New classification criteria for antiphospholipid syndrome — 2023

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Summary

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by the clinical presence of thrombotic episodes, and — in women — obstetric complications with the laboratory presence of antiphospholipid antibodies in blood. The main objective of this report is to present in detail the new American College of Rheumatology (ACR)/Alliance of Associations for Rheumatology (EULAR) APS classification criteria. According to EULAR methodology they include entry criterion indispensable to initiate classification process and contain 8 clinical and laboratory domains allowing to classify patient as having APS with 99% specificity.

Keywords: antiphospholipid syndrome; antiphospholipid antibodies; lupus anticoagulant; thrombosis; obstetric complications; classification criteria

Introduction

Antiphospholipid syndrome (APS) is characterized by clinical symptoms of venous or arterial thrombosis (and obstetric complications in women) and the presence of antiphospholipid autoantibodies (aPL) in the patient’s plasma. These include lupus anticoagulant (LA) detected by coagulation-based functional assay as well as anti-cardiolipin antibodies (aCL) and anti-β2-glycoprotein I antibodies (aβ2-GPI) directed against complexes of proteins and negatively charged phospholipids detected by solid-phase assays.

APS is a systemic autoimmune disorder (probably one of the most common), the etiology of which is unknown and the pathogenesis includes a role of heterogeneous group of antiphospholipid autoantibodies. Clinical manifestations co-existing with the occurrence of these autoantibodies are quite common and in the general population may be attributable to other causes. It is therefore necessary to single out and describe the laboratory and clinical features characteristic for this syndrome in order to develop classification criteria allowing research in a relatively homogeneous groups of patients. Such criteria are primarily used to include patients into clinical trials on pathogenesis, diagnostics and management of the disease.

APS classification criteria were last developed at the Sapporo congress and published in 2006 [1]. In brief: the Sapporo criteria for APS require that the patient meets at least one clinical criterion (macrovascular, or microvascular thrombosis, and in women — obstetric complications) and one laboratory criterion (presence of lupus anticoagulant LACand/or aCL and/or aβ2-GPI antibodies of the IgG or IgM class in moderate to high titers).

From the very beginning it was pointed out that the suggested criteria did not include some clinical and laboratory aspects. Firstly, they did not

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consider several other clinical manifestations not suggestive of thrombosis but often co-existing with aPL such as thrombocytopenia, hemolytic anemia, valvular heart lesions, nephropathy, and a number of less frequent thrombotic microangiopathy — related symptoms. At that time, this was explained mostly by low specificity of these symptoms. Moreover, since the publication of these criteria new types of antiphospholipid antibodies have been described which strongly correlated with thrombotic symptoms of the syndrome. Most prominent among them are antibodies against domain I of β2-glycoprotein I (aDI) — the domain against which most pathogenic antiphospholipid antibodies were to be directed [2]. Other antibodies manifesting strong correlation with the presence of lupus anticoagulant are antibodies directed against phosphatidylserine/prothrombin (aPS/PT) complexes [3]. They were even included in the proposed global anti-phospholipid syndrome score (GAPSS) [4]. Questions have also been raised about the possible independent role of IgA antiphospholipid antibodies [5].

It also became obvious that the risk of developing clinical symptoms, mostly thrombotic events, varies and depends on the type, titer and nature (persistent/transient) of the detected antibodies. On the other hand, in some patients, symptoms of thrombosis (as well as others) may have been explained by risk factors not related to antiphospholipid antibodies, e.g. by classic cardio-vascular risk factors.

In light of the above and based on the new scientific data published after 2006, an attempt was made to develop new classification criteria following recommendations of the European Alliance of Associations for Rheumatology (EULAR). Already at the initial stage of work, the number of considered clinical symptoms was reduced, and aDI, aPS/PT and IgA antibodies were eliminated, mainly because they showed no independent diagnostic value (independent of co-occurring aPL, hitherto included in the APS diagnostic criteria), with no additional contribution to the specificity of existing laboratory criteria [6]. Therefore, only lupus anticoagulant, anticardiolipin antibodies and antibodies to β2-glycoprotein I of IgG and IgM class remained as in original list of the Sapporo criteria.

In 2023 the new antiphospholipid syndrome classification criteria were finally published, following the standardized EULAR methodology. The new set of criteria was developed by a group of experts of the American College of Rheumatology (ACR) and EULAR [7, 8]. The new criteria differ from the Sapporo criteria in several aspects [7, 8].

Firstly, entry criteria were introduced which had to be fulfilled for the patient to be classified (Fig. 1). The maximum interval between the occurrence of the clinical symptom/clinical criterion and detection of antiphospholipid antibody was reduced to 3 years. Clinical symptoms and laboratory criteria were divided into domains and in each of them the symptoms and laboratory test results were assigned certain weight expressed as score-points. The list of clinical symptoms was markedly expanded to include a number of new ones as well as some omitted from the Sapporo version. As regards thrombosis transfusion-related clinical symptoms, much emphasis was devoted to deciding whether the observed symptom, (non-specific to APS only) may be otherwise explained. In the current APS classification only criterion with the highest weight within one domain should be included. A patient who meets the entry criteria and accumulates at least 3 points from each of the clinical and laboratory domains is classified as having APS.

According to EULAR methodology, the latest criteria allow to classify patients as having APS with 99% specificity and 84% sensitivity. It is worth mentioning here that classification criteria should not be confused with diagnostic criteria. The former are used to single out homogeneous groups of patients for further research.

Figure 1 presents the classification process and the clinical and laboratory domains. We then present fairly detailed definitions of classification criteria with their specific ontology and explanation.

### Definitions of criteria used in antiphospholipid syndrome classification [7, 8]

#### Clinical criteria

**Domain 1. Macrovascular (venous thromboembolism)**

Venous thromboembolism (VTE) otherwise unexplained and confirmed by appropriate testing for: pulmonary embolism, deep vein thrombosis of lower extremities, splanchnic and renal vein thrombosis, cerebral venous thrombosis and retinal vein occlusion as well as others. 

**High VTE risk profiles:**

- **any VTE high risk factor such as:**
  - **active malignancy** — ongoing curative treatment (hormonal therapy included); disease
ENTRY CRITERIA
At least one documented clinical criterion, included in domains 1–6 and a positive antiphospholipid antibody (aPL) test result (lupus anticoagulant or moderate to high titer of antiphospholipid antibodies, or anti-β2-glycoprotein I antibodies (IgG or IgM) within 3 years of identification of the aPL-related clinical criterion

Absent — do not attempt to classify as APS; present — apply additive criteria

CLINICAL AND LABORATORY ADDITIVE CRITERIA
Do not accept as clinical criterion if there exists an equally, or more likely explanation than APS
In each domain, consider solely the highest weight (score) criterion

DOMAINS AND CLINICAL CRITERIA

Weight

D1. Macrovascular (venous thromboembolism [VTE])
— High risk profile for VTE* 1
— No high risk profile for VTE 3

D2. Macrovascular (arterial thrombosis — AT)
— High risk CVD profile for AT* 2
— No high risk CVD profile for AT 4

D3. Microvascular
Suspected one of the following:
— livedo racemosa (physical examination1)
— livedoid vasculopathy lesions (physical examination)
— acute/chronic aPL-related nephropathy (physical examination or laboratory tests2)
— pulmonary hemorrhage (physical examination or imaging3)
Established one of the following:
— livedoid vasculopathy (physical examination or pathology4)
— acute/chronic aPL-related nephropathy (pathology)
— pulmonary hemorrhage (BAL5 or pathology)
— myocardial disease (imaging or pathology)
— adrenal hemorrhage (imaging or pathology)

D4. Obstetric complications
— ≥ 3 consecutive pregnancy losses at the (pre-fetal (< 10 weeks), or early fetal stage (10 weeks 0 days–15 weeks 6 days) 1
— Fetal death (16 weeks 0 days–33 weeks 6 days) in the absence of preeclampsia (PEC) with severe placental insufficiency (PI) 1
— Severe PEC (< 34 weeks 0 days) or severe PI (< 34 weeks 0 days) with, or without fetal death 3
— Severe PEC (< 34 weeks 0 days) and severe PI (< 34 weeks 0 days) with, or without fetal death 4

D5. Cardiac valve
— Valve thickening 2
— Valve vegetation 4

D6. Hematology
Thrombocytopenia (20–130 × 109/L) 2

DOMAINS AND LABORATORY CRITERIA

Weight

D7. aPL test by coagulation-based functional assay (lupus-anticoagulant test, LAC)
— Positive LAC (one time) 1
— Positive LAC (persistent) 5

D8. aPL test by solid-phase assay (anti-cardiolipin (aCL) ELISA and/or anti-β2-glycoprotein I antibody (aβ2GPI) ELISA (persistent)
— Moderate/high6 positive IgM (aCL and/or aβ2GPI) 1
— Moderate positive IgG (aCL and/or aβ2GPI) 4
— high positive (IgG) aCL or aβ2GPI 5
— high positive (IgG) aCL and aβ2GPI 7

TOTAL
Classify as antiphospholipid syndrome for research studies when there are at least 3 points from clinical domains AND 3 points from laboratory domains

Figure 1. Antiphospholipid syndrome (APS) classification criteria — 2023 ACR/EULAR [7, 8]

Factors related to VTE and AT risk — see below; 1physical examination — the suspicion based on physical examination; 2lab. — clinical suspicion based on laboratory findings; 3imaging — clinical suspicion based on imaging; 4pathol. — diagnosis based on histo-pathological tests; 5BAL — bronchoalveolar lavage; 6moderate positive antibodies 40–79 U, high positive ≥ 80 U
recurrence/progression during/ despite treatment of the VTE episode;
— emergency hospitalization with at least 3 day bed confinement within 3 months prior to the VTE event;
— major trauma with limb fractures, spinal cord injury within one month prior to the VTE event;
— surgery with general/spinal/epidural anesthesia for > 30 minutes within 3 months prior to VTE event; or
b) at least two minor risk factors, i.e.:
— active systemic autoimmune disease or active inflammatory bowel disease;
— acute/active infection, e.g.: sepsis, pneumonia, SARS-CoV-2;
— central venous catheter in the same vascular bed;
— hormone replacement therapy, with estrogen containing oral contraceptives or ongoing in vitro fertilization treatment;
— long distance travel (> 8 hours);
— obesity (BMI ≥ 30 kg/m²);
— pregnancy or postpartum period (within 6 weeks of delivery);
— prolonged immobilization for other reasons than those already mentioned i.e. lower limb injury associated with reduced mobility or out-of-hospital confined to bed > 3 day;
— surgical procedure — as above but with general/spinal/epidural anesthesia of < 30 minutes within 3 months prior to VTE event.

Domain 2. Macrovascular (arterial thrombosis)

Arterial thrombosis otherwise unexplained and confirmed by appropriate testing for: myocardial infarction, peripheral/splanchnic/retinal artery thrombosis, stroke, and other organ infarcts (kidney, liver, or spleen) — in the absence of visualised thrombus.

High risk cardiovascular disease (CVD) profile — presence of one or more than one high-risk CVD factors or three or more moderate-risk CVD factors if timeline/severity is associated with the event based on the investigator/s judgement.

a) High risk factors for CVD any of the following at the time of the event:
— arterial hypertension, with systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 110 mmHg;
— chronic kidney disease with estimated glomerular filtration rate (GFR) ≤ 60 mL/min, for more than 3 months;
— diabetes mellitus with organ damage or long duration (type 1 ≥ 20 years, type 2 ≥ 10 years);
— hyperlipidemia (severe); total cholesterol ≥ 310 mg/dL (8 mmol/L) or low-density lipoprotein (LDL)-cholesterol > 190 mg/dL (4.9 mmol/L);

b) moderate CVD risk factors:
— arterial hypertension on treatment, or with systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg;
— current tobacco smoking;
— diabetes mellitus, with no organ damage and short duration (type 1 < 20 years; type 2 < 10 years);
— hyperlipidemia (moderate) on treatment or total cholesterol above normal but < 310 mg/dL (8 mmol/L), or LDL-cholesterol < 190 mg/dL (4.9 mmol/L);
— obesity (BMI ≥ 30 kg/m²).

Domain 3. Microvascular

Suspected (based on physical examination, clinical symptoms, imaging or laboratory tests):
— livedo racemosa — violaceous, net-like, blotchy motting of the skin. irregular, patchy, persistent skin lesions, reticulated and asymmetrical, nonuniform, irreversible; broken and asymmetric persistant discoloring should be differentiated from livedo reticularis with uniform, reversible, unbroken and symetric discoloration and should not be scored. Livedo reticularis is not included in the APS classification criteria;
— livedoid vasculopathy lesions — otherwise unexplained painful papules and violaceous purpuric plaques, which may rapidly evolve into hemorrhagic vesicles or bullae; if ruptured, may result in small, painful ulcers or reticulate, confluent, geometric and painful ulcers;
— antiphospholipid antibody (aPL) nephropathy.

Otherwise unexplained, persistent:

a) arterial hypertension — new-onset hypertension or deterioration of previously well-controlled hypertension;

b) proteinuria ≥ 0.5 g/24 hour urine specimen or protein creatinine ratio 0.5 (mg/mg, or 50 mg/m; /day or protein/creatinine ratio ≥ 0.5 mg/mg (50 mg/mmol);

c) acute renal failure serum (creatinine level increased above normal), or

d) glomerular microscopic hematuria.
Pulmonary hemorrhage (by clinical symptoms and imaging): respiratory symptoms (dyspnea, cough, hemoptysis) and otherwise unexplained pulmonary infiltrates or imaging suggestive of pulmonary hemorrhage.

Confirmed/established:
- livedoid vasculopathy — by pathology, once livedoid vasculopathy lesions are present. Otherwise unexplained thrombosis of the small dermal vessels and/or endothelial proliferation.
- aPL nephropathy (by pathology once suspected aPL nephropathy definition is fulfilled): a) acute glomerular or and renal vascular thrombotic microangiopathy lesions including fibrin thrombi in the arterioles or glomeruli, without inflammatory cells and immune complexes, b) chronic glomerular and renal vascular lesions, described as: arterial or arteriolar microthrombi with or, without recanalization; fibrous, or fibrocellular occlusion of vessels; focal cortical atrophy; fibrous and fibrocellular (arterial or arteriolar) occlusions, focal cortical atrophy with or without hydroidization, fibrous intimal hyperplasia or chronic/organized glomerular thrombi. Note: in patients with systemic lupus erythematosus, aPL nephropathy occurs independent of lesions attributable to lupus nephritis;
- pulmonary hemorrhage — by histopathology or bronchoalveolar lavage (BAL) — otherwise unexplained progressive hemorrhagic return on BAL or hemosiderin-laden macrophages (> 20%) or lung biopsy demonstrating capillaritis or microthrombosis;
- myocardial disease (by imaging, or histopathology). Otherwise unexplained non-ST segment elevation myocardial infarction and with a normal coronary angiogram (myocardial infarction with nonobstructive coronary arteries, MINOCA) and cardiac magnetic resonance imaging (CMRI) abnormalities including: a) late gadolinium enhancement, b) T2 abnormalities, or c) perfusion MRI abnormalities. OR histologically by thrombosis of the small vessels of the heart.

Adrenal hemorrhage or microthrombosis (by imaging or pathology). Otherwise unexplained CT or MRI demonstrating hemorrhage, histologically by thrombosis of the adrenal(micro) vasculature, eg. adrenal plexus, adrenal vein.

Domain 4. Obstetric complications

Prefetal death (preembryonic or embryonic loss) — otherwise unexplained pregnancy loss before 10 weeks and 0 days of gestation.

Fetal death — otherwise unexplained pregnancy loss between 10. w. 0 d. and 15 w. 6 d. of gestation (early fetal death), or between 16 w. 0 d. and 34 w. 0 d. of gestation. Note: If a detailed analysis of the fetal morphology or genetic constitution are unavailable, reasonable clinical judgement should be used based on review of available medical records.

Preeclampsia with severe features

Preeclampsia, defined as hypertension; systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg on 2 occasions at least 4 hours apart after 20 weeks of gestation in a previously normotensive or hypertensive patient (a sudden blood pressure elevation and/or proteinuria after 20 weeks of pregnancy), and proteinuria (also after 20 weeks of pregnancy), determined as a) proteinuria ≥ 0.3 mg/mg (30 g/mmol) in a random urine specimen, or b) dipstick protein ≥ 2+ strip test.

The definition of severe preeclampsia includes the above symptoms plus at least one of the following severe features:
- severe blood pressure elevation — systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 110 mmHg on 2 occasions, at least 4 hours apart, when the patient is on bed rest (antihypertensive therapy can be started on confirmation of severe blood pressure elevation in which case the 4-hour wait criterion does not apply);
- central nervous system dysfunction (CSN): new-onset headache, not accounted for by other diagnosis and unresponsive to medication;
- visual disturbances;
- pulmonary edema;
- impaired liver function — elevated blood concentrations of liver enzymes (more than twice the upper limit of normal concentration) or severe, persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by another diagnosis;
- renal dysfunction — serum creatinine concentration > 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease;
- thrombocytopenia platelet count of < 100 × 10⁹/L.
Placental insufficiency with severe features:
— intrauterine fetal growth restriction defined as biometry indicating estimated fetal weight of less than the 10th percentile for gestational age or postnatal birth weight less than the 10th percentile for gestational age in the absence of fetal-neonatal syndromes or conditions associated with growth restriction and;
— abnormal or non-reassuring fetal surveillance tests suggestive of fetal hypoxemia;
— abnormal doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia;
— severe intrauterine fetal growth restriction — suggested by fetal biometry indicating an estimated fetal or postnatal weight of < 3rd percentile for gestational age;
— oligohydramnios — according to obstetric criteria;
— maternal vascular malperfusion on histology — suggested by placental thrombosis/infarction, inadequate remodelling of the uterine spiral arteries (decidual vasculopathy), decreased vasculosyncytial membranes, increased syncytial knots, or decidual inflammation. These findings are not specific for APS.

Domain 5: Cardiac valves
Valve thickening (otherwise unexplained) — based on echocardiographic criteria, mitral valve thickening is defined as > 4 mm between ages 20–39 years and > 5 mm for those older than age 40 years; and > 3 mm for other valves for any age. Valve thickening can be associated with valvular dysfunction (regurgitation or stenosis).

Valve vegetations (otherwise unexplained) — based on the American Society of Echocardiography guidelines [9], valve vegetation is defined as shaggy, lobulated or rounded masses typically located on the atrial side of the atrioventricular valves (mitral and tricuspid valves) or ventricular side of the aortic valve, variable in size, usually < 1 cm. Unlike lesions in infective endocarditis, they are not related to valve damage but may be associated with regurgitation or valve stenosis.

Domain 6: Hematology
Thrombocytopenia — otherwise unexplained lowest platelet count ever between 20 and $130 \times 10^9/L$, confirmed by peripheral blood smear and repeat testing.

Laboratory criteria

Domain 7. Antiphospholipid antibody test (aPL) by coagulation-based functional assay
Lupus anticoagulant (LAC) assay used and interpreted based on ISTH guidelines [10]. A three-step procedure is recommended. Results of LAC testing should be interpreted with caution because false positive or false negative test results can occur during anticoagulation treatment as acute-phase response due to acute-phase reactants or in pregnancy due to increase in blood coagulation factors. Samples from patients receiving anticoagulants should be marked positive or negative only by individuals with expertise in performing and interpreting the LAC assay.

Domain 8. Antiphospholipid antibodies (aPL) determined by solid phase-based assay
Anticardiolipin antibodies (aCL) and anti-$\beta_2$-glycoprotein I antibody (a$\beta_2$GPI) — thresholds of moderate (40–79 U) and high (≥ 80 U) should be determined based on standardized immunoenzymatic assays (ELISA) with solid-phase antigen binding. New automated platforms with variations of the solid-phase modifications (e.g. magnetic microparticles and microspheres) and various detection systems (e.g. chemiluminescent immunoassay (CLIA), multiplex flow immunoassay (MFI) or flow cytometry) should not be used for the purpose. The correlation of the numerical values between the moderate/high values of ELISA and automated platforms varies substantially. Therefore these data can only provide guidance but for classification purposes they can be used only after additional validation studies and publication of new guidelines issued by the SSC subcommittee of Lupus Anticoagulant (LAC/aPL) of ISTH.

Conclusions
The presented classification criteria allow to identify patients with high likelihood of having antiphospholipid syndrome (APS) and to include them into clinical trials devised to improve diagnosis and management of APS. Presently however, the very determination of the type and titer of antiphospholipid antibodies is sufficient to assess the future risk of clinical complications [11] and to make appropriate decisions regarding anticoagulant treatment and duration [12, 13].
Conflict of interest: none declared

References


