Hypercoagulable states
Robert McDonald
Phlebology Course, 2007

Venous thromboembolism
• Incidence 1-2:1000
  age dependent
  – 20s  1:10,000
  – 50s  1:1000
  – 80s  >1:100
• Mean age 1st VTE event 62 years

Venous thromboembolic disease
• Presentations
  – Superficial thrombophlebitis
  – Deep venous thrombosis
  – Pulmonary embolism, sudden death
  – Post-thrombotic syndrome
  – Pulmonary hypertension

VTE Aetiology
• Acquired
• Hereditary
• Multifactorial
  Interplay of genetic & environmental influences
Acquired – risk factors

General
• Age
• Immobilisation >3 days
• Pregnancy and postpartum
• Major surgery previous 4 wks
• Long plane or car trips(<4h) in prev 4 wks

Medical
• Cancer
• Previous DVT
• Stroke
• AMI
• CHF
• Sepsis, nephrotic syn, ulcerative colitis

Trauma
• Multiple trauma
• CNS/spinal injury
• Burns
• Lower extremity fractures

Vasculitis
• SLE and lupus anticoagulant
• Behcet syndrome
• homocystinuria
Haematologic
• Polycythaemia rubra vera
• Thrombocytosis
• Inherited disorders of coagulation
• Antithrombin III, protein C, S deficiency
• Dysfibrinogenaemias and disorders of plasminogen activation

Drugs/medications
• IV drug abuse
• Oral contraceptives
• Oestrogens
• tamoxifen
• Heparin-induced thrombocytopenia

Oral Contraceptives and VTE
• Low dose (30-40 microg ethinylestradiol) assoc with increase risk 3-6x
• Risk highest if 1st year of use
• Absolute risk 3-4 per 10,000 person years cf 1 per 10,000 in nonusers
• HRT assoc with 2-4x increased risk, probably not significant after 1 year

Influence of Progestins
• Higher risk with 3rd generation progestins desogestrel, gestodene cf 2nd generation levonorgestrel, norgestrel
• Progestin only OC have lower risk than combined OC
**Inherited thrombophilia**

**Common**
1. Mutation in factor V gene (factor V Leiden)
2. Mutation in prothrombin (FII) gene
3. Homozygous methylenetetrahydrofolate reductase (MTHFR) gene mutation

**Frequency of Inherited Thrombophilias**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Prevalence in general population %</th>
<th>Prevalence in DVT pts %</th>
<th>Relative risk of DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden</td>
<td>5</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>Prothrombin G20210A</td>
<td>2*</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>0.2-0.4</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>0.7</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>0.02</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>1/355,000</td>
<td>&lt;0.1</td>
<td>2.5</td>
</tr>
</tbody>
</table>

**Normal control of coagulation**

Coagulation reactions

**Protein C Pathway**

Protein C Pathway

Activated Protein C

Factor Va, VIIIa inactivation

Endothelial cell

Protein C

Activated Protein C

Factor V, VIIIa

Protein S phospholipid

Antithrombin-heparin sulfate

Normal control of coagulation

Coagulation reactions

**PROTHROMBIN** → **THROMBIN** → **COAGULATION** → **PROTEIN C PATHWAY** → **ANTITHROMBIN**
Mechanisms of Thrombosis

- Factor V Leiden
- Prothrombin mutation
- Protein C, S deficiencies
- Antithrombin deficiency

PROTHROMBIN THROMBIN THROMBOSIS

Factor V Leiden

- Factor V protein resistant to inactivation by APC
- Single base substitution – adenine for guanine at position 1691 in the factor V gene
- Translated protein has AA glutamine instead of arginine at residue 506
- 506 is the 1st of 3 sites of cleavage by APC
- *In vitro* - Failure of activated protein C to prolong the aPTT (APC resistance)

Factor V Leiden accounts for 95% genetic abnormalities in APC resistance.
- Found in 20% VTE pts, 5% general population
- VTE risk in carriers variable, prevalence of 13-25%, RR 5-10X (much higher if coinherit other thrombophilias)
- 2/3s VTE associated with an environmental precipitant

Acquired APC resistance
- Pregnancy
- OCP
- Elevated factor VIII
- APL syndrome
- Oral anticoagulants
- Anti-protein C antibodies
- Stroke
Prothrombin G20210A

- Adenine substitution for guanine at nucleotide position 20210
- Increased prothombin levels
- ?altered processing of mRNA
- Found in 6% pts with VTE, 2% healthy subjects

Hyperhomocysteinaemia

- Genetic and acquired forms
- Arterial & venous thrombosis
- Increases VTE risk in pts with the common inherited thrombophilias

Transsulfuration Pathway

- Transfer of sulfur atom from methionine to cysteine

- Methionine
- THF
- Methyl THF
- Methylene THF
- Methyl THF: homocysteine methyltransferase, hydroxyB12
- Cystathione B-Synthase
- Pyridoxal phosphate
- THF

Hyperhomocysteinaemia

- Acquired causes
  - Folate, B12, B6 deficiency
  - Renal failure
  - Hypothyroidism
  - Increasing age
  - Smoking
- Tx: folic acid supplement, plus B6 and B12 if normal homocysteine levels not achieved
C677T MTHFR gene mutation

- Thermolabile variant of MTHFR with reduced activity
- 5-15% of caucasians, East Asians
- Mild hyperhomocysteinemia in persons with folate deficient diet
- ?risk factor for VTE

Thrombophilia - hereditary

Consider when:

- No acquired risk factors for VTE*
- Unusual site – cerebral, visceral, axillary*
- Family history VTE
- <45-50yo
- Female with multiple miscarriages, stillbirths

>50% associated with known acquired risk factor

*Most present with DVT of legs and/or PE

Thrombophilia Panel

- Antithrombin activity
- Protein C, S activity
- Activated protein C resistance or factor V Leiden
- Prothrombin gene mutation
- Homocysteine levels
- Anticardiolipin Ab, lupus anticoagulant
- Factor VIII activity

Thrombophilia screen

First line tests Seligsohn, NEJM 2001

- Activated protein C resistance
- Factor V mutation
- G20210A prothrombin mutation
- Homocysteine level
- Factor VIII level
- Lupus anticoagulant
**Intermediate priority**
- Protein C activity, protein S Ag
- Antithrombin activity
- Anticardiolipin antibody titres

**Low priority**
- Dysfibrinogenaemia (normal-low fibrinogen level and prolonged thrombin time)
- Increased fibrinogen
- Increased factor IX, XI activity
- MTHFR C677T mutation

**False positives**
- Thrombosis – low antithrombin levels, elevated factor VIII
- Heparin – low antithrombin levels
- Warfarin – low protein C, S
- Increased factor VIII – acute phase response, stress, pregnancy, oral contraceptive, older age

**Decreased protein C, S levels**
- Vit K deficiency
- Liver disease
- warfarin
- DIC
- Acute phase response (protein S)
- Factor V Leiden interferes with coagulation assays of C and S