Hypercoagulable State Practice Guidelines
Washington State Clinical Laboratory Advisory Council
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Definition: Hypercoagulable state: balance of the coagulation system is tipped toward thrombosis, due to either acquired or inherited increase in pro-coagulant elements (e.g. cancer pro coagulant) or decrease in anti-coagulant elements (e.g. Protein C deficiency).

Hypercoaguable states are suspected in patients who have:
1) "Spontaneous" thrombosis without obvious associated risk factors
2) Thrombosis, even with a concomitant risk factor, at an early age (e.g. less than 40)
3) Recurrent thrombosis, especially in different sites
4) Family history of recurrent venous thrombosis at an early age.
5) Thrombosis in unusual locations (for example: visceral thrombosis or upper extremity thrombosis)

Acquired Disorders and applicable laboratory test

<table>
<thead>
<tr>
<th>Initial testing for all patients: PT, aPTT, TT, Platelet, Fibrinogen</th>
<th>Refer to Coagulation Guideline for Unexplained Bleeding Disorders on the reverse side</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Antiphospholipid antibody (aPL) Syndrome (Lupus anticoagulant)</td>
<td>Tests: 1:1 mix showing inhibitor</td>
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<td></td>
<td>Hexagonal phase lupus inhibitor assay or dilute Russell viper venom time (dRVVT)</td>
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<tr>
<td></td>
<td>Anticardiolipin or anti-beta-2-GPI antibodies by ELISA (with titers)</td>
</tr>
<tr>
<td>2) Heparin induced thrombocytopenia (HIT) in appropriate clinical setting. Two types:</td>
<td>Test: Platelet Factor 4 Antibody (PF4)</td>
</tr>
<tr>
<td>HIT Type I - usually clinically mild and non-progressive</td>
<td></td>
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<tr>
<td>HIT TYPE II - acute, severe, progressive, immuno-mediated and may develop life threatening paradoxical thrombosis.</td>
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<tr>
<td>3) Cancer</td>
<td>Test: Use what is general practice for cancer diagnosis based on the clinical presentation</td>
</tr>
<tr>
<td>4) Persistent elevation of factor VIII with normal CRP</td>
<td>Test: Factor VIII activity and CRP</td>
</tr>
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</table>

Inherited Disorders and applicable laboratory test

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<tr>
<th>Initial testing for all patients: PT, aPTT, TT, Platelet, Fibrinogen</th>
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<tr>
<td>1) Factor V Leiden/aPC resistance (most common)</td>
<td>Test: aPC (activated Protein C) resistance assay OR DNA analysis for factor V Leiden - both can determine if patient is heterozygote or homozygote</td>
</tr>
<tr>
<td>2) Factor II (Prothrombin G20210) polymorphism</td>
<td>Test: Factor II DNA Analysis</td>
</tr>
<tr>
<td>3) Protein C Deficiency, Protein S Deficiency, or Antithrombin III Deficiency</td>
<td>Test together with: Protein C activity, Protein S free antigen assay, Antithrombin activity assay</td>
</tr>
<tr>
<td>4) Persistent elevation of factor VIII with normal CRP</td>
<td>Test: Factor VIII activity and CRP</td>
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Notes:
Factor V Leiden/Activated Protein C Resistance, Factor II DNA analysis, antiphospholipid antibody and HIT testing can be done at any time.

At time of acute thrombosis:
1) Protein C, Protein S, antithrombin may be falsely low due to ongoing thrombosis. If normal, deficiency is ruled out, if abnormal they should be repeated when the patient is asymptomatic and off antithrombotic medications for 2 weeks.
2) May identify reactive (not causative) antiphospholipid antibodies.
3) Factor VIII is an acute-phase reactant.

When on heparin/ coumadin:
1) Antithrombin is decreased 20-30% during heparin therapy.
2) Protein C and S are decreased during warfarin therapy.

References:
1. CAP Consensus Conference XXXVI, Diagnosis Issues in Thrombophilia, Nov.2001
4. Tsai AW; Cushman M; Rosamond WD; Heckbert SR; Tracy RP; Aleksic N; Folsom AR. Coagulation factors, inflammation markers, and venous thromboembolism: the longitudinal investigation of thromboembolism etiology (LITE). Am J Med 2002 Dec 1;113(8):636-42.
Patient History & Physical Exam
Important points to consider in interpreting guidelines:
1) Early onset bleeding (platelets) versus late onset (humoral factor deficiency).
2) Pregnancy (effects on circulatory levels)
3) Hereditary and/or personal history of bleeding disorders- possible (autosomal, recessive, dominant, sex-linked).

Basic Coagulation Workup (BCW): aPTT, PT, TT, Fibrinogen, Platelet count

- PT- Normal
  - aPTT- Normal
    - aPTT 1:1 Mix
      - No or incomplete correction (immediate inhibitor)
        - Do Lupus anti-coagulant workup (contact reference lab)
      - Complete after 60 minutes (slow acting inhibition)
        - Do Factor VIII Inhibitor workup
  - PT- Prolonged
    - aPTT- Normal
      - FVII Deficiency, Liver Disease, Vitamin K Deficiency
      - Full Correction
        - Deficiency of:
          - F VIII (hemophilia A, Type I VWD), F IX (hemophilia B), F XI, F XII (Hageman Factor deficiency, No bleeding)
      - Do Factor VIII inhibitor workup
    - aPTT- Prolonged
      - Common Pathway Deficiency
        - -FX, FII (ex: Warfarin RX, Vit K deficiency)
        - -FVX II (ex: liver disease)

- TT- Prolonged
  - Add protamin sulfate
    - No Correction
      - Heparin contamination
      - Antibody against bovine thrombin/dysfibrinogen
        - Fibrin Split Products
        - DIC
        - Dysfibrinogen
      - Pos
      - Neg
      - Workup for Isolated Thrombocytopenia
  - D-Dimer

- Fibrinogen-Low
  - Platelet- Low
    - Platelet Decreased
    - Other Tests - Normal

- Normal Coagulation Workup Bleeding Patient

Possible Causes
a) Mild FVII
b) VWD type II a/II b (autosomal dominant)
c) FX III (autosomal recessive)
d) Fibrinolytic work-up:
  - -PAI-1 deficiency
  - -TPA excess
  - -Alpha 2 antiplasmin deficiency

Abbreviations:
  aPTT: Activated Partial Thromboplastin Time
  CRP: C-Reactive Protein
  DIC: Disseminated Intravascular Coagulation
  F: Factor
  PAI: Plasminogen Activator Inhibitor
  PT: Prothrombin Time
  TPA: Tissue Plasminogen Activator
  TT: Thrombin Time
  VWD: Von Willebrand's Disease

NOTE: Bleeding time or platelet function assay maybe useful as an additional diagnostic tool for familial or acquired platelet disorders such as Von Willebrand's disease or Ticlopidine medication. In general, it is not a predictor of bleeding for surgical procedures.

REFERENCES: Work up extracted from literature and modified by University of Washington Department of Laboratory Medicine.

(Hypercoagulable State Practice Guidelines on reverse side)