A review on management of antiphospholipid syndrome in clinical practice

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ABSTRACT

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by thrombotic or obstetric events occurring in patients with persistent antiphospholipid antibodies. Thrombotic APS is characterized by venous, arterial, or microvascular thrombosis. The diagnosis is accepted when both one clinical and one laboratory criteria according to the updated Sapporo classification are established. APS may occur in combination with other autoimmune diseases, mainly systemic lupus erythematosus, or in its primary form. Long-term anticoagulation with a vitamin K antagonist is the standard of care for patients who develop thrombosis, considering the high rate of recurrent thrombosis. The current international guidelines are not in favor of recommending direct oral anticoagulants for secondary prevention of thrombotic antiphospholipid syndrome, especially in the context of arterial thrombosis and triple-positive antiphospholipid patients. The most common approach, endorsed by the American College of Chest Physicians guidelines is the combination of heparin and low-dose aspirin (75-100 mg) daily for women who fulfill the clinical and serologic criteria for obstetric APS. New potential therapeutic approaches are under evaluation but actually the anticoagulation remains the cornerstone of treatment.

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Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by thrombotic or obstetric events occurring in patients with persistent antiphospholipid antibodies (APLA), including lupus anticoagulant (LA), anti-β2-glycoprotein I (anti-β2GPI) and/or anti-cardiolipin (aCL) antibodies.[1] Thrombotic APS is characterized by venous, arterial, or microvascular thrombosis. The most frequently affected venous and arterial sites are deep veins of the lower extremities and the cerebral arterial circulation.[2] However the hepatic veins, visceral veins, or cerebral venous circulation are possible, although unusual, sites of thrombosis in APS.

Two specific forms of APS are the catastrophic antiphospholipid syndrome (CAPS) and the obstetrical antiphospholipid syndrome. Only a small number of patients (<1%) develop CAPS,[1,3,4] an extremely aggressive form of APS characterized by multi-organ thrombosis usually caused by a triggering event such as infection.[4-6] CAPS is associated with high (50%) mortality, mostly due to cerebral and cardiac thrombosis, infections, and multi-organ failure.[3,7]

The obstetrical APS is characterized by fetal loss after the 10th week of gestation, recurrent early miscarriages, intrauterine growth restriction, or severe preeclampsia.[1] The definition of clinically significant APLA positivity is not well established, although criteria for classification of the APS have been proposed.[1]

Of note, thrombotic and pregnancy morbidities are

traditional features of APS. However, other clinical manifestations should also be considered to postulate diagnosis. Hematologic disorders (thrombocytopenia, hemolytic anemia), heart valve thickening or vegetation, nephropathy, cognitive dysfunction, and livedo reticularis/racemosa may be a sign of APS.[8]

The purpose of this review is to help both general practitioners and specialists recognize and accurately diagnose APS. Our recommendations are evidence-based whenever possible, however, given the limited number of well-designed, randomized, and controlled trials often reflect expert opinion.

Diagnosis

APS may occur in combination with other autoimmune diseases, mainly systemic lupus erythematosus (SLE), or in its primary form (primary APS).[1,7] The Sapporo classification criteria for APS were first proposed in 1999,[9] and updated at the Eleventh International Congress on Antiphospholipid Antibodies in Sydney in 2006.[1] To diagnose APS, patients must have both clinical and laboratory criteria. Clinical criteria include either objectively confirmed arterial, venous, or small vessel thrombosis; obstetric morbidity such as the premature birth of one or more morphologically normal neonates before the 34th week of gestation, the unexplained death of one or more morphologically normal fetuses at or beyond the 10th week of gestation, and/or three or more unexplained, consecutive spontaneous abortions before the 10th week of gestation.[1] Transient ischemic attack and stroke are the most common arterial events; while the most common venous events are lower-extremity deep-vein thrombosis, pulmonary embolism, or both. According to the Sydney classification scheme, laboratory criteria include: a LA detected according to guidelines published by the International Society on Thrombosis and Hemostasis,[10,11] aCL antibodies (IgG or IgM) exceeding 40 IgG or IgM antiphospholipid units, or anti-β2GPI antibodies (IgG or IgM) at levels exceeding the 99th percentile, measured by enzyme-linked immunosorbent assay (ELISA). Furthermore, to minimize the risk of making a diagnosis based on transient APLA, the recommendations are to perform assays on two separate occasions, at least twelve weeks apart.[10,11]

However, patients who are positive for APLA may present with no related symptoms. Such patients are usually identified during evaluation for other problems, such as early miscarriages, systemic autoimmune diseases, and an elevated activated partial-thromboplastin time. The only presence of antiphospholipids antibodies (aPL) in asymptomatic patients for vascular events or in patients with SLE may be associated with an increased risk of vascular thrombosis but it is not sufficient to establish a clinical diagnosis of APS.

Patients risk stratification: "antiphospholipid profile"

The risk of thrombotic and obstetric complications is strictly associated with the "aPL profile". The aPL type, the titre of the antibody, the persistence of aPL positivity in repeated measurements, and the single or multiple antibody positivity define the "aPL profile" spectrum. It is possible to recognize and correlate some spectrum with increasing risk of clinical potential vascular events and consequently to justify the choice of the intensity of treatment. It is generally accepted as:

- High-risk aPL profile: four different conditions are considered in this profile if the presence of positive titres is demonstrated in two or more occasions at least 12 weeks apart.
  - LA
  - Double positive (any combination of aCL, anti-β2GPI)
  - Triple positive
  - Presence of persistently high titre of aPL.
- Medium-high aPL titres:
  - aCL antibody IgG/IgM isotype in titres >40 IGG phospholipid (GPL) units or >40 IgM phospholipid (MPL) units or >99th percentiles, measured by ELISA.
  - anti-β2GPI antibody of IgG/ IgM isotype in titre >99th percentiles, measured by ELISA.
- Low-risk aPL profile: single positive antibody of aCL or anti-β2GPI at low-medium titres, especially if the positive titre is transient.[11]

Vitamin K antagonists: the standard of care

Long-term anticoagulation with a vitamin K antagonist (VKA) is the standard of care for patients who develop thrombosis, considering the high rate of recurrent thrombosis in patients with APS.[13] A systematic review of 8 prospective studies of patients with a first APS-related thrombotic event reveals that the rate of recurrent thrombosis after stopping anticoagulation in patients with APLA was 40% higher than in those with venous thromboembolism (VTE) unrelated to APLA [unadjusted relative risk 1.4 (95% CI 0.99-2.36).[14] However, a significant proportion of patients with APS develop recurrent thrombosis while on therapeutic anticoagulation.[7,15] Patients with only positivity for LA deserve a special mention. In the Vienna APS study, a prospective observational cohort, LA-positive patients, with or without thrombosis, had higher mortality at 10 years (cumulative relative

survival 87%) compared with a reference population matched for age, sex, and inclusion year.[16] VKA remains the standard of care even in this subgroup of patients. However, physicians should be aware that due to the subtle effects of LA on the international normalized ratio (INR), the INR in patients with LA may be highly dependent upon the thromboplastin used in the assay.[17] One report found that approximately 10% of patients with LA treated with VKA may have a falsely elevated INR when therapeutic ranges were directly compared with a chromogenic factor X assay.[18]

Asymptomatic antiphospholipid-positive subjects: primary thromboprophylaxis?

Asymptomatic patients with confirmed positive aPL are not considered for the diagnosis of APS, however, clinicians should assess aPL antibody risk and subsequent evaluation for treatment if required. A primary prevention treatment with low-dose aspirin (LDA) 75-100 mg daily is recommended in asymptomatic patients with a high-aPL risk profile.[8,19,20] In patients with low-risk aPL profile, LDA as primary thromboprophylaxis may be considered.[21,22] Other non-anticoagulant drugs have been proposed in aPL-positive subjects for primary thromboprophylaxis. The 16th International Congress on Antiphospholipid Antibodies and EULAR recommendations have suggested the use of statins in patients with additional cardiovascular risk factors, although their role remains unclear.[8,23] The beneficial effect of statins in patients with VTE has just been previously studied in randomized trials, meta-analyses, and Choort studies.[24-34]

Management of venous thrombosis in antiphospholipid syndrome

The standard treatment for patients with venous thrombosis in APS is initial anticoagulation with unfractionated heparin or low molecular weight heparin transitioned to a VKA, commonly warfarin, which is continued indefinitely. A target INR of 2.5 (2.0-3.0) is recommended. Because a significant subset of these patients develop recurrent thrombosis despite anticoagulation, the adequacy of this INR target has been questioned. However, two randomized trials that compared standard intensity (INR 2.0-3.0) versus high intensity (INR 3.0-4.0) anticoagulation with warfarin in patients with APS found no difference in the rates of recurrent thrombosis or major bleeding, supporting the use of standard intensity anticoagulation.[35,36] The current recommendation is that anticoagulation should be continued indefinitely for these patients, also considering secondary prophylaxis. However, the optimal duration of anticoagulation is still unclear.[37] Furthermore, the type of VTE (provoked/unprovoked) and the aPL profile are important elements to consider for the duration of anticoagulant treatment. In patients with provoked first venous thrombosis, the therapy should be continued as for patients without APS, according to international guidelines. In this subgroup of patients, prolonged treatment should be considered only in high-risk aPL profile patients or in the presence of additional risk factors for recurrence (VTE).[38] Long-term anticoagulation in first-provoked VTE patients remains unclear. To our knowledge, there are no studies on this topic and this recommendation is based only on expert opinion.[20]

While the authors agree with this recommendation, we emphasize that all cases should be considered on an individual basis, and the duration of anticoagulation should be dictated by the patient-specific risk-benefit ratio, weighing the risk of recurrent thrombosis, against the likelihood of bleeding, falls, and compliance.

Management of arterial thrombosis in antiphospholipid syndrome

The 2011 report by a task force of the 13th International Congress on APLA suggested that patients with definite APS and arterial thrombosis should be treated with warfarin at an INR>3.0 or combined anti-platelet and anticoagulant (INR 2.0-3.0) therapy.[37] However, there was no consensus on the use of high-intensity anticoagulation and several members of the task force opined that standard-intensity anticoagulation (INR 2-3) is adequate for secondary thromboprophylaxis of arterial events.[37] In the setting of inadequate data concerning efficacy and safety, we believe that high-intensity anticoagulation should be used very judiciously, if at all in APS patients, and reserved for those with a high-risk APLA profile and additional cardiovascular risk factors in whom the potential benefit outweighs the risk of bleeding. Different therapeutic approaches have also been evaluated. The Antiphospholipid Antibodies and Stroke study, a subgroup of the Warfarin-Aspirin Recurrent Stroke Study, evaluated warfarin versus aspirin for secondary stroke prevention in patients with APLA. The rate of recurrent stroke was similar in the warfarin (INR 1.4-2.8) and aspirin groups;[39] however, these results may not be generalizable, since APLA were tested only once at baseline and low titer aCL antibodies were included. A small, randomized trial reported a lower rate of recurrent stroke in patients treated with aspirin plus warfarin versus aspirin alone.[40] However, this study had an unexpectedly high incidence rate of recurrent stroke (8 of 11 in the aspirin arm and 3 of 11 in the combination arm) over a mean follow-up of approximately 4 years.

Is the use of direct oral anticoagulant possible?

The use of VKA is difficult in some patients due to numerous food-drug interactions, frequent monitoring, and the direct effect of LA on accurate INR monitoring. Hence, theoretically, direct oral anticoagulants (DOACs) are an attractive alternative. Published data on their use in APS was limited to anecdotal reports in case studies and case series with variable results.[41-44] Three case series including a total of 69 patients with thrombotic APS reported acceptable safety profiles for DOACs with low rates of recurrent thrombosis.[8,26,35,45-47] However, other studies have reported a high rate of recurrent thrombosis, including arterial events, in patients with thrombotic VTE who switched to DOACs, raising significant concerns about their efficacy. DOACs, on the other hand, are not universally recommended for these patients and their use should be limited to those who are refractory or intolerant to VKA or low molecular weight heparin. In the meantime, DOACs could be considered in patients with a clear contraindication to VKA (intolerance or allergy) or those not able to achieve a target INR despite good adherence to VKA. The current international guidelines are not in favor of recommending DOACs for secondary prevention of thrombotic APS, especially in the context of arterial thrombosis and triple-positive aPL patients. In the other clinical context (VTE) or aPL profile (*e.g.*, single or double positive) the use of DOACs is highly debated and further studies are needed to clarify their efficacy.[20,48]

Management of refractory thrombotic antiphospholipid syndrome

Refractory thrombotic APS is defined as rates of recurrent thrombosis in excess of 30% in anticoagulated patients with APLA.[7] The management of these cases is difficult, and evidence is insufficient to consider a standardized approach. First, we suggest verifying that the patient is adequately anticoagulated with a target INR in the therapeutic range, as well as a therapeutic factor X level;[37,49] second, to consider higher intensity anticoagulation. For still refractory patients, adjunctive non-anticoagulant therapies such as statins, hydroxychloroquine, and rituximab may be an option,[37] but no well-designed clinical studies support their use.

Management of catastrophic antiphospholipid syndrome

In patients without a known history of APLA, CAPS can be difficult to diagnose and delays can have lethal consequences. Due to its rapidly, progressive and potentially fatal condition, early diagnosis is essential. The optimal treatment of CAPS is unknown and prospective trials for treatments of CAPS have not been conducted. Based on observational data and expert opinion, anticoagulation with heparin and high-dose steroids (methylprednisolone 1000 mg daily for 3 days or longer) are the mainstay of therapy.[50] Additional recommendations include searching for and treating any precipitating factor such as infection and debriding/amputating any necrotic tissues to limit inflammation. Plasma exchange has been shown to improve mortality in the CAPS registry.[3] Intravenous immunoglobulin alone does not appear to be beneficial in patients with CAPS.[3] Eculizumab has been reported to successfully treat patients with refractory CAPS.[51-55]

The pathogenesis of APS supports the use of biologic agents as a targeted treatment approach and new drugs are investigated for patients with refractory APS or CAPS.

New evidence underlines the potential efficacy of biologics such as anti-CD38 monoclonal antibody (Daratumumab), BAFF/Blys inhibitor (Belimumab), BTK inhibitor (Zanubrutinib), Anti-TNF-a monoclonal antibody (adalimumab, certolizumab).[56] Although anticoagulation still remains the main therapy of APS, the specificity of biologics makes them promising options for the development of more appropriate tailored therapies.

Management of obstetric antiphospholipid syndrome

Pregnancy in APS is regarded as a "high-risk pregnancy" and the main aim of surveillance and treatment in pregnant women with aPL is to optimize maternal and fetal pregnancy outcomes. Management of obstetrical APS remains controversial. The most common approach, endorsed by the American College of Chest Physicians guidelines is the combination of heparin (unfractionated or low molecular weight; prophylactic or intermediate dose) and low-dose aspirin (75-100 mg) daily for women who fulfill the clinical and serologic criteria for obstetric APS.[57] A prospective observational study reported live births in 71% of pregnancies treated with aspirin in combination with either heparin or low molecular weight heparin (LMWH).[58] Two randomized studies comparing aspirin have demonstrated an increased rate of live births with aspirin and unfractionated heparin compared with aspirin alone, though different doses of heparin were employed.[59,60] In women with APS and prior thrombosis, aspirin, and therapeutic dose LMWH should be employed. Women who are anticoagulated with VKA should be switched to LMWH since warfarin has been linked to fetal malformations.

Conclusions

The APS has a broad spectrum of thrombotic and non-thrombotic clinical manifestations due to a thrombo-inflammatory autoimmune disease. The main manifestations concern vascular events and pregnancy morbidity. The diagnosis requires positive APLA tests in the presence of a typical clinical manifestation and the "aPL profile" is important in choosing the most appropriate treatment. Thus, both misdiagnosis due to underrecognition of signs or symptoms and overdiagnosis due to overinterpretation of antiphospholipid-antibody tests are common. Vitamin K antagonists seem to offer more protection in triple-positive APS and in patients with arterial thrombotic events and remain the most appropriate treatment in secondary prevention. New potential therapeutic approaches are under evaluation but actually, the anticoagulation remains the cornerstone of APS treatment.

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