ICU Corner
Hypercoagulable states: A concise review

Mark P. Prosciak, MD 1, S. Peter Stawicki, MD 2,3

1 Junior Scientist, OPUS 12 Foundation, Columbus Chapter, Ohio, USA
2 Principal Scientist, OPUS 12 Foundation, Columbus Chapter, Ohio, USA
3 Dept of Surgery, Division of Critical Care, Trauma, and Burn, The Ohio State University Medical Center, Columbus, OH, USA

ABSTRACT
Over 200,000 new cases of venous thromboembolism (VTE) occur annually in the United States. The risk of VTE is increased in hospitalized patients, and deep venous thrombosis (DVT) is a relatively common complication in patients who are acutely ill or undergo surgery. With better identification of hereditary and acquired risk factors for VTE, the modern clinician is presented with an ever-growing number of laboratory tests that can be ordered in such patients. There is considerable controversy as to how this newly available information should be utilized in clinical patient management. Goals of this article include: (a) an overview of the epidemiology of venous thrombosis and its associated risk factors (including recently discovered genetic abnormalities); (b) current indications for testing for thrombophilia; (c) the appropriate choice for timing and type of testing; and (d) the interpretation of test results. Sections in the latter part of the manuscript include a description of each respective hypercoagulable condition, including diagnosis, treatment, prognostic factors, complications, and long-term care implications.


Correspondence to: S. P. Stawicki, MD. OPUS 12 Foundation, 1011 Rutherglen Drive, Columbus, OH 43235 USA.

Keywords: Venous thromboembolism, Deep venous thrombosis, Genetic predisposition, Laboratory testing, Overview of treatment.

INTRODUCTION
More than 200,000 new cases of venous thromboembolism (VTE) occur annually in the United States. Among the affected patients, up to one third die within 30 days, with approximately one fifth suffer sudden death due to pulmonary embolism (PE). In addition, about one third of patients develop recurrent VTE within 10 years of the initial event.1 Because of high morbidity and mortality associated with VTE, several pre-test probability scoring systems have been devised in order to help identify patients with PE (Tables 1-3). The risk of VTE is increased in hospitalized patients, and deep venous thrombosis (DVT) is a relatively common complication in patients with acute medical illness or those who undergo surgery (Table 4). Recognizing this, The Centers for Medicare & Medicaid Services (CMS) is proposing to expand the list of conditions it refers to as reasonably preventable to include active thrombosis may affect the validity of certain laboratory tests. Finally, one must choose the most appropriate test(s) and interpret the results correctly and carefully. This article will provide an overview of the epidemiology of venous thrombosis, risk factors associated with VTE, including the newly discovered genetic abnormalities, current indications for testing for thrombophilia, the choice of diagnostic tests and when these tests should be ordered, as well as the interpretation of test results. Each of the following sections includes a description of the respective hypercoagulable condition, its diagnosis, treatment, prognostic factors, and patient care implications.

Table 1. Charlotte criteria for rapidly ruling out pulmonary embolism using D-dimer and alveolar dead space

<table>
<thead>
<tr>
<th>If any two are present, patient is unsafe for ruling out of pulmonary embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age &gt;50 years or heart rate &gt; systolic blood pressure</td>
</tr>
<tr>
<td>2. Recent (past four weeks) surgery requiring anesthesia</td>
</tr>
<tr>
<td>3. Unilateral leg swelling (i.e., asymmetry on visual examination)</td>
</tr>
<tr>
<td>4. Hemoptysis</td>
</tr>
<tr>
<td>5. Unexplained room air pulse oximetry &lt;95% in a patient who is a non-smoker, non-asthmatic, and has no chronic obstructive pulmonary disease</td>
</tr>
</tbody>
</table>

BACKGROUND
In 1856, Virchow described the essential risk factors for venous thrombosis – the so-called Virchow’s Triad of vascular stasis, vascular damage, and hypercoagulability (3). Hypercoagulability or hypercoaguable state includes both acquired and hereditary conditions that increase the risk factors for venous thrombosis. In other words, an inherited and/or acquired imbalance between procoagulant and anticoagulant factors combined with an appropriate trigger results in thrombosis. Identification of acquired or inherited thrombophilia may predict the subset of patients exposed to known risk factors who are more likely to actually develop VTE.5 Molecular defects such as deficiencies of antithrombin III, protein C, or protein S, as well as the presence of anticardiolipin antibody, lupus anticoagulant,
prothrombin G20210A mutation, or factor V Leiden mutation all predispose to spontaneous thromboembolic disease and further magnify a patient’s risk for thrombosis during trauma, surgery, or hospitalization/bedrest.

In addition, screening for select hypercoagulable states is appropriate in patients with no other apparent risk factors who develop PE. Furthermore, patients with a history of VTE who undergo major surgery or periods of immobility, or who are hospitalized for serious medical illnesses should receive appropriate prophylactic regimen consisting of various subcutaneously administered anticoagulant agents.

Table 2. Wells criteria for the assessment of pretest probability of pulmonary embolism.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected DVT</td>
<td>3.0</td>
</tr>
<tr>
<td>An alternative diagnosis is less likely than PE</td>
<td>3.0</td>
</tr>
<tr>
<td>Heart rate &gt; 100 beats/minute</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization or surgery in previous 4 weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1.0</td>
</tr>
<tr>
<td>Maligany (on treatment or treated within past 6 weeks)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Table 3. Wicki criteria for the assessment of pretest probability of pulmonary embolism.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 60–70</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt;79</td>
<td>2</td>
</tr>
<tr>
<td>Prior DVT or PE</td>
<td>3</td>
</tr>
<tr>
<td>Recent surgery</td>
<td>2</td>
</tr>
<tr>
<td>Heart rate &gt;100 beats/minute</td>
<td>3</td>
</tr>
<tr>
<td>PaCO₂ &lt;36</td>
<td>4</td>
</tr>
<tr>
<td>PaO₂ &gt;30-36</td>
<td>5</td>
</tr>
<tr>
<td>PaO₂ &gt;30-38</td>
<td>4</td>
</tr>
<tr>
<td>PaO₂ &gt;30-40</td>
<td>3</td>
</tr>
<tr>
<td>PaO₂ &gt;30-50</td>
<td>2</td>
</tr>
<tr>
<td>PaO₂ &gt;30-71</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 4. Risk factors for venous thrombosis. Legend: TAFI = thrombin activated fibrinolysis inhibitor; APC = activated protein C.

ANTIPHOSPHOLIPID SYNDROME (APS)
The antiphospholipid antibody syndrome (APS) is a disorder characterized by the presence of various antibodies that are associated with both arterial and venous thrombotic events. Antiphospholipid (aPL) antibodies belong to family of antibodies that react with negatively charged phospholipids (PLs) including cardiolipin, phosphatidyglycerol, phosphatidylseritol, phosphatidylyserine, phosphatidylcholine, and phosphatidic acid. There are three primary classes of antibodies associated with APS: (a) antiardiolipin antibodies (aCL); (b) the lupus anticoagulant (LA) and (c) antibodies directed against specific molecules including a molecule known as β2-glycoprotein 1 (β₂GPI).

Historically, antiphospholipid antibodies were first noted in patients who had positive tests for syphilis without signs of infection. Subsequently, a specific clotting disorder was associated with patients with systemic lupus erythematosus (SLE). A link between recurrent pregnancy loss and what is now called the lupus anticoagulant was established in the 1950s. In addition, the association between aPL and arterial as well as venous thrombotic events is well described.
There are two main classifications of the antiphospholipid antibody syndrome. In primary APS the patient has no known underlying autoimmune disorder. Secondary APS is usually seen in patients with an underlying autoimmune disorder, such as SLE. In fact, about half of those diagnosed with SLE have antiphospholipid antibodies. This abnormal plasma phenotype has also been found in the course of infections, neoplastic disease, associated with certain drugs, and in apparently healthy individuals.5

Lupus Anticoagulants (LA) are antibodies directed against plasma proteins, which also bind to phospholipid surfaces. They are usually of IgG, IgM, or mixed types, and frequently interfere with standard phospholipid-dependent coagulation tests. Many LA are discovered incidentally such as when a prolonged activated partial thromboplastin time (aPTT) is discovered during a preoperative evaluation. Importantly, the clotting test abnormalities caused by LA are in vitro phenomena. In vivo clotting factor activities are not diminished and, except in extremely rare cases where there are specific antibodies directed against clotting factor II, there is no danger of a bleeding diathesis. It should also be recognized that most patients with LA do not have lupus erythematosus or other systemic autoimmune disorders.10

<table>
<thead>
<tr>
<th>Hypercoagulable state</th>
<th>General population (%)</th>
<th>Patients with single VTE (%)</th>
<th>Families with thrombophilia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden</td>
<td>3-7</td>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td>Prothrombin G20210A</td>
<td>1-3</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>Antithrombin III deficiency</td>
<td>0.02</td>
<td>1</td>
<td>4-8</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>0.2-0.4</td>
<td>3</td>
<td>6-8</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>N/A</td>
<td>1-2</td>
<td>3-13</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>5-10</td>
<td>10-25</td>
<td>N/A</td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
<td>0-7</td>
<td>5-15</td>
<td>N/A</td>
</tr>
</tbody>
</table>

N/A = not readily available or unknown.

Table 5. Prevalence of major hypercoagulable states in different patient populations.8

The exact etiology of LA is unclear. These antibodies are commonly found in asymptomatic elderly individuals. Patients with HIV infection may also have increased incidence of LA during the course of their disease. Of interest, a number of drugs (most notably procainamide, hydralazine, isoniazid, dilantin, phenothiazines, quinidine, and angiotensin converting enzyme inhibitors) have been associated with induction of LA. However, most patients with drug-induced LA have no systemic autoimmune disease or any other underlying disorder and exhibit no clinical manifestations traditionally seen with LA.4

Lupus Anticoagulants: Risk of Thrombosis. Although only minority of patients with LA present with recurrent episodes of thrombosis, LA belong to some of the most common acquired pro-thrombotic conditions. They are associated with cerebral, deep venous, renal venous thromboses, as well as with pulmonary emboli and arterial occlusions, particularly stroke.11-12

Laboratory Diagnosis of LA. Anticoagulant therapy may interfere with the detection of LA.12 The typical screening test is a prolongation of the standard aPTT that fails to correct when the patient’s plasma is mixed with normal plasma. However, this screening alone is inadequate to establish the presence of a LA because many affected patients, especially pregnant women, may have normal aPTT. Consensus guidelines recommend screening for LA with two or more phospholipid-dependent coagulation tests, including the activated partial thromboplastin time (aPTT), dilute Russell viper venom time (dRVV), kaolin clotting time, dilute prothrombin time (dPT), textarin time, or taipan time.12-13

<table>
<thead>
<tr>
<th>Symptoms and Signs</th>
<th>% Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>84%</td>
</tr>
<tr>
<td>Pluritic chest pain</td>
<td>74%</td>
</tr>
<tr>
<td>Feeling of “apprehension”</td>
<td>59%</td>
</tr>
<tr>
<td>Cough</td>
<td>53%</td>
</tr>
<tr>
<td>Hemoptyis</td>
<td>30%</td>
</tr>
<tr>
<td>Sweating</td>
<td>27%</td>
</tr>
<tr>
<td>Nonpleuritic chest pain</td>
<td>14%</td>
</tr>
<tr>
<td>Physical signs commonly seen in PE</td>
<td></td>
</tr>
<tr>
<td>Tachycardia &gt;16 beats/min</td>
<td>92%</td>
</tr>
<tr>
<td>Pulmonary ratios</td>
<td>58%</td>
</tr>
<tr>
<td>Accentuated S2</td>
<td>53%</td>
</tr>
<tr>
<td>Tachycardia &gt;100 beats/min</td>
<td>44%</td>
</tr>
<tr>
<td>Temperature &gt;37.8°C</td>
<td>43%</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>36%</td>
</tr>
<tr>
<td>S3 or S4 gallop</td>
<td>34%</td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td>32%</td>
</tr>
<tr>
<td>Lower extrematy edema</td>
<td>24%</td>
</tr>
<tr>
<td>Cardiac murmur</td>
<td>23%</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>19%</td>
</tr>
</tbody>
</table>

Table 6. Symptoms and signs commonly associated with pulmonary embolism.9

Anticardiolipin antibodies share a common in vitro binding affinity for cardiolipin and can be detected using enzyme-linked immunosorbent assays (ELISA). The immunoglobulin isotype may be IgG, IgM, or IgA. It is believed that the IgG isotype is most strongly associated with thrombotic events, although this has not been verified in large prospective studies. ELISA tests for aCL are poorly standardized and aCL testing has shown poor concordance between laboratories. Anticardiolipin antibodies are reported as a titer specific to the isotype (IgG, IgM, or IgA phospholipid antibody titer), but because the accuracy and reliability of assays are limited, consensus guidelines recommend semiquantitative result reporting (low, medium, or high titer).14

Anti–β-2-Glycoprotein 1 Antibodies (β2-GP1). The clinical relevance of anti–β-2-glycoprotein 1 antibodies is uncertain, although there is some evidence that these antibodies are more specific for APS.15

Epidemiology of APS. The estimated prevalence of antiphospholipid antibody syndrome in the general population is approximately 7%. Most cases of APS (80%) occur in women. Among patients with the antiphospholipid antibody syndrome, about 50% have primary APS. About 50% of patients with SLE will develop the APS. In general, anticardiolipin antibodies (aCL) are more common than lupus anticoagulant and occur approximately five times more often than the lupus anticoagulant
in patients with APS. However, a recent review has questioned the association between isolated aCL and thrombosis. In patients with an initial presentation of primary APS, approximately 10% will eventually go on to be diagnosed with an autoimmune disorder such as SLE or a mixed connective tissue disorder.

Antiphospholipid Antibody Syndrome: Associated Risks. Overall, the risk of thrombosis in patients with both primary and secondary APS is increased approximately 10-fold. Patients with SLE have a high prevalence of thrombosis even in the absence of antiphospholipid antibodies (aPL). The aPL antibodies account for 65-70% of cases of thrombotic episodes in women with venous thromboses in less common sites (e.g., cerebral portal, splenic, subclavian and mesenteric veins). About one fourth of thrombotic events occur during pregnancy or the postpartum period. These observations suggest that women with documented APS should avoid estrogen-progestin combination oral contraceptives. Recurrent thrombotic events, both arterial and venous, may also be seen with APS. Most studies suggest that patients who experience a recurrent episode often experience it in a similar blood vessel type. However, it is not infrequent for patients to have thrombotic events involving different types of vessels. The risk of thrombosis among healthy patients who are incidentally found to have aPL is low (<1% per year).

Pregnancy and APS. The APS is associated with adverse events during pregnancy. These complications can include miscarriages, preterm labor, low birth-weight, and preeclampsia. Fetal deaths at or beyond 20 weeks gestation have been attributed to APS involvement. In fact, the rate of fetal loss may exceed 90% in untreated patients who have APS. Thus, pregnant women with APS are considered high-risk obstetric patients. Pre-pregnancy counseling and close prenatal monitoring are the norm. Medical therapy during pregnancy is a subject of active investigation at this time. Several studies have examined the use of heparin, low-molecular weight heparin, along with low-dose aspirin throughout the pregnancy and have demonstrated improved fetal outcomes. In fact, the use of medical therapy (including aspirin and heparin) can reduce the rate of fetal loss to about 25%. Diagnosis and Testing of Antiphospholipid Antibodies. Various physical findings are more likely in patients with secondary APS but may be associated with primary APS. aPTT is a useful screen for aPL antibody. aPTT mixing study may be able to distinguish between APS and disseminated intravascular coagulation (DIC). Diagnosis of APS requires at least one clinical and one laboratory criterion. Briefly, clinical criteria are: (a) Vascular thrombosis - One or more clinical episodes of arterial, venous, or small-vessel thrombosis, occurring within any tissue or organ; and (b) Complications of pregnancy - One or more unexplained deaths of morphologically normal fetuses at or after 10 weeks' gestation, one or more premature births of morphologically normal fetuses at or before 34 weeks' gestation, or three or more unexplained consecutive spontaneous abortions before 10 weeks' gestation.

Briefly, laboratory criteria include: (a) Anticardiolipin antibodies - Anticardiolipin IgG or IgM antibodies present at moderate or high levels in the blood on two or more occasions at least 6 weeks apart; and (b) Lupus anticoagulant – LA antibodies detected in the blood on two or more occasions at least 6 weeks apart, according to the guidelines of the International Society on Thrombosis and Hemostasis.

Management of Antiphospholipid Antibody Syndrome. In patients with APS, the risk of recurrence is relatively high for both arterial and venous thrombotic events. Thus, patients are generally placed on long-term (often life-long) oral anticoagulation. Assessment of anticoagulation with heparin in patients with prolonged aPTT due to a lupus anticoagulant can be accomplished by anti-factor Xa activity assay. Although PT is less affected by LA than aPTT, the chromogenic factor X assay may be used to determine the accuracy of the international normalized ratio (INR) in patients with LA. With drug-induced LA, discontinuing the inciting agent will usually cause any abnormal clotting tests to revert to normal in 2-3 weeks. Again, majority of patients with clinically symptomatic APS are placed on long-term (if not life-long) anticoagulation with warfarin. At times, low molecular weight heparins (LMWH) can be used therapeutically instead of warfarin (i.e., during pregnancy), or in combination with other pharmacologic treatments. Among other therapeutic considerations, anti-platelet drugs, such as aspirin, have been used in APS. In the case of patients who are discovered to have the antiphospholipid antibodies without any known thrombotic problems, the question of prophylactic treatment is unresolved. According to some sources, aspirin is the general recommendation.

ANTITHROMBIN III DEFICIENCY
Antithrombin III deficiency (ATIIIId) was initially described in the 1960’s and was the first trait found to be associated with thrombophilia. It exists as both a genetically acquired trait and an acquired condition caused by some forms of hepatic and renal disease.

Pathophysiology of ATIIIId. The ATIIIId is most commonly associated with venous thrombosis. Antithrombin is a potent inhibitor of the reactions of the coagulation cascade. It is a non-vitamin K-dependent protease that inhibits coagulation by lysing thrombin and factor Xa. Although the name, antithrombin, implies that it works only on thrombin, it actually serves to inhibit virtually all of the coagulation enzymes to at least some extent. The primary enzymes it inhibits include factor Xa, factor IXa and thrombin (factor IIa). It also has inhibitory actions on factor XIIa, factor XIa and factor VIIa-tissue factor complex. Its ability to limit coagulation through multiple interactions makes it one of the primary natural anticoagulant proteins.

Potentiation of antithrombin III activity is the main mechanism by which both heparin and low molecular weight heparin result in anticoagulation.

Congenital ATIIIId is an autosomal dominant disorder in which an individual inherits one copy of a defective gene. This condition leads to increased risk of venous and arterial thrombosis, with an onset of clinical manifestations typically appearing in young adulthood. This form is commonly diagnosed during childhood by screening after an affected family member has been identified or after a child has had a thrombotic event. Heterozygote newborns are typically normal in appearance and do not commonly develop purpura fulminans unless other problems coexist. Individuals may remain asymptomatic until well into middle age.
Severe congenital ATIIId, in which the individual inherits two defective genes, is a rare condition associated with increased thrombogenesis, typically noted in the neonatal period or early infancy. Homozygote deficient newborns may have purpura fulminans-type presentation with embolic lesions in the skin.25

Acquired ATIIId is commonly due to increased coagulation secondary to endothelial injury or the presence of APL (i.e., lupus anticoagulant). In both of these situations, ATIII is consumed at increased rates due to abnormal activation of a coagulation pathway or a synthetic defect, often from medication (i.e., L-asparaginase) or liver disease. Common conditions that result in acquired ATIIId include disseminated intravascular coagulation (DIC), microangiopathic hemolytic anemia due to endothelial damage (i.e., hemolytic uremic syndrome), and veno-occlusive disease (VOD) in patients undergoing bone marrow transplant. Other reported mechanisms of acquired ATIIId include protein loss due to ascites or nephrotic syndrome.

There are two primary types of antithrombin III deficiency - Type I and Type II. Type I ATIIId, the most common type, is characterized by inadequate amounts of normal antithrombin present to inactivate the coagulation factors. In type II ATIIId (i.e., unclassified ATIII deficiency) the amount of antithrombin present is normal, but the enzyme function is reduced. Frequently, the antithrombin in type II ATIIId has lower affinity for heparin, with several molecular defects having been described.25-27

Epidemiology of ATIIId. Antithrombin deficiency is estimated to be present in about 0.2% of the population. However, some studies have cited rates as high as 1.1% of the population. In addition, ATIIId is seen in 0.5-7.5% of patients who have had venous thromboembolism.25-27

Specific Risks Associated with ATIIId. Patients with ATIIId are at higher risk for thrombosis than patients with any other congenital thrombophilic state. In fact, approximately 60% of patients with ATIIId will experience an episode of venous thrombosis by age 60 years.28 The overall estimated incidence (annual occurrence) of DVT is one episode for every 1000 persons. This estimate does not discriminate between patients who had predisposing conditions from those who do not. In patients who are homozygous for type II ATIIId, severe venous thrombosis and arterial thrombotic events have been reported. Homozygous type I ATIIId is thought to be incompatible with life, leading to fetal death.29

ATIIId: Diagnosis and Testing. No specific physical stigmata are associated with congenital ATIIId. A thrombotic challenge, such as placement of a central venous catheter or other vascular catheters, frequently unMASKS an underlying procoagulant condition and thus should prompt further evaluation. Antithrombin III measurement should be the first test performed, even before heparin anticoagulation is started (heparin administration interferes with this test). Prothrombin time (PT) and activated partial thromboplastin time (aPTT) allow evaluation of the presence of inappropriate activation of the coagulation system.

Management of ATIIId. Personal history of thrombosis is particularly important in terms of treatment. Patients with congenital ATIIId who have had one spontaneous thrombotic event (particularly in the mesenteric or splanchnic systems) are much more likely to experience recurrent thrombi. These patients are usually treated with indefinite anticoagulant therapy. In ATIIId, the activity of LMWH is not as reliable as it is in an otherwise healthy person. Consider alternative anticoagulation medications (e.g., warfarin) for that reason. In patients on LMWH, careful monitoring of anti-Xa activity in the patient should be instituted. Asymptomatic carriers should not receive anticoagulation therapy because the risk of thrombosis does not appear to exceed the bleeding risk associated with anticoagulation therapy. ATIIId may be quickly corrected with infusions of antithrombin III concentrates.28-32 Of interest, antithrombin III is relatively abundant in fresh frozen plasma (FFP). Long-term therapy for congenital deficiency is generally not indicated, as the asymptomatic period may last for decades.

Pregnancy and ATIIId. Oral anticoagulation with warfarin is not recommended during pregnancy and should be discontinued. In patients with a history of thrombosis and ATIIId, alternative anticoagulation can be instituted with heparin or LMWH.32

FACTOR V LEIDEN MUTATION AND ACTIVATED PROTEIN C RESISTANCE

Factor V Leiden (Factor V R506Q) is a genetically acquired trait manifesting as the phenomenon of activated protein C resistance (APCR). Subsequent to the first description of APCR in 1993, Factor V Leiden, discovered in 1994, was found to be present in over 95% of patients with APCR.33

Factor V Leiden: Mechanism of Action. Factor V Leiden is characterized by the Activated Protein C Resistance (APCR) phenomenon where factor V genetic point mutation makes it resistant to degradation by activated protein C (APC) during coagulation. The result of this resistance is an increased level of thrombin in the blood and an increased risk of VTE.34

Epidemiology of Factor V Leiden. Factor V Leiden has an approximate prevalence of 5%, making it the most common genetic factor that predisposes to thrombotic events.34-42 It is found in 20% of unselected patients and in up to 50% of selected patients with venous thrombosis (i.e., positive family history in first degree relatives, first event prior to age 50).36

Specific Risks Associated with Factor V Leiden. Factor V Leiden increases the risk of venous thrombosis three- to eight-fold in heterozygous carriers, and fifty- to eighty-fold in homozygous individuals. Homozygosity is found in about 1 per 5000 persons in the general population.35,37 Factor V Leiden is thus a relatively weak risk factor for developing VTE. In fact, most people who are heterozygous for factor V Leiden never develop thrombosis. At this time, available data do not suggest any solid association between factor V Leiden and arterial thrombosis (stroke, heart attack).

Factor V Leiden: Diagnosis and Testing. The initial screening test for factor V Leiden is activated protein C (APC) resistance testing. About 95% of the time, patients who have APC resistance are found to have factor V Leiden mutation.43 Consequently, if resistance is present, then a test for the factor V Leiden gene mutation is performed, both to confirm the diagnosis and to determine whether the patient is heterozygous or homozygous for the mutation.
Management of Factor V Leiden Mutation. After a standard course of anticoagulation is completed, continuation is generally not indicated in factor V Leiden heterozygotes after a single thromboembolic episode. Patients who experienced multiple thromboembolic episodes or are at high risk of further episodes (for example, those with multiple concurrent deficiencies or factor V Leiden homozygotes) are more likely to require long-term anticoagulation. In women with factor V Leiden mutation, oral contraceptive use and pregnancy both increase the risk for venous thrombosis four to seven fold. Women with factor V Leiden mutation are also at increased risk for venous thrombotic complications associated with hormone replacement therapy and perhaps with tamoxifen and selective estrogen receptor modulators (SERM).

PROTHROMBIN GENE MUTATION 20210A

The prothrombin gene mutation 20210A is a genetically acquired trait and was first described in 1996. It is a variant form of prothrombin caused by a genetic point mutation in the 3’-untranslated region of prothrombin at position 20210 (G to A, PT20210A).

Mechanism of Action of Prothrombin. Prothrombin is the precursor to thrombin in the coagulation cascade (Figure 1). Thrombin is required in order to convert fibrinogen into fibrin, which is the primary goal of the coagulation cascade. The PT20210A mutation leads to increased amount of circulating thrombin. It is thought that the increased amount of circulating prothrombin lowers the pro-thrombotic threshold, resulting in uncontrolled activation of the clotting cascade.

Figure 1. Schematic representation of the coagulation cascade, including the intrinsic system (left), the extrinsic/cellular injury system (right), and the final common pathway (bottom).

Epidemiology of PT20210A. The prothrombin gene mutation PT20210A is seen in about 3% of the Caucasian population with regional variations in prevalence ranging from 1% to 6%. This mutation is found in 5% to 10% of patients presenting with venous thrombosis and about 15% of patients being investigated for thrombophilia. Diagnosis and Testing. The PT20210A mutation is diagnosed via direct genetic testing for the gene mutation, followed by the determination of whether the patient is heterozygous or homozygous. Although thrombin levels are usually moderately elevated in the setting of this mutation and can be measured, this is not clinically useful. Likewise, screening the general population is not recommended.

PT20210A Mutation: Specific Risks. The overall risk for venous thrombosis in patients with this disorder is relatively low, and most patients with PT20210A mutation do not experience an episode of venous thrombosis by age 50 years.

Management of PT20210A Mutation. Evidence is lacking with regards to the use of long-term anticoagulation in the setting of PT20210A gene mutation. Studies in patients with factor V Leiden (in which the risk of thrombotic events is similar to that with prothrombin gene mutation) suggest that the risk of bleeding from anticoagulation may outweigh the potential benefits of anticoagulation. Patients with history of multiple thromboembolic episodes or those who are at an otherwise high risk of future thrombotic episodes (i.e., those with more than one hypercoagulable disorder) may be started on long-term anticoagulation.

HYPERHOMOCYSTEINEMIA

Elevated levels of homocysteine are associated with both venous and arterial thrombotic events. Hyperhomocysteinemia (HHC) is most often an acquired condition (low folate intake, low vitamin B6 or vitamin B12 intake) and only rarely due to heterozygous cystathionine synthase (CS) deficiency. The congenital form is most commonly due to mutations affecting the cystathionine β-synthase (CBS) gene or the methylenetetrahydrofolate reductase (MTHFR) gene. These mutations generally cause mild increases in homocysteine levels. Homozygous deficiency of CBS is quite rare. It causes high plasma levels of homocystine, homocystinuria, atherosclerosis, arterial disease, and venous thrombosis occurring at a young age. The most common hereditary abnormality associated with hyperhomocysteinemia, the heterozygous MTHFR mutation (thermolabile or heat-inactivated variant), does not appear to be significantly associated increased risk of thrombotic events. It is associated with increased homocysteine levels only in homocysteinemic patients in the presence of coexisting deficiencies of folate, vitamin B12, or vitamin B6. Again, the precise relationship between this mutation and thrombotic events, even in homocysteinemic patients with hyperhomocysteinemia, is still controversial.

In some populations, up to 50% of unselected patients are heterozygous for this mutation and 15% are homozygous.

Pathophysiology of HHC. The mechanism by which HHC predisposes to thrombosis is unclear. The presence of homocysteine is required in several intracellular reactions. Three enzymes, including methylenetetrahydrofolate reductase (MTHFR), cystathionine beta-synthase (CBS) and methionine synthase (MS) are associated with elevated levels of homocysteine. Methionine synthase requires vitamin B12 (methylcobalamin) in order to convert homocysteine to methionine. MTHFR is required to produce 5-methyl
tetrahydrofolate, which is required to convert homocysteine to methionine.

Epidemiology of HHC. Mildly elevated levels of homocysteine (over 18 μmol/L) are found in 5-10% of the general population and roughly double the risk of venous thrombosis. Heterozygosity for the CBS mutation is thought to occur in 0.4% to 1.4% of the population. Homozygosity for the CBS mutation is much less frequent.53-57

HHC: Specific Risks. The thermolabile MTHFR variant is most likely to predispose to thrombotic events when it is co-inherited with other risk factors.50,61

HHC: Diagnostic Testing. Specialized testing is available for the common homozygous mutation (C677T) encoding the heat-labile form of MTHFR. Studies have shown, however, that this genetic variant either does not represent a significant prothrombotic risk or carries a lower relative risk for thrombosis than simple elevations of fasting plasma homocysteine level. Therefore, testing for this genetic mutation is not recommended routinely.53,55

Management of HHC. Although folate supplementation has been shown to lower homocysteine levels, little data is available concerning the impact of this therapy on risk of venous or arterial thrombosis. Management of proven thromboembolic events should follow the established treatment protocols.

PROTEIN C DEFICIENCY

Pathophysiology of Protein C Deficiency. Protein C deficiency (PCd) is a congenital defect first described in the early 1980s.62 Protein C is a potent anticoagulant that functions to inactivate factor Va and factor VIIIa. The reaction requires the presence of specific cofactor, protein S. First, protein C is activated by thrombin complexed to thrombomodulin. Activated protein C then combines with protein S on the surface of platelets where it can then degrade factor Va and factor VIIIa.

There are two types of PCd. In Type I, the amount of protein C is insufficient to properly regulate the coagulation process. In this type, both antigenic and functional levels are decreased. Type II PCd is characterized by reduced functional levels but preserved antigenic levels. Numerous variations of abnormal protein C molecule have been described.63-65

A condition mimicking PCd has been described in which patients have a reduced level of an endothelial receptor for protein C and cannot generate normal levels of activated protein C (and thus are predisposed to VTE).66 Complete absence of protein C production results from a homozygous mutation characterized by diffuse venous thrombosis in the newborn known as neonatal purpura fulminans. The condition can be fatal unless the patient receives protein C in the form of concentrate or plasma.67 A homozygous mutation that results in reduced but not absent protein C production, or inheritance of two different mutations associated with reduced protein C production, can present with deep venous thrombosis in the adulthood or skin necrosis following exposure to warfarin. These patients have protein C levels less than 20% of normal.68-70

Epidemiology of PCd. Protein C deficiency is relatively rare. It is present in approximately 0.2% of the normal population and in 2.5% to 6% of patients with venous thrombosis.53,71-73

PCd: Specific Risks. In general, protein C deficiency appears to increase the risk of venous thromboembolism approximately 10-fold in heterozygous individuals.74-75

Management of PCd. In asymptomatic patients found to have decreased protein C levels, no specific therapeutic intervention is usually needed. However, one should consider prophylactic measures during periods of increased thrombotic risk, such as the peripartum period, perioperatively, or during periods of prolonged immobilization (including prolonged air or land travel). In addition, the potential for increased risk of thrombotic disease during oral contraceptive therapy should be considered.62

PROTEIN S DEFICIENCY

Mechanism of Action of Protein S Deficiency. First described in the mid-1980s, protein S deficiency (PSd) is a congenital defect.76-77 Protein S functions as a cofactor to protein C to inactivate factor Va and factor VIIIa. The first step in this process is the activation of thrombomodulin by thrombin. Subsequently, protein C combines with thrombomodulin in order to produce activated protein C. Activated protein C then combines with protein S on the platelet surface and can then degrade factor Va and factor VIIIa.63-65

Table 7. Recommended laboratory evaluation for patients suspected of having an underlying hypercoagulable state

<table>
<thead>
<tr>
<th>Screening Tests</th>
<th>Confirmatory Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated protein C resistance</td>
<td>Factor V Leiden PCR</td>
</tr>
<tr>
<td>Prothrombin G20210A mutation testing by PCR</td>
<td>Antigenic assays for antithrombin, protein C, and/or protein S</td>
</tr>
<tr>
<td>Antithrombin, protein C, and protein S activity (functional) levels</td>
<td>Confirmatory tests for lupus anticoagulants*</td>
</tr>
<tr>
<td>Factor VIII activity level</td>
<td></td>
</tr>
<tr>
<td>Screening tests for lupus anticoagulants (sensitive aPTT, aPTT mixing studies, dilute Russell viper venom time)</td>
<td></td>
</tr>
<tr>
<td>Anticardiolipin antibody testing by ELISA</td>
<td></td>
</tr>
<tr>
<td>Fasting total plasma homocysteine level</td>
<td></td>
</tr>
</tbody>
</table>

* Include at least one of the following: platelet neutralization procedure, hexagonal phase phospholipids, Textarin/Ecarin test, platelet vesicles, DVV Confirm. PCR=polymersase chain reaction; aPTT=activated partial thromboplastin time; ELISA=enzyme-linked immunosorbent assay.

Protein S exists in the body in two primary forms or states—free and bound. Only the free form is active. Most patients with VTE and hereditary PSd have free protein S levels that are about 50% to 75% of normal.76 There are three types of PSd. Type I results from an inadequate amount of protein S in both the free and bound forms. Type II is characterized by reduced functional and preserved antigenic
levels. Type III denotes reduced free protein S levels and is due to mutations that enhance the interaction between protein S and C4b-binding protein.78

Epidemiology of PSd. The incidence of PSd in the general population is not known. In the Caucasian population, protein S deficiency has been found in between 1% and 5% of persons who experience a venous thrombotic event.59,79

Specific Risks of PSd. About one third of patients with protein S deficiency will have venous thrombosis by age 60 years.73,80-82 Homozygotes for the defect can manifest purpura fulminans, which involves severe widespread systemic thrombosis with associated tissue necrosis.67,78,79 Warfarin-induced skin necrosis has also been reported in patients with protein S deficiency, and is related to differences in production and turnover of various coagulation cascade components during the early warfarin administration period.85 Warfarin-induced skin necrosis, although very rare, can be prevented with temporary bridging administration of therapeutic intravenous heparin or fully therapeutic doses of subcutaneous LMWH until the international normalized ratio (INR) reaches target therapeutic levels.

Management of PSd. Because studies have demonstrated an increased risk of recurrent venous thromboembolic events in patients with protein S deficiency, long-term oral anticoagulation is recommended. Use of fresh frozen plasma (FFP) can be helpful in life-threatening thrombosis from protein S deficiency.67,83-85 The current recommendation is to begin warfarin therapy on the first or second day of heparin or LMWH treatment and discontinue heparin treatment on the fifth day.86

SUMMARY

Treatment of Initial Thrombosis. Treatment of the initial thrombotic event in patients with hypercoagulable states does not generally differ from treatment of other patients with VTE. Venous thromboembolism, regardless of any pre-existing thrombophilic state(s) warrants therapeutic anticoagulation in all affected patients without acute contraindications to such therapy. This can be accomplished with several different pharmacologic agents: (a) heparin; (b) warfarin; and (c) LMWH. Among more recent therapeutic developments, fondaparinux sodium – a synthetic Factor Xa inhibitor – became available for prophylaxis and treatment of VTE.

Therapeutic anticoagulation is generally continued for 3-6 months, unless lifetime risk of thrombotic events has been clearly established and life-long anticoagulation is thus indicated.30,86 Patients who experienced multiple thromboembolic episodes or are at high risk of further thromboembolic episodes (for example, patients with multiple co-existing hypercoagulable states as described above) may be considered for long-term oral anticoagulation with oral warfarin or therapeutically-dosed subcutaneous LMWH.86 Long-term anticoagulation has risks associated with it, including the probability of approximately 3% per year of major hemorrhage, of which approximately 20% may be fatal. Therefore, the decision to begin long-term anticoagulation is influenced by the patient's overall risk of recurrent thrombosis balanced against risks associated with long-term anticoagulation and is best undertaken on case-by-case basis.

Clinical data suggest that the incidence of recurrent venous thromboembolism following the cessation of therapy in patients presenting with a first episode of unprovoked symptomatic venous thromboembolism is 5-15% in the first year and 20-30% at four years.87-90 However, estimates of the risk of fatal pulmonary embolism in patients following adequate treatment for an initial episode of symptomatic DVT or pulmonary embolism are very low at approximately 0.4% per year.91-92 Recurrences occur much less frequently when the initial event is associated with only transient risk factors (i.e., traumatic injury, prolonged immobility, surgery, etc).92-94

<table>
<thead>
<tr>
<th>3 months</th>
<th>If VTE is due to a transient or provoked event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifelong</td>
<td>If VTE and:</td>
</tr>
<tr>
<td></td>
<td>• Uncontrolled cancer</td>
</tr>
<tr>
<td></td>
<td>• Homozygous Factor V Leiden</td>
</tr>
<tr>
<td></td>
<td>• Antiphospholipid syndrome</td>
</tr>
<tr>
<td></td>
<td>• Antithrombin III deficiency</td>
</tr>
<tr>
<td></td>
<td>• ≥ 2 hereditary abnormalities</td>
</tr>
<tr>
<td></td>
<td>• Multiple VTEs</td>
</tr>
<tr>
<td></td>
<td>• Life-threatening VTE</td>
</tr>
</tbody>
</table>

Table 8. Recommended duration of treatment for venous thromboembolism.

Screening for hypercoagulable states in patients with VTE. Individuals with VTE should be screened in the presence of any of the following conditions: (a) age under 50 years; (b) recurrent VTE; (c) positive family history of VTE in first-degree relative; (d) recurrent fetal loss; (e) DVT and/or PE while on the birth control pill or hormone replacement; or (f) while pregnant/post-partum.

Screening tests for hypercoagulable states can be affected by multiple conditions and therapies (e.g., medications, pregnancy, infections, active thrombotic process). Because it is unlikely that the detection of a hematologic abnormality will alter the intensity of anticoagulant therapy, screening for a hypercoagulable state one to two months after the anticoagulant therapy has been stopped is recommended.

Individuals who develop VTE and have a hypercoagulable state do not usually need lifelong anticoagulation. If there is no VTE, and the hypercoagulable state was detected during routine screening, the decision to treat should be based on individual risk factors and the type of hypercoagulable state. Many patients, however, may benefit from prophylaxis during high-risk periods (e.g., surgery and pregnancy).

CONCLUSIONS

Venous thrombotic events result from multiple and complex interactions between genetic and acquired factors. Congenital thrombophilic disorders are often found in patients with venous thrombosis. Many patients have either factor V Leiden or the prothrombin gene mutation, which are associated with a lower risk for thrombosis than the less common deficiencies of protein C, protein S, or antithrombin III. Advanced knowledge of specific risk factors, particularly of the complex interactions

Copyright 2007-2008 OPUS 12 Foundation, Inc.

12
between multiple risk factors, will enable clinicians to develop clinical approaches customized to each patient. Pulmonary embolism is difficult to diagnose and continues to be characterized by high mortality and morbidity. Preventing DVT in high-risk populations is therefore preferable to treating the condition and its complications following the acute event.

REFERENCES


[27] Lane DA, Bayston T, Olds RJ, Fitches AC, Cooper DN, Millar DS, McAvoy A. Value of autoantibodies to beta(2)-glycoprotein 1 in the diagnosis of antiphospholipid syndrome. Rheumatology (Oxford) 2002;41:550-553.


[33] Dahlback B, Hildebrand B. Inherited resistance to activated protein C is corrected by anticoagulant cofactor activity found to be a property of factor V. Proc Natl Acad Sci U S A 1994;91:1396-1400.


