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 thrombosis (venous, arterial, or microvascular) 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). The term ‘obstetric APS’ denotes the condition of APS with pregnancy morbidity but without thrombosis.

DIAGNOSIS:
The diagnosis of APS should be made carefully and in consultation with a specialist because of the potential for both false positive and false negative 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 (revised Sapporo criteria) and requires the presence of at least one laboratory and one clinical criterion.

Laboratory criteria:
If laboratory testing is undertaken in a patient with a history of recent thrombosis, it should be performed after a minimum of 3 months of anticoagulant therapy has been completed. 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 (LMWH), or direct oral anticoagulants (DOACs) given the potential for false positive or false negative results. LA testing should also be avoided 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 of microvascular thrombosis). 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.

**Antithrombotic therapy of APS:**

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

**Acute venous thrombosis:** LMWH is 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. Patients with a known high-risk APL profile (either triple positivity, or persistently positive lupus anticoagulant +/- moderate-to-high titre ACL IgG or beta-2-glycoprotein-I IgG antibodies) and those with arterial events should be treated with warfarin administered to a target INR of 2.0 to 3.0 (see “DOACs in APS” below). Whether DOACs can be used in lower risk patients is unknown although available evidence supports the safety of this approach (see below).

**Acute arterial thrombosis:** The treatment of patients with an acute arterial thrombosis is controversial as data are limited. However, most guidelines currently recommend anticoagulation therapy with warfarin in this setting.

A study assessed secondary ischemic stroke prevention with acetylsalicylic acid (ASA) 325 mg daily versus warfarin (international normalized ratio [INR] target of 1.4 – 2.8). A subset of this study included patients with antiphospholipid antibodies present and found no difference between the two treatment arms. However, the antibodies were generally low titre and only measured once, making it unclear if these patients truly had APS. Antiplatelet therapy or anticoagulant therapy are seen as
options in this setting but anticoagulant therapy with warfarin administered to a target INR of 2.0 to 3.0 is generally preferred.

**DOACs in APS:** Randomized clinical trials have found rivaroxaban to be less effective than warfarin administered to a target INR of 2.0 to 3.0 in preventing recurrent thrombosis in patients with APS. This includes patients with triple positivity and patients with a high-risk APL profile (persistent lupus anticoagulant positive +/- moderate-to-high titre ACL IgG or beta-2-glycoprotein-I IgG antibodies). In these studies, patients on rivaroxaban experienced more thrombotic episodes and bleeding than those on warfarin.

A patient-level data meta-analysis of 47 studies analyzed data of rivaroxaban (n = 290), apixaban (n = 13), and dabigatran (n = 144) users with APS. Recurrent thrombosis occurred 16.9% of rivaroxaban/apixaban users and 15% of dabigatran users at a mean follow up of 12.5 months. A prior history of arterial thrombosis was also associated with a higher risk of recurrent thrombosis.

Therefore, warfarin administered to a target INR of 2.0 to 3.0 is currently the preferred long-term anticoagulant for patients with a high-risk APL profile. Patients who decline warfarin or who cannot tolerate warfarin should be informed about the available evidence, possible reduced benefit of DOACs relative to warfarin, and referred to a hematologist or thrombosis specialist. There is uncertainty about which antithrombotic therapy is preferred for non-high-risk profiles and consultation with a hematologist or thrombosis specialist is recommended.

**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 INR range of 2.0-3.0. Randomized controlled trial data supports this suggestion.

There is limited data with regards to patients who develop 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), therapeutic-dose LMWH, or the combination of low dose ASA and conventional warfarin therapy. In all cases the suspected recurrence should be objectively confirmed, and the adequacy of anticoagulation assessed before an event is labelled a recurrence, given the long-term implications of failure of therapeutic anticoagulation.

**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. Point of care INR determinations appear to be particularly prone to error in patients with APS. Periodic reconfirmation of the reliability of test results is required for patients being monitored with point of care devices.
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 previously missed. 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 other manifestations such as immune thrombocytopenia and livedo reticularis; there is no evidence to support treatment with anticoagulants for those conditions alone. A small study examined use of ASA for primary prophylaxis in patients with APS and found no benefit.

Pregnant women with antiphospholipid antibodies: It is recommended that pregnant women who meet criteria for obstetric APS without a history of venous/arterial thrombosis 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 pregnancy 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. Post-partum prophylaxis is also frequently used in these patients even in the absence of a prior history of thrombosis, although this practice is not evidence-based.

Catastrophic antiphospholipid antibody syndrome: Catastrophic antiphospholipid antibody syndrome (CAPS) is a rare clinical manifestation presenting with a fulminant onset of multiorgan microvascular thrombosis, oftentimes in patients without a prior history of APS. Management consists of aggressive anticoagulation, plasmapheresis, and immunosuppression. Despite treatment, there is a high rate of long-term morbidity and mortality. Diagnosis requires identification of one or more antiphospholipid antibodies but does not require tissue biopsy evidence of microvascular thrombosis in a compatible clinical setting. Management should occur in expert centers under the direction of experienced clinicians. Anti-complement therapy may be of benefit in selected patients and should be considered for critically ill patients and those not responding to “standard” therapies.

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.

OTHER RELEVANT THROMBOSIS CANADA CLINICAL GUIDES:

- Deep Vein Thrombosis (DVT): Treatment
- Pregnancy: Thromboprophylaxis
- Pregnancy: Venous Thromboembolism Treatment
- Pulmonary Embolism (PE): Treatment
• Unfractionated Heparin, Low Molecular Weight Heparin, and Fondaparinux
• Warfarin

REFERENCES:
Lim W. Prevention of thrombosis in antiphospholipid syndrome. Hematology 2016:1;707-713.

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