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# Antiphospholipid Syndrome

Diane George[a,*], Doruk Erkan[b]

[a]*Department of Rheumatology, Yale School of Medicine, New Haven, CT*
[b]*Barbara Volcker Center for Women and Rheumatic Diseases, Hospital for Special Surgery, Weill Medical College of Cornell University, New York, NY*

**Abstract** The antiphospholipid syndrome (APS) is an autoimmune systemic disease that is diagnosed when there is vascular thrombosis and/or pregnancy morbidity occurring with persistently positive antiphospholipid antibodies (aPL) (lupus anticoagulant test, anticardiolipin antibodies, and/or anti–$\beta_2$-glycoprotein I antibodies). Although International APS Classification Criteria have been formulated to provide a uniform approach to APS research, aPL may cause a spectrum of clinical manifestations, some of which are not included in these criteria. The main aPL-related cardiac manifestations include valve abnormalities (vegetations and/or thickening), myocardial infarction (MI), intracardiac thrombi, and myocardial microthrombosis. In this article, we will review the definition, etiopathogenesis, clinical manifestations, diagnosis, and treatment of aPL-related clinical events with emphasis on cardiac manifestations. (Prog Cardiovasc Dis 2009;52:115-125)


*Keywords:* Antiphospholipid syndrome; Anticardiolipin antibodies; Lupus anticoagulant; Myocardial infarction

The antiphospholipid syndrome (APS) is a multisystem disorder defined as vascular thromboses (venous, arterial, or small vessel) and/or pregnancy morbidity (fetal loss, premature birth, or recurrent embryonic losses) occurring in those with persistent autoantibodies directed against phospholipid-binding plasma proteins (antiphospholipid antibodies [aPL]).[1] Although a broad spectrum of aPL exists, the universally accepted diagnostic aPL tests are lupus anticoagulant (LA) functional coagulation assay; anticardiolipin antibody (aCL) enzyme-linked immunosorbent assay (ELISA); and anti–$\beta_2$-glycoprotein I antibody (a$\beta_2$GPI) ELISA. An international consensus statement on the APS classification was published in 1999 after a workshop in Sapporo, Japan,[1] and updated in 2006 after another workshop in Sydney, Australia[2] (Table 1).

Antiphospholipid antibodies were first described in 1906 in patients with syphilis. These complement-fixing antibodies (aCL) reacting with extracts from bovine hearts (mitochondrial phospholipid cardiolipin)[3] formed the basis for the serologic syphilis test (Venereal Disease Research Laboratory [VDRL] assay). Mass population screening for syphilis demonstrated that patients with systemic lupus erythematosus (SLE) without clinical syphilis had persistently false-positive VDRL tests.[4,5] As false-positive VDRL tests in patients with SLE were also found to be associated with prolonged in vitro coagulation, the term *lupus anticoagulant* was introduced. It was not until the early 1980s that an association between thrombotic events and aPL was recognized, and not until the early 1990s that the primary target antigen that aPL bind (phospholipid-binding plasma protein $\beta_2$GPI) were identified.

## Epidemiology

Antiphospholipid syndrome can occur in otherwise healthy persons without an underlying systemic autoimmune disease (primary APS) or in the presence of other systemic autoimmune diseases, particularly SLE. The prevalence of aPL ranges from 1% to 10% in the general population (usually transient low-titer aCL with the

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* Address reprint requests to Diane George, MD, Department of Rheumatology, Yale School of Medicine, 300 Cedar Street, TAC 541, PO BOX 208031, New Haven, CT 06520.
*E-mail address:* dtg24@pantheon.yale.edu (D. George).

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Table 1
Updated Sapporo classification criteria for the antiphospholipid syndrome[2]

*Clinical criteria*

1. Vascular thrombosis
   One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ.
2. Pregnancy morbidity
   (a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th wk of gestation, *or*
   (b) One or more premature births of a morphologically normal neonate before the 34th wk of gestation because of eclampsia, severe preeclampsia, or recognized features of placental insufficiency, *or*
   (c) Three or more unexplained consecutive spontaneous abortions before the 10th wk of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

*Laboratory criteria*

1. Lupus anticoagulant present in plasma, on 2 or more occasions at least 12 wk apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis
2. Anticardiolipin antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (ie, >40 GPL or MPL, or greater than the 99th percentile), on 2 or more occasions, at least 12 wk apart, measured by a standardized ELISA.
3. Anti–$\beta_2$-glycoprotein I antibody of IgG and/or IgM isotype in serum or plasma (in titer greater than the 99th percentile) present on 2 or more occasions, at least 12 wk apart, measured by a standardized ELISA

Definite APS is present if at least one of the clinical criteria and one of the laboratory criteria are met. Classification of APS should be avoided if less than 12 weeks or more than 5 years separate the positive aPL test and the clinical manifestation. In studies of populations of patients who have more than one type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to (a), (b), or (c) above.
*Abbreviation*: ELISA, Enzyme-linked immunosorbent assay.

elderly at the higher end of the range), 16% in patients with rheumatoid arthritis, and 30% to 40% in patients with SLE.[6,7]

The strength of association between aPL and thrombosis varies among studies (from no to strong association), depending on the aPL test type, study design, and clinical populations studied. Based on a limited number of uncontrolled and not risk-stratified studies, asymptomatic (no history of vascular or pregnancy events) aPL-positive patients have 0% to 4% risk of annual thrombosis. Patients with other autoimmune diseases such as SLE are at the higher end of the range.[8] Approximately 5% to 20% of patients presenting with thrombosis possess aPL.[7,9]

## Etiopathogenesis

Antiphospholipid antibodies are a heterogeneous family of autoantibodies directed against phospholipid-binding plasma proteins, most commonly the natural anticoagulant $\beta_2$GPI. The predominant hypothesis regarding the origin of aPL states that an incidental exposure to environmental agents with $\beta_2$GPI-like peptides induces aPL in susceptible individuals (molecular mimicry).[10]

Table 2
The clinical apectrum of aPL

1. Antiphospholipid syndrome with vascular events
2. Antiphospholipid syndrome with only pregnancy morbidity
3. Noncriteria aPL manifestations: livedo reticularis, thrombocytopenia, hemolytic anemia, antiphospholipid antibody nephropathy, cardiac valve disease
4. Catastrophic antiphospholipid syndrome
5. Asymptomatic* aPL positivity

* No history of thrombosis or pregnancy morbidity as per the Sapporo Criteria.[1]

In experimental models, passive and active immunization with aPL induces fetal loss as well as the serologic and hematologic manifestations of aPL.[11] The proposed mechanism of aPL-mediated thrombosis is the binding of aPL to endothelial cells (via $\beta_2$GPI) inducing a procoagulant state through the induction of adhesion molecules, tissue factor expression (a physiologic initiator of coagulation and thrombin formation), and complement activation (C3 and C5a are potent mediators of platelet and endothelial cell activation).[12,13]

In humans, although cross-sectional and prospective cohort studies demonstrate a predictive role of aPL for future vascular events, a direct casual association between aPL and thrombosis does not exist. However, there is substantial support that other thrombotic risk factors in aPL-positive individuals influence the risk of thrombosis in an additive manner.[14] In the currently accepted "second-hit hypothesis," a trigger event (such as oral contraceptives or surgical procedures), which may not be otherwise clinically important alone to cause thrombosis, is required for an aPL-positive patient to develop a vascular event.

## Clinical manifestations

A spectrum of aPL-related clinical manifestations exists (Table 2). Although persistently aPL-positive patients with vascular and/or pregnancy events fulfill the Updated Sapporo APS Classification Criteria,[2] asymptomatic (no history of vascular and/or pregnancy events) aPL-positive patients as well as those with only noncriteria aPL features are also included in this spectrum.

### *Vascular events*

Although any vasculature can be affected by thrombosis, stroke and transient ischemic attack are the most common presentations of arterial thrombosis, whereas deep vein thrombosis (with or without pulmonary embolism) is the most common presentation of venous thrombosis in APS. Antiphospholipid antibodies can cause both arterial and venous thrombosis in the same patient; recurrent thromboses tend to occur in the same vascular distribution (ie, arterial followed by arterial, and venous followed by venous).[15]