

Thrombophilia or Hypercoagulable States

1. Definition: tendency to have thrombosis as a result of an inherited or acquired molecular defect.
2. Hypercoagulability disorders can be correctly diagnosed in about 85% of cases. Clinical thrombosis often arises from more than one "hit", e.g., trauma including surgery or oral contraceptives in a previously asymptomatic patient with an inherited disorder. Some individual defects are more thrombogenic than others, as are multiple abnormalities.
3. Risk factors: Autoimmune disease, cancer, cardiac disease, cardiac valve replacement, catheters, chemotherapy, dehydration, drugs (e.g., phenothiazines, phenytoin), hyperlipidemia, infection especially sepsis, Kawasaki's disease, liver disease, oral contraceptives, pregnancy, renal disease, sickle cell disease, surgery, thalassemia and trauma.
4. Individual Inherited Syndromes: Most significant inherited disorders are deficiencies of antithrombin, protein C and S, activated protein C resistance/factor V Leiden mutation, antiphospholipid syndrome (lupus anticoagulant and anticardiolipin antibody), homocystinemia, plasminogen abnormalities, prothrombin G20210A mutation and sticky platelet syndrome.
5. Mnemonic - CALMSHAPES: protein C deficiency, Antiphospholipid syndrome, factor V Leiden, Malignancy, protein S deficiency, Homocystinemia, Antithrombin 3 deficiency, Prothrombin G20210A mutation, Elevated factor VIII, Sticky platelet syndrome.
6. Investigation: Clinical features that suggest hypercoagulability include thromboembolism early in life, positive family history, thrombosis at unusual sites (e.g. upper extremity), spontaneous or recurrent episodes
7. Confirmatory tests for children with thromboembolic events.

Location	Gold standard	Current practice
DVT in upper system	Venography	Venography and USG of internal jugulars
DVT in lower system	Venography	USG then proceed to venography if needed
Pulmonary embolism	V/Q scan	V/Q scan; value of spiral CT not certain
Tip of CVL	Echocardiogram	Echocardiogram; USG
Arterial thrombosis	Angiography	Doppler may suffice, may need angiography
Ischemic stroke	Angiography	MRI, MRA
Sinovenous thrombosis	MRI, MRA	MRI, MRA

8. Laboratory Studies: Complete laboratory work-up is generally unreliable during acute thrombosis or while on anticoagulants. Basic work-up for thrombotic disorders should include the following: PT, PTT, Factor V Leiden assay, protein C and S levels, cardiolipin antibodies, lupus anticoagulant, ANA titer, antithrombin III assay, prothrombin G20210A mutation, fibrinogen, plasminogen activator inhibitor-1 assay, platelet aggregation and

- homocysteine level. Appropriate studies to rule out acquired risk factors listed above should also be considered.
9. Screening of healthy children of adults diagnosed with thromboembolic risk factors: the thrombotic risk of healthy children with a single thrombophilic defect is extremely low, therefore screening in these children under 15 years is unjustified as being non-cost-effective.
 10. Treatment: Low-molecular weight heparin (LMWH) 1 mg/kg SQ q12 hours has become the most often used therapy, both acute and long term. Advantages are predictable pharmacology, more certain compliance, lack of interference from drugs or diet, lower risk of heparin-induced thrombocytopenia (HIT), and probably lower risk of osteoporosis. Single-dose (q24hrs) is quite often used in adult hematology practice. Initial monitoring with anti-Xa levels with desired results between 0.5 and 1.0 is recommended.
 11. Oral anticoagulants (e.g., warfarin), can also be used, which reduce plasma levels of vitamin-K-dependent factors (II, VI, IX, X, PC, PS). Start with 2 – 5 mg PO qd and adjust based on the INR, with a target level of 2.5. Alterations in dosage may be needed with concurrent use of antibiotics, steroids, anticonvulsants, and TPN, especially in infancy, when oral anticoagulants are best avoided. Long term use is associated with osteoporosis. Because of their less predictable pharmacokinetics, laboratory monitoring must be carried out more frequently than when using LMWH.