



Antiphospholipid antibody syndrome

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The antiphospholipid antibody syndrome (APS) is defined by the persistent presence of antiphospholipid antibodies in patients with recurrent venous or arterial thromboembolism or pregnancy morbidity. Antithrombotic therapy is the mainstay of treatment given the high risk of recurrent thromboembolism that characterizes this condition. Despite the prothrombotic nature of APS, thrombocytopenia is present in a proportion of patients, which can complicate management and limit the use of antithrombotic therapy. The mechanism of APS-associated thrombocytopenia is multifactorial and its relation to thrombotic risk poorly characterized. However, the presence of thrombocytopenia does not appear to reduce thrombotic risk in patients with APS, who can develop thromboembolic complications necessitating antithrombotic treatment. In these cases, treatment of the thrombocytopenia may be necessary to facilitate administration of antithrombotic agents. Clinical trials have demonstrated that patients with antiphospholipid antibodies and venous thromboembolism should be treated with vitamin K antagonists (warfarin); that ischemic stroke may be treated with aspirin or warfarin; and that women with recurrent pregnancy loss should receive prophylactic-dose heparin and aspirin. However, application of these trial results to patients with APS-associated thrombocytopenia can be challenging since there are limited data on the optimal use of antithrombotic agents in this setting. Issues such as determining the platelet threshold at which antithrombotic agents can be safely used and managing patients with both bleeding and thromboembolic complications remain unresolved. Ultimately the risks and benefits of antithrombotic therapy, balanced against the severity of the thrombocytopenia and its potential bleeding risks, need to be assessed using an individualized patient approach.

Antiphospholipid antibodies, including lupus anticoagulant (LA), anticardiolipin antibodies (aCL) and anti- β 2-glycoprotein-1 (anti- β 2-GPI) antibodies, are associated with an increased risk of arterial and venous thromboembolism. The antiphospholipid antibody syndrome (APS) is a prothrombotic condition characterized by the presence of these antibodies in patients with recurrent pregnancy morbidity and/or thromboembolic complications. Thrombocytopenia is a frequent finding in patients with APS, and balancing the need for anticoagulation when faced with significant thrombocytopenia can be a considerable challenge for clinicians managing such patients.

Diagnosing APS

The diagnosis of APS is based on clinical criteria of pregnancy morbidity or thromboembolism, and laboratory findings of medium or high titer antiphospholipid antibodies that are present on two or more occasions at least 12 weeks apart (Table 1).¹ These international consensus criteria were designed to facilitate clinical studies of treatment and causation in APS and were not intended to be diagnostic criteria for clinical practice. Nonetheless, these criteria can be useful to assess the applicability of the

results of clinical trials to an individual patient. It is notable that patients with APS may have other clinical characteristics, including thrombocytopenia, livedo reticularis, valvular heart lesions and nephropathy, but these features are not formally part of the consensus diagnostic criteria. Similarly, these patients may have antiphospholipid antibodies other than LA, aCL and anti- β 2-GPI, including antibodies against prothrombin and other proteins or phospholipids that are not included in the current consensus criteria.

Rarely, patients with antiphospholipid antibodies have multiorgan failure resulting from widespread thrombotic disease, known as catastrophic APS. Preliminary criteria for the classification of catastrophic APS have been published.² The clinical manifestations,³ treatment and prognosis⁴ of catastrophic APS are beyond the scope of this review.

Laboratory Measurement of Antiphospholipid Antibodies

The measurement of antiphospholipid antibodies has potential limitations. Screening for LA is done using at least two phospholipid-dependent coagulation tests.⁵ LA

Table 1. Revised classification criteria for the antiphospholipid antibody syndrome.¹⁴**Clinical criteria (one or more)**

1. Vascular thrombosis: One or more objectively confirmed episodes of arterial, venous or small vessel thrombosis occurring in any tissue or organ
2. Pregnancy morbidity:
 - a) one or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation; or
 - b) one or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia, pre-eclampsia or placental insufficiency; or
 - c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation

Laboratory criteria (one or more, present on 2 or more occasions at least 12 weeks apart using recommended procedures)

1. Lupus anticoagulant, detected according to the guidelines of the International Society on Thrombosis and Haemostasis
2. Anticardiolipin antibody of IgG and/or IgM isotype, present in medium or high titer (greater than 40 GPL or MPL, or greater than the 99th percentile), measured by a standardized ELISA
3. Anti- β_2 -glycoprotein-1 antibody of IgG and/or IgM isotype, present in titer greater than the 99th percentile, measured by a standardized ELISA

detection can be problematic in patients receiving oral anticoagulants or unfractionated heparin, since clotting times will be prolonged on screening, and mixing and confirmatory testing can be similarly prolonged, resulting in false-positive results.⁶ Although there are techniques that may overcome this limitation, testing for LA should ideally be done when antithrombotic agents have been discontinued. In contrast to LA, both aCL and anti- β_2 -GP1 antibodies are detected using enzyme-linked immunosorbent assay (ELISA) techniques. Many of these assays are not standardized and have significant batch-to-batch variability.⁷

Thrombocytopenia in Patients with APS

Thrombocytopenia, defined by a platelet count less than $100\text{--}150 \times 10^9/\text{L}$, is found in approximately 20% of patients with APS and is found in more than 40% of patients who have APS associated with underlying systemic lupus erythematosus.⁸⁻¹⁰ The degree of thrombocytopenia observed in patients with APS is usually moderate, in the range of $100\text{--}150 \times 10^9/\text{L}$.^{9,10} A minority of patients have thrombocytopenia with platelets less than $50 \times 10^9/\text{L}$.¹⁰

There are likely different mechanisms resulting in thrombocytopenia in patients with APS. Many patients are initially diagnosed with idiopathic thrombocytopenic purpura (ITP), and autoantibodies directed against platelet glycoproteins have been detected in patients with antiphospholipid antibodies¹¹ as well as in patients with APS.¹² Thrombocy-

topenia in these patients may be due to immune-mediated clearance of platelets, as in patients with ITP. However, the frequent finding of thrombocytopenia and thrombosis in patients with APS suggests that antiphospholipid antibodies interact with platelets in a manner that triggers platelet aggregation and thrombosis. In vitro and in vivo studies have demonstrated that antiphospholipid antibodies can bind platelets, increasing platelet aggregation and activation in the presence of subthreshold concentrations of thrombin, adenosine diphosphate or collagen.¹³ The intracellular events following platelet binding remain incompletely elucidated, but activation of arachidonic acid, thromboxane production and expression of glycoprotein IIb/IIIa have all been shown to occur following antiphospholipid antibody binding to platelets.¹⁴

Mechanisms for Thrombosis in Patients with APS

The mechanism of thrombosis in patients with antiphospholipid antibodies is still unknown, although several mechanisms have been proposed.¹⁴ There are data suggesting that antiphospholipid antibodies induce thrombosis through any one or more of several mechanisms: (1) antiphospholipid antibody interference with endogenous anticoagulant mechanisms (disruption of the annexin A5 anticoagulant shield,¹⁵ inhibition of protein C pathway, inhibition of antithrombin), (2) binding and activation of platelets, (3) interacting with endothelial cells and inducing expression of adhesion molecules and tissue factor, and (4) activation of the complement cascade.

Bleeding Versus Thrombotic Risk in Patients with APS

Despite the prolongation in the activated partial thromboplastin time that may be observed in patients with antiphospholipid antibodies, APS predominantly presents as a prothrombotic disorder. It is one of few conditions that can manifest with both arterial and venous thromboembolism and can affect both large and small vessels. Interestingly, the presence of thrombocytopenia in patients with APS is not typically associated with hemorrhagic complications.^{9,10} In the retrospective Italian Registry of Antiphospholipid Antibodies, there were no bleeding complications among 44 patients with moderate thrombocytopenia ($50\text{--}100 \times 10^9/\text{L}$), and 14 (32%) of these patients actually suffered thrombotic events.¹⁰ In the 32 patients with severe thrombocytopenia (less than $50 \times 10^9/\text{L}$), 2 (6%) patients had bleeding complications and 3 (9%) patients had thrombosis. Although limited, this suggests that thrombotic events still occur in severely thrombocytopenic patients with APS, although the risk may be lower compared to patients with moderate thrombocytopenia.

Distinguishing APS from Other Prothrombotic and Thrombocytopenic Conditions

The differential diagnosis in patients with APS presenting with thrombocytopenia includes thrombotic thrombocytopenic purpura (TTP), heparin-induced thrombocytopenia (HIT) and disseminated intravascular coagulation (DIC). Distinguishing these conditions can be challenging. As described earlier, diagnosing APS requires documentation of persistent antiphospholipid antibodies in combination with compatible clinical features of thrombosis or pregnancy morbidity. However, antiphospholipid antibodies have been documented in TTP and other thrombotic microangiopathies including hemolytic uremic syndrome and HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome,¹⁶ as well as in cases of HIT. Patients with TTP present with microangiopathic hemolytic anemia, manifest with schistocytes on the blood smear and evidence of hemolysis, which is not a typical feature seen in APS. Measurement of the ADAMTS-13 metalloprotease, if available, may be helpful in these situations given that TTP is associated with ultra-large von Willebrand factor multimers that result from a deficiency in ADAMTS-13. Patients with HIT have a history of heparin exposure, a typical decrease in platelet count occurring 5 to 10 days following this exposure and serologic evidence of the HIT antibody. Notably, false-positive HIT antigen tests have been reported in patients with APS, presumably related to autoantibodies against platelet factor 4 (PF4) that can be distinguished from true HIT antibodies by using enzyme immunoassays for PF4/heparin complexes tested with heparin excess or with use of functional assays.¹⁷ Patients with DIC typically test negative for antiphospholipid antibodies and frequently present with evidence of thrombocytopenia, coagulopathy and thrombotic or hemorrhagic complications in the setting of a compatible clinical picture precipitating DIC.

Antithrombotic Treatment of APS

Given the high risk of recurrent thromboembolism that characterizes this condition, the mainstay of treatment in patients with APS is antithrombotic therapy. However, the optimal antithrombotic management of patients with APS can be challenging because of the lack of standardized laboratory tests to confirm the diagnosis, limited data on its natural history and a paucity of randomized treatment trials. Further complicating this is the balance between thrombosis and hemorrhage in an individual patient with APS, who may have concomitant thrombocytopenia and other comorbidities contributing to increased bleeding risks. Treatment recommendations are therefore taken in light of individual patient characteristics and preferences.

Antithrombotic Management of Patients with Antiphospholipid Antibodies and Venous Thromboembolism

Deep vein thrombosis of the lower extremities is the most common initial manifestation among patients with APS, occurring in approximately 30% of patients who meet consensus diagnostic criteria.⁸ Patients with APS and a first episode of venous thromboembolism have a high risk of recurrent venous thromboembolism if anticoagulants are discontinued, based on data from retrospective studies of untreated patients or studies of patients followed prospectively after their anticoagulants have been discontinued.^{18,19} Prospective data suggest that the risk of recurrence in these patients is between 50% to 67% per year.^{18,19} Notably, many of the patients in these studies do not meet the current consensus definition for APS where documentation of antiphospholipid antibodies is required on more than one occasion. Retrospective studies in patients who received no antithrombotic therapy report recurrent venous thromboembolism occurring in 52% to 69% of patients during 5 to 6 years of follow-up regardless of the type of antithrombotic therapy.^{20,21} This is in contrast to the rate of recurrent venous thromboembolism in patients without APS, where rates of recurrence are approximately 10% to 12% after 1 year, 20% to 25% after 3 years, 30% after 5 years and 40% after 10 years.²²

Antithrombotic Recommendations

Initial Treatment

Initial treatment of venous thromboembolism in patients with APS is identical to that for patients without APS. In the absence of a contraindication to heparin therapy (active bleeding, allergy to heparin or documented HIT), initial therapy consisting of unfractionated heparin, low molecular weight heparin or pentasaccharide for at least 4 to 5 days overlapping with warfarin therapy is recommended.²³ In patients with APS and significant thrombocytopenia, there may be a preference for initial treatment with unfractionated heparin in the event that the patient develops bleeding complications.

Long-term Treatment

Warfarin (or other vitamin K antagonists) administered with a target international normalized ratio (INR) of 2.0 to 3.0 is recommended for the long-term treatment of patients with APS.²³ This recommendation is based on two randomized controlled trials demonstrating that high-intensity warfarin (INR greater than 3.0) was not superior to standard-intensity warfarin (INR 2.0-3.0) for preventing recurrent thrombosis in patients with APS.^{24,25} No difference in bleeding rates was observed with the two intensities of warfarin. In patients with APS and thrombocytopenia, long-term warfarin

treatment likely warrants closer monitoring of the INR and hemoglobin levels to ensure that the INR is in the target range and to detect any asymptomatic decrease in hemoglobin that might signify bleeding.

Duration of Treatment

The optimal duration of anticoagulation to prevent recurrent venous thromboembolism in patients with APS is unknown. Based on the high risk of recurrent venous thromboembolism and the comparatively lower risk of major bleeding in these patients, expert opinion recommendations suggest that these patients receive anticoagulation indefinitely.²³ However, this recommendation must be taken in light of the individual patient's risk factors and preferences. Patients who are poor candidates for anticoagulation, either because of recurrent bleeding complications or non-compliance with therapy, may not necessarily benefit from indefinite anticoagulation.

Antithrombotic Management of Patients with Antiphospholipid Antibodies and Arterial Thromboembolism

The most common presentation of arterial disease in APS is ischemic stroke, observed in 13%, and transient ischemic attack in 7% of patients meeting consensus diagnostic criteria.⁸ Population-based case control studies suggest that the presence of LA or aCL is associated with a 2-fold increase in first time ischemic stroke,²⁶ and anti- β 2-GPI antibodies may be associated with a 2-fold increase in myocardial infarction.²⁷ However, the risk of recurrent arterial thromboembolism in patients with APS is not well defined.

Antithrombotic Recommendations

Initial and Long-term Treatment

Antithrombotic recommendations for ischemic stroke are based on the results of the APL and Stroke Study (APASS),²⁸ a prospective cohort study within the Warfarin Aspirin Recurrent Stroke Study (WARSS),²⁹ a randomized double-blind trial comparing warfarin (INR 1.4-2.8) and aspirin 325 mg/day for preventing recurrent stroke or death. The patients in this study had only one measurement of antiphospholipid antibodies prior to randomization in the study and patients with aCL levels that would be considered low titer were included; neither feature would meet the current diagnostic criteria. Patients treated with warfarin had a similar relative risk of recurrent ischemic stroke or death as patients treated with aspirin, and there was no difference whether patients were antiphospholipid antibody positive or negative. Based on this finding, both warfarin and aspirin appear to be reasonable antithrombotic treatment options for patients presenting with a first time ischemic stroke. Since aspirin does not require INR moni-

toring and has a lower bleeding risk compared with warfarin, aspirin is typically the first choice in these patients and is the recommendation of current consensus guidelines.³⁰ It is notable that the median INR in the patients receiving warfarin in this study was 1.9, which is a level where there are no data supporting efficacy for the treatment of arterial thromboembolism. The optimal management of patients meeting consensus diagnostic criteria for APS and who have had ischemic stroke remains controversial since no prospective study has comprehensively examined optimal treatment in such patients. The presence of APS-associated thrombocytopenia in these patients does not necessarily contraindicate use of aspirin or warfarin, but patients should be aware of bleeding symptoms.

No clinical study data are available on which to base treatment recommendations for arterial thromboembolism in patients with APS aside from ischemic stroke. Patients with myocardial infarction and peripheral arterial thromboembolism are typically treated with long-term warfarin therapy administered to achieve an INR of 2.0 to 3.0 based on data extrapolated from the venous thromboembolism studies.

Duration of Treatment

There are no studies evaluating optimal duration of treatment for patients with APS and arterial thromboembolism. As a result, these patients are often treated similarly to the patients with venous thromboembolism and receive indefinite therapy. These recommendations must be taken in light of the individual patient's risk factors and preferences.

Antithrombotic Management of Patients with Antiphospholipid Antibodies and Recurrent Pregnancy Loss

Pregnancy morbidity in the form of fetal loss or premature birth is a common finding in women with APS. The mechanism of fetal loss is believed to be due to binding of antiphospholipid antibodies to trophoblast cells, resulting in defective placentation.³¹ Thrombotic complications within the uteroplacental circulation has also been proposed as a contributing mechanism.³² There are no specific data evaluating thrombocytopenia in the setting of antiphospholipid antibodies and pregnancy loss.

Antithrombotic Recommendations During Pregnancy

The goal of antithrombotic treatment in these women is aimed at prevention of further pregnancy loss, as opposed to treatment of thrombosis. In women with antiphospholipid antibodies and recurrent pregnancy loss with no history of thrombosis, consensus guidelines recommend low-dose aspirin in combination with prophylactic or intermediate-dose unfractionated heparin or prophylactic

dose low molecular weight heparin, administered in the antepartum period.³³ This recommendation is based on the results of prospective studies demonstrating higher live birth rates using the combination of aspirin and heparin,^{34,35} and consistent, but preliminary data using low molecular weight heparin.^{37,38}

Treatment of APS-associated Thrombocytopenia

Treatment of APS-associated thrombocytopenia may be required to facilitate antithrombotic treatment and minimize bleeding complications. There are no trials evaluating optimal management in this setting, and no guidelines exist regarding when treatment is required and what treatments should be used. In general, treatment of APS-associated thrombocytopenia is indicated in the presence of overt bleeding or when the risk of bleeding outweighs the risks associated with treatment. In patients with ITP, consensus guidelines recommend that patients with a platelet count of less than 20 to $30 \times 10^9/L$ receive treatment,³⁸ and this threshold can be extrapolated to patients with APS-associated thrombocytopenia. However, this threshold may be higher based on presence of bleeding symptoms or need for antithrombotic therapy. Patients with APS-associated thrombocytopenia who present with bleeding require treatment for the thrombocytopenia irrespective of the platelet count. Similarly, patients with APS who have thromboembolic complications despite being thrombocytopenic may require treatment to increase the platelet count to at least 30 to $50 \times 10^9/L$ before antithrombotic therapy can be administered. Varying the intensity of anticoagulant therapy based on the degree of thrombocytopenia to reduce bleeding risk may be considered in individual cases, but is controversial. Clinical trial data from the venous thromboembolism literature in non-thrombocytopenic patients suggest that lower intensity warfarin therapy is not effective for secondary prevention of thrombotic events.³⁹

Patients with APS-associated thrombocytopenia are treated in a similar manner to patients with ITP since there are limited data suggesting that anticoagulation is an effective therapy for thrombocytopenia in these patients. Treatment options include glucocorticoids, intravenous immune globulin (IVIg), immunosuppressive agents (azathioprine, cyclophosphamide) and off-label use of newer agents such as rituximab. There are individual case reports of successful treatment of thrombocytopenia in patients with APS using danazol,⁴⁰ aspirin,⁴¹ dapsone⁴² and chloroquine.⁴³ Pregnant women with APS and thrombocytopenia often require treatment to facilitate use of epidural anesthesia and to ensure adequate hemostasis at the time of delivery or cesarian section. In these cases, IVIg and early delivery, if possible, are favored.⁴⁵

Treatment of Bleeding in Patients with APS

Bleeding is a less frequent complication than thrombosis in patients with APS. Severe thrombocytopenia can result in bleeding; less commonly, patients with APS may have antibodies directed against prothrombin, resulting in increased clearance of prothrombin and low prothrombin levels.⁴⁵ The site and severity of bleeding will dictate how the bleeding is managed and how urgently this is undertaken. In general, if the bleeding results from antithrombotic therapy, the antithrombotic agent needs to be discontinued, a specific antidote administered (protamine sulfate for heparins, vitamin K for warfarin) and transfusional support given (frozen plasma for heparins or warfarin, prothrombin complex concentrates for warfarin and consideration for red cell transfusions for symptomatic anemia). If the bleeding is associated with thrombocytopenia, or if the patient is taking aspirin, platelet transfusions may be given in addition to treatments that increase the platelet count. Off-label use of recombinant factor VIIa may be considered for severe bleeding unresponsive to other therapies.

Rarely, patients with APS may present with both bleeding and thrombotic complications, and the dominant presentation or most life-threatening complication will dictate how patients are ultimately managed. Patients who are assessed to be at high risk of bleeding should have their anticoagulants withheld or anticoagulants administered using a lower intensity target range while measures to decrease bleeding should be sought. Patients who are assessed to be at high risk of thromboembolic complications despite thrombocytopenia should be anticoagulated and treatments to improve platelet count should be initiated.

Conclusions

APS is a prothrombotic disorder with various manifestations, most commonly venous and arterial thromboembolism and recurrent pregnancy loss. Diagnosis of APS can be challenging due to evolving criteria, potential limitations in the laboratory assays used to measure antiphospholipid antibodies and overlapping characteristics with other prothrombotic thrombocytopenic disorders. Thrombocytopenia is a frequent finding in patients with APS, but this does not appear to decrease thrombotic risk. Consequently, the mainstay of APS treatment is antithrombotic therapy, which must be carefully balanced against the bleeding risks associated with thrombocytopenia. Treatment of APS-associated thrombocytopenia may be required, using agents typically used in patients with immune thrombocytopenia. Although broad antithrombotic treatment recommendations can be made, decisions regarding antithrombotic treatment must be individualized in light of patient-specific risk factors and preferences.

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