VTE – Thrombophilia Testing and Treatment

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Hypercoagulable States - VTE

• Who should be tested
• When to Test
• Why Test
• What to Test
• How to Treat
• How long to Treat
Virchow’s Triad

- Inherited
  - Factor V Leiden
  - Prothrombin Gene
  - Protein C
  - Protein S
  - Anti thrombin Deficiency
  - Rare causes – Elevated Factor VIII, dysfibrongemia

- Acquired
  - Cancer
  - Antiphospholipid antibody
  - Drugs – OCP, Chemotherapy
  - PNH
  - Inflammatory Bowel Disease
  - Pregnancy
  - Trauma
Case 1

• 26 y women otherwise healthy on estrogen based OCP’s presents with new onset left lower extremity DVT. No family history of clots. No prior history of clots. No surgery and no long distance car travel.
Case 2

• 19 Y male ISU student presenting with unprovoked DVT (no trauma, no long distance travel or no recent surgery history, no OCP use). Mother had DVT in her 30’s. Uncle had PE in his 40’s
Prevalence of Thrombophilic Defects

• Factor V Leiden- 12 to 40%
• Prothrombin G20210A gene mutation - 6 to 18%
• Deficiencies of Antithrombin, protein C, protein S - 5 to 15%

Note: The lower percentage for each condition is for unselected patients; the higher percentage is for those with first events prior to age 50 or with a history of venous thrombosis in first-degree relatives.

• Homocysteine levels and mutational analysis for the responsible gene, methylene tetrahydrofolate reductase (MTHFR), should NOT be tested.
## Inherited States - Probability of First DVT or PE

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>1</td>
</tr>
<tr>
<td>Heterozygous factor V Leiden</td>
<td>5</td>
</tr>
<tr>
<td>Heterozygous prothrombin 20210A</td>
<td>5</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>10</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>10</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>15-20</td>
</tr>
<tr>
<td>Homozygous factor V Leiden</td>
<td>60-80</td>
</tr>
<tr>
<td>OCP</td>
<td>4-5</td>
</tr>
<tr>
<td>Heterozygous factor V Leiden + OCP</td>
<td>30-35</td>
</tr>
<tr>
<td>Pregnancy and Post Partum</td>
<td>5-10</td>
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</tbody>
</table>
Factor V Leiden

- Most common hereditary risk factor for venous thrombosis - 4% of Caucasian population
- Caused by a point mutation in Factor V (R506Q)
- Poor anticoagulant response to activated protein C (APC Resistance
Prothrombin Gene Mutation

• Second most common hereditary risk factor for venous thrombosis - 2% of Caucasian population
• Caused by a point mutation (G20210A) in the 3’ UTR of prothrombin gene
• Elevated levels of prothrombin in plasma
Antithrombin Deficiency

• Antithrombin (also called AT III) inhibits thrombin, factor Xa and other clotting factors
• Activity enhanced by heparin
• Risk factor for venous thrombosis, especially during pregnancy
Why Test

• Prophylactic anticoagulation during high risk Conditions such as surgery, pregnancy

• Extended duration of anticoagulation after a thrombotic event
  • Antiphospholipid antibody
  • Antithrombin deficiency
  • Two or more thrombophilic alleles
  • Homozygous Factor V Leiden, Prothrombin 20210A

• Family genetic counseling

• Birth Control Recommendations
Timing of Testing

• Acute thrombosis can reduce the plasma concentrations of antithrombin, protein C, and protein S.
• Heparin can reduce the plasma concentration of antithrombin and falsely lead to the detection of a lupus anticoagulant (LA).
• Warfarin can reduce the functional activity, and to some extent levels of, protein S and protein C, and can affect the detection of LA.
Case 3

• 46 y women presented to ER with shortness of breath for 2 weeks and new onset right side weakness. High Speed CT in the ER showed saddle PE. USG showed Right lower extremity extensive DVT. Brain MRI showed features consistent with a stroke. Echo shows right heart strain.

• She was previously healthy, No history of recent surgery, no recent long distance travel and not on any medications. No family history of clots. Mammogram and pap smear 3 months ago was negative.
Antiphospholipid Antibody Syndrome

• Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by venous or arterial thrombosis and/or pregnancy loss in the presence of persistent laboratory evidence of antiphospholipid antibodies (aPL)

• Can occur as a primary or secondary to underlying autoimmune conditions (like SLE)

• What to Test
  • pTT
  • Mixing study – does not correct
  • Anticardiolipin antibodies (aCL);
  • Anti-beta2-GP I antibodies;
  • Lupus Anticoagulant

• When to Test
  • Initial – during the acute event – can be falsely positive
  • Confirmatory – repeat > 12 weeks after initial event
  • aCL and anti-beta2-GP I antibodies are unaffected by the presence of an anticoagulant
Antiphospholipid Antibody Syndrome

Clinically significant aPL profile is defined as the presence of one or more of the aPLs on two or more occasions at least 12 weeks apart: revised Sapporo APS Classification Criteria

• A positive LA test, based on the guidelines of International Society of Thrombosis and Haemostasis
• aCL IgG or IgM, with a titer ≥40 units
• anti-beta2-GP I IgG or IgM, with a titer ≥40 units
Catastrophic APS

- History of APS and/or antiphospholipid antibodies (aPL)
- Three or more new organ thromboses within a week
- Biopsy confirmation of a microthrombus
- Exclusion of other causes of multiple organ thromboses or microthromboses
APS - Treatment

- Target INR 2-3 or
- Some antiphospholipid antibodies interfere with INR: 2.5-3.5 or 3-4
- Alternative method to monitor anticoagulation - Chromogenic factor X levels
- Occasionally have to add ASA
- Catastrophic APS
  - High Intensity Heparin gTT
  - Plasma Exchange
  - Steroids
  - Rituxan
Case 4

• 45 Y women with no past significant medical history presenting with abdominal pain worsening over the last week or two. Imaging showed acute portal vein thrombosis. No prior history of abdominal surgery. Not on any medications. Is up to date on cancer screening tests.

• Labs – WBC – 10k, Hg -15g, Platelets – 460K
Myeloproliferative Neoplasms

- ET, PV and Primary Myelofibrosis
- Jak2 V617F testing on blood
- May need bone marrow biopsy
- Anticoagulation
- Disease Modifying Agents - Hydrea
Case 5

• 28 y male presenting with acute onset abdominal pain. Has been having worsening fatigue over the last 6 months. Diminished exercise tolerance. Erectile dysfunction. On examination abdominal distention. Labs showed – WBC 6k, with normal Diff, Hg -11 g, Platelets 230K. MCV 102, Retic count elevated. Ultrasound showed hepatic vein thrombosis
PNH – Triad of Clinical Features

- Hemolysis/Haemoglobinuria
- Thrombosis
- Aplastic anemia
PNH Testing

Anemia
Elevated reticulocyte count, LDH and Retic Count
Decreased haptoglobin
Negative direct antiglobulin (Coombs) test (DAT)
Flow Cytometry
PNH - Pathophysiology

- Acquired mutation in the PIGA gene
- PIGA protein is involved in the first step in the synthesis of the glycosylphosphatidylinositol (GPI) anchor, a glycolipid that links dozens of cell-surface proteins to the plasma membrane on hematopoietic cells
- Cells become vulnerable to complement mediated lysis
- Pathogenesis of thrombosis in PNH is multifactorial and incompletely understood –
  - Free hemoglobin released from RBCs scavenges nitric oxide (NO), which in turn leads to vasoconstriction and possibly endothelial cell activation and expression of tissue factor.
  - Procoagulant microparticles may be released from platelets undergoing complement-mediated attack
PNH - Treatment

• Acute thromboses managed with anticoagulation similarly to patients without PNH
• Eculizumab $$$$$
Case 6

• 59 y Professor otherwise healthy admitted for unprovoked DVT of right lower extremity. No personal history of clots, and no family history of clots. On further questioning no change in BM and no weight loss. No fevers/night sweats. Colonoscopy 9 years ago was normal. Recent PSA was normal.
VTE – Testing for Cancer

• Screening for Occult Malignancy in Patients with Idiopathic Venous Thromboembolism (SOME) trial was a multicenter, open-label, randomized clinical trial comparing comprehensive CT of the abdomen and pelvis in addition to limited occult-cancer screening with limited occult-cancer screening alone in patients with unprovoked venous thromboembolism.

• Overall Incidence of cancer at 1 year after unprovoked VTE is low (3.9%) (However A systematic review and meta-analysis of the literature that pooled data from older clinical studies showed a rate of occult-cancer detection of up to 10% at 12 months after a diagnosis of unprovoked venous thromboembolism)

• No significant difference in median time to diagnosis of a malignancy or in cancer–related mortality between the groups.

VTE – Testing for Cancer

• In general, other than age-appropriate cancer screening, routine evaluation for occult malignancy in unselected patients with a diagnosis of venous thromboembolism (VTE) is **not** recommended

• High risk patient population – more testing may be beneficial
  • Symptoms or signs suggestive of an underlying malignancy
  • Recurrent VTE
Case 7

- 66 y male with metastatic pancreatic cancer on chemotherapy presenting with new diagnosis of pulmonary embolism.
Management of VTE in cancer

LMW Heparin VS Coumadin

• Meta analysis - Cochrane Database Syst Rev. 2014;
  • Reduced the rate of recurrent VTE
  • No Survival benefit
  • No difference in major bleeding events

• Randomized Clinical Trials
  • CLOT trial (Warfarin vs Dalteparin – 17% vs 9 % risk of VTE recurrence)
  • LITE trial (Warfarin vs Tinzaparin – 16% vs 7 % risk of VTE recurrence)
  • CANTHANOX trial (Warfarin vs Enoxaparin – no difference - terminated early due to poor recruitment)
  • ONCENOX trial (Warfarin vs Enoxaparin – no difference - terminated early due to poor recruitment)
Management of VTE in cancer - DOACS

Oral direct factor Xa inhibitors - Rivaroxaban (Xarelto); Apixaban (Eliquis); Edoxaban (Savaysa)

Oral direct thrombin inhibitors - Dabigatran (Pradaxa)

• Fixed-dose oral agents
• Do not require routine laboratory monitoring and dose adjustments
• Bridging therapy is not required when switching from initial treatment
• Avoid these agents in patients with severe renal insufficiency
• Most of these trials were performed in stable patients
• Most Trials were noninferiority trials that compared it with standard anticoagulation
Management of VTE in cancer - DOACS

• Anticoagulant effect cannot be reversed by fresh frozen plasma
• Idarucizumab (Praxbind) – approved for dabigatran reversal
• Unactivated 4-factor PCC (Kcentra) – for direct factor Xa inhibitor reversal.
• Andexanet is showing reversal activity for direct factor Xa inhibitor– pending FDA approval
Management of VTE in cancer - DOACS

• Most of these studies either excluded or included only a small number of patients with cancer
• Cancer patients included in these major trials were heterogeneous
• Meta-analysis of studies that approved these agents showed similar rates of VTE recurrence and major bleeding
• Several studies evaluating the efficacy and safety of DOACs in these high-risk populations are underway
Case 8

45 Y male admitted after MVA, Had surgery to right arm, Post op day 1 started on DVT prophylaxis with Lovenox, CBC - WBC 12, Hg 14 g, Platelets 390K. Discharged home doing well.

8 days later noted to have increasing swelling of left lower extremity. Presented to PCP. Ultrasound showed DVT. CBC – WBC 10, Hg 12 g, Platelet 195K

Started on Lovenox BID and Coumadin and sent home

3 days later presented to ER with acute shortness of breath. High speed CT showed acute PE, WBC 11, Hg 13g, Platelets 140K
HIT - Iceberg Model

- Multiple thrombosis (white clot syndrome) 0.01-0.1%
- Isolated thrombosis 30-80% of below groups
- Asymptomatic thrombocytopenia 30-50% of below group
- HIT - IgG seroconversion 0-10%

Warkentin TE, et al. 1994;75-127
Evolution of the HIT immune response in relation to clinical manifestations.

Grace M. Lee, and Gowthami M. Arepally Hematology 2013;2013:668-674
## HIT – 4T score

<table>
<thead>
<tr>
<th>Category</th>
<th>2 points</th>
<th>1 point</th>
<th>0 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Thrombocytopenia</td>
<td>Platelet count decrease &gt; 50% and platelet nadir ≥ 20 × 10^9 L^-1</td>
<td>Platelet count decrease 30%-50% or platelet nadir 10-19 × 10^9 L^-1</td>
<td>Platelet count decrease &lt; 30% or platelet nadir &lt; 10 × 10^9 L^-1</td>
</tr>
<tr>
<td>2. Timing of platelet count decrease</td>
<td>Clear onset between days 5 and 10 or platelet decrease ≤ 1 day (prior heparin exposure within 30 days)</td>
<td>Consistent with day 5-10 decrease, but not clear (eg, missing platelet counts) or onset after day 10 or decrease ≤ 1 day (prior heparin exposure 30-100 days ago)</td>
<td>Platelet count decrease &lt; 4 days without recent heparin exposure</td>
</tr>
<tr>
<td>3. Thrombosis or other sequelae</td>
<td>New thrombosis (confirmed) or skin necrosis at heparin injection sites or acute systemic reaction after IV heparin bolus</td>
<td>Progressive or recurrent thrombosis or nonnecrotizing (erythematous) skin lesions or suspected thrombosis (not proven)</td>
<td>None</td>
</tr>
<tr>
<td>4. Other causes for thrombocytopenia</td>
<td>None apparent</td>
<td>Possible</td>
<td>Definite</td>
</tr>
</tbody>
</table>

Total score of ≥ 8 points, high probability of HIT; 4-5 points, intermediate probability of HIT; ≤ 3 points, low probability of HIT.
Diagnostic algorithm.

1. Thrombocytopenia in a patient receiving heparin or LMWH*
   - Apply clinical scoring system

2. High clinical suspicion (4Ts=6-8)
   - Discontinue heparin; start alternative therapy
     - Immunoassay
     - Positive HIT confirmed (post-test probability of HIT ~55%)*
     - Negative HIT unlikely (post-test probability of HIT ~3-16%)*
     - Consider functional assay

3. Intermediate (4Ts=4-5)
   - Discontinue heparin; start alternative therapy
     - Immunoassay
     - Positive HIT possible (post-test probability of HIT ~60%)*
     - Negative HIT unlikely (post-test probability of HIT <0.5%)*

4. Low clinical suspicion for HIT (4Ts<3)
   - Continue heparin therapy

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Grace M. Lee, and Gowthami M. Arepally Hematology
2013;2013:668-674

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HIT – Management

• Low clinical suspicion of HIT, no further testing and recommend continuation of heparin therapy.
• For patients with an intermediate or high clinical suspicion of HIT, we discontinue heparin and initiate an alternative anticoagulant.
• DTI – Argatroban etc.
HIT- Management

• Current guidelines recommend up to 4 weeks of anticoagulation with warfarin for patients with isolated HIT and a minimum of 3 months for patients with HIT complicated by thrombosis.

• Whether sensitized patients with or without HIT can receive future heparin therapy is unresolved.

• For patients with refractory or progressive thromboses on DTI - plasmapheresis with fresh-frozen plasma replacement as salvage therapy to reduce antibody burden
Case 9

• 60 Y practicing lawyer presents with right lower extremity DVT. No recent surgery, On HTN and cholesterol medications. No travel history. Colon cancer and prostate cancer screening 2 months ago.

• Has been on 3 months of Rivaroxiban. He would like to stop given the bleeding risks.
VTE – Length of Anticoagulation

• D-Dimer one month and 3 months after stopping anticoagulation
  • PROLONG randomized trial - showed that a normal D-dimer (D-d) 1 month after anticoagulation suspension for unprovoked venous thromboembolism (VTE) was associated with a low risk of late recurrences (4.4% patient years).
  • PROLONG II randomized trial – showed that Patients in whom D-dimer became abnormal at the third month and remained abnormal afterward had a higher risk of recurrence than patients in whom D-d remained normal at the third month and afterward
  • Recurrence occurred in 27.7% of patients with previous DD>0.63mg/L and in 5.9% of patients with previous DD< 0.63mg/L – ASH 2015 abstract # 3554

• Residual Thrombosis (hypo-echogenicity by Doppler ultrasound) new thrombotic events were diagnosed in 75% of patients - – ASH 2015 abstract # 3554
VTE – Length of Anticoagulation

- VTE, major transient risk factor
- VTE due to minor transient risk, woman with VTE on hormones
- Woman, unprovoked VTE
  - DVT
  - PE
- Man, unprovoked VTE
  - DVT
  - PE
VTE – Length of Anticoagulation

1. Risk factors for recurrent VTE
   (a)....., (b)....., (c) ..... 

2. Risk factors for bleeding
   (a)....., (b)....., (c) ..... 

3. Patient preference
   “Warfarin hate factor” or
   “NOAC dislike factor”
Risk Factors for Bleeding on Anticoagulant Therapy

- Age >65
- Age >75
- Previous bleeding
- Cancer
- Metastatic cancer
- Renal failure
- Liver failure
- Thrombocytopenia
- Previous stroke

- Diabetes
- Anemia
- Antiplatelet therapy
- Poor anticoagulant control
- Comorbidity and reduced functional capacity
- Recent surgery
- Frequent falls
- Alcohol abuse
- NSAID use

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>0 risk factors</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>1 risk factor</td>
</tr>
<tr>
<td>High risk</td>
<td>≥2 risk factors</td>
</tr>
</tbody>
</table>
My Approach

• Low Risk Group
  • Superficial venous thrombosis 4-6 weeks
  • Provoked DVT or PE 3-6 months (including patients with one genetic risk factor)

• Intermediate Risk
  • Unprovoked DVT or PE (6 months to indefinite)
  • Unprovoked DVT or PE with one genetic risk factor (indefinite)

High Risk - Indefinite Anticoagulation
  • Two unprovoked DVT or PE
  • Life-threatening venous thrombosis
  • Unprovoked DVT or PE with antiphospholipid antibody,
  • Two or more genetic risk factors,
  • Active cancer
Summary

• There is general consensus among experts that testing for inherited thrombophilia’s should **not** be routinely recommended in most unselected patients with VTE

• In most patients with VTE, the identification of an inheritable defect does not alter therapeutic or prophylactic anticoagulant management, and consequently it has not been associated with improved outcomes

• Venous and arterial Clot think about APS

• Low Yield in testing inherited risk factors for arterial thrombosis (Stoke and MI)

• VTE in unusual locations think about PNH, Myeloproliferative cancers, APS

• Remember to think about HIT in hospitalized or recently hospitalized patients with new clots

• Duration of anticoagulation is a balance
Additional References

- Br J Haematol. 2010;149(2):209
- J Thromb Haemost. 2008;6(9):1474
- Blood 2014 124:196-203;
- Blood 2010 115:481-488
- Uptodate.com
- NCCN.org
- ASH
- ASCO
Thank You