Hematology

Emerging Insights Into Diagnosis, Prevention and Treatment of Thrombophilia
Clinical Implications of Thrombosis

- Approx 900,000 cases per year of VTE
- Two thirds DVT and PE not diagnosed
- VTE is life-threatening
  - 30d case fatality 5% DVT/33% PE
  - ~20% of all VTE are PE
  - ~25% of PE present as fatal PE
- Arterial thrombosis is still most common cause of death in western world
Predictors of Death after Surviving a First VTE

Olmsted County MN, Residents With First Lifetime VTE Diagnosed, 1966–1990

- Age (#1!)
- Obesity
- Tobacco use
- Congestive heart failure
- Chronic lung disease
- Chronic renal disease
- Cancer
- Serious neurologic disease

Pathogenesis of Thrombosis

Virchow’s Triad

- Endothelial Injury
- Vascular catheters
- Trauma
- Tumors
- Biochemical injury

- Venous Stasis
  - Immobility/travel
  - Pulmonary HTN
  - CHF
  - Venous obstruction

- Blood Coagulation
  - Venous obstruction
Thrombophilia: Imbalance in Clot Generating Systems

- Enhanced Initiation/Propagation
- Deficient Termination
- Resistance to Lysis
Enhanced Initiation/Propagation Phase

- Elevated Fibrinogen and Factor VII
  - Clear association with increased risk of arterial athero-thrombosis

- Elevated Factor VIII, IX, and XI
  Association with modest elevated risk of VTE (~2 fold)
Enhanced Initiation/Propagation Phase

- Consistent high levels of coagulation factors are most likely hereditary
  - Prothrombin Gene Polymorphism (G20210A) is assoc with 4-5 fold increase in thrombosis risk
    - 1-3% of Caucasians are heterozygotes
    - 5-10% of patients with idiopathic VTE

- Levels should be checked 3-6 months after any clinical event
  - Many are acute phase reactants and/or are consumed during clot formation

- Certain drugs effect levels: OCPs, HRT
Disorders in Termination Phase

- Protein C/S system deficiencies
- Antithrombin III deficiency
- ZPI/Protein Z mutations/deficiency
- ?TFPI deficiency
Protein C “Anticoagulant” System

Protein C → APC → Protein S

Thrombin

EPCR

PAR

Tm

EC activation

Endothelial Cell

Va VIIIa

Vi VIIIi
Inherited Deficiency States

• Rare heterozygous null mutations
  – 0.1 to 0.3% of general pop are heterozygous (40-50% of normal levels)
  – RR is ~5 for heterozygous PC/PS
    • Risk of thrombosis not uniform in all kindreds
    • Purpura fulminans in PC homozygous state
  – AT deficiency is high risk (RR is ~20)

• Functional Mutations: Factor V Leiden:
  • Arg506Gln removes aPC cleavage site
  • Prevalence in general population varies with ethnicity and race (rare in Africa and Asia)
  • RR is probably 4-5
Acquired Deficiency States

• Common
  – Consumption (DIC, post-op, massive thrombi)
  – Renal/GI loss (nephrosis, malabsorption)
  – Synthesis defect (warfarin, L-asparaginase, liver disease)
  – Fraction of PS circulates in inactive form bound to C4bBP
    • C4bBP is an acute phase reactant
Other Primary Hypercoagulable States

• **Defects in Clot Stabilization/Lysis**
  – Plasmin generation system
    • Plasminogen deficiency
    • PAI-1 excess
  – Fibrinogen mutations
    • plasmin resistance

• **Others:**
  – Sickle Cell Disease/?Trait
  – Other hereditary hemolytic states
  – Homocysteinemia
Hyperhomocysteinemia

• Can be genetic or acquired or both
• Associated with both VTE and arterial athero-thrombosis
• Relative risks are in the 2-3 range
• Lowering homocysteine levels is easy with vitamin therapy (Folate/B6/B12)
• Lowering homocysteine levels with vitamins does not reduce thrombosis risk
VTE at unusual sites

• Mesenteric and Portal Systems
  – PNH
  – Occult MPN
    • JAK2 mutation
• Cerebral sinus
  – Children with ALL and L-asparaginase
• Retinal vein
  – ?G20210A
Acquired Thrombophilia

- **HOSPITALIZATION** – by far the biggest risk factor
  - Internists/hospitalists need to be advocates for prophylaxis
  - Post op states (not just orthopedic surgery)
  - Trauma, ICU, “sick” medical patients
- **Age**
- **Cancer:** Solid tumors, MM, APL, MPN
- **Immune thrombophilia**
  - Anti-phospholipid syndrome:
    - Heparin associated thrombocytopenia
- **Travel**
- **Pregnancy**
- **PNH**
- **Diabetes/Obesity/Metabolic Syndrome**
- **Immobility**
- **Drug-related:** Estrogens, Chemotherapy, Thalidomide
- **Protein-losing states:** Nephrosis; Bowel Diseases
- **CHF/Renal Failure/Low flow states**
Incidence Rate DVT/PE

Rates 3x greater above age 65 compared to 45-64
PE rates increase more with age than DVT

p < 0.05 M vs W
What About Travel?

- RR for fatal PE is ~ 6 for airplane travel
  - Correlates with duration of flight (? threshold)
  - 4.8/million/yr for flights >10,000 Km
- RR for any long travel is >1
  - 4-8 hours = 1.8; 8-12 hrs = 2.8; >12hrs = 8.0
  - Risk increases for short stature (esp airplane)
- Mechanisms include hyper-responsiveness to hypobraric hypoxia
  - Subjects with V Leiden or OCP had increased TAT on 8hr flight c/w watching movies or ADL
Cancer and Thrombosis - Risks

- **Prandoni et al (NEJM, 10/92):**
  - 250 patients with first episode DVT
    - compare idiopathic and secondary
    - two year follow up (prospective)
    - 16/153 (10.5%) of idiopathic DVT developed cancer; 6/35 with recurrent thrombosis
    - 2/107 with secondary DVT developed cancer

- **Monreal et al (Cancer, 1991):**
  - 23% vs 6% incidence of cancer (more invasive diagnostics)
Cancer Thrombophilia: Unanswered Questions

• Is extensive cancer evaluation indicated in patients who present with idiopathic VTE?

• Is there a role for prophylactic anticoagulation therapy in cancer patients receiving chemotherapy?

• What is the role for anticoagulation in maintenance of central venous catheters?
Immune Thrombophilia: Heparin Associated Thrombocytopenia

- **HIT**
  - Associated with severe thrombosis
  - Rapid drop of 50% or more
    - Does not have to be “thrombocytopenia”
    - Good idea to follow platelet count postop from day 1
  - Can be severe
  - Less common with LMW heparins
Pathophysiology of HIT

From Aster, NEJM. 1995; 332:1374

Diagnostic tests

ELISA (anti-PF4)
- High sensitivity for presence of antibody
- Specificity for clinical syndrome not well defined
- Probably low
- Heparin dependent platelet serotonin release
- Cumbersome and radioactive
Heparin-induced thrombocytopenia is a severe thrombophilia: 40-50% absolute risk.
Treatment of HIT Syndrome

• Confirm diagnosis if possible

• **Interrupt the immune response**
  – Discontinue heparin immediately
  – Be wary of catheter flushes

• **Inhibit thrombin generation**
  – Treat active thrombosis
  – Prevent new thrombosis
    • Parenteral FXa or Direct thrombin inhibitors: Lepirudin/Bivalirudin, Agatrobam, Fondaparinox
    • Oral FXa inhibitors or DTIs: rivaroxiban, apixaban (not FDA approved for this)
  – Avoid platelet transfusions
Warfarin in HIT

• Warfarin alone is considered contraindicated in patients with acute HIT until the platelet count has recovered (or >100,000)

• Use during acute HIT only with an agent that reduces thrombin generation or inhibits thrombin

• Associated with progression of deep venous thrombosis to venous limb gangrene

• Caution if INR >4
Immune Thrombophilia: Antiphospholipid Antibody Syndrome

- Clinical syndrome characterized by:
  - Venous Thrombosis
  - Fetal loss
  - Thrombocytopenia
  - Neurologic disease
  - Cardiac valvular disease
  - Athero-thrombosis
    - Helsinki Heart Study and others identify aPL as independent risk factor for MI
Antiphospholipid Antibody Syndrome

- Often associated with systemic lupus erythematosus or other autoimmune disease
  - Up to 50% of SLE patients have aPL antibodies
- May be idiopathic - Primary Antiphospholipid Antibody Syndrome (PAPS)
Diagnostic Testing for APL

- **Functional Tests: Lupus Anticoagulant**
  - Inhibition of PL-dependent clot formation (aPTT)
    - Mixing 50:50 with normal plasma - does not correct
  - dRVVT (dilute Russel’s Viper Venom) is more sensitive than aPTT,
    - Needs a confirmatory test

- **Immunologic Tests (ELISA)**
  - Anti-cardiolipin antibody
  - Anti-β2GPI antibody
Indications for Screening for Causes of Hypercoagulable States

• **Classic Indications:**
  – Idiopathic thrombosis at young age (<50)
  – Recurrent thrombosis (especially during AC treatment)
  – Unusual site (cerebral, retinal, portal/mesenteric, hepatic)
  – Thrombosis in setting of + family history

• **“Newer” Indications**
  – Recurrent fetal loss (normal karyotype)
  – Severe or recurrent intrauterine growth retardation or preeclampsia
  – Idiopathic osteonecrosis
  – Maybe nearly every patient with unprovoked VTE
Diagnostic Evaluation of Thrombophilia is Usually Informative

Does this make it worthwhile?
Will it influence type, intensity or duration of AC therapy?
Will it aid in family or lifestyle counseling?
## Prevalence of Defects in Patients with Idiopathic Venous Thrombosis (and Risk)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence (%)</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden</td>
<td>0-40%</td>
<td>RR 5</td>
</tr>
<tr>
<td>Homozygous FV Leiden</td>
<td>0-1%</td>
<td>RR 10-20</td>
</tr>
<tr>
<td>Prothrombin Mutation G20210A</td>
<td>6-18%</td>
<td>RR 3-5</td>
</tr>
<tr>
<td>Deficiencies of AT3</td>
<td>2%</td>
<td>RR 20</td>
</tr>
<tr>
<td>Deficiency of PC or PS</td>
<td>2-3%</td>
<td>RR 2-10</td>
</tr>
<tr>
<td>Elevated Factors VIII, XI, IX</td>
<td>5-15%</td>
<td>RR &lt;2</td>
</tr>
<tr>
<td>MTHFR polymorphisms</td>
<td>high</td>
<td>RR &lt;2</td>
</tr>
<tr>
<td>Antiphospholipid Ab Syndrome</td>
<td>5-10%</td>
<td>RR 5-10</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>low</td>
<td>RR 3-5</td>
</tr>
<tr>
<td>Studies using GWAS or candidate genes</td>
<td>likely</td>
<td>RR &lt;2</td>
</tr>
</tbody>
</table>

*What is the value of testing given the low absolute risks and moderate to low relative risks? What is the population attributable risk?*
Screening for OCP as Example

• Absolute risk is 1:10,000/yr in young adults
• OCP RR is 4-5; V Leiden is 7; combined is 35
• Pop prevalence of V Leiden is 3%
• 10,000 young white women on OCP: expect 4-5 VTE/yr
• If you screen: 300 will be carriers
• RR in this group is 35. Absolute risk is 35 X 1:10,000 (~1 in 300 per year)
• Therefore, screening 10,000 women will prevent less than one additional event per year while denying 300 women OCPs!
“Multi-Hit” Hypothesis: Thrombosis is the result of a combination of risk factors

• Thrombotic events in patients with known thrombophilia usually occur in settings of increased risk
  – Airplane trips, trauma, pregnancy
  – Risks increase with age

• Some risk factors synergize in combination
VTE Risk Factor Model

**Genes**
- Anticoagulant deficiencies
- Factor V Leiden
- Prothrombin 20210A

**Acquired RFs**
- Age
- Previous VTE
- Cancer
- Obesity
- Varicose Veins
- Hormone Treatments

**Intrinsic Thrombosis Risk**

**Triggering Factors**
- Pregnancy
- Surgery
- Immobilization
- Trauma
- Air Travel

**Prophylaxis**

**Thrombosis Threshold**

**VTE**
How long should patients with idiopathic VTE be treated with OAC?
Thrombosis Recurrence After Cessation of Warfarin

Subgroup Analysis:
Those with “provoked” VTE did well with 6 weeks
DVT Recurrence

- **Cumulative Incidence**
  - 2 years: 17.5%
  - 5 years: 24.6%
  - 8 years: 30.3%

- **Predictors of Recurrence**
  - Older age (**#1 predictor; 17% higher risk per decade of age**)
  - Idiopathic or malignancy-related first event
  - Male sex
  - Neurologic disease
  - Higher BMI
  - Certain hemostatic defects
  - PE as first event predicts recurrent PE
  - Number of prior VTE (RR 2 with 2; 3 with 3)

*Prandoni, Ann Intern Med 125:1-7, 1996*
*Heit, Arch Intern Med 2000 160: 761-8*
*Shrivastava, submitted 2006*
Candidates for Long Term AC

- Multiple recurrent VTE
- Single life threatening event?
- Thrombosis at an unusual site (portal vein)
- ? Multiple risk factors
- ? Cancer, obesity, older age
- Thrombophilia evaluations can be helpful
  - AT3 deficiency (RR20), aPL/LAC (RR8-10), homozygous Factor V Leiden (RR80), compound heterozygous states (RR15-20), and PC or PS with strong +FH are associated with significant increased risk
  - Except for aPL/LAC these are relatively uncommon (<5% in total)
PROLONG: D-dimer testing to determine the duration of OAC (3mos + 30d)

(Palareti et al. NEJM 2006)
What is the pathophysiologic meaning of a persistent positive d-dimer?

• Possible marker for systemic thrombophilia
  >50% of the recurrent events were contralateral

Caveats:
  – d-dimer levels tend to increase with age
  – d-dimer is known to increase in the setting of chronic inflammatory disorders

• Conclusion:
  – Segregating risk in VTE patients is an attainable goal
  – Need to develop more sensitive and specific biomarkers to detect persistent underlying thrombophilia in subjects who have suffered VTE.
Risk of Recurrence of Venous Thromboembolism in Patients Randomly Assigned to Aspirin or Placebo

11% vs 6.6% recurrence with no differences in bleeding

100mg ASA for 2yr
400 subjects
Unprovoked VTE
Double blind, placebo
Post-Thrombotic Syndrome

- Cumulative Incidence 30-50% after DVT
- Risk Factors (little information available)
  - Age
  - Male Sex
  - Overweight
  - Proximal vs distal DVT (debated)
- Compression stockings for all DVT patients appear to be effective prevention

Stain M, JTH 3:2671-6, 2005