Updates on the Antiphospholipid syndrome

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Abstract
Antiphospholipid syndrome (APS) is an acquired autoimmune thrombophilia characterized by venous or arterial thrombosis, and/or pregnancy loss or complications in the presence of persistently positive antiphospholipid antibodies. Organ involvement, referred to as non-criteria manifestations, includes livedo reticularis, thrombocytopenia and nephropathy. Non-thrombotic inflammatory mechanisms are increasingly identified in the pathogenesis of APS, alongside a recognition that obstetric APS may be a specific subset of APS. Treatment remains focused on lifelong anticoagulation and prevention of further thrombosis or obstetric complications. Identification of novel mechanisms are, however, leading the development of diagnostic tests and more targeted therapies to improve disease management.

Keywords
β2-Glycoprotein-1 antibodies
anticardiolipin antibodies
anticoagulation
antiphospholipid syndrome
complement
lupus anticoagulant
MRCP
obstetric morbidity
thrombosis

Key points
•Antiphospholipid syndrome (APS) is an appreciable cause of unprovoked thrombosis and acquired pregnancy morbidity
•Obstetric and thrombotic APS have distinct phenotypes and mechanisms
•Triple antiphospholipid antibody positivity confers the highest risk of clinical events
•Non-thrombotic, non-criteria, manifestations are increasingly recognized
•Current treatment remains focused on anticoagulation

Introduction
Clinical manifestations of venous or arterial thrombosis and/or certain forms of pregnancy loss in the presence of persistently positive antiphospholipid antibodies (aPLs) are required to classify antiphospholipid syndrome (APS) according to international criteria (Table 1). These criteria, primarily intended to create well-defined cohorts for research studies are routinely applied in clinical practice to aid diagnosis, were last revised in 2006. New criteria using data and consensus driven methodology are being developed and are likely to include additional manifestations that currently fall outside existing criteria[1]. Current criteria aPL tests include detection of: anticardiolipin antibodies (aCLs) and/or anti-β2-glycoprotein I (β2GPI) antibodies by enzyme-linked immunosorbent assay (ELISA); and/or positive lupus anticoagulant (LA) assay by prolongation of *in vitro* phospholipid-dependent clotting assays that can be corrected by addition of excess phospholipid.

Epidemiology

Estimates of aPL in the general population vary around 1–5%, with increased prevalence: in elderly patients; with various medications (including procainamide and phenothiazines); in infections (including human immunodeficiency virus, varicella, hepatitis C, syphilis, malaria and leprosy); in lymphoproliferative disorders; and in other autoimmune rheumatic diseases (ARDs), principally systemic lupus erythematosus (SLE). The precise prevalence of APS is estimated at 40-50 per 100,000, with an incidence of around 5 cases per 100,000 per year. The AntiPhospholipid Syndrome Alliance for Clinical Trials and International Networking (APS ACTION) systematically analysed published studies to produce estimates of aPL prevalence of 6% in pregnancy morbidity, 10% in deep vein thrombosis (DVT), 11% in myocardial infarction, 14% in stroke and 17% in stroke in individuals <50 years of age[2].

An observational European study (Euro-Phospholipid project) defined the characteristics of 1000 patients with APS.[2] Of these, 82% were female. Most (53.1%) had primary APS in the absence of another disease; the remainder had APS in association with another ARD, most commonly SLE. These cases are reported as ARD-associated APS. Although aPLs are found in up to 40% of patients with SLE, only 40% of those patients develop APS. A more severe variant with widespread microvascular thrombosis and high morbidity/mortality – catastrophic APS (CAPS) – occurs in 1% of patients with APS.

Pathogenesis

Animal models and *in vitro* studies provide direct evidence that aPLs cause thrombotic and obstetric APS (OAPS) manifestations.[3] One of the main distinguishing properties of pathogenic aPLs is their binding to β2GPI, a protein composed of five regions called domains (D) I-V that contains an important epitope for pathogenic aPL on DI. Other antibodies identified in APS include those directed against prothrombin, protein C, protein S, annexin V and factor Xa. Interestingly, antibodies directed against β2GPI and prothrombin are responsible for the prolongation of clotting times observed *in vitro* in LA tests.

Pathogenic aPLs have been shown to have inflammatory, thrombotic and adverse obstetric effects. The binding of aPL (principally via β2GPI) on cellular surfaces results in endothelial cell, monocyte, platelet and complement activation leading to inflammation, neointimal proliferation, thrombosis and pregnancy complications (Figure 1).

A ‘two-hit’ hypothesis has been proposed: the first hit is an aPL-induced prothrombotic/inflammatory state, and the second is exposure to an acute precipitating event such as surgery, immobilization, exogenous oestrogen or pregnancy. Pregnancy itself does not serve purely as a precipitating prothrombotic state, because comparison of products of conception from aPL-positive and aPL-negative women with recurrent early miscarriage demonstrates a specific defect in decidual endovascular trophoblast invasion in OAPS and shows placental infarction is not unique to APS.

Experimental evidence is increasingly implicating non-thrombotic mechanisms in the pathogenesis of OAPS by aPL-mediated complement activation, inflammation and impairment of placental development and function (Figure 1). In addition, clinical data from the European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS) on 247 patients with OAPS demonstrated that progression to thrombosis and SLE is low compared with patients with thrombotic APS[4], thus lending credence to the hypothesis that OAPS is a specific subset of APS.

Clinical features

Although vascular thrombosis and certain adverse pregnancy outcomes are the main clinical features of APS, other non-classification criteria clinical features are increasingly recognized (Table 2) and indicate the variety of non-thrombotic effects of aPL. For instance, in the Euro-Phospholipid project, the most common presenting non-criteria features were thrombocytopenia (21.9%), livedo reticularis (20.4%), superficial thrombophlebitis (9.1%) and haemolytic anaemia (6.6%).

Vascular thrombosis

Thrombotic events, most commonly venous events in the lower limbs, are the hallmark of APS. The presence of aPL increases the risk of venous thrombosis in patients with SLE 2-fold for aCL and 6-fold for LA, compared with healthy populations. In patients without an underlying ARD, venous thrombotic risk is increased 1.5-fold for aCL and up to 10-fold for LA, while arterial thrombosis is increased 3-fold (aCL) and 4-fold (LA). The risk of recurrent thrombosis or thromboembolism can further increase in patients with triple positivity to LA, aCL and anti-β2GPI antibodies.

Given that aPL positivity is found in 17% of patients experiencing a stroke at <50 years of age (compared with 0.7% of control participants), the British Society of Haematology guidelines on investigation and management of APS recommend that anyone <50 years of age presenting with an ischaemic stroke should be screened for aPL.

Obstetric manifestations

Table 1 shows the current classification of OAPS. Recurrent miscarriages are a hallmark of APS. In the Euro-Phospholipid project, the most common fetal complications were early fetal loss (35.4%), late fetal loss (16.9%) and premature birth (10.6% of live births). The most common obstetric complications in the mother were pre-eclampsia (9.5% of pregnant women), eclampsia (4.4%), and abruptio placentae (2.0%). The strongest association between criteria aPLs and pregnancy complications was found for LA and triple aPL positivity.

Non-criteria manifestations

Although many multisystem manifestations of APS (Table 2) are thrombotic in nature, it is increasingly recognized that aPLs have other immune-mediated effects producing manifestations that fall outside current APS classification criteria. These non-criteria manifestations involve multiple organ systems. Patients can present with valvular heart disease, and develop a sterile endocarditis (Libman–Sacks endocarditis) that gives rise to embolic complications.

Livedo reticularis is the most common dermatological manifestation; when associated with aPL and stroke, known as Sneddon's syndrome. Less commonly, skin ulceration occurs. Other non-ischaemic neurological complications include chorea, psychiatric disorders, Guillain–Barré syndrome, transverse myelopathy, dementia and seizures.

Thrombocytopenia is a common finding on laboratory investigation, as is a prolonged activated partial thromboplastin time (aPTT), yet bruising is rarely seen. An APS nephropathy has been described in which aPLs cause renal endothelial intimal hyperplasia independently of thrombosis because of activation of the mammalian target of rapamycin (mTOR) pathway.

Catastrophic APS

CAPS is a rare form of APS with high mortality that presents as a microangiopathic storm in the presence of aPLs with no other likely diagnosis. Classification criteria have been developed and require presence of aPLs, rapid onset of microthrombi in three or more organs within a week, biopsy confirmation of microthrombi and exclusion of other causes. In 65% of cases, there is a precipitating cause such as infection, a surgical procedure or cessation of anticoagulation. It typically presents with multiorgan failure of the kidneys, lungs, bowel, heart and brain. Mortality is high (44%) without treatment.

Non-criteria APS

Increasing recognition of non-criteria manifestations (Table 2) has led to the concept of non-criteria APS that has been proposed to occur in patients with either: typical thrombotic or obstetric manifestations satisfying APS classification criteria plus non-criteria manifestations but persistently negative criteria aPLs; non-criteria manifestations plus aPL positivity fulfilling APS laboratory criteria; clinical APS criteria and low titre positivity not-fulfilling APS laboratory criteria; or clinical APS criteria, with persistently negative or low titre criteria aPL and positive non-criteria aPL. These alternative ‘non-criteria’ assays have been developed to identify other aPLs not recognized in standard criteria tests. Particular attention has focused on assays to detect antibodies against other phospholipids (e.g. phosphatidylethanolamine, phosphatidylserine), other proteins of the coagulation cascade (e.g. prothrombin, phosphatidylserine–prothrombin complexes) and specific domains (particularly DI) of β2GPI, as well as on a functional assay measuring annexin A5 resistance. In addition, there is increasing interest in detection of IgA aCL and anti-β2GPI. None of these assays however, have been validated for routine clinical use (Table 3).

Diagnosis

The diagnosis of APs should be considered in the presence of any of the following that are otherwise unexplained: one or more thrombotic events; specific adverse pregnancy events; thrombocytopenia; or prolongation of clotting assay. Antibody testing for aPLs should then be performed.

Diagnosis is usually made according to classification criteria (Table 1) and based on the presence of one or both major clinical (thrombotic or obstetric) manifestations and persistent positivity of criteria aPLs. Although the classification criteria are routinely used to diagnose APS, this diagnosis

can be considered in certain patients who do not fulfil these criteria; including individuals with otherwise unexplained thrombocytopenia, heart valve disease or renal thrombotic microangiopathy, or those with aPL-related clinical events and borderline positive aPL testing. In these circumstances consultation with a clinician with expertise in the diagnosis of APS is advised to consider the possibility of non-criteria APS.

Investigations

Laboratory tests

Current criteria aPL tests consist of two direct ELISAs that detect antibodies against cardiolipin or β2GPI, and the LA assay. Interpretation of the LA test is often challenging; a true-positive result requires positivity in two clotting assays, one of which must be the factor Xa-dependent dilute Russell venom viper time, with the other commonly aPTT. The diagnosis of APS requires persistently positive (on at least two occasions, 12 or more weeks apart) IgG/M aCL and/or IgG/M anti-β2GPI and/or LA tests. There are no data to validate this time interval, but it is designed to avoid inclusion of transiently positive (non-pathogenic) aPLs that may be caused by infections and are not typically associated with clinical features of APS. Importantly, LA but not ELISA tests are affected by anticoagulant administration.

Further investigations are required to exclude other associated conditions or causes of thrombotic/obstetric manifestations (Table 3). Standard blood tests are useful to examine for complications, coexistent ARD and alternative causes of positive aPLs including infections, medications, malignancy and other coagulopathies. Thrombocytopenia is a frequent finding in APS. Raised inflammatory markers, such as erythrocyte sedimentation rate, may indicate coexisting inflammatory disease.

Renal function testing is required, with a protein:creatinine ratio to exclude renal involvement. Immunology tests including antinuclear antibody, extractable nuclear antigen, complement 3/4 and anti-double-stranded DNA antibodies are important to examine for associated ARDs, particularly SLE.

Imaging

If respiratory symptoms are the predominant feature, a chest X-ray is required, followed by a ventilation/perfusion scan or a computed tomography pulmonary angiogram to exclude pulmonary embolism (PE). If neurological deficits are apparent, imaging of the brain is required to examine for cerebrovascular disease. Doppler ultrasound is required to confirm suspected DVTs.

Other tests

Electrocardiography may display left ventricular hypertrophy in acute or chronic PE. Echocardiography may be required to detect heart valve lesions.

Histology

Histopathological confirmation is rarely required in primary APS but can help if there is diagnostic uncertainty with manifestations. A typical finding in APS is thrombosis without evidence of inflammation in the vessel wall. Renal biopsies in renal APS carry high mortality due to haemorrhagic risk particularly in those who are LA positive. The biopsy is rarely indicated unless there is uncertainty over the aetiology of renal impairment, such as in SLE/APS. In patients with primary APS, vasculo-occlusive lesions in small renal vessels can cause fibrous intimal hyperplasia and thrombotic microangiopathy.

Management

The management of APS is outlined in Table 4.

Asymptomatic patients

The risk of thrombosis in asymptomatic aPL carriers depends on the type, titre and number of positive aPL antibodies. A prospective study following aPL-positive patients with no previous thrombosis found that the risk of thrombosis if only one aPL antibody was present was the same as for the general population (0.65% per year). This risk increased to 5.3% per year if the patient was triple aPL antibody-positive. There is limited evidence to support routine thromboprophylaxis in asymptomatic aPL carriers and other modifiable vascular risk factors should be actively managed, smoking cessation encouraged and oestrogen-containing therapies avoided. In transient situations of increased thrombotic risk such as hospitalization or prolonged immobility, short-term heparin prophylaxis is advisable. European League Against Rheumatism (EULAR) evidence-based

recommendations advise prophylactic low dose aspirin (75-100mg/day) in all asymptomatic aPL carriers with high risk profile (persistent LA, high aPL titres, double or triple aPL antibody positivity), including during pregnancy. In women with coexistent SLE, the administration of low-dose aspirin has the additional benefit of reducing the risk of pre-eclampsia in pregnancy. Other consensus and evidence-based guidelines advise LDA and prophylactic dose heparin in asymptomatic aPL in pregnancy with high risk aPL profile and individualised stratification/counselling is required for each patient.

Vascular thrombosis

Anticoagulation treatment is required long-term for any patient with persistently positive aPLs and a history of unprovoked thromboembolism. Anticoagulation is usually initiated with heparin and continued with warfarin.

The intensity of anticoagulation has been much debated, and the current standard of care for long-term management of venous thrombosis in APS to maintain an international normalized ratio (INR) of 2–3 is based on two randomized controlled trials that found no benefit of high-intensity (INR >3) over low-intensity (INR 2–3) warfarin in preventing recurrent thrombosis. Given that the recurrence rate and number of arterial events was low in these studies, the optimal management of arterial thrombosis in APS remains a matter of debate; some experts recommend a combination of warfarin (INR 2–3) with low-dose aspirin, while others advocate warfarin, with a higher INR of 3–4. It is important to note that as the anticoagulant target dose is increased, so too is the risk of haemorrhage. Current EULAR guidance after a first thrombotic event and definite APS diagnosis, recommends lifelong warfarin with a target INR of 2-3. Long-term high or standard intensity plus antiplatelet is only recommended for those with arterial thrombosis or recurrent VTE despite standard therapy

Direct oral anticoagulants (DOAC) are no longer attractive alternatives to warfarin in patients with APS. Non-inferiority of rivaroxaban (a direct FXa inhibitor) compared with warfarin based on a laboratory surrogate of coagulation was shown in one randomised controlled trial (RCT), the Rivaroxaban in APS (RAPS) study. In contrast, another RCT, the Trial of Rivaroxaban in APS (TRAPS) study, of high risk triple aPL positive patients with a history of thrombosis, was terminated early, due to increased thrombosis rates in the DOAC group (12%) vs warfarin (0%). Similarly, an RCT of Rivaroxaban versus vitamin K antagonists (VKAs) in APS found rivaroxaban did not show noninferiority to VKA for thrombotic APS and had a non-significant near doubling of risk for recurrent thrombosis[3]. Therefore, the European Medicines Agency have issued a special warning that DOACs are not recommended for patients with APS and a history of thromboses, particularly if triple aPL positive. EULAR guidance is similar although it does state that DOACs may be considered in patients with APS who are unable to achieve target INR despite good adherence to VKA or are unable to tolerate a VKA[4].

Despite compliance with anticoagulation, 17.7% of patients with APS will have a recurrent thrombotic event. Thrombosis is the major cause of death in APS, and accounts for 3x as many deaths as haemorrhagic complications. For recurrent thrombosis on warfarin, options include increasing the target INR to 3–4 if recurrence occurs at INR 2–3, addition of low-dose aspirin (or clopidogrel) or switching to low-molecular-weight heparin (LMWH).

Other potential adjunctive agents include: hydroxychloroquine, with proven anti-inflammatory and anti-thrombotic properties in SLE, although primary prophylaxis in primary APS is unknown; statins, which have anti-inflammatory and anti-thrombotic properties in small APS cohorts and reduce venous thromboembolism in large population cohorts; and sirolimus, an mTOR inhibitor that has been shown to reduce renal vasculopathy after renal transplantation for APS nephropathy. Multiple case reports/series have shown benefit for rituximab in refractory APS, and evidence of efficacy in controlling some non-criteria manifestations (particularly thrombocytopaenia and skin ulceration) in an open-label Phase IIa descriptive pilot, rituximab in APS (RITAPS), study. Small cohort studies also show a specific benefit in SLE-APS at preventing thrombosis previously refractory to conventional treatment. Potential alternative and future therapies are outlined in Table 5.

Pregnancy

In patients with previous OAPS only (and hence with no thrombosis), low-dose aspirin and LMWH are advised throughout pregnancy. The level of evidence for this therapeutic regimen varies for different aPL-related obstetric manifestations, with some studies supporting aspirin alone. Overall, however, systematic reviews and consensus documents support combination of LMWH and aspirin. If aspirin and heparin are not enough to result in a successful term pregnancy, there are few evidence-based

options[5]. In patients with SLE/APS, consideration should be given to concomitant treatment with medications to control disease activity that are compatible with pregnancy, such as corticosteroids and hydroxychloroquine. Current trials underway include looking into use of HCQ vs placebo in aPL positive women planning to conceive (HYPATIA), and pravastatin in those with pre-eclampsia, after preliminary evidence has shown an improvement in blood flow and prolongation of gestation in women with pre-eclampsia and IUGR despite LDA and LMWH.

In patients with thrombotic APS, warfarin is not recommended throughout pregnancy because of its teratogenic effects on the fetus; it should be switched to therapeutic heparin at confirmation of pregnancy. Pre-pregnancy counselling is advisable to warn patients of pregnancy risks and these therapeutic requirements.

Catastrophic APS

Management of this rare condition is based on collective experience from the international CAPS registry. The McMaster RARE-Best Practices Clinical guidelines proposes initial triple therapy with anticoagulation (heparin), high-dose intravenous glucocorticoids, plasma exchange and/or intravenous immunoglobulin, particularly in ARD-associated APS. For those failing triple therapy, rituximab or complement inhibitor eculizumab have shown benefit in case reports.

Prognosis

The 10-year follow-up data from the Euro-phospholipid project of patients having standard treatment for APS revealed a re-thrombosis rate of 15.3%. Although the most common presenting thrombotic event was a DVT, arterial thrombotic events increased in incidence during the course of the disease. The most common obstetric complication was early pregnancy loss, in 16.5% of patients. Despite 72.9% of pregnancies succeeding in producing one or more live births, there remained a high degree of fetal morbidity (48.2% of babies being premature). A total of 9.3% of patients died during the 10-year period, with severe thrombotic events accounting for most deaths (myocardial infarction, strokes and PE for 36.5%, and haemorrhages for 10.7%).

Classification criteria for APS

Clinical criteria:

- Vascular thrombosis
  - Arterial, venous or small vessel thrombosis in any tissue or organ (excluding superficial thrombosis), confirmed by appropriate imaging or histopathology
- Pregnancy morbidity – at least one of the following:
  - ≥ 1 unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation
  - ≥1 premature births or a morphologically normal neonate before the 34th week of gestation owing to eclampsia or severe pre-eclampsia or placental insufficiency
  - ≥ 3 unexplained consecutive spontaneous abortions before the 10th week of gestation, with hormonal, chromosomal or maternal anatomic causes excluded

Laboratory criteria: any must be present on two or more occasions at least 12 weeks apart:

- LA present in plasma, detected according to the guidelines of the International Society on Thrombosis and Haemostasis
- IgG and/or IgM isotype aCL present in medium to high titre (i.e. >40 IgG phospholipid units or IgM phospholipid units) as measured by standard ELISA
- IgG and/or IgM isotype anti-β2GP1 antibody in serum or plasma, present in medium/high titre (e.g. >99th centile)

To fit the classification, one feature from each set of the clinical and laboratory criteria is required. The classification criteria are primarily a research tool, and do not include all clinical features or manifestations.

Table 1.

Criteria and non-criteria clinical manifestations of APS

Clinical manifestations in the APS criteria	
Vascular	Venous/arterial thromboembolic disease
Neurological	Stroke, transient ischaemic attack
Obstetric	Recurrent miscarriage, intrauterine fetal death, stillbirth, early severe pre-eclampsia, placental insufficiency
Non-criteria clinical manifestations of APS	
Cardiovascular	Valvular heart disease (mitral >aortic), Libman–Sachs endocarditis with embolism
Obstetric	HELLP syndrome, intrauterine growth restriction
Neurological	Chorea, dementia, psychiatric disorders, transverse myelopathy, seizures, Guillain–Barré syndrome, Sneddon's syndrome, cognitive dysfunction
Haematological	Autoimmune thrombocytopenia, autoimmune haemolytic anaemia, prolonged aPTT
Dermatological	Livedo reticularis, skin ulceration, superficial thrombophlebitis, livedoid vasculopathy (poorly healing ulcers)
Renal	Microthrombotic nephropathy, renal artery stenosis, hypertension, aPL-associated nephropathy

aPTT, activated partial thromboplastin time; HELLP, haemolysis, elevated liver enzymes, low platelets.

Table 2.

Summary of investigations for suspected APS

Laboratory tests

- Standard tests
  - FBC
  - Renal and liver function
  - ESR
  - CRP
  - Coagulation
  - Fasting lipids
  - Glucose and HbA1c
- Urinalysis
  - Urine protein:creatinine ratio
- Immunology
  - IgG/M anticardiolipin antibodies
  - IgG/M anti-β2GPI antibodies
  - LA
  - ANA, ENA, C3/C4, dsDNA
- ± Thrombophilia screen
  - Protein S, protein C, antithrombin, factor V Leiden

Imaging/other tests

- ECG
- CXR
- ± Doppler US (exclude DVT)
- ± CTPA (exclude PE)
- ± Brain MRI (exclude stroke)
- ± Echocardiography (exclude heart valve lesions)

Potential future tests (not currently clinically validated)

- IgG/M Anti PS–PT complex
- IgA anticardiolipin
- IgA anti-β2GPI
- IgG/M Anti-D1

ANA, antinuclear antibody; C3, complement C3; CRP, C-reactive protein; CTPA, computed tomography pulmonary angiogram; CXR, chest radiograph; dsDNA, double-stranded DNA; ECG, electrocardiogram; ENA, extractable nuclear antigen; ESR, erythrocyte sedimentation rate; FBC, full blood count; HbA1c, glycated haemoglobin; MRI, magnetic resonance imaging; PS/PT, phosphatidylserine–prothrombin; US, ultrasound.

Table 3.

Management of APS

Management of APS-positive patients	Treatment regimen
Previous VTE not on anticoagulation	Warfarin (target INR 2–3) or (DOAC only in exceptional circumstances)
Previous VTE on anticoagulation	Warfarin (target INR 3–4)
Previous arterial TE not on anticoagulation*	Warfarin (target INR 2–3) + low-dose aspirin *or* Warfarin (target INR 3–4)
Recurrent arterial TE on anticoagulation	Warfarin (target INR 3–4)
Recurrent thrombosis	Low-dose aspirin or clopidogrel + warfarin
Management of pregnancy in aPL-positive women	**Recommendations**
No previous thrombosis + aPL	Low-dose aspirin ± LMWH (prophylaxis dose) if high risk aPL profile
SLE/APS	Low-dose aspirin + LMWH (+hydroxychloroquine)
Previous thrombosis	Low-dose aspirin + LMWH (therapeutic dose)
Recurrent early miscarriage	Low-dose aspirin + LMWH (prophylaxis dose)
Late fetal loss/severe pre-eclampsia/previous IUGR	Low-dose aspirin + LMWH (prophylaxis dose)

DOAC, direct oral anticoagulants; INR, international normalized ratio; IUGR, intrauterine growth retardation; LMWH, low-molecular-weight heparin; TE, thromboembolism; VTE, venous thromboembolism.
*Conflicting expert opinion.

Table 4.

Alternative and future potential therapies and diagnostic assays in APS

Potential adjunctive therapies	
Statins	Some benefit in recurrent TE despite anticoagulation. Potential adjunctive therapy
Eculizumab	C5 inhibitor. Case reports of its use in preventing APS-associated thrombotic microangiopathy after renal transplantation, as well as recurrent CAPS
Sirolimus	Blocks B and T cell activation by inhibiting mTOR. No recurrence of APS nephropathy in renal transplant patients being given sirolimus, and decreased vascular proliferation
Autologous stem cell transplant	Promising early studies in SLE and APS, but high rates of adverse events
Belilumab	2 case reports in primary APS improving recurrent pulmonary necrotizing neutrophilic capillaritis, and skin uceration
Novel therapies in development	
NFκB and p38 MAPK inhibitors	Effective in reducing the *in vitro* proinflammatory/prothrombotic effect of APS and reduced TF expression
Recombinant DI	Inhibit development of anti-β2GPI antibodies and inhibits aPL-mediated prothrombotic effects in animal models
A1-A1	Dimeric inhibitor selectively targets β2GPI in β2GPI–antibody complexes, interfering with *in vitro* interaction with anionic phospholipids and ApoER2

ApoER2, apolipoprotein E receptor 2; MAPK, mitogen-activated protein kinase; NFkB, nuclear factor κB; TE, thromboembolism; TF, tissue factor.

Table 5.

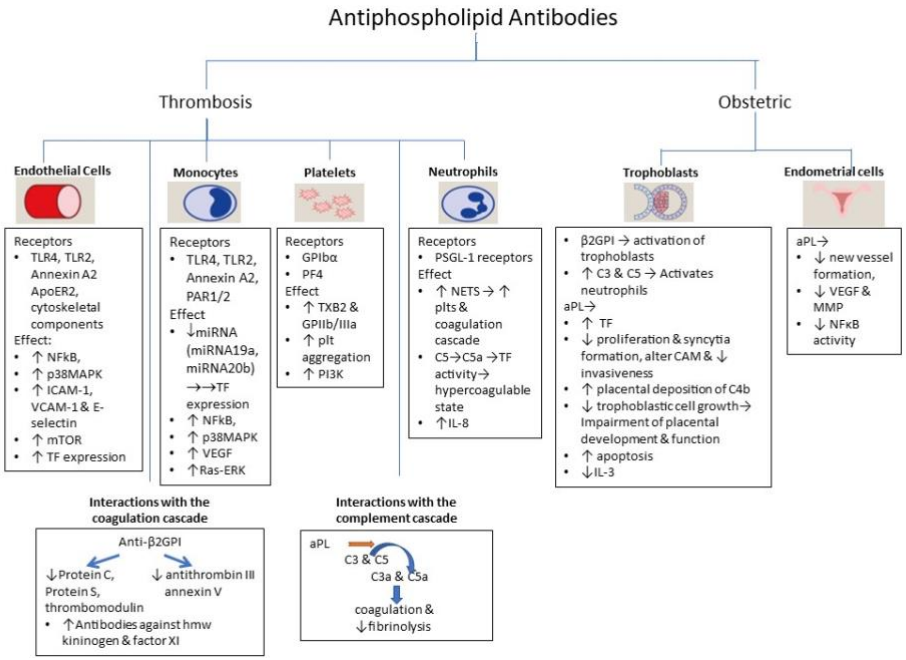

Figure 1. Pathogenesis of thrombotic and obstetric APS.
Abbreviations: ApoER, apolipoprotein E receptor; CAM, cellular adhesion molecule; GP1bα, glycoprotein 1bα; GPIIb/IIIa, glycoprotein IIb/IIIa; hmw, high-molecular-weight; miRNA, microRNA; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin; NETS, neutrophil extracellular traps; NFkB, nuclear factor κB; p38MAPK, p38 mitogen-activated protein kinase; PAR, protease activated receptor; plt, platelets; PI3K, phosphoinositide 3-kinase; PSGL-1, P-selectin glycoprotein ligand 1; Ras-ERK, extracellular signal-regulated kinase; TF, tissue factor; TLR, Toll-like receptor; TXB2, thromboxane B2; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor.

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 35 year old lady is referred after one first trimester miscarriage at 9 weeks gestation in her first pregnancy. The GP has done blood tests and found IgM aCL antibodies are mildly raised, but LA and B2GPI are negative.

How would you advise the patient?

a) You reassure them patient that a low-titre aCL can be seen in up to 5% of healthy population and the occurrence of only one first trimester miscarriage is not suggestive of APS and no further treatment is required.
b) You confirm a diagnosis of APS and initiate low dose aspirin to reduce her chance of miscarriage in subsequent pregnancy.
c) You confirm a diagnosis of APS but advise that after only one miscarriage treatment is not required.
d) You confirm a diagnosis of APS and initiate subcutaneous heparin to be continued until she has a successful pregnancy.
e) You reassure the patient that they do not have APS, but will need her antibodies repeated in 4 weeks from the initial test to see if they remain positive.

The correct answer is A. This patient does not meet clinical or laboratory criteria for APS with only one first trimester miscarriage and a weak positive IgM aCL. Current APS criteria specify three consecutive first-trimester miscarriages with medium/high titre IgM aCL that are persistently positive on two occasions at least 12 weeks apart.

Question 2

A 25 year old man is referred by his GP with cold hands and positive lupus anticoagulant assay. He has a past medical history of schizophrenia maintained on chlorpromazine. He has no other past medication history, other than a recent cellulitis on his shin, which resolved after a course of flucloxicillin. On examination he has slightly cool peripheries with normal peripheral pulses and nil else to find.

What would you do next?

a) Reassure him that he does not have any clinical manifestations of APS and that flucloxicillin can give rise to false positive aPL tests so they should be repeated in 12 weeks.
b) Given the positive LA test, he is at high risk of clots, and should be initiated on anticoagulation.
c) The patient is likely to have thrombotic APS and requires treatment with aspirin alone.
d) Reassure him that he does not have any clinical manifestations of APS and that chlorpromazine can give rise to false positive LA tests.
e) Patients with thrombotic APS and LA positivity alone do not require anticoagulation.

The correct answer is D. This patient does not have any evidence of vascular thrombosis so lacks clinical criteria for APS and false positive LA tests are reported with chlorpromazine.

Question 3

A 42 year old previously healthy woman presented 2 weeks ago with a swollen right calf. Doppler USS confirmed a DVT and she was initiated on heparin. She had no obvious triggers for its development and is not on any medication. She is referred to you to investigate whether she has an underlying diagnosis of APS.

Which statement is true?

a) Tests for anti-β2GPI antibodies can be measured while she is on heparin.
b) Any LA test can be measured whilst she is on heparin.
c) Investigations are not required. She will need life-long anticoagulation regardless of the underlying diagnosis.
d) The patient should be switched to a DOAC for ease of monitoring while investigations are taking place.
e) If aPL tests confirm APS she only requires 6 months treatment.

The correct answer is A. Only LA tests are affected by anticoagulation so the ELISA tests can be performed once that treatment has begun. The presence of persistently positive aPL tests and thus confirmation of APS will require long-term anticoagulation instead of 6 months only if no underlying cause for this first DVT is found. DOAC are not recommended in APS unless the patient cannot tolerate VKA.