Nuevas evidencias en el síndrome antifosfolipídico

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Nuevas evidencias en el síndrome antifosfolipídico: Nuevos criterios clasificatorios

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Diagnóstico de enfermedades minoritarias

Diagnóstico de enfermedades minoritarias

Enfermedades genéticas

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Diagnóstico de enfermedades minoritarias

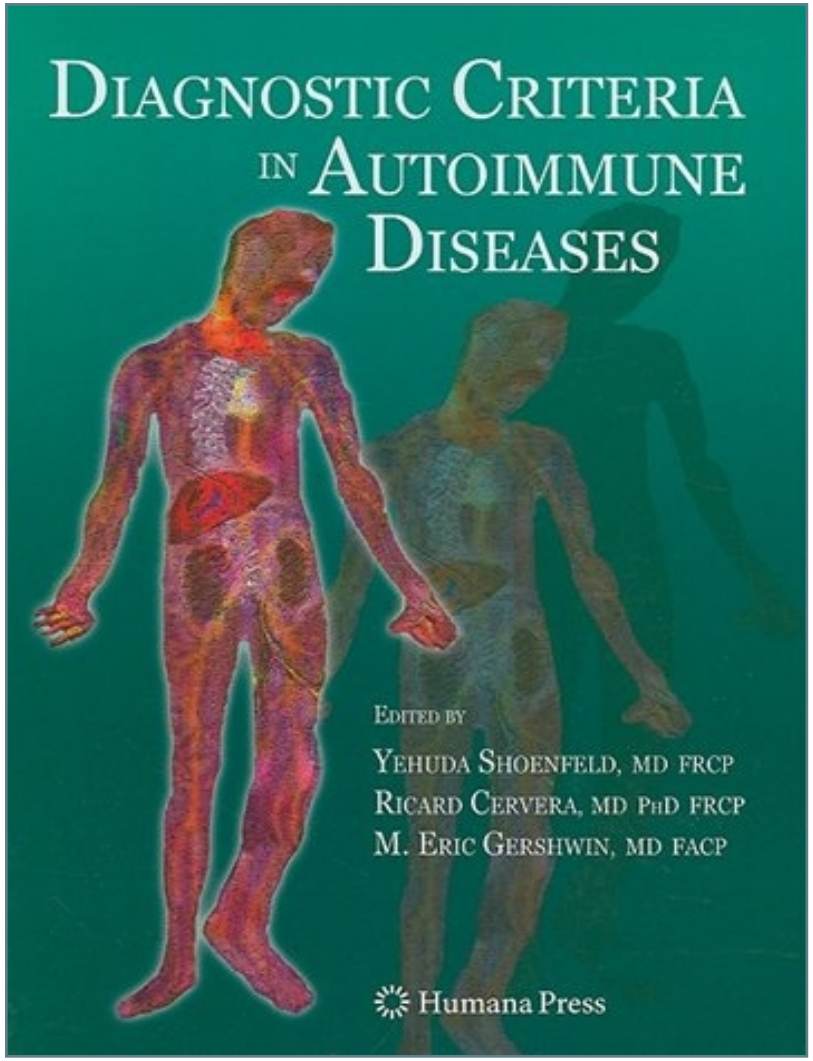
Enfermedades infecciosas

Clínic Barcelona | Universitat de Barcelona

Diagnóstico de enfermedades minoritarias

Clínic Barcelona | Universitat de Barcelona

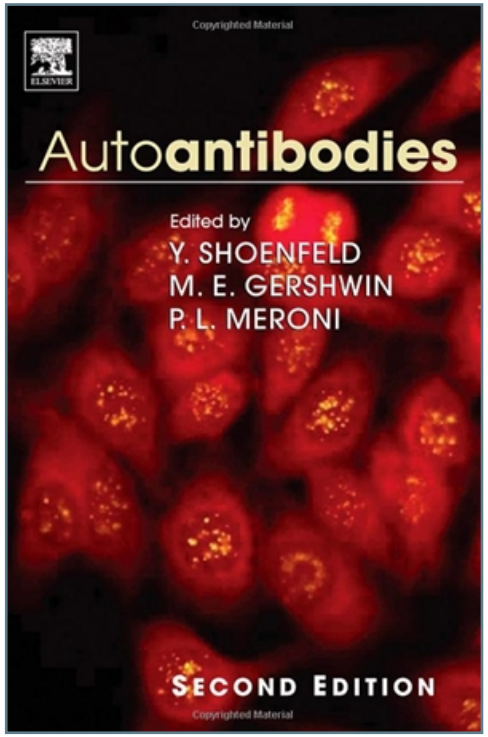
Diagnóstico de enfermedades minoritarias



Shoenfeld Y, Cervera R, Gershwin ME. Humana Press, 2008.

Enfermedades autoinmunes

ANA
ds-DNA
SLE
APS
RNP
SS-A/Ro
SSc
PM
MS
CAPS
Sm
RF
SS
MCTD
DM
LA
WG
c-ANCA
Scl-70
aCL
IBD
p-ANCA
PM
PAN
PAM
Anticentromer
a-β2GPI
SS-B/La



Shoenfeld Y, Gershwin ME, Meroni PL. Elsevier, 2007.

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Diagnóstico de enfermedades minoritarias

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Diagnóstico de enfermedades minoritarias

Criterios diagnósticos

Criterios clasificatorios

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Diagnóstico de enfermedades minoritarias

Criterios diagnósticos

- Enfoque altamente individualizado sobre un solo paciente que puede incluir toda la información disponible.
- A menudo iterativo y depende en gran medida de la exclusión de otras entidades.
- Provisional.
- La **sensibilidaad** es más importante en el diagnóstico.

Criterios clasificatorios

- Enfoque científico que utiliza una definición positiva basada en un número limitado de variables.
- Pretende combinar grupos relativamente homogéneos de pacientes con una determinada enfermedad.
- Más específico y, por tanto, no debería ser erróneo casi nunca.
- La **especificidad** es clave para la clasificación.

Aringer M, Johnson SR. Rheumatol (Oxford). 2020; 59 Suppl 5:v 4-11.
Cervera R. Med Clin (Barc). 2022; 159: 187-8.

Criterios clasificatorios para el síndrome antifosfolipídico

1983

BRITISH MEDICAL JOURNAL VOLUME 287 8 OCTOBER 1983

Thrombosis in systemic lupus erythematosus: striking association with the presence of circulating lupus anticoagulant

M L BOEY, C B COLACO, A E GHARAVI, K B ELKON, S LOIZOU, G R V HUGHES

Thrombosis, abortion, cerebral disease, and the lupus anticoagulant

BRITISH MEDICAL JOURNAL VOLUME 287 15 OCTOBER 1983

GRAHAM R V HUGHES

Consultant Physician,
Hammersmith Hospital,
London W12 0HS

Boey ML, et al.. Br Med J. 1983; 287:1021-3.
Hughes GRV. Br Med J 1983; 287:1088-9.

Criterios clasificatorios para el síndrome antifosfolipídico

8th International Congress on Antiphospholipid Antibodies (Sapporo, Japan, 1998)

Sapporo Criteria

1999

Arthritis & Rheumatism

Official Journal of the American College of Rheumatology

SPECIAL ARTICLE

INTERNATIONAL CONSENSUS STATEMENT ON PRELIMINARY CLASSIFICATION CRITERIA FOR DEFINITE ANTIPHOSPHOLIPID SYNDROME

Report of an International Workshop

WENDELL A. WILSON, AZZUDIN E. GHARAVI, TAKAO KOIKE, MICHAEL D. LOCKSHIN, D. WARE BRANCH, JEAN-CHARLES PIETTE, ROBIN BREY, RONALD DERKSEN, E. NIGEL HARRIS, GRAHAM R. V. HUGHES, DOUGLAS A. TRIPLETT, and MUNTHER A. KHAMASHTA

Clinical criteria†

1. Vascular thrombosis

   One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by imaging or doppler studies or histopathology, with the exception of superficial venous thrombosis. For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.

2. Pregnancy morbidity

   (a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or

   (b) One or more premature births of a morphologically normal neonate at or before the 34th week of gestation because of severe preeclampsia or eclampsia, or severe placental insufficiency (18,19), or

   (c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

In studies of populations of patients who have more than 1 type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to a, b, or c above.

Laboratory criteria

1. Anticardiolipin antibody of IgG and/or IgM isotype in blood, present in medium or high titer, on 2 or more occasions, at least 6 weeks apart, measured by a standardized enzyme-linked immunosorbent assay for β_2-glycoprotein I–dependent anticardiolipin antibodies (7,20).

2. Lupus anticoagulant present in plasma, on 2 or more occasions at least 6 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis (Scientific Subcommittee on Lupus Anticoagulants/Phospholipid-Dependent Antibodies) (21), in the following steps:

   (a) Prolonged phospholipid-dependent coagulation demonstrated on a screening test, e.g., activated partial thromboplastin time, kaolin clotting time, dilute Russell's viper venom time, dilute prothrombin time, Textarin time.

   (b) Failure to correct the prolonged coagulation time on the screening test by mixing with normal platelet-poor plasma.

   (c) Shortening or correction of the prolonged coagulation time on the screening test by the addition of excess phospholipid.

   (d) Exclusion of other coagulopathies, e.g., factor VIII inhibitor or heparin, as appropriate.

Definite antiphospholipid antibody syndrome is considered to be present if at least 1 of the clinical criteria and 1 of the laboratory criteria are met.

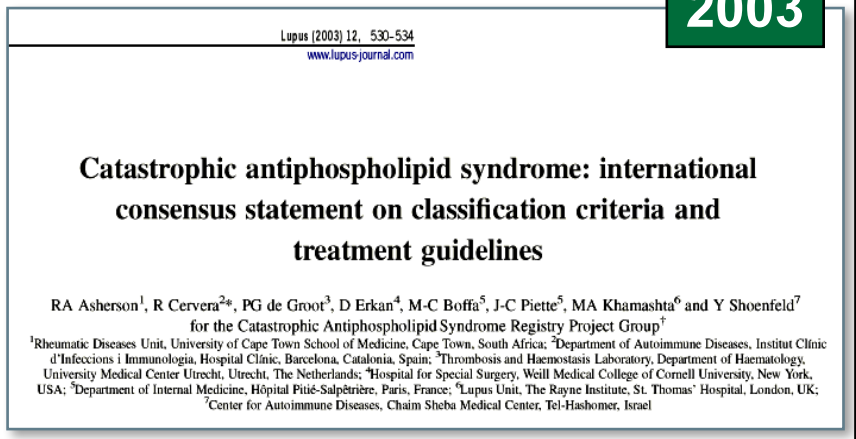
Wilson WA, et al. Arthritis Rheum. 1999; 42: 1309-11.

Criterios clasificatorios para el síndrome antifosfolipídico

10th International Congress on Antiphospholipid Antibodies (Taormina, Italy, 2002)

CAPS Criteria

2003



Lupus (2003) 12, 530–534
www.lupus-journal.com

Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines

RA Asherson[1], R Cervera[2]*, PG de Groot[3], D Erkan[4], M-C Boffa[5], J-C Piette[5], MA Khamashta[6] and Y Shoenfeld[7] for the Catastrophic Antiphospholipid Syndrome Registry Project Group[†]

[1]Rheumatic Diseases Unit, University of Cape Town School of Medicine, Cape Town, South Africa; [2]Department of Autoimmune Diseases, Institut Clínic d'Infeccions i Immunologia, Hospital Clínic, Barcelona, Catalonia, Spain; [3]Thrombosis and Haemostasis Laboratory, Department of Haematology, University Medical Center Utrecht, Utrecht, The Netherlands; [4]Hospital for Special Surgery, Weill Medical College of Cornell University, New York, USA; [5]Department of Internal Medicine, Hôpital Pitié-Salpêtrière, Paris, France; [6]Lupus Unit, The Rayne Institute, St. Thomas' Hospital, London, UK; [7]Center for Autoimmune Diseases, Chaim Sheba Medical Center, Tel-Hashomer, Israel

Table 1 Preliminary criteria for the classification of catastrophic APS

1) Evidence of involvement of three or more organs, systems and/or tissues[a]
2) Development of manifestations simultaneously or in less than a week
3) Confirmation by histopathology of small vessel occlusion in at least one organ or tissue[b]
4) Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies)[c]

Definite catastrophic APS

- All four criteria

Probable catastrophic APS

- All four criteria, except for only two organs, systems and/or tissues involvement
- All four criteria, except for the absence of laboratory confirmation at least six weeks apart due to the early death of a patient never tested for aPL before the catastrophic APS
- 1, 2 and 4
- 1, 3 and 4 and the development of a third event in more than a week but less than a month, despite anticoagulation

Asherson RA, et al. Lupus. 2003;12:530-4.

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Criterios clasificatorios para el síndrome antifosfolipídico

11th International Congress on Antiphospholipid Antibodies (Sydney, Australia, 2006)

Updated Sapporo (Sydney) Criteria

2006

Journal of Thrombosis and Haemostasis, **4**: 295–306

SPECIAL ARTICLE

International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS)

S. MIYAKIS,* M. D. LOCKSHIN,† T. ATSUMI,‡ D. W. BRANCH,§ R. L. BREY,¶ R. CERVERA,** R. H. W. M. DERKSEN,†† P. G. DE GROOT,†† T. KOIKE,‡ P. L. MERONI,‡‡ G. REBER,§§ Y. SHOENFELD,¶¶ A. TINCANI,*** P. G. VLACHOYIANNOPOULOS††† and S. A. KRILIS*

*St George Hospital, University of New South Wales, Sydney, Australia; †Hospital for Special Surgery, Cornell Medical Center, New York, NY, USA; ‡Hokkaido University, Sapporo, Japan; §University of Utah Health Sciences Center, Salt Lake City, UT; ¶University of Texas Health Science Center, San Antonio, TX, USA; **Hospital Clinic, Barcelona, Spain; ††University Medical Center, Utrecht, The Netherlands; ‡‡Istituto Auxologico Italiano, University of Milan, Milan, Italy; §§University Hospital, Geneva, Switzerland; ¶¶Sheba Medical Center, Tel-Hashomer and Tel Aviv University, Israel; ***Spedali Civili, University of Brescia, Italy; and †††Department of Pathophysiology, University of Athens, Greece*

Clinical criteria	Vascular thrombosis	⩾1 clinical episodes of arterial, venous or small-vessel thrombosis in any tissue or organ.
	Pregnancy morbidity (one of the following)	⩾1 fetal death (at or beyond the 10th week of gestation). ⩾1 premature birth before the 34th week of gestation because of eclampsia, severe preeclampsia or placental insufficiency. ⩾3 consecutive (pre)embryonic losses (before the 10th week of gestation.
Laboratory criteria	Lupus anticoagulant positivity on ⩾2 occasions at least 12 weeks apart. aCL (IgG and/or IgM) in medium or high titre (i.e. >40 or above the 99th percentile) on two or more occasions at least 12 weeks apart. Anti-β2GPI antibody (IgG and/or IgM) in medium or high titre (i.e. above the 99th percentile) on two or more occasions at least 12 weeks apart.	

Definite APS is present if at least one of the clinical criteria and one of the laboratory criteria are met.

Miyakis S, et al. J Thromb Haemostas. 2006; 4: 295-306.

Criterios clasificatorios para el síndrome antifosfolipídico

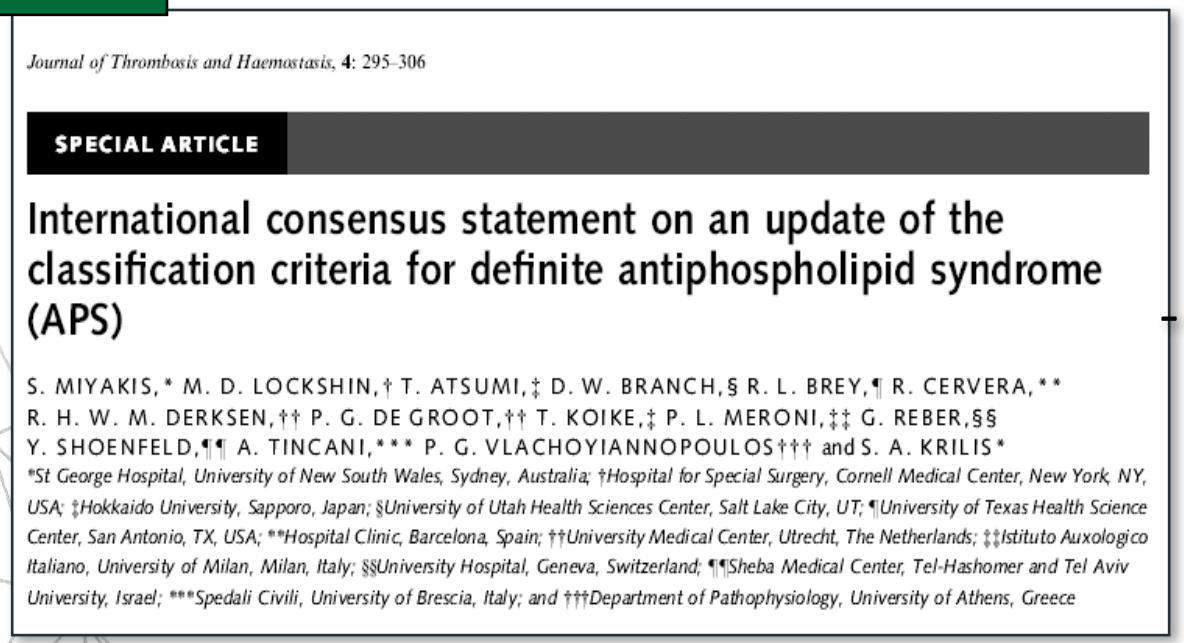
11th International Congress on Antiphospholipid Antiboides (Sydney, Australia, 2006)

2006

Updated Sapporo (Sydney) Criteria

Grey zones

- Non-criteria clinical features:
  - Heart valve disease
  - Livedo reticularis
  - Thrombocytopenia
  - Renal involvement
- Non-criteria laboratory findings:
  - aCL or anti-β_2GPI levels below 40GPL/MPL
  - IgA aCL and IgA anti-β_2GPI
- Other aPL (antiprothrombin, ….)



Journal of Thrombosis and Haemostasis, **4**: 295–306

SPECIAL ARTICLE

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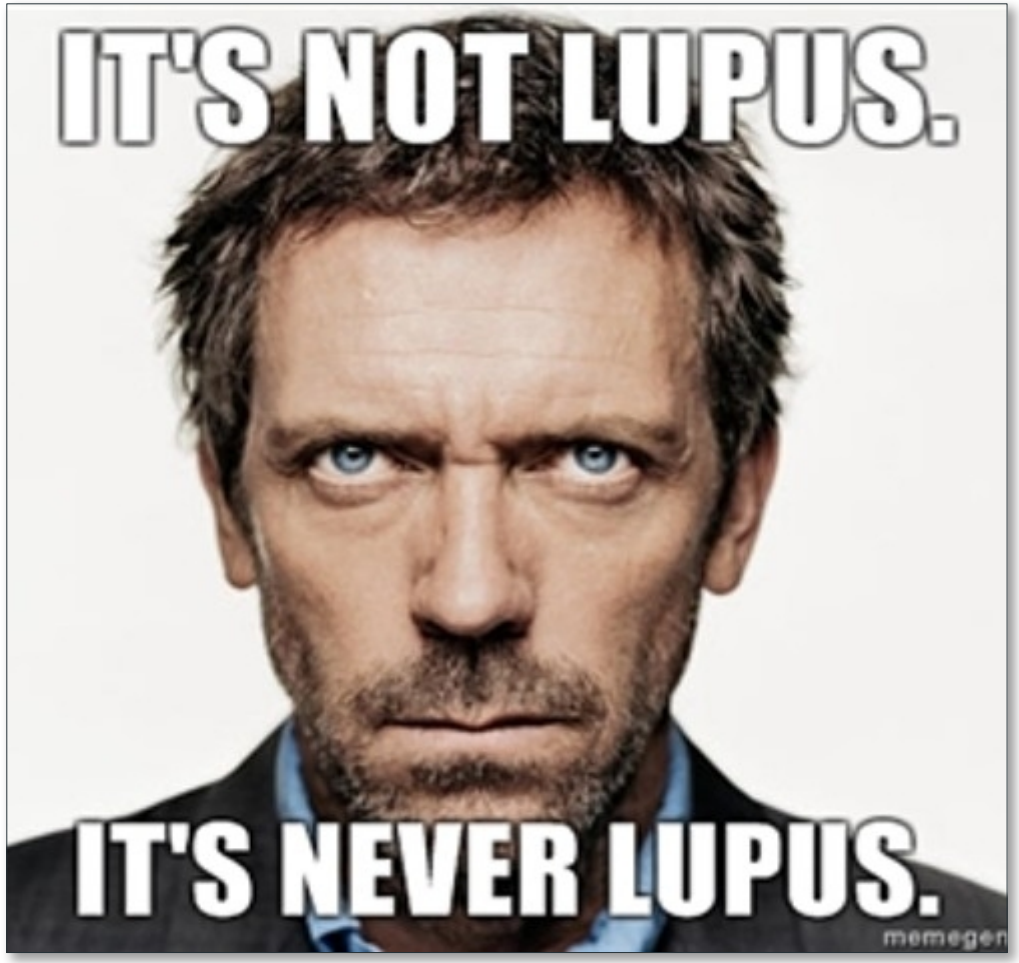
Miyakis S, et al. J Thromb Haemostas. 2006; 4: 295-306.

Criterios clasificatorios para el lupus eritematoso sistémico



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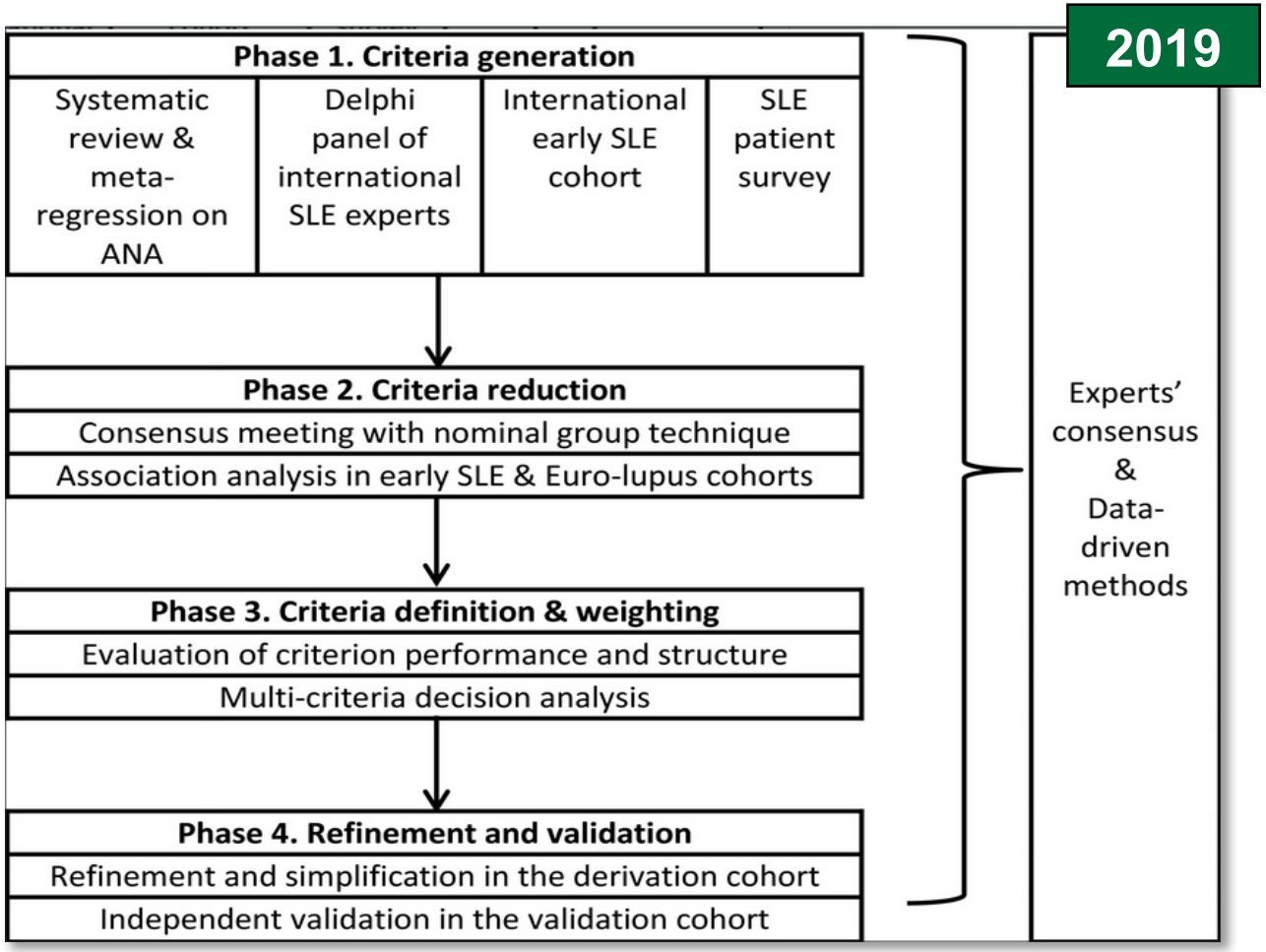
Criterios clasificatorios para el lupus eritematoso sistémico

ACR/EULAR

Criteria

2019 European League Against Rheumatism/ American College of Rheumatology classification criteria for systemic lupus erythematosus

Martin Aringer,[1] Karen Costenbader,[2] David Daikh,[3] Ralph Brinks,[4] Marta Mosca,[5] Rosalind Ramsey-Goldman,[6] Josef S Smolen,[7] David Wofsy,[8] Dimitrios T Boumpas,[9,10] Diane L Kamen,[11] David Jayne,[12] Ricard Cervera,[13] Nathalie Costedoat-Chalumeau,[14] Betty Diamond,[15] Dafna D Gladman,[16] Bevra Hahn,[17] Falk Hiepe,[18] Søren Jacobsen,[19] Dinesh Khanna,[20] Kirsten Lerstrøm,[21] Elena Massarotti,[22,23] Joseph McCune,[20] Guillermo Ruiz-Irastorza,[24] Jorge Sanchez-Guerrero,[25,26] Matthias Schneider,[27] Murray Urowitz,[28] George Bertsias,[29] Bimba F Hoyer,[18,30] Nicolai Leuchten,[1] Chiara Tani,[31] Sara K Tedeschi,[23,32] Zahi Touma,[33] Gabriela Schmajuk,[3] Branimir Anic,[34] Florence Assan,[35] Tak Mao Chan,[36] Ann Elaine Clarke,[37] Mary K Crow,[38] László Czirják,[39] Andrea Doria,[40] Winfried Graninger,[41] Bernadett Halda-Kiss,[39] Sarfaraz Hasni,[42] Peter M Izmirly,[43] Michelle Jung,[37] Gábor Kumánovics,[39] Xavier Mariette,[44,45] Ivan Padjen,[34] José M Pego-Reigosa,[46] Juanita Romero-Diaz,[47] Íñigo Rúa-Figueroa Fernández,[48] Raphaèle Seror,[35] Georg H Stummvoll,[49] Yoshiya Tanaka,[50] Maria G Tektonidou,[51] Carlos Vasconcelos,[52] Edward M Vital,[53,54] Daniel J Wallace,[55] Sule Yavuz,[56] Pier Luigi Meroni,[57] Marvin J Fritzler,[58] Ray Naden,[59] Thomas Dörner,[18] Sindhu R Johnson[60,61]



Aringer M, et al. Ann Rheum Dis. 2019; 78:1151-59.

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Criterios clasificatorios para el lupus eritematoso sistémico

2019

ACR/EULAR

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Entry criterion

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria

Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight
Constitutional	
Fever	2
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous OR discoid lupus	4
Acute cutaneous lupus	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis	6
Musculoskeletal	
Joint involvement	6
Renal	
Proteinuria >0.5g/24h	4
Renal biopsy Class II or V lupus nephritis	8
Renal biopsy Class III or IV lupus nephritis	10

Immunology domains and criteria	Weight
Antiphospholipid antibodies	
Anti-cardiolipin antibodies OR	
Anti-β2GP1 antibodies OR	
Lupus anticoagulant	2
Complement proteins	
Low C3 OR low C4	3
Low C3 AND low C4	4
SLE-specific antibodies	
Anti-dsDNA antibody* OR	
Anti-Smith antibody	6

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

Aringer M, et al. Ann Rheum Dis. 2019; 78:1151-59.

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Criterios clasificatorios para el síndrome antifosfolipídico

European Forum on Antiphospholipid Antibodies

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Criterios clasificatorios para el síndrome antifosfolipídico

ACR/EULAR

2021

American College of Rheumatology
Empowering Rheumatology Professionals

Arthritis Care & Research
Vol. 73, No. 10, October 2021, pp 1490–1501
DOI 10.1002/acr.24520
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Development of a New International Antiphospholipid Syndrome Classification Criteria Phase I/II Report: Generation and Reduction of Candidate Criteria

Medha Barbhaiya,[1] Stephane Zuily,[2] Yasaman Ahmadzadeh,[3] Mary-Carmen Amigo,[4] Tadej Avcin,[5] Maria Laura Bertolaccini,[6] D. Ware Branch,[7] Guilherme de Jesus,[8] Katrien M. J. Devreese,[9] Camille Frances,[10] David Garcia,[11] Francis Guillemin,[12] Steven R. Levine,[13] Roger A. Levy,[14] Michael D. Lockshin,[1] Thomas L. Ortel,[15] Surya V. Seshan,[16] Maria Tektonidou,[17] Denis Wahl,[2] Rohan Willis,[18] Ray Naden,[†] Karen Costenbader,[19] and Doruk Erkan,[1] on behalf of the New APS Classification Criteria Collaborators

Table 1. Phase I/II methodology of the new antiphospholipid syndrome (APS) classification criteria development

Phase I: Item generation
Part A
Item generation survey with open-ended questions (54 collaborators)
Part B
Item expansion to incorporate negatively weighted responses and APS subgroups (20 steering committee members)
Literature screening for thrombosis risk factors and additional criteria not identified by survey responses
Phase II: Item reduction
Part A
Item reduction survey A with Likert scale (61 collaborators) (low-specificity items [Likert score <1] eliminated)
Systematic literature reviews and meta-analyses
Part B
Item reduction survey B (19 steering committee members) (low-specificity items [Likert score <2] eliminated)
Systematic literature reviews and meta-analyses

Barbhaiya M, et al. Arthritis Care Res (Hoboken). 2021; 73: 1490-1501.

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Criterios clasificatorios para el síndrome antifosfolipídico

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Barbhaiya M, et al. Arthritis Care Res (Hoboken). 2021; 73: 1490-1501.

Criterios clasificatorios para el síndrome antifosfolipídico

Phase I: Item generation

ction surveys during the new antiphospholipid syndrome (APS) classification criteria development*

	Survey question and response option	Goal	Response rate†	Respondents	Results summarized	Final no. of candidate criteria
Phase I						
Question 1	Question: "Describe all features (historical, clinical, laboratory, radiological, and pathological) that in your experience can occur as part of aPL/APS spectrum." Response option: open-ended.	Identify potential candidate criteria with positive weight	41/54 (76)	Of 41, 18 were rheumatologists, 5 hematologists, 5 clinical immunologists, 5 nephrologists, cardiologists, or neurologists, 4 internists, 2 pediatric rheumatologists, and 2 obstetricians.	Distribution of potential aPL/APS spectrum candidate criteria by system: neurologic (n = 25); laboratory (aPL) (n = 23); obstetric (n = 16); dermatologic (n = 15); renal (n = 12); vascular (n = 10); cardiac (n = 9); laboratory (non-aPL) (n = 9); other (n = 7); hematology (n = 5); pulmonary (n = 5); gastrointestinal (n = 4); musculoskeletal (n = 4); endocrinologic (n = 3); ophthalmology (n = 2); auditory (n = 2); family history (n = 1)	152 items (based on question 1) expanded to 261 to include negatively weighted criteria and subgroups. Of note, some items were reported as both positive and negative candidate criteria; we included those items in the expanded list.

Barbhaiya M, et al. Arthritis Care Res (Hoboken). 2021; 73: 1490-1501.

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Criterios clasificatorios para el síndrome antifosfolipídico

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	Survey question and response option	Goal	Response rate†	Respondents	Results summarized	Final no. of candidate criteria
Phase I						
Question 1	Question: "Describe all features (historical, clinical, laboratory, radiological, and pathological) that in your experience can occur as part of aPL/APS spectrum." Response option: open-ended.	Identify potential candidate criteria with positive weight	41/54 (76)	Of 41, 18 were rheumatologists, 5 hematologists, 5 clinical immunologists, 5 nephrologists, cardiologists, or neurologists, 4 internists, 2 pediatric rheumatologists, and 2 obstetricians.	Distribution of potential aPL/APS spectrum candidate criteria by system: neurologic (n = 25); laboratory (aPL) (n = 23); obstetric (n = 16); dermatologic (n = 15); renal (n = 12); vascular (n = 10); cardiac (n = 9); laboratory (non-aPL) (n = 9); other (n = 7); hematology (n = 5); pulmonary (n = 5); gastrointestinal (n = 4); musculoskeletal (n = 4); endocrinologic (n = 3); ophthalmology (n = 2); auditory (n = 2); family history (n = 1)	152 items (based on question 1) expanded to 261 to include negatively weighted criteria and subgroups. Of note, some items were reported as both positive and negative candidate criteria; we included those items in the expanded list.

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Criterios clasificatorios para el síndrome antifosfolipídico

Phase I: Item generation

ction surveys during the new antiphospholipid syndrome (APS) classification criteria development*

	Survey question and response option	Goal	Response rate†	Respondents	Results summarized	Final no. of candidate criteria
Phase I						
Question 1	Question: "Describe all features (historical, clinical, laboratory, radiological, and pathological) that in your experience can occur as part of aPL/APS spectrum." Response option: open-ended.	Identify potential candidate criteria with positive weight	41/54 (76)	Of 41, 18 were rheumatologists, 5 hematologists, 5 clinical immunologists, 5 nephrologists, cardiologists, or neurologists, 4 internists, 2 pediatric rheumatologists, and 2 obstetricians.	Distribution of potential aPL/APS spectrum candidate criteria by system: neurologic (n = 25); laboratory (aPL) (n = 23); obstetric (n = 16); dermatologic (n = 15); renal (n = 12); vascular (n = 10); cardiac (n = 9); laboratory (non-aPL) (n = 9); other (n = 7); hematology (n = 5); pulmonary (n = 5); gastrointestinal (n = 4); musculoskeletal (n = 4); endocrinologic (n = 3); ophthalmology (n = 2); auditory (n = 2); family history (n = 1)	152 items (based on question 1) expanded to 261 to include negatively weighted criteria and subgroups. Of note, some items were reported as both positive and negative candidate criteria; we included those items in the expanded list.

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Empowering Rheumatology Professionals

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Development of a New International Antiphospholipid Syndrome Classification Criteria Phase I/II Report: Generation and Reduction of Candidate Criteria

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Table 1. Phase I/II methodology of the new antiphospholipid syndrome (APS) classification criteria development

Phase I: Item generation
Part A
Item generation survey with open-ended questions (54 collaborators)
Part B
Item expansion to incorporate negatively weighted responses and APS subgroups (20 steering committee members)
Literature screening for thrombosis risk factors and additional criteria not identified by survey responses
Phase II: Item reduction
Part A
Item reduction survey A with Likert scale (61 collaborators) (low-specificity items [Likert score <1] eliminated)
Systematic literature reviews and meta-analyses
Part B
Item reduction survey B (19 steering committee members) (low-specificity items [Likert score <2] eliminated)
Systematic literature reviews and meta-analyses

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Criterios clasificatorios para el síndrome antifosfolipídico

Phase II: Item reduction

	Survey question and response option	Goal	Response rate†	Respondents	Results summarized	Final no. of candidate criteria
Phase II						
Survey A	Question: "Consider 2 patients who are exactly the same except that one has the clinical feature presented and the other does not. Please rate each feature in terms of how strong this feature is in differentiating APS from other similar conditions, i.e., specific for APS" using a Likert scale (–5 to +5). Response option: "Please rate each item based on a scale of –5 to +5, with +5 being extremely specific for APS."	Item reduction by elimination of low specificity items and organizing higher specificity items into separate domains	43/61 (71)	Of 43, 22 were rheumatologists, 4 hematologists, 4 nephrologists, cardiologists, neurologists, or vascular specialists, 4 internists, 3 clinical immunologists, 3 pediatric rheumatologists, 2 pediatric hematologists, and 1 obstetrician.	See Table 3	132 items (reduced to 64 items and 10 domains when overlapping items were eliminated)
Survey B	"Consider 2 patients who are exactly the same except that one has the clinical feature presented and the other does not. Please rate each feature in terms of how strong this feature is in differentiating APS from other similar conditions, i.e., specific for APS" using a Likert scale (–5 to +5). Response option: "Please rate each item based on a scale of –5 to +5, with +5 being extremely specific for APS."	Further item reduction to goal of ~30 candidate criteria	19/19 (100)	Of 19, 8 were rheumatologists, 2 hematologists, 2 cardiologists or vascular medicine specialists, 2 immunologists, 2 obstetricians, 1 pediatric rheumatologist, 1 neurologist, and 1 classification criteria methodologist.	See Table 4	27 items and 6 domains

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Phase II: Item reduction

Table 3. Phase II survey A results and subsequent steering committee and domain subcommittee decisions and rationale for item reduction during the new antiphospholipid syndrome (APS) classification criteria development*

Candidate criteria and domains	Committee consensus supported by the literature review for items eliminated (despite score >2) or retained (despite score <2)
Laboratory part I	
Retained: Lupus anticoagulant test	
Laboratory part II	
Retained: IgG/IgM aCL,† IgG/IgM anti-β_2GPI antibodies†	IgM aCL and anti-β_2GPI: Wide variation in survey scores for IgM aPL ELISA based on titer level and single/persistent positivity. IgM aPL ELISA is noted to have lower specificity than IgG for APS. Final decision was to collect detailed aPL ELISA isotype and titer information during phase 3 (48,49).
Eliminated: Anti-DI antibodies,‡ anti-PS/PT,‡ IgA aCL, IgA anti-β_2GPI, antiprothrombin antibodies	Anti-DI and anti-PS/PT: Limited commercial availability; additional research needed to define feasibility, clinical correlation, and standardization.

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Criterios clasificatorios para el síndrome antifosfolipídico

2023 ACR/EULAR antiphospholipid syndrome classification criteria

ACR/EULAR

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Barbhaiya M, et al. Ann Rheum Dis 2023;82:1258–1270.

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Entry Criteria[a]
At least one documented[b] 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[b] of the clinical criterion

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

Additive clinical and laboratory criteria[a]
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 and criteria	Weight	Clinical domains and criteria	Weight
D1. Macrovascular (Venous Thromboembolism [VTE])		**D2. Macrovascular (Arterial Thrombosis [AT])**	
VTE with a high-risk VTE profile[c]	1	AT with a high-risk CVD profile[c]	2
VTE without a high-risk VTE profile[c]	3	AT without a high-risk CVD profile[c]	4
D3. Microvascular		**D4. Obstetric**	
Suspected (one or more of the following)	2	≥3 Consecutive pre-fetal (<10w) and/or early fetal (10w 0d -15w 6d) deaths	1
Livedo racemosa (exam)			
Livedoid vasculopathy lesions (exam)			
Acute/chronic aPL-nephropathy (exam or lab)			
Pulmonary hemorrhage (symptoms and imaging)		Fetal death (16w 0d – 33w 6d) in the absence of pre-eclampsia (PEC) with severe features or placental insufficiency (PI) with severe features	1
Established (one of more of the following)	5		
Livedoid vasculopathy (pathology[d])			
Acute/chronic aPL-nephropathy (pathology[d])		PEC with severe features (<34w 0d) or PI with severe features (<34w 0d) with/without fetal death	3
Pulmonary hemorrhage (BAL or pathology[d])		PEC with severe features (<34w 0d) and PI with severe features (<34w 0d) with/without fetal death	4
Myocardial disease (imaging or pathology)			
Adrenal hemorrhage (imaging or pathology)			
D5. Cardiac Valve		**D6. Hematology**	
Thickening	2	Thrombocytopenia (lowest 20-130x10^9/L)	2
Vegetation	4		
Laboratory (aPL) domains and criteria[e]	**Weight**		
D7. aPL test by coagulation-based functional assay (lupus anticoagulant test [LAC])		**D8. aPL test by solid phase assay (anti-cardiolipin antibody [aCL] ELISA and/or anti-β_2-glycoprotein-I antibody [aβ_2GPI] ELISA [persistent])**	
Positive LAC (single – one time)	1	Moderate or high positive (IgM) (aCL and/or aβ_2GPI)	1
Positive LAC (persistent)	5	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

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

Criterios clasificatorios para el síndrome antifosfolipídico

2023

Entry Criteria[a]

At least one documented[b] 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[b] of the clinical criterion

↓

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

↓

Additive clinical and laboratory criteria[a]

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.

↓

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

Criterios clasificatorios para el síndrome antifosfolipídico

2023

Entry Criteria[a]
At least one documented[b] 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[b] of the clinical criterion

D1. Macrovascular (Venous Thromboembolism [VTE])

VTE with a high-risk VTE profile[c]	1
VTE without a high-risk VTE profile[c]	3

High VTE Risk Profile

Major VTE Risk Factors (≥1)
- Active malignancy
- Hospital admission
- Major trauma
- High risk surgery

Minor VTE Risk Factors (≥2)
- Active systemic autoimmune disease or active inflammatory bowel disease
- Acute/active severe infection
- Central venous catheter
- HRT, estrogen containing oral contraceptives, or ongoing IVF
- Long distance travel
- Obesity
- Pregnancy or postpartum period
- Prolonged immobilization or low risk surgery

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

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Criterios clasificatorios para el síndrome antifosfolipídico

2023

Entry Criteria[a]
At least one documented[b] 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[b] of the clinical criterion

2023 ACR/EULAR antiphospholipid syndrome classification

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D2. Macrovascular (Arterial Thrombosis [AT])

AT with a high-risk CVD profile[c]	2
AT without a high-risk CVD profile[c]	4

High CVD Risk Profile

High CVD Risk Factors (≥1)
- Severe arterial hypertension
- Long lasting diabetes mellitus
- Severe hyperlipidemia
- Chronic kidney disease

Moderate CVD Risk Factors (≥3)
- Non severe arterial hypertension
- Diabetes mellitus
- Moderate hyperlipidemia
- Current tobacco smoking
- Obesity

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ith	4
death	
	2
olipin antibody antibody	
$a\beta_2$GPI)	1
	4
	5
	7

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

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Criterios clasificatorios para el síndrome antifosfolipídico

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Aurelien Delluc,[23] Sheetal Desai,[24]
Reyhan Diz-Kucukkaya,[28] Ali Duarte
Jean-Christophe Gris ,[32] Natash
Jason S Knight ,[36] Carl Laskin,[37]
Roger A Levy ,[41,42] Maarten Lim
Jack Musial,[45] Pier Luigi Meroni
Vittorio Pengo ,[49] Michelle Petri
Jose A Gomez-Puerta,[52] Quentin Ra
Surya V Seshan,[56] Savino Sciascia
Denis Wahl,[2] Rohan Willis,[60] Cécile
Karen Costenbader ,[63] Doruk Er
Classification Criteria Collaborators

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D3. Microvascular

Suspected (one or more of the following) 2

- Livedo racemosa (exam)
- Livedoid vasculopathy lesions (exam)
- Acute/chronic aPL-nephropathy (exam or lab)
- Pulmonary hemorrhage (symptoms and imaging)

Established (one of more of the following) 5

- 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)

Entry Criteria[(a)]
At least one documented[(b)] 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-β₂-glycoprotein-I antibodies [IgG or IgM])

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rds the total score.

	Weight
terial Thrombosis [AT])	
D profile[(c)]	2
CVD profile[(c)]	4
l (<10w) and/or	1
w 6d) deaths	
3w 6d) in the absence of	1
vith severe features or	
(PI) with severe features	
es (<34w 0d) or PI with	3
0d) with/without fetal death	
es (<34w 0d) and PI with	4
0d) with/without fetal death	
rest 20-130x10⁹/L)	2
ase assay (anti-cardiolipin antibody	
ti-β₂-glycoprotein-I antibody	
tent])	
ve (IgM) (aCL and/or aβ₂GPI)	1
) (aCL and/or aβ₂GPI)	4
L or aβ₂GPI)	5
L and aβ₂GPI)	7

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aboratory domains

Criterios clasificatorios para el síndrome antifosfolipídico

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2023 ACR/EULAR antipl
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Florian Manneville,[5] Mary-Carmen Am
Laura Andreoli ,[9] Bahar Artim-Eser
Michael H Belmont ,[13] Maria Laura
Graziela Carvalheiras,[16] Alessandro Ca
Nathalie Costedoat-Chalumeau ,[20]
Aurelien Delluc,[23] Sheetal Desai,[24] Ma
Reyhan Diz-Kucukkaya,[28] Ali Duarte-G
Jean-Christophe Gris ,[32] Natasha J
Jason S Knight ,[36] Carl Laskin,[37] Al
Roger A Levy ,[41,42] Maarten Limpe
Jack Musial,[45] Pier Luigi Meroni ,[46]
Vittorio Pengo ,[49] Michelle Petri
Jose A Gomez-Puerta,[52] Quentin Raim
Surya V Seshan,[56] Savino Sciascia
Denis Wahl,[2] Rohan Willis,[60] Cécile Ye
Karen Costenbader ,[63] Doruk Erka
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Entry Criteria[a]
At least one documented[b] 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])

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	Weight
ombosis [AT])	
le[c]	2 4
nd/or ths	1
he absence of features or severe features	1
d) or PI with ithout fetal death	3
d) and PI with ithout fetal death	4
x10⁹/L)	2
(anti-cardiolipin antibody protein-I antibody	
CL and/or aβ₂GPI) /or aβ₂GPI) PI) GPI)	1 4 5 7

re
lomains

D4. 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

Criterios clasificatorios para el síndrome antifosfolipídico

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2023 ACR/EULAR antiphospholipid syndrome classification criteria

ACR/EULAR

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D5. Cardiac Valve

Thickening	2
Vegetation	4

D6. Hematology

Thrombocytopenia (lowest 20-130x10^9/L)	2

Entry Criteria[a]
At least one documented[b] 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[b] of the clinical criterion

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

Additive clinical and laboratory criteria[a]
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 and criteria	Weight		Weight
Acute/chronic aPL-nephropathy (pathology[d])		PEC with severe features (<34w 0d) or PI with severe features (<34w 0d) with/without fetal death	3
Pulmonary hemorrhage (BAL or pathology[d])		PEC with severe features (<34w 0d) and PI with severe features (<34w 0d) with/without fetal death	4
Myocardial disease (imaging or pathology)			
Adrenal hemorrhage (imaging or pathology)			
D5. Cardiac Valve		**D6. Hematology**	
Thickening	2	Thrombocytopenia (lowest 20-130x10^9/L)	2
Vegetation	4		

Laboratory (aPL) domains and criteria[e]	Weight		
D7. aPL test by coagulation-based functional assay (lupus anticoagulant test [LAC])		**D8. aPL test by solid phase assay (anti-cardiolipin antibody [aCL] ELISA and/or anti-β_2-glycoprotein-I antibody [aβ_2GPI] ELISA [persistent])**	
Positive LAC (single – one time)	1	Moderate or high positive (IgM) (aCL and/or aβ_2GPI)	1
Positive LAC (persistent)	5	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

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

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Criterios clasificatorios para el síndrome antifosfolipídico

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2023 ACR/EULAR antiphospholipid syndrome classification criteria

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Entry Criteria[a]
At least one documented[b] 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[b] of the clinical criterion

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

Laboratory (aPL) domains and criteria[e]	Weight
D7. aPL test by coagulation-based functional assay (lupus anticoagulant test [LAC])	
Positive LAC (single – one time)	1
Positive LAC (persistent)	5
D8. aPL test by solid phase assay (anti-cardiolipin antibody [aCL] ELISA and/or anti-β_2-glycoprotein-I antibody [aβ_2GPI] ELISA [persistent])	
Moderate or 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

Thickening 2
Vegetation 4
Thrombocytopenia (lowest 20-130x10^9/L) 2

Laboratory (aPL) domains and criteria[e] Weight

D7. aPL test by coagulation-based functional assay (lupus anticoagulant test [LAC])
Positive LAC (single – one time) 1
Positive LAC (persistent) 5

D8. aPL test by solid phase assay (anti-cardiolipin antibody [aCL] ELISA and/or anti-β_2-glycoprotein-I antibody [aβ_2GPI] ELISA [persistent])
Moderate or 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

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

Barbhaiya M, et al. Ann Rheum Dis 2023;82:1258–1270.

Criterios clasificatorios para el síndrome antifosfolipídico

2023 ACR/EULAR antiphospholipid syndrome classification criteria

ACR/EULAR

Medha Barbhaiya ,[1] Stephane Zuily ,[2] Ray Naden,[3] Alison Hendry,[4] Florian Manneville,[5] Mary-Carmen Amigo,[6] Zahir Amoura,[7] Danieli Andrade ,[8] Laura Andreoli ,[9] Bahar Artim-Esen,[10] Tatsuya Atsumi,[11] Tadej Avcin,[12] Michael H Belmont ,[13] Maria Laura Bertolaccini,[14] D Ware Branch,[15] Graziela Car… Nathalie Co… Aurelien Del… Reyhan Diz… Jean-Christo… Jason S Knig… Roger A Lev… Jack Musial,[45] Pier Luigi Meroni ,[46] Giovanni Orsolini ,[47] Thomas L Ortel,[48] Vittorio Pengo ,[49] Michelle Petri ,[50] Guillermo Pons-Estel ,[51] Jose A Gomez-Puerta,[52] Quentin Raimboug,[53] Robert Roubey,[54] Giovanni Sanna,[55] Surya V Seshan,[56] Savino Sciascia ,[57,58] Maria G Tektonidou ,[59] Angela Tincani,[9] Denis Wahl,[2] Rohan Willis,[60] Cécile Yelnik,[61] Catherine Zuily,[62] Francis Guillemin,[5] Karen Costenbader ,[63] Doruk Erkan ,[1] on Behalf of the ACR/EULAR APS Classification Criteria Collaborators

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

2023

Entry Criteria[a]
At least one documented[b] 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[b] of the clinical criterion

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

Additive clinical and laboratory criteria[a]
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 and criteria	Weight		Weight
D1. Macrovascular (Venous Thromboembolism [VTE])		**D2. Macrovascular (Arterial Thrombosis [AT])**	
			2
			4
			1
			1
Acute/chronic aPL-nephropathy (pathology[c])		PEC with severe features (<34w 0d) or PI with	3
Pulmonary hemorrhage (BAL or pathology[d])		severe features (<34w 0d) with/without fetal death	
Myocardial disease (imaging or pathology)		PEC with severe features (<34w 0d) and PI with	4
Adrenal hemorrhage (imaging or pathology)		severe features (<34w 0d) with/without fetal death	
D5. Cardiac Valve		**D6. Hematology**	
Thickening	2	Thrombocytopenia (lowest 20-130x10^9/L)	2
Vegetation	4		

Laboratory (aPL) domains and criteria[e]	Weight		
D7. aPL test by coagulation-based functional assay (lupus anticoagulant test [LAC])		**D8. aPL test by solid phase assay (anti-cardiolipin antibody [aCL] ELISA and/or anti-β_2-glycoprotein-I antibody [aβ_2GPI] ELISA [persistent])**	
Positive LAC (single – one time)	1	Moderate or high positive (IgM) (aCL and/or aβ_2GPI)	1
Positive LAC (persistent)	5	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

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

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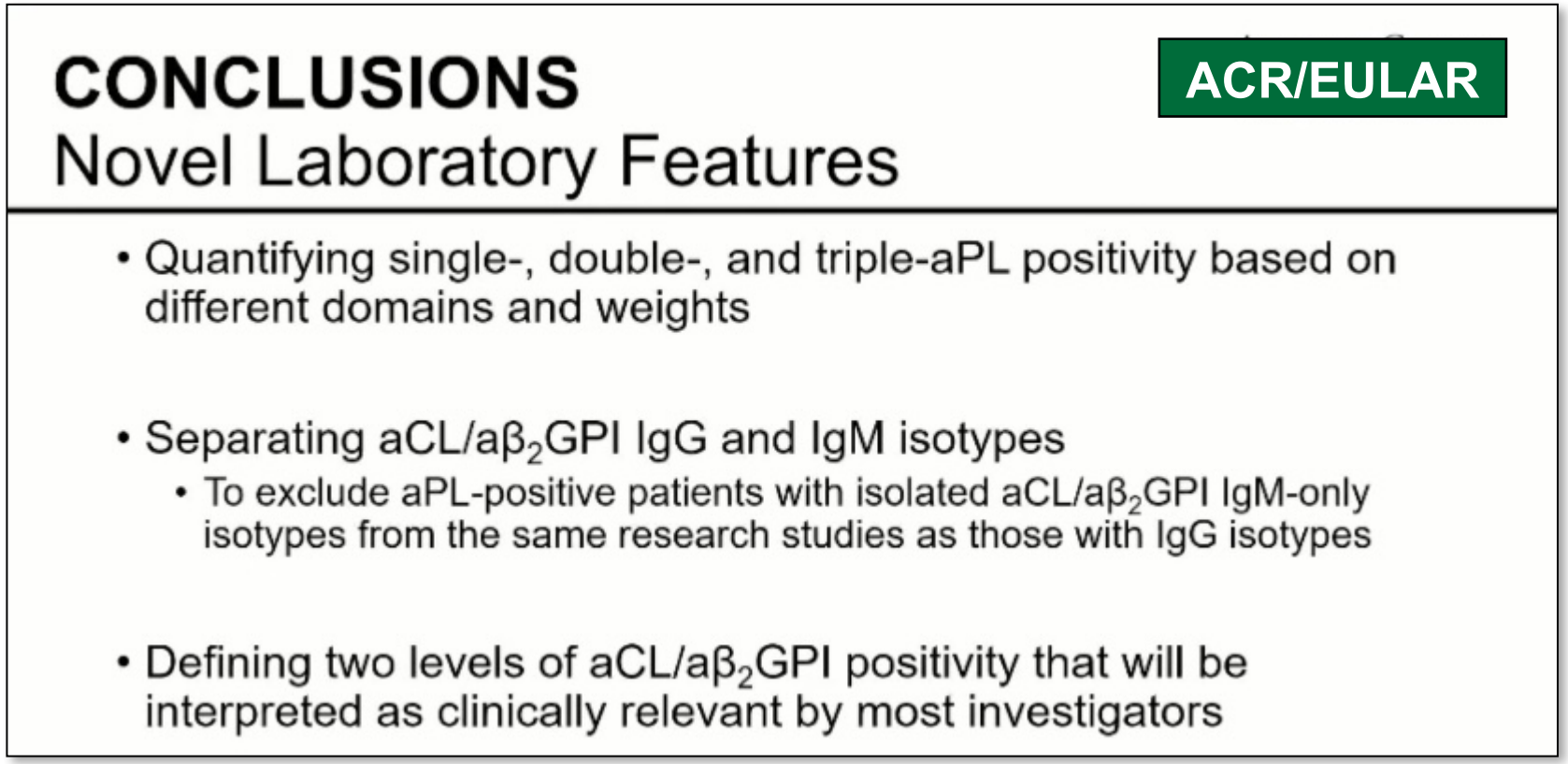
Criterios clasificatorios para el síndrome antifosfolipídico

CONCLUSIONS:
Novel Clinical Features

ACR/EULAR

- Risk stratification of macrovascular events by traditional thrombosis risk factors
- Well-defined microvascular domain items
- Re-defined pregnancy morbidity definitions
- The addition of cardiac valve disease and thrombocytopenia

Criterios clasificatorios para el síndrome antifosfolipídico



Criterios clasificatorios para el síndrome antifosfolipídico

European Forum on Antiphospholipid Antibodies

APS ACTION

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Criterios clasificatorios para el síndrome antifosfolipídico

European Forum on Antiphospholipid Antibodies

Stephane Zuily

APS ACTION

Doruk Erkan

Clínic Barcelona

Universitat de Barcelona

Ricard Cervera

Spain

NEW CLASSIFICATION CRITERIA FOR THE ANTIPHOSPHOLIPID SYNDROME

18-05-2024 | 10:30 - 12:00

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