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The 2023 ACR/EULAR Classification Criteria for Antiphospholipid Syndrome: Implications for the Inclusion of Participants in Research vs Diagnosis in Clinical Practice

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Background

Antiphospholipid syndrome (APS) was first described in patients with systemic lupus erythematosus in 1983,¹ and the primary version in 1989.² Multiple clinical manifestations have been associated with antiphospholipid antibodies (aPL) including venous and arterial

thromboses, transient ischemic attack (TIA), obstetric complications, thrombocytopenia, hemolytic anemia, livedo reticularis, transverse myelitis, cognitive dysfunction, cutaneous ulcers, Libman-Sacks endocarditis, and a peculiar type of nephropathy.³ Antiphospholipid antibodies include lupus anticoagulant (LAC), anticardiolipin antibodies (aCL) IgG and IgM, and

anti-beta-2-glycoprotein antibodies (a β_2 GPI) IgG and IgM. Other antibodies such as anti-prothrombin and anti-prothrombin/phosphatidylserine have been proposed as biomarkers of APS, particularly in cases where the standard antibodies are negative, but they are not officially accepted.

Since 1999, the original Sapporo Criteria⁴ and its revised 2006⁵ version have been used for the classification of patients in research studies and for the diagnosis of patients with APS. Despite the broad spectrum of clinical manifestations and serological markers considered by physicians as part of the APS, the original and revised versions of Sapporo Criteria include only venous, arterial and microvascular thrombotic events and specific obstetric events among the clinical manifestations, and aCL IgG and IgM antibodies, a β_2 GPI-IgG and IgM or lupus anticoagulant as the serological markers. Consequently, APS was diagnosed as obstetric and/or thrombotic syndrome, not considering other non-criteria manifestations associated to aPL antibodies. The major limitation of these criteria is that they do not reflect the systemic nature of APS.

Due to the importance of classification criteria in research, the ACR and EULAR assumed the responsibility of encouraging the development and validation of new and improved classification criteria for various rheumatic diseases, including APS, based on the current standards of measurement.⁶

The 2023 ACR/EULAR Classification Criteria for Antiphospholipid Syndrome

The recently published 2023 ACR/EULAR APS classification criteria aimed to have *high specificity for use in observational studies and trials*.^{7,8} The objective is to restrict the inclusion of research study participants to subjects with selected (not all) clinical manifestations associated solely with the standard aPL antibodies. To make the classification stricter, the new criteria provide different weights to the clinical manifestations and the serology. Even more so, acknowledging that competing factors may be associated with the development of clinical manifestations, the weight of a manifestation varies between patients if the presence of competing factors is different between them. Additionally, if a manifestation can be explained by a concurrent disease, the weight is less, or the manifestation is not scored. Obstetrical manifestations are

strictly defined, and future research studies in this area must include investigators with expertise in applying the various definitions. The laboratory criteria include: **a)** aPL test by coagulation-based functional assay (lupus anticoagulant assay); and **b)** aPL test by solid phase-based assay (anticardiolipin antibody and anti- β_2 -glycoprotein-I antibodies) (**Table 1**).

The new criteria include an entry criterion of at least one positive antiphospholipid (aPL) antibody test within 3 years of identification of an aPL-associated clinical criterion, followed by additive weighted criteria (score range 1–7 points each) clustered into 6 clinical domains and two laboratory domains. Patients accumulating at least 3 points each from the clinical and laboratory domains are classified as having APS. The laboratory criteria de-prioritize the IgM isotypes of aCL and a β_2 GPI. As a result, having the IgM isotype only of aCL and/or a β_2 GPI antibodies at either a moderate or high level does not fulfill the laboratory criterion. However, having persistent IgG aCL or a β_2 GPI at a medium (40–79 units) or high level (80 or higher), or persistent LAC, is sufficient to fulfill it. So, the clinician has to identify specifically the isotype and levels of the antibodies reported as well as the dates when the tests were performed as persistence of the antibodies or LAC means at least 2 consecutive results at medium or high levels, at least 12 weeks apart.

In clinical practice, the assessment, diagnosis, and treatment of a patient with APS differ from a research setting. While in research, a patient with non-criteria manifestations associated with aPL antibodies will be excluded to participate in the investigation, when consulting with a treating physician, the same patient will be managed under the diagnosis of APS. Diagnosing APS requires experience and judgement by the clinician, who must continue to weigh clinical manifestations against aPL profiles and other potential risk factors.

Classification and diagnostic criteria typically differ from each other. Classification criteria are developed for research purposes, not for clinical diagnosis. Developing diagnostic criteria is much more challenging than classification criteria due to the variety of clinical manifestations that can be seen among the diversity of patients with the same diagnosis. Developing diagnostic criteria with 95–100% sensitivity is virtually impossible; however, developing classification criteria with

ENTRY CRITERIA

At least one documented clinical criterion listed below (domains 1–6)

plus

A positive antiphospholipid antibody (aPL) test
(a lupus anticoagulant test, or moderate-to-high titers of anticardiolipin, or
anti- β_2 -glycoprotein-I antibodies [IgG or IgM]) within three years of the clinical criterion



If absent, do not attempt to classify as APS; If present, apply additive criteria



Additive clinical and laboratory criteria

Do not count a clinical criterion if there is an equally or more likely explanation than APS
Within each domain, only count the highest weighted criterion towards the total score

Clinical Domains	Criteria	Weight
1. Macrovascular (Venous Thromboembolism [VTE])	• VTE with a high-risk VTE profile ^c	• 1
	• VTE without a high-risk VTE profile ^c	• 3
2. Macrovascular (Arterial Thrombosis [AT])	• AT with a high-risk CVD profile ^c	• 2
	• AT without a high-risk CVD profile ^c	• 4
3. Microvascular	Suspected (one or more of the following): • Livedo racemosa (exam) • Livedoid vasculopathy lesions (exam) • Acute/chronic aPL-nephropathy (exam or lab) • Pulmonary hemorrhage (symptoms and imaging)	• 2
	Established (one or more of the following): • Livedoid vasculopathy (pathology ^d) • Acute/chronic aPL-nephropathy (pathology ^d) • Pulmonary hemorrhage (BAL or pathology ^d) • Myocardial disease (imaging or pathology) • Adrenal hemorrhage (imaging or pathology)	• 5
4. Obstetric	• ≥ 3 consecutive pre-fetal (< 10w) and/or early fetal (10w 0d- 15w 6d) deaths	• 1
	• Fetal death (16w 0d–33w 6d) in the absence of pre-eclampsia (PEC) with severe features or placental insufficiency (PI) with severe features	• 1
	• PEC with severe features (<34w 0d) or PI with severe features (<34w 0d) with/without fetal death	• 3
	• PEC with severe features (<34w 0d) and PI with severe features (<34w 0d) with/without fetal death	• 4
5. Cardiac Valve	• Thickening	• 2
	• Vegetation	• 4
6. Hematology	• Thrombocytopenia (lowest 20–130 × 10 ⁹ /L)	• 2
Laboratory Domains	Criteria	Weight
7. aPL test by coagulation-based functional assay (lupus anti-coagulant [LAC] test)	• Positive LAC (single-one time)	• 1
	• Positive LAC (persistent)	• 5
8. aPL test by solid phase assay (anti-cardiolipin antibody [aCL] ELISA and/or anti-β ₂ -glycoprotein-I antibody [aβ ₂ GPI] ELISA persistent)	• Moderate or high positive (IgM) (aCL and/or aβ ₂ GPI)	• 1
	• Moderate or positive (IgG) (aCL and/or aβ ₂ GPI)	• 4
	• High positive (IgG) (aCL or aβ ₂ GPI)	• 5
	• Moderate or positive (IgG) (aCL and aβ ₂ GPI)	• 7

Table 1. 2023 ACR/EULAR APS clinical and laboratory domains, criteria and weightings.^{7,8}

99% specificity, such as with the new APS criteria, is feasible.

It is important to understand the meaning of sensitivity versus specificity. In clinical practice, a diagnostic test or criteria should have high sensitivity because the aim is to identify as many patients as possible with the disease/diagnosis. In research, classification criteria should be highly specific because the aim is to avoid including patients without the disease/diagnosis of interest in an investigation study.

The validation of the new APS criteria showed 99% specificity in two cohorts, while the 2006 Sapporo criteria showed specificity of 91% and 86%, respectively. However, the sensitivity of the 2023 APS criteria was 83% and 84% in the two cohorts, while the 2006 Sapporo Criteria had sensitivity of 100% and 99% in both cohorts. The meaning of these values is that among patients with a clinical diagnosis of APS according to the treating physicians, the new criteria failed to identify 16%–17% of APS patients; however, among those who fulfilled the criteria, only 1% did not have APS.

In the manuscript reviewing the new APS criteria, the authors identified the following false-negative clinical scenarios that failed to meet the APS classification criteria.^{7,8}

1. Patients with an acceptable clinical criterion and moderate- or high-titer IgM aCL/anti- β_2 GPI alone; i.e. a young patient with stroke, or VTE/PE with persistently positive IgM aCL or β_2 GPI only.
2. VTE or arterial thrombosis alone in patients with high-risk profiles for VTE or CVD with an acceptable laboratory criterion; i.e. patient with stroke or VTE/PE with medium-high levels of IgG aCL or β_2 GPI antibodies or LAC with comorbidities such as diabetes, artery hypertension, heavy smoker, dyslipidemia, etc.
3. Occurrence of 3 or more consecutive pre-fetal deaths and/or early fetal deaths, or 1 or more fetal deaths alone in the context of an acceptable laboratory criterion

Other potential false-negative scenarios will continue to be identified.

Due to the lack of a gold standard for diagnosing many rheumatic diseases, clinicians tend to use classification criteria to support the clinical diagnosis. The correlation between classification and diagnosis will be perfect only when the criteria have 100% sensitivity and specificity. It is important for clinicians to understand the limitations of using classification criteria for diagnosis because ultimately, many more physicians caring for patients with APS will read and use the classification criteria than investigators applying the same criteria in clinical studies/trials.

From the clinical perspective, the *2023 ACR/EULAR APS criteria capture the systemic nature of APS* incorporating some of the non-criterion clinical manifestations associated with aPL antibodies including thrombocytopenia, livedoid vasculopathy, nephropathy, valvular disease, pulmonary hemorrhage, and adrenal hemorrhage. As a result, APS will no longer be solely an obstetric and/or thrombotic syndrome.

Conclusion

The 2023 ACR/EULAR APS classification criteria comprise an additive, weighted system, assessing an individual's relative probability of APS and defining a threshold for APS classification for *research purposes*, not diagnosis purposes.

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None declared.

References

1. Hughes GRV. Thrombosis, abortion, cerebral disease and the lupus anticoagulant. *Br Med J*. 1983;287:1088-1089
2. Alarcón-Segovia D, Sanchez-Guerrero J. Primary antiphospholipid syndrome. *J Rheumatol*. 1989;16:482-8.
3. Alarcón-Segovia D, Delezé M, Oria CV, et al. Antiphospholipid antibodies and the antiphospholipid syndrome in systemic lupus erythematosus. A prospective analysis of 500 consecutive patients. *Medicine (Baltimore)*. 1989;68:353-65.
4. Wilson WA, Gharavi AE, Koike T, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. *Arthritis Rheum*. 1999;42:1309-11.
5. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost*. 2006;4:295-306.
6. Kirshner B, Guyatt G. A methodological framework for assessing health indices. *J Chronic Dis*. 1985;38:27-36.
7. Barbhaiya M, Zully S, Naden R, et al. The 2023 ACR/EULAR Antiphospholipid Syndrome Classification Criteria. *Arthritis Rheumatol*. 2023;75:1687-702.
8. Barbhaiya M, Zully S, Naden R, et al. 2023 ACR/EULAR Antiphospholipid Syndrome Classification Criteria. *Ann Rheum Dis*. 2023;82:1258-70.