



TARGET AUDIENCE: All Canadian health care providers (i.e. primary care physicians, internists, subspecialists, surgeons, pharmacists, nurse practitioners, nurses, pharmacists, dentists).

OBJECTIVE:

To outline the main clinical and laboratory features of the antiphospholipid antibody syndrome, and to describe anticoagulant management.

ABBREVIATIONS:

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| aCL | anticardiolipin |
| APS | antiphospholipid antibody syndrome |
| aPTT | activated partial thromboplastin time |
| ASA | acetyl salicylic acid |
| INR | international normalized ratio |
| LA | lupus anticoagulant |
| LMWH | low-molecular-weight heparin |
| UFH | unfractionated heparin |
| VTE | venous thromboembolism |

BACKGROUND:

Antiphospholipid antibody syndrome (APS) is an acquired hypercoagulable state caused by antibodies against cell membrane phospholipids that is associated with venous and arterial thromboembolism, as well as pregnancy complications such as miscarriage, stillbirth or pre-eclampsia. The clinical manifestations of APS are similar whether the condition is on its own (primary APS), or whether it occurs in the setting of underlying connective tissue disease such as systemic lupus erythematosus, in which case it is referred to as secondary APS.

DIAGNOSIS:

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 may have important treatment implications because if APS is confirmed such patients may require indefinite (or lifelong) anticoagulant therapy. The diagnosis of APS requires the presence of at least one laboratory and one clinical criterion.

Laboratory criteria:

- a) A positive lupus anticoagulant (LA), also referred to as a non-specific inhibitor, because it can cause an elevated activated partial thromboplastin time (aPTT), present on 2 or more occasions at least 12 weeks apart. The presence of LA is more strongly associated with thrombosis risk than the presence of other laboratory criteria listed below.
- b) Anticardiolipin (aCL) antibody (IgG or IgM), present in medium or high titre (i.e. > 40 GPL units or > 99th percentile) on 2 or more occasions at least 12 weeks apart.
- c) Anti-beta2 glycoprotein-I antibody (IgG or IgM) (in titre > 99th percentile) present on 2 or more occasions at least 12 weeks apart.

Laboratory testing should be done at a time remote from an acute thrombotic event because of the potential for false positive laboratory tests in this clinical setting.

Clinical criteria:

- a) Objectively confirmed arterial or venous thrombosis.
- b) Obstetrical complications:
 - ≥ 1 pregnancy loss ≥ 10 weeks gestation
 - ≥ 3 consecutive spontaneous abortions < 10 weeks gestation
 - ≥ 1 premature births (≤ 34th week gestation) of a normal neonate delivered because of severe pre-eclampsia, eclampsia, or severe placental insufficiency.

ANTICOAGULANT THERAPY:

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 acute thrombosis in a patient with APS is 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 monitoring UFH in this situation. There are no data to support the use of corticosteroids or other immunosuppressive therapy in patients with APS.

Long-term anticoagulant management: The risk of recurrent thrombosis in patients with APS is high. Consultation with a specialist is recommended for patients with APS.

- **Duration of anticoagulant therapy:** In general, anticoagulation should be continued indefinitely in patients with thrombosis (venous or arterial) and confirmed APS. 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 aCL antibodies.

- **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, treatment options include higher-intensity warfarin (INR range: 3.0-4.0) or therapeutic-dose LMWH. The benefit of adding acetyl salicylic acid (ASA) in patients with arterial thrombosis is not clear and is likely to increase the risk of bleeding.
- **Laboratory monitoring of anticoagulant therapy:** Occasionally, patients with a positive LA test will have a prolongation in the INR before anticoagulant therapy is commenced. In such patients, alternate monitoring approaches may be necessary.

MANAGEMENT OF PREGNANCY:

It is recommended that pregnant women with APS who have had previous thrombosis or have suffered obstetrical complications (i.e. recurrent pregnancy loss) receive prophylactic-dose LMWH/UFH combined with low-dose ASA for the duration of their pregnancy, but the efficacy and safety of such management has not been validated in well-designed clinical trials. Please refer to the Thromboprophylaxis: Pregnancy guide. 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.

SPECIAL CONSIDERATIONS:

Asymptomatic (without thrombosis) patients with positive APS tests:

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 recent past events indicating that the patient was probably a missed case of APS. Although asymptomatic patients with both LA and APS markers may be at increased risk for thrombotic complications, there is no consensus on the role of antithrombotic prophylaxis.

PEDIATRICS:

For children with venous thromboembolism (VTE) in the setting of antiphospholipid antibodies, anticoagulate as per general recommendations for VTE management in children (see pediatrics guide). 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 an adult hematologist, supported by consultation with an experienced pediatric hematologist, is recommended.

REFERENCES:

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