Antiphospholipid Syndrome: A Review
Hossain MM¹, Hossain MA², Rahman Y³, Hasan MK⁴

Abstract
Antiphospholipid syndrome (APS) is an autoimmune disease characterized by venous thromboembolism, arterial thrombosis, and obstetric morbidities in the setting of persistently positive levels of antiphospholipid antibodies. It may be primary or secondary. The latest classification criteria (Sydney 2006) recognize just three tests to define this syndrome-lupus anticoagulant, anticardiolipin antibodies and anti-β2-glycoprotein-1 antibodies. Treatment of thrombotic events involves lifelong anticoagulation with vitamin K antagonist warfarin. Antiphospholipid antibody syndrome (APS) with only pregnancy morbidity is treated with thromboprophylaxis with heparin during pregnancy and postpartum for 6 weeks. In this review we discuss the pathogenesis, diagnosis, treatment and prognosis of the APS.

Keywords: antiphospholipid syndrome, autoimmune disease.

Introduction
Antiphospholipid syndrome (APS) is an autoantibody-mediated acquired thrombophilia characterized by recurrent arterial, venous or small vessel thrombosis and/or pregnancy morbidity in the presence of antiphospholipid antibodies.¹ The major autoantibodies detected in the patient's serum are directed against phospholipid (PL) binding plasma proteins, mainly against a 43 kDa plasma apolipoprotein known as β2-glycoprotein 1 (β2GPI) and prothrombin. Other autoantibodies detected in the patient's serum are antibodies against cardiolipin(aCL) and lupus anticoagulant (LA). Patients with APS often possess antibodies recognizing Treponema pallidum-PL/cholesterol complexes, which is responsible for biologic false positive VDRL test.²,³ APS may occur alone (primary) or in association with any other autoimmune disease (secondary). Catastrophic APS (CAPS) is defined as a rapidly progressive thromboembolic disease involving simultaneously three or more organs, organ systems, or tissues leading to corresponding functional defects.⁴,⁵

The discovery of this syndrome can be traced back to the 1950s with the finding of prolonged activated partial thromboplastin time (aPTT) and even earlier with the biologic false positive syphilis test. Subsequently, in the 1980s with the detection of antibodies against cardiolipin, it was named the anticardiolipin syndrome, later revised to antiphospholipid syndrome (APS).⁶ This review synthesises the current information on this syndrome.

Epidemiology
Anti-PL (aPL) -binding plasma protein antibodies occur in 1-5% of the general population. Their prevalence increases with age. One-third of patients with systemic lupus erythematosus (SLE) possess these antibodies and about 6 to15% in other autoimmune connective tissue disorders, e.g. systemic sclerosis (PSS), Sjögren's syndrome, dermatomyositis and rheumatoid arthritis. One-third of aPL-positive individuals experience thrombotic events or pregnancy morbidity.²

Pathogenesis
The trigger for the induction of antibodies to PL-binding proteins is not known. However, infections, oxidative stress, major physical stresses such as surgery and discontinuation of anticoagulant treatment may induce the exacerbation of the disease.²,⁷ Experimental data have shown that these phenomena are induced via:

1. Conformational changes of β2-GPI either complexed with microbial antigens or dimerization through interaction with endothelial cell surface receptor annexin 2/TLR, the platelet receptors apolipoprotein E receptor 2' (apoER2') and/or GpIIb/IX/V receptor and/or the chemokine platelet factor 4 (PF4).
2. Impaired defensive mechanisms such as reduced generation of endothelial nitric oxide synthase.²,⁷-10

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These induces activation of endothelial cells, platelets and monocytes and causes secretion of proinflammatory cytokines, IL-1, IL-6 and IL-8. These change the phenotype of above cells to a prothrombotic form. In addition, anti-β2-GPI antibodies induce foetal injury through complement activation. Furthermore, the binding of antiphospholipid antibody to β2-GPI suppresses the activity of the tissue factor pathway inhibitor, reduces activated protein C activity and activates complement.

Clinical Features

Incidence is more in female like other autoimmune diseases, F:M = 4.5:1. APS has an onset in the middle aged, i.e. 30-40 years old, although, the Euro-Phospholipid Cohort Study found around 10% patients who were older than 50 years and 2.5% below 15 years of age. Antiphospholipid syndrome (APS) can be primary that is, not associated with any other connective tissue diseases and it is most common about 50%. Secondary antiphospholipid syndrome (APS) is associated with other connective tissue diseases, most common with systemic lupus erythematosus around 35%. Clinical manifestations represent mainly a direct or indirect expression of venous or arterial thrombosis and/or pregnancy morbidity. Venous thrombosis being most common. Common clinical manifestations with their incidence are shown in table-I and table-II.

Obstetric and foetal complications include early and late pregnancy losses, pre-eclampsia, premature births, abruptio placentae and postpartum cardiopulmonary syndrome. Recurrent Miscarriage Syndrome (RMS) which is defined as three or more consecutive miscarriages before mid-second trimester, is an important manifestation of APS. Antiphospholipid-antibody found in about 10-15% of RMS patient.

APS also causes intrauterine growth retardation (IUGR) due to placental insufficiency and prematurity. Women with only obstetric manifestations of APS are also at risk for thrombotic events. In a prospective study, the risk of thrombosis during pregnancy was 5% among women with known APS (compared with 0.025 to 0.10% in the general).

Table I: Clinical Manifestations of Antiphospholipid Syndrome (APS)

<table>
<thead>
<tr>
<th>Venous thrombosis and related consequences</th>
<th>Arterial thrombosis and related consequences</th>
<th>Obstetric manifestations</th>
<th>Foetal manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep vein thrombosis (39%)</td>
<td>Stroke (20%)</td>
<td>Preeclampsia (10%)</td>
<td>Early foetal loss (&lt;10 weeks) (35%)</td>
</tr>
<tr>
<td>Livedo reticularis (24%)</td>
<td>Cardiac valve thickening / dysfunction and/or Liebman-Sacks vegetations (14%)</td>
<td>Eclampsia (4%)</td>
<td>Late foetal loss (&gt;10 weeks) (17%)</td>
</tr>
<tr>
<td>Pulmonary embolism (14%)</td>
<td>Transient ischemic attack (11%)</td>
<td></td>
<td>Premature birth among the live births (11%)</td>
</tr>
<tr>
<td>Superficial thrombophlebitis (12%)</td>
<td>Myocardial ischemia (infarction or angina) and coronary bypass thrombosis (10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombosis in various other sites (11%)</td>
<td>Leg ulcers and/or digital gangrene (9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arterial thrombosis in the extremities (7%)</td>
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<td></td>
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<tr>
<td></td>
<td>Retinal artery thrombosis / amaurosis fugax (7%)</td>
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<tr>
<td></td>
<td>Ischemia of visceral organs or avascular necrosis of bone (6%)</td>
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</tr>
<tr>
<td></td>
<td>Multi-infarct dementia (3%)</td>
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<td></td>
</tr>
</tbody>
</table>

Some uncommon manifestations of arterial thrombosis are cognitive dysfunction, avascular necrosis of bone, infarcts of spleen, pancreas, and adrenals. Glomerular lesions are manifested with hypertension, mildly elevated serum creatinine levels, proteinuria and mild haematuria. Histologically, these lesions are characterized in an acute phase by thrombotic microangiopathy involving glomerular capillaries and in a chronic phase with fibrous intima hyperplasia, fibrous and/or fibrocellular occlusions of arterioles and focal cortical atrophy. Premature atherosclerosis has been recognized as a rare feature of APS.
A minority of patients have *Catastrophic Antiphospholipid Syndrome (CAPS)*, which is characterized by multiple simultaneous vascular occlusions occurring in a small span of time, first described by Asherson in 1992 and hence the eponym 'Ashersons syndrome'. Manifestations are usually in the form of cutaneous (skin purpura, necrosis, splinter haemorrhages), renal failure, Pulmonary (ARDS), cardiac failure and neurologic (seizures and stroke) and gastrointestinal (mesenteric ischemia). Other unusual manifestations include focal hepatic necrosis, bone-marrow necrosis, adrenal, splenic infarctions and polyneuropathy. Large vessel involvement may also occur concomitantly. Laboratory findings include thrombocytopenia in a majority (3/4th) which is often mild to moderate, haemolytic anaemia (1/4th patients), disseminated intravascular coagulation (1/4th) and occasionally schistocytes.3,29 Precipitating factor for catastrophic antiphospholipid syndrome (CAPS) are infections, surgery or sudden stoppage of anticoagulation and up to 6% of CAPS seems to be associated with pregnancy and preeclampsia.3,30

**Criteria for Diagnosis of Antiphospholipid Syndrome**

The diagnosis of APS is based on the occurrence of the clinical features of APS in the context of persistent positivity for antiphospholipid antibodies (APLA). Classification criteria were initially proposed in 1998 in Sapporo (Japan) and known as 'Sapporo criteria'. These were subsequently revised in 2006 and known as the 'revised Sapporo' or 'Sydney criteria'.24,25

### Laboratory Findings

Unlike other autoimmune disease, where even in the absence of autoantibodies, clinical features alone can be used to diagnose the disease like SLE, antiphospholipid syndrome requires the detection of autoantibodies. On the other hand, similar to other autoimmune diseases, even persistently positive

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**Table II: Other Clinical Manifestations of Antiphospholipid Syndrome (APS)**

<table>
<thead>
<tr>
<th>Neurologic manifestations</th>
<th>Renal manifestations</th>
<th>Osteoarticular</th>
<th>Hematologic manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine (20%)</td>
<td>Renal artery thrombosis (3%)</td>
<td>Arthralgia (39%)</td>
<td>Thrombocytopenia (30%)</td>
</tr>
<tr>
<td>Epilepsy (7%)</td>
<td>Renal vein thrombosis (3%)</td>
<td>Arthritis (27%)</td>
<td>Coombs positive</td>
</tr>
<tr>
<td>Chorea (01%)</td>
<td>Glomerular thrombosis (3%)</td>
<td></td>
<td>autoimmune</td>
</tr>
<tr>
<td>Cerebellar ataxia (01%)</td>
<td>Fibrous intima hyperplasia (3%)</td>
<td></td>
<td>haemolytic anaemia (10%)</td>
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<tr>
<td>Transverse myelopathy (0.5%)</td>
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</tbody>
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**Table III: Revised Sapporo or Sidney Criteria for Diagnosis of APS**

**Clinical criteria**

The presence of either vascular thrombosis or pregnancy morbidity, defined as follows:

**Vascular thrombosis:** One or more episodes of venous, arterial, or small vessel thrombosis with unequivocal imaging or histologic evidence of thrombosis in any tissue or organ. Superficial venous thrombosis is not included.

**Pregnancy morbidity:** Unexplained foetal death at ≥10 weeks gestation of a morphologically normal foetus, or one or more premature births before 34 weeks of gestation because of eclampsia, pre-eclampsia, or placental insufficiency or three or more embryonic (<10-week gestation) pregnancy losses unexplained by maternal or paternal chromosomal abnormalities or by maternal anatomic or hormonal causes.

**Laboratory criteria**

Presence of aPL, on two or more occasions at least 12 weeks apart and no more than five years prior to clinical manifestations, as demonstrated by one or more of the following:

1. IgG and/or IgM aCL in moderate or high titre (>40 units GPL or MPL or >99th percentile for the testing laboratory).
2. Antibodies to β2-glycoprotein I (anti-β2GPI) of IgG or IgM isotype at a titre >99th percentile for the testing laboratory when tested according to recommended procedures.
3. Lupus anticoagulant (LA) activity detected according to guidelines established by International Society of Thrombosis and Haemostasis.

**Presence of at least one clinical and one laboratory findings is essential to fulfil the diagnostic criteria.**1,3,11
antibodies are not diagnostic without clinical features. In a case control study in 73 such women who had persistently positive antibodies, there was no difference with respect to pregnancy outcomes compared to controls. Indeed, positivity of antiphospholipid antibodies may reach up to 10% in some populations and 50% in SLE, most not manifesting the clinical features of the syndrome.

The three main tests which are included in the diagnostic criteria are:

1. Anticardiolipin antibody
2. Anti-β2GP1 antibody
3. Lupus anticoagulant.

**Anticardiolipin antibody test:** The anticardiolipin antibody test is the most commonly performed test for the detection of this syndrome done by ELISA are 90% positive in APS patients.

**Anti-β2GP1 antibody test:** This test is detecting the antibodies against a protein called β2-glycoprotein-1 (β2-GP1) in ELISA plates, this test is less sensitive than anticardiolipin antibody test.

**Lupus anticoagulant test:** The 'lupus anticoagulant' is both a phenomenon and a test. The phenomenon is increases APTT values but a paradoxical thrombosis also occurs at the same time. It was first recognized in patients with systemic lupus erythematosus (SLE). A large study found that 50% of all patients of antiphospholipid syndrome had lupus anticoagulant positive and a positive lupus anticoagulant is associated with the highest risk of thrombosis. All these tests are considered positive only if they are persistently found to be positive even after 12 weeks.

**Other blood test for thrombophilia:**

1. Full blood count with platelet count and PBF study
2. Coagulation tests: prothrombin time (PT), activated partial thromboplastin time (APTT), d-dimer assay, fibrinogen concentration, bleeding time,
3. Measurement of plasma levels of protein C, protein S, antithrombin (AT), factorV Leiden, homocyisteine,
4. Activated Protein C Resistance (APCR)
5. Prothrombin gene mutation
6. Coombs' test
7. Haemoglobin electrophoresis to exclude hereditary haemolytic anaemia
8. Serum calcium level
9. Liver function tests
10. ANA, Anti-ds DNA and extractable nuclear antigen antibodies to exclude SLE and other connective tissue diseases.

**Other tests of Antiphospholipid Syndrome:** Other tests are done according to clinical presentations and to exclude other causes of thrombophilia. Common tests are following:

1. Duplex ultrasound: Most common test to diagnose venous and arterial thrombosis.
2. Venography: This test is used if ultrasound doesn't provide a clear diagnosis.
3. MRI and CT scan with MR & CT angiogram: These tests provide pictures of organs and tissues and also done if there is suspected pulmonary embolisms, CNS, eye, joint, bone or renal involvement.
4. ECG: If coronary artery diseases suspected.
5. Echocardiogram: If cardiac valve disease or vegetation suspected.
6. Ventilation-perfusion (V/Q) scan: In suspected pulmonary embolisms.
7. USG of renal system, urine R/E, serum creatinine, BUN, Ccr: If there is renal involvement.
8. USG of pregnancy profile with colour Doppler study and foetal anomaly scan with TVS if needed.

**Treatment**

The treatment of antiphospholipid syndrome is evolving. However, the current treatment protocols are mentioned here. The management of aPL-positive patients is focused on antithrombotic therapies and the variety of clinical presentations together with the heterogeneity of the aPL antibodies make it difficult to give definite therapeutic guidelines for the treatment of APS. After a first episode of thrombosis, patients with aPL antibodies have a higher risk of recurrent thrombosis than patients without the antibodies.

**Treatment of a patient with venous or arterial thrombosis:** The treatment strategy consists of anticoagulation of the patient for life. Treatment usually start with injection heparin for the initial few days (till oral anticoagulant starts working) followed by oral anticoagulant (warfarin or new anticoagulants) to achieve INR of 2-3 to be continued life long. Unfractionated heparin can be given as an infusion or by subcutaneous injections. Low molecular weight heparin is often preferred, because of ease of administration, lack of requirement to adjust APTT and less risk of
heparin induced thrombocytopenia and osteoporosis. The drug of choice for oral anticoagulation in APS is warfarin with dose adjustment to achieve an INR of 2-3. The role of the newer anticoagulants like direct thrombin inhibitors (Dabigatran etexilate) or direct Xa inhibitors (Rivaroxaban, Apixaban and Edoxaban) though proven in most settings to be equal to warfarin but still under evaluation and cannot replace warfarin in APS. It is not certain that addition of low dose aspirin gives any extra benefit but it has been recommended in case of arterial thrombosis. Unlike other autoimmune diseases, immunomodulatory drugs have very little role in APS except in catastrophic APS. Some studies have found that Hydroxychloroquine use is protective in preventing thrombosis in SLE patients with aPL positivity but its utility in primary APS is unclear. Recent few studies suggest that Rituximab (a chimeric monoclonal antibody directed against CD20) used in APS, not responding to conventional anticoagulation, thrombocytopenia associated with APS and in catastrophic APS appeared to have a beneficial clinical effect and aPL-antibody levels were significantly decreased.

Treatment of antiphospholipid syndrome in pregnancy: aPL-positive patients who have no history of thrombosis, the current recommendation of treatment is heparin and low dose aspirin for the duration of the pregnancy and postpartum at least 6 weeks. It has also been recommended that low dose aspirin be started pre-conceptionally in these women. Low-dose aspirin during pregnancy is often suggested in these patients but no data support this strategy. In pregnant women who have already suffered a thrombotic event with or without an obstetric complication, the therapeutic approach differs and includes full dose anticoagulation with heparin during pregnancy and lifelong anticoagulation with warfarin. If this patient wants to conceive in future then warfarin should be discontinued before pregnancy because of its teratogenic properties and re-started again after delivery. Some recent studies report that low dose steroids show some benefit in first trimester in refractory obstetric APS. Intravenous immunoglobulins have also been tried in refractory patients with antiphospholipid syndrome. The role of newer anticoagulants like fondaparinux (pentasaccharide which inhibits Xa) is unclear.

Treatment of the catastrophic antiphospholipid syndrome: Early treatment is critical in patients with catastrophic antiphospholipid syndrome (CAPS). It requires a multi-pronged strategy that deals with the inciting event and anticoagulation. Multi-pronged strategies are -

i) Antibiotics for any infection,

ii) Removal of the plasma mediators of inflammation as well as antiphospholipid antibodies by plasma exchange,

iii) Pharmacologic control of inflammatory cascade (pulse steroids- iv methyl prednisolone 250-1000 mg/day for 3 days or intravenous immunoglobulins1-2 g/kg over 3-5 days ± other immunosuppressants like cyclophosphamide or azathioprine or mycophenolate mofetil, especially in case of associated systemic lupus).

iv) Daily plasma exchange is considered to be the most effective treatment.

v) Removal of necrotic tissues like finger/toe amputations may help to reduce thrombotic storm.

Some newer immunomodulatory agents are under trial for the treatment of catastrophic antiphospholipid syndrome (CAPS) as well as other thrombotic features of APS are - Eculizumab, Sirolimus, Defibrotide.

Treatment of asymptomatic aPL-positive patients (Primary Thrombosis Prevention): The absolute risk of a first thrombosis in aPL-positive patients who do not have other risk factors is probably less than 1% per year. The role of aspirin to prevent thrombosis in asymptomatic aPL positive patients and obstetric complications is controversial. One randomized trial found no benefit of aspirin. But a recent meta-analysis which included 11 studies with 1208 patients found that low dose aspirin reduced the risk of first thrombosis in aPL positive asymptomatic subjects and those with SLE. So, aspirin should be given to those patients with high risk such as patients with triple positivity and with additional cardiovascular risk factors.

Prognosis

Prognosis is very good with anticoagulation treatment. Five years follow up with oral anticoagulants shows only 2.1% developed new DVT, 2.4% developed new strokes and 2.3% developed new transient ischemic attacks. If not treated with anticoagulant, majority of patients with APS will develop recurrent thrombosis in the next 5 years. The prognosis of patients with pregnancy morbidity in with oral anticoagulation is also good. Successful pregnancy outcome rate increases from 74% to 81.8% with oral anticoagulation in between pregnancies in 5 years follow up. Survival of patients of catastrophic antiphospholipid syndrome
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(CAPS) using the multimodal therapy was 70%. The overall mortality rate is 5.3%.3,4,24,62

Conclusions

The antiphospholipid syndrome (APS) has a broad spectrum of thrombotic and non-thrombotic clinical manifestations with newer manifestations being recognized on an ongoing basis. The current classification criteria (Sydney 2006) require the presence of one clinical and one laboratory criteria for diagnosis. Treatment includes life long anticoagulation in case of thrombosis and in case of isolated obstetric APS, prophylactic heparin is given in pregnancy. Low dose aspirin is often added to both regimens. APS remains an exciting area for research and encompasses all areas of medical science presenting as young stroke to a neurologist, venous thrombosis to an internist, leg ulcers and digital gangrene to a surgeon, poor obstetric history to an obstetrician, valvular disease or myocardial infarctions to a cardiologist, and renal involvement to a nephrologist.

References


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