Updates on the antiphospholipid syndrome

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Abstract

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by arterial, venous or microvascular thrombosis, and/or pregnancy morbidity or non-thrombotic manifestations in the presence of persistently positive antiphospholipid antibodies. APS can occur alone or in association with other autoimmune rheumatic disease and affects around 1 in 2000 people. 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 the prevention of further thrombosis or obstetric complications. The identification of novel mechanisms is, however, leading the development of diagnostic tests and more targeted therapies to improve disease management.

Keywords β_2-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 manifestations are recognized
- Current treatment remains focused on anticoagulation

Introduction

Clinical manifestations of arterial, venous or microvascular thrombosis and/or certain forms of pregnancy morbidity or non-thrombotic manifestations in the presence of persistently positive antiphospholipid antibodies (aPLs) are required to classify antiphospholipid syndrome (APS) according to international criteria (Table 1).[1] These criteria, primarily intended to create well-defined cohorts for research studies are routinely applied in clinical practice to aid diagnosis.

Current criteria aPL tests include the detection of: anticardiolipin antibodies (aCLs) and/or anti-β_2-glycoprotein I (β2GPI) antibodies by enzyme-linked immunosorbent assay (ELISA); and/or positive lupus anticoagulant (LA) assay by the prolongation of *in vitro* phospholipid-dependent clotting assays that can be corrected by the addition of excess phospholipid.

Epidemiology

Estimates of aPL in the general population vary around 1–5%, with increased prevalence in several situations: elderly patients; with various medications (including procainamide and phenothiazines); infections (including HIV, hepatitis C and coronavirus disease (COVID-19)); lymphoproliferative disorders; and 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. 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.[2] 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. 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).

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Classification criteria for APS

Clinical domains		Weight
VTE	With high VTE risk profile	1
	Without high VTE risk profile	3
Arterial thromboembolism	With high CVD risk profile	2
	Without high CVD risk profile	4
Microvascular involvement[a]	Suspected	2
	Confirmed	5
Obstetric involvement	≥3 consecutive pre-fetal losses (<10 weeks) and/or ≥1 early fetal death ($10-15^{+6}$ weeks)	1
	Fetal death ($16-33^{+6}$ weeks) without pre-eclampsia or placental insufficiency	1
	Pre-eclampsia **or** placental insufficiency <34 weeks	3
	Pre-eclampsia **and** placental insufficiency <34 weeks	4
Cardiac valve	Thickening	2
	Vegetation	4
Thrombocytopenia	Lowest platelets of $20-130 \times 10^9$/litre	2
Laboratory domains		
LA positivity	Single	1
	Persistent	5
aCL/anti-β2GP1 positivity	IgM only	1
	IgG moderate (40–79 units)	4
	IgG high (≥80 units) for anticardiolipin **or** anti- β_2GP1 (40–79 units)	5
	IgG high for anticardiolipin **and** anti-β_2GP1 (40–79 units)	7

Consider APS classification if there is a score of ≥1 point from the clinical domains **and** ≥1 point from the laboratory domains within 3 years. For classification as APS, ≥3 points must be scored from the clinical domains **and** ≥3 points from the laboratory domains. The classification criteria are primarily a research tool and do not include all clinical features or manifestations.

CVD, cardiovascular disease. For other abbreviations, see text.

[a] Includes livedo racemosa, livedoid vasculopathy, acute/chronic aPL nephropathy, pulmonary haemorrhage, myocardial disease, adrenal haemorrhage or microthrombosis.

Table 1

Complement hyperactivity has been associated with triple aPL positivity, and recurrent thromboses. Neutrophil extracellular traps (NETs) fragments are increased in patients with APS, and are a current focus for potential therapeutic targets. NETs activate the complement system, endothelium and platelets through the release of chromatin scaffolds, triggering thromboses. In aPL nephropathy the aPLs cause renal endothelial intimal hyperplasia independently of thrombosis by activation of the mammalian target of rapamycin (mTOR) pathway.

A 'two-hit' hypothesis has been proposed: the first hit is an aPL-induced prothrombotic/inflammatory state; the second is exposure to an acute precipitating event such as surgery, immobilization or pregnancy. Pregnancy does not serve purely as a precipitating prothrombotic state, because a comparison of products of conception from aPL-positive and aPL-negative pregnancies with recurrent early miscarriage demonstrates a specific defect in decidual endovascular trophoblast invasion in OAPS and shows that 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 on 247 patients with OAPS supported the notion of OAPS being a specific subset of APS, given that few patients progressed to thrombotic APS.[1]

Clinical features

The American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR; formerly the European League Against Rheumatism) updated their APS classification criteria in 2023. These revised criteria now include six clinical and two laboratory domains with hierarchically clustered, weighted and risk-stratified criteria that better represent the full disease spectrum of APS compared with previous criteria (Table 2).

Vascular thrombosis

The 2023 ACR/EULAR classification criteria now include microvascular as well as arterial and venous thrombotic domains. 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, the 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

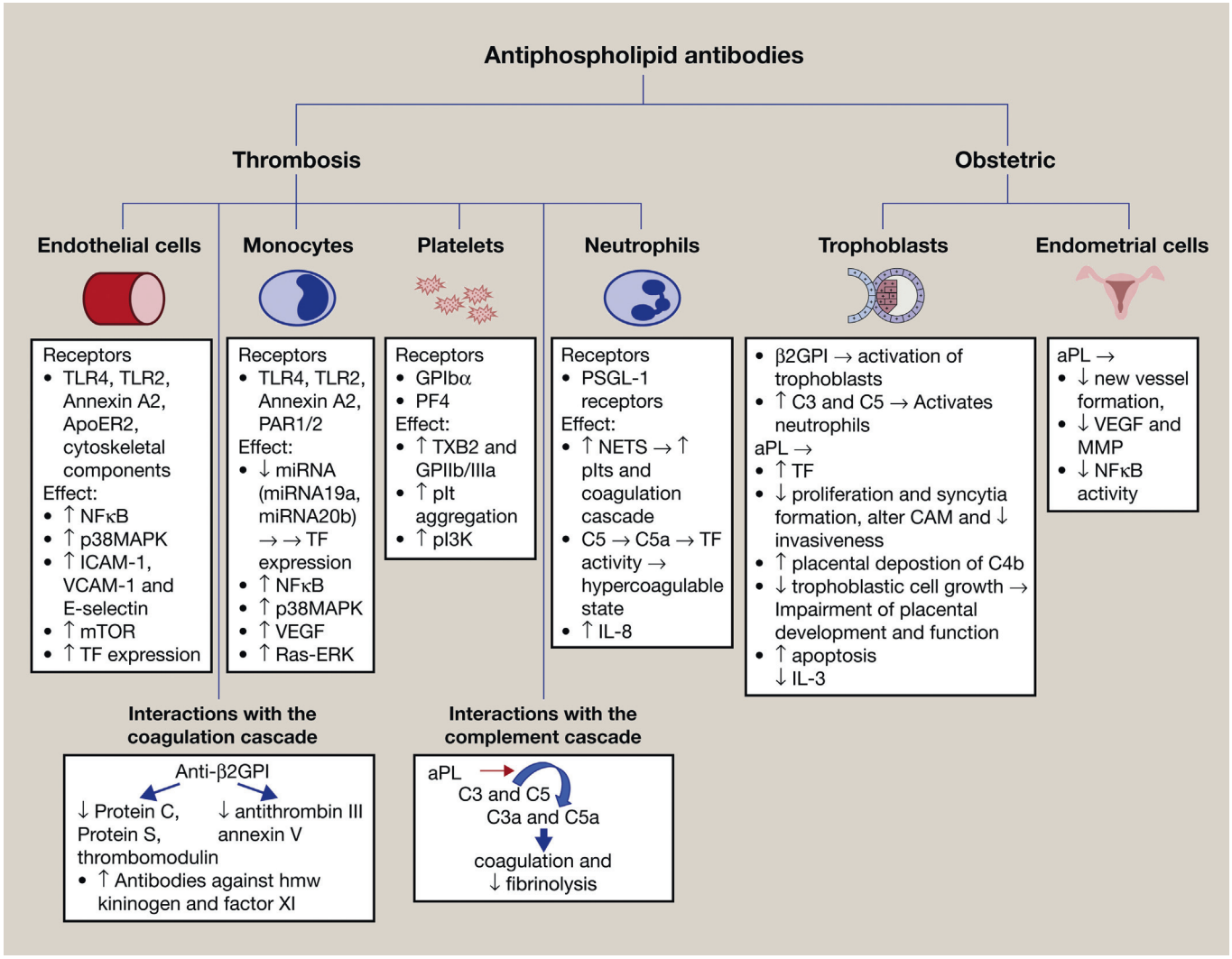

Figure 1 Pathogenesis of thrombotic APS and OAPS. ApoER2, apolipoprotein E receptor 2; C3, C4, C5, complement factors; CAM, cellular adhesion molecule; GP1bα, glycoprotein 1bα; GPIIb/IIIa, glycoprotein IIb/IIIa; hmw, high molecular weight; miRNA, microRNA; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; MMP, matrix metalloproteinase; NFκB, nuclear factor κB; p38MAPK, p38 mitogen-activated protein kinase; PAR, protease activated receptor; PF4, platelet factor 4 pI3K, phosphoinositide 3-kinase; plt, platelet; 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.

in patients with triple positivity to LA, aCL and anti-β2GPI antibodies.

Microvascular manifestations include livedo racemosa, otherwise unexplained aPL nephropathy, pulmonary haemorrhage, myocardial disease or adrenal haemorrhage or microthrombosis.

Obstetric manifestations

Table 1 shows the re-structured classification of OAPS. Recurrent miscarriages are a hallmark of APS. The most common fetal complications are early fetal loss (35.4%), late fetal loss (16.9%) and premature birth (10.6% of live births). The most common maternal complications are pre-eclampsia (9.5%), eclampsia (4.4%) and abruptio placentae (2.0%).[3] The strongest association between criteria aPLs and pregnancy complications was found for LA and triple aPL positivity, although fetal growth restriction has a stronger association with aCL and β2GPI.

Other clinical manifestations

The 2023 ACR/EULAR classification criteria recognize other immune-mediated complications through the addition of new domains. There are now clinical domains for otherwise unexplained cardiac valve thickening or vegetation, and for thrombocytopenia. Thrombocytopenia is a common finding on laboratory investigation (affecting 21.9%), as is a prolonged activated partial thromboplastin time, yet bruising is rarely seen.

Catastrophic antiphospholipid syndrome

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, a rapid onset of microthrombi in ≥3 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

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
Dermatological	Livedo racemosa, livedoid vasculopathy lesions (poorly healing ulcers)
Renal	Acute/chronic aPL nephropathy, adrenal haemorrhage
Respiratory	Pulmonary haemorrhage
Cardiovascular	Myocardial disease, valvular disease (thickened mitral > aortic), Libman-Sacks endocarditis
Haematology	Thrombocytopenia (autoimmune)
Non-criteria clinical manifestations of APS	
Obstetric	HELLP syndrome
Neurological	Chorea, dementia, psychiatric disorders, transverse myelopathy, seizures, Guillain–Barré syndrome, Sneddon syndrome, cognitive dysfunction, retinal ischaemia
Haematological	Autoimmune haemolytic anaemia, prolonged aPTT, Evans syndrome
Dermatological	Livedo reticularis, skin ulceration, superficial thrombophlebitis, Raynaud phenomenon
Renal	Microthrombotic nephropathy, renal artery stenosis, hypertension
Musculoskeletal	Arthralgia/arthritis, avascular necrosis

Sneddon syndrome is generalized livedo reticularis, hypertension and neurologic symptoms. Evans syndrome is an autoimmune condition that presents with two or more cytopenias.
aPTT, activated partial thromboplastin time; HELLP, haemolysis, elevated liver enzymes, low platelets.

Table 2

anticoagulation. It typically presents with multiorgan failure of the kidneys, lungs, bowel, heart and brain. Mortality is high (44%) without treatment.

Non-criteria antiphospholipid syndrome

Non-criteria APS includes patients with typical thrombotic or obstetric manifestations satisfying APS classification criteria but persistently negative criteria aPLs, as well as clinical manifestations not currently included in the classification criteria. Non-criteria manifestations include chorea, psychiatric disorders, Guillain–Barré syndrome, transverse myelopathy, dementia and seizures.

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 the detection of immunoglobulin (Ig) A anti-β2GPI, which may be an independent risk factor for thrombosis, and IgA aCL. None of these assays has, however, been validated for routine clinical use and they were not included in the 2023 revision of the APS classification criteria (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; cardiac valve disease; thrombocytopenia; or prolongation of the clotting assay.

Summary of investigations for suspected APS

Laboratory tests

- Standard tests
  - FBC
  - Renal and liver function
  - ESR
  - CRP
  - Coagulation
  - Fasting lipids
  - Glucose and HbA_{1c}
- 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
- Chest X-ray
- ± Doppler ultrasonography (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
- Anti-LBPA/EPCR
- Anti-β2GPI/HLA class II complex antibodies
- Anti-NET antibodies

ANA, antinuclear antibody; C3, complement C3; CRP, C-reactive protein; CTPA, computed tomography pulmonary angiography; CXR, chest radiograph; dsDNA, double-stranded DNA; ECG, electrocardiography; ENA, extractable nuclear antigen; ESR, erythrocyte sedimentation rate; FBC, full blood count; HbA_{1c}, glycated haemoglobin; LBPA/EPCR, lysobisphosphatidic acid/endothelial protein C receptor; MRI, magnetic resonance imaging; PE, pulmonary embolism; PS–PT, phosphatidylserine–prothrombin.

Table 3

Diagnosis is usually made according to the classification criteria (Table 1). The 2023 APS criteria consist of eight domains containing multi-weighted criteria, six representing clinical criteria and two, laboratory domains. A score of ≥3 points from the clinical domains and ≥3 points from the laboratory domains meets the classification for APS. The 2023 APS criteria better represent the full disease spectrum through the inclusion of many features excluded from previous classification criteria.

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 weeks apart) IgG/M aCL and/or IgG/M anti-β2GPI and/or LA tests, although the 2023 classification criteria give minimal weighting to a positive LA at one time point. There are no data to validate this time interval, but it is designed to avoid the 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 and non-thrombotic 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 computed tomography pulmonary angiography to exclude pulmonary embolism (PE). If neurological deficits are apparent, imaging of the brain is required to examine for cerebrovascular disease. Doppler ultrasonography 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 of microvascular manifestations is now included in the 2023 APS criteria. A typical finding in APS is thrombosis without evidence of inflammation in the vessel wall. Renal biopsies in renal APS carry high mortality because of risk of haemorrhage, particularly in those who are LA positive. The biopsy is rarely indicated unless there is uncertainty over the aetiology of renal impairment, 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.

EULAR recommendations advise prophylactic low-dose aspirin (75–100 mg/day) in all asymptomatic aPL carriers with a 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 low-dose aspirin and prophylactic dose heparin in asymptomatic aPL in pregnancy with a high-risk aPL profile, and individualized stratification/counselling is required for each patient.

Vascular thrombosis

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

The intensity of anticoagulation has been much debated. The current standard of care for the 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 warfarin with above standard target INR plus antiplatelet treatment is only recommended for

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[a]	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) (± HCQ if maternal risk factors)
Recurrent early miscarriage	Low-dose aspirin + LMWH (prophylaxis dose)
Late fetal loss/severe pre-eclampsia/previous IUGR	Low-dose aspirin + LMWH (prophylaxis dose)
OAPS, with high-risk aPL profile ± maternal risk factors	LMWH (therapeutic dose) ± HCQ
Non-criteria OAPS	Low-dose aspirin ± LMWH (prophylaxis dose) if high-risk aPL profile
OAPS with pregnancy failure despite treatment	Low-dose aspirin + LMWH (therapeutic dose) ± HCQ ± low-dose prednisolone ± intravenous immunoglobulin

HCQ, hydroxychloroquine; IUGR, intrauterine growth retardation; TE, thromboembolism. For other abbreviations, see text.
[a] Conflicting expert opinion.

Table 4

those with arterial thrombosis or recurrent venous thromboembolism (VTE) despite standard therapy.[2]

Direct oral anticoagulants (DOAC) have been found in multiple trials to be ineffective at preventing recurrent thromboses in high-risk triple aPL-positive patients with a history of thrombosis. The European Medicines Agency has issued a special warning that DOACs are not recommended for patients with APS and a history of thromboses, particularly if they are triple aPL positive. EULAR guidance is similar, although it states that DOACs can be considered in patients with APS who are unable to achieve target INR despite good adherence to vitamin K antagonists or are unable to tolerate a vitamin K antagonist.

Despite compliance with anticoagulation, 17.7% of patients with APS have a recurrent thrombotic event. Thrombosis is the major cause of death in APS, and accounts for three times 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 the following: 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 VTE in large population cohorts; and sirolimus, an mTOR inhibitor that has been shown to reduce renal vasculopathy after renal transplantation for APS nephropathy.[4]

Rituximab can be considered for use for particular APS manifestations. Studies confirm its ability to significantly decrease aCL titres and improve multiple vascular and non-ischaemic manifestations including venous and arterial thrombosis, thrombocytopenia, haemolytic anaemia, pulmonary haemorrhage and skin ulceration. Small cohort studies also show a specific benefit in SLE-APS for preventing thrombosis previously refractory to conventional treatment. Potential alternative and future therapies are outlined in Table 5.

Pregnancy

In patients with previous OAPS only (thus no thrombosis), low-dose aspirin and LMWH are advised throughout pregnancy (Table 4).[3] 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 a 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. 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. The currently underway HYPATIA trial includes looking into use of hydroxychloroquine versus placebo in aPL-positive women planning to conceive.

Pregnant women with APS should also undergo increased monitoring during the course of their pregnancy. This is especially important in the third trimester to identify fetal growth restriction, growth arrest or small for gestational fetuses early. Monthly Doppler ultrasonography is recommended.

Patients with thrombotic APS should be switched to therapeutic heparin at confirmation of pregnancy as warfarin is teratogenic. Pre-pregnancy counselling is advisable to warn patients of pregnancy risks and these therapeutic requirements.

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. May also have benefit for APS treatment during pregnancy. Phase II clinical trial of use in renal transplantation with history of CAPS has closed, but results not reported yet
Sirolimus	Blocks B and T cell activation by inhibiting mTOR. No recurrence of APS nephropathy in renal transplant patients given sirolimus, and decreased vascular proliferation
Autologous stem cell transplant	Promising early studies in SLE and APS, but high rates of adverse events
Belilumab	Anti-BAFF monoclonal antibody. Case reports in primary APS of improving recurrent pulmonary necrotizing neutrophilic capillaritis and skin ulceration. Current phase II pilot trial underway
Rituximab	Anti-CD20 monoclonal antibody — evidence of benefit in thrombocytopenia, haemolytic anaemia or other aPL-mediated haematological and microthrombotic manifestations. Alternative option for CAPS, refractory OAPS and paediatric CAPS
Obinutuzumab	Anti-CD20 monoclonal antibody, alternative option to rituximab
Daratumumab	Anti-CD38 monoclonal antibody. Potential treatment for refractory APS
Zanubrutinib	BTK inhibitor. Currently clinical trial for treatment of APS with secondary thrombocytopenia
Anti-TNF therapy	Adalimumab and certolizumab have been tried in refractory OAPS with positive results in 70% of cases
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; BAFF, B cell activating factor; BTK, Bruton tyrosine kinase; C5, complement 5; MAPK, mitogen-activated protein kinase; NκB, nuclear factor κB; TE, thromboembolism; TF, tissue factor.[4]

Table 5

Management of catastrophic antiphospholipid syndrome

Management of this rare condition is based on collective experience from the international CAPS registry. The McMaster RARE-Best Practices Clinical guidelines propose initial triple therapy with anticoagulation (heparin), high-dose intravenous glucocorticoids, plasma exchange and/or intravenous immunoglobulin, particularly in ARD-associated APS. For patients failing triple therapy, rituximab and the 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 rethrombosis 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 ≥1 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%). ◆

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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 38-year-old woman presented with a swollen left calf after a long-haul flight from Australia. She had no past medical history and was taking the oral contraceptive pill. Her body mass index was 28 kg/m^2.

Investigations

- IgM β2GPI positive
- IgG negative
- Doppler ultrasonography confirmed a venous thrombosis in the left calf

What action should be taken?

A. Lifelong anticoagulation
B. Repeat the antiphospholipid screen in 12 weeks after initial treatment for a deep vein thrombosis (DVT)
C. Treat DVT for 6 weeks with treatment dose anticoagulation then stop. No further tests required.
D. Perform further coagulation studies in 6 weeks but counsel patient to remain on lifelong anticoagulation
E. Initiate aspirin

Question 2

A 37-year-old woman presented 4 weeks pregnant. She had had three previous pregnancies that had all ended in a miscarriage (at 4 weeks, 8 weeks and 3 weeks, respectively). Previous laboratory findings had confirmed a persistently raised lupus anticoagulant. She had no other past medical history and was taking no medication.

Investigations

- Haemoglobin 107 g/litre (115–165)
- Platelets 128 × 10^9/litre
- Activated partial thromboplastin time 48 seconds (30–40)
- Antinuclear antibody positive 1/80
- Double-stranded DNA negative
- Complement C3 79 mg/dl (65–190)
- Extractable nuclear antigen negative

What is the most appropriate management?

A. Low-dose aspirin alone
B. Low-dose aspirin and prophylactic dose of low-molecular-weight heparin (LMWH)
C. Treatment-dose LMWH and low-dose aspirin
D. Treatment dose LMWH and hydroxychloroquine
E. Initiation of warfarin

Question 3

A 32-year-old woman presented with left-sided hemiplegia, and investigations confirm a stroke. She has a background of systemic lupus erythematosus (SLE) (diagnosed age 25), lupus nephritis and hypertension. She was taking azathioprine, hydroxychloroquine and ramipril.

Investigation

- Lupus anticoagulant positive at the time of diagnosis of SLE, and repeat at presentation confirms persistent lupus anticoagulant positivity.

What is the significance of the positive lupus anticoagulant result in this patient?

A. This is likely a false-positive and will need repeating in 12 weeks time.
B. Its presence now signifies a need for lifelong anticoagulant therapy
C. All the antiphospholipid antibodies if positive carried a similar risk for a thrombotic in SLE
D. The patient should have been anticoagulated when first diagnosed with SLE
E. The patient only requires 6 weeks of treatment dose anticoagulation, and then will require repeat antibody testing following that.