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ORIGINAL ARTICLE

Diagnosing and treating antiphospholipid syndrome: a consensus paper

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KEYWORDS

Antiphospholipid syndrome, antiphospholipid antibodies, thrombosis, pregnancy morbidity, catastrophic antiphospholipid syndrome, treatment

ABSTRACT

Introduction. The antiphospholipid syndrome (APS) is defined by the occurrence of venous and/or arterial thrombosis and/or pregnancy-related morbidity, combined with the presence of antiphospholipid antibodies (aPL) and/or a lupus anticoagulant (LAC). Large, controlled, intervention trials in APS are limited. This paper aims to provide clinicians with an expert consensus on the management of APS.
Methods. Relevant papers were identified by literature search. Statements on diagnostics and treatment were extracted. During two consensus meetings, statements were discussed, followed by a Delphi procedure. Subsequently, a final paper was written.
Results. Diagnosis of APS includes the combination of thrombotic events and presence of aPL. Risk stratification on an individual base remains challenging. 'Triple positive' patients have highest risk of recurrent thrombosis. aPL titres > 99th percentile should be considered positive. No gold standard exists for aPL testing; guidance on assay characteristics as formulated by the International Society on Thrombosis and Haemostasis should be followed. Treatment with vitamin K-antagonists (VKA) with INR 2.0-3.0 is first-line treatment for a first or recurrent APS-related venous thrombotic event. Patients with first arterial thrombosis should be treated with clopidogrel or VKA with target INR 2.0-3.0. Treatment with direct oral anticoagulants is not recommended. Patients with catastrophic APS, recurrent thrombotic events or recurrent pregnancy morbidity should be referred to an expert centre.
Conclusion. This consensus paper fills the gap between evidence-based medicine and daily clinical practice for the care of APS patients.

Introduction

The antiphospholipid syndrome (APS) is defined by the occurrence of venous and/or arterial thrombotic events and/or pregnancy-related morbidity (≥ 3 unexplained consecutive spontaneous abortions < 10 weeks with exclusion of chromosomal causes, foetal death or severe pre-eclampsia before 34th week of gestation), combined with the presence of circulating antiphospholipid antibodies (aPL) and/or a lupus anticoagulant (LAC),

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Table 1. *Classification criteria for the antiphospholipid syndrome*[1]
A patient can be classified as having the antiphospholipid syndrome when at least one clinical and one laboratory criterion is present. We consider arterial thrombosis in the eye as a defining clinical event for antiphospholipid syndrome; venous thrombosis of the eye is not considered a defining event. We prefer to use the 99th percentile cut-off value for anticardiolipin antibodies and do not use the > 40 GPL-cut-off.

Clinical criteria	
1. Vascular thrombosis (confirmed by imaging studies or histopathological studies)	a. One or more clinical episodes of arterial, venous or small-vessel thrombosis, in any tissue or organ
2. Pregnancy morbidity	a. Three or more sequential spontaneous abortions before 10th week of gestation; or b. Unexplained foetal death of a morphologically normal foetus after 10th week of gestation; or c. Early birth before 34th week of gestation of a morphologically normal foetus due to eclampsia, severe pre-eclampsia or confirmed placental failure
Laboratory criteria	
	a. Lupus anticoagulant (LAC) present in plasma, confirmed on minimally two occasions with an interval of at least 12 weeks b. Anticardiolipin-antibodies (aCL), IgG- or IgM-isotype, present in serum or plasma, with elevated titre (> 99th percentile), confirmed on minimally two occasions with an interval of at least 12 weeks c. Anti-β2 glycoprotein-I-antibodies, IgG- or IgM-isotype, present in serum or plasma (with titre > 99th percentile), confirmed on minimally two occasions with an interval of at least 12 weeks

see table 1.[1] Formally, LAC is the result of aPL binding to plasma proteins, mainly β2-glycoprotein, that have affinity for the negatively-charged phospholipids; therefore, the pathologic auto-antibodies are not directed against phospholipids. In this paper, the term 'aPL' refers to both LAC and anticardiolipin (aCL)/anti-β2-glycoprotein-I (anti-β2GPI) antibodies, following clinical practice and literature. APS is considered a primary autoimmune disease, but is often diagnosed as being secondary to other auto-immune diseases; 30-40% of patients with systemic lupus erythematodes (SLE) also have APS, and APS can be diagnosed secondary to rheumatoid arthritis, systemic sclerosis, dermatomyositis or other autoimmune diseases.[2] Large, controlled, randomised clinical trials for interventions in APS are limited, and the quality of current data is not sufficient to develop a structured guideline or assess evidence-based management strategies. However, clinically-relevant questions about diagnostic criteria and treatment of APS patients arise on a daily basis.
We aim to provide clinicians with an expert consensus on the management of APS, with a focus on classification, diagnostics, risk stratification, and treatment.

Methods

A literature review was performed (KdL and ML) with the following Pubmed search terms: 'antiphospholipid syndrome', "Antiphospholipid Syndrome"[Mesh], 'antiphospholipid antibodies', "Antibodies, Antiphospholipid"[Mesh], 'obstetric antiphospholipid syndrome', 'catastrophic antiphospholipid syndrome', 'laboratory diagnostics', 'Clinical Laboratory Techniques"[Mesh] 'diagnosis', "Diagnosis"[Mesh], 'treatment' and "Therapeutics"[Mesh]; papers focusing on diagnostics and/or treatment for APS were included. Non-English papers and papers published before 2000 were excluded. The literature search was performed on April 3rd, 2018; papers published after that date but with high impact according to the writing committee were included until September 1st, 2018. Statements on APS diagnostics and treatment were extracted from the papers selected, and a first draft of the consensus paper was written (KdL and ML). This draft was circulated amongst all authors and comments were

Table 2. *Non-criteria clinical manifestations of antiphospholipid syndrome*

Livedo reticularis/racemosa
Heart valve lesions/Libman-Sacks endocarditis
Thrombocytopenia
Superficial venous thrombosis
Nephropathy
Migraine
Chorea
Epilepsy
Myelitis transversa
'SLE-like' symptoms (e.g. alopecia, aphthous ulcers)

SLE = systemic lupus erythematosus

collected. On June 6th, 2018, a first consensus meeting was held in Utrecht, The Netherlands. Based on the outcomes of this meeting, a second draft of the paper was written (JS, ML) and circulated again for comments. On November 5th, 2018, a second consensus meeting was held in Utrecht, The Netherlands. Degree of consensus on statements was assessed by a Delphi procedure and a final report was written afterwards (see table 3).

Diagnosis, classification, risk stratification

Diagnosis of APS

No *diagnostic* criteria for APS exist. If a patient meets the classification criteria – developed for research purposes – for APS (e.g., a thrombotic event and/or pregnancy morbidity, combined with repeated presence of antiphospholipid antibodies (aPL); see table 1), most likely a clinical diagnosis of APS will be made, although thrombotic and pregnancy complications are not necessarily causally related to circulating aPL.

In addition to the thrombotic or pregnancy-related events listed in the classification criteria, APS may be associated with a variety of *non-criteria manifestations*, such as superficial vein thrombosis, thrombocytopenia, renal microangiopathy, heart valve disease, livedo reticularis or racemosa, migraine, chorea, seizures and myelitis; see table 2. As a result, a *clinical* diagnosis of APS can be made in patients who do not fulfil the classification criteria.[3]

An even more complicating factor is the concept of seronegative APS, a term coined to include patients with clinical (criteria and non-criteria) features suggestive of APS, but who are persistently negative for aPL.[4] The existence of seronegative APS is a point of international discussion among experts. If the suspicion of seronegative APS arises, we suggest referral to an expert centre.

Catastrophic antiphospholipid syndrome (CAPS) is the most extreme APS variant that includes simultaneous multiple organ thrombosis and develops in a short period of time with a high mortality rate. Although strongly associated with the presence of LAC, no other laboratory or clinical determinants are known to be associated with CAPS.[2]

Risk stratification in APS

Several assessment tools to risk-stratify patients have been proposed, mainly focusing on presence and levels of aPL and/or on clinical parameters. For aPL, the presence of LAC is the strongest risk factor for both arterial and venous thrombosis in APS.[5,6] For aCL and anti-β2GPI, the association between (levels of) antibodies and thrombosis is less clear. It has been suggested that anti-β2GPI-dependent LAC has a strong association with thrombotic risk.[7] In several studies, it has been demonstrated that the risk of arterial and venous thrombosis increases with the number of positive tests for aPL, with the highest risks in patients with both LAC, aCL and anti-β2GPI antibodies, so-called 'triple positive patients'.[6,8] In clinical practice, risk stratification does not affect treatment decisions in most situations. The antiphospholipid score (aPL-S) has been developed to predict the risk of APS-related clinical events in patients with APS and other autoimmune diseases (such as SLE, rheumatoid arthritis, and Sjögren's syndrome) based on the presence of aPL.[9] The global APS score (GAPSS) is another clinical score, including both aPL and conventional cardiovascular risk factors, predicting the risk of thrombotic events in patients with SLE.[10] The GAPSS has been validated in a cohort of APS patients, and a correlation between higher GAPSS values and recurrence of thrombotic events was observed.[11] However, these scores are not sufficient to design treatment strategies for the individual patient. We consider triple positive patients to be at highest risk for recurrent thrombosis.

Laboratory diagnostics in APS

The classification criteria for APS indicate three different antibody subsets of aPL. For two of these, the antigen is well-defined: aCL antibodies recognize the plasma glycoprotein β2GPI in complex with the anionic phospholipid cardiolipin, and anti- β2GPI antibodies recognize the protein β2GPI in the absence of cardiolipin. Both antibody subtypes can be detected with quantitative solid phase assays in which the antigen is immobilized on a surface. The third aPL subtype, known as LAC, is detected with a functional assay: these antibodies manifest as phospholipid-dependent inhibitors of *in vitro* coagulation. They are detected with phospholipid sensitive coagulation assays. Although the exact antigen to which LAC are directed is currently unclear, there is ample evidence that antibodies against β2GPI as well as antibodies against prothrombin can induce the LAC phenomenon.[12,13]

The diagnosis of APS is made in cases of persistent presence of aPL (titre > 99th percentile), assessed in two separate samples taken with an arbitrarily defined interval of at least twelve weeks. This is an important distinction, as several aPL occur transiently in relation to viral and bacterial infections and are of uncertain clinical relevance.[14] Moreover, since aPL is prevalent (1-5%) in the general population,[15] aPL status should only be tested in patients considered at risk of having APS, such as those < 50 years of age, unprovoked arterial or venous thrombosis, thrombosis at an unusual site, recurrent thrombosis, and thrombotic/pregnancy complications with or without association with a systemic autoimmune disease.[16-18]

Unfortunately, gold standards for aPL detection are lacking, although aCL assays based on pooled human serum have been in use for over 20 years.[19] Reports have

been published of new standards based on human(ized) monoclonal antibodies against β2GPI and purified patient-derived polyclonal antibody preparations, but these are not yet available.[20] No such standards exist for LAC-positive plasmas. For further harmonization of results between diagnostic laboratories, centres performing these tests participate in diagnostic surveys as part of laboratory accreditation.

Measurement of anticardiolipin and anti-β2-glycoprotein I antibodies

The classification criteria for APS specify that both immunoglobin G (IgG) and IgM class immunoglobulins against cardiolipin or β2GPI should be measured. Several commercial entities supply kits to measure these antibodies and many laboratories have developed their own solid phase assays. To minimize the effect of the lack of gold standards and the large number of assays in use for detection of aPL on assay standardization, guidance on assay characteristics has been provided by the Scientific Standardization Committee of the International Society on Thrombosis and Haemostasis.[16] Detection of aCL and β2GPI antibodies can be performed in both trisodium citrate anticoagulated plasma and in serum. Since aCL antibodies associated with APS are β2GPI-dependent, diagnostic laboratories should use assays in which cardiolipin is saturated with human β2GPI. Samples should be considered positive when the value obtained in these assays exceeds the 99th percentile of the normal population, rather than antibody levels exceeding 40 arbitrary units as indicated in the classification criteria, as this appears to be more specific for APS.[21] We recommend that the laboratory report mentions both a cut-off value (< 99th or > 99th percentile, e.g., negative or positive) and a continuous numeric value.

Detection of lupus anticoagulant

LAC are phospholipid-dependent coagulation inhibitors and are detected with sensitive coagulation assays in trisodium citrate anticoagulated plasma. Plasma samples should be double centrifuged to minimize contamination with platelets, as they are a major source of phospholipid and might therefore interfere with LAC detection.[17,18] LAC can be detected with any phospholipid-dependent coagulation assay, however, no gold standard for LAC testing exists. For this reason, it is warranted to perform two tests based on a different assay principle for LAC detection, preferably a dilute Russell's viper venom time (dRVVT) and a LAC-sensitive activated partial thromboplastin time (APTT).[17] In order to be deemed LAC-positive, a sample should have a prolonged clotting time when a reagent with a low phospholipid content is used (screening test), which should correct when a reagent with a high phospholipid content is used (confirmatory test), indicating phospholipid-dependence of the prolongation. The presence of a coagulation inhibitor as the cause of the prolongation should be shown with a mixing test, in which patient plasma is mixed with an equal volume of pooled normal plasma. This will normalise any coagulation factor deficiencies that are present, and any remaining prolongation of the clotting time is therefore caused by an inhibitor. Cut-off values for LAC should be determined locally in each diagnostic laboratory, based on the 99th percentile of the local normal population or alternatively, on the mean + 2 standard deviation (SD) of the clotting time of the normal population. The strength of the LAC should be expressed as a ratio between screen and confirm clotting times, preferably normalized on the mean of the normal population, according to the following equation:

$$\text{normalized LAC ratio} = \frac{\text{Screen(patient)/Screen(normal)}}{\text{(Confirm(patient)/Confirm(normal)}}$$

Samples are deemed positive for LAC when one or both tests for LAC detection (APTT and dRVVT-based tests) indicate the presence of LAC.

The use of anticoagulant drugs interferes with detection of LAC, possibly resulting in false-positive test results. Samples for LAC-detection should therefore be collected before treatment with anticoagulants has started, or sufficiently long after cessation of treatment to minimize confounding effects. However, it should be avoided to use samples obtained in the acute phase after a thrombotic event or during infection, as this is associated with high Factor VIII levels, which might interfere with LAC detection by APTT-based assays. Although LAC can be determined in samples from patients receiving vitamin K antagonists when they are mixed with an equal volume of pooled normal plasma, the outcome of LAC tests in samples with an INR within therapeutic range (INR 2-3) should be interpreted with caution and measurement of LAC in samples with an international normalised ratio (INR) > 3 is not recommended. Mixing antagonists with normal plasma dilutes the titre of LAC and thus reduces the sensitivity of the assay. On the other hand, the mixing test may not completely correct the clotting time for samples in the high INR range and may lead to false-positive interpretation. Temporary discontinuation of vitamin K antagonists (or co-administration of vitamin K and continuing vitamin K antagonists) and bridging with low molecular weight heparin is possible. Unfractionated heparin, however, is incompatible with LAC testing, as is the use of direct oral anticoagulants, even at trough levels of factor Xa or thrombin inhibitors, with factor Xa inhibitors producing false-positive LAC.[22] No alternatives exist for LAC detection in samples containing direct

thrombin inhibitors. A possible means to detect LAC in samples containing rivaroxaban is the Taipan snake venom time/Ecarin clotting time combination, as these tests are insensitive to factor Xa-inhibitors.[23] More studies on the specificity and sensitivity for LAC of this test combination are required before these tests will be widely adopted for LAC detection.

Non-criteria aPL

There are several reports on the association between various non-criteria aPL subtypes and thrombosis. Amongst these are IgA anti-β2GPI antibodies,[24-26] antibodies against the phospholipid phosphatidylethanolamine (PE),[27] antibodies against the complex between the phospholipid phosphatidylserine, and the coagulation factor prothrombin (aPS/PT).[28] Currently, however, there is insufficient evidence of their clinical relevance to warrant routine detection of these antibodies.

Treatment

Venous thrombosis in APS

A first venous thrombotic event (VTE; amongst others including deep vein thrombosis and pulmonary embolism, abdominal vein thrombosis, cerebral vein thrombosis) should be treated according to the current guidelines for treatment of VTE; no routine testing for aPL is indicated in the general population. In cases of recurrent thrombosis (both provoked and unprovoked), or patients with a pre-existing autoimmune disease (and in particular, SLE), additional testing for aPL should be performed.

Low molecular weight heparin (LMWH) in therapeutic doses and subsequent vitamin K antagonists (VKA) are first-line treatments for a first or recurrent APS-related venous thrombotic event (VTE). Treatment with direct oral anticoagulants (DOACs; see separate section below) is not recommended. For APS patients with a first VTE, life-long anticoagulation is recommended. After treatment with LMWH in the acute phase, treatment will be switched to VKA, with an INR target range of 2.0-3.0 for venous events.[29,30] High-intensity treatment with an INR ≥ 3.0 after a first VTE is not recommended.[31,32]

Arterial thrombosis in APS

Optimal long-term treatment for arterial thrombosis (other than cerebral arterial thrombosis; see below) is still a matter of debate; either anti-platelet therapy such as aspirin or clopidogrel, VKA with an INR target range of 2.5-3.5 or combined therapy with VKA with an INR target range of 2.0-3.0 and anti-platelet therapy has been recommended.[30] As combined therapy, VKA and anti-platelet therapy has not been shown to be superior to anti-platelet therapy alone, and since more major bleeding complications were observed in the combination group,[33] we do not recommend up-front combined treatment with both VKA and anti-platelet therapy. Based on expert opinion and in slight contrast with international recommendations, we prefer treatment with either clopidogrel or VKA with an INR target range of 2.0-3.0 in these patients.[33,34]

In patients with a cerebral ischemic event (transient ischemic attack (TIA) or ischemic stroke) as clinical manifestation, there is no evidence supporting one therapy over the other. A prospective, comparative study in aPL-positive stroke patients showed no benefit of warfarin over aspirin (325 mg/day) on recurrent events; more (minor) haemorrhagic complications in the warfarin group were observed. However, these patients did not necessarily fulfil APS criteria.[35] A small (n = 20), randomized, controlled trial in APS patients with ischemic stroke compared VKA and low-dose aspirin with low-dose aspirin alone, and demonstrated less recurrent stroke in the combined-therapy group.[36] In APS patients with a first ischemic stroke or TIA without any cause other than APS on work-up, we propose treatment with either VKA with an INR target range of 2.0-3.0 or clopidogrel (since this is superior to aspirin for stroke prevention in a general population suffering from atherosclerotic cerebrovascular disease).[37]

Position of direct oral anticoagulants in APS

DOACs such as dabigatran, rivaroxaban, apixaban, and edoxaban, were shown to be non-inferior to VKAs for treatment and secondary prevention of venous thromboembolic events and prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.[38] Furthermore, these drugs have some advantages compared to VKAs as it is a fixed dose, no monitoring is required, interaction is limited, and there is a lower risk of intracranial and other major bleeding. Nonetheless, few studies are published concerning the use of DOACs in known APS. A recent review summarised the available data, including one randomized controlled trial (RAPS trial) and case series.[39]

From all available case series and case reports, 122 patients were analysed.[39] High-risk APS patients with triple positivity or with several clinical criteria for definite APS, developed recurrent thrombosis more frequently while on DOACs in comparison to warfarin. The RAPS trial, comparing 54 APS patients treated with rivaroxaban to 56 APS patients treated with warfarin, demonstrated that the *in vitro* anticoagulant effect of rivaroxaban may be inferior to that of warfarin.[40] A randomized controlled clinical trial in triple positive patients, comparing VKA treatment with rivaroxaban, was terminated early due to more thrombotic events in the rivaroxaban-arm, with particularly more ischemic strokes in the DOAC group.[41]

At this moment VKAs, compared to DOACs, remain the standard of care in the treatment of APS, especially in high-risk APS patients. DOACs might be an alternative

treatment modality for only those patients with instable INR or poor adherence to INR monitoring, and we anticipate more data from future trials using DOACs in thrombotic APS.

Recurrent venous thrombotic events while using anticoagulation therapy

Recurrent thrombosis in APS patients, despite adequate anticoagulation therapy (INR target range, 2.0-3.0) is common and occurs in up to one-third of all patients.[2] However, recurrent thrombosis is uncommon in APS patients with a higher INR target range of 2.5-3.5 and most patients treated with a VKA with recurrent thrombosis, appear to have an INR target < 3.0.[42] Therefore, anticoagulation therapy should be intensified with a INR target range of 2.5-3.5 in case of a recurrent venous event despite adequate INR. When a recurrent venous thrombosis is diagnosed with a suboptimal INR (< 2.0), therapeutic LMWH should be given for a period of two weeks and the INR treatment range should not be changed. Note that the INR value can be underestimated due to interference of thromboplastin and LAC, although this is mostly problematic with higher INR values, i.e. > 4.0.[43]

If the target INR cannot be reached and/or maintained with VKA, referral to an expert centre is recommended.

Based on expert opinion, in patients with recurrent venous thrombosis, despite an adequate INR target range of 2.5-3.5 and after two weeks of therapeutic LMWH, additional long-term use of aspirin can be recommended, or intensifying of VKA therapy with to an INR target range of 3-4. Alternatively, a permanent switch to therapeutic LMWH can be considered.

Combining VKA with hydroxychloroquine may also decrease the risk of recurrent venous thrombosis, although randomized studies with hydroxychloroquine in APS are still lacking.[44,45]

Until now, no clinical support for the use of statins in patients with recurrent venous thrombosis despite anticoagulation exists. However, based on *in vitro* work and surrogate endpoints, a beneficial role of statins has been suggested.[46,47]

Recurrent arterial thrombotic events while using anticoagulation therapy

No consensus on treatment of recurrent arterial thrombosis was reached at the last meeting of the APS task force.[30] Optimal treatment strategies for recurrent arterial thrombotic events have not been studied. In recurrent arterial thrombosis, including TIA or ischemic stroke, despite treatment with clopidogrel, we suggest switching treatment to VKA with an INR target range of 2.0-3.0.

If recurrent arterial thrombosis occurs despite adequate treatment with VKA, referral to an expert centre is recommended.

We do not recommend to routinely perform brain magnetic resonance imaging (MRI) in APS patients with an ischemic stroke. However, some experts believe that if neurological symptoms, including migraine or cognitive performance, deteriorate, a repeat brain MRI is indicated and new white matter abnormalities may lead to intensifying treatment. The possible benefits of this strategy have not been confirmed in clinical studies, and for patients with deterioration of neurological symptoms, referral to an expert centre is recommended.

Catastrophic antiphospholipid syndrome (CAPS)

CAPS is a rare complication of APS and occurs in approximately 1% of APS patients. CAPS is a severe condition, including massive (mostly arterial) thrombosis of small vessels, causing multi-organ failure. Mortality in CAPS is high, up to 50%. Adequate and fast treatment initiation slightly improves clinical outcomes (mortality 20-40%) and treatment should be carried out in an expert centre.[48,49] A combination of anticoagulant drugs (mostly unfractionated heparin with APTT ratio 2-2.5), intravenous corticosteroids (methylprednisolone 500-1000 mg/day for 3-5 days), therapeutic plasma exchange (TPE) and/or intravenous immunoglobulins (IVIG) (1 g/kg, for a time period of 3 days) is associated with highest survival rates. Combination of heparin-corticosteroids-plasmapheresis with or without additional IVIG results in 69-78% patient survival.[50-52] TPE should be started when the clinical suspicion of CAPS arises, within a minimum of 5 days.[52] Clinical response dictates the duration of TPE and no single clinical or laboratory parameter is used to determine when to discontinue treatment.

For patients with CAPS and underlying SLE, treatment with cyclophosphamide (750 mg/m^2 monthly) has been proposed.[48,53] Rituximab (anti-CD20) has been administered to patients with refractory CAPS and may be of adjunctive value in a selected population of patients. Eculizumab (anti-complement 5) has been reported in case reports as a last resort, and could be considered in those patients refractory to all other therapies.[54,55]

Pregnancy and antiphospholipid antibodies

Pregnancy complications of APS include recurrent first trimester pregnancy loss, intrauterine growth restriction (IUGR), preeclampsia (PET), premature birth, and intrauterine death (IUD). Early miscarriages are reported in 26-35% and aPL-related PET, premature birth or foetal death are seen in 10–20% of APS pregnancies.[2,56]

Women with positive aPL do not all carry the same obstetric risk. The following parameters are associated with an increased risk: the presence of LAC, more than one

aPL (especially triple positivity), IgG aPL (instead of IgM), previous thrombosis, previous pregnancy complications, associated autoimmune condition, and hypocomplementemia.[57] At present, however, risk stratification does not direct different treatment strategies.

The current standard treatment, based on low-dose aspirin and LMWH, increases the percentage of a successful pregnancy from 20% to 54-80%.[58] In patients with obstetrical APS, aspirin and a prophylactic dose of LMWH should be administered. Depending on the context (concurrent SLE, maternal age, non-criteria clinical features), treatment of patients with fewer than three miscarriages, and therefore, formally not classified as having APS, can be considered. To prevent overtreatment in these cases, confirmation of miscarriage by ultrasound is recommended. During pregnancy, regular clinical pregnancy follow-up is sufficient; only in specified subpopulations (e.g. patients with SLE, chronic kidney disease, morbid obesity, triple positive antibody profile, and patients with a thrombotic event during pregnancy), follow-up (of foetal growth and hypertensive pregnancy complications) should be intensified. Platelets should be checked at least once every 10-14 days after starting LMWH to exclude heparin-induced thrombocytopenia. If pregnancy complications (foetal death or miscarriage) still occur despite combined treatment with low-dose aspirin and prophylactic dose of LMWH, the dose of LMWH can be increased to a therapeutic dose; reverting back to a prophylactic dose of LMWH after 36 weeks of gestation can be considered.

Based on expert opinion, patients with APS who already use therapeutic anticoagulation before pregnancy, should be switched to therapeutic dose of LMWH and low-dose aspirin should be added. Anti-factor Xa levels should be periodically monitored (at least once every trimester) in patients receiving therapeutic doses of LMWH, depending on the context.

If this strategy fails, further treatment should take place in an expert centre. The recommendations are again based on expert opinion and retrospective cohort studies and include, for example, the addition of hydroxychloroquine or intravenous immunoglobulins. This should however, be confirmed in randomized controlled trials.[59-61]

In the postpartum period there is an increased risk for thrombosis. Patients with APS with an indication of therapeutic anticoagulation before pregnancy, should be switched to VKA or continue with therapeutic LMWH. Obstetrical APS patients should receive prophylactic or intermediate doses (a randomized clinical trial to investigate optimal dosing is currently underway[62]) of LMWH during a period of six weeks postpartum.[57]

Withdrawal of antithrombotic treatment in APS

As mentioned above it is recommended to treat thrombotic APS patients lifelong. However, as long-term anticoagulation therapy is associated with haemorrhagic complications, the question arises whether it is possible to withdraw this therapy in selected patients, especially those who have a long-term event free period or who no longer have positive aPL, also called seroconversion. Only a few (uncontrolled and small) studies have addressed this question. Criado-Garcia *et al* described the effects of anticoagulation withdrawal in six primary APS patients in whom aPL had disappeared.[63] None of these patients experienced a thrombotic event during a follow-up of 21 ± 4.9 months. It should be mentioned, however, that these patients were at low risk for recurrence, as they only had a venous thrombosis history. Similar results were found by Coloma Bazan *et al*, who reported no thrombotic recurrences after anticoagulation withdrawal durign a median follow-up of 20 months in 11 primary APS patients (seven with history of venous thrombosis and four with obstetrical APS).[64] However, in a more recent study, 30 APS patients with anticoagulation withdrawal were compared to a thrombotic APS control population without withdrawal. During a median follow-up of 51 months, anticoagulation withdrawal was associated with a higher risk of thrombotic relapse (HR 4.82). Predictive factors were male gender, anti-β2GPI-positivity and triple positivity at onset as well as persistence positivity over time. Predictive factors for low risk of relapse were aspirin prescription and aPL disappearance during follow-up.[65]

In conclusion, data is insufficient to draw firm conclusions concerning anticoagulation withdrawal in APS patients. The available data suggests that anticoagulation could be withdrawn in APS patients with a single provoked venous thrombotic event in the presence of a known transient precipitating risk factor (such as smoking, disease activity, oral contraceptive use) together with disappearance of aPL. In all other situations, the high risk of thrombotic relapse favours the continuance of anticoagulation treatment. Randomized studies with larger sample sizes are still needed to confirm these statements.[66,67]

The decision to withdraw anticoagulation in APS patients should be made in an expert centre.

Position of rituximab, hydroxychloroquine, intravenous immunoglobulins

Several immunomodulatory drugs are suggested for the treatment for patients with APS, although their exact use in the treatment of APS is unclear; these include. rituximab, hydroxychloroquine (HCQ), and IVIG. Most evidence is based on cohort studies, case series or expert opinion. Only a few randomised controlled trials (RCTs) are published. Furthermore, their application is strongly dependent on the different clinical situations. For example, in secondary APS in SLE patients, HCQ is strongly recommended, as it has been shown that HCQ has 'thrombo-protective' effects, resulting in fewer

venous and arterial thrombotic events.[68] In primary APS, limited data is available. One retrospective cohort study demonstrated strong reduction of aPL titres and a decrease in the incidence of arterial thrombosis recurrence by using HCQ.[69,70] One RCT randomizing 40 APS patients to VKAs versus VKAs with HCQ showed a protective effect of adding HCQ upon venous thrombotic events.[45] At this moment, HCQ is not included in standard care of primary APS, but refractory cases, including refractory obstetrical APS, might benefit from this treatment. Treatment with HCQ (200-400 mg per day) is safe during pregnancy and lactation.

Rituximab and IVIG may be used in difficult-to-treat APS patients, especially in those with CAPS or recurrent haematological non-criteria manifestations as thrombocytopenia, but not as standard of care of APS.[71,72]

Prophylaxis in aPL-positive patients without earlier events

The question remains whether patients with obstetric APS or individuals with positive aPL without thrombotic events should be treated to prevent thrombosis (primary thromboprophylaxis). At present, there is insufficient evidence to support prophylactic treatment for all of these patients.[8,73] However, in patients with more risk factors for thrombosis (such as obesity, smoking, higher age) and/or high-risk aPL profile (e.g., triple positive), low dose aspirin might be beneficial. In any case, attention should be paid to avoid or to treat any associated cardiovascular risk factors, e.g. using antihypertensives or cholesterol-lowering agents and avoidance of smoking, etc. Also, the administration of oral contraceptives should be used with caution and with counselling.[74] Lastly, prophylaxis of venous thrombosis using LMWH is required for patients in situations associated with increased risk of thrombosis, such as surgical procedures, plaster casts, and those requiring bed rest.

Box 1. *Recommendations for consultation and/or referral of patients to an APS expert*

- Recurrent thromboembolic events despite adequate treatment with VKA and/or anti-platelet therapy
- Recurrent obstetric events despite therapy with low dose aspirin and LMWH in prophylactic dose
- Strong suspicion of APS with negative aPL
- Positive aPL but only non-criteria manifestations
- APS-patients with deterioration of neurological symptoms
- (Suspected) CAPS
- Withdrawal of anticoagulation in APS patients

VKA = vitamin K antagonists; LMWH = low molecular weight heparin; APS = antiphospholipid syndrome; aPL = antiphospholipid antibodies; CAPS = community-acquired pneumonia

Conclusion

APS is a rare and heterogeneous disease and as a result, well-designed and well-conducted clinical trials are scarce and the development of a formal guideline is difficult. However, by combining data from completed clinical intervention trials together with observational data and data from research in other thrombotic and/or inflammatory conditions, recommendations for clinical practice can be formulated. Current national and international initiatives – such as the Dutch Arthritis Research and Collaboration Hub (ARCH) and the European Reference Network on Rare and Complex Connective Tissue and Musculoskeletal Diseases (ERN-ReConnet) – are aiming to structure the care for APS patients to offer a unique future opportunity to collect longitudinal clinical data on APS treatment and outcomes. Until a formal guideline has been made, this consensus paper fills the gap between evidence-based medicine and daily clinical practice for the care of APS patients.

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DISCLOSURES

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Table 3. *Degree of consensus according to Delphi procedure outcome. 1 Denotes 'totally disagree', 10 denotes 'fully agree'*

Nr	Statement	Average	Range
1	Seronegative APS is acceptable as a clinical entity	6.1	3 - 10
2	Triple positive patients have highest risk of recurrent thrombosis	9.3	8 - 10
3	Non-citeria aPL should not be tested routinely	8.3	1 - 10
4	Low molecular weight heparin (LMWH) in therapeutic doses and subsequent vitamin K antagonists (VKA) is first-line treatment for a first or recurrent APS-related thrombosis	9.3	7 - 10
5	Treatment with direct oral anticoagulants is not recommended for APS patients	8.5	6 - 10
6	For APS patients with a first thrombotic event, life-long anticoagulation is recommended	7.4	1 - 10
7	For APS patients with 1st VTE, VKA with INR 2-3 is recommended	9.5	7 - 10
8	For APS patients with 1st VTE, high-intensity treatment with an INR ≥ 3.0 is not recommended	9.8	9 - 10
9	For APS patients with first arterial event including TIA or ischemic stroke, treatment with either VKA with target INR 2.0-3.0 or clopidogrel is recommended	8.1	3 - 10
10	Anticoagulation therapy should be intensified with a target INR between 2.5-3.5 in case of a recurrent venous event despite adequate INR (2.0-3.0)	9.6	8 - 10
11	If the target INR cannot be reached and/or maintained with VKA in patient with recurrent VTE, continuous treatment with therapeutic dosing of LMWH can be considered	8.6	8 - 10
12	In patients with recurrent VTE despite an adequate target INR 2.5-3.5, after two weeks of therapeutic LMWH, additional long-term use of aspirin can be recommended, or intensifying of VKA therapy to a target INR 3-4	8,5	3 - 10
13	In recurrent arterial thrombosis, including TIA or ischemic stroke, despite treatment with clopidogrel, we suggest switching treatment to VKA with a target INR 2.0-3.0	9.3	7 - 10
14	If neurological symptoms – including migraine or cognitive performance – in APS patients deteriorate, repeating brain MRI is indicated and new white matter abnormalities may lead to intensifying treatment	7.7	2 - 10
15	For the treatment of CAPS, a combination of heparin/methylprednisolone/PE and/or IVIG is recommended	9.2	8 - 10
16	In patients with obstetrical APS, aspirin and prophylactic dose of LMWH should be given	8.7	3 - 10
17	For pregnant patients with APS, regular clinical pregnancy follow-up is sufficient; follow-up should be intensified only in specified subpopulations (patients with chronic kidney disease, morbid obesity, triple positive antibody profile and patients with a thrombotic event during pregnancy)	7.2	3 - 10
18	If pregnancy complications still occur despite treatment with low dose aspirin and prophylactic LMWH, the dose of LMWH can be increased to a therapeutic dose	8.7	6 - 10
19	Patients with primary or secondary APS who already use therapeutic anticoagulation before the pregnancy, should be switched to therapeutic dose of LMWH and low-dose aspirin should be added	8.9	3 - 10
20	Obstetrical APS patients should receive prophylactic LMWH during a period of 6 weeks, post-partum	9.5	8 - 10
21	Anticoagulation could be withdrawn in APS patients with only a single venous thrombotic event in the presence of a known transient precipitating risk factor (e.g., smoking, disease activity, oral contraceptive use) together with disappearance of aPL	7.9	4 - 10
22	Patients with seronegative APS with recurrent thrombosis need long-term anticoagulation therapy	8.6	1 - 10
23	Women with seronegative APS and recurrent pregnancy complications should receive the same treatment as established APS patients	6.6	1 - 10
24	In patients with more risk factors for thrombosis and/or high-risk aPL profile (e.g., triple positive), low dose aspirin might be beneficial as primary prophylaxis	7.8	6 - 10
25	Prophylaxis of venous thrombosis using LMWH is required for aPL positive individuals in situations associated with increased risk of thrombosis, such as surgical procedures, plaster casts, those requiring bed rest	9.2	7 - 10

APS = antiphospholipid syndrome; aPL = antiphospholipid antibodies; LMWH = low molecular weight heparin; VKA = vitamin K antagonists; VTE = venous thromboembolism; INR = international normalized ratio; TIA = transient ischemic attack; MRI = magnetic resonance imaging; PE = plasma exchange; IVMP = intravenous methylprednisolone

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