

THROMBOPHILIA: ANTIPHOSPHOLIPID ANTIBODY SYNDROME



Thrombosis Canada
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OBJECTIVE:

To outline the main clinical and laboratory features of the antiphospholipid antibody syndrome (APS) and to describe its anticoagulant management.

BACKGROUND:

APS is an acquired hypercoagulable state characterized by the persistent presence of autoantibodies against proteins bound to cell membrane phospholipids. It is associated with venous and/or arterial thromboembolism, and/or pregnancy complications such as recurrent miscarriage, late pregnancy loss or pre-eclampsia. There may be accompanying features such as thrombocytopenia, livedo reticularis, renal disease and neurologic symptoms. APS may occur in the setting of underlying autoimmune disease such as systemic lupus erythematosus (**secondary APS**) or may occur in isolation (**primary APS**). APS associated with pregnancy morbidity and no thrombosis is often termed obstetric APS.

DIAGNOSIS OF APS:

The diagnosis of APS should be made carefully and in consultation with a specialist because of the potential for false positive laboratory tests. In addition, a diagnosis of APS has important treatment implications because such patients may require long-term anticoagulant therapy. APS is diagnosed based on expert consensus criteria (Sapporo criteria) and requires the presence of at least one laboratory and one clinical criterion for definite APS.

Laboratory criteria:

Laboratory testing should be done at a time remote from an acute thrombotic event and preferably off anticoagulants because of the potential for false positive laboratory tests in this clinical setting. A positive result requires confirmation and documentation of persistent positivity at least 3 months later.

Currently, 3 types of antibodies are accepted for the laboratory criteria for definite APS:

- 1) **Lupus anticoagulant (LA)** or non-specific inhibitor. These antibodies are present (positive) or absent (negative). Note that in laboratories that use a lupus-sensitive activated partial thromboplastin time (aPTT) reagent, LA can result in an elevated aPTT. The presence of LA is more strongly associated with thrombosis than the presence of other antibodies listed below. LA testing should not be performed in patients who are receiving heparin, low molecular weight heparin or direct oral anticoagulants given the potential for false positive results. LA testing must be done with caution in patients taking Vitamin K antagonists (VKA) such as warfarin, and in patients with factor deficiencies, as these can also result in a false positive result.

- 2) **Anticardiolipin (aCL) antibody** (IgG or IgM) present in medium or high titre (i.e. >40 GPL units or >99th percentile).
- 3) **Anti-beta2 glycoprotein-I antibody** (IgG or IgM) with a titre >99th percentile.

Patients testing positive for all 3 antibodies (“triple positivity”) appear to have the highest risk of thrombotic events.

Clinical criteria:

1) Vascular thrombosis:

- One or more clinical episodes of arterial, venous or small vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by objective criteria (i.e. unequivocal findings on appropriate imaging studies or histopathology). For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall. Superficial venous thrombosis is not part of the criteria.

2) Obstetrical complications:

- Three or more unexplained, consecutive spontaneous abortions before the 10th week of gestation, with exclusion of maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes, or
- One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or
- One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe pre-eclampsia according to standard definitions or (ii) recognized features of placental insufficiency.

ANTICOAGULANT THERAPY OF APS:

Due to the complexity and potential severity of APS, treatment of patients with APS should be undertaken in consultation with a specialist.

Acute thrombosis: The treatment of an acute venous thrombosis in a patient with APS is generally the same as for patients without APS. Low molecular weight heparin (LMWH) may be preferred over unfractionated heparin (UFH) in patients with venous thrombosis whose baseline aPTT is prolonged by a LA because of the difficulties with monitoring UFH in this situation. Clinical trials evaluating the DOACs are ongoing and indirect data using laboratory endpoints suggest DOACs may be less effective in these patients. The treatment of patients with an acute arterial thrombosis is controversial, with antiplatelet therapy or anticoagulant therapy as options. There are no data to support the use of corticosteroids or other immunosuppressive therapy in patients with APS.

Long-term anticoagulant management: Since the risk of recurrent thrombosis in patients with APS is high, long-term anticoagulation is usually required. Consultation with a specialist is recommended for patients with APS. All patients with APS should have aggressive reduction of their modifiable cardiovascular risk factors. Patients who also have systemic lupus erythematosus may benefit from the addition of hydroxychloroquine. It is not known whether anticoagulation may be stopped safely if the laboratory criteria for APS are no longer present on later follow-up.

Intensity of anticoagulant therapy: Most patients with venous or arterial thrombosis and APS should receive conventional warfarin therapy, administered to achieve an international normalized ratio (INR) range of 2.0-3.0. In patients with recurrent thrombosis, despite conventional doses of warfarin and optimal time in therapeutic range, treatment options include higher-intensity warfarin (INR range: 3.0-4.0) or therapeutic-dose LMWH. The benefit of adding acetylsalicylic acid (ASA) in patients with arterial thrombosis is not clear and is likely to increase the risk of bleeding.

Laboratory monitoring of anticoagulant therapy: Some patients with APS have a prolongation in the INR before anticoagulant therapy is commenced. In such patients, alternate monitoring approaches may be necessary. Consultation with an expert is strongly suggested to prevent under-treatment.

Direct Oral Anticoagulants (DOACs) in APS: The role of the direct oral anticoagulants (apixaban, dabigatran, edoxaban, rivaroxaban) is unclear in patients with APS at this time; trials are currently addressing their efficacy.

SPECIAL CONSIDERATIONS:

Asymptomatic (without thrombosis) patients with positive antiphospholipid test results:

Due to the widespread use of the aPTT in clinical practice, a LA may be detected in otherwise asymptomatic patients who do not have the clinical criteria for APS. A detailed clinical history should be taken to exclude thrombotic events that were missed previously. Although asymptomatic patients with both LA and other APS markers may be at increased risk for thrombotic complications, there is no consensus on the role of primary antithrombotic prophylaxis. These individuals should receive aggressive thromboprophylaxis in high-risk situations. 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 alone.

Pregnant women with antiphospholipid antibodies: It is recommended that pregnant women with persistent antiphospholipid antibodies who have suffered recurrent pregnancy loss receive prophylactic-dose LMWH/UFH combined with low-dose ASA for the duration of their pregnancy; however, it is important to note that the efficacy and safety of such management has not been validated in well-designed clinical trials. The role of prophylactic-dose LMWH/UFH and low-dose ASA in women with persistent antiphospholipid antibodies and a single late loss has not been well studied. Low-dose ASA is often used in pregnant women with persistent antiphospholipid antibodies to reduce the risk of pre-eclampsia.

Pediatrics: For children with venous thromboembolism (VTE) in the setting of antiphospholipid antibodies, anticoagulation as per general recommendations for VTE management in children is recommended. Pediatricians with expertise in thromboembolism should manage, where possible, pediatric patients with thromboembolism. When this is not possible, a combination of a neonatologist/pediatrician and a pediatric hematologist or an adult hematologist, supported by consultation with an experienced pediatric hematologist, is recommended.

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OTHER RELEVANT THROMBOSIS CANADA CLINICAL GUIDES:

- Deep Vein Thrombosis (DVT): Treatment

- Pediatric Thrombosis
- Pregnancy: Thromboprophylaxis
- Pregnancy: Venous Thromboembolism Treatment
- Pulmonary Embolism (PE): Treatment
- Unfractionated Heparin, Low-molecular-weight Heparin and Fondaparinux
- Warfarin

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Date of Version: 2017Sept13

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