



## Clinical Guide - Antiphospholipid Syndrome

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### 1. DEFINITION

- The antiphospholipid syndrome (APS) is increasingly recognized as an important clinical disorder, but one which has engendered confusion in both its clinical and laboratory aspects. APS is an acquired condition and should not be evaluated in patients undergoing a work-up of familial hypercoagulability.

According to consensus guidelines, the diagnosis of APS requires the presence of both clinical and laboratory criteria<sup>(1,2)</sup>.

#### Clinical Criteria:

##### Thrombosis

- objectively confirmed arterial or venous thrombosis

##### Obstetrical complications

- One or more pregnancy loss(es)  $\geq 10$  weeks
- $\geq 3$  consecutive spontaneous abortions  $< 10$  weeks
- $\geq 1$  premature births ( $\leq 34$ th week of gestation) of a normal normal neonate delivered because of severe pre-eclampsia, eclampsia, or severe placental insufficiency

The manifestations of APS are similar whether the condition is primary, or whether it occurs in the setting of underlying connective tissue disease (e.g. lupus erythematosus) in which case it is referred to as "secondary" APS.

The clinical manifestations associated with APS are not unique to this disorder; thus laboratory evaluation is critical to determine whether a clinical event is attributable to APS in a given patient.

Although not included in "consensus conference" definitions of the syndrome, thrombocytopenia (which may be severe and is due to an ITP-like mechanism) is also common in patients with APS.

#### Laboratory criteria:

Many laboratory tests have been used to detect antiphospholipid antibodies. These assays fall in two general categories: Coagulation assays and antibody binding assays.

**Lupus anticoagulants:** An antibody that interferes with a phospholipid-dependent coagulation test is referred to as a "lupus anticoagulant" (LA). This is a misnomer as many patients with a LAC do not have lupus erythematosus and about 60% of patients with lupus erythematosus have a detectable lupus anticoagulant. These antibodies rarely exhibit an anticoagulant effect in vivo.

**Anticardiolipin antibodies (aCL):** Antibodies identified in assays of this type may bind directly to phospholipids or, more commonly, to other proteins bound to phospholipids, of which beta-2-glycoprotein I appears to be the most important. Assays which detect only antibodies directed against beta-2-glycoprotein 1 antibodies (beta-2-GP1 antibody) are available. Whether they better predict complications of APS is unknown.

- By the consensus guidelines, the diagnosis of APS requires at least one of the clinical criteria plus the presence of either a LA, an aCL, or a direct beta-2-glycoprotein 1 antibody
- The LA, aCL, or beta-2-GP1 antibody must persist for at least 12 weeks before the diagnosis of APS may be made.

In clinical practice the consensus guidelines may be overly restrictive. For example, a patient with a positive lupus anticoagulant test that is repeated and confirmed on at least 2 occasions 12 weeks apart, who has persistent thrombocytopenia, and who suffers recurrent transient ischemic attacks does not meet "consensus criteria" for harbouring APS. However most experts would consider this patient to have manifestations of their antiphospholipid antibodies, and many would label them as having APS.

## 2. LABORATORY TESTING

When investigating patients with thrombosis for suspected hypercoagulability, other investigations, in addition to tests for antiphospholipid antibodies, are generally in order. As APS is not a hereditary condition, antiphospholipid antibody tests are not indicated in the work up of familial hypercoagulability. Please refer to the guideline, "Investigation of Hypercoagulable States". Lupus anticoagulant assays

Clinical laboratories should offer lupus anticoagulant testing as a specific service. Because of the variable effect of lupus anticoagulants on different assays, laboratories should perform at least two different coagulation-based tests (1). Numerous tests for LA are available including:

- APTT. The most widely used test is the aPTT, performed using a sensitive reagent. Note: Although a prolonged aPTT may reflect a LA, the sensitivity of aPTT reagents to prolongation by LA is highly variable and different reagents will give different results for individual patients with APS. Hence, a normal aPTT obtained with a standard reagent does not rule out a LA.
- dilute Russell viper venom time (DRVVT)
- dilute prothrombin time
- thromboplastin inhibition test

Lupus anticoagulants are more strongly associated with thrombosis than are aCL or Beta-GP1 antibodies

### Anticardiolipin assays

The aCL is an ELISA type assay, and is usually performed with separate assays for IgG and IgM antibodies.

Although several variations on this test have been described, there is no consensus yet that other phospholipid based binding assays should be used in place of or in addition to the aCL in routine practice.

- IgG aCL may be more strongly associated with thrombosis than IgM aCL.
- Only higher titres of aCL (e.g. above 40 units) are clearly associated with thrombotic risk.

### Beta-2-GPI assays

These assays are also ELISA but are not dependent on negatively charged phospholipid (i.e. cardiolipin as in aCL). They may be either IgG or IgM.

## 3. TREATMENT

### Thrombosis

The immediate treatment of an acute thrombotic event in a patient with APS is the same as for other patients with thrombosis (usually anticoagulation with heparin or low molecular weight heparin). Low molecular weight heparin (LMWH) may be preferred in patients whose baseline aPTT is prolonged by a LA because of the difficulties monitoring unfractionated heparin in this situation. Alternately, unfractionated heparin may be used and monitored by heparin levels. There are no trial data to support the use of corticosteroids or other immunosuppressive treatments in patients with primary APS.

The risk of recurrent thrombosis in patients with APS is high. The controversial issues are the duration of the anticoagulation, the intensity of anticoagulation, and the best way to monitor warfarin. Consultation with a specialist is recommended for most patients with APS.

Duration: It is generally suggested that anticoagulation be continued indefinitely if the thrombotic event was otherwise unprovoked, though this has not been prospectively validated in clinical trials. It is not known whether anticoagulation may be stopped safely if the laboratory criteria for APS are no longer present on later follow-up; this approach seems most reasonable in patients with primary APS and repeatedly negative tests on follow-up, particularly those whose only laboratory manifestation were low or

moderate titre anticardiolipin antibodies.

**Intensity:** Most patients with venous or arterial thrombosis and APS do well with conventional warfarin treatment (target INR 2.0 - 3.0) <sup>(3)</sup>. It is recommended that patients with recurrent thrombosis despite conventional doses of warfarin should maintain an INR of 3.0 - 4.0 or should receive an alternate therapy such as therapeutic dose low molecular weight heparin (LMWH). The benefit of adding aspirin in arterial disease is not clear, and is likely to increase the risk of bleeding.

**Monitoring:** Occasionally, a LA will prolong the INR. In such patients, alternate monitoring approaches may be necessary <sup>(4)</sup>.

### **Pregnancy**

For women with APS-associated complications of pregnancy, prophylaxis with LMWH or heparin, with or without ASA, should be considered although clear evidence that this intervention improves outcome is lacking.

Prophylactic LMWH or heparin for pregnant women with APS and previous thrombosis is recommended by extrapolation from the experience with other thrombophilic disorders, but this has not been specifically addressed in trials. Please refer to the guideline, "Thrombosis in Pregnancy". Specialist referral is appropriate in either of these circumstances.

Although APS may be associated with a number of other manifestations such as thrombocytopenia and livedo reticularis, there is no evidence to support treatment with anticoagulants for those conditions.

### **References**

1. Miyakis S et al. International consensus statement of an update of the classification criteria for definite antiphospholipid syndrome. *J Thromb and Haemostas* 4:295-306,2006
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