment. Thrombophilia testing for these indications must be discussed with a haematology consultant (preferably with an interest in thrombosis and haemostasis).

(4) Arterial thromboembolism

Testing for heritable thrombophilia is **not indicated** in patients with arterial thrombosis.(1)

(5) Repeat testing

There is **no benefit** in repeating normal thrombophilia screens. This is only likely to result in further anxiety for the patient.

In the event of an abnormal result, requests for confirmatory testing should be limited to the relevant deficiency only.

(6) Referrals from General Practice

It is suggested that General practitioners **DO NOT** request Thrombophilia screens without review of this guideline AND discussion with haematology. At UHCW we can review any queries for thrombophilia screening via our online advice and guidance (A and G) service. A and G is available at Warwick hospital and George Eliot. Thrombophilia testing is rarely performed urgently, there is time to wait for a written response if online A and G is not available in your area.

Testing for Hereditary Thrombophilia Screening (code = TPS)

This screen includes protein C, protein S & antithrombin levels, and a test for the prothrombin gene mutation (20210A). An 'activated protein C resistance' (APCR) test is also done as a screen for Factor V Leiden – if this is abnormal, then DNA analysis for Factor V Leiden is performed. It is a recommended approach to 'target' isolated thrombophilias if possible as the different tests vary in their clinical utility, rather than selecting all thrombophilias.

PLEASE ADD AS MUCH CLINICAL INFORMATION AS POSSIBLE ON REQUEST FORM. IN THE ABSENCE OF CLINICAL INFORMATION ALL REQUESTS WILL BE REJECTED AND THE SAMPLE FROZEN PENDING FURTHER INFORMATION. (All samples that do not appear to fulfil criteria will be stored for 1 month, the requesting clinician is advised to discuss the case with Consultant Haematologist at UHCW if they feel the test is warranted)

Indications for Hereditary Thrombophilia Screening

Personal history of VTE / related problems:

(1) Neonates and children with purpura fulminans (urgent protein S and C – discuss with haematologist) (1, 2))

(2) Patients with cerebral venous sinus thrombosis aged <60 years [++]

(3) History of warfarin induced skin necrosis (test after warfarin treatment withdrawn) (2)

(4) Women with a history of second trimester miscarriage, placental abruption, Intrauterine Growth Retardation (IUGR), unexplained stillbirth / intrauterine death (3-6) [++] (**NOT** as part of pre IVF work up / implantation failure investigation unless another qualifying factor)

(5) Antithrombin levels in patients with recurrent VTE while receiving heparin based anticoagulation

(6) Consider testing Antithrombin levels in patients with unprovoked thrombosis in whom you plan to stop anticoagulation as a positive result 'may' influence risk of recurrence. (12,13) Please only test if this will affect management.

[++]At discretion of clinician in individual cases and only after appropriate counselling regarding the limitations of the test. Testing for these indication has uncertain predictive value and there is currently no clear evidence that result should influence therapy intensity or duration. (1)

Contraindications

Do not screen patients when a positive result will not affect management

- Patients with unprovoked VTE in whom you are continuing anticoagulation (7,8,9)
- Do not screen for factor V leiden, Prothrombin gene mutation, protein C or S in unprovoked thrombosis. (Current evidence suggests that these thrombophilias do not increase risk for recurrence or have a minor effect and should not be used to aid decision making for long term anticoagulation. (8,15))
- Provoked VTE
- Retinal vein occlusion
- Abdominal thromboses

('Unprovoked' means no recent history of surgery within the preceding 3 months, immobility, fracture, cancer, oestrogen therapy, pregnancy).

Family screening

(7) Women planning pregnancy with a family history of VTE at a young age (<40years) in at least 1 first degree relative OR family history of known thrombophilic defect – please only test if it will affect management as per Green top guidelines (6)

(8) Women planning use of HRT with a strong family history of VTE (1 or more 1st degree relatives) should be discussed with a haematology consultant with an interest in thrombosis and haemostasis prior to testing (11)

Do not screen patients when a positive result will not affect management

- Women planning use of combined oral contraceptive pill with a family history of VTE <45 - screening is **not** recommended as COCP is not recommended on history alone.(1,10)
- Women planning use of COCP with a family member with VTE and known thrombophilia - screening is **not** recommended. COCP is not recommended, a negative thrombophilia test in this clinical situation does not exclude an increased risk of thrombosis.(1,10)

Sample Requirements

Hereditary Thrombophilia Screen:

X3 blue citrate (adult) for functional factor assays
X1 purple EDTA (adult) for molecular tests (PT gene mutation +/- FV Leiden)

End of clinical content
Guideline Governance

Implementation
Text Widespread involvement and dissemination of guideline as per sections 2.1-2.3 To appear on pathology network internet site (for primary care)
Training
Undergraduate and postgraduate training programmes
Patient Information
Nil

Audit & Monitoring				
Aspect being monitored	**Monitoring method**	**Responsible department(s)**	**Frequency**	**Group / committee receiving report & responsible for actions**
Frequency of rejected requests	Manual – haematology laboratory	Haematology	Continuous	Ben Bailiff
End of Governance content				

Guideline References

CEBIS Evidence Summary
(1) T Baglin et al. Clinical guidelines for testing for heritable thrombophilia (BCSH) Br J Haem 2010 149(2): 209-220 (2) T Baglin. Guidelines for thrombophilia testing. Thrombus 2010: 14(1) 6-8 (3) Royal college of Obstetricians and Gynaecologists Green Top Guideline No 17. The Investigation and Treatment of Couples with Recurrent First-trimester and Second-trimester Miscarriage (2011) (4) Royal College of Obstetricians and Gynaecologists Green Top Guideline No 63. Antepartum Haemorrhage (2011) (5) Royal College of Obstetricians and Gynaecologists Green Top Guideline No 55. Late Intrauterine Fetal Death and Stillbirth (2010) (6) Royal College of Obstetricians and Gynaecologists Green Top Guideline No 37a. 'Reducing the risk of thrombosis and embolism during pregnancy and the puerperium' (2015) (7) Christiansen SC et al. Thromobophilia, clinical factors and recurrent venous thrombotic events. JAMA 2005;293:2352-61. (8) Coppens M et al. Testing for thrombophilia does not reduce the recurrence of venous

thrombosis. J Thrombosis Haemost 2008;6:1474-7
(9) Couturaud et al. Factors that predict thrombosis in relatives of patients with venous thromboembolism. Blood 2014.;124:21214-30
(10) Faculty of sexual and reproductive healthcare. UKMEC. For oral contraceptive use (2016)
(11) NICE guideline NG23. Menopause: diagnosis and management. (2015)
(12) J.Sokol et al. Mild antithrombin deficiency and risk of recurrent venous thromboembolism: results from the MEGA follow-up study. J Thromb and Haemost 2018; 16:680-688
(13) Di Minno MND et al. Mild antithrombin deficiency and risk of venous thrombosis. Circulation 2014;129:497-503
(14) Di Minno MND et al. Natural anticoagulant deficiency and the risk of venous thromboembolism: a meta analysis of observational studies. Thrombosis research 135 (2015) 923-932
(15) Stevens S et al. Guidance for the evaluation and treatment of hereditary and acquired thrombophilia. J Thromb Thrombolysis 2016. 41:154-164

References cited in guideline	Grade*
T Baglin et al. Clinical guidelines for testing for heritable thrombophilia (BCSH) Br J Haem 2010 149(2): 209-220	1-2

***Grade:- The references are graded through the CEBIS process according to the criteria outlined below.**

Grade of evidence	**Based on**
1	Systematic review or meta-analysis
2	Randomised controlled trial/s
3	Controlled study without randomisation (e.g. case controlled) or quasi-experimental study, such as a cohort study
4	Descriptive studies such as case series and reports.
5	Expert opinion, narrative review

Add any Appendices below

(Please use a "Page Break" before each appendix, and list each clearly in the section on the title page. Appendices may include a summary, a flowchart, a proforma, or other materials, but its purpose must be clearly identified)