APS ACTION 5-MINUTE READS #1

Antiphospholipid Syndrome (APS): Distinguishing APS Classification from APS Diagnosis

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Antiphospholipid syndrome (APS) is an autoimmune disorder mostly characterized by blood clots and pregnancy complications. However, the spectrum of APS-related clinical symptoms is broad, and APS can cause other problems such as chronic kidney disease, heart valve abnormalities, low platelet counts, anemia, and livedo (reddish-purple discoloration in a lace-like pattern, associated with the damage to small blood vessels) in the skin. As awareness of APS grows, so does the need to distinguish between **APS Classification** used for research and **APS Diagnosis** used in clinical care.

For medical research, classification criteria are developed to identify patient populations with well-defined and uniform disease characteristics. These criteria intentionally include selected disease characteristics to ensure that enrolled patients in studies share similar clinical profiles. In contrast, diagnostic approaches in clinical practice must be more inclusive, allowing physicians to recognize the full spectrum of disease even when symptoms fall outside of established classification sets. The goal of diagnostic criteria is to maximize the number of patients that can be identified as having a particular disease, which contrasts with more stringent classification criteria that aim to identify a more specific cohort of patients (1). Although there are two different classification criteria for APS (2-4), there are no universally accepted diagnostic criteria.

Antiphospholipid Syndrome Classification:

The **Revised Sapporo APS Classification Criteria**, introduced in 1999 and updated in 2006, were a key step in standardizing APS research (2). Based on these criteria, APS classification

requires at least one clinical event (blood clots or pregnancy-related clinical problems) and one positive laboratory marker (lupus anticoagulant test [LA], anticardiolipin antibodies [aCL], or anti-β_2-glycoprotein-I antibodies [aβ_2GPI]). A simplified version of the Revised Sapporo APS Classification Criteria is shown in Table 1.

Table 1: Revised Sapporo APS Classification Criteria (simplified) (2)

Clinical criteria - Blood clots within arteries, veins, or small blood vessels or - Adverse outcomes during pregnancies ▪ Three or more spontaneous abortions before 10th week of pregnancy or, ▪ Unexplained fetal deaths at or beyond 10th week of pregnancy or, ▪ Premature births before 34th week of pregnancy due to severe preeclampsia (high blood pressure and protein in the) or eclampsia (a severe form of preeclampsia that can also cause seizures and coma in the mother).
Laboratory criteria (antiphospholipid antibody tests) - Positive lupus anticoagulant test. - Positive anticardiolipin antibody (aCL) IgG or IgM. - Positive anti-Beta-2-glycoprotein-I antibody (aβ_2GPI) IgG or IgM.
Final Assessment: Classify as "Antiphospholipid Syndrome" for research purposes if there is at least one clinical criterion and one positive aPL test.

While helpful for research, the Revised Sapporo APS Classification Criteria do not capture some of the other well-recognized APS manifestations, lack clear thresholds for aCL/aβ_2GPI positivity, and do not factor in coexisting risk factors that may influence blood clotting. To address these gaps, the American College of Rheumatology (ACR) – European Alliance of Associations for Rheumatology (EULAR) APS Classification Criteria were introduced in 2023 a more detailed, point-based classification system, which was developed based on a four-step methodology approved by these organizations. These point-based weighted criteria include eight domains (six clinical and two laboratory), and also include an entry requirement (at least one relevant clinical event and a positive aPL test). Patients who score three or more

points in both clinical and laboratory domains are classified as APS for research. This new model reflects the evolving understanding of APS as a heterogeneous disease and improves the specificity of patient selection in studies (Table 2).

Table 2: 2023 ACR/EULAR APS Classification Criteria (simplified) (3,4)

Step 1: Entry Criteria	
At least one clinical criterion listed below (domains 1 to 6) plus positive antiphospholipid antibody (aPL) test (lupus anticoagulant test, or moderate-to-high titers of anticardiolipin or anti-Beta-2-glycoprotein-I (aβ_2GPI) antibodies [IgG or IgM]) within three years of the clinical criterion.	
Step 2: Clinical Domains	
Domain 1. Macrovascular (Venous Thromboembolism [VTE])	**Weight**
VTE with a high VTE risk profile	1
VTE without a high VTE risk profile	3
Domain 2. Macrovascular (Arterial Thrombosis [AT])	**Weight**
AT with a high CVD risk profile	2
AT without a high CVD risk profile	4
Domain 3. Microvascular*	**Weight**
Suspected	2
Established	3
* Suspected: Livedo racemosa, livedoid vasculopathy (skin-related microvascular disease) lesions by physical examination, or acute/chronic aPL-nephropathy (renal disease) by physical examination and/or laboratory tests, or pulmonary hemorrhage by symptoms and imaging. Established: Livedoid vasculopathy by pathology; acute/chronic aPL-nephropathy by pathology; pulmonary hemorrhage by bronchoalveolar lavage or pathology; myocardial (heart muscle) disease by imaging or pathology; or adrenal hemorrhage (bleeding) by imaging or pathology.	
Domain 4. Obstetric	**Weight**
Three or more consecutive pre-fetal (<10 weeks [w] of pregnancy) and/or early fetal (10w 0 days [d] -15w 6d) deaths	1
Fetal death (16w 0d – 33w 6d) in the absence of preeclampsia (PEC) with severe features or placental insufficiency (PI) (alternations in fetal well-being due to	1

problems with the placenta) with severe features	
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
Domain 5. Cardiac Valve	**Weight**
Thickening	2
Vegetation**	4
** Debris of coagulated tissue that sits on heart valves which develop due to damage caused by aPL to valves	
Domain 6. Hematology	**Weight**
Thrombocytopenia (decreased platelet count) (lowest 20-130x109/L)	2
Step 3: Laboratory (aPL) domains	
Domain 7. aPL test by coagulation-based functional assay (lupus anticoagulant test [LA])	**Weight**
Positive LA (single – one time)	1
Positive LA (persistent)	5
Domain 8. aPL test by solid phase assay (anti-cardiolipin antibody [aCL] ELISA and/or anti-Beta-2-glycoprotein-I antibody [aβ2GPI] ELISA [persistent])* **	**Weight**
Moderate-high positive (IgM) (aCL and/or aβ_2GPI)	1
Moderate positive (IgG) (aCL and/or aβ_2GPI)	4
High positive (IgG) (aCL *or* aβ_2GPI)	5
High positive (IgG) (aCL *and* aβ_2GPI)	7
*** Moderate (40-79U) and high (≥80U) level aCL/(aβ2GPI) are based on enzyme-linked immunosorbent assays (ELISA)	
Step 4: Final Assessment – Total Score	
Classify as "Antiphospholipid Syndrome" for research purposes if there are at least 3 points from clinical domains AND at least 3 points from laboratory domains	

Antiphospholipid Syndrome Diagnosis:

In clinical practice, there are no universally accepted APS diagnostic criteria. Thus, APS diagnosis depends on the careful assessment of patient's APS-related clinical symptoms,

interpretation of the aPL results (for instance one-time *versus* persistent aPL positivity, low *versus* moderate-to-high aCL/aβ_2GPI positivity, or triple *versus* double *versus* single aPL positivity), and the incorporation of the other factors that may be responsible for the clinical problem, for instance, blood clots. It is important to note that blood clots are many times multi-factorial, and aPL-positive patients, when they develop a blood clot, may have other risk factors for blood clots (for instance hypertension or estrogen use) (1). In addition, not all patients with positive aPL tests have APS, and not all aPL-positive patients with APS-related clinical symptoms meet APS classification criteria.

Conclusion:

The goal of the APS classification criteria is to identify patients that have a high likelihood of having APS based on common and typical APS-related clinical manifestations. A common misconception is that the classification criteria for APS should also be used as diagnostic criteria. Although APS classification criteria may guide physicians in making a diagnosis, it should not be substituted for a doctor's clinical judgment, which is based on a complete evaluation of the patient. Diagnosing APS remains challenging. It can be missed when symptoms are attributed to other risk factors, or over-diagnosed, for instance based on a single time weakly positive aPL test. Clinical vigilance, along with the integration of standardized aPL testing and careful interpretation of the results, is crucial for accurate diagnosis and optimal management.

References

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