

Diagnosis and therapy of antiphospholipid syndrome

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KEY WORDS

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ABSTRACT

Antiphospholipid syndrome (APS) is a clinical condition that has not been well defined yet. Although the clinical component is well established, the laboratory part is a mood issue. According to current guidelines, 3 tests (lupus anticoagulant, anticardiolipin, and anti β_2 -glycoprotein I antibodies) are officially recommended to assess the presence of antiphospholipid antibodies. According to test positivity, patients are classified into categories in clinical studies. However, it is now clear that classification categories have a different impact on the clinical course of APS. Indeed, patients and healthy carriers with a full positive antibody profile (triple positivity) are those at the highest risk of events. Patients with a single test positivity are those at a lower risk. In this review, on the basis of a laboratory profile, we grade the diagnosis of APS into definite, probable/possible, and uncertain. We also discuss secondary prevention of thrombotic APS, prevention of pregnancy morbidity, and treatment of catastrophic APS. Finally, new tools in laboratory diagnosis and treatment are highlighted.

Introduction Antiphospholipid syndrome (APS) is a complex clinical condition characterized by the presence of circulating antiphospholipid (aPL) antibodies in patients with thrombosis or pregnancy morbidity. As thrombosis and pregnancy loss are common clinical conditions, the diagnosis is essentially based on the detection of aPL antibodies.

Diagnosis of antiphospholipid syndrome After several previous proposals for the criteria of APS, an international consensus statement for definite APS was formulated during a postconference workshop held on October 10, 1998, in Sapporo, Japan, following the Eighth International Symposium on Antiphospholipid Antibodies.¹ The classification criteria considered definite APS to be a condition in which at least 1 clinical criterion (thrombosis or pregnancy loss) and 1 of the laboratory criteria (the presence of β_2 -glycoprotein I [β_2 GPI]-dependent anticardiolipin [aCL] antibodies or lupus anticoagulant [LAC]) were met. These criteria were retained in the Sydney consensus conference, with the addition of anti- β_2 -GPI antibody positivity to other laboratory tests.²

The Sydney criteria no longer required the aCL enzyme-linked immunosorbent assay (ELISA) to be β_2 GPI-dependent. Positive laboratory results had to be confirmed after a minimum of 12 weeks.

Using these criteria, a single positive test confirmed upon repeat testing allows to diagnose APS. This is of major concern because sole positivity for LAC is not associated with thrombosis³ or with clinical manifestations of APS.⁴ The same conclusions were drawn from the Leiden thrombophilia case-control study,⁵ in which LAC positivity in the absence of anti- β_2 GPI or antiprothrombin antibodies was not associated with a higher risk of deep vein thrombosis (odds ratio, 1.3; 95% confidence interval, 0.3–6.0). Although previous studies and a meta-analysis⁶ have shown that LAC is associated with thrombosis, the analysis did not consider isolated LAC positivity (with negative aCL and a β_2 GPI ELISAs). The antibody present in the plasma of patients who are positive for LAC alone is not the relevant anti- β_2 GPI antibody. This denotes the presence of a different disease process with a different pathogenesis, and, most likely, with different clinical consequences. Recently, in a prospective study that

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TABLE 1 Diagnosis of antiphospholipid syndrome^a

Definite thrombotic and/or obstetric antiphospholipid syndrome (APS)
<p>Triple-positive patients (lupus anticoagulant [LAC] positive, immunoglobulin [Ig] G, or IgM anticardiolipin [aCL] antibodies >99th percentile, and IgG or IgM anti-β_2-glycoprotein I [anti-β_2GPI] antibodies >99th percentile, same isotype) and proven venous/arterial thrombosis and/or pregnancy loss (as defined by the 2006 International Consensus statement).²</p> <p>Remarks: This is a high-risk group of patients with an observed high recurrence rate of thrombosis and pregnancy loss despite appropriate anticoagulant treatment.^{20,23} Young age (less than 50 years), unprovoked venous thromboembolism (VTE) or VTE at unusual site or in microcirculation, late pregnancy morbidity (including fetal death, eclampsia/severe preeclampsia or placental insufficiency), IgG isotype, high titer of aCL and anti-β_2GPI antibodies, and strong LAC test (LAC potency is significantly stronger when both dRVVT and activated partial thromboplastin time are positive),¹⁴ all reinforce the diagnosis of definite APS.^{19,20,23} Additional test reinforcing the diagnosis of definite APS include anti-domain I antibodies (detected by a chemiluminescent assay).²⁵ Positivity on 2 or more occasions, at least 12 weeks apart² may not be necessary, as positivity is seldom transient in triple-positive patients.²⁶ No firm association is present between the IgM isotype and thrombotic APS with a predominant or only the IgM isotype. These patients differ from those with the IgG isotype as they are significantly older and more frequently present an atherothrombotic event at diagnosis.²³</p>
Probable/possible thrombotic and/or obstetric antiphospholipid syndrome
<p>These are generally lower-risk patients with double positivity (mostly LAC negative but with aCL IgG or IgM >99th, anti-β_2GPI IgG or IgM > 99th percentile, same isotype) and proven venous/arterial thrombosis and/or pregnancy loss.²</p> <p>Remarks: In this context, possibly relevant anti-β_2GPI antibodies are involved at a titer that is not sufficient to induce LAC activity in plasma. Typically, positivity for dilute Russell's viper venom time becomes evident only when the concentration of aCL exceeds 50 GPL units.¹⁶ The clinical significance of lower amounts of antibodies remains unclear; however, this laboratory observation may be relevant in pregnancy morbidity, where lower titers of antibodies are frequently encountered.^{3,8} Treatment in these patients should mainly consider the clinical picture rather than the presence of antibodies.</p>
Uncertain thrombotic and/or obstetric antiphospholipid syndrome
<p>Single-positive patients for LAC, aCL, or anti-β_2GPI antibodies (classification categories IIa, IIb, and IIc)² and proven venous/arterial thrombosis and/or pregnancy loss.</p> <p>Remarks: Older age (>60 years), weak LAC, low-titer aCL or anti-β_2GPI antibodies, IgM isotype,²⁷⁻²⁹ as well as the presence of other possible risk factors for venous/arterial thrombosis, are all observations that support the exclusion of this group from definite, or even probable, APS. Autoantibodies different from pathogenic anti-β_2GPI appear to be primarily involved in these patients.³⁰ In a recent paper, aCL positivity alone was often found in pregnancy loss but not in patients with thromboembolic events.⁸ The explanation for why lower titers of antibodies may be clinically relevant in APS patients with pregnancy morbidity remains unclear. One possible explanation is that the pathogenic mechanism involved in placental injury may be different from that involved in thrombosis.^{31,32} Pregnancy loss and thromboembolism should be regarded as separate entities in the frame of APS patients. Further studies on homogeneous cohorts of these patients with single positivity are required. Treatment in these patients should be driven by clinical event rather than by the presence of a single positive test.</p>

a Note on detection of aPL antibodies: a) lupus anticoagulant guidelines for LAC detection have been updated.³³ After double centrifugation, the obtained plasma should be used for both coagulation tests and for solid phase assays; b) aCL and anti- β_2 GPI enzyme-linked immunosorbent assays: there are recently published recommendations on both assays that should be followed.^{34,35} Several additional issues for users of either commercial or home-made kits are as follows: 1) run a known positive sample on each plate and stop the color approximately at the same optical density in each working session; 2) run on each plate 2 known negative samples whose optical density should be within the normal values for the laboratory; 3) individual laboratories should establish their own 99th percentile (using plasma from at least 40 healthy individuals). As there are no solid data for IgA aPL or for antiphosphatidylserine, phosphatidylinositol, or antiphosphatidic acid (offered by some reference laboratories), these tests at present should be reserved for research use only. Anti-a β_2 GPI-domain I, a β_2 GPI-domain 4/5, and anti-phosphatidylserine/prothrombin antibodies require further validation studies.

considered individuals with a laboratory diagnosis of isolated LAC positivity (defined as positive LAC in the absence of anti- β_2 GPI antibodies) without

the clinical features of APS, we have shown that the risk of thrombosis is low.⁷

Concerning isolated aCL antibody positivity (with negative LAC and anti- β_2 GPI ELISAs), there is no association between thromboembolic events and laboratory measurements of aCL at low or high titer.^{3,8-10} Moreover, being negative for anti- β_2 GPI, the isolated aCL positivity is detecting a non- β_2 GPI-dependent antibody directed to other cardiolipin-binding proteins or cardiolipin itself (true cardiolipin-specific antibodies).¹¹ In summary, when a LAC or aCL ELISA is the sole positive test result, it is unclear what antibody is detected and what is the clinical significance of the isolated result. On the other hand, sole anti- β_2 GPI positivity (with negative LAC and aCL ELISAs) is not associated with thrombosis although specific autoantibodies are identified.^{3,12} This may be related to the fact that only some anti- β_2 GPI antibodies are those relevant to the syndrome, specifically those directed against domain I of the β_2 GPI molecule.¹³ In conclusion, previous studies and meta-analyses considered the association of a single type of aPL antibodies (ie, aCL or LAC or anti- β_2 GPI antibodies) with thrombosis or pregnancy loss without taking into account the complete laboratory profile. Thus, the strength of association with thromboembolic events in these studies has been undermined by the lack of a correct classification of the laboratory profile.

In the most recent guidelines,² investigators were advised to classify APS patients in categories according to the positivity of 1 or more aPL antibody tests. This implies that all 3 tests are performed and data are confirmed after 12 weeks. The aim of this useful suggestion is to promote clinical studies on cohorts of patient with a homogeneous aPL pattern. However, classification criteria are often mistaken for diagnostic criteria, and patients fulfilling such criteria were often put together in clinical studies (triple-, double-, and single-positive patients). Moreover, it must be emphasized that the lack of accuracy in LAC^{14,15} and ELISA tests,¹⁶ as well as the lack of reference materials, have made study reports difficult to interpret and directly compare with one another. It is now recognized by many groups that patients with positive results of more than 1 test,^{17,18} and particularly those with positive results of all aPL antibody tests^{3,19,20} (referred to as triple positivity), are those in whom the association with clinical events (ie, vascular thrombosis and pregnancy morbidity) and the recurrence of events is the highest.

This is most likely related to the fact that only a particular anti- β_2 GPI antibody with LAC activity, the one directed to domain I of the molecule is highly associated with the clinical features of APS.^{13,21} Evidence that triple positivity can identify anti-domain I antibodies in triple-positive patients comes from studies on affinity purification of antibodies to β_2 GPI from the plasma of these patients: when spiked into normal plasma, they reproduce the positivity in all 3 tests as

the original plasma.²² Therefore, waiting for a direct validated measurement of anti-domain I antibodies, positivity both in the anti- β_2 GPI ELISA and in LAC ELISA, allows us to identify anti- β_2 GPI autoantibodies with LAC activity that appears to be directed against domain I of the molecule. As the standardization of the anti- β_2 GPI ELISA remains poor,¹⁶ a concurrent positivity in aCL ELISA of the same isotype, helps substantiate the result obtained in the anti- β_2 GPI ELISA (ie, triple positivity). Recent clinical studies confirm that triple-positive patients with APS and carriers of triple positivity are at high risk of developing a thrombotic event in their clinical course.^{23,24} Moreover, at variance with single positivity, recent data have shown that high-risk subjects with triple-positive aPL profiles are identified early at the time of the initial screening tests without the need for confirmation after 12 weeks.²⁵ In light of these more recent contributions to the field, new updated criteria for the laboratory component of the diagnosis of APS should be developed.

Treatment of thrombotic antiphospholipid syndrome

The choice of treatment as well as its intensity and duration should be tailored to the type of the event. Patients with venous thromboembolism (VTE) usually do not need to be checked for aPL antibodies close to the index event. Indeed, the treatment with heparin followed by vitamin K antagonists (VKAs) will continue unchanged irrespective of the presence of aPL, and LAC may be false-positive due to the anticoagulant treatment. Non-vitamin K oral anticoagulants (NOACs) should not be used when thrombotic APS is suspected, as there is no solid data on their effectiveness in this setting. The use of rivaroxaban versus warfarin in thrombotic APS is currently assessed in our Phase III clinical trial (TRAPS trial, ClinicalTrials.gov Identifier: NCT02157272C).

In secondary prevention of VTE in APS, we are still facing the problems of the intensity and duration of treatment because the evidence for what is best is scarce. Most studies addressing these issues are retrospective or subgroup analyses of randomized clinical trials.³⁶ Only 2 randomized prospective controlled studies have explored the benefit of high-intensity anticoagulation (international normalized ratio [INR], 3.0–4.0) in aPL patients.^{37,38} The Canadian trial randomized 114 patients (most of whom were diagnosed with VTE) to receive VKAs at standard (INR, 2.0–3.0; n = 58) or high-intensity (INR, 3.1–4.0; n = 56). Randomized patients were heterogeneous in terms of the aPL antibody profile. Most of them had either IgG aCL or LA positivity only with a wide age range. Titers of aPL antibodies increase with age; thus, many patients with doubtful APS and a few at high-risk may have been included. Moreover, it should be underlined that it is difficult to reach and maintain a high INR target. The WAPS trial included 109 patients (most of whom had VTE) with a higher-risk aPL profile (56% were positive

in more than 1 test) as compared with the Canadian study. Both trials concluded that the recurrence rate was lower in patients treated with standard-intensity VKAs (INR, 2.0–3.0), and this regimen was also safer in terms of major and minor bleeding. Other examples of benefit in the lower-intensity group are reported in the literature in the setting of prosthetic heart valves and atrial fibrillation.³⁹

Duration of treatment is a major issue, and the following items should be considered: 1) whether the VTE was provoked or unprovoked or associated with permanent risk factors; 2) the aPL profile and titer; 3) the site of VTE (deep vein thrombosis or pulmonary embolism or both). Long-term treatment should be advised if VTE was unprovoked or associated with permanent risk factors such as concurrent thrombophilic states or an autoimmune disease, if the event was a pulmonary embolism or in the presence of a “high-risk” aPL profile (triple positivity).²³ Short-term duration might be considered when VTE was provoked in patients with a single positive aPL test. In case of recurrence despite VKA treatment, the quality of anticoagulation (time in therapeutic range) should be checked because low adherence to treatment is not unusual in young subjects as in those with APS. Educational programs explaining the clinical importance of well-monitored oral anticoagulant treatment may help increase compliance in these patients.⁴⁰

When APS is diagnosed in a patient with arterial thromboembolism, a complete evaluation in relation to the site of thrombosis (cerebral, cardiac, or peripheral) should be made. Transthoracic and transesophageal echocardiography and other specific tests to evaluate the possible source of cardiac embolism are mandatory. Warfarin is the treatment of choice when ischemic stroke is of cardioembolic origin. Aspirin may be given if no clear feature of cardioembolism is present.⁴¹ However, the clinical course of APS is complicated by fewer thromboembolic events when patients are treated with warfarin as compared with aspirin.²³ Secondary stroke prevention should include standard intensity VKAs (INR, 2.0–3.0). Although recommended by some experts,^{36,42,43} the use of high-intensity anticoagulation in arterial APS is still under debate.

In high-risk patients with triple positivity or multiple ischemia in cerebral imaging, or in those with more than 1 clinical event, the addition of low-dose aspirin (100 mg/d) to VKAs should be considered in the absence of a high risk of bleeding. In patients with a triple-positive laboratory profile and previous myocardial infarction, a long-term VKA plus low-dose aspirin is recommended.⁴⁴ High-risk patients with APS (triple positivity) who undergo percutaneous coronary interventions and stent implantation should be treated with full antithrombotic regimens (VKA at INR 2.0–3.0, clopidogrel loading dose of 600 mg, clopidogrel maintaining dose of 75 mg/d, and aspirin dose of 100 mg/d).

Treatment of obstetric antiphospholipid syndrome

Pregnant women with APS should receive personalized treatment strategies. According to 3 clinical trials, APS patients with a history of pregnancy morbidity but no vascular thrombosis are usually treated with prophylactic doses of heparin plus low-dose aspirin (LDA) to prevent pregnancy loss.⁴⁵⁻⁴⁷ Two trials did not, however, find a significant improvement in pregnancy outcome in patients treated with low-molecular-weight heparin plus LDA with respect to those treated with LDA alone.^{48,49} According to a meta-analysis, the combination of heparin and aspirin is superior to aspirin alone in achieving more live births.⁵⁰ Although specific clinical trials are lacking, women with a history of vascular thrombosis alone or associated with pregnancy morbidity are usually treated with therapeutic heparin doses generally in association with LDA in the attempt to prevent both thrombosis and pregnancy morbidity. The protocols outlined above fail in about 20% to 30% of pregnant APS women, and additional treatments including intravenous immunoglobulins,⁵¹⁻⁵⁵ low-dose prednisolone,⁵⁶ or apheresis procedures such as plasma exchange and immunoadsorption have, at times, been prescribed.⁵⁷⁻⁶² Identifying risk factors associated to pregnancy failure when conventional therapies are utilized is an important step in establishing guidelines to manage these high-risk patients. Several studies have attempted to identify variables predictive of complications during conventionally treated pregnancies. In 2011, a relatively large case-control multicenter study reported that previous thrombosis and the presence of systemic lupus erythematosus and triple aPL positivity were associated with pregnancy failure during conventional therapy.⁶³ More recently, in a European multicentre retrospective study, pregnant patients with APS with thrombosis and triple aPL positivity treated with additional therapy were found to have a significantly higher live birth rate in comparison with those receiving conventional therapy alone.⁶⁴ However, at present, there are no guidelines on the ideal additional treatment strategy in APS women at high risk of pregnancy failure, probably because of the rarity of this disorder. Future studies on larger numbers of patients will be able to identify the benefits and limits of different additional treatment strategies and indicate which is associated with the best pregnancy outcome.

Treatment of catastrophic antiphospholipid syndrome

In 1992, Asherson coined the term catastrophic APS to describe an accelerated form of the syndrome with multiorgan thrombotic failure. As this condition is fatal in around half of affected individuals, many therapeutic options have been proposed. In our center, intravenous heparin, methylprednisone administered as a 1-gram daily bolus for a few days, intravenous immunoglobulins, and plasma exchange have been employed in these patients.^{65,66} Other treatment in

the follow-up period may include cyclophosphamide (if associated SLE), rituximab (anti-CD 20), and eculizumab (anti-C5a).

Conclusions Future clinical studies in patients with aPL antibodies should first consider triple-positive APS patients or triple-positive aPL carriers. The aPL laboratory profile should be confirmed in 1 or more reference laboratories. Interventional trials using old or new antithrombotic agents should consider patients or carriers with triple aPL positivity given the high rate of events in the follow-up period that have been found by other studies. The clinical significance of double-positivity and single-positivity status for aPL also needs to be confirmed in prospective clinical studies.

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Rozpoznanie i leczenie zespołu antyfosfolipidowego

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SŁOWA KLUCZOWE

artykuł poglądowy,
ciąża, rozpoznanie,
zakrzepica, zespół
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STRESZCZENIE

Zespół antyfosfolipidowy (*antiphospholipid syndrome* – APS) jest stanem klinicznym, który wciąż nie został dobrze zdefiniowany. Chociaż znane są jego składowe kliniczne, to składowe laboratoryjne pozostają kwestią dyskusyjną. Zgodnie z aktualnymi wytycznymi, w celu oceny obecności przeciwciał antyfosfolipidowych oficjalnie zaleca się wykonywanie trzech testów: w kierunku obecności antykoagulantu toczniowego, przeciwciał antykardiolipinowych oraz przeciwciał przeciwko β_2 -glikoproteinie I. Jeśli wyniki tych testów są dodatnie, pacjentów klasyfikuje się w badaniach klinicznych do różnych kategorii. Obecnie wiadomo, że w zależności od kategorii przebieg kliniczny APS jest różny. Rzeczywiście – chorzy i zdrowi „nosiciele” z całkowicie dodatnim profilem (dodatnie wyniki wszystkich trzech testów) należą do osób obciążonych największym ryzykiem wystąpienia zdarzeń związanych z tym zespołem. Chorzy z dodatnim wynikiem jednego z tych badań są obciążeni mniejszym ryzykiem. W tym artykule poglądowym podzielono – w odniesieniu do profilu laboratoryjnego – rozpoznanie APS na: ostateczne, prawdopodobne/możliwe i niepewne. Omówiono również wtórną profilaktykę APS związanego z zakrzepicą, zapobieganiu powikłaniom u kobiet w ciąży oraz leczeniu katastrofalnego APS. Podkreślono też znaczenie nowych narzędzi stosowanych w diagnostyce laboratoryjnej i leczeniu.

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