Disclosure (s)

• Relevant financial relationship(s)
  • None

• Off-label usage
  • None

• Change in slide set
  • You betcha! (YES!)
Learning Objectives

• Explain the concept of thrombophilia
• Recognize the congenital and acquired thrombophilias
• State the practical application of thrombophilia in patient management
• Understand limitations of selected assays
• Realize the value of algorithmic approach to testing
Multifactorial Disease

Acquired + inherited

Thrombosis

Acquired

Inherited

Acquired + acquired

Inherited + inherited
Thrombophilia

Hereditary

Coagulopathy

• Activated protein C resistance  
  • Factor V Leiden
• Prothrombin G20210A
• Selected dysfibrinogenemia variants
• Antithrombin
• Protein C
• Protein S

Acquired

Coagulopathy

• Antiphospholipid antibodies  
  • Lupus anticoagulant
  • Anti-cardiolipin
  • Anti-beta-2 GP I
• Clinical Risk factors  
  • Numerous
Acquired Clinical Risk Factors for VTE
Nested Case-Control Study (625 Case-Control Pairs)

- Surgery
- Trauma
- Inpatient
- Malignancy with chemotherapy
- Malignancy without chemotherapy
- Central venous catheter or pacemaker
- Neurologic disease
- Superficial vein thrombosis
- Varicose veins/age 45 yr
- Varicose veins/age 60 yr
- Varicose veins/age 70 yr
- CHF, VTE incidental on autopsy
- CHF, antemortem VTE/causal for death
- Liver disease

Odds ratio

Algorithmic approach

- Pre-analytical:
  - Patient selection

- Analytical:
  - Types and sequence of testing
Patient Population

• Asymptomatic individual
  
  General screening $\rightarrow$ NOT indicated

  Anticipated exposure to an acquired thrombophilia
  Hospitalization, surgery, pregnancy, orthopedic surgery
  oral contraceptive (OCP), hormone replacement (HRT)

• Symptomatic patient thromboembolism
# Odds Ratio of Risk of VTE with HRT

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>VTE events n/N</th>
<th>No VTE events n/N</th>
<th>OR (random) 95% CI</th>
<th>OR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Use of hormone replacement therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herrington et al</td>
<td>32 / 40</td>
<td>60 / 105</td>
<td>3.00 (1.26-7.13)</td>
<td></td>
</tr>
<tr>
<td>Rosendaal et al</td>
<td>31 / 61</td>
<td>37 / 153</td>
<td>3.24 (1.74-6.04)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>101</strong></td>
<td><strong>258</strong></td>
<td><strong>3.16 (1.90-5.23)</strong></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2=0.02$, df=1 (P=0.89), $I^2=0%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $z=4.45$ (P&lt;0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Factor V Leiden</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herrington et al</td>
<td>2 / 10</td>
<td>4 / 49</td>
<td>2.81 (0.44-18.00)</td>
<td></td>
</tr>
<tr>
<td>Rosendaal et al</td>
<td>8 / 38</td>
<td>8 / 124</td>
<td>3.87 (1.34-11.15)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>48</strong></td>
<td><strong>173</strong></td>
<td><strong>3.58 (1.43-8.97)</strong></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2=0.09$, df=1 (P=0.77), $I^2=0%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $z=2.71$ (P=0.007)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Factor V Leiden and use of hormone replacement therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herrington et al</td>
<td>8 / 38</td>
<td>2 / 118</td>
<td>15.47 (3.12-76.66)</td>
<td></td>
</tr>
<tr>
<td>Rosendaal et al</td>
<td>6 / 14</td>
<td>3 / 48</td>
<td>11.25 (2.32-54.44)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>52</strong></td>
<td><strong>166</strong></td>
<td><strong>13.15 (4.28-40.47)</strong></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2=0.08$, df=1 (P=0.78), $I^2=0%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $z=4.50$ (P&lt;0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Odds Ratio vs Absolute Risk of HRT-Related VTE in FV Leiden Carriers

Assumption: Up to 15-fold increase in risk of VTE

Absolute incidence: 900-1800 per 100,000 women-years or 1-2% per woman-year

In comparison with no screening, universal pre-HRT FV Leiden screening was found to be cost effective (in the U.K.)

Cushman M et al: JAMA 292:1573, 2004
Patient Population

- Asymptomatic individual

  General screening

  Anticipated exposure to an acquired thrombophilia
  Hospitalization, surgery, pregnancy, orthopedic surgery
  oral contraceptive (OCP), hormone replacement (HRT)

- Symptomatic patient thromboembolism
Patient selection: A suggested approach

Arterial thrombosis

Antiphospholipid Antibodies
Dysfibrinogenemia etc

Venous thrombosis
Temporary risk factor

Testing not indicated
The ASH Choosing Wisely® Campaign: five hematologic tests and treatments to question

### Recommendations

1. ..... Transfuse the minimum number of RBCs...to relive symptoms of anemia to return Hb to safe range

2. ..... Do not order thrombophilia testing for VTE occurring in associating with a transient VTE risk factor...

3. ..... Do not routinely insert IVC filters...

4. ..... Do not administer FFP or PCC except in emergency circumstances...

5. ..... Limit surveillance CT scans in asymptomatic patient after curative intent lymphoma treatment...

Blood 2013; 122: 3879
Patient selection

Arterial thrombosis

Antiphospholipid antibodies

Testing not indicated

Venous thrombosis

Temporary risk factor

Idiopathic with or without family history

Testing possibly indicated
Phases of anticoagulation

- **Initial Rx**  
  - **Acute VTE Rx**  
    - Parenteral
    - 0-7 days
  - **Long term**  
    - VKA or other agent  
    - 3 months
  - **Extended**  
    - Secondary prophylaxis of VTE  
    - > 3 months

- **No effect of thrombophilia**
- **Multifactorial effect**

Kearon C et al Chest 2012;141 (2)(Suppl)e419S-e494S
Thrombophilia Profile

Testing begins with:
- Prothrombin Time (PT), Plasma
- Activated Partial Thromboplastin Time (APTT), Plasma
- Dilute Russells Viper Venom Time (DRVVT), Plasma
- Thrombin Time (Bovine), Plasma
- Fibrinogen, Plasma
- D-Dimer, Plasma
- Soluble Fibrin Monomer
- Antithrombin Activity, Plasma
- Protein C Activity, Plasma
- Protein S Antigen, Free, Plasma
- Prothrombin G20210A A Mutation, Blood
- Activated Protein C Resistance V (APCRV), Plasma
- Special Coagulation Interpretation

All initial testing within reference ranges for age and gender:
- No evidence of thrombotic diathesis
- No further testing is performed

Possible factor inhibitor

Evidence of inhibition

Evidence of coagulation factor deficiency

PT: ≥14.0 seconds

APTT: >36 seconds

DRVVT: ≥1.2 seconds

Thrombin Time (Bovine)

APCRV: <2.3 OR
Prolonged baseline APTT

Protein C Activity: <70%

Protein S Antigen, Free:
- Males <65%
- Females <50 years: <50%
  ≥50 years: <65%

Antithrombin Activity:
- <80%
- No evidence of an acquired deficiency

PT Mix 1:1

APTT Mix 1:1

DRVVT Mix 1:1

Evidence of inhibition

Evidence of coagulation factor deficiency

≥14.0 <14.0 ≤36 >36 ≥1.2 <1.2

Normal – no evidence of heparin or dys/hypofibrinogenemia

Repitlase Time

15-23 sec >23 sec

Anticoagulant effect:
- Possible dys/hypofibrinogenemia

Factor V Leiden (R506Q) Mutation

Protein C Antigen

Protein S Antigen, Total

Possible factor inhibitor

Antithrombin Antigen, Plasma

No evidence of heparin in sample

Platelet neutralization procedure (PNP)

Does not shorten

Shortens by 4-5 seconds

Evidence of lupus-like anticoagulant

No diagnostic of lupus-like anticoagulant

Additional assays may be performed if further information is necessary. These may include:
- Coagulation Factor Assays
- Staclot Lupus Anticoagulant
- Protein S Activity

**Unfractionated/low-molecular weight heparin or direct thrombin inhibitor (eg, dabigatran, argatroban)

An interpretive report is provided that includes all profile tests (always performed) and any reflex tests performed (if appropriate).
Thrombophilia Profile

Testing begins with:
- Prothrombin Time (PT), Plasma
- Activated Partial Thromboplastin Time (APTT), Plasma
- Dilute Russell's Viper Venom Time (DRVVT), Plasma
- Thrombin Time (Bovine), Plasma
- Fibrinogen, Plasma
- D-Dimer, Plasma
- Soluble Fibrin Monomer
- Antithrombin Activity, Plasma
- Protein C Activity, Plasma
- Protein S Antigen, Free, Plasma
- Prothrombin G20210A A Mutation, Blood
- Activated Protein C Resistance V (APCRV), Plasma

All initial testing within reference ranges for age and gender:
- No evidence of thrombotic diathesis
- No further testing is performed

PT: ≥14.0 seconds
- PT Mix 1:1
  - ≥14.0
  - <14.0
- Evidence of inhibition*
- Evidence of coagulation factor deficiency*

APTT: >36 seconds
- APTT Mix 1:1
  - ≤36
  - >36
- Evidence of inhibition*
- Evidence of coagulation factor deficiency*

DRVVT: ≥1.2 seconds
- DRVVT Mix 1:1
  - ≥1.2
  - <1.2
- Evidence of coagulation factor deficiency*

Thrombin Time (Bovine)
- Normal – no evidence of heparin or dys/hypofibrinogenemia
- Reptilase Time
  - ≤1.2
  - >1.2
- Evidence of inhibition*
- Evidence of inhibition*
- Reptilase Time
  - 14-23 sec
  - >23 sec
- Anticoagulant effect **
  - Possible dys/hypofibrinogenemia*

No evidence of heparin in sample
- Platelet neutralization procedure (PNP)
  - Does not shorten
  - Shortens by 4-5 seconds
- Possible factor inhibitor*

Evidence of lupus-like anticoagulant
- DRVVT Confirmation
  - ≥1.2
  - <1.2
- Not diagnostic of lupus-like anticoagulant
- Possible dys/hypofibrinogenemia*
Thrombophilia Profile

Testing begins with:

- Prothrombin Time (PT), Plasma
- Activated Partial Thromboplastin Time (APTT), Plasma
- Dilute Russells Viper Venom Time (DRVVT), Plasma
- Thrombin Time (Bovine), Plasma
- Fibrinogen, Plasma
- D-Dimer, Plasma
- Soluble Fibrin Monomer
- Antithrombin Activity, Plasma
- Protein C Activity, Plasma
- Protein S Antigen, Free, Plasma
- Prothrombin G20210A A Mutation, Blood
- Activated Protein C Resistance V (APCRV), Plasma

All initial testing within reference ranges for age and gender:

- No evidence of thrombotic diathesis
- No further testing is performed

**PT:**

- PT: ≥ 14.0 seconds

**APTT:**

- APTT: > 36 seconds

**DRVVT:**

- DRVVT: ≥ 1.2 seconds

**Thrombin Time (Bovine):**

- Normal – no evidence of heparin or dys/hypofibrinogenemia

**APCRV:**

- APCRV: < 2.3 OR Prolonged baseline APTT

**Protein C Activity:**

- Protein C Activity: < 70%
- Males < 65%
- Females < 50 years: < 50%
  ≥ 50 years: < 65%

**Protein S Antigen, Total:**

- Plus/minus: < 80%
  Factor V Leiden (R506Q) Mutation

**Protein S Antigen, Free:**

- Males < 65%
- Females < 50 years: < 50%
  ≥ 50 years: < 65%

**Antithrombin Activity:**

- Antithrombin Activity: < 80%
  No evidence of an acquired deficiency

**Factor V Leiden (R506Q) Mutation**

Factor V Leiden (R506Q) Mutation

- Evidence of inhibition
- Evidence of coagulation factor deficiency

**Protein C Antigen**

Protein C Antigen

- Evidence of inhibition
- Evidence of coagulation factor deficiency

**Protein S Antigen, Total**

Protein S Antigen, Total

- Evidence of lupus-like anticoagulant
  No diagnostic of lupus-like anticoagulant

**Antithrombin Activity**

- Antithrombin Activity: < 80%
  No evidence of an acquired deficiency

**Antithrombin Activity**

Antithrombin Activity

- Evidence of lupus-like anticoagulant
  No diagnostic of lupus-like anticoagulant

*Additional assays may be performed if further clarification or confirmation is necessary. These may include:

- Coagulation Factor Assays
- Staclot Lupus Anticoagulant
- Protein S Activity

**Unfractionated/low-molecular weight heparin or direct thrombin inhibitor (e.g., dabigatran, argatroban)**

An interpretive report is provided that includes all profile tests (always performed) and any reflex tests performed (if appropriate).
Activated Protein C Resistance and Factor V Leiden

• Most common congenital hereditary thrombophilia among whites

• Protein phenotype
  • Normally: Activated protein C (APC) inactivates activated factor V (fVa)
  • APC resistance: Mutated factor V resists inactivation by APC

• Genetic basis
  • Factor V Leiden (R506Q) mutation

• Testing strategy
  • Initial APC-R assay, FV Leiden only if indicated
Review of APC-R and FV Leiden Test Ordering Patterns (MML reference laboratory clients)

• January 2010 to October 2010
• Data pull: 917 APC-R test orders (and associated FVL)
• APC-R normal: 471/917 (51%)
  • Factor V Leiden ordered separately by providers
    • (FV Leiden was not indicated)
  • All 471 FV Leiden results were negative
• Root cause: APCR-Reflex available to Mayo and no MML Clients. (Making this available in near future)
APC Resistance assay: Normal

Baseline aPTT
(30 sec)

aPTT after addition of APC
(inactivates factor V, prolongs aPTT)
(90 sec)

APCR ratio \[ \frac{\text{APC aPTT (90)}}{\text{aPTT (30)}} = 3.0 \]
APC Resistance assay: Abnormal (FV Leiden)

Baseline aPTT
(30 sec)

aPTT after addition of APC
(inactivates factor V, prolongs aPTT, but not as much as normal)
(60 sec)

APCR ratio
\[
\frac{\text{APC aPTT (60)}}{\text{aPTT (30)}} = 2.0
\]
Coagulation and Transfusion Medicine  /  Screening for Factor V Leiden

Screening With the Activated Protein C Resistance Assay Yields Significant Savings in a Patient Population With Low Prevalence of Factor V Leiden

Laura J. Taylor, MT(ASCP), Robert A. Oster, PhD, George A. Fritsma, MS, MT(ASCP), Patricia H. Tichenor, MT(ASCP), Cari E. Reed, MT(ASCP), Barbara M. Eiland, MT(ASCP), Christine L. Hudson, MT(ASCP), and Marisa B. Marques, MD

Key Words: Factor V Leiden; Activated protein C resistance; Cost savings

DOI: 10.1309/4370VLY9PBDDEWF6

Taylor LJ et al Am J Clin Pathol 2008; 129: 494
# Cost Savings by Screening With APCR in a Population With Low Prevalence of FVL

## Test ordered

<table>
<thead>
<tr>
<th></th>
<th>FVL</th>
<th>APCR</th>
<th>Tests (no.)</th>
<th>Total cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline (1998/99: 2 yr)</strong> (Send out tests)</td>
<td>299 × $187 = $55,913</td>
<td>75 × $45 = $3,375</td>
<td>374</td>
<td>$59,288</td>
</tr>
<tr>
<td><strong>Theoretical cost without interventions for subsequent 6 yr</strong></td>
<td>1,980 × $187 = $370,260</td>
<td>495 × $45 = $22,275</td>
<td>2,475</td>
<td>$392,535</td>
</tr>
<tr>
<td><strong>Actual cost with interventions for subsequent 6 yr</strong></td>
<td>154* × $80 = $12,320</td>
<td>710 × $4.50 (2 yr) + 1,765 × $5.36 (4 yr) = $12,655</td>
<td>2,475*</td>
<td>$24,975†</td>
</tr>
</tbody>
</table>

* All 154 patients also had an APCR assay
† Impact of interventions after 6 years: $392,535 – $24,975 = $367,560 or $61,260/year

The laboratory took control over sequence of testing

---

Taylor LJ et al Am J Clin Pathol 2008; 129: 494
Mayo Clinic, Rochester experience vs Optum labs

• Optum labs data warehouse
  • >100 million enrollees
  • Medical claims data for laboratory testing etc
• Inpatient and outpatient
# Mayo APCR/FV Leiden vs Optum Labs database

<table>
<thead>
<tr>
<th>Test description</th>
<th>Mayo Sp Coag Lab</th>
<th>Optum Labs</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC-R</td>
<td>1256</td>
<td>5,395</td>
</tr>
<tr>
<td>FV Leiden</td>
<td>268</td>
<td>80,129 (78,525)</td>
</tr>
<tr>
<td>Ratio: APCR:FVL</td>
<td>~1: 0.2</td>
<td>~1:15</td>
</tr>
</tbody>
</table>
APC-R without FV deficient plasma premix (ECAT 2015-3): heterozygous FV Leiden sample (8 different kits)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Homozygous FVL</th>
<th>Heterozygous FVL</th>
<th>Non-conclusive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>10</td>
<td>14</td>
<td>6</td>
</tr>
</tbody>
</table>
APC-R with FV deficient plasma premix (ECAT 2015-3): heterozygous FV Leiden sample

<table>
<thead>
<tr>
<th>Classification</th>
<th>Homozygous FVL</th>
<th>Heterozygous FVL</th>
<th>Non-conclusive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n=178 laboratories) 10 different kits</td>
<td>6</td>
<td>121</td>
<td>22</td>
</tr>
</tbody>
</table>
## Annual review of molecular testing data

<table>
<thead>
<tr>
<th>Assay</th>
<th>Results (n)</th>
<th>% positive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factor V R506Q</strong></td>
<td>22535</td>
<td></td>
</tr>
<tr>
<td>Heterozygous</td>
<td>3618</td>
<td>16%</td>
</tr>
<tr>
<td>Homozygous</td>
<td>109</td>
<td></td>
</tr>
<tr>
<td><strong>PTG20210A</strong></td>
<td>21101</td>
<td></td>
</tr>
<tr>
<td>Heterozygous</td>
<td>1086</td>
<td>5%</td>
</tr>
<tr>
<td>Homozygous</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td><strong>MTHFR C677T</strong></td>
<td>10033</td>
<td></td>
</tr>
<tr>
<td>Heterozygous</td>
<td>4453</td>
<td>44%</td>
</tr>
<tr>
<td>Homozygous</td>
<td>1202</td>
<td>12%</td>
</tr>
<tr>
<td><strong>MTHFR 1298</strong></td>
<td>2611</td>
<td></td>
</tr>
<tr>
<td>Heterozygous</td>
<td>1084</td>
<td>42%</td>
</tr>
<tr>
<td>Homozygous</td>
<td>226</td>
<td>9%</td>
</tr>
</tbody>
</table>
Thrombophilia Profile

- **APCRV:**
  - <2.3
  - OR
  - Prolonged baseline APTT

- **Protein C Activity:** <70%
- **Protein S Antigen, Free**
  - Males <65%
  - Females
    - <50 years: <50%
    - ≥50 years: <65%

- **Antithrombin Activity:** <80%
- **Factor V Leiden (R506Q) Mutation**
- **Protein C Antigen**
- **Protein S Antigen, Total**
- **Antithrombin Antigen, Plasma**
- **No evidence of an acquired deficiency**
## Classification of protein C deficiency

<table>
<thead>
<tr>
<th></th>
<th>PC activity</th>
<th>PC Ag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Type IIa</td>
<td>Decreased</td>
<td>Normal</td>
</tr>
<tr>
<td>Type IIb (detected by clotting assay)</td>
<td>Decreased</td>
<td>Normal</td>
</tr>
</tbody>
</table>

**Acquired:** neonates, children, liver disease, VKA therapy, acute thrombosis, DIC etc
Classification of protein S deficiency

<table>
<thead>
<tr>
<th></th>
<th>PS activity</th>
<th>Free PS Ag</th>
<th>Total PS Ag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Type 2</td>
<td>Decreased</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Type 3</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Normal</td>
</tr>
</tbody>
</table>
Limitations of PS activity assays

• PS activity measurements in normals:
  • Levels reduced in 10 to 15% normal donors
    • Upon recheck-levels returns to normal

• Subject to technical limitations
  • Measuring a cofactor function
  • Significantly affected by biological and analytical variables

Reference ranges: lab established vs manufacturer provided information

<table>
<thead>
<tr>
<th>Assay</th>
<th>%below established reference range</th>
<th>%below manufacturer’s reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free PS Ag</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Kit A PS activity</td>
<td>11%</td>
<td>13%</td>
</tr>
<tr>
<td>Kit B PS activity</td>
<td>18%</td>
<td>38%</td>
</tr>
<tr>
<td>Kit C PS activity</td>
<td>24%</td>
<td>Not available</td>
</tr>
<tr>
<td>Kit D PS activity</td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
<td>Total PS Ag</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Limitations of PS activity assays

• Measurement of a cofactor activity
• Influenced by different biological and preanalytical variables.

• Interferences:
  • Artifactual elevation of PS activity:
    • Lupus anticoagulants
  • Artifactual reduction of PS activity
    • Elevated factor VIII:C
    • Factor V Leiden mutation (selected assays)
## ECAT Proficiency testing: PS deficiency sample (2015-3)

<table>
<thead>
<tr>
<th>Total Group</th>
<th>Assigned value</th>
<th>Range of results</th>
</tr>
</thead>
<tbody>
<tr>
<td>155 Laboratories (5 different kits)</td>
<td>34%</td>
<td>21-111</td>
</tr>
</tbody>
</table>

### Classification Table

<table>
<thead>
<tr>
<th>Classification</th>
<th>Normal</th>
<th>Borderline normal</th>
<th>Borderline abnormal</th>
<th>Abnormal</th>
<th>No classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>147</td>
<td>2</td>
</tr>
</tbody>
</table>

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Conclusions: Algorithmic approach to thrombophilia testing

• Algorithmic approach begins with patient selection
  • Judicious ordering of Thrombophilia testing if it affects patient management

• If testing is indicated, profile of testing should be considered
  • Multifactorial nature of VTE

• Algorithmic approach within thrombophilia profiles provides the most cost effective approach to testing
Thrombophilia Profile

**THROMBOPHILIA PROFILE**

- **Testing begins with:**
  - Prothrombin Time (PT), Plasma
  - Activated Partial Thromboplastin Time (aPTT), Plasma
  - Dilute Russell Viper Venom Time (dRVVT), Plasma
  - Thrombin Time (bovine), Plasma
  - Fibroglycan, Plasma
  - D-Dimer, Plasma
  - Soluble Flavin Mononucleotide
  - Antithrombin Activity, Plasma
  - Protein C Activity, Plasma
  - Protein S Antigen, Free, Plasma
  - Prothrombin 20210A Mutation, Blood
  - Activated Protein C Resistance V (APCRR), Plasma
  - Special Coagulation Interpretation

**Initial Testing with Reference Ranges for Age and Gender:**
- No evidence of thrombophilic diathesis
- No further testing is performed

**All initial testing with reference ranges for age and gender:**
- No evidence of thrombophilic diathesis
- No further testing is performed

**Platelet Function:**
- Platelet function evaluation procedure (PFP)

**DRVT Confirmation:**
- Evidence of factor deficiency
- Evidence of inhibition

**Normal - no evidence of heparin or lack of hypotrombogenemia:**
- Factor V Leiden (506G) Mutation
- Protein C Antigen
- Protein C Activity - 50%
- Protein C Antigen, Total
- Antithrombin Activity - 50%
- No evidence of an acquired deficiency

**Antithrombin Activity:**
- <50%
- Normal range

**Coagulation Factor Assays:**
- Factor IX Deficiency
- Heterozygous Factor V Leiden
- Protein C Antigen
- Protein C Activity
- Protein S Antigen, Free
- Protein S Antigen, Total
- Protein C activity - 50%
- Protein C Antigen - 50%
- Antithrombin Activity - 50%
- No evidence of an acquired deficiency

**Unfractionated low-molecular weight heparin or direct thrombin inhibitor (eg, dabigatran, argatroban):**

An interpretive report is provided that includes all profile tests always performed and any reflex tests performed (if appropriate).

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