ANTIPHOSPHOLIPID antibodies are a family of autoantibodies that exhibit a broad range of target specificities and affinities, all recognizing various combinations of phospholipids, phospholipid-binding proteins, or both. The term “antiphospholipid syndrome” was first coined to denote the clinical association between antiphospholipid antibodies and a syndrome of hypercoagulability.\cite{1,2} Revision of the criteria for diagnosis of the antiphospholipid syndrome and the terminology used to describe the disease is an ongoing process\cite{3} (Table 1).

**BACKGROUND**

The first antiphospholipid antibody, a complement-fixing antibody that reacted with extracts from bovine hearts, was detected in patients with syphilis in 1906.\cite{10} The relevant antigen was later identified as cardiolipin, a mitochondrial phospholipid.\cite{31} This observation became the basis for the Venereal Disease Research Laboratory (VDRL) test for syphilis that is currently used. Mass screening of blood for syphilis led to the finding that many patients with systemic lupus erythematosus had a positive VDRL test, without clinical or serologic evidence of syphilis.\cite{12} In 1983, a solid-phase immunoassay for antiphospholipid antibodies was developed.\cite{13} This assay was several hundred times more sensitive than the VDRL test for detecting antiphospholipid antibodies in patients with systemic lupus erythematosus, and the antiphospholipid antibodies detected were strongly associated with lupus anticoagulant antibodies, false positive VDRL tests, and thrombosis.\cite{13}

In the early 1990s, two groups discovered that some antiphospholipid antibodies require the presence of the plasma phospholipid-binding protein $\beta_2$-glycoprotein I in order to bind to cardiolipin.\cite{14,15} This requirement is a feature of antiphospholipid antibodies from patients with systemic lupus erythematosus or the antiphospholipid syndrome but not from patients with syphilis or other infectious diseases.\cite{14,16} Antibodies in the latter group of patients react directly with cardiolipin; they are not only independent of $\beta_2$-glycoprotein I but are also inhibited by it.\cite{16} The demonstration that autoimmune antiphospholipid antibodies are directed against a phospholipid-binding protein rather than against a phospholipid led to the discovery that some autoantibodies bind directly to $\beta_2$-glycoprotein I in the absence of phospholipids.\cite{14,17} This has resulted in a change of focus from phospholipids to phospholipid-binding proteins.\cite{6}

**DETECTION OF CLINICALLY RELEVANT ANTIPHOSPHOLIPID ANTIBODIES**

The most commonly detected subgroups of antiphospholipid antibodies are lupus anticoagulant antibodies, antiphospholipid antibodies, and anti-$\beta_2$-glycoprotein I antibodies. Division into these subgroups is broadly based on the method of detection (Table 2). Lupus anticoagulant antibodies are identified by coagulation assays, in which they prolong clotting times. In contrast, antiphospholipid antibodies and anti-$\beta_2$-glycoprotein I antibodies are detected by immunoassays that measure immunologic reactivity to a phospholipid or a phospholipid-binding protein (cardiolipin and $\beta_2$-glycoprotein I, respectively). Despite the frequent concordance between lupus anticoagulant antibodies and either antiphospholipid\cite{19} or anti-$\beta_2$-glycoprotein I\cite{20} antibodies, these antibodies are not identical. Some lupus anticoagulant antibodies react with phospholipids other than cardiolipin or proteins other than $\beta_2$-glycoprotein I,\cite{1,18} whereas some antiphospholipid\cite{19} and anti-$\beta_2$-glycoprotein I\cite{20} antibodies have no lupus anticoagulant activity. Most $\beta_2$-glycoprotein I–dependent antiphospholipid antibodies recognize $\beta_2$-glycoprotein I equally well whether bound to cardiolipin or bound to other anionic phospholipids. This is because $\beta_2$-glycoprotein I interacts strongly with anionic phospholipids but weakly with phospholipids with a net neutral charge.\cite{22} In general, lupus anticoagulant antibodies are more specific for the antiphospholipid syndrome, whereas antiphospholipid antibodies are more sensitive.\cite{23} The specificity of antiphospholipid antibodies for antiphospholipid syndrome increases with titer and is higher for the IgG than for the IgM isotope. However, there is no
definitive association between specific clinical manifestations and particular subgroups of antiphospholipid antibodies. Therefore, multiple tests for antiphospholipid antibodies should be used, since patients may be negative according to one test yet positive according to another.

Despite their name, lupus anticoagulant antibodies are associated with thromboembolic events rather than clinical bleeding. Antiphospholipid antibodies can interfere with both anticoagulant and procoagulant pathways. Anticardiolipin antibodies present at moderate or high levels in the blood on two or more occasions at least six weeks apart. Lupus anticoagulant antibodies detected in the blood on two or more occasions at least six weeks apart, according to the guidelines of the International Society on Thrombosis and Hemostasis§.

**Laboratory criteria**

- Anticardiolipin antibodies
  - Anti–β2-glycoprotein I antibodies present at moderate or high levels in the blood on two or more occasions at least six weeks apart.
- Lupus anticoagulant antibodies
  - Lupus anticoagulant antibodies detected in the blood on two or more occasions at least six weeks apart, according to the guidelines of the International Society on Thrombosis and Hemostasis§.

*A diagnosis of definite antiphospholipid syndrome requires the presence of at least one of the clinical criteria and at least one of the laboratory criteria. No limits are placed on the interval between the clinical event and the positive laboratory findings.*

†The following antiphospholipid antibodies are currently not included in the laboratory criteria: anticardiolipin IgA antibodies, anti–β2-glycoprotein I antibodies, and antiphospholipid antibodies directed against phospholipids other than cardiolipin (e.g., phosphatidylserine and phosphatidylethanolamine) or against phospholipid-binding proteins other than cardiolipin-bound β2-glycoprotein I (e.g., prothrombin, annexin V, protein C, or protein S).§

‡The threshold used to distinguish moderate or high levels of anticardiolipin antibodies from low levels has not been standardized and may depend on the population under study. Many laboratories use 15 or 20 international “phospholipid” units as the threshold separating low from moderate levels of anticardiolipin antibodies. Others define the threshold as 2.0 or 2.5 times the median level of anticardiolipin antibodies or as the 99th percentile of anticardiolipin levels within a normal population. Until an international consensus is reached, any of these three definitions seems reasonable.

§Guidelines are from Brandt et al.9

**PATHOGENESIS**

Several hypotheses have been proposed to explain the cellular and molecular mechanisms by which antiphospholipid antibodies promote thrombosis (Table 3). The first implicates activation of endothelial cells. Binding of antiphospholipid antibodies induces activation of endothelial cells, as assessed by up-regulation of the expression of adhesion molecules, the secretion of cytokines, and the metabolism of prostacyclins. Antiphospholipid antibodies recognize β2-glycoprotein I bound to resting endothelial cells, although the basis for the interaction of β2-glycoprotein I with viable endothelial cells remains unclear.

A second theory focuses on oxidant-mediated in-
Antiphospholipid antibodies interfere with the regulatory functions of prothrombin, protein C, annexin V, and tissue factor have also been proposed.\textsuperscript{7,22,25,34,35}

Finally, thrombosis in the antiphospholipid syndrome has been likened to that in heparin-induced thrombocytopenia.\textsuperscript{36} Both syndromes induce thrombosis in multiple arterial and venous beds.\textsuperscript{36,37} In heparin-induced thrombocytopenia, the site of thrombosis is often determined by prior cardiovascular disease, whereas in the antiphospholipid syndrome, there is a high rate of recurrence of similar thrombotic events. A “second hit” such as vascular injury may be necessary for thrombosis to occur in both syndromes.

It remains unclear which cellular phospholipids and phospholipid-binding proteins are targeted by antiphospholipid antibodies in vivo. The absence of anionic phospholipids on the cell surface and the apparent lack of reactivity of antiphospholipid antibodies with intact cells suggest that perturbation of the cell

### Table 2. Classification and Detection of Antiphospholipid Antibodies.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Method of Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupus anticoagulant antibodies</td>
<td>The first step is prolongation of coagulation in at least one phospholipid-dependent in vitro coagulation assay with the use of platelet-poor plasma.\textsuperscript{<em>}† These assays can be subdivided according to the portion of the coagulation cascade that they evaluate as follows‡: The extrinsic coagulation pathway (dilute prothrombin time) The intrinsic coagulation pathway (activated partial-thromboplastin time, dilute activated partial-thromboplastin time, colloidal-silica clotting time, and kaolin clotting time) The final common coagulation pathway (dilute Russell’s viper-venom time, Taipan venom time, and Textrarin and Ecarin times).§ The second step is a failure to correct the prolonged coagulation time by mixing the patient’s plasma with normal plasma.\textsuperscript{††} The third step is confirmation of the presence of lupus anticoagulant antibodies by shortening or correction of the prolonged coagulation time after the addition of excess phospholipid or platelets that have been frozen and then thawed.\textsuperscript{</em>} The fourth step is ruling out other coagulopathies with the use of specific factor assays if the confirmatory test is negative or if a specific factor inhibitor is suspected.\textsuperscript{*}</td>
</tr>
<tr>
<td>Anticardiolipin antibodies</td>
<td>Solid-phase immunoassay (usually enzyme-linked immunosorbent assay) is performed on cardiolipin-coated plates, usually in the presence of bovine serum β\textsubscript{2}-glycoprotein I. Anticardiolipin antibodies from patients with the antiphospholipid syndrome are β\textsubscript{2}-glycoprotein I–dependent; antibodies from patients with infectious diseases are β\textsubscript{2}-glycoprotein I–independent.¶</td>
</tr>
<tr>
<td>Anti–β\textsubscript{2}-glycoprotein I antibodies</td>
<td>Solid-phase immunoassay (usually enzyme-linked immunosorbent assay) is performed on human β\textsubscript{2}-glycoprotein I–coated plates (usually γ-irradiated polystyrene). Anti–β\textsubscript{2}-glycoprotein I antibody assays detect antibodies to human β\textsubscript{2}-glycoprotein I, rather than bovine β\textsubscript{2}-glycoprotein I (as in anticardiolipin antibody assays).</td>
</tr>
</tbody>
</table>

*Data are from Brandt et al.\textsuperscript{*}†The use of two or more assays sensitive to lupus anticoagulant antibodies is recommended before the presence of lupus anticoagulant antibodies is excluded. At least one of these assays should be based on low phospholipid concentration (dilute prothrombin time, dilute activated partial-thromboplastin time, colloidal-silica clotting time, kaolin clotting time, or dilute Russell’s viper-venom time). The two assays should evaluate distinct portions of the coagulation cascade (e.g., activated partial-thromboplastin time and dilute Russell’s viper-venom time).

‡Data are from Triplet.\textsuperscript{18}

§The Ecarin-time assay differs from the other coagulation assays listed in that it is a phospholipid-independent assay. It should be used in combination with the phospholipid-dependent Textrarin time as a confirmatory test for lupus anticoagulant antibodies. In the presence of lupus anticoagulant antibodies, Textrarin times are prolonged, whereas Ecarin times are unaffected.

¶Data are from Galli et al.,\textsuperscript{14} McNeil et al.,\textsuperscript{15} and Hunt et al.\textsuperscript{16}

||Data are from Rouby.\textsuperscript{9}
CLINICAL MANIFESTATIONS OF THE ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid antibodies are found among young, apparently healthy control subjects at a prevalence of 1 to 5 percent for both anticardiolipin antibodies and lupus anticoagulant antibodies.\(^5\) As with other antibodies, the prevalence of antiphospholipid antibodies increases with age, especially among elderly patients with coexistent chronic diseases.\(^5\) Among patients with systemic lupus erythematosus, the prevalence of antiphospholipid antibodies is much higher, ranging from 12 to 30 percent for anticardiolipin antibodies\(^5\) and 15 to 34 percent for lupus anticoagulant antibodies.\(^5\)

Many patients have laboratory evidence of antiphospholipid antibodies without clinical consequences. For otherwise healthy control subjects, there are insufficient data to determine what percentage of those with antiphospholipid antibodies will eventually have a thrombotic event or a complication of pregnancy consistent with the antiphospholipid syndrome. In contrast, the antiphospholipid syndrome may develop in 50 to 70 percent of patients with both systemic lupus erythematosus and antiphospholipid antibodies after 20 years of follow-up.\(^4,5\) Nonetheless, up to 30 percent of patients with systemic lupus erythematosus and anticardiolipin antibodies lacked any clinical evidence of the antiphospholipid syndrome over an average follow-up of seven years.\(^4\)

Prospective studies have shown an association between antiphospholipid antibodies and the first episode of venous thrombosis,\(^5,4\) the first myocardial in-

### Table 3. Opposing Effects of Antiphospholipid Antibodies on Coagulation.\(^*\)

<table>
<thead>
<tr>
<th>Procoagulant Effect</th>
<th>Anticoagulant Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition of the activated protein C pathway</td>
<td>Inhibition of activation of factor IX</td>
</tr>
<tr>
<td>Up-regulation of the tissue factor pathway</td>
<td>Inhibition of activation of factor X</td>
</tr>
<tr>
<td>Inhibition of antithrombin III activity</td>
<td>Inhibition of activation of prothrombin to thrombin</td>
</tr>
<tr>
<td>Disruption of annexin V shield on membranes</td>
<td>Disruption of annexin V shield on membranes</td>
</tr>
<tr>
<td>Activation of endothelial cells</td>
<td>Activation of endothelial cells</td>
</tr>
<tr>
<td>Enhanced expression of adhesion molecules by endothelial cells and adherence of neutrophils and leukocytes to endothelial cells</td>
<td>Enhanced expression of adhesion molecules by endothelial cells and adherence of neutrophils and leukocytes to endothelial cells</td>
</tr>
<tr>
<td>Activation and degranulation of neutrophils</td>
<td>Activation and degranulation of neutrophils</td>
</tr>
<tr>
<td>Potentiation of platelet activation</td>
<td>Potentiation of platelet activation</td>
</tr>
<tr>
<td>Enhanced platelet aggregation</td>
<td>Enhanced platelet aggregation</td>
</tr>
<tr>
<td>Enhanced binding of B2-glycoprotein I to membranes</td>
<td>Enhanced binding of B2-glycoprotein I to membranes</td>
</tr>
<tr>
<td>Enhanced binding of prothrombin to membranes</td>
<td>Enhanced binding of prothrombin to membranes</td>
</tr>
</tbody>
</table>

*Two major factors that probably modulate the balance between procoagulant and anticoagulant effects of antiphospholipid antibodies are the phospholipid surface on which the reaction takes place and the antigenic specificity of the antibody.

### CRITERIA FOR CLASSIFICATION AND DIAGNOSIS

A recent consensus statement provides simplified criteria for the diagnosis of the antiphospholipid syndrome\(^6\) (Table 1). A patient with the antiphospholipid syndrome must meet at least one of two clinical criteria (vascular thrombosis or complications of pregnancy [as defined in Table 1]) and at least one of two laboratory criteria. None of the other protein clinical manifestations of the antiphospholipid syndrome, such as thrombocytopenia, are included in the clinical criteria. Although such features have been associated with antiphospholipid antibodies, they occur in a variety of disease states other than the antiphospholipid syndrome, and the strength of their association does not reach that of vascular thrombosis.

The antiphospholipid syndrome may be divided into several categories. “Primary” antiphospholipid syndrome occurs in patients without clinical evidence of another autoimmune disease, whereas “secondary” antiphospholipid syndrome occurs in association with autoimmune or other diseases. Since systemic lupus erythematosus is by far the most common disease with which the antiphospholipid syndrome occurs, tentative exclusion criteria have been proposed to distinguish primary antiphospholipid syndrome from that related to systemic lupus erythematosus.\(^4\) The link between antiphospholipid antibodies and other rheumatologic diseases, with the exception of rheumatoid arthritis,\(^48\) is more tenuous and is based largely on case reports. Many cases of Sneddon’s syndrome, defined as the clinical triad of stroke, livedo reticularis, and hypertension, may represent undiagnosed antiphospholipid syndrome.\(^49\) Although antiphospholipid antibodies also occur in association with other conditions (including infections, cancer, and the use of drugs or hemodialysis), they are usually IgM antibodies that are present at low levels and are not associated with thrombotic events.\(^50\) “Catastrophic” antiphospholipid syndrome will be discussed separately.

### EPIDEMIOLOGY

Antiphospholipid antibodies are found among young, apparently healthy control subjects at a prevalence of 1 to 5 percent for both anticardiolipin antibodies and lupus anticoagulant antibodies.\(^5\) As with other antibodies, the prevalence of antiphospholipid antibodies increases with age, especially among elderly patients with coexistent chronic diseases.\(^5\) Among patients with systemic lupus erythematosus, the prevalence of antiphospholipid antibodies is much higher, ranging from 12 to 30 percent for anticardiolipin antibodies\(^5\) and 15 to 34 percent for lupus anticoagulant antibodies.\(^5\)

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Prospective studies have shown an association between antiphospholipid antibodies and the first episode of venous thrombosis,\(^5,4\) the first myocardial in-
Figure 1. Detection of Lupus Anticoagulant Antibodies by in Vitro Coagulation Assays.

The various coagulation tests used to detect lupus anticoagulant activity are indicated in italics, and the figure shows a simplified schematic diagram of the coagulation pathway evaluated by each of these tests. The coagulation cascade is a result of the enzymatic conversion of each factor (orange boxes) to its activated, or enzymatic, form (blue boxes), which then, in combination with an activated cofactor, catalyzes the subsequent reaction. The intrinsic coagulation pathway is initiated by contact activation on glass, silica, or kaolin (as in the activated partial-thromboplastin time [APTT], colloidal-silica clotting time [CSCT], and kaolin clotting time [KCT] assays), whereas the extrinsic coagulation pathway is initiated by the formation of a complex between tissue factor (TF) and factor VIIa (as in the dilute prothrombin time [dPT] assay). Both the intrinsic and extrinsic pathways result in the conversion of factor X to activated factor X (factor Xa). Finally, both intrinsic and extrinsic pathways converge on the final common pathway, the activation of prothrombin to thrombin followed by the conversion of fibrinogen to fibrin. Russell's viper venom directly activates factor X. Taipan, Textarin, and Ecarin snake-venom extracts directly activate prothrombin but have different cofactor requirements. Taipan venom activation of prothrombin requires phospholipid and calcium but not factor Va. Textarin activation of prothrombin requires phospholipid, calcium, and factor Va, whereas Ecarin activation of prothrombin is independent of cofactors and does not require phospholipid, calcium, or factor Va. The activation of prothrombin to thrombin, like several other reactions in the coagulation cascade, requires the presence of phospholipid and calcium. These phospholipid-dependent reactions are believed to be targeted by lupus anticoagulant antibodies in vitro. Although both the intrinsic and extrinsic pathways are invaluable for understanding clot formation in vitro, the extrinsic pathway has the dominant role in vivo.
With the presence of antiphospholipid antibodies is a factor for thromboembolism. Associated with the nephrotic syndrome, itself a risk factor for lupus anticoagulant antibodies, and an elevated level of IgG anticardiolipin antibodies, each of which increases the risk of thrombosis up to five times, although not all studies agree. Persistence of antiphospholipid antibodies also appears to increase the risk of thrombosis. Except for a previous thrombotic event, none of the above individual risk factors are sufficiently predictive to warrant treatment.

DIFFERENTIAL DIAGNOSIS

The antiphospholipid syndrome is one of several prothrombotic states in which thrombosis occurs within both the venous and arterial beds (Table 4). Although other conditions predisposing the patient to venous and arterial thrombosis (e.g., heparin-induced thrombocytopenia, homocysteinemia, myeloproliferative disorders, and hyperviscosity) can be detected through routine laboratory testing, the sole abnormality in a patient with primary antiphospholipid syndrome may be the existence of antiphospholipid antibodies. It is important to note that since a normal activated partial-thromboplastin time does not exclude the presence of lupus anticoagulant antibodies (Table 2), a patient presenting with a first thrombotic event should be screened for anticardiolipin antibodies and with other assays that are sensitive to lupus anticoagulant antibodies. The diagnosis may be unsuspected in patients in whom the antiphospholipid syndrome results in a chronic, more indolent process, leading to ischemia and slow, progressive loss of organ function.

Secondary risk factors that increase the tendency to thrombosis should be pursued. Such factors can affect the venous or arterial beds and include stasis, vascular injury, the use of medications such as oral contraceptives, and traditional risk factors for atherosclerotic disease. Eliminating or reducing the effect of these factors is especially important, since the mere presence of antiphospholipid antibodies may be insufficient to generate thrombosis; a “second hit,” in combination with antiphospholipid antibodies, may be required for thrombosis to occur. Finally, even in patients with documented antiphospholipid syndrome, disentangling cause and effect can at times be difficult. For example, the antiphospholipid syndrome is associated with the nephrotic syndrome, itself a risk factor for thromboembolism.

CLINICAL FEATURES

Although the association of clinical manifestations with the presence of antiphospholipid antibodies is clearest in primary antiphospholipid syndrome, there are no major differences in the clinical consequences of antiphospholipid antibodies between patients with primary antiphospholipid syndrome and those with secondary antiphospholipid syndrome. Virtually any organ can be involved, and the range of disorders observed within any one organ system spans a diverse spectrum (Table 5). The effects of antiphospholipid antibodies are best appreciated from a pathogenetic point of view, with emphasis placed on two key features: the nature and size of the vessels involved and the acuteness or chronicity of the thrombotic process.

Venous thrombosis, especially deep venous thrombosis of the legs, is the most common manifestation of the antiphospholipid syndrome, occurring in 29 to 55 percent of patients with the syndrome during an average follow-up of less than six years. Up to half these patients have pulmonary emboli. Arterial thromboses are less common than venous thromboses and most frequently manifest with features consistent with ischemia or infarction. The severity of presentation relates to the acuteness and extent of occlusion. The brain is the most common site, with strokes and transient ischemic attacks accounting for almost 50 percent of arterial occlusions. Coronary occlusions account for an additional 23 percent; the remaining 27 percent involve diverse beds, including subclavian, renal, retinal, and pedal arteries. It should be emphasized that thrombotic episodes associated with the antiphospholipid syndrome may occur in vascular beds that are infrequently affected by other prothrombotic states (Table 5).

Not all arterial episodes of ischemia or infarction are thrombotic in origin. Emboli, especially from mitral-valve or aortic-valve vegetations, can also lead to cerebral events. The frequency of cardiac valvular abnormalities appears to be quite high, with up to 63 percent of patients with the antiphospholipid syndrome revealing at least one valvular abnormality on echocardiography. Although many of these abnormalities are of little clinical consequence, vegetations of the mitral or aortic valves are present in approximately 4 percent of patients with primary or secondary antiphospholipid syndrome.

Acute involvement at the level of the capillaries, arterioles, or venules often results in a clinical picture virtually indistinguishable from those of the hemolytic–uremic syndrome and thrombotic thrombocytopenic purpura as well as other thrombotic microangiopathies. Thrombotic microangiopathy may also occur as a more chronic process, resulting in slow, progressive loss of organ function, the underlying reason for which may only be determined by biopsy. Thus, organ involvement in patients with the antiphospholipid syndrome can present on a spectrum from rapidly progressive to clinically silent and indolent...
lent. Depending on the size of the vessels affected, organ failure has two predominant causes, thrombotic microangiopathy and ischemia secondary to thromboembolic events.

Other prominent manifestations of the antiphospholipid syndrome include thrombocytopenia (in 40 to 50 percent of patients), hemolytic anemia (in 14 to 23 percent), and livedo reticularis (in 11 to 22 percent). Although renal manifestations are a very common feature of systemic lupus erythematosus, they were only recently recognized as part of the antiphospholipid syndrome. Among patients with the antiphospholipid syndrome with renal involvement, hypertension is almost invariably present.63

PATHOLOGICAL FEATURES

The histopathological features of the antiphospholipid syndrome reflect a combination of several major pathophysiological processes: thrombotic microangiopathy, ischemia secondary to upstream arterial thromboses or emboli, and peripheral embolization from venous, arterial, or intracardiac sources.62,63,64 The histopathological features of arterial and venous thromboses seen in association with the antiphospholipid syndrome do not differ from those seen in other prothrombotic states. Similarly, regions of ischemia and infarction downstream from thrombotic or embolic occlusions lack unique features.

Thrombotic microangiopathy, an emerging clinical concern in the antiphospholipid syndrome, is a consequence of microvascular involvement. Its histologic features also are not specific to the antiphospholipid syndrome and can be seen in a variety of other diseases and syndromes, including hemolytic–uremic syndrome and thrombotic thrombocytopenic purpura, malignant hypertension, scleroderma, radiation-induced injury, pregnancy-associated renal failure, and various thrombotic microangiopathies induced by

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TABLE 4. DISEASE STATES AND RISK FACTORS PREDISPOSING PATIENTS TO THROMBOEMBOLISM.

<table>
<thead>
<tr>
<th>ABNORMALITY</th>
<th>VENOUS AFFECTED VASCULAR BEDS</th>
<th>VENOUS AND ARTERIAL AFFECTED VASCULAR BEDS</th>
<th>ARTERIAL AFFECTED VASCULAR BEDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defects in coagulation factors</td>
<td>Resistance to activated protein C (factor V)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leiden</td>
<td>Deficiency of protein C</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Deficiency of protein S</td>
<td>Deficiency of antithrombin III</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mutation of prothrombin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defects in clot lysis</td>
<td>Deficiency of plasminogen</td>
<td>Dysthrombogenemia*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Deficiency of tissue plasminogen activator</td>
<td>Deficiency of plasminogen activator inhibitor type 1*</td>
<td></td>
</tr>
<tr>
<td>Metabolic defects</td>
<td>Homocystinemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet defects</td>
<td>Heparin-induced thrombocytopenia and thrombosis</td>
<td>Paroxysmal nocturnal hemoglobinuria*</td>
<td>Polycythemia vera (with thrombocytosis)</td>
</tr>
<tr>
<td>Stasis</td>
<td>Immobilization</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Congestive heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperviscosity</td>
<td>Polycythemia vera</td>
<td>Atherosclerosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Waldenstrom’s macroglobulinemia</td>
<td>Turbulence</td>
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<td></td>
<td>Sickle cell anemia</td>
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<td></td>
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<tr>
<td></td>
<td>Acute leukemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defects in vessel walls</td>
<td>Trauma</td>
<td>Antiphospholipid syndrome</td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>Vasculitis</td>
<td>Foreign bodies</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Other</td>
<td>Cancer (Trousseau’s syndrome)</td>
<td>Cycloxygenase-2 inhibitors†</td>
<td>Smoking</td>
</tr>
<tr>
<td></td>
<td>Use of oral contraceptives</td>
<td></td>
<td>Arterial fibrillation</td>
</tr>
<tr>
<td></td>
<td>Estrogen therapy</td>
<td></td>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td></td>
<td>Pregnancy or puerperium</td>
<td></td>
<td>Chronic inflammation</td>
</tr>
<tr>
<td></td>
<td>Nephrotic syndrome</td>
<td></td>
<td>Systemic lupus erythematosus‡</td>
</tr>
</tbody>
</table>

*In this disorder, the venous involvement far exceeds the arterial involvement.
†Specific inhibitors of cycloxygenase-2 reduce systemic production of the antithrombotic prostaglandin prostacyclin. A recent series described four patients with secondary antiphospholipid syndrome in whom acute thrombosis developed in conjunction with a cycloxygenase-2 inhibitor.62
‡A prothrombotic effect of systemic lupus erythematosus, separate from that of antiphospholipid antibodies, has been suggested but not definitely established.
drugs (cyclosporine, tacrolimus, and chemotherapeutic agents such as mitomycin C). Although the acute changes of thrombotic microangiopathy are usually fairly prominent, the chronic changes can be quite subtle and easily overlooked. Acute changes include capillary congestion and intracapillary fibrin thrombi, generally without inflammation. Immuno-fluorescence reveals a predominance of fibrin-related antigens. Immune complexes are not seen. Chronic changes, ranging from ischemic hypoperfusion to atrophy and fibrosis, reflect healing and scarring of acute lesions. Vascular involvement extends from the nonmuscular precapillary arterioles to small muscular arteries. During the acute phase, fibrin thrombi containing fragmented blood cells narrow or occlude the vascular lumen. Thrombi eventually organize into fibrocellular and fibrous vascular occlusions. Blood flow may be restored by the development of new endothelialized channels that traverse the occlusion. True vasculitis is rarely, if ever, seen in primary antiphospholipid syndrome. Vasculitis in secondary antiphospholipid syndrome is attributable to systemic lupus erythematosus, not the antiphospholipid syndrome. Although there is enormous confusion regarding terminology for the vascular lesions associated with systemic lupus erythematosus, vaso-occlusive disease associated with the antiphospholipid syndrome, irrespective of the size of the vessel involved, is universally due to thrombosis.

OBSTETRICAL CONSIDERATIONS

Women with antiphospholipid antibodies have an unusually high proportion of pregnancy losses within the fetal period (10 or more weeks of gestation). In contrast, in unselected women with sporadic or recurrent miscarriage, pregnancy losses occur more commonly in the preembryonic period (less than six weeks of gestation) or the embryonic period (six to nine weeks of gestation). Pregnancies in women who...
are positive for antiphospholipid antibodies can also be complicated by premature delivery due to pregnancy-associated hypertensive disease and uteroplacental insufficiency.\textsuperscript{70,71} More recent studies have extended the deleterious effects of antiphospholipid antibodies to women with recurrent preembryonic and embryonic losses,\textsuperscript{2–74} among whom 10 to 20 percent have antiphospholipid antibodies without other medical conditions.\textsuperscript{72–77} The 1999 international consensus statement provides separate criteria for these two seemingly different populations\textsuperscript{9} (Table 1).

Adverse pregnancy outcomes in women with the antiphospholipid syndrome may result from poor placental perfusion\textsuperscript{78} due to localized thrombosis, perhaps through interference with trophoblastic annexin V that is mediated by antiphospholipid antibodies.\textsuperscript{35} Antiphospholipid antibodies may also impair trophoblastic invasion and hormone production, thereby promoting not only preembryonic and embryonic loss but also fetal loss and uteroplacental insufficiency.\textsuperscript{79}

Treatment has evolved considerably. Early enthusiasm for glucocorticoids waned when a small, randomized trial found heparin administered to pregnant women to be as effective as prednisone.\textsuperscript{80} Recently, two prospective trials showed that heparin plus low-dose aspirin is more effective than aspirin alone for achieving live births among women with antiphospholipid antibodies and predominantly preembryonic and embryonic pregnancy loss.\textsuperscript{75,76} A third prospective trial of women who were positive for antiphospholipid antibodies and had repeated pregnancy loss but no history of thrombosis or systemic lupus erythematosus found similar rates of live births (approximately 80 percent) with the use of either low-dose aspirin or placebo,\textsuperscript{77} suggesting that treatment may be unnecessary in some women. Although intravenous immune globulin has been used to treat some autoimmune conditions in pregnancy, a randomized, controlled study found no benefit of intravenous immune globulin as compared with heparin and aspirin in reducing adverse obstetrical outcomes in women with the antiphospholipid syndrome.\textsuperscript{81}

Concern about patient selection notwithstanding,\textsuperscript{82} most experts recognize the antiphospholipid syndrome as a proven, treatable cause of recurrent pregnancy loss.\textsuperscript{83} Currently, heparin administered to pregnant women after ultrasonographic demonstration of a live embryo is the treatment of choice, although the dose is debated. Women with recurrent preembryonic and embryonic pregnancy loss and no history of thromboembolism may be treated with 5000 U of heparin twice daily,\textsuperscript{75} but experts recommend higher doses, sufficient to produce full anticoagulation, for women with prior thromboembolism.\textsuperscript{84} The optimal treatment for women with pregnancy loss during the fetal period but no history of thromboembolism is controversial because of the potential risk of maternal thromboembolism. Generous thromboprophylaxis (15,000 to 20,000 U of heparin per day) or adjusted thromboprophylaxis is favored by some,\textsuperscript{70,71,80} but there are no properly designed studies for guidance. Experts agree that low-molecular-weight heparin may be substituted for standard heparin in the treatment of pregnant women with the antiphospholipid syndrome.\textsuperscript{84}

CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME

In most patients with the antiphospholipid syndrome, thrombotic events occur singly. Recurrences may occur months or years after the initial event. However, a minority of patients with the antiphospholipid syndrome present with an acute and devastating syndrome characterized by multiple simultaneous vascular occlusions throughout the body, often resulting in death. This syndrome, termed “catastrophic antiphospholipid syndrome,” is defined by the clinical involvement of at least three different organ systems over a period of days or weeks with histopathological evidence of multiple occlusions of large or small vessels.\textsuperscript{85} Although the same clinical manifestations seen with primary and secondary antiphospholipid syndrome also occur as part of catastrophic antiphospholipid syndrome, there are important differences in prevalence and in the caliber of the vessels predominantly affected. Our discussion will rely heavily on a comprehensive review through 1998 of 50 cases of catastrophic antiphospholipid syndrome.\textsuperscript{85}

Venous or arterial thrombosis of large vessels is less common in patients with catastrophic antiphospholipid syndrome, who tend to present with an acute thrombotic microangiopathy affecting small vessels of multiple organs.\textsuperscript{85} The kidney is the organ most commonly affected (in 78 percent of patients), followed by the lungs (in 66 percent), the central nervous system (in 56 percent), the heart (in 50 percent), and the skin (in 50 percent). Disseminated intravascular coagulation, which does not occur in primary or secondary antiphospholipid syndrome, occurs in approximately 25 percent of patients with catastrophic antiphospholipid syndrome. Microvascular manifestations include renal thrombotic microangiopathy, adult respiratory distress syndrome, cerebral microthrombi and microinfarctions, and myocardial microthrombi. Most patients with renal involvement have hypertension, often malignant, and approximately 25 percent require dialysis. The mortality rate is 50 percent, and death is usually due to multiorgan failure.\textsuperscript{85} Precipitating factors of catastrophic antiphospholipid syndrome include infections, surgical procedures, withdrawal of anticoagulant therapy, and the use of drugs such as oral contraceptives.\textsuperscript{85} Although the
pathophysiology of this disorder is poorly understood, thrombosis can be self-perpetuating in patients with an underlying hypercoagulable state. Thus, an initial thrombosis in a patient with the antiphospholipid syndrome may upset the balance of hemostasis and set in motion a process termed “thrombotic storm,” leading to multiple coagulative events throughout the body.86

Recommendations for the treatment of catastrophic antiphospholipid syndrome are based entirely on case reports. In the above series of 50 patients, recovery occurred in 14 of 20 patients (70 percent) treated with a combination of anticoagulants and steroids plus either plasmapheresis or intravenous immune globulin.85 The rationale for plasmapheresis derives from its documented effectiveness in treating the hemolytic–uremic syndrome and thrombotic thrombocytopenic purpura. The fibrinolytic agents streptokinase and urokinase have also been used to treat acute thrombotic microangiopathy with varying success.85,86 Since thrombosis tends to be a self-perpetuating process,86 an aggressive therapeutic approach is warranted in these patients.

TREATMENT

Treatments decisions fall into four main areas: prophylaxis, prevention of further thromboses of large vessels, treatment of acute thrombotic microangiopathy, and management of pregnancy in association with antiphospholipid antibodies. This section will review data on treatment in the first two areas. Treatment of thrombotic microangiopathy and management of pregnancy have been covered in the sections on catastrophic antiphospholipid syndrome and obstetrical considerations, respectively.

Prophylaxis

A case–control study nested within the Physicians’ Health Study examined the role of aspirin (325 mg per day) as a prophylactic agent.54 Aspirin did not offer protection against deep venous thrombosis and pulmonary embolism in male physicians with anticardiolipin antibodies.54 In contrast, aspirin may provide protection against thrombosis in women with the antiphospholipid syndrome and previous pregnancy loss.87 Hydroxychloroquine may be protective against thrombosis in patients with systemic lupus erythematosus and secondary antiphospholipid syndrome.88 Certainly, any factors predisposing the patient to thrombosis (Table 4) should be eliminated. In addition, modification of secondary risk factors for atherosclerosis seems prudent, given the putative role of vascular injury in promoting thrombosis associated with antiphospholipid antibodies89,90 and the association between antiphospholipid antibodies and oxidized LDL.31,32,36

Treatment after a Thrombotic Event

A beneficial role for anticoagulation in decreasing the rate of recurrent thrombosis has been shown in three retrospective studies.60,89,90 In a small series of 19 patients with the antiphospholipid syndrome, the rate of recurrence at eight years was 0 percent for the patients receiving oral anticoagulants.90 Among patients whose anticoagulant therapy was stopped, the rate of recurrence was 50 percent at two years and 78 percent at eight years.90 In two larger series, the level of protection against venous and arterial thrombosis correlated directly with the level of anticoagulation.60,89 Among 70 patients with the antiphospholipid syndrome, warfarin treatment of intermediate intensity (to achieve an international normalized ratio [INR] of 2.0 to 2.9) and high intensity (INR, 3.0 or more) significantly reduced the rate of recurrent thrombosis, whereas low-intensity treatment (INR, 1.9 or less) did not confer significant protection.89 Similar results were found in a series of 147 patients with the antiphospholipid syndrome.60 In both studies, aspirin alone was ineffective in reducing the rate of recurrent thrombosis.60,89

Several additional points warrant mention. First, discontinuation of warfarin seems to be associated with an increased risk of thrombosis89,60,90,91 and even death,69 especially in the first six months after anticoagulant therapy is stopped. Since the rate of recurrence among patients who have not received optimal anticoagulation can be as high as 70 percent,60,89,90 treatment with warfarin should probably be long term, if not lifelong. Second, it remains unclear whether patients with the antiphospholipid syndrome can be safely treated with intermediate-intensity warfarin treatment (INR, 2.0 to 2.9) or whether they require high-intensity treatment (INR, 3.0 or more). This is an important unresolved issue, since high-intensity warfarin carries a higher risk of hemorrhagic complications.92 In some studies, intermediate-intensity warfarin has appeared to be fully effective in suppressing coagulation, as assessed according to the levels of prothrombin fragments93 and the prevention of recurrent thrombosis.59,91,94,95 Finally, monitoring the level of anticoagulation in patients with the antiphospholipid syndrome is complicated by the lack of standardized reagents for the determination of the INR and the potential interference of antiphospholipid antibodies in this measurement.96

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