Hypercoagulability Syndromes

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Hypercoagulability can be defined as the tendency to have thrombosis as a result of certain inherited and/or acquired molecular defects. Clinical manifestations of hypercoagulability can be devastating and even lethal. In the past 20 years, the origin of most of these diverse hypercoagulability syndromes has been elucidated. Currently, hypercoagulability disorders can be correctly diagnosed in approximately 80% to 90% of patients. Defining the cause of hypercoagulability may determine the type and duration of treatment for the associated thrombosis. The discovery of an occult carcinoma allows for the possibility of early and possibly curative treatment. Finding a genetic defect in coagulation allows for testing of asymptomatic family members as well. The purpose of this review is to provide internists with a logical approach to the identification and treatment of hypercoagulability syndromes.

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Most commonly, thrombosis is the result of more than one “hit.” For example, patients with the factor V Leiden defect may be asymptomatic until they start taking oral contraceptives. Patients with antithrombin deficiency may go on without incident until they undergo a hernia repair. Also, multiple genetic defects predispose one to thrombosis much more than does a single defect.1,2 Some defects are known to be more powerful predictors than others. Therefore, hypercoagulability is not a uniform disease process but rather a host of predisposing conditions that may or may not be expressed as thrombosis, depending on environmental insults and the strength and number of predisposing factors.

INDIVIDUAL SYNDROMES

The following is a list of the disorders that cause hypercoagulability and their approximate incidences. Since these were derived from different studies, percentages cannot be exact. Also, incidences may vary, depending on the ethnic backgrounds of persons in a particular geographic area.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Incidence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiphospholipid antibody syndrome</td>
<td>28</td>
</tr>
<tr>
<td>Activated protein C resistance</td>
<td>25</td>
</tr>
<tr>
<td>Elevated coagulation factor VIII levels</td>
<td>25</td>
</tr>
<tr>
<td>Malignancy</td>
<td>15</td>
</tr>
<tr>
<td>Sticky platelet syndrome</td>
<td>14</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>10</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>10</td>
</tr>
<tr>
<td>Homocystinemia</td>
<td>10</td>
</tr>
<tr>
<td>Prothrombin G20210A</td>
<td>5–10</td>
</tr>
<tr>
<td>Plasminogen deficiency</td>
<td>2–3</td>
</tr>
<tr>
<td>Dysfibrinogenemia</td>
<td>1.5</td>
</tr>
<tr>
<td>Plasminogen activator inhibitor increase</td>
<td>1–3</td>
</tr>
<tr>
<td>Tissue plasminogen activator deficiency</td>
<td>1</td>
</tr>
</tbody>
</table>

Antiphospholipid Antibody Syndrome

The antiphospholipid antibody syndrome is probably the most common of the hypercoagulable disorders. It is caused by a heterogeneous family of immunoglobulins that bind to plasma proteins that have an affinity for phospholipid surfaces. These antigens include B2 glycoprotein I, pro-
thrombin, high- and low-molecular-weight kininogens, annexin V, activated protein C, and activated protein S. It is usually acquired and can be divided into the lupus anticoagulant syndrome and the antiphospholipid antibody syndrome. Both of these syndromes may be associated with other disorders, such as collagen vascular diseases or infections, but are more often primary. Antiphospholipid antibody syndrome can also be associated with use of the following medications: phenytoin, quinidine, hydralazine, procainamide hydrochloride, phenothiazines, interferon, cocaine, quinine, and the combination product of pyrimethamine and sulfadoxine.

Usually, a patient will have one syndrome or the other but not both. Multiple mechanisms as to the reason for hypercoagulability have been postulated, but the exact cause is unknown at this time. The risk of thrombosis is 5.5% per year for symptomatic patients.

The lupus anticoagulant is directed against phospholipids, which then causes an in vivo prolongation in the prothrombin time (PT), partial thromboplastin time (PTT), or the Russell viper venom time. These values do not correct with normal plasma. However, the addition of phospholipids will correct the abnormality. Despite the prolonged coagulation times, thrombosis is the predominant feature of this syndrome. The PT and PTT are not sensitive enough to be used as a screening tool for the lupus anticoagulant. Instead, the Russell viper venom time must be used. Venous thrombosis is much more common than arterial thrombosis in these patients.

The antiphospholipid antibody syndrome is 5 times more common than the lupus anticoagulant syndrome. Antibodies can be detected by enzyme-linked immunosorbent assay. Both IgG and IgM are associated with thrombosis. A total of 1% to 7% of asymptomatic individuals have low titers of these antibodies. Even asymptomatic persons have a 1% risk per year of thrombosis. This increases to 6% in those with high titers. This contrasts with a 0.1% risk per year in the general population. Venous and arterial thrombi are equally common. Other manifestations include valvular abnormalities, livedo reticularis, superficial thrombophlebitis, ulcers, adrenal hemorrhage, fatal wastage, chorea, transverse myelopathy, and thrombocytopenia.

The treatment of patients with antiphospholipid antibody syndrome who have had thrombosis is long-term anticoagulation until the antibody has been absent for at least 6 months. The drug of choice is low-molecular-weight heparin sodium since in 65% of patients warfarin sodium therapy fails and the international normalized ratio is unreliable in monitoring the intensity of therapy. If warfarin must be used, an international normalized ratio target range of 3 to 4 should be sought. The treatment of fetal wastage syndrome is beyond the scope of this review. There is no clear indication for therapy in asymptomatic persons; however, aspirin therapy would be reasonable in this population because the risk of thrombosis is higher than normal. Other treatments, such as corticosteroids, cyclophosphamide, and plasma exchange, have been used for severely symptomatic disease, but their roles in routine management are not well established.

Activated Protein C Resistance

Activated protein C resistance (eg, factor V Leiden) is the most common inherited disorder that causes hypercoagulability. Factor V Leiden is present in 5% of whites but virtually absent in Africans and Asians. However, 1% of African Americans have the mutation, reflecting racial mixing. It results from a point mutation in the factor V gene, which causes the substitution of glutamine for arginine at position 506. Several rare factor V gene mutations that can lead to activated protein C resistance have also been described. Consequently, 1 of 3 activated protein C cleavage sites is lost. The result is an impaired inactivation of factor V by activated protein C. Venous thromboses and fetal wastage may occur. It is not an important risk factor for arterial disease except in the presence of smoking or other known risk factors. Those with factor V Leiden have a 2- to 3-fold risk for venous thrombosis compared with healthy subjects. The risk in homozygotes is 80-fold. Heterozygous factor V Leiden is, therefore, a relatively mild risk factor for thrombosis. The annual rate of thrombosis is 0.28%. Six percent of patients will have a thrombosis by the age of 65 years. Sixty percent of patients who experience thrombosis have a predisposing event, such as oral contraceptive use or pregnancy. The presence of this mutation does not appear to affect life expectancy, and many patients will remain asymptomatic. Therefore, patients with no history of thrombosis should not be treated prophylactically with long-term anticoagulation. Functional tests for activated protein C resistance should be used to screen for the disorder, and positive results should be confirmed with polymerase chain reaction for the genetic mutation. However, patients with phenotypic resistance to activated protein C have an increased risk of thrombosis even if it is not due to factor V Leiden. Functional tests may still be performed while patients undergo anticoagulation.

Elevated Coagulation Factor VIII Levels

Elevated coagulation factor VIII levels appear to be nearly as common a risk factor for thrombosis as factor V Leiden. The Leiden Thrombophilia Study found an 11% incidence in healthy controls and a 25% incidence in patients with venous thrombosis. The odds ratio for thrombosis was 4.8 for subjects with levels greater than 150 IU/dL vs those with levels less than 100 IU/dL. For every 10-IU/dL rise in levels, the risk for a single episode of deep venous thrombosis (DVT) increases 10% and the risk for recurrent DVT increases 24%. Levels of coagulation factor VIII are not elevated because of the acute-phase reaction but appear to be constitutively increased in most patients with thrombosis, since coagulation factor VIII levels are elevated independently of C-reactive protein and fibrinogen, and 94% of patients continue to have high levels throughout long-term follow-up. Pregnancy and oral contraceptive use may also raise levels. The use of oral contraceptives in patients with increased coagulation factor VIII levels raises the risk of thrombosis 10-fold over pa...
tients with neither risk factor.28 The genetic basis for increased coagulation factor VIII levels is not well understood at this time; however, one small study25 showed high concordance rates for first-degree adult family members.

Malignancy

Cancer is the second most common acquired cause of hypercoagulability, accounting for 10% to 20% of spontaneous DVTs. Indeed, 15% of patients with cancer have clinical thromboses and about 50% have thromboses on autopsy.29 Cancer not only causes hypercoagulability but may also produce endothelial injury and venous stasis. Hypercoagulability is especially frequent in mucin-secreting adenocarcinomas, brain tumors, acute promyelocytic leukemia, and myeloproliferative disorders.

Arterial thrombosis is much less common than venous thrombosis and is most often the result of nonbacterial thrombotic endocarditis or disseminated intravascular coagulation. Ninety percent of patients with cancer have clotting abnormalities, such as increased fibrinogen, clotting factors, fibrin degradation products, and platelets.30,31 Overt disseminated intravascular coagulation is rare. There is no consensus as to the value of measuring coagulation markers in predicting thrombosis in individual patients with cancer.

Some cancers underlying spontaneous DVT are occult, early stage, and curable. However, there is no proof that aggressive diagnostic testing leads to improvement in survival. Most experts recommend a thorough history and physical examination, routine blood tests, chest x-ray examination, urinalysis, and age- and sex-specific screening, such as prostate-specific antigen, Papanicolaou smear, lower endoscopy, mammography, and fecal occult blood testing. Suspicious findings should be aggressively evaluated. In addition, patients without evidence of cancer should be followed up closely for the ensuing 2 years, during which time virtually all occult cancers will become clinically apparent.

The initial treatment of thromboses is the same as in patients without cancer. However, treatment should be continued indefinitely until the patient is cured of the malignancy and is no longer receiving chemotherapy. If anticoagulation is contraindicated as with cerebral or pericardial metastases, primary brain tumors, or severe thrombocytopenia, an inferior vena cava filter may be placed. Long-term treatment may be with low-molecular-weight heparin or warfarin, although anecdotal evidence suggests that heparin may lead to fewer thrombotic recurrences than warfarin.32 Certainly, warfarin failure should lead to a switch to heparin. If heparin fails, an inferior vena cava filter should then be placed. Thrombo-lytic agents should only be used in patients with cancer who have a good prognosis and either pulmonary embolism with hemodynamic compromise or severe iliofemoral thrombosis of less than 4 days’ duration. Of course, aggressive DVT prophylaxis with low-dose subcutaneous heparin or low-molecular-weight heparin (depending on severity and number of risk factors) should be carried out in patients with cancer who are hospitalized, immobilized, or undergoing surgery.

Sticky Platelet Syndrome

The sticky platelet syndrome is an autosomal dominant disorder that results in platelets that are hyperaggregable to epinephrine and/or adenosine diphosphate. Venous or arterial thrombosis may occur.33 Episodes are more common during emotional stress. Retinal vascular thrombosis appears to be associated with this entity. Fetal wastage may also occur. It is diagnosed with platelet aggregation studies. Treatment is with low-dose aspirin (81 mg). If platelet aggregability does not normalize, aspirin, 325 mg, may be tried.34 If there is still no response, then clopidogrel (an adenosine diphosphate receptor antagonist similar to but better tolerated than ticlopidine hydrochloride) may be used.

Protein C Deficiency

Protein C deficiency is an autosomal dominant trait that may be caused by a decrease in absolute levels of protein C or a decrease in its function. Deficiency of protein C occurs in 1 of 250 controls.35 Protein C is made in the liver and is vitamin K dependent. It acts to inactivate factor V and factor VIII:C. It requires factor S as a cofactor and is activated by thrombin, when thrombin is bound to thrombomodulin.

In families with thromboses and protein C deficiency, thromboses begin in the late teens.36 Seventy-five percent of affected individuals will have 1 or more events.37 The relative risk is 7.3.38 The annual incidence is 1%.39 Seventy percent of episodes are spontaneous.37 Both DVT and pulmonary embolism are the most common manifestations. Superficial thrombophlebitis is also common.38 Arterial events are rare.

The optimal time to investigate is at least 10 days after warfarin therapy is stopped, since both warfarin and acute thrombosis decrease protein C levels. Levels below 53% of normal are likely to be genetically deficient; 55% to 65% is borderline. Abnormal results should always be repeated for confirmation and family studies performed.39

The short-term management of thrombosis is with heparin or low-molecular-weight heparin. Warfarin may be used for long-term treatment; however, doses should be started low and titrated upward slowly only after heparin is therapeutically because of the risk of warfarin necrosis.40 In fact, one third of patients with warfarin necrosis have an underlying protein C deficiency.

Protein S Deficiency

Protein S is vitamin K dependent and is synthesized by hepatocytes and megakaryocytes. It acts as a cofactor for protein C. Fifty percent circulates free and 50% circulates bound to C4b binding protein. Deficiency is transmitted autosomally dominant and can be quantitative or qualitative.

Seventy-four percent of patients develop DVT; 72% develop superficial thrombophlebitis.41 The relative risk of thrombosis is 8.5.18 The annual incidence is 1%;19; 56% of episodes are spontaneous. Arterial events are uncommon. One half of patients who develop thromboses do so by the age of 25 years.41
Homocystinemia

Elevated levels of homocysteine are known to be a risk factor for arterial and venous thrombosis and fetal wastage. Homocysteine is an intermediate of methionine metabolism and, therefore, elevated levels may result from cystathionine β-synthase deficiency, homozygous expression of the thermolabile form of methylenetetrahydrofolate reductase, or from B_{12} or folate acid deficiency. Mild-to-moderate increases in homocysteine occur in 5% to 10% of the population. The relative risk of thrombosis is 2.6. Elevated homocysteine levels are thought to cause thromboses via several mechanisms, including (1) decreased protein C activation, (2) increased factor V activity, (3) induction of endothelial cell tissue factor activity, (4) inhibition of thrombomodulin expression and activation, (5) decreased antithrombin activity, and (6) enhanced affinity of lipoprotein(a) and fibrin.

Measurement of homocysteine levels is not well standardized, and acute thrombosis may raise homocysteine levels. Dietary supplementation with vitamin B_{6}, B_{12}, and folic acid can lower homocysteine levels. However, reduction of homocysteine levels has not been shown to reduce thrombotic complications. Folate supplementation (400 µg/d) may decrease levels by 30% to 42%. B_{12} supplementation (100 µg/d) may decrease levels by 15%. B_{6} supplementation (3 µg/d) only reduces levels if there is a pre-existing deficiency. Thrombosis is treated in standard fashion in addition to vitamin supplementation.

Antithrombin Deficiency

Antithrombin is made in the liver and endothelial cells. It inactivates thrombin and other serine proteases. Deficiency is an autosomal dominant disorder and occurs in 1 of 5000 healthy blood donors. The protein can be absent or dysfunctional. The normal concentration is 150 µg/mL. Thrombosis may occur at less than 75% of this amount. Patients may present with DVT or pulmonary embolism. Mesenteric vessels appear to be particularly susceptible. Arterial events are rare. Fifty percent of patients are asymptomatic. Thromboses occur early in life, with two thirds of patients presenting by the age of 35 years. Forty percent of thromboses are spontaneous. The relative risk of thrombosis is 8.1, and the annual incidence of thrombosis is 1%. Acute thrombosis, heparin, and other systemic diseases may decrease antithrombin levels. Warfarin may raise deficient levels into the normal range. Therefore, low levels in a patient during acute thrombosis or while taking heparin should be confirmed when the patient is not undergoing therapy. Likewise, normal levels while the patient is taking warfarin should be confirmed when the patient is not undergoing therapy.

Treatment of acute thrombosis is with low-molecular-weight heparin because deficiency may cause resistance to unfractionated heparin. In fact, heparin resistance may be a clue to the presence of this deficiency. Lifelong therapy should be considered for spontaneous or recurrent thromboses. Prophylactic treatment of asymptomatic individuals is controversial but usually is limited to high-risk situations, such as pregnancy or surgery. Antithrombin concentrate may be used for thromboses, which both thrombosis and bleeding may occur, such as labor and delivery, where anticoagulation might be contraindicated.

Dysfibrinolysis

There are 5 major forms of dysfibrinolysis: (1) congenital plasminogen deficiency, (2) tissue plasminogen activator deficiency, (3) increased plasminogen activator inhibitor, (4) congenital dysfibrinogenemia, and (5) factor XII deficiency. Long-term treatment may be with warfarin or low-molecular-weight heparin for all patients.

Congenital plasminogen deficiency is a rare autosomal dominant disorder caused by either absent or dysfunctional plasminogen. Clinically, it mimics protein C and S deficiencies. Symptoms usually begin in the late teens. Most commonly, it presents with DVT or pulmonary embolism. Arterial events are uncommon. Events usually occur when plasminogen levels are less than 40% of the normal values. The results of routine coagulation studies are normal. Treatment is standard.

Congenital deficiency of tissue plasminogen activator and congenital increases of plasminogen activator inhibitor are exceedingly rare. Acquired abnormalities are more common. They may occur with diabetes mellitus, inflammatory bowel disease, and coronary atherosclerosis.

Most congenital dysfibrinogenemias occur in asymptomatic individuals (55% of patients) or cause mild hemorrhagic disorders (20%). Only 20% are associated with thrombosis. Venous thrombosis is most common but arterial events may occur. They are usually autosomal dominant. They may be detected with abnormal thrombin times or reptilase clotting times. Treatment of thrombosis consists of heparin or low-molecular-weight heparin followed by warfarin.

Factor XII deficiency is inherited in autosomal dominant fashion. It is involved in plasmin generation. Thus, patients will have a prolonged PTT, yet have a thrombotic diathesis. Arterial and venous thromboses and fetal wastage are common. Approximately 8% of deficient subjects develop thromboses. Factor XII deficiency should be suspected when a patient with thrombosis has a prolonged PTT that corrects with the addition of normal plasma. A factor XII assay should then be performed. Treatment is with low-molecular-weight heparin followed by warfarin or continuation of low-molecular-weight heparin. Stan-
Prothrombin G20210A

Prothrombin G20210A mutation is a relatively recently discovered defect in which there is a G to A transition at nucleotide position 20210. This mutation increases prothrombin activity and levels. It is found in 2.3% of healthy controls. The incidence is twice as high in people from southern Europe than from northern Europe, and it is rare in Africans and Asians. It may be detected through DNA analysis. At this time, it must be considered a very mild risk factor for venous and arterial thrombosis. The relative risk is approximately 2 to 3 times that of individuals without the mutation.

Other Hypercoagulable Syndromes

Heparin cofactor II inhibits thrombin by mimicking the cleavage sites of thrombin and forming a stable complex with it, thus acting as a “suicide” substrate. Deficiency is rare and could theoretically cause thrombotic potential, but its exact role is controversial. Heparin is effective in the presence of heparin cofactor II deficiency.

Tissue factor pathway inhibitor is a plasma component that binds and inhibits factor Xa directly. This complex then binds to the tissue factor–factor VIIa complex, blocking its activity as well. Unstimulated plasma levels do not appear to be related to thrombosis. However, plasma levels measured 10 minutes after intravenous heparin, 7500 U, is administered correlate with venous thrombosis. The role of tissue factor pathway inhibitor and its incidence in thrombophilia are currently unknown.

Thrombomodulin mutations have also been implicated in thrombophilia but prevalence and degree of risk are unknown. The Wein-Penzing defect is an extremely rare deficiency of the lipoxynase metabolic pathway that results in the compensatory increase of the cyclooxygenase pathway and, therefore, elevated thromboxane levels. Thus, platelets are in a state of increased activation.

INVESTIGATION OF HYPERCOAGULABILITY

Various clinical features should suggest hypercoagulability, including thrombosis at an early age (<50 years), family history of thrombosis, recurrent idiopathic thrombosis, thrombosis at an unusual site (except for effort-related upper extremity DVT), spontaneous thrombosis or only mild provocation, unexplained spontaneous abortions, massive thrombosis, and warfarin-induced skin necrosis. Information from the history and physical examination determines the likelihood of the underlying disorder. For example, a young patient who presents with a strong family history of thrombosis suggests a genetic disorder. A patient with systemic lupus erythematosus is likely to have the antiphospholipid antibody syndrome. An older patient with weight loss, early satiety, and epigastric pain is likely to have a gastric carcinoma.

All patients should have a complete blood count performed, including platelets, to exclude myeloproliferative disorders. Abnormalities in PT and PTT suggest either the lupus anticoagulant or factor XII deficiency. Antiphospholipid antibodies should be obtained. Screening for cancer as outlined earlier should be performed. Patients in whom this evaluation is negative and all patients with a positive family history of thrombosis should undergo testing for the common genetic disorders (Table 1). Table 2 provides a list of the approximate costs of the various tests for hypercoagulability. Laboratory investigation for these disorders is generally unreliable during acute thrombosis and while undergoing anticoagulant therapy. Thus, studies are optimally performed while the patient is not taking anticoagulants and is in the asymptomatic state. If tests are performed while the patient is taking anticoagulants, knowledge of the alteration of the individual factors by the specific anticoagulant is essential. Depending on the level of suspicion for

**Table 1. Genetic Disorders That Cause the Hypercoagulable Syndrome**

<table>
<thead>
<tr>
<th>Common</th>
<th>Uncommon</th>
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<tbody>
<tr>
<td>Sticky platelet syndrome</td>
<td>Plasminogen activator inhibitor excess</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>Heparin cofactor II deficiency</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>Wein-Penzing defect</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>Dysfibrinogenemia</td>
</tr>
<tr>
<td>Homocystinemia</td>
<td>Tissue plasminogen activator deficiency</td>
</tr>
<tr>
<td>Prothrombin G20210A</td>
<td>Plasminogen deficiency</td>
</tr>
<tr>
<td>Increased factor VIII</td>
<td>Tissue factor pathway inhibitor</td>
</tr>
</tbody>
</table>

**Table 2. Costs of Hypercoagulable Workup at the University of Miami**

<table>
<thead>
<tr>
<th>Test</th>
<th>Cost, $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete blood cell count with platelets</td>
<td>30.00</td>
</tr>
<tr>
<td>Prothrombin and partial thromboplastin time</td>
<td>64.50</td>
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<tr>
<td>Anticardiolipin antibodies</td>
<td>130.00</td>
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<tr>
<td>Lupus anticoagulant</td>
<td>240.00</td>
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<tr>
<td>Activated protein C resistance</td>
<td>75.00</td>
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<tr>
<td>Confirmatory polymerase chain reaction for factor V Leiden</td>
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</tr>
<tr>
<td>Factor VIII</td>
<td>90.00</td>
</tr>
<tr>
<td>Prothrombin G20210A</td>
<td>175.00</td>
</tr>
<tr>
<td>Platelet aggregation studies</td>
<td>360.00</td>
</tr>
<tr>
<td>Protein C (functional)</td>
<td>105.00</td>
</tr>
<tr>
<td>Antigen</td>
<td>110.00</td>
</tr>
<tr>
<td>Protein S (functional)</td>
<td>105.00</td>
</tr>
<tr>
<td>Free</td>
<td>100.00</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>324.00</td>
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</table>

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Approach to treatment of hypercoagulability.

A genetic defect, referral to a hematologist for testing of the rarer defects may be indicated if the prior workup is unrewarding. A useful mnemonic for the common causes of hypercoagulability is CALMSHAPES: protein C deficiency, Antiphospholipid antibody syndrome, factor V Leiden; Malignancy, protein S deficiency, Homocystinemia, Antithrombin deficiency, Prothrombin G20210A, increased factor VIII levels (Eight), Sticky platelet syndrome.

**TREATMENT**

When considering a patient for indefinite therapy, many factors must be considered: (1) the number, site, and severity of thromboses; (2) spontaneous vs provoked thrombus; (3) the sex and lifestyle of the patient; (4) the strength of the predictive value for thrombosis of the particular hypercoagulable disorder; (5) the compliance of the patient; and (6) the patient’s personal value construct.

Few guidelines exist for indefinite therapy in hypercoagulable patients. A recent study that favored indefinite therapy in anyone with an unprovoked thrombosis was terminated prematurely. Bauer divides patients with hereditary defects into 2 groups: high risk (≥2 spontaneous episodes, 1 spontaneous life-threatening thrombosis, 1 thrombosis at an unusual site, or 1 thrombosis in the presence of >1 defect) and moderate risk (asymptomatic individuals or 1 thrombosis in response to a prothrombotic stimulus). In the high-risk group, he recommends indefinite anticoagulation. In the moderate-risk group, he recommends vigorous prophylaxis only for high-risk situations. Since no long-term studies have been performed comparing lifetime anticoagulation treatment with short-term anticoagulation therapy, definitive recommendations cannot be made at this time. Until these studies are performed, the Figure may be used as a guide to the evaluation and management of hypercoagulable disorders.

**CONCLUSIONS**

The evaluation and treatment of a patient suspected of having hypercoagulability cannot be generalized at this time. The clinician must consider many patient factors with statistical probabilities to determine what conditions should be investigated. When a hypercoagulable syndrome is diagnosed, further judgment must be exercised to then decide the best course of treatment. Oversimplifications on the evaluation and treatment of hypercoagulable syndromes are not helpful and may result in harm to individual patients.

**REFERENCES**


