

# Antiphospholipid Thrombosis Syndromes

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Rodger L. Bick and William F. Baker, Jr

### The Relationship Between the Antiphospholipid Syndrome and Heparin-Induced Thrombocytopenia

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Debra A. Hoppensteadt and Jeanine M. Walenga

Antiphospholipid syndrome (APS) and heparin-induced thrombocytopenia (HIT) are immune-mediated thrombotic conditions caused by antibodies targeted to a protein-antigen complex. Although each disorder is attributed to two distinct antibodies, these autoimmune disorders are characterized by a similar pathogenesis that includes a hypercoagulable state, platelet activation, damage to the vascular endothelium, and inflammation. APS and HIT share similarities in the clinical presentation because each is associated with thrombocytopenia, a high risk of thrombosis in all venous and arterial sites, and catastrophic thrombotic outcomes occur if untreated. Understanding the disease process for one disorder could potentially aid in understanding the other disorder.

### Laboratory Evaluation of the Antiphospholipid Syndrome

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Debra A. Hoppensteadt, Nancy Fabbrini, Rodger L. Bick, Harry L. Messmore, Cafar Adiguzel, and Jawed Fareed

Antiphospholipid syndrome (APLS) is among the most common acquired blood protein defects that have been identified as leading to thrombosis. This article describes the laboratory diagnosis of APLS, including the detection of lupus anticoagulants, anticardiolipin antibodies, and subtypes of antiphospholipid antibodies.

### The Clinical Spectrum of Antiphospholipid Syndrome

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William F. Baker, Jr and Rodger L. Bick

Antiphospholipid syndrome (APS) is a disorder characterized by a wide variety of clinical manifestations. Virtually any organ system or tissue may be affected by the consequences of large- or small-vessel thrombosis. There is a broad spectrum of disease among individuals with antiphospholipid antibodies (aPL). Patients may exhibit clinical features suggesting APS but not fulfill the International Criteria for a “definite”

diagnosis. Seronegative APS patients demonstrate typical idiopathic thromboses but aPL are not initially detected. Patients defined with definite APS demonstrate nearly identical sites of venous and arterial thrombosis, regardless of the presence or absence of systemic lupus erythematosus. Microangiopathic APS may present with isolated tissue and organ injury or as the overwhelming “thrombotic storm” observed in catastrophic APS.

## **Antiphospholipid Antibody Syndrome and Autoimmune Diseases**

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Rochella A. Ostrowski and John A. Robinson

The arbitrary division between antiphospholipid antibody syndrome and secondary antiphospholipid antibody syndrome has not proven useful. Antiphospholipid antibodies in the absence of antiphospholipid antibody syndrome often occur as epiphenomena in many autoimmune diseases. They are very common in systemic lupus erythematosus. Antiphospholipid antibody syndrome is a significant comorbidity in lupus but is uncommon in Sjögren’s syndrome, rheumatoid arthritis, scleroderma, and systemic vasculitis. Evidence is growing that antiphospholipid antibodies may have a pathogenic role in pulmonary hypertension and accelerated atherosclerosis of autoimmune diseases.

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Sari Weinstein and Warren Piette

Many different cutaneous lesions or cutaneous-systemic syndromes can be the presenting sign of antiphospholipid antibody syndrome (APS), or can develop during the course of disease. None of these conditions are specific for APS. Livedo reticularis or racemosa is commonly seen in APS, but it is one of the least specific findings. Other diseases are less commonly seen, in either their idiopathic or APS-associated form, but are more suggestive of APS. APS should be considered in patients who may appear to have idiopathic livedo reticularis with cerebrovascular accidents (Sneddon’s syndrome), atrophic blanche, livedoid vasculitis, malignant atrophic papulosis, or anetoderma. Finally, retiform (branching, stellate) purpura or necrosis is perhaps the most characteristic cutaneous lesion of many different cutaneous microvascular occlusion syndromes, including APS.

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Brian R. Long and Ferdinand Leya

The antiphospholipid syndrome (APS) is associated with various cardiovascular manifestations. These include accelerated atherosclerosis, valvular heart disease, intracardiac thrombi, myocardial and pericardial involvement, cerebral and peripheral vascular disease, and premature

restenosis of vein grafts and coronary stents. This article reviews the prevalence and proposed mechanisms of the various cardiovascular diseases associated with APS. It concludes with a discussion of current recommendations for treatment of these conditions.

### **Antiphospholipid Syndrome: Role of Antiphospholipid Antibodies in Neurology**

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Rima M. Dafer and José Biller

Antiphospholipid antibodies (aPLs) are acquired antibodies against anionic phospholipid containing moieties in cell membranes. Their presence often is associated with the antiphospholipid syndrome (APS), an acquired autoimmune prothrombotic syndrome associated with thrombosis in the arterial and venous circulations, recurrent unexplained fetal loss, and thrombocytopenia. The association of aPLs with other nonthrombotic neurological disorders remains of unclear significance. This article reviews the definition of APS, its clinical presentations, and therapeutic approaches.

### **Antiphospholipid Syndrome in Pregnancy**

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Rodger L. Bick

During the past 5 years the author and his colleagues have assessed carefully 351 women referred for evaluation of thrombosis and hemostasis after they had suffered recurrent miscarriages. This article describes the flow protocol the author and associates follow to maximize success and keep the costs of evaluation of recurrent miscarriage syndrome/infertility at a minimum while providing the best chances for defining a cause and thus providing optimal therapy for successful term pregnancy outcome. It presents the outcomes of the author's protocol and those of others in treating women who have antiphospholipid syndrome and who have suffered recurrent miscarriages.

### **Antiphospholipid Antibodies and Malignancy**

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Chi Pham and Yu-Min Shen

Antiphospholipid antibody syndrome is characterized clinically by venous or arterial thrombosis, recurrent fetal loss, or placental insufficiency in women. This article describes the prevalence of malignancy, the manifestations, and the prognosis for this condition.

### **Antiphospholipid Syndromes in Infectious Diseases**

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Navin M. Amin

Antiphospholipid antibodies are essential in the diagnosis of antiphospholipid syndrome (APS), or the classic "Hughes syndrome," which is a systemic disorder that is autoimmune in nature. They are also found in various infections in low titers without any evidence of thrombotic manifestations of APS. However, in a few infections, when antiphospholipid antibodies are associated with protein cofactor, there

can be associated thrombosis. Different infections are also responsible for triggering a subset of lethal APS, acute catastrophic APS. This situation requires prompt diagnosis and aggressive treatment of the infection to prevent severe complications.

### **Treatment Options for Patients Who Have Antiphospholipid Syndromes**

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Rodger L. Bick and William F. Baker, Jr

The antiphospholipid thrombosis syndrome, associated with anticardiolipin (aCL) or subgroup antibodies, can be divided into one of six subgroups (I–VI). There is little overlap (about 10% or less) between these subtypes, and patients usually conveniently fit into only one of these clinical types. Although there appears to be no correlation with the type, or titer, of aCL antibody and type of syndrome, the subclassification of thrombosis and aCL antibody patients into these groups is important from the therapy standpoint. This article also reviews the clinical presentations associated with each of these six subgroups.

### **Controversies and Unresolved Issues in Antiphospholipid Syndrome Pathogenesis and Management**

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William F. Baker, Jr, Rodger L. Bick, and Jawed Fareed

While much is understood concerning the clinical features of patients with antiphospholipid syndrome (APS), many issues remain. The proper designation of patients with “definite” APS and the correct categorization of patients by both laboratory and clinical features are matters of ongoing debate. Recent proposals have identified new subsets of patients who have many typical features of APS but either do not fit the criteria for a “definite” diagnosis or have initially negative laboratory tests for antiphospholipid antibodies. Meanwhile, decisions about laboratory tests are based on expert opinion, rather than the results of controlled trials. As for treatment, many guidelines are offered, but few are backed by data from strong clinical trials. This article summarizes the clinical questions remaining to be answered and debates concerning pathogenesis, diagnosis, and management.

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