

Antiphospholipid syndrome: advances in diagnosis, pathogenesis, and management

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Abstract

Antiphospholipid syndrome (APS) is a thrombo-inflammatory disease propelled by circulating autoantibodies that recognize cell surface phospholipids and phospholipid binding proteins. The result is an increased risk of thrombotic events, pregnancy morbidity, and various other autoimmune and inflammatory complications. Although antiphospholipid syndrome was first recognized in patients with lupus, the stand alone presentation of antiphospholipid syndrome is at least equally common. Overall, the diagnosis appears to affect at least one in 2000 people. Studies of antiphospholipid syndrome pathogenesis have long focused on logical candidates such as coagulation factors, endothelial cells, and platelets. Recent work has shed light on additional potential therapeutic targets within the innate immune system, including the complement system and neutrophil extracellular traps. Vitamin K antagonists remain the mainstay of treatment for most patients with thrombotic antiphospholipid syndrome and, based on current data, appear superior to the more targeted direct oral anticoagulants. The potential role of immunomodulatory treatments in antiphospholipid syndrome management is receiving increased attention. As for many systemic autoimmune diseases, the most important future direction is to more precisely identify mechanistic drivers of disease heterogeneity in pursuit of unlocking personalized and proactive treatments for patients.

Introduction

Antiphospholipid syndrome (APS) is a thrombo-inflammatory disease that complicates up to one third of cases of systemic lupus erythematosus, where it portends more organ damage over time.¹⁻⁴ Primary antiphospholipid syndrome can also occur in the absence of other systemic autoimmune disorders. Antiphospholipid syndrome is propelled by circulating antiphospholipid antibodies that cause vascular thrombosis and obstetrical complications.⁵ Antiphospholipid antibodies engage phospholipids and phospholipid binding proteins at cell surfaces to activate the endothelium, platelets, and leukocytes—thereby tipping the circulating intravascular milieu toward in situ thrombosis while also promoting other autoimmune and inflammatory complications.^{6,7} Beyond a history of at least one thrombotic or obstetric morbidity, the most recent antiphospholipid syndrome classification criteria (2006, **table 1**) seek the persistent presence of anticardiolipin antibodies or anti-beta-2 glycoprotein I antibodies (a β ₂GPI).⁵ Furthermore, the lupus anticoagulant test—a panel of functional assays that screens for antiphospholipid antibodies based on paradoxical prolongation of phospholipid

dependent clotting times—is also part of the classification criteria. This review endeavors to tackle the current landscape of antiphospholipid syndrome diagnosis, pathogenesis, and management with a particular focus on updates from the past five years. The intended audience is individuals interested in learning more about the clinical care and research of patients with antiphospholipid syndrome.

Epidemiology

The estimated population prevalence of antiphospholipid syndrome is 40 to 50 cases per 100 000, with an annual incidence of 1 to 2 per 100 000.^{8,9} Antiphospholipid syndrome is typically diagnosed in relatively younger individuals with just 12.7% of patients diagnosed after the age of 50 in one study of 1000 patients.¹⁰ The epidemiology of antiphospholipid syndrome remains understudied, and population based studies of patients with diverse ages and ethnic backgrounds are needed. The population prevalence of persistently positive antiphospholipid antibodies among healthy individuals has yet to be rigorously determined. Although pediatric antiphospholipid syndrome is thought of as rare, it could plausibly be

Table 1 | Classification criteria for antiphospholipid syndrome⁵

Clinical criteria*	Vascular thrombosis	≥1 clinical episode of arterial, venous, or small vessel thrombosis
	Pregnancy morbidity	<ul style="list-style-type: none"> a) ≥1 unexplained death of a morphologically normal fetus at ≥10 weeks' gestation b) ≥1 premature delivery of a morphologically normal fetus at <34 weeks' gestation because of: <ul style="list-style-type: none"> i) Severe pre-eclampsia or eclampsia defined according to standard definition ii) Recognized features of placental insufficiency c) ≥3 unexplained consecutive miscarriages at <10 weeks' gestation, with maternal and paternal factors (anatomic, hormonal, or chromosomal abnormalities) excluded
Laboratory criteria	The presence of antiphospholipid antibodies on ≥2 occasions ≥12 weeks apart, identified as one or more of the following: <ul style="list-style-type: none"> a) Lupus anticoagulant, defined as: <ul style="list-style-type: none"> i) Prolongation of a phospholipid dependent clotting test (eg, aPTT or dilute Russell viper venom test); ii) Evidence for an inhibitory effect in patient plasma (eg, mixing with normal plasma does not correct the prolonged clotting time as would be expected for a simple factor deficiency); and iii) Evidence that the inhibitory activity can be quenched via the addition of excess phospholipids b) Moderate to high titer anticardiolipin antibodies of IgG or IgM isoforms, defined as >40 (moderate) to >80 (high) GPL or MPL units, or greater than the 99th centile, determined by the laboratory providing the test c) Moderate to high titer anti-β₂GPI antibodies of IgG or IgM isoforms, defined as greater than the 99th centile, determined by the laboratory providing the test 	

aPTT=activated partial thromboplastin time; β₂GPI=beta-2 glycoprotein I.

*Antiphospholipid syndrome is present if at least one of the clinical criteria and one of the laboratory criteria are met.

underdiagnosed for a variety of reasons, including that pregnancy (and associated morbidity) will be less common in this group.¹¹ One registry of 121 children reported a mean age at onset of antiphospholipid syndrome of 10.7 years.¹² Non-thrombotic manifestations of antiphospholipid syndrome such as thrombocytopenia and autoimmune hemolytic anemia might be more common in the pediatric population.¹³

Sources and selection criteria

PubMed was searched using the terms “antiphospholipid syndrome”, “antiphospholipid antibodies”, “anticardiolipin”, “lupus anticoagulant”, and “beta-2 glycoprotein I”. All English language studies published between 1 January 2017 and 15 June 2022, were considered. Relevant publications outside this timeline were selected based on review of article bibliographies. Studies were prioritized for discussion based on their level of evidence (eg, randomized controlled trials and meta-analyses preferred), their pursuit of mechanistic insights with rigorously defined reagents, and their time of publication (more recent studies preferred).

Clinical manifestations

Thrombotic manifestations of antiphospholipid syndrome

Deep veins and cerebral arteries of the lower extremities are the most frequent sites of venous and arterial thrombosis in APS, respectively.^{14 15} Thrombi can also form in sites which do not commonly form thrombi in the general population, including the arteries that supply the intestinal viscera and the dural venous sinuses of the brain.^{14 15} Patients with antiphospholipid syndrome are also at risk for microvascular thrombosis in the skin, eyes, heart, lungs, kidneys, and other organs.

A meta-analysis reported that lupus anticoagulant test positivity (odds ratio >10) carries more risk for thromboembolism than do anticardiolipin antibodies.¹⁶ A well characterized cohort of patients

with triple positive antiphospholipid syndrome (ie, positivity for anticardiolipin antibodies, aβ₂GPI, and the lupus anticoagulant test) has shown the high risk associated with that profile, including a 44.2% (95% confidence interval 38.6 to 49.8) prevalence of thrombosis by 10 years¹⁷; this risk was more than twice as high (hazard ratio 2.4, 95% confidence interval 1.3 to 4.1) in the subset of patients not taking anticoagulants. In another report, the site of recurrence was arterial in >90% of those patients with an initial arterial thrombotic event, and venous in 76% of those patients with an initial venous thrombotic event.¹⁸ Whether this seeming predilection for particular vascular beds is attributable to fine autoantibody specificity not revealed by current clinical testing, or other factors inherent to each individual, is an area deserving of further exploration.

Obstetric manifestations of antiphospholipid syndrome

When considering fetal death at ≥10 weeks' gestation, a meta-analysis of publications through 2009 concluded that the presence of a lupus anticoagulant and anticardiolipin antibodies were significantly associated with fetal death, but found “insufficient evidence to establish a significant link between [aβ₂GPI] antibodies and pregnancy morbidity.”¹⁹ Two more recent systematic reviews and meta-analyses also found a lack of evidence associating aβ₂GPI with fetal death,^{20 21} whereas they found that lupus anticoagulant test positivity was strongly associated with fetal death.²⁰ Investigating the association from a different perspective, a multicenter, population based case-control study comparing 582 stillbirths with 1547 live births found positive tests for antiphospholipid antibodies (anticardiolipin antibodies or aβ₂GPI) in 9.6% (56/582) of fetal deaths at ≥20 weeks' gestation, and therefore threefold to fivefold increased odds of stillbirth.²² In patients with known antiphospholipid syndrome, the likelihood of fetal death remains higher even when treated with heparins and low dose aspirin; two prospective, observational studies

Box 1: Preliminary criteria for classification of catastrophic antiphospholipid syndrome (reproduced with permission from Asherson et al)³¹

1. Evidence of involvement of three or more organs, systems, and/or tissues*
2. Development of manifestations simultaneously or in less than a week
3. Confirmation by histopathology of small vessel occlusion in at least one organ or tissue†
4. Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies)‡

Definite catastrophic antiphospholipid syndrome

- All four criteria

Probable catastrophic antiphospholipid syndrome

- All four criteria, except for only two organs, systems, and/or tissues involvement
- All four criteria, except for the absence of laboratory confirmation at least six weeks apart due to the early death of a patient never tested for antiphospholipid antibodies before the catastrophic antiphospholipid syndrome
- 1, 2, and 4
- 1, 3, and 4 and the development of a third event in more than a week but less than a month, despite anticoagulation

*Usually, clinical evidence of vessel occlusions, confirmed by imaging techniques when appropriate. Renal involvement is defined by a 50% rise in serum creatinine, severe systemic hypertension ($>180/100$ mm Hg), and/or proteinuria (>500 mg/24 hours).

†For histopathological confirmation, significant evidence of thrombosis must be present, although vasculitis can coexist with small vessel occlusion occasionally.

‡If the patient had not been previously diagnosed as having antiphospholipid syndrome, the laboratory confirmation requires that presence of antiphospholipid antibodies must be detected on two or more occasions at least six weeks apart (not necessarily at the time of the event), according to the proposed preliminary criteria for the classification of definite antiphospholipid syndrome.

of patients with antiphospholipid syndrome found fetal death rates of 10-12% despite the use of the standard treatments.^{23 24}

Preterm delivery for pre-eclampsia with severe features or placental insufficiency (ie, fetal growth restriction) is likely the most specific obstetric criterion for antiphospholipid syndrome. A 2011 meta-analysis of case-control studies found that the presence of a lupus anticoagulant and anticardiolipin antibodies were significantly associated with pre-eclampsia, with odds ratios of 2.34 (95% confidence interval 1.18 to 4.64) and 1.52 (95% confidence interval 1.05 to 2.20), respectively¹⁹; fewer data were available for $a\beta_2$ GPI, although a potential association with pre-eclampsia was noted based on two cohort studies.¹⁹ In the same meta-analysis, lupus anticoagulant test positivity was associated with fetal growth restriction with an odds ratio of 4.65 (95% confidence interval 1.29 to 16.71).¹⁹ A meta-analysis performed in 2022 found fetal growth restriction associated with anticardiolipin antibodies (odds ratio 2.25, 95% confidence interval 1.55 to 2.94) and $a\beta_2$ GPI (odds ratio 1.31, 95% confidence interval 1.12 to 1.49), but not with lupus anticoagulant test positivity.²⁵ A single center prospective study of pre-eclampsia with severe features or placental insufficiency in consecutive general obstetric patients who delivered for medical indications before 36 weeks of gestation found that 11.5% of cases were positive for antiphospholipid antibodies (LA, anticardiolipin antibodies, or $a\beta_2$ GPI), compared with 1.4% of matched controls.²⁶ Prospective observational studies have found that 9-10% of pregnant women with antiphospholipid syndrome develop pre-eclampsia with severe features despite standard treatments.^{23 24}

Recurrent early miscarriage (<10 weeks' gestation) is the obstetric complication for which

a diagnosis of antiphospholipid syndrome is most often considered, but for which the role of antiphospholipid antibodies is least clearly defined. Limitations of the literature include lack of discrimination between losses before and after 10 weeks' gestation, incomplete evaluation for other causes of pregnancy loss, inclusion of minimally positive antiphospholipid antibodies, and absence of confirmatory autoantibody testing. A review of studies through 2011 concluded that the median frequencies of lupus anticoagulant, anticardiolipin antibodies, and $a\beta_2$ GPI in such patients were 0%, 2%, and 4%, respectively.²⁷ A subsequent meta-analysis of studies published before 2014 found that the frequencies of lupus anticoagulant test positivity and anticardiolipin antibodies in patients with recurrent early miscarriage ranged widely from 1.8% to 36.5% and 2% to 88.1%, respectively.²⁸ A recent single center retrospective cohort study and systematic analysis concluded that the prevalence of antiphospholipid antibodies in patients with recurrent early miscarriage is similar to that of the general population.²⁹ Well designed studies to better define the association between antiphospholipid antibodies and early miscarriage are needed.³⁰

Catastrophic antiphospholipid syndrome

Catastrophic antiphospholipid syndrome is characterized by the rapid onset of thrombosis in multiple vascular beds leading to multiorgan failure and a high risk of mortality.^{31 32} Fortunately, this complication only develops in a small subgroup of patients with antiphospholipid syndrome. Catastrophic antiphospholipid syndrome is a systemic thrombo-inflammatory state, and must be distinguished from other systemic thrombotic disorders such as thrombotic thrombocytopenic purpura, hemolytic-uremic syndromes, and

Other manifestations sometimes associated with APS

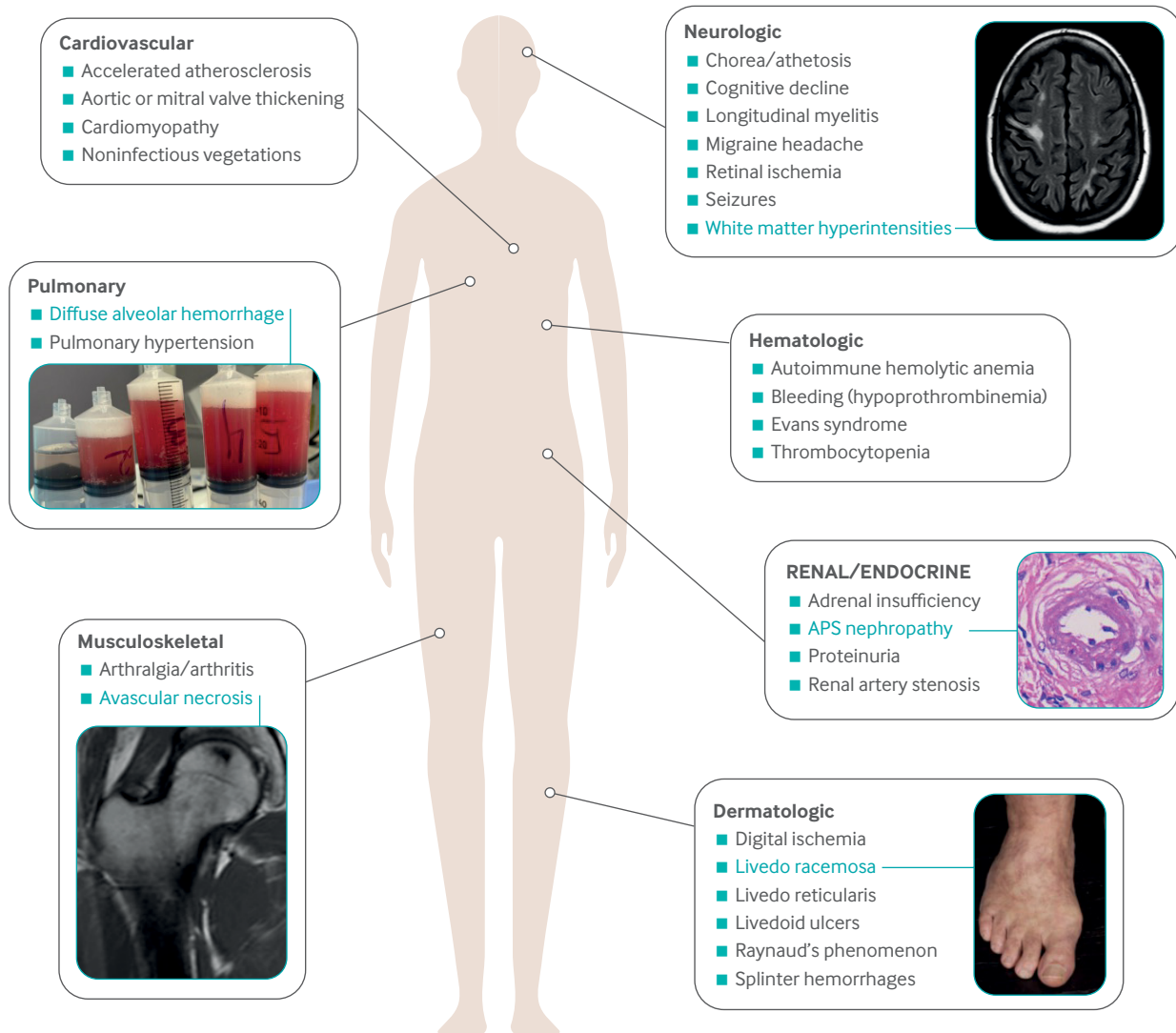


Fig 1 | Other clinical manifestations sometimes associated with antiphospholipid syndrome. Clinical images showing (clockwise from top right) white matter hyperintensities, a thickened vessel wall associated with antiphospholipid syndrome associated nephropathy, livedoid skin changes, avascular necrosis of the hip, and serial bloody return from the bronchoalveolar lavage of a patient with diffuse alveolar hemorrhage

heparin induced thrombocytopenia.³³ Although not universal, a triggering factor such as infection, neoplasm, surgery, or anticoagulation withdrawal can commonly be identified.³⁴ Mutations in complement regulatory genes have also been noted as a potential risk factor.³⁵ The central nervous system, skin, and kidneys are all commonly affected, while the heart, lungs, liver, and gastrointestinal tract can also be affected. Classification criteria for catastrophic antiphospholipid syndrome are shown in box 1.

Other manifestations of antiphospholipid syndrome Antiphospholipid syndrome is associated with a variety of autoimmune and inflammatory manifestations (fig 1). These features are sometimes referred to as “non-criteria” manifestations as they were not deemed specific enough for inclusion

in the 2006 classification criteria despite being regularly appreciated in clinical practice. Common non-criteria features include thrombocytopenia and livedo reticularis or racemosa.³⁶ Less common manifestations such as cardiac valve damage, diffuse alveolar hemorrhage, and antiphospholipid antibody associated nephropathy are also associated with organ threatening morbidity.³⁶ From the patient's perspective, physical and emotional quality of life are negatively affected by the long term obligation to take medications such as vitamin K antagonists, as well as the burden of non-criteria manifestations like fatigue, pain, and premature cognitive dysfunction. Indeed, one study administered the Short Form 36 to 270 people living with antiphospholipid syndrome (either with or without lupus) and identified pain and fatigue, lack of healthcare professional/public awareness, and medication unpredictability as major


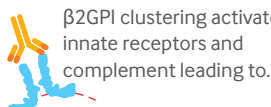
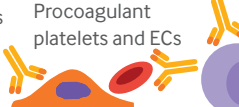
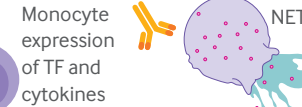


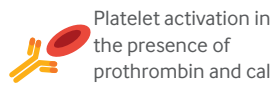








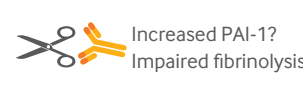




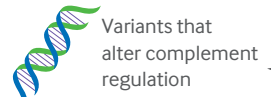
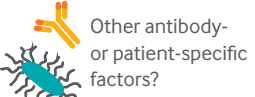


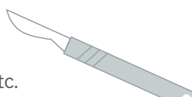


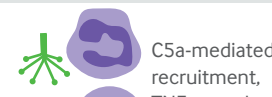

Potential mechanisms	Relevant testing	Potential implications for thrombosis and inflammation
 β 2GPI	a β 2GPI; aCL; LA; [a β 2GPI DI]	 β 2GPI clustering activates innate receptors and complement leading to...  Procoagulant platelets and ECs  Monocyte expression of TF and cytokines  NETosis
 Prothrombin	LA; [aPS/PT]	 Platelet activation in the presence of prothrombin and calcium  EC activation?  Accelerated prothrombinase activity?
 LBPA/EPCR	aCL?	 Dendritic cell type I IFN production  Monocyte activation including TF decryption
 Protein C, other pro- and anti-clotting factors	APC resistance; protein C activity	 Protein C \blacktriangle FVa \blacktriangle FVIIIa  Defective regulation by antithrombin  Increased PAI-1? Impaired fibrinolysis?
 Nucleosomes, NETs	ANA? Anti-chromatin? [anti-NET ELISA]	  Protection of NETs from nucleases  Immune complex formation and complement activation?
Exaggerated complement activation	Genetic testing; [modified Ham's test]	 Variants that alter complement regulation  Other antibody- or patient-specific factors?  Increased risk for CAPS
Other risk factors	Regular screening and education	 Risk factors for CVD: hypertension, hyperlipidemia, smoking, etc.  Risk factors for venous thrombosis: hormones, cancer, surgery etc.
Potential implications for obstetric morbidity		
 β 2GPI (others likely contribute, but are not well studied)	a β 2GPI; aCL; LA (best predictor of risk)	 Trophoblast dysfunction: \blacktriangle apoptosis, \blacktriangledown migration  C5a-mediated recruitment, TNF- α production  Disruption of annexin A5 shield

Fig 2 | Some potential mechanisms of antiphospholipid syndrome. Columns indicate potential mechanisms, relevant laboratory testing, and impact on thrombosis, inflammation, or obstetric morbidity. Laboratory tests in brackets are not widely available for clinical use. ECs=endothelial cells; IFN=interferon; LBPA/EPCR=lysobisphosphatidic acid/endothelial protein C receptor; NETs=neutrophil extracellular traps; PAI=plasminogen activator inhibitor; PS/PT=phosphatidylserine/prothrombin; TF=tissue factor; TNF=tumor necrosis factor

factors detracting from quality of life.³⁷ In addition, recent studies have shown an association between damage accrual (as measured by the damage index for antiphospholipid syndrome)^{38 39} and quality of life.^{40 41} An international effort to update the classification criteria for antiphospholipid syndrome is currently under way, and is likely to better represent the full disease spectrum of antiphospholipid syndrome.⁴²

Clinical laboratory identification of antiphospholipid antibodies

In addition to a history of at least one clinical event, antiphospholipid syndrome classification criteria (table 1) require the stable presence of one or more

of the following autoantibodies: anticardiolipin antibodies, a β ₂GPI, or a lupus anticoagulant. The three tests should be performed concurrently and be repeated at least once after a minimum interval of 12 weeks,⁵ although in some situations clinical decisions need not wait for this second round of testing. Antibodies of low positivity are most likely to disappear over 12 weeks.

Anticardiolipin antibodies

Antiphospholipid syndrome classification criteria are fulfilled by moderate to high titer anticardiolipin antibodies of the IgG or IgM isotype, although the clinical importance of IgM antibodies is debated.^{43 44} Assays for anticardiolipin antibodies are solid phase

Box 2: Disruptions in coagulation and fibrinolysis that might contribute to antiphospholipid syndrome**Coagulation**

- Anti- β_2 GPI antibodies (in complex with β_2 GPI) disrupt the annexin A5 “anticoagulant shield” that neutralizes procoagulant phospholipids on cell surfaces⁸⁹
- Antibodies against protein C (and potentially other targets) contribute to an acquired “activated protein C resistance” whereby protein C does not efficiently inactivate coagulation factors Va and VIIIa^{90,91}
- Antibodies associated with antiphospholipid syndrome limit the interaction between antithrombin and the heparan pentasaccharides that license antithrombin’s full activation⁹²
- Autoantibodies target factor II,⁹³ factor IX,⁹⁴ and factor X,⁹⁵ preventing their negative regulation by antithrombin

Fibrinolysis

- Autoantibodies disrupt the function of fibrinolytic mediators such as annexin A2, tissue type plasminogen activator (tPA), and plasmin itself⁹⁶
- Anti- β_2 GPI antibodies inhibit fibrinolysis by disrupting the ability of β_2 GPI to potentiate cleavage and activation of plasminogen by tPA⁹⁷
- Upregulation of anti-fibrinolytic factors such as plasminogen activator inhibitor-1 through unknown mechanisms⁹⁸

and optimized to recognize $\alpha\beta_2$ GPI antibodies, as phospholipid binding β_2 GPI protein present in patient serum or sample diluent provides a bridge between antibody and cardiolipin⁴⁵⁻⁴⁷; indeed, guidance recommends that laboratories test for β_2 GPI dependent anticardiolipin antibodies to increase specificity of the result.⁴⁸ Results are typically expressed as IgG and IgM phospholipid units, but one must be cautious assigning definitive status to a particular number, given the imperfect correlation between the values obtained from assays provided by different manufacturers.⁴⁹ In practice, the clinician could be confronted with values above the manufacturer’s threshold but less than moderately positive (≥ 40 units by enzyme linked immunosorbent assay (ELISA)); the clinical significance of these low positive results is unclear.

Anti- β_2 GPI antibodies

$\alpha\beta_2$ GPI of the IgG and IgM isotypes, present at moderate to high titer and detected by solid phase assays, are used for diagnosis and classification of antiphospholipid syndrome. Again, IgG antibodies have more clinical relevance than IgM.^{43, 44} Units are typically defined by the manufacturer, and antiphospholipid syndrome classification criteria recommend only considering antibodies positive at the 99th centile or greater.⁵ While a strong mechanistic case can be made for the importance of $\alpha\beta_2$ GPI in antiphospholipid syndrome pathogenesis,⁵⁰⁻⁵² it should be noted that a recent systematic review found few prospective data to support added diagnostic value beyond testing for anticardiolipin antibodies and lupus anticoagulant.²¹ To complicate such analyses, clinically relevant assays to detect anticardiolipin antibodies will also routinely detect $\alpha\beta_2$ GPI, as discussed in the preceding section. Furthermore, at least some $\alpha\beta_2$ GPI have lupus anticoagulant activity.⁵³⁻⁵⁵

IgA anticardiolipin antibodies and $\alpha\beta_2$ GPI can also be detected in antiphospholipid syndrome, commonly in combination with other isotypes. While one retrospective study found isolated IgA $\alpha\beta_2$ GPI to be an independent risk factor for thrombosis and also showed potential pathogenicity in a preclinical model,⁵⁶ no recommendations currently support of

testing for IgA anticardiolipin antibodies or $\alpha\beta_2$ GPI in the diagnostic workup for antiphospholipid syndrome.

Lupus anticoagulant

Although the association between lupus anticoagulant test positivity and thrombotic complications has been appreciated since the 1960s,⁵⁷ the assay was not formalized until the early 1990s.^{58, 59} Conceptually, a lupus anticoagulant test should have three characteristics: (a) prolongation of a phospholipid dependent clotting test, (b) evidence for an inhibitory effect in patient plasma, and (c) evidence that the inhibitory effect can be quenched by excess phospholipids (table 1). Samples for lupus anticoagulant testing are ideally collected from patients not receiving anticoagulant treatment.^{60, 61} Vitamin K antagonists have been associated with both false positive and false negative results, and successful interpretation of results requires experienced laboratory staff.⁶⁰ More problematic are direct oral anticoagulants such as rivaroxaban, which cause false positive results even at low concentrations.⁶⁰ While absorbents have been developed that can remove the interference of direct oral anticoagulants,⁶² such agents are not widely available. Emerging strategies for lupus anticoagulant testing, such as use of the Taipan venom time, could eventually help resolve concerns about concomitant anticoagulation use.⁶³ Testing for a lupus anticoagulant should also be interpreted with caution in the acute clinical setting, as elevated levels of acute phase reactants can interfere with test results.⁶⁰

Antiphospholipid profile

A persistently positive lupus anticoagulant test is the single most powerful predictor of thrombotic risk,^{16, 64} as well as pregnancy morbidity.⁶⁵ Patients who are “triple positive” for all three standard assays are at highest risk for development of thrombotic and obstetric complications.⁶⁶⁻⁶⁸ As will be discussed in more detail below, triple positive patients also appear to be more likely to develop thrombotic events while under treatment with direct oral anticoagulants (compared with vitamin K antagonists).

Box 3: Mechanisms of (and possible approaches to blocking) the release of neutrophil extracellular traps (NETs) in antiphospholipid syndrome**Mechanisms of NET release in antiphospholipid syndrome**

- Triggered by anti- β_2 GPI antibodies¹⁵¹
- Requires TLR4 signaling and downstream generation of reactive oxygen species by NADPH oxidase¹⁵¹
- Mac-1 mediated adhesion also required for efficient NET release¹⁵²

Strategies that reduce antiphospholipid syndrome mediated NET release and thrombosis in mice

- Neutrophil depletion¹⁵³
- Deoxyribonuclease administration¹⁵³
- PSGL-1 inhibition¹¹¹
- Activation of neutrophil surface adenosine receptors^{154,155}
- Administration of phosphodiesterase inhibitors¹⁵⁶

New assays

While risk stratification is somewhat informed by an individual's antiphospholipid antibody profile, these profiles themselves are not proven to allow for strategic or pre-emptive therapeutic interventions. Emerging autoantibody classes associated with antiphospholipid syndrome include anti- β_2 GPI domain I antibodies,⁶⁹ antiphosphatidylserine/prothrombin antibodies (anti-PS/PT),⁷⁰ antilyso-bisphosphatidic/endothelial protein C receptor antibodies (anti-LBPA/EPCR),⁷¹ anti- β_2 GPI/HLA class II complex antibodies,⁷² and antineutrophil extracellular trap antibodies.⁷³ More research is needed and none of these antibodies currently have a defined role in the clinic.⁷⁴ An open question is whether the answer to disease heterogeneity will eventually be unlocked by comprehensively defining each individual's circulating autoantigenome. Alternatively, it could be that the same antibodies drive distinct disease manifestations based on the genetic, epigenetic, and metabolic landscapes of various circulating and tissue resident cells.

Timing of antiphospholipid antibodies testing in relation to thrombotic events and pregnancy

For practical reasons, initial testing is usually done shortly after a clinical event, followed by confirmatory testing at least 12 weeks later.⁵ Some nuances should be discussed though. At the time of an acute thromboembolic event, acute phase reactants such as C reactive protein, factor VIII, and fibrinogen might be markedly increased, altering coagulation test results (either increasing or decreasing times) and making it particularly important that lupus anticoagulant testing is repeated once the patient is stable. In addition, acute events have long been known to trigger the appearance of transient anticardiolipin antibodies,⁷⁵ especially of low titer. Because of reports that antiphospholipid antibodies levels can fluctuate during pregnancy, either decreasing or increasing,⁷⁶⁻⁷⁸ current International Society on Thrombosis and Haemostasis guidelines recommend that antiphospholipid antibodies results obtained during pregnancy be interpreted with caution.⁶⁰ Results of a prospective observational

study of 152 pregnant patients positive for antiphospholipid antibodies enrolled in the late first or early second trimesters found that 25% of lupus anticoagulant positive patients became negative in the second or third trimesters.⁷⁹ IgG antiphospholipid antibodies levels were also significantly lower during the second and third trimesters, but among patients testing positive, IgG anticardiolipin antibodies and $\alpha\beta_2$ GPI results remained in the positive range through pregnancy in 93% and 85% of patients, respectively.⁷⁹ Guidelines recommend that confirmation or exclusion of antiphospholipid antibodies positivity be confirmed after the postpartum period.⁶⁰ Although the optimal timing of such testing is not established, one study found that lupus anticoagulant test results returned to baseline status three months after delivery.⁷⁹

Pathogenesis of antiphospholipid syndrome

The evidence that IgG antibodies targeting domain I of β_2 GPI contribute to the prothrombotic state of antiphospholipid syndrome is convincing.⁵⁰ Meanwhile, data also support roles for other isotypes of $\alpha\beta_2$ GPI, antibodies that target heterotypic complexes of phospholipids and phospholipid binding proteins, and antibodies that target phospholipids directly.^{80, 81} Given that most mechanistic studies have focused on either polyclonal IgG fractions isolated from patients with antiphospholipid syndrome or IgG anti- β_2 GPI, we unfortunately could not build a nuanced model of how diverse species of antiphospholipid antibodies conspire to cause various manifestations of antiphospholipid syndrome. Some potential mechanisms downstream of individual autoantibodies are highlighted in fig 2.

Since circulating antiphospholipid antibodies are typically unaffected by immunomodulatory treatments,⁸² the antibody producing cells of antiphospholipid syndrome likely reside among long lived plasma cells. Meanwhile, evidence suggests that some antiphospholipid antibodies have undergone extensive affinity maturation from original germ-line sequences,⁸³ indicating a role for helper T cells in shaping the antiphospholipid syndrome antibody repertoire.⁸⁴ The best defined B cell epitope relevant to antiphospholipid syndrome is in domain I of β_2 GPI,⁸⁵ while the best defined T cell epitope is in domain V of the same protein.⁸⁶

As has been recently reviewed,⁸⁷ several reports have found genetic associations with HLA class II alleles in antiphospholipid syndrome (again supporting a role for helper T cells in pathophysiology); only two genetic loci outside of the HLA region (STAT4 and C1D) have reached the threshold for significance at the genome wide level. Larger collaborative studies are needed.

Thrombotic events

It has been posited that "two hits" are necessary to trigger a thrombotic event in antiphospholipid syndrome.⁸⁸ This hypothesis argues that antiphospholipid antibodies provide the first hit by

Table 2 | Randomized clinical trials for the treatment of patients with thrombotic antiphospholipid syndrome*

Study	No subjects	Previous TE	AT treatment	Primary outcome	Results	Notes
Crowther, 2003	58	45 VTE (78%)	warfarin, INR 2-3	Recurrent TE	2 TE (3.4%)	HR 3.1 (95% CI, 0.6 to 15.0); P=0.15
	56	42 VTE (75%)	warfarin, INR 3.1-4		6 TE (10.7%)	
Finazzi, 2005	55	38 VTE; 23 ATE	warfarin, INR 2-3	Composite outcome of vascular death, non-fatal major VTE and/or ATE	3 TE (5.5%)	HR 1.63 (95% CI, 0.39 to 6.83); P=0.5043
	54	37 VTE; 21 ATE	warfarin, INR 3-4.5		5 TE (9.3%)	
Cohen, 2016	57	32 DVT; 25 PE	rivaroxaban, 20 mg/day*	Percentage change in ETP from randomization to day 42†	1086 nmol/L per min (957-1233)	Treatment effect 2.0 (95% CI 1.7 to 2.4); P<0.0001 No TE in either group at day 21‡
	59	37 DVT; 22 PE	warfarin, INR 2-3		548 nmol/L per min (484-621)	
Pengo, 2018	59	11 ATE; 38 VTE; 10 ATE+VTE	rivaroxaban, 20 mg/day	Composite outcome of TE, MB, and vascular death	7 ATE; 4 MB	HR (all events) 6.7 (95% CI 1.5 to 30.5); P=0.01 [as treated analysis]
	61	14 ATE; 39 VTE; 8 ATE+VTE	warfarin, INR 2-3		2 MB	
Ordi-Ros, 2019	95	37 ATE; 69 VTE; 11 ATE+VTE	rivaroxaban, 20 mg/day	New TE	9 ATE; 1 VTE; 1 ATE+VTE	HR (all events) 1.94 (95% CI 0.72 to 5.24); P=0.190 [as treated analysis]
	95	34 ATE; 70 VTE; 9 ATE+VTE	VKA, INR 2-3		3 ATE; 3 VTE	
Woller, 2022	23	6 ATE; 20 VTE	apixaban, 2.5 mg twice daily‡	Combined rate of ATE, VTE, and vascular death	6 ATE, all strokes; no VTE, no deaths	1 MB in the warfarin arm; no MB in the apixaban arm
	25	11 ATE; 18 VTE	warfarin, INR 2-3		No TE events or deaths	

AT=anti-thrombotic; ATE=arterial thromboembolism; CI=confidence interval; DVT=deep vein thrombosis; ETP=endogenous thrombin potential; HR=hazard ratio; INR=international normalized ratio; MB=major bleeding; PE=pulmonary embolism; TE=thromboembolic events; VKA=vitamin K antagonist; VTE=venous thromboembolism.

*Two patients treated with rivaroxaban 15 mg/day owing to creatinine clearance of 30-49 mL/min.

†Secondary outcomes included the occurrence of thromboembolism up to 210 days after randomization.

‡Dose of apixaban increased to 5 mg twice daily after the first 25 patients were enrolled. No patients with ATE were randomized to the study after the first 30 patients were enrolled.

creating a generalized procoagulant state, which conspires with a second hit (often cryptic and potentially the result of subclinical vascular injury, stasis, or inflammation) that triggers thrombosis.

Inappropriate activation of hemostatic factors (clotting cascade, endothelium, and platelets)

Breakdowns in natural anticoagulant systems were among the first prothrombotic consequences of antiphospholipid antibodies to be reported (box 2); however, as is true for many of the mechanisms that follow, the weight that should be attributed to each concept in a particular vascular bed remains mostly unknown. A recent report found that β_2 GPI deficiency in mice creates a prothrombotic environment independent of antiphospholipid antibodies,⁹⁹ an observation that has the potential to shine new light on the interplay between this abundant plasma protein and other clotting regulators in antiphospholipid syndrome.

In vitro, antiphospholipid antibodies appear to activate endothelial cells by co-opting pathways normally associated with non-autoimmune inflammatory stimuli.¹⁰⁰ Potential surface receptors for the complex of β_2 GPI and $\alpha\beta_2$ GPI include apolipoprotein E receptor 2 (apoER2),¹⁰¹ and the complex of annexin A2 and TLR4.¹⁰² Implicated pathways downstream of antiphospholipid antibodies include the activation of p38 MAPK and NF- κ B and the suppression of homeostatic Krüppel-like factors.¹⁰³⁻¹⁰⁵ Modulation of these pathways by antiphospholipid antibodies leads to a reduction in nitric oxide synthesis and increased expression of tissue factor and cell adhesion molecules.¹⁰⁶⁻¹⁰⁹ Concordantly, mice can be protected from antiphospholipid antibodies mediated thrombosis by disrupting the function of various selectins, selectin ligands, and integrins.¹¹⁰⁻¹¹³ Endothelium derived microparticles can be detected at

increased levels in the circulation of patients with antiphospholipid syndrome, indicating that the endothelium is activated and primed for interactions with platelets and leukocytes.¹¹⁴⁻¹¹⁶ All the above phenotypes have either been attributed to $\alpha\beta_2$ GPI or have been elicited with polyclonal IgG fractions isolated from patients with antiphospholipid syndrome.

When studied in vitro, unstimulated platelets resist binding by β_2 GPI protein; however, when platelets are exposed to either shear stress or thrombin, β_2 GPI complexes with apoER2 and platelet glycoprotein Ib, enabling $\alpha\beta_2$ GPI to trigger platelet activation.¹¹⁷⁻¹¹⁸ Antiphospholipid syndrome patient derived antiprothrombin antibodies have also recently been shown to activate healthy platelets in the presence of calcium and prothrombin¹¹⁹; the authors proposed that this might explain why vitamin K mediated depletion of prothrombin (in contrast with anticoagulation with factor Xa targeting direct oral anticoagulants) might be especially effective in antiphospholipid syndrome.¹¹⁹ In a mouse model of antiphospholipid syndrome, platelets are recruited to the injured endothelium in exuberant fashion where they support fibrin generation in the thrombus.¹²⁰ While there have been only a few direct characterizations of antiphospholipid syndrome patient platelets,¹²¹⁻¹²² it has also been shown that circulating platelet leukocyte aggregates are present at increased levels in patients with antiphospholipid syndrome.¹²³

Immunothrombosis (complement, monocytes, and neutrophils)

After early work showed a requirement for complement in animal models of antiphospholipid antibodies mediated pregnancy loss,¹²⁴ attention turned to its potential role in thrombosis. In a femoral vein model, antagonizing any of complement C3, C5, or C6 protects against thrombosis.¹²⁵⁻¹²⁸

Blocking either C5 or C6 is protective in a model of antiphospholipid antibodies mediated mesenteric thrombosis.¹²⁹ Studies in patients found evidence of smoldering complement activation,¹³⁰ via both the classical pathway and alternative pathway.¹³¹⁻¹³³

Another mechanism of complement activation in antiphospholipid syndrome could require mannose binding lectin bound to β_2 GPI.¹³⁴ A notable recent study used a “modified Ham test” to show complement activity in antiphospholipid syndrome sera as measured by C5b-9 deposition and complement mediated cell death³⁵; complement hyperactivity associated with both triple positive status and recurrent thrombosis.

In vitro, $\alpha\beta_2$ GPI engage TLR4 signaling and trigger monocytes to express tissue factor and proinflammatory cytokines such as TNF- α and IL-1 β ,^{135 136} via signaling that depends on p38 MAPK and NF κ B.¹³⁷ Cofactor independent antiphospholipid antibodies such as anti-LBPA/EPCR are also able to activate monocytes via endosomal NADPH oxidase.^{71 138 139} Patients with antiphospholipid syndrome show enhanced monocyte production of tissue factor as well as VEGF and its receptor Flt-1.¹⁴⁰⁻¹⁴² Unbiased transcriptomic profiling has found upregulation of proinflammatory genes including TLR8, CD14, and others associated with inflammation and oxidative stress.¹⁴³⁻¹⁴⁵ Microparticles derived from monocytes are detected at increased levels in antiphospholipid syndrome blood,^{146 147} where they present tissue factor.¹¹⁵

Although $\alpha\beta_2$ GPI were shown to activate neutrophils many years ago,¹⁴⁸ interest in this concept intensified recently based on emerging connections between neutrophil extracellular traps (NETs) and thrombosis. NETs are extracellular web-like scaffolds of decondensed chromatin decorated with microbicidal proteins,¹⁴⁹ which trigger thrombosis in the original place through multiple mechanisms including activation of coagulation factors, the endothelium, platelets, and the complement system.¹⁵⁰ Relevant mechanisms and inhibitors of NET release are discussed in box 3. High levels of NET remnants are found in the circulation of patients with antiphospholipid syndrome even in the absence of active thrombosis.^{151 157} The prothrombotic and complement activating properties of NETs might also be further amplified by anti-NET antibodies.^{73 158}

Catastrophic antiphospholipid syndrome

Most of what is known about catastrophic antiphospholipid syndrome has been inferred through collaborative international cohort studies.³¹ One small study found high levels of von Willebrand factor and P-selectin in patients with active disease, consistent with endothelial/platelet activation.¹⁵⁹ A role for complement activation has been indirectly suggested by complement gene variants in 60% of patients who experience a catastrophic antiphospholipid syndrome event.³⁵ The likely role of complement in catastrophic

antiphospholipid syndrome is also supported by reports of successful use of eculizumab in some, but not all, patients refractory to standard treatment.^{160 161}

Obstetric morbidity

A meta-analysis of placental histopathology found that thrombosis is actually a rare feature of antiphospholipid syndrome pregnancies; rather, common abnormalities included decidual inflammation, deposition of complement split product C4d, impaired spiral artery remodeling by extravillous trophoblasts, and decreased vasculosyncytial membranes.¹⁶² Unlike most other cells in the body, trophoblasts and decidual endothelial cells constitutively display β_2 GPI on their surfaces,^{163 164} making the placenta a target for binding of pathogenic $\alpha\beta_2$ GPI.

In vitro, $\alpha\beta_2$ GPI interfere with extravillous trophoblast proliferation and invasion.^{165 166} Like endothelial cells and platelets, the low density lipoprotein receptor apoER2 has been implicated in antiphospholipid antibodies mediated trophoblast dysfunction.¹⁶⁷ β_2 GPI and apoER2 are clustered by $\alpha\beta_2$ GPI on the cell surface, which triggers protein phosphatase 2A (PP2A) activation.¹⁶⁸ Notably inhibition/deletion of either apoER2 or PP2A protects antiphospholipid syndrome mice from maternal hypertension, proteinuria, and fetal growth restriction.¹⁶⁸ Beyond apoER2, in vitro studies have also implicated the TLR4/MyD88 pathway in anti- β_2 GPI mediated trophoblast dysfunction.¹⁶⁹ Downstream of TLR4, endogenous uric acid contributes to inflammasome activation,¹⁷⁰ while miR-146a-3p activates TLR8.¹⁷¹ The extent to which other autoantibodies associated with antiphospholipid syndrome beyond $\alpha\beta_2$ GPI contribute to trophoblast dysfunction has not been rigorously investigated.

In addition to trophoblast dysfunction, antiphospholipid antibodies also promote complement activation in the placenta, which could explain the effectiveness of heparins in reducing antiphospholipid syndrome obstetric morbidity.¹⁷² Notably, mice deficient in C3 are almost completely protected from fetal injury when they receive IgG from patients with antiphospholipid syndrome.¹⁷³ Subsequent studies implicated both C4 (classical pathway) and factor B (alternative pathway) in mediating the full antiphospholipid syndrome phenotype in mice.^{174 175} Downstream of complement, neutrophils are activated in C5a receptor dependent fashion with inflammation further amplified by TNF- α and tissue factor.^{174 176} Studies in patient cohorts have shown that blood markers of complement activation (Bb, soluble C5b-9) predict pregnancy morbidity in patients positive for antiphospholipid antibodies.¹⁷⁷ Notably, NETs have also been found in the intervillous space of antiphospholipid syndrome placentas where they could contribute to reduced trophoblast function.¹⁷⁸

Occlusive vasculopathy

Although this antiphospholipid antibodies related pathology was initially reported and is still best defined in the renal microvasculature,¹⁷⁹⁻¹⁸⁰ occlusive lesions are likely under-recognized in tissues that are not commonly biopsied such as brain, heart, and mesentery.¹⁸¹⁻¹⁸³ The chronic vasculopathy of antiphospholipid syndrome is characterized by progressive expansion of the intima,¹⁸¹⁻¹⁸³ which could be partially attributable to endothelial cell proliferation, but might also require infiltration of vascular smooth muscle cells and deposition of proteoglycan rich extracellular matrix. The molecular pathways that propel these vascular lesions have not been studied in detail, although one report posited that the mTOR/Akt pathway is an important mediator of antiphospholipid syndrome nephropathy and therefore a potential pharmacological target.¹⁸⁴

Management of thrombotic antiphospholipid syndrome

Risk factor reduction

Given that many patients with persistent antiphospholipid antibodies will also have other cardiovascular risk factors such as hypertension, dyslipidemia, and obesity,¹⁸⁵ attention should be given to correcting reversible predispositions whenever possible. The importance of such factors is emphasized by an easy-to-use thrombosis risk prediction tool called the adjusted Global Antiphospholipid Syndrome Score (aGAPSS), which includes hypertension and hyperlipidemia in addition to the traditional antiphospholipid antibody tests discussed above.¹⁸⁶

Primary prevention

Antiphospholipid antibodies can be detected during evaluations of patients with rheumatic disease, obstetric morbidity, thrombocytopenia, or livedo reticularis/racemosa, or during further assessment for a false positive syphilis test or prolonged activated partial thromboplastin time. Data to guide management of such patients are limited.¹⁸⁷⁻¹⁸⁹ A prospective observational study of 258 individuals with persistently positive antiphospholipid antibodies (54.3% using primary prophylaxis) showed an annual thrombotic incidence rate of 1.86%.¹⁹⁰ By contrast, when 104 carriers of triple positive antiphospholipid antibodies were followed for an average of 4.5 years, annual thrombosis incidence was 5.3%¹⁹¹; in this cohort, use of low dose aspirin was not associated with a reduced risk of thrombosis.

One randomized controlled trial has evaluated the effectiveness of aspirin (n=48) versus placebo (n=50) for prevention of first thrombotic event in individuals persistently positive for antiphospholipid antibodies¹⁹²; the trial found no difference between groups, albeit with a low event rate as a clear limitation.¹⁹² A recent Cochrane systematic review found insufficient evidence to support the use of aspirin for primary thrombosis prevention in asymptomatic carriers of antiphospholipid

antibodies.¹⁹³ Some observational studies have suggested a protective effect of aspirin,¹⁹⁴⁻¹⁹⁶ which might be most relevant in patients with lupus or thrombocytopenia.¹⁹⁶ Such data informed the recommendations by EULAR¹⁹⁷ and the 16th International Congress on Antiphospholipid Antibodies Task Force on APS Treatment Trends¹⁹⁸ to provide low dose aspirin prophylaxis in subjects with a high risk profile, defined as persistently positive for lupus anticoagulant or with triple positive status, or both. At this point, the decision regarding primary prophylaxis remains individualized and should consider other thrombotic risk factors.

Treatment and secondary prevention

Key trials that have informed the approach to treatment and secondary prevention of thromboembolism are highlighted in table 2. Vitamin K antagonists are the recommended treatment for thrombotic antiphospholipid syndrome. Several early observational studies suggested that optimal anticoagulation regimens were those that maintained the INR between 3.0 and 4.0 (so called high intensity anticoagulation).^{18 199 200} Conversely, two randomized controlled trials in 2003 and 2005 found no difference between INR goals of 2.0-3.0 and 3.1-4.0,^{201 202} other than a higher risk of hemorrhagic complications with the high intensity regimen.²⁰² Many patients in the high intensity arms did not routinely achieve the higher INR target, and a minority of patients with a history of arterial thrombosis were included; some experts therefore continue to endorse the use of high intensity anticoagulation, especially for patients with arterial thrombosis. Such an approach can be supported by a systematic review that found only seven of 180 recurrent thrombotic events occurred in patients when the INR was >3.0,²⁰³ while noting that recent EULAR guidelines did not reach a consensus on this topic.¹⁹⁷ Whether a higher target INR is better for certain subsets of patients with recurrent venous thromboembolism or an initial arterial event remains controversial.²⁰³⁻²⁰⁵ Rather than targeting a higher goal INR, some favor the combination of aspirin and standard intensity anticoagulation for secondary prevention of arterial thrombosis, which can be supported by observational data.²⁰⁶

Several randomized controlled trials have investigated the use of direct oral anticoagulants in patients with thrombotic antiphospholipid syndrome. One randomized controlled trial of 116 patients with antiphospholipid syndrome (28% triple positive) compared rivaroxaban with the vitamin K antagonist warfarin.²⁰⁷ While the study did not meet its primary endpoint (change in endogenous thrombin potential), no thrombosis or major bleeding was observed in either group over seven months.²⁰⁷ Another trial evaluated rivaroxaban compared with warfarin in 120 triple positive patients with antiphospholipid syndrome.²⁰⁸ The composite primary outcome of thrombotic events, major bleeding, and vascular mortality

was higher in the rivaroxaban group (hazard ratio 7.4, 95% confidence interval 1.7 to 32.9).²⁰⁸ A second study also failed to show non-inferiority of rivaroxaban compared with warfarin as a secondary thromboprophylaxis agent.²⁰⁹ Finally, a randomized controlled trial of apixaban versus warfarin was stopped early after the primary outcome, stroke, occurred in six of 23 patients randomized to apixaban (albeit three receiving prophylactic rather than therapeutic dosing), as compared with 0 of 25 patients randomized to warfarin.²¹⁰ A recent meta-analysis found no evidence of a higher risk of recurrent venous thromboembolism in patients with antiphospholipid syndrome treated with direct oral anticoagulants compared with those treated with warfarin²¹¹; this was in contrast to a significantly increased risk of recurrent arterial thrombosis.²¹¹ Moreover, risk of recurrent arterial thrombosis tended to be more frequent in patients with a history of arterial thrombosis.²¹¹ These results are in line with international guidelines which recommend not to use direct oral anticoagulants in patients with antiphospholipid syndrome with a history of arterial thrombosis, but raise the question of the efficacy of direct oral anticoagulants to prevent venous thrombosis in a subset of patients with antiphospholipid syndrome.^{198 212} At present, our opinion is that direct oral anticoagulants should be avoided when possible in patients with a history of arterial thrombosis or with triple positive antiphospholipid syndrome, regardless of whether the initial thromboembolic event was venous or arterial, pending further well designed clinical trials.

Treatment with long term anticoagulation unfortunately brings with it an increased risk of bleeding complications. At a traditional INR target (eg, 2.0-3.0), the risk of major bleeding in patients with antiphospholipid syndrome is similar to that observed in patients receiving vitamin K antagonists because of inherited thrombophilia or prosthetic mitral valve replacement.²¹³ The risk of bleeding is higher when vitamin K antagonists are either combined with aspirin,²¹⁴ or administered at a higher intensity in pursuit of an INR target such as 3.0-4.0.²⁰² The risk of bleeding is increased in patients with poor anticoagulant control, and optimally, these patients would be managed by experienced providers to minimize the bleeding risk.²⁰⁰ Novel approaches to anticoagulation in antiphospholipid syndrome that might reduce bleeding risk, such as factor XI inhibitors,²¹⁵ are currently being studied in different patient populations. We also need to identify patients with antiphospholipid syndrome who might be able to eventually discontinue anticoagulation altogether,²¹⁶ such as in individuals with marginally positive antibodies at baseline that eventually disappear.

If a patient develops a thrombotic event while on a vitamin K antagonist, alternative treatments, such as the addition of aspirin, a switch to low

molecular weight heparin, or initiation of high intensity anticoagulation (eg, vitamin K antagonist with a target INR>3.0), would typically be considered first.²¹⁷

Catastrophic antiphospholipid syndrome

In addition to recognizing and treating any underlying triggers (eg, infection), so called “triple therapy” with anticoagulation (typically unfractionated heparin), corticosteroids, and plasmapheresis or intravenous immunoglobulin (or both) is typically utilized in patients with catastrophic antiphospholipid syndrome^{218 219}; this approach has improved survival as evidenced by a large retrospective case series (471 patients).²²⁰ Specifically, triple therapy was positively associated with a higher chance of survival when compared with non-treatment (odds ratio 9.7, 95% confidence interval 2.3 to 40.6) or treatment with other combinations of drugs included in the triple therapy (odds ratio 1.7, 95% confidence interval 1.2 to 2.6).²²⁰ Rituximab is sometimes used as adjuvant treatment in catastrophic antiphospholipid syndrome.²²¹ Furthermore, while it seems likely that complement inhibiting treatments would benefit a subset of patients with catastrophic antiphospholipid syndrome who present with features of a complement mediated thrombotic microangiopathy, real world experience has not found such treatment to be universally effective. More research is therefore needed to identify the patients most likely to benefit.^{160 161}

Management of obstetric antiphospholipid syndrome

Patients positive for antiphospholipid antibodies without history of thrombotic events or obstetric morbidity

Two randomized controlled trials and one retrospective study of pregnant individuals with positive antiphospholipid antibodies (but without systemic lupus erythematosus) did not show a difference in live birth rate with low dose aspirin.²²²⁻²²⁴ A large randomized controlled trial of patients with pregnancies at risk for pre-eclampsia (n=1176), including a minority with antiphospholipid syndrome, found a significant decrease in the rate of preterm pre-eclampsia with low dose aspirin at a dose of 150 mg daily started at 11-14 weeks' gestation.²²⁵ Various professional organizations recommend aspirin doses of 75 to 150 mg daily beginning ≥ 12 weeks' gestation,²²⁶⁻²³⁰ and ideally by 16²²⁷ to 20²²⁶ weeks' gestation to reduce the rate of pre-eclampsia in at risk patients. The optimal low dose aspirin dose is uncertain because dose comparison trials are lacking. Specifically regarding patients with antiphospholipid antibodies without antiphospholipid syndrome, American expert guidelines call for prophylactic low dose aspirin (81 or 100 mg daily) during pregnancy beginning before 16 weeks' gestation.²³¹ European guidelines recommend low dose aspirin (75-100 mg daily) for patients with lupus anticoagulant or who are double positive for antiphospholipid antibodies.¹⁹⁷ Most

experts also recommend careful monitoring of fetus and mother.^{197 232}

Individuals with antiphospholipid syndrome based on recurrent early miscarriage (no thrombosis history)

While some trials have found improved live birth rates with the combination of low dose aspirin and prophylactic dose heparin,²³³⁻²³⁵ other studies have not shown a benefit.^{236 237} A systematic review highlighted the many limitations of the literature characterizing antiphospholipid antibodies in the setting of recurrent early miscarriage.²³⁸ A Cochrane systematic review including 1295 pregnancies from five qualifying studies concluded that treatment with low dose aspirin and prophylactic dose heparin might increase the number of live births (relative risk 1.27, 95% confidence interval 1.09 to 1.49), but the characteristics of participants and adverse events were not uniformly reported and the evidence was judged to be of low certainty.²³⁹ In most cases, combination treatment with low dose aspirin and prophylactic dose heparin is ultimately recommended in the clinic.¹⁹⁷

Individuals with antiphospholipid syndrome based on history of thrombosis or of second trimester or third trimester morbidity

Well designed trials to determine the efficacy of treatments (including low dose aspirin and heparin) and to improve obstetric outcomes in patients diagnosed with antiphospholipid syndrome are lacking. Against a background of increased maternal risk for thrombosis owing to antiphospholipid antibodies positivity and results from retrospective case series, current European and American guidelines recommend patients with antiphospholipid syndrome based on a history of second trimester or third trimester morbidity and without a history of thrombosis be treated during pregnancy with low dose aspirin and prophylactic dose low molecular weight heparin, while those with a history of thrombosis should be treated with low dose aspirin and therapeutic dose low molecular weight heparin.^{197 231} American guidelines also conditionally recommend treatment during pregnancy with hydroxychloroquine.²³¹ Clinicians should recognize that despite treatment with low dose aspirin and heparin, patients with lupus anticoagulant, and perhaps particularly those that are triple positive, have a 30% or higher risk of adverse pregnancy outcomes.^{23 65 240} Given the risks of pre-eclampsia and placental insufficiency in these patients, experts recommend careful monitoring of fetus and mother.^{197 232}

Other considerations

Given that the postpartum period represents the highest risk for pregnancy related thrombosis, antiphospholipid antibodies-positive individuals who have never had thrombosis should receive 6-12 weeks of prophylactic low molecular weight heparin,

while participants with antiphospholipid syndrome and history of thrombosis should resume full anticoagulation.^{7 232} Beyond hydroxychloroquine, other treatments such as intravenous immunoglobulin and corticosteroids are sometimes trialed in refractory cases, albeit without compelling evidence from the literature.

Considerations regarding covid-19

Critical and severe cases of covid-19 are associated with an increased risk of thrombosis in arterial, microcirculatory, and venous vascular beds.²⁴¹ Reports from early in the pandemic found antiphospholipid antibodies at high titers in a small number of patients with covid-19 who experienced macrovascular thrombotic events.^{241 242} Studies of hospitalized covid-19 patients have detected both traditional antiphospholipid antibodies (such as IgG and IgM isotypes of anticardiolipin antibodies) and non-criteria antiphospholipid antibodies (including IgG and IgM isotypes of anti-PS/PT, as well as IgA isotypes of anticardiolipin antibodies and $\alpha\beta_2$ GPI). Studies show significant heterogeneity in terms of both overall prevalence of antiphospholipid antibodies (some as high as 50%) and which antiphospholipid antibodies species are most commonly detected.²⁴³⁻²⁴⁵ While most studies have not found a clear link between circulating antiphospholipid antibodies and large vessel thrombosis,²⁴⁶ some evidence has been found that IgG fractions isolated from patients with covid-19 have prothrombotic properties in vitro and in mice.²⁴⁵ Future studies are required to further clarify whether antiphospholipid antibodies found in patients with severe covid-19 are similar to antiphospholipid antibodies seen in patients with antiphospholipid syndrome.

Vaccination with adenovirus based covid-19 vaccines has been associated with rare complications of thrombocytopenia and thrombosis, likely attributable to antiplatelet factor 4 antibodies²⁴⁷; this complication has not been seen with other types of covid-19 immunizations, including mRNA vaccines. Nevertheless, both patients and providers have questioned the extent to which patients with antiphospholipid syndrome might be at increased risk for vaccine associated complications. Fortunately, this does not appear to be the case with multiple studies showing no thrombosis or serious adverse events in 102,²⁴⁸ 146,²⁴⁹ and 44²⁵⁰ vaccinated patients positive for antiphospholipid antibodies.

Emerging treatments

Hydroxychloroquine and statins

Both hydroxychloroquine and statins were highlighted as emerging treatments by recent International Congress on Antiphospholipid Antibodies task forces on APS treatment trends.^{198 251} Hydroxychloroquine appears to be protective against thrombosis in people with lupus, whether characterized by positive antiphospholipid antibodies or not.¹⁹⁵

In animal models of antiphospholipid syndrome, hydroxychloroquine reduces thrombus size.²⁵² In vitro, hydroxychloroquine prevents antiphospholipid antibodies mediated disruption of the annexin A5 shield that coats phospholipid bilayers.²⁵³ In patients, a reduced type I interferon signature is observed in patients with antiphospholipid syndrome taking hydroxychloroquine, as compared with those who are not.²⁵⁴ Based on these mechanistic data and its excellent safety profile, hydroxychloroquine is regularly deployed in patients with antiphospholipid syndrome with high risk antibody profiles, breakthrough thrombotic events, or other disease manifestations that are progressing despite anticoagulation.

HMG-CoA reductase inhibitors, known as statins, have been widely used for primary and secondary cardiovascular disease prevention, and clearly have a role in patients with antiphospholipid syndrome who also have hypercholesterolemia. Beyond their impact on cholesterol, administration of fluvastatin to mice with antiphospholipid syndrome reduces leukocyte adhesion to endothelial cells as well as thrombus size.²⁵⁵ Small mechanistic clinical trials of fluvastatin in patients with antiphospholipid syndrome have shown reduced tissue factor expression by monocytes,²⁵⁶ and modulation of proinflammatory and prothrombotic biomarkers.²⁵⁷ Like hydroxychloroquine, statins are sometimes prescribed to patients with antiphospholipid syndrome with breakthrough manifestations or at high risk of recurrent events.

Other less common agents

Case reports have described the successful use of rituximab in patients with antiphospholipid syndrome with severe thrombocytopenia, autoimmune hemolytic anemia, skin ulcers, and antiphospholipid antibodies associated nephropathy.²⁵⁸ A pilot open label phase II clinical trial found rituximab to exhibit potential efficacy for non-criteria manifestations of antiphospholipid syndrome.⁸² Eculizumab is a humanized monoclonal antibody that prevents complement C5 cleavage and is approved for treatment of atypical hemolytic uremic syndrome and paroxysmal nocturnal hematuria.^{259 260} Case reports and series have suggested efficacy of eculizumab in treating refractory antiphospholipid syndrome especially in the setting of catastrophic antiphospholipid syndrome.^{160 161 261} Regarding pregnancy morbidity, one ongoing study aims to determine whether the addition of tumor necrosis factor alpha blockade to standard of care treatment can improve outcomes as compared with historical controls (NCT03152058); to date (December 2022), this study has recruited 43 patients with a pre-prescribed target of 50.

Other agents that might warrant further study include sirolimus,¹⁸⁴ adenosine receptor agonists such as dipyridamole,¹⁵⁴ and plasma cell depleting agents such as daratumumab.²⁶² Patients are also interested in further study of supplements

such as CoQ10, ginger, and vitamin D that have shown promise in preclinical and mechanistic studies.^{156 263 264} A review of clinicaltrials.gov in September 2022 identified antiphospholipid syndrome trials recruiting subjects for interventions targeting B cells (belimumab, telitacicept, zanubrutinib), tumor necrosis factor (certolizumab), and innate immunity (hydroxychloroquine).

Guidelines

Currently, researchers rely on an international consensus statement for classification of definite antiphospholipid syndrome published in 2006.⁵ An international effort to update these criteria is under way and is likely to take into account features of antiphospholipid syndrome beyond thrombosis and pregnancy morbidity,⁴² such as thrombocytopenia, heart valve damage, and livedo racemosa. Other risk factors surrounding venous (malignancy, major surgery) and arterial (hypertension, hyperlipidemia) thromboemboli are also likely to be better accounted for in the new criteria. Other notable guidelines include expert guidance from the scientific and standardization committee for lupus anticoagulant/antiphospholipid antibodies of the International Society on Thrombosis and Haemostasis,⁶⁰ and EULAR recommendations for the management of antiphospholipid syndrome in adults,¹⁹⁷ both of which are referenced above. Areas to watch in future include the development of pediatric specific criteria, continued refinements for best laboratory practices in patients receiving anticoagulant therapy, and more nuanced recommendations for which patients are most likely to benefit from medications beyond warfarin.

Conclusion

In summary, antiphospholipid syndrome is a thrombo-inflammatory autoimmune disease driven by autoantibodies that recognize cell surface phospholipids and phospholipid binding proteins. The result is an increased risk of thrombotic events, pregnancy morbidity, and other autoimmune or inflammatory complications. Vitamin K antagonists remain the most appropriate treatment for most patients with thrombotic antiphospholipid syndrome and, based on current data, appear superior to direct oral anticoagulants. Beyond anticoagulants and anti-aggregants, recent research has highlighted additional potential therapeutic targets within the innate immune system, including the complement system and NETs. The potential role of immunomodulatory treatments in antiphospholipid syndrome management is rightly receiving increased attention.

Some of the most pertinent and persistent questions for the antiphospholipid syndrome field are highlighted in the Questions for future research box. While mechanistic in vitro and in vivo studies will likely continue to prove valuable, we are fortunate that recent advances in biomedical and clinical sciences have created unprecedented

research opportunities to understand disease causes more deeply, and ultimately, improve outcomes through an approach personalized to the care of each individual living with antiphospholipid syndrome. It will be imperative in the coming decade to introduce individual and multiomics approaches to the study of carefully phenotyped patient cohorts, including during interventional clinical trials. Profiling circulating and tissue resident cells,¹⁴⁵ as well as cytokines,²⁶⁵ metabolism,²⁶³ microbiome,²⁶⁶ and other areas is likely to be necessary to identify the next generation of safer and more effective treatments for patients.

QUESTIONS FOR FUTURE RESEARCH

- What adjuvant agents can best suppress breakthrough antiphospholipid syndrome manifestations, especially those that target the microvasculature and thereby threaten organ function?
- Will agents that decrease antibody titers (neonatal Fc receptor inhibitors, plasma cell depleting agents) find a role in the management of antiphospholipid syndrome?
- Can lupus anticoagulant functional panels eventually be replaced with a combination of solid phase assays? If so, what will be the relative roles of IgG and IgM autoantibodies in antiphospholipid syndrome?
- How can we explain the heterogeneity of antiphospholipid syndrome? Will it be defined by a comprehensive understanding of autoantibodies or by other patient specific factors?
- Anti- β_2 GPI antibodies clearly contribute to antiphospholipid syndrome pathogenesis; how might these antibodies conspire with autoantibodies such as anti-PS/PT and anti-LBPA/EPCR?

PATIENT INVOLVEMENT

A draft of the manuscript was shared with three patients who are living with antiphospholipid syndrome. Their feedback led to numerous improvements to the manuscript, especially in the sections that describe non-criteria manifestations of antiphospholipid syndrome, the impact of antiphospholipid syndrome on quality of life, the risks and benefits of currently available treatments, and future directions for antiphospholipid syndrome treatment.

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