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Clinical Guide - Investigation & Management of Hypercoaguable States (September 2006)

Principal Developer: M. Mant
Secondary Developers: D. Houston, L. Vickars

BACKGROUND

Hypercoagulable states, also referred to as thrombophilias or prothrombotic disorders, are disorders that increase a subject's risk to venous, and sometimes to arterial, thromboembolism.Their Identification may be useful to identify a cause of thrombosis, to better select duration of anticoagulation, to help clarify future risk of thrombosis in asymptomatic relatives and for management of pregnancy in subjects who have had a prior thrombotic episode. A prothrombotic disorder should be considered in patients as outlined below. However, an indiscriminate search for underlying hypercoagulable states is usually unrewarding and may result in false positive results that inappropriately label patients as "clotters".

Long-term anticoagulation is probably never justified in asymptomatic subjects with thrombophilia. Identification of a thrombophilia should not normally affect choice of anticoagulant intensity. There is controversy regarding testing of family members. Informed consent should always be obtained. Results can create problems. Testing must be followed by appropriate counseling. Testing of minors is rarely, if ever, warranted. The main potential benefit is for younger females who might wish to use oral contraception or become pregnant.

A thrombophilia may contribute more strongly or weakly to initial or recurrent venous thromboembolic risk. Some thrombophilias (e.g. Factor V Leiden, Factor II 20210A), contribute weakly or not at all to thrombosis recurrence risk, although families with high clinical penetrance may be exceptions. However, protein C, S and antithrombin deficiencies, homozygosity for Factor V Leiden, combined heterozygosity for both Prothrombin 20210A and Factor V Leiden, and lupus anticoagulant almost certainly increase thromboembolic risk after discontinuing anticoagulant therapy. This increased risk applies particularly following idiopathic thromboembolism. However, recurrence risk largely depends on the original context of the episode. Because the influence of a thrombophilia may change recurrence risk only slightly, according to some data, some experts no longer recommend testing as an aid to recommending duration of anticoagulation. An alternate view is that long-term treatment should be individualized and that presence or absence of a thrombophilia, and its type, may be an important component of this choice.

Some hypercoagulable states are associated with late fetal and recurrent pregnancy loss, intrauterine growth retardation and probably other obstetric complications. This clinical guide will not address this area further as it is rapidly evolving and best management in most situations cannot yet be defined.

ACQUIRED RISK FACTORS

Most acquired causes of a predisposition to venous thromboembolism (VTE) can be elicited from the history and physical examination. Transient or reversible causes include immobilization, trauma or major surgery, use of oral contraceptives, hormone replacement therapy, and prolonged travel. Causes that are generally irreversible include malignancy, myeloproliferative disorders, nephrotic syndrome, antiphospholipid syndrome, and paroxysmal nocturnal hemoglobinuria. Long term anticoagulation should be undertaken, or at least considered, in patients whose thrombotic event is associated with continued immobilization or any of the irreversible acquired causes

INHERITED RISK FACTORS

These include deficiencies of antithrombin, protein C and protein S; elevated Factor VIII; Factor V Leiden (activated protein C resistance); Factor II 20210A; and dysfibrinogenemia. Most of these are autosomal dominantly inherited. Hyperhomocysteinemia may be inherited or acquired and non-inherited factors influence Factor VIII levels. High levels of other clotting factors have also been associated with VTE. However, their measurement is not currently recommended.

WHOM TO CONSIDER FOR INVESTIGATION FOR THROMBOPHILIA

- Thrombosis occurring at a young age (i.e. < 45 yrs)
- Idiopathic VTE
- Recurrent VTE
- Thrombosis at an unusual site
- Family history of VTE or of inherited prothrombotic disorder
- Warfarin-induced skin necrosis
- Recurrence/extension of thrombosis while adequately anticoagulated.

PITFALLS AND CAUTIONS IN INVESTIGATION OF PROTHROMBOTIC DISORDERS

- Assays performed during acute illness or while patient is anticoagulated may be unreliable, leading to misdiagnosis. For example, anticoagulant therapy with warfarin may influence the levels of protein C and S and antithrombin, tests for lupus anticoagulants, and some tests for APC resistance, while heparin may influence the measurement of antithrombin. Recent thrombosis, inflammatory disease and pregnancy may also affect some of these tests. Normal levels in children may differ from those in adults.
- With the exception of oral contraceptives, hyperhomocysteinemia, and antiphospholipid antibodies, risk factors that predispose to VTE probably do not normally predispose to arterial thromboembolism. Other thrombophilic disorders should not be routinely tested for in this setting, although stroke in some young people may be an exception.
- Abnormal results for inherited prothrombotic disorders should in general be confirmed by a second measurement obtained under ideal circumstances.
- Confirmation of the presence of a familial abnormality in first degree relatives of patients with functional test abnormalities is desirable.
- Comprehensive testing is recommended. Subjects with VTE often have more than one abnormality.
- The significance of anticardiolipin antibodies in subjects with VTE is currently controversial.

MANAGEMENT

Subjects who develop VTE during transient high-risk clinical settings (e.g. post-surgery), are unlikely to develop recurrent thrombosis after a 3 month period of treatment. They should, however, have appropriate thromboprophylaxis for future high-risk situations, and if they fall into a category where a prothrombotic disorder is likely, they may warrant further investigations.

Patients who develop VTE with ongoing malignancy, lupus anticoagulants, and those with PNH or other continued risk factors have a high-risk of recurrent VTE. Long-term anticoagulation should be considered. For most of these patients **(e.g. antiphospholipid syndrome) expert advice is recommended.**

Subjects with inherited hypercoagulable states require appropriate counselling, including the advisability of testing of first degree relatives. They should be considered for prolonged anticoagulation after a first episode of spontaneous VTE. However, long-term management should be individualized, and will depend on such factors as the precise nature of the disorder or disorders, circumstances of thrombosis, anticoagulant risk and patient preference. **Expert advice is recommended for all patients.** Recommendations may change as new knowledge related to natural history and results of clinical trials become available.

Subjects with inherited and some acquired thrombophilias are at increased, but variable, risk of VTE with pregnancy and with use of oral contraceptives and hormone replacement therapy. Management in these settings should be guided by expert advice and an informed patient's preferences.

New causes of thrombophilia continue to be identified. These may also lead to changes in recommended management.

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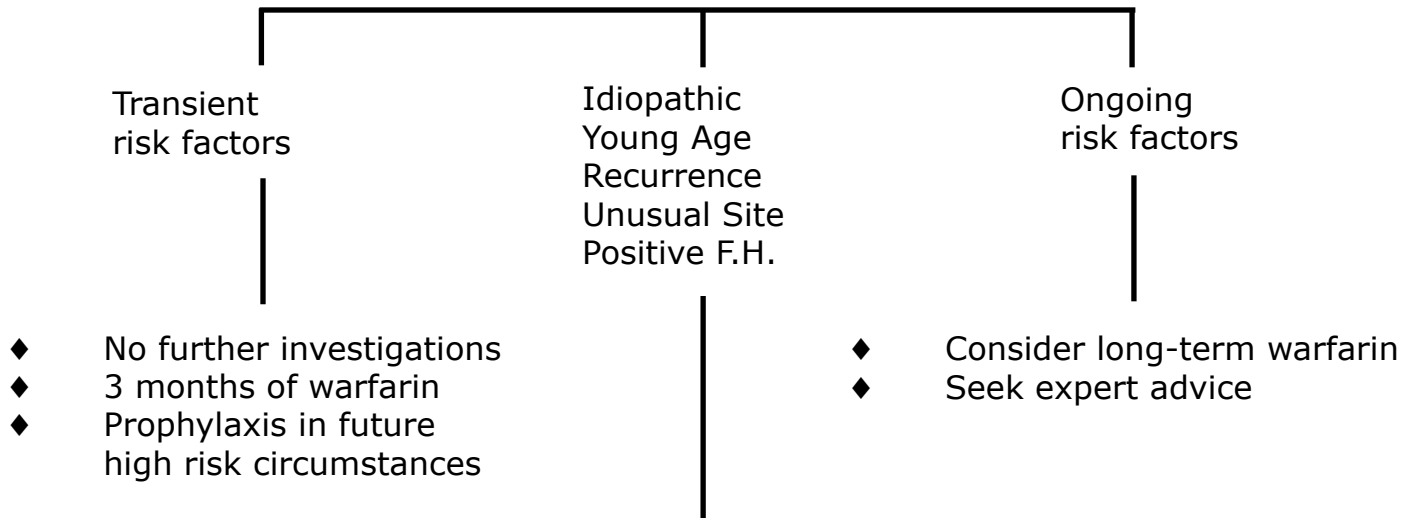
IIINITIAL THROMBOTIC EVENT



INVESTIGATIONS

- Investigate for inherited or acquired prothrombotic disorder
- Seek expert advice

CLINICAL SETTING WITH HIGH PROBABILITY OF RECURRENT VENOUS THROMBOSIS

- Idiopathic
- Metastatic carcinoma
- Antiphospholipid syndrome
- Deficiency of coagulation inhibitor
- Nephrotic syndrome
- PNH or myeloproliferative disease

TESTS FOR HYPERCOAGUABLE STATE

- CBC, PT, PTT
- Proteins C and S
- Antithrombin
- Factor V Leiden (and/or APC resistance)
- Factor VIII C
- Factor II 20210 A
- Fasting homocysteine
- Lupus anticoagulant
- Anticardiolipin antibody