

# Treatment of antiphospholipid antibody syndrome

Antiphospholipid antibody syndrome (APS) is a systemic autoimmune disease with thrombotic predilection resulting in vascular thrombotic events and obstetric complications. Management of APS focuses on anticoagulation; however, despite the solid evidence suggesting that this is the best treatment option available, a lot of debate persists regarding the intensity and duration of anticoagulation needed in the various subsets of APS. Thus, there are currently no uniformly agreed upon management algorithm for APS. This article reviews the clinical and serological criteria defining this syndrome and presents the latest evidence with regard to the optimal management of the various aspects of APS. Here we present our evidence-based recommendations for proper APS management. We conclude by shedding light on possible therapeutic options that may be available in the near future.

**KEYWORDS:** antiphospholipid antibodies ■ antiphospholipid syndrome  
■ clinical aspects ■ management ■ prophylaxis

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## Learning objectives

Upon completion of this activity, participants should be able to:

- Distinguish antiphospholipid antibody syndrome (APS) from genetic thrombophilias
- Describe the types of categories of APS
- Describe the diagnostic criteria for APS
- Identify the criteria for management of APS with anticoagulation
- Describe optimal treatment of APS during pregnancy

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Antiphospholipid antibody syndrome (APS) is an autoimmune vascular thrombotic disorder. It is often characterized by recurrent thrombosis and/or obstetric morbidity in patients with persistently positive antiphospholipid antibodies (aPLs) [1]. In the early 1980s, it was observed that amongst patients suffering from systemic lupus erythematosus (SLE) there was an association between the presence of circulating aPLs and thrombosis, pregnancy loss and thrombocytopenia [2]. However, years later it became clear that APS can occur in the absence of an underlying systemic autoimmune disease (primary APS) [3]. Lately, a lot of publications have focused on the remarkable similarity between APS and SLE in terms of systemic clinical manifestations and serologic markers. This has led Shoenfeld *et al.* to speculate that these entities might represent variants within a continuum of the same disease [4].

At present, APS is recognized as one of the most common causes of acquired thrombophilia in young adults. Unlike genetic thrombophilias that lead to venous thromboembolic phenomenon, thrombosis in APS can affect any vascular bed (e.g., arterial and venous) of any size [5]. Deep vein thrombosis with or without pulmonary embolism, along with strokes and transient ischemic attacks, are the most common manifestations and major causes of morbidity in this disease [3]. Interestingly, according to a recent paper by Cervera *et al.*, the major causes of mortality include bacterial infections, myocardial infarctions and strokes [6]. This observation holds significance owing to the possibility that an infectious process might be an important triggering factor in the etiopathogenesis of the disease.

Anticoagulation is currently the mainstay of management of APS patients, but there remain several controversies in the management algorithm of the disease (e.g., intensity of anticoagulation, duration of anticoagulation and whether or not to anticoagulate asymptomatic patients who are serologically aPL positive). Experience has shown us that some APS patients still develop disease progression despite optimal anticoagulation [6]. Moreover, as our understanding of the disease advances, we are facing certain clinical manifestations of APS that are not related to the thrombotic tendency of the disease. All this calls for a thorough review of the available literature in order to devise the optimal management protocol of various APS patients. This also shows that a deeper understanding of the pathogenetic etiology of the disease is required in order to provide better therapeutic options (not only thrombosis targeted) for the disease process.

In this article, we will review the clinical and serological criteria of APS. We will also present a critical review of the available data regarding the treatment of various categories of APS patients. Based on this review, we will provide updated evidence-based treatment guidelines for the management of APS patients. We will also shed light on the future of the management of APS as we present certain agents that have been shown to be promising in APS research studies.

### Clinical aspects of APS

Antiphospholipid antibody syndrome was first described in patients with SLE and abnormal lupus anticoagulant test results along with thrombotic tendency [2]. However, it was noted later that this syndrome could occur independently without any associated systemic autoimmune disease. Thus, the distinction between secondary APS, which occurs in the setting of a pre-existing autoimmune disease, and primary isolated APS became necessary.

Antiphospholipid antibody syndrome is well known for its hypercoagulable state, leading to both venous and arterial thrombotic events. This was noted in the international preliminary (Sapporo) classification criteria for APS (Box 1) [1]. The thrombotic events can show in different clinical presentations ranging from superficial thrombosis, to large vessel thrombosis, to life-threatening catastrophic APS (CAPS), which presents with widespread microangiopathy and leads to a syndrome that is difficult to distinguish from disseminated intravascular coagulation and thrombotic thrombocytopenic purpura [7,8]. Other thrombotic presentations include osteonecrosis and venous occlusion of solid organs, such as the liver (Budd–Chiari syndrome) [9], kidneys [10] and the adrenal glands with resulting adrenal insufficiency [9,11]. Furthermore, any vessel can be involved with thrombosis in APS, including the iliac, femoral, retinal or the inferior vena cava [12,13]. Mesenteric and colonic vasculature can be the setting of the thrombotic processes with bowel infarction, pancreatitis or even colonic perforation [14]. In addition to thrombotic predilection, aPLs have been associated with accelerated atherosclerosis. The pathophysiology of this observation has been extensively studied. Matsuura *et al.* recently published a review regarding this topic, demonstrating that APS is associated with facilitated intracellular accumulation of oxidized low-density lipoprotein in macrophages as well as endothelial damage and vascular inflammation [15]. Another presentation of the thrombotic predilection of

**Box 1. The international preliminary (Sapporo) classification criteria for antiphospholipid syndrome.****Clinical criteria**

- Vascular thrombosis:
  - One or more clinical episodes of arterial, venous or small-vessel thrombosis in any tissue or organ.
- Pregnancy morbidity (one of the following):
  - One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation;
  - One or more premature births of a morphologically normal neonate before the 34th week of gestation due to eclampsia, severe pre-eclampsia or recognized features of placental insufficiency;
  - Three or more unexplained, consecutive, spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities, and maternal and paternal chromosomal causes excluded.

**Laboratory criteria**

- Lupus anticoagulant present in plasma on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis.
- Anticardiolipin antibody (IgG and/or IgM isotype) in serum or plasma, present in medium or high titers on two or more occasions at least 12 weeks apart, measured by a standardized ELISA.
- Anti- $\beta_2$  glycoprotein I antibody (IgG and/or IgM isotype) in serum or plasma, present on two occasions at least 12 weeks apart, measured by a standardized ELISA.

*The diagnosis of definite antiphospholipid antibody syndrome could be made only if one clinical criterion occurs along with one of the laboratory criteria. International preliminary (Sapporo) classification criteria for antiphospholipid antibody syndrome [1].*

APS is the obstetric morbidity of the disease. This includes recurrent spontaneous abortions, fetal deaths, intrauterine growth restriction, pre-term delivery and pre-eclampsia. Interestingly, some clinical presentations of APS do not stem from the systemic thrombotic tendency associated with disease and are therefore not caused by thrombosis. These include thrombocytopenia, livedo reticularis and heart valve lesions, in addition to a spectrum of neurological disorders such as chorea, epilepsy, memory loss, transverse myelitis and multiple sclerosis-like disease [16–23]. It should be noted that some of these nonthrombotic manifestations are among the most common presentations of APS [24]. These manifestations sometimes precede the occurrence of frank thrombotic attacks by years. However, as noted in the updated Sapporo criteria of APS, these manifestations are not part of the diagnostic algorithm [1]. We speculate that these nonthrombotic, yet common, APS presentations will be part of the classification criteria in the near future, providing solid scientific evidence becomes available to justify the change.

Following the publication of the revised Sapporo classification criteria for APS, several research groups tried to validate these recommendations in comparison to the initial Sapporo criteria. Kaul *et al.* examined this topic in a descriptive study of 200 aPL-positive patients and concluded that the revised criteria will have positive implications in APS research and will limit overdiagnosis of APS [25]. Bobba *et al.* further emphasized the positive impact of the revised criteria in a review concluding that these criteria have incremental face and content validity over the initial Sapporo criteria [26].

A possible association between APS and malignancy is noteworthy. In a recent article by Tincani *et al.*, the authors concluded that despite the obvious lack of sufficient evidence, patients with certain neoplasms that are associated with elevations in aPLs demonstrated a higher thrombosis risk than the general population [27]. Moreover, it was also found that asymptomatic aPL-positive patients have an increased risk of developing a malignancy (particularly hematologic). This association warrants further investigation. Box 2 stratifies the clinical manifestations of APS by organ system and summarizes the various presentation of each system.

**Antiphospholipid antibodies**

Antiphospholipid antibodies comprise a family of heterogeneous antibodies that share the ability to bind phospholipid-binding proteins including, and most commonly,  $\beta$ -2 glycoprotein I ( $\beta$ 2GPI) [12]. Other less commonly encountered target proteins include prothrombin, tissue plasminogen activator, annexin A2 and thrombin [28,29]. Despite the broad range of existing aPLs, only three tests are commonly used to detect the presence of aPLs in patients' blood. The three tests are the lupus anticoagulant functional coagulation assay, anticardiolipin (aCL) ELISA and anti- $\beta$ -2GPI antibody ELISA (Box 1) [1]. Additional antibodies can be detected via different laboratory tests. These include IgA aCL antibodies, IgA anti- $\beta$ -2GPI antibodies, antiphosphatidylserine antibodies, antiphosphatidylethanolamine antibodies, antiprothrombin antibodies and antiphosphatidylserine–prothrombin complex antibodies [1]. As illustrated in Box 1, these antibodies are not incorporated

**Box 2. Antiphospholipid antibody syndrome: clinical features.****Cardiovascular**

- Myocardial infarction [81]
- Accelerated atherosclerosis [82]
- Heart valve lesions<sup>†</sup>
- Syndrome X [83]
- Deep vein thrombosis

**Pulmonary**

- Pulmonary hypertension<sup>†</sup>
- Diffuse alveolar hemorrhage<sup>†</sup>
- Acute respiratory distress syndrome<sup>†</sup>

**CNS** [22,84,85]

- Strokes
- Transient ischemic attacks
- Chorea and movement disorders<sup>†</sup>
- Epilepsy<sup>†</sup>
- Transverse myelitis<sup>†</sup>
- Multiple sclerosis-like disease<sup>†</sup>
- Memory loss<sup>†</sup>

**Ophthalmic** [86]

- Visual problems (CRVO, CRAO, PRVO and PRAO)

**Ear nose throat**

- Sudden sensorineural hearing loss [87,88]
- Balance disturbances [89]

**Blood**

- Thrombocytopenia<sup>†</sup>

**Endocrine**

- Adrenal insufficiency
- Pituitary infarction

**Orthopedic** [90]

- Osteonecrosis [91]
- Avascular necrosis<sup>†</sup>

**Renal** [92,93]

- RAS and renal HTN
- Renal vein thrombosis
- Renal failure<sup>†</sup>

**Gastroenterology**

- Mesenteric ischemia (acute–chronic) [94]
- Pancreatitis [95]
- Peptic ulcer disease [96]
- Bowel ischemia and perforation [97]
- Budd–Chiari syndrome

**Skin** [98]

- Livedo reticularis<sup>†</sup>
- Skin ulcers

**Reproductive (obstetric)**

- Spontaneous abortions
- Fetal loss<sup>†</sup>
- Premature births
- Fetal growth restriction
- Pre-eclampsia

<sup>†</sup>May not be secondary to thrombosis.

<sup>†</sup>May have a thrombotic and a nonthrombotic component.

CRAO: Central retinal artery occlusion; CRVO: Central retinal vein occlusion; HTN: Hypertension; PRAO: Peripheral retinal artery occlusion; PRVO: Peripheral retinal vein occlusion; RAS: Renal artery stenosis.

into the revised Sapporo criteria for classification of APS because they lack the required specificity and their corresponding tests lack standardization [1]. It is worth mentioning that a high variability in the performance of clinical laboratories with respect to sensitivity and specificity of lupus anticoagulant tests has been reported. To address this, a helpful update of the detection guidelines for lupus anticoagulant detection was recently published by Pengo *et al.*, with recommendations for appropriate detection of lupus anticoagulant highlighting proper patient selection, blood collection and interpretation of results [30]. The efficacy of these guidelines in terms of improved test measures should be validated in further studies.

Interestingly, some individuals demonstrate positive aPL test results without any vascular or obstetric thrombotic manifestations. These should be labeled as asymptomatic aPL-positive patients rather than APS patients, although they do have an increased lifetime risk of acquiring the disease [31]. Conversely, the term seronegative APS has recently been used in the literature to delineate typical APS clinical presentation with negative serological markers. It has been proposed that these patients may only have aPLs other than those included in the Sapporo criteria. Sanmarco *et al.* suggested that antiphosphatidylethanolamine may be an important serological marker responsible for the thrombotic manifestations in seronegative APS [32]. More studies are required in order to identify the added value of this (or other) serological markers to the panel of tested antibodies currently available.

### Management of persistently aPL-positive patients

It is not surprising that management of aPL-positive patients focuses on anticoagulation and antithrombotic therapies (Box 3). However, owing to the low prevalence of the disease, randomized controlled trials (RCTs) have faced limitations in recruiting sufficient participants to represent the wide spectrum of the disease and thus empower the study design. As a consequence of this problem, much of the evidence-based practice in the management of APS has relied on the methodologically weaker observational studies. This has led to controversy and debate regarding what the best practice really is.

### ■ Management of asymptomatic aPL-positive patients

Asymptomatic aPL-positive patients have an estimated 0–3.8% thrombosis risk per year [6,33]. However, the actual annual risk is difficult to

estimate accurately owing to the important impact of confounding factors when it comes to the issue of thrombosis. These factors include diabetes, hypertension, hyperlipidemia, smoking, estrogen-containing oral contraceptive pills and hormone replacement therapy [34]. It makes sense that management of asymptomatic persistently aPL-positive individuals should start with modification of these non-aPL thrombosis risk factors. However, in their recent prospective study, Cervera *et al.* failed to demonstrate any association between the occurrence of thrombotic manifestations and any of the non-aPL thrombotic risk factors mentioned previously [6].

Information regarding the effectiveness of aspirin for primary thromboprophylaxis in asymptomatic aPL-positive individuals is contradictory. While some studies show a reduction in thrombosis events with the use of aspirin for prophylaxis, other studies failed to show any added benefit over placebo [33,34]. Given the low rate of thrombosis in this group of individuals, it would require a large number of patients to yield a powerful and conclusive study (as many as 30,000 patients according to one commentary) [35]. Considering the disparity in the available literature regarding primary thromboprophylaxis, we recommend a risk-stratified approach to the management of these patients. Stratification should include the immunological profile of the patient. For example, a positive lupus anticoagulant test yields the highest thrombosis risk when compared with other aPLs [36]. Therefore, in patients with a high-risk immunological profile (i.e., high aPL titers, especially for lupus anticoagulant test) or those with other non-aPL thrombosis risk factors (e.g., smoking, oral contraceptive pills, hormone replacement therapy, hypertension, diabetes and postpartum depression) we recommend aspirin for thromboprophylaxis. Those patients with a low-risk profile should not receive aspirin as the risks and expense outweigh the benefits. We also recommend the use of aspirin thromboprophylaxis in all patients with an underlying systemic autoimmune disease since these patients are at a relatively higher risk of thrombosis.

Hydroxychloroquine has also been used for primary prophylaxis in asymptomatic aPL-positive patients, particularly those with another connective tissue disease, and was found to confer added thromboprophylaxis [6,37,38].

Note that in high-risk situations such as the postoperative period and periods of prolonged immobilization, we recommend using prophylactic doses of heparin in patients with asymptomatic persistently positive aPLs [39].

### ■ Secondary thrombosis prevention in persistently aPL-positive (APS) patients

Secondary thrombosis prevention in APS also requires a risk-stratified management plan and the elimination of non-aPL thrombotic risk factors. The risk of thrombosis recurrence varies depending on whether the initial event involved a vein or an artery. Recurrence rates appear to be lowest in patients with a first venous thrombotic event as compared with those with recurrent venous thrombosis or an index arterial thrombotic event [40–42]. The current accepted and agreed upon recommendation is lifelong anticoagulation [40,43,44]. However, the duration and the intensity of therapy are still subject to debate, with two recent systematic reviews (one by

#### Box 3. Recommendations for management of persistently antiphospholipid antibody-positive patients.

##### Asymptomatic aPL-positive patients<sup>†</sup>

- High thrombosis risk:
  - Lifestyle modifications and aspirin/hydroxychloroquine
- Low thrombosis risk:
  - Lifestyle modifications only

##### Secondary thrombosis prevention<sup>‡</sup>

- Index venous event:
  - Lifelong anticoagulation with INR (2–3)
- Index arterial: event/recurrent event
  - Lifelong anticoagulation with INR (3–4)<sup>§</sup>

##### Obstetric APS patients

- Clinical criteria vascular:
  - Major/recent event: aspirin and therapeutic dose UFH/LMWH
  - Minor/remote event: aspirin and prophylactic dose UFH/LMWH
- Clinical criteria obstetric:
  - Aspirin and prophylactic dose UFH/LMWH

##### Catastrophic APS<sup>¶</sup>

- Life threatening:
  - Anticoagulation, intravenous corticosteroids, and IVIG and/or plasma exchange
- Stable:
  - Anticoagulation and intravenous corticosteroids, ± IVIG and/or plasma exchange

##### Noncriteria manifestations

- Thrombocytopenia (clinically significant):
  - Corticosteroids, rituximab, IVIG or splenectomy
- Cardiac valvular disease:
  - Anticoagulation (in the presence of atrial fibrillation or other thrombosis risk factors)
- Nephropathy:
  - Anticoagulation and angiotensin-converting enzyme inhibitor
- Cognitive dysfunction:
  - No available therapeutic intervention

<sup>†</sup>Aspirin is always recommended in this group in the context of an underlying autoimmune disorder. Prophylactic heparin is indicated in high-risk situations (postoperative, prolonged immobilization).

<sup>‡</sup>Lifestyle modifications and control of non-aPL-related thrombotic risk factors are also important.

<sup>§</sup>This recommendation is supported by observational studies only.

<sup>¶</sup>In case of lack of stabilization despite full management, rituximab or cyclophosphamide could be employed.

aPL: Antiphospholipid antibody; APS: Antiphospholipid antibody syndrome; INR: International normalization rate; IVIG: Intravenous immunoglobulins; LMWH: Low-molecular-weight heparin; UFH: Unfractionated heparin.



Lim *et al.* and another by Ruiz-Irastorza *et al.*) tackling the subject and yielding conflicting conclusions and recommendations [45,46].

Lim *et al.* conducted a systematic review including only well-designed RCTs [45]. Owing to the previously mentioned limitations in designing proper RCTs, only three studies were included in the review [41,42,47]. This review concluded that APS patients who suffered a first venous or arterial noncerebral thrombotic event should be treated with regular intensity anticoagulation with a target international normalization rate (INR) of 2.0–3.0. It also concluded that those patients who suffered cerebral artery thrombosis should be treated with aspirin (325 mg/day) or moderate-intensity anticoagulation (INR: 1.4–2.0) [45].

It may seem logical that inclusion of only optimally designed RCTs in a systematic review should yield the highest level of evidence and thus provide the best recommendations. However, considering the limitations that researchers face while designing adequate RCTs in this subject, as well as the low number of participants that are enrolled in the study designs, it seems probable that these studies might not actually be representative of the APS patient population. Furthermore, inherent limitations of each of the quoted RCTs further weaken the conclusions and the recommendations of this systematic review. The studies conducted by Crowther *et al.* [41] and Finazzi *et al.* [42] were both RCTs comparing conventional-intensity anticoagulation (INR: 2.0–3.0) to high-intensity anticoagulation (INR: 3.0–4.0) in patients with criteria-based APS. However, as expected, the researchers failed to recruit the intended sample size, leaving the studies underpowered. Event rate in both of these studies was lower than expected, further diminishing the strength of the study designs. These RCTs both concluded that there was no difference in outcome between the two arms of the study [41,42]. However, it should be noted that the researchers used an intention-to-treat design to analyze the results of the study. This analysis might obscure the benefit of higher intensity anticoagulation if the level of anticoagulation in this arm of the study had been inadequate. In fact, Crowther *et al.*'s high-intensity arm was subtherapeutic in 43% of cases, whilst Finazzi *et al.*'s high-intensity arm had a mean INR of 3.2, suggesting that the levels were subtherapeutic in a substantial percentage of cases [39]. More importantly, it was noted that six out of eight thrombotic events in the high-intensity anticoagulation group of Crowther

*et al.*'s study occurred when the INR was below 3.0. Under such circumstances and taking all these observations into account, it appears that the intention-to-treat analysis might not be the best analysis modality to compare the two study groups.

The third study included in this review, the Antiphospholipid Antibody Stroke Study (APASS), was actually a subgroup analysis of the Warfarin Aspirin Recurrent Stroke Study (WARSS) [47]. This was a large prospective study that aimed to evaluate the relation between aPLs and the risk of stroke recurrence and response to therapy. It should be noted that the target population in this study was not patients with definite APS and that the Sapporo criteria were not used as part of the study's inclusion criteria. Furthermore, 41% of the individuals tested were found to be positive for aPLs, which is significantly higher than the expected incidence of persistent aPL positivity whether symptomatic or not. This points to the fact that a significant number of the enrolled patients had only a transitory aPL positivity. The study concluded that there was no difference between low-intensity anticoagulation and aspirin therapy in preventing stroke recurrence. However, given the aforementioned discussion, the validity of extrapolating this result to the APS population is debatable.

Another systematic review by Ruiz-Irastorza *et al.* [46] has drawn conclusions and made recommendations that contradict those in Lim *et al.*'s review. This review employed a study design that allowed a wider integration of the research body. Overall, nine cohort studies (prospective and retrospective) [40,43,44,48–53], five subgroup analyses [47,54–57] and two RCTs [41,45] were included in the review. Despite the fact that some of the included studies have obvious inherent design limitations, the approach was perhaps chosen in order to better represent the APS patient population [39]. Several important conclusions were generated by Ruiz-Irastorza *et al.* from this review. Importantly, among patients with definite APS as per the Sapporo clinical and laboratory criteria, risk of recurrence was lowest in those with first venous event than those with first arterial thrombotic event or recurrent events [46]. Usual-intensity anticoagulation (INR: 2.0–3.0) protected those with first venous thrombosis, whereas in patients with arterial or recurrent thrombosis, higher intensity anticoagulation (INR: 3.0–4.0) achieved better thromboprophylaxis. Another extremely important conclusion drawn by Ruiz-Irastorza *et al.* is that thrombosis recurrence was more frequent

and associated with a higher morbidity and mortality than the hemorrhagic complications of high-intensity anticoagulation therapy [46].

With the current state of knowledge, we recommend indefinite anticoagulation at an INR of 2.0–3.0 for patients with APS presenting with first venous events. Debate persists regarding those with arterial thromboses. It is our view that APS patients with arterial disease or recurrent events merit a more aggressive approach, which might include warfarin with a target INR of more than 3.0 or combined antithrombotic therapy. We acknowledge that evidence supporting this recommendation comes from observational studies only. It is also of absolute importance to control the non-aPL thrombosis risk factors, including diabetes, hypertension, hyperlipidemia and smoking.

Another nonresolved dilemma in the management plan of APS patients includes the duration of treatment following the index venous thrombotic event. Some authorities recommend indefinite anticoagulation [39], while others advocate a finite treatment period depending on whether or not a reversible risk factor could be identified [38]. However, we recommend long-term anticoagulation following the index venous thrombotic event in the context of APS, although it still unclear whether long-term anticoagulation is needed in patients whose index venous thrombotic event occurred within the setting of a reversible non-aPL prothrombotic risk factor.

As hard as it seems, well-designed RCTs with a large number of definite APS patients are called for in order to solidify the current available evidence and clarify the optimal management guidelines.

### ■ Prevention of pregnancy morbidity in APS patients

Obstetric complications are a major aspect of APS and an integral component of the Sapporo classification criteria. Complications include maternal thrombosis, recurrent spontaneous abortions before 10 weeks of gestation and late adverse pregnancy outcomes (e.g., fetal demise, pre-eclampsia, placental insufficiency, intrauterine growth restriction and preterm birth). Even with the optimal management according to the current guidelines, adverse outcomes still occur in approximately 20–30% of cases [58,59].

Different management options have been proposed in pregnant APS patients, including aspirin, unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), steroids and intravenous immunoglobulins (IVIG). It is agreed upon that the gold standard for the

management of these patients is combined aspirin and heparin therapy. Two prospective randomized trials demonstrated that treatment with aspirin and UFH was superior to aspirin alone in terms of completed successful pregnancies [60,61]. A Cochrane systematic review and meta-analysis by Empson *et al.* concluded that dual therapy with aspirin and UFH reduces pregnancy loss by 54% in patients with aPLs and previous pregnancy loss [62]. Information regarding the use of LMWH and aspirin is still not conclusive, although two small studies showed no difference between UFH and LMWH when either is combined with aspirin [63,64]. In order to further clarify this point a three-arm trial is needed, comparing UFH and aspirin in one arm, LMWH and aspirin in another and aspirin alone in the third arm.

The use of IVIG and steroids in the management of APS pregnant patients have been reported to be effective in case reports, although studies have failed to demonstrate any beneficial effect when compared with aspirin and heparin [39].

Based on the current available evidence, we recommend the use of aspirin and UFH/LMWH for thromboprophylaxis in pregnant APS patients. Patients who are maintained on long-term anticoagulation should be given therapeutic-dose UFH/LMWH during pregnancy. Similarly, patients with a recent history of a major thrombotic episode should receive therapeutic-dose anticoagulation throughout pregnancy. Patients with a remote vascular phenomenon, those with mild vascular disease (superficial thrombophlebitis) or those who meet the Sapporo criteria based solely on obstetric complications should receive prophylactic-dose UFH/LMWH. Moreover, we recommend against the standard use of IVIG or steroids in the management of APS pregnant patients, except in cases where these therapeutic interventions have another coexisting indication (autoimmune thrombocytopenia or SLE, respectively); however, in the context of failure of standard therapy, it might be reasonable to try these alternative measures.

### ■ Management of catastrophic APS

Although less than 1% of APS patients develop CAPS, these usually present in a life-threatening state and most of these patients end up in the intensive care unit [65]. A high index of suspicion and careful investigation are required to make an early diagnosis [31]. The highest survival rates are achieved via employment of combination therapy with effective anticoagulation and

intravenous corticosteroids, as well as IVIG and/or plasma exchange [38,66]. Based on the available data, we recommend stratification of patients presenting with CAPS into either 'life threatening' or 'stable'. For stable patients, we recommend effective anticoagulation in addition to intravenous steroids. In the case of no clinical improvement, IVIG and/or plasma exchange should be employed. For patients presenting with life-threatening CAPS, management plans should be more aggressive, utilizing anticoagulation, corticosteroids, IVIG and/or plasma exchange as soon as possible. In case of a deteriorating clinical situation despite exhaustion of standard treatment options, additional agents such as rituximab or cyclophosphamide could be utilized. It should be noted that there is some concern about possible upregulation of the aPLs following cyclophosphamide therapy stemming from the documented upregulation of the antibodies in SLE patients following initiation of cyclophosphamide [67].

#### ■ Management of nonthrombotic APS manifestations

As noted previously, some of the manifestations of APS are not thrombosis dependent. They are termed noncriteria aPL manifestations. Despite the importance of these manifestations, a few studies addressed their pathogenesis and treatment. Thrombocytopenia is the most common noncriteria aPL manifestation. However, most APS patients with thrombocytopenia will never become clinically symptomatic and, thus, will not require therapy. Whenever a clinically significant drop in platelet number occurs, and although not established in the medical literature, it makes sense to utilize corticosteroids, IVIG, rituximab or even splenectomy [31].

For aPL-related nephropathy, no treatment has been shown to be effective. Experts in the field recommend treating those patients with anticoagulation in addition to a renoprotective angiotensin-converting enzyme inhibitor [31].

No data exist regarding whether antiplatelet, anticoagulation or even immunosuppressive therapy is beneficial for aPL-related cardiac valvular disease. Experts recommend anticoagulation in the context of chronic atrial fibrillation or the presence of multiple non-aPL thrombotic risk factors [31].

Cognitive dysfunction is also part of the extending spectrum of non-aPL-related manifestations. There is currently no established treatment modality, but therapeutic studies are underway [31].

#### ■ Future of APS management

As more insight is being gained about the pathophysiology of the disease and the involved receptors and intracellular pathways utilized, targeted treatment modalities have been proposed as possible alternatives to the current treatment options. Anti-inflammatory and immunomodulatory approaches have been increasingly investigated by different research groups.

Statins are being extensively investigated and have been shown in clinical trials to reverse the prothrombotic tendency in APS patients [31]. Rituximab, a chimeric monoclonal antibody that targets CD20 of B lymphocytes, has been reported in case reports as being utilized successfully in APS patients with thrombocytopenia, autoimmune hemolytic anemia, livedo reticularis or skin ulcers [68]. Further studies reported success in treating refractory systemic autoimmune diseases with rituximab [69–71]. Hydroxychloroquine, an antithrombotic and anti-inflammatory agent used in the management of some systemic autoimmune diseases (e.g., SLE) [72] has also been reported in preclinical trials to reverse the thrombotic manifestations of APS [73]. Other agents that target specific elements involved in the pathophysiology of the disease process, including receptor molecules, postreceptor mediators and effector proteins, are also being studied. These agents include glycoprotein (GPIIb/IIIa) inhibitors of platelets (abciximab), tissue factor inhibitors, angiotensin-converting enzyme inhibitors, defibrotide (adenosine receptor agonist), dilazep (adenosine uptake inhibitor), complement inhibitors, anti-TNF agents, p38MAPK inhibitors, and NF- $\kappa$ B inhibitors [73–80].

#### Conclusion & future perspective

Antiphospholipid syndrome is a systemic autoimmune disease with a thrombotic tendency manifesting as vascular (arterial and venous) thrombotic events and obstetric morbidity (e.g., fetal loss, recurrent miscarriages, premature deliveries and placental insufficiency), in the presence of persistent aPL (aCL, lupus anticoagulant and anti- $\beta$ 2GPI) positivity for a period of 12 weeks. Being the most devastating consequence of APS and the major cause of morbidity and mortality, thrombosis has been the target of therapeutic interventions. Therefore, treatment has been restricted to antithrombotic medications and anticoagulation; however, due to study design restrictions, several questions remain unanswered concerning the optimal



management of these patients. These include, amongst others, whether primary prophylaxis is needed in persistently aPL-positive patients, the intensity and duration of anticoagulation required following a thrombotic episode, the optimum management plan for CAPS and the treatment options for the nonthrombotic manifestations of the disease. This necessitates well-designed studies in the future to further solidify the evidence relating to our current management algorithm.

Despite documented adequate anticoagulation, recurrent thrombotic events have occurred in some cases. Moreover, the need for higher intensity anticoagulation for thromboprophylaxis in some cases has led to an increase in the hemorrhagic complications. This clearly demonstrates that we are in need of new, more efficacious treatment modalities. Perhaps our developing understanding of the disease's pathophysiology will provide the answer to our quest in the near future with targeted therapy being the key.

### Executive summary

#### **Antiphospholipid antibody syndrome is an autoimmune vascular thrombotic disorder**

- Antiphospholipid antibody syndrome (APS) is characterized by recurrent vascular thrombotic events or obstetric complications in patients with persistently positive antiphospholipid antibodies (aPLs).
- It is one of the most common causes of acquired thrombophilia in young adults.

#### **Clinical aspects of APS**

- Clinical presentations of thrombotic events range from superficial thrombosis, to large vessel thrombosis, to life-threatening catastrophic microangiopathy.
- Deep vein thrombosis and strokes are the most common causes of morbidity and mortality.
- Obstetric complications include fetal loss, recurrent miscarriages, premature births, pre-eclampsia and placental insufficiency.
- Some clinical manifestations are not thrombotic in nature (e.g., cognitive disorders, thrombocytopenia, livedo reticularis and heart valve lesions).

#### **Antiphospholipid antibodies**

- aPLs comprise a heterogeneous group of antibodies that share the ability to bind phospholipid-binding proteins.
- The three tests included in the Sapporo criteria are: lupus anticoagulant functional coagulation assay, anticardiolipin ELISA and anti- $\beta$ -2GPI antibody ELISA.

#### **Management of persistently aPL-positive patients**

- Thromboprophylaxis in asymptomatic aPL-positive patients requires a risk-stratified approach.
- Secondary thrombosis prevention in APS patients requires lifelong anticoagulation with target international normalization rate (INR) of 2–3 following an index venous event, and INR of 3–4 following an arterial index event or recurrent events.
- Aspirin and heparin are recommended for pregnant APS patients.
- Catastrophic microangiopathy management usually includes effective anticoagulation and intravenous steroids  $\pm$  intravenous immunoglobulins and/or plasma exchange, depending on the clinical picture.

#### **Future in the management of APS**

- As our understanding of the disease's pathophysiology deepens, new potential targeted therapeutic options appear on the horizon.
- These include statins, hydroxychloroquine, rituximab, complement inhibitors, tissue factor inhibitors, GPIIb/IIIa inhibitors, anti-TNF agents, p38MAPK inhibitors and NF- $\kappa$ B inhibitors.

#### **Conclusion**

- We are in need of well-designed studies in order to establish the optimal treatment plan for APS patients.
- As the pathophysiology of the disease is being elucidated, several possible therapeutic agents are being proposed.
- In the future, targeted therapy might be the answer to many questions in the management of APS.

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**Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.**

	1	2	3	4	5
The activity supported the learning objectives.					
The material was organized clearly for learning to occur.					
The content learned from this activity will impact my practice.					
The activity was presented objectively and free of commercial bias.					

**1. Which of the following best describes the difference between antiphospholipid antibody syndrome (APS) and genetic thrombophilias?**

- A** Thrombosis can affect any vascular bed
- B** Thrombosis is arterial only
- C** Thrombosis affects large vessels
- D** Thrombosis affects small vessels

**2. Which of the following best distinguishes categories of APS?**

- A** Type A versus type B
- B** Large-vessel versus small-vessel disease
- C** Primary versus secondary
- D** Autoimmune versus carcinogenic

3. A 35-year-old woman is positive for anticardiolipin ELISA antibody, negative for lupus antibody, and negative for anti- $\beta$ 2-GPI antibody. She has a history of three consecutive spontaneous abortions before 10 weeks' gestation. Which of the following is the most likely diagnosis?

- A Antiphospholipid antibody-positive APS
- B Seronegative APS
- C Systemic lupus erythematosus
- D None of the above

4. Which of the following patients has the greatest indication to receive thromboprophylaxis with aspirin?

- A Smoker with lupus anticoagulant-positive antibody
- B Asymptomatic patient with elevated anticardiolipin antibodies
- C Asymptomatic patient with positive anti- $\beta$ 2-GPI antibody
- D None of the above

5. A 34-year-old pregnant woman is diagnosed with APS. Which of the following treatment strategies is considered optimal therapy for best pregnancy outcome?

- A Low-molecular-weight heparin alone
- B Aspirin alone
- C Aspirin and unfractionated heparin
- D Low-molecular-weight heparin and intravenous immunoglobulins