The antiphospholipid syndrome has been recognized only during the past 20 years. It is characterized by a thrombotic vasculopathy involving both arterial and venous blood vessels, recurrent fetal wastage, and thrombocytopenia. An international consensus on the primary classification criteria for the antiphospholipid syndrome was recently published. The evolving information has described 2 major clinical criteria. The first criterion is 1 or more clinical episodes of arterial venous thrombosis, confirmed by imaging or dipolar studies. Histopathology should demonstrate thrombosis without significant information. The second clinical manifestation is increased fetal wastage beyond the 10th week of gestation, with no evidence of abnormal fetal morphology as determined by ultrasonography or direct examination of the fetus. The syndrome is also characterized by 1 or more premature births of normal neonates at or before the 34th week of gestation secondary to severe pre eclampsia, eclampsia, or placental insufficiency. Furthermore, the syndrome may be characterized by 3 or more unexplained spontaneous miscarriages before the 10th week of gestation.

The laboratory criteria for the diagnosis of antiphospholipid syndrome involve 2 classes of antibody determination. These methods of determination are the standard enzyme-link immunoabsorption assay for beta-2 glycoprotein I-dependent anticardiolipin antibodies and a functional assay called the lupus anticoagulant. Numerous tests to detect prolonged anticoagulation time have been employed. These tests include activated partial thromboplastin time, kaolin clotting time, dilute Russell's viper venom time, and dilute prothrombin time. The lupus anticoagulant cannot be corrected by mixing with normal platelet-poor plasma; however, shortening or correction of the prolonged coagulation time can occur with the addition of excess phospholipid. A definite diagnosis of the antiphospholipid syndrome is made if one of the clinical criterion plus one of the laboratory criterion is met.

Information concerning the antiphospholipid syndrome is rapidly evolving. Anticardiolipin antibodies have been known since the turn of the last century, when a complement fixating extract of bovine hearts was employed to detect syphilis. In the 1940s, the antigen was determined to be cardiolipin. Further studies in patients with systemic lupus erythematosus determined a significant number of these patients had a false-positive test for syphilis using the Venereal Disease Research Laboratory assay. Unlike the syphilitic anticardiolipin antibody, which is not associated with thrombosis, patients with the primary or secondary (most commonly associated with systemic lupus erythematosus) antiphospholipid syndrome characteristically have a hypercoagulable state. The anticardiolipin antibody found in syphilis and other infectious diseases, such as leprosy, is directed against phospholipids. The functional assay fails to reveal the lupus anticoagulant.

The anticardiolipin antibody in primary and secondary antiphospholipid syndrome is directed against an anionic phospholipid bound to beta-2 glycoprotein I. Some anticardiolipin antibodies are directed against beta-2 glycoprotein I alone. These antibodies are associated with a positive lupus anticoagulant test.

The exact mechanisms by which antiphospholipid antibodies induce a hypercoagulable state are unknown, but judging by the multitude of specificities of the antiphospholipid antibodies, several theoretical mechanisms may be operative. These mechanisms include inhibition of activated protein seed pathway, upregulation of tissue factor pathway, inhibition of antithrombin III activity, disruption of annexin V shield on membranes, inhibition of anticoagulant activity of beta-2 glycoprotein I, inhibition of fibrinolysis, activation of endothelial cells, enhanced expression of adhesion molecules by endothelial cells, adherence of neu-
trophils and leukocytes to endothelial cells, activation and degranulation of neutrophils, potentiation of platelet activation, enhanced platelet aggregation, enhanced binding of beta-2 glycoprotein I to membranes, and enhanced binding of prothrombin to membranes.

These autoantibodies may also exert an anticoagulant effect by inhibiting activation of factor IX, inhibiting activation of factor X, and inhibiting of activation of prothrombin to thrombin.

**Clinical Manifestations**

All blood vessels, venous and arterial, are at risk for thrombosis in patients with this syndrome. Risks include deep vein thrombosis of the legs, hepatic portal vein and inferior vena cava thromboses, renal vein thromboses, pulmonary emboli, retinal artery and vein thromboses, and recurrent vascular events frequently resulting in multi-infarct dementia, intestinal infarction, infarction of the gall bladder, Budd-Chiari syndrome, adrenal infarction, angiomyocardial infarction, and nonbacterial thrombotic endocarditis (Libman-Sacks syndrome).

The cutaneous manifestations of the antiphospholipid syndrome are listed in the Table and include livedo reticularis with or without ulceration, acrocyanosis, acral infarcts with crusted ulcerations around the nail beds, peripheral gangrene, widespread hemorrhagic necrosis, recurrent deep vein thrombosis, necrotizing purpura and atrophie blanche-like ulcerations around the ankles. On rare occasions, malignant atrophic papulosis (Degos disease), characterized by wedge-shaped cutaneous ischemia and infarction, has been associated with anticardiolipin antibodies. The atrophie blanche is characterized by smooth, wide, scarred areas, predominantly on the lower legs and feet associated with telangectasia surrounding hyperpigmentation. These small ulcerations are quite painful and notoriously slow to heal.

**Treatment**

Managing thrombosis in patients with antiphospholipid syndrome has been an area of great interest. There is some evidence, but not strong evidence, indicating that 325 mg aspirin daily offered no protection against deep venous thrombosis in male patients with anticardiolipin antibodies. However, aspirin may provide protection against thrombosis in women with the antiphospholipid syndrome and previous pregnancy loss. Hydroxychloroquine may provide protection from thrombosis in patients with systemic lupus erythematosus.

The best evidence indicates anticoagulation is of value in decreasing the rate of recurrent thrombosis. Studies indicate high-intensity treatment (international normalized ratio [INR], 3.0 or more), is very effective in reducing the frequency of recurrent thrombosis in patients with antiphospholipid syndrome. However, high-intensity warfarin confers high risk of hemorrhagic complications. Unfortunately, it remains is unclear whether intermediate-range warfarin treatment (INR, 2.0–2.9) is effective in treating patients who have recurrent thrombosis secondary to the antiphospholipid syndrome.

**References**


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Table. Cutaneous Manifestations of Antiphospholipid Syndrome

- Livedo reticularis with or without ulcerations
- Peripheral ischemia - Raynaud's-like syndrome
- Acrocyanosis
- Acral infarcts with crusted ulcerations around nail beds
- Peripheral gangrene
- Atrophie blanche-like lesions about ankles
- Rarely, Degos disease