International Journal of Biomedicine 16(1) (2026) 14-16
http://dx.doi.org/10.21103/Article16(1)_RA2

BRIEF REVIEW

INTERNATIONAL JOURNAL OF BIOMEDICINE

Evolution of the Classification Criteria for Antiphospholipid Syndrome: From Hughes Syndrome to ACR/EULAR Criteria

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Abstract

Antiphospholipid syndrome (APS) is an autoimmune disorder defined by thrombotic events or obstetrical morbidity in the presence of persistent antiphospholipid antibodies, such as lupus anticoagulant (LAC), anticardiolipin (aCL), and ß2-glycoprotein I (ß2-GPI). The need for standardized classification criteria has been recognized as essential for diagnosis, patient stratification, research consistency, and comparison of clinical studies since their initial description. The classification criteria for APS have evolved over the years in response to advances in clinical practice and laboratory standardization. First, based on clinical observations, the preliminary Sapporo criteria highlighted an association among thrombosis, pregnancy morbidity, and antiphospholipid antibodies. The Sydney criteria, an international consensus statement, introduced structured clinical and laboratory criteria and incorporated persistence of antiphospholipid antibodies to improve specificity. The recent classification criteria of the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR), published in 2023, introduced a weighted point system across clinical and laboratory domains, with the aim of achieving high specificity for research. (**International Journal of Biomedicine. 2026;16(1):14-16.**)

Keywords: antiphospholipid syndrome • Sapporo criteria • Sydney criteria • ACR/EULAR criteria

For citation: Toska I, Rapushi E, Shkurti R, Mitre A. Evolution of the Classification Criteria for Antiphospholipid Syndrome: From Hughes Syndrome to ACR/EULAR Criteria. International Journal of Biomedicine. 2026;16(1):14-16. doi:10.21103/Article16(1)_RA2

Abbreviations

APS, antiphospholipid syndrome; **aCL**, anticardiolipin; **LAC**, lupus anticoagulant; **ß2-GPI**, ß2-glycoprotein I; **SLE**, systemic lupus erythematosus.

Introduction

Antiphospholipid syndrome (APS) is an autoimmune disorder defined by thrombotic events or obstetrical morbidity in the presence of persistent antiphospholipid antibodies.[1] Antiphospholipid syndrome was initially described in the early 1980s, based on recurrent associations between thrombosis, pregnancy losses, and the presence of lupus anticoagulant (LAC), especially in patients with systemic lupus erythematosus (SLE).[2] This early conceptualization, even without formalized criteria, provided the fundamental recognition of APS as a clinical entity. Given the clinical and immunological heterogeneity of the syndrome, standardized classification criteria were necessary to ensure homogeneity within the research population and to facilitate comparisons across studies. Classification criteria for APS have undergone multiple revisions in response to clinical evidence and advances in laboratory diagnostics (Table 1).

Hughes Syndrome: Early Clinical Description

The earliest descriptions of APS, known as Hughes syndrome, were based on clinical observations linking thrombotic events and recurrent pregnancy loss with the presence of lupus anticoagulant. These were largely

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descriptive, and APS was not defined by formal classification criteria.[3]

Table 1.

Evolution of APS classification criteria

1983	1999	2006	2023
Hughes Syndrome	Sapporo Criteria	Syndey Criteria	ACR/EULAR
Clinical observation	First Consensus	Revised Criteria	Score-point system
Thrombosis, Pregnancy loss	Clinical + Laboratory Criteria	Added Anti-ß2GPI	Research purposes
LAC	LAC, aCL IgG/IgM	Persistent positivity within 12 weeks	High specificity
	Persistent positivity within 6 weeks		

Sapporo Criteria

The need for standardized classification criteria for APS became more evident in 1990, with the increase in heterogeneous clinical studies reported, characterized by variable clinical manifestations and laboratory findings. The first international consensus classification criteria were established at the Eighth International Symposium on Antiphospholipid Antibodies in 1999 in Sapporo (Japan).

The Sapporo criteria required the coexistence of clinical manifestations and laboratory evidence of antiphospholipid antibodies to classify as APS. Clinical criteria included vascular thrombosis and pregnancy morbidity. Vascular thrombosis is represented by one or more confirmed episodes of arterial, venous, or small vessel thrombosis in any organ or tissue. Pregnancy morbidity included: one or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, one or more premature births of a morphologically normal neonate before the 34th week of gestation due to severe preeclampsia, eclampsia or placental insufficiency, three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, excluding maternal anatomical or hormonal abnormalities and chromosomal causes.

Laboratory criteria comprise the detection of LAC and/or anticardiolipin antibodies IgM/IgG in medium or high titer, on two or more occasions within six weeks.[4]

Sydney Criteria

Although the Sapporo criteria represented an important step in standardizing the definition of APS, their application in clinical studies revealed some limitations regarding laboratory characterization, heterogeneity of clinical manifestations, and antibody persistence. The Sapporo criteria did not include anti-β2GPI antibodies, lacked strict rules for repeat testing, and exhibited limited standardization of laboratory assays.[5]

The international consensus meeting, held in Sydney in 2006, revised the previously established criteria for the APS classification. For the first time, the Sydney criteria included anti-ß2GPI antibodies (IgG or IgM) as a laboratory criterion, based on evidence of their pathogenic and diagnostic relevance. Additionally, revised criteria expanded the interval for persistence of antiphospholipid antibody positivity from 6 to 12 weeks.[5] In this way, the cases with transient antibody positivity related to other conditions can be excluded. Regarding clinical criteria, the obstetric domain is more precisely defined with clearer distinctions for fetal loss, preterm birth, and recurrent pregnancy loss. Revised criteria improved the APS classification and homogeneity in research studies. This way, the revised Sapporo criteria became the gold standard for APS classification, widely used for years in clinical and practical research.[6]

ACR/EULAR 2023 Classification Criteria

The Sydney classification criteria also demonstrated limitations, particularly for research in heterogeneous populations. According to clinical experience, thrombotic events don't carry the same diagnostic weight, and in the laboratory setting, LAC positivity carries a higher risk than other antiphospholipid antibodies. The ACR/EULAR initiated an effort to develop APS classification criteria with high specificity for use in observational studies and trials.[7] For the first time, "entry criteria" were introduced, which had to be met for the patient to be classified as having APS.

The maximum interval between the occurrence of one clinical symptom and the detection of antiphospholipid antibodies was reduced to three years. Clinical manifestations are organized in domains including venous thromboembolism, arterial thrombosis, microvascular thrombosis, obstetric morbidity, cardiac valve disease, and hematology. Each has a specific score reflecting its association with APS. Laboratory criteria were also structured as a weighted scoring system and included LAC, anti-cardiolipin IgM/IgG titers (medium or high), and anti-ß2GPI IgG/IgM titers (medium or high). To be classified as APS, it is required to accumulate at least three points from the clinical domain and at least three points from the laboratory domain.[8,9] The new ACR/EULAR 2023 classification can improve specificity and provide a robust framework for APS research and clinical trials; however, new criteria may exclude patients with non-criteria manifestations. As understanding of APS evolves, the validity of the latest criteria and their revisions are likely to follow.

Discussion and Recommendations

For more than four decades, all knowledge of APS has been reflected in the evolution of classification criteria. From the earliest to the latest criteria, each iteration has sought to address the limitations of its predecessors as scientific evidence has evolved. Early descriptive observations prioritized sensitivity, enabling recognition of a broad clinical phenotype, whereas subsequent criteria increased specificity and reproducibility, particularly for research.

The Sapporo criteria defined APS by combining clinical and laboratory evidence. They improved standardization and facilitated epidemiological research. Nevertheless, they had limitations, including the absence of anti-β2GPI antibodies, insufficient specificity, and insufficient emphasis on antibody persistence, which led to the Sapporo-revised criteria (Sydney). They improved standardization and were the gold standard for clinical and research applications. Even the Sydney criteria showed limitations: their binary structure, inability to account for antibody profiles, and differential risk contributed to heterogeneity in study populations and limited interpretation of clinical outcomes. The new ACR/EULAR 2023 classification introduced a weighted, point-based system that emphasized specificity, antibody profiling, and pathogenic relevance. New criteria, by prioritizing specificity and homogeneity, are optimized for research. As noted above, they may exclude patients with non-criteria clinical manifestations, underscoring the importance of ongoing clinical judgment in practice. From a research perspective, a weighted point-based classification system improves homogeneity across studies, whereas stratification by antibody profiles enables precise risk assessment. Elimination of non-criteria patients highlights the limitations of current classification, underscoring the need for research to integrate non-criteria manifestations into clinical frameworks to bridge the gap between classification and clinical complexity.

Competing Interests

The authors declare that they have no conflicts of interest.

References

1. Alijotas-Reig J, Esteve-Valverde E, Anunciación-Llunell A, Marques-Soares J, Pardos-Gea J, Miró-Mur F. Pathogenesis, Diagnosis and Management of Obstetric Antiphospholipid Syndrome: A Comprehensive Review. J Clin Med. 2022 Jan 28;11(3):675. doi: 10.3390/jcm11030675. PMID: 35160128; PMCID: PMC8836886.

2. Hughes GR. The antiphospholipid syndrome: ten years on. Lancet. 1993 Aug 7;342(8867):341-4. doi: 10.1016/0140-6736(93)91477-4. PMID: 8101587.

3. Hughes GR. Thrombosis, abortion, cerebral disease, and the lupus anticoagulant. Br Med J (Clin Res Ed). 1983 Oct 15;287(6399):1088-9. doi: 10.1136/bmj.287.6399.1088. PMID: 6414579; PMCID: PMC1549319.

4. Wilson WA, Gharavi AE, Koike T, Lockshin MD, Branch DW, Piette JC, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum. 1999 Jul;42(7):1309-11. doi: 10.1002/1529-0131(199907)42:7<1309::AID-ANR1>3.0.CO;2-F. PMID: 10403256.

5. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, Derksen RH, DE Groot PG, Koike T, Meroni PL, Reber G, Shoenfeld Y, Tincani A, Vlachoyiannopoulos PG, Krilis SA. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost. 2006 Feb;4(2):295-306. doi: 10.1111/j.1538-7836.2006.01753.x. PMID: 16420554.

6. Schreiber K, Sciascia S, de Groot PG, Devreese K, Jacobsen S, Ruiz-Irastorza G, Salmon JE, Shoenfeld Y, Shovman O, Hunt BJ. Antiphospholipid syndrome. Nat Rev Dis Primers. 2018 Jan 11;4:17103. doi: 10.1038/nrdp.2017.103. Erratum in: Nat Rev Dis Primers. 2018 Jan 25;4:18005. doi: 10.1038/nrdp.2018.5. PMID: 29321641.

7. Cervera R. Antiphospholipid syndrome. Thromb Res. 2017 Mar;151 Suppl 1:S43-S47. doi: 10.1016/S0049-3848(17)30066-X. PMID: 28262233.

8. Barbhaiya M, Zuily S, Naden R, Hendry A, Manneville F, Amigo MC, et al.; ACR/EULAR APS Classification Criteria Collaborators. 2023 ACR/EULAR antiphospholipid syndrome classification criteria. Ann Rheum Dis. 2023 Oct;82(10):1258-1270. doi: 10.1136/ard-2023-224609. Epub 2023 Aug 28. PMID: 37640450.

9. Musiał J. New classification criteria for antiphospholipid syndrome — 2023. Journal of Transfusion Medicine [Internet]. Journal of Transfusion Medicine 2023;16(3):103-109. doi: 10.5603/jtm.97795