Autoantibodies are a very heterogeneous group of antibodies with respect to their specificity, induction, effects, and clinical significance. Testing for autoantibodies can be helpful or necessary for the diagnosis, differential diagnosis, prognostication, or monitoring of autoimmune diseases. In case of limited *(forme fruste)* disease or a single disease manifestation, the detection of serum autoantibodies can play an important role in raising the suspicion of evolving disease and forecasting prognosis. This book and reference guide is intended to assist the physician in understanding and interpreting the variety of autoantibodies that are being used as diagnostic and prognostic tools for patients with systemic rheumatic diseases. Autoantibodies observed in systemic autoimmune diseases are described in alphabetical order in Part 1 of this reference guide. In Part 2, systemic autoimmune disorders as well as symptoms that indicate the possible presence of an autoimmune disease are listed. Systemic manifestations of organ-specific autoimmune diseases will not be covered in this volume. Guide marks were inserted to ensure fast and easy cross-reference between symptoms, a given autoimmune disease and associated autoantibodies. Although the landscape of autoantibody testing continues to change, this information will be a useful and valuable reference for many years to come.

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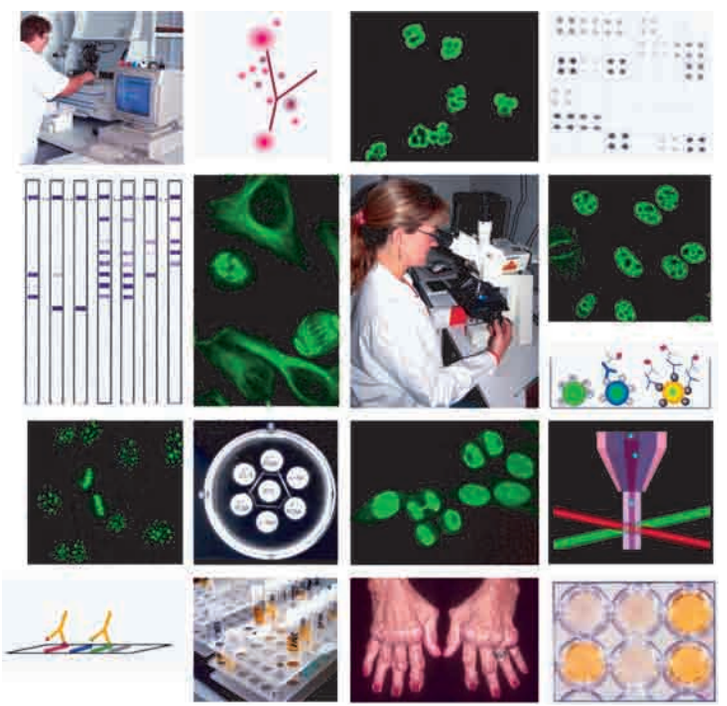
K. Conrad, W. Schößler, F. Hiepe, M. J. Fritzler
Autoantibodies in Systemic Autoimmune Diseases

2nd edition

Karsten Conrad, Werner Schößler, Falk Hiepe, Marvin J. Fritzler

Autoantibodies in Systemic Autoimmune Diseases

A Diagnostic Reference



AUTOANTIGENS, AUTOANTIBODIES, AUTOIMMUNITY
Volume 2, second Edition – 2007

PABST

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A Diagnostic Reference

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Part 2
Systemic Autoimmune Diseases — Syndromes, Diagnostic Criteria, Symptoms

Preface, 2nd edition

The determination of autoantibodies has become an integral part of the diagnosis and differential diagnosis, as well as the estimation of the prognosis and development of autoimmune diseases. Furthermore, because many disease-associated autoantibodies are detectable in preclinical stages, they have assumed a potential role in the very early diagnosis or risk assessment of disease development. The growing knowledge about the pathogenic and diagnostic value of autoantibodies in systemic diseases, and the discovery of novel autoantibodies and changes in classification criteria necessitated the publishing of a revised and supplemented 2nd edition. Besides the clinically relevant autoantibodies also antibodies that may serve as tools in molecular, cell and tumor biological studies have been included. However due to the rapid development, the alphabetical catalogue of relevant or potential relevant autoantibodies is incomplete. Therefore, the authors appreciate helpful comments for future editions.

Karsten Conrad
Marvin J. Fritzler
Falk Hiepe
Werner Schößler

Preface, 1st edition

Among the challenges facing the new millennium physician are tremendous changes in biomedical and information technologies that are rapidly changing the nature and complexity of clinical practice. Since the discovery of the LE cell over 50 years ago, there has been a logarithmic increase in the description and clinical application of autoantibodies in an ever-widening spectrum of diseases. Systemic rheumatic diseases are among the most complex of these diseases because the clinical presentation and constellation of findings are in part reflected by the spectrum of autoantibodies found in these conditions. The litany of autoantibody acronyms, designations and descriptors include Sm, dsDNA, SS-A/Ro, SS-B/La, U1RNP, Jo-1, topo-I, CENP, Ku, Ki, Sa, and ribo P, to name a few. This 'antibody alphabet soup' has threatened to move clinical diagnostics into a literal Tower of Babel.

It is important to appreciate how the 'antibody alphabet soup' can be useful in the diagnosis and management of systemic rheumatic diseases. The applications are as varied and rich as are the multiplicity of the autoantibody specificities. Certainly, autoantibody testing is not required to make a diagnosis in a woman who presents with a photosensitive skin rash, pericarditis, glomerulonephritis, anemia and psychosis. This patient clearly has SLE and the detection of autoantibodies confirms the obvious. What may not be as clear is that the presence of anti-dsDNA could correlate with nephritis and the presence of anti-ribo P may indicate manifestations of central nervous system lupus in the presence of confounding factors such as infections and drug use. In addition, not all patients present with classical "textbook" features of systemic rheumatic diseases. Unfortunately, in many cases the time interval from the onset of symptoms to a confirmed diagnosis and meeting established criteria for the classification of disease, can be measured in decades. Thus, when there is limited (*forme fruste*) disease or a single disease manifestation, the detection of serum autoantibodies can play an important role in raising the suspicion of evolving disease and forecasting prognosis. A good example is the use of autoantibodies in the initial evaluation of Raynaud's phenomenon. If the ANA and other autoantibody tests are negative, the likelihood that his patient has primary Raynaud's disease is likely and the concern that the clinical course will transform into systemic rheumatic disease is lessened. On the other hand, ample

clinical studies have shown that the presence of anti-topo-I (Scl-70) is a harbinger of diffuse scleroderma, antibodies to CENP are more predictive of the limited form of the disease, and the presence of anti-PM/Scl, indicates a scleroderma-polymyositis overlap syndrome. There many other examples of the clinical utility of autoantibody testing in isolated clinical scenarios such as polyarthritis, myositis, neuropathies, cytopenias, and vasculopathies that are characteristic, but not specific for, any single systemic rheumatic disease. In many of these instances the presence of one or more 'alphabet soup' antibodies can be a prologue to diseases that are likely to evolve during patient follow-up.

While the diagnosis of *forme fruste* disease is an important use of autoantibody testing, another valuable use is that they provide an understanding of the pathogenesis. This has been clearly illustrated with the subsets of disease such as neonatal lupus syndrome, subacute cutaneous lupus, homozygous C2 deficiency, interstitial lung disease, granulocytopenia, and Sjögren's syndrome that are strongly associated with anti-SS-A/Ro. Compelling evidence shows that anti-SS-A/Ro binds with the cognate antigen in the fetal heart and in keratinocytes exposed to ultraviolet light. On the other hand, it is not clear how or if the same antibody participates in the development of keratoconjunctivitis sicca. The demonstration that ribosomal P proteins and other autoantigens are found on the surface of some normal and apoptotic cells may provide an important clue to their potential pathogenic role. The notion that some autoantibodies may be fingerprints incriminating a cause or etiology of the disease are also being clarified. For example, antibodies to fibrillarin (U3-RNP) are induced in certain strains of mice by heavy metal exposure and systemic sclerosis patients with these autoantibodies have high levels of urinary mercury.

The future of autoantibody testing can be cast into at least four arenas. First, the rapid advancement of new technologies (autoantigen arrays, microfluidics and nanotechnology) will change the complexion of the autoantibody testing by providing a wealth of serological information that will almost certainly challenge current paradigms and clinical associations. It is now possible to use a drop of blood to analyze serum for the presence of over 100 different autoantibodies in a single test that can be completed and reported within minutes. Second, it is anticipated that autoantibody testing will be a critical part of monitoring and evaluating patients placed on a variety of the newer biological therapeutics. For example, it is increasingly clear that interferon and tumor necrosis factor blockade therapies are associated with the induction of autoantibodies and, in some cases, full blown disease. Interestingly, these observations fall on the historical evidence that drugs such as procainamide and hydralazine can induce autoantibodies and lupus syndromes. Third, it is likely that autoantibody testing will replace more invasive and costly diagnostic techniques such as the salivary gland biopsy for Sjögren's syndrome, the small bowel biopsy for coeliac disease, the nerve and skin biopsy for vasculitis, the muscle biopsy for myositis, and many others. Fourth, carefully designed

studies that assess the cost effectiveness of autoantibody testing are required. On one hand, there is the notion that in many patients, including the woman with unequivocal features of SLE described above, that even the relatively inexpensive autoantibody test is superfluous and not cost effective. However, the implications of longer term health care costs of missing an early diagnosis in a patient with *forme fruste* disease must also be carefully considered. A cost-effective and rational approach to autoantibody testing algorithms and clinical practice guidelines are overdue. Clinical studies to address these issues will prove worthwhile and save patients from needless, expensive and invasive tests, and missed diagnosis that can lead to significant morbidity and mortality.

This book and reference guide is intended to assist the physician understand and interpret the variety of autoantibodies that are being used as diagnostic and prognostic tools for patients with systemic rheumatic diseases. Although the landscape of autoantibody testing continues to change, this information will be a useful and valuable reference for many years to come.

Marvin J. Fritzler

Notes for the Use of this Book

This reference book on the serological diagnosis of systemic autoimmune diseases is divided into two main sections. The autoantibodies observed in autoimmune diseases are described in alphabetical order in Part 1, and autoimmune disorders as well as symptoms that indicate the possible presence of an autoimmune disease are listed in Part 2. Guide marks (the symbol "➢") were inserted to ensure fast and easy cross-reference between symptoms, a given autoimmune disease and associated autoantibodies. Bibliographic references were omitted due to the broad scope of the subject matter. Only the first authors of historical or some important recent publications have been named.

With some exceptions (e. g., antinuclear antibodies) the prefix "anti-" was omitted for better clarity of alphabetization. Anticentromere antibodies, for example, are listed as "centromere antibodies". In as far as they were known to the authors, synonyms or alternative names for the antibodies were also listed. Obsolete terminology is indicated as such, and the names preferred by the authors are used in the alphabetical index.

The autoantibody description section begins, in some cases, with a brief introduction or historical account. This is followed by information on the target structures (autoantigens), detection methods, clinical relevance, and indications for testing of the autoantibody.

The authors' rating of the clinical relevance of each autoantibody listed in the book is indicated using variable coloring and lettering.

White Letters on Green Background

These are autoantibodies of high diagnostic relevance (markers for diagnosis, prognosis or monitoring) that can usually be determined in all laboratories.

Black Letters on Medium Green Background

These are diagnostically relevant autoantibodies that are not measurable in all laboratories and therefore are determined in specialized laboratories only.

Black Letters on Light Green Background

The clinical relevance of these antibodies is (still) unclear due to their very low frequency of detection, discrepancies between the findings of different studies (lack of comparability due to differences in study design, methodology, ethnic differences, etc.), methodological problems, or preliminary nature of study findings.

Black Letters on White Background

These autoantibodies are currently not clinically relevant, are no longer clinically relevant, or are clinically relevant only in isolated cases. This can also include disease-specific autoantibodies if their testing does not provide any added diagnostic advantages over other parameters.

Part 1

Autoantibodies in Systemic Autoimmune Diseases

GWB Antibodies

Synonym: Anti-GW bodies also referred to as mammalian processing (P) bodies.

Autoantigens

GWB autoantigens include a group of 3 GW proteins referred to as GW182, GW2 and GW3 as well as other components such as Ago2, Ge-1/Hedls and RAP55. They are localized to discrete cytoplasmic structures that are involved in mRNA processing. The GW antigens were so-named because they contain numerous glycine (G) and tryptophan (W) repeats and have a calculated molecular mass of 182 kDa) and they bind to mRNA as well as Ago2, and are key components of the RNA interference silencing complex (RISC) (reviewed in Jakymiw et al., 2007). The most common target antigen of GWB antibodies is Ge-1/Hedls followed by GW182 (Bhanji et al., 2007).

Detection Methods

- IIF using monolayers of tissue culture or tumor cells, e. g., HEp-2 cells (Fig. 12).

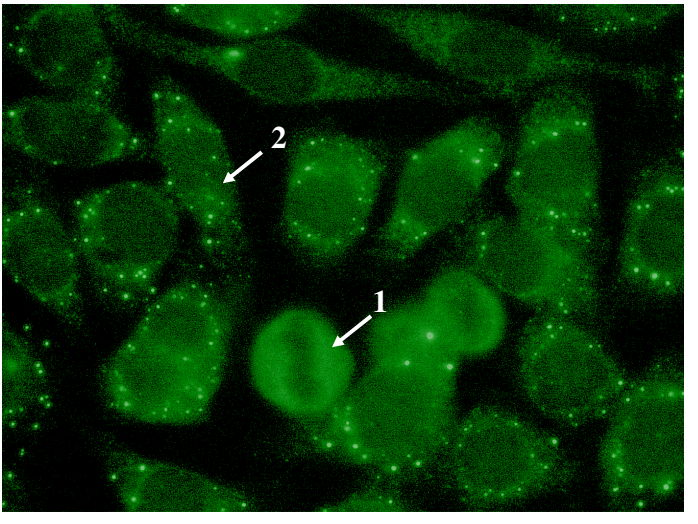

Figure 12. IIF pattern on HEp-2 cells (Immuno Concepts Ltd, Sacramento, USA) of an anti-GWB antibody positive serum: distinctive cytoplasmic dots varying in number from zero in mitotic cells (1) to more than 30 in interphase cells (2).

Note: The frequency of detection of anti-GWB depends on the cell line and tissue that is used for the assay because GWB are most highly expressed in rapidly proliferating cells and in testis and a subset of neural cells. In addition, anti-GWB may be obscured by high titer anti-cytoplasmic antigens such as anti-mitochondrial antibodies.

- IIF using monoclonal anti-GW182 for co-localization
- IB using whole cell extracts or purified GWB fractions.
- EIA or ALBIA using recombinant GW, Ago2, Ge-1/Hedls and RAP55 proteins.
- IP of recombinant protein produced by *in vitro* transcription and translation of cDNA of respective antigens.

Clinical Relevance

- Moderate to high titers of anti-GWB are found in ~0.4 % of routine screening using HEp-2 cells (Stinton et al., 2004). They are primarily associated with ➢ Sjögren's syndrome, ataxia and other neuropathies, ➢ systemic lupus erythematosus (SLE), primary biliary cirrhosis (Bloch et al., 2005) and also found in other systemic autoimmune rheumatic diseases.
- A systematic study of cohorts of various autoimmune diseases is needed now that rapid and sensitive array technology (e. g. ALBIA) is available.
- It is important to note that the detection of anti-GWB may be masked by other autoantibodies (i. e. antimitochondrial antibodies in primary biliary cirrhosis) or overlooked in the presence of strong ANA.

Indications

None currently established.

Comments: If the typical cytoplasmic discrete speckled pattern is found during screening with HEp-2 cells, serological follow-up to rule out reactivity with other cytoplasmic antigens that give a similar pattern (i. e. EEA-1, lysosome) is required. This can be partly accomplished by co-localization studies. However, it should be noted that GWB are quite heterogeneous with respect to content of any one of the components. Thus, analyses of autoantibodies with multiplexed array technologies are preferred once the distinctive staining pattern is identified. At the clinical interface, examinations should be performed, e. g., to detect the potential development of connective tissue disease (Sjögren's syndrome) and neurological conditions such as ataxia and sensory/motor neuropathies. Cooperation with a research laboratory can be useful, e. g., for determination of the specificity and further evaluation of the potential clinical relevance of these antibodies.

Heat Shock Protein (Hsp) Antibodies

Collective term for all autoantibodies directed against **h**eat **s**hock **p**roteins/heat stress proteins (Hsp).

Autoantigens

Various heat shock proteins (heat-stress-induced proteins) like Hsp60, Hsp70 and Hsp90.

Detection Methods

- WB using cell extracts after one- or two-dimensional separation.
- EIA using biochemically purified or recombinant heat shock proteins.

Clinical Relevance

Hsp antibodies occur in a number of autoimmune and non-autoimmune diseases (especially infections) as well as in healthy individuals.

Indications

None related to systemic autoimmune diseases. The use of Hsp antibodies for diagnosis of arteriosclerosis and autoimmune diseases of the inner ear is being evaluated.

Histidyl-tRNA (tRNA^{His}) Synthetase (HRS) Antibodies

See ➤ Jo-1 antibodies, ➤ Aminoacyl-tRNA synthetase antibodies.

Histone Antibodies

Synonym: Anti-histone antibodies (AHA).

History: Histone antibodies appear to be involved in the LE cell phenomenon that was first described in 1948. H2A-H2B antibodies and, more recently, H1 antibodies have been implicated in this phenomenon, which was an important milestone in the discovery of autoantibodies associated with SLE (➢ LE cell factor).

Autoantigens

Histones can be found in almost all eukaryotic cell nuclei. The histone family contains the following five basic proteins: H1 (26.5 kDa), H2A (14 kDa), H2B (13.8 kDa), H3 (15.3 kDa) and H4 (10.2 kDa). Histones form complexes with double-stranded DNA, called nucleosomes. The DNA thereby wraps around dimeric H2A-H2B and H3-H4, while H1 binds to DNA on the surface of the nucleosome. The bead-like nucleosomes help bundle the DNA into a more compact chromatin structure. All histones and histone complexes can be targeted by autoantibodies.

Detection Methods

- IIF using HEp-2 cells: Chromatin can be visualized like the pattern produced by ➢ dsDNA antibodies (homogeneous staining of interphase nuclei and of the chromatin region in mitotic cells).
  Note: A negative immunofluorescence does not exclude the presence of AHA.
- EIA, ALBIA and LIA using isolated histones or histone mixtures.
- RIA using isolated histones or histone mixtures.
- WB.

Comments: The conformational epitopes may be altered or destroyed due to solid phase binding (EIA) and/or the use of SDS-polyacrylamide gel electrophoresis (WB).

Clinical Relevance

- With the possible exception of anti-H1, AHA are not specific for any one disease, but can be detected in a number of autoimmune diseases, especially rheumatic disorders: ➢ Systemic lupus erythematosus (SLE; 50–80 %), ➢ drug-induced lupus (DIL; 92–95 %), ➢ rheumatoid arthritis (RA; up to 11 %), RA vasculitis (up to 75 %), ➢ Felty's syndrome (up to 79 %), ➢ juvenile idiopathic arthritis (JIA; up to 51 %), systemic sclerosis (SSc; up to 30 %), ANA positive undifferentiated connective tissue diseases (up to 90 %), primary biliary cirrhosis (up to 55 %), autoimmune hepatitis (up to 35 %). Furthermore, AHA are detectable in patients with neoplastic diseases, subacute sensoric neuropathies and infections.

- *High titers* of AHA are found almost exclusively in patients with SLE and DIL. The detection of high AHA titers in the absence of SLE marker antibodies is characteristic of **drug-induced lupus**.
- AHA can be of the IgG, IgM or IgA isotype. IgG AHA appear to be related to the disease activity of lupus.
- In patients with SSc, AHA are associated with lung, heart and kidney involvement (Hesselstrand et al., 2003). A strong correlation of AHA with the number of morphea lesions and the number of involved areas of the body have been described in patients with localized sclerodema (Takehara et al., 2005).

Indications

1. Suspicion of drug-induced lupus (especially after procainamide, hydralazine, isoniazid, chlorpromazine, methyldopa, beta blockers, anticonvulsant, sulfasalazine or captopril use).
   Note: To establish the diagnosis of drug-induced lupus, the potential presence of SLE marker antibodies (i. e., ➢ dsDNA and ➢ Sm antibodies) must be ruled out using the appropriate tests. Antihistone antibodies tend to disappear within one year of discontinuing the causative drug.
2. Differential recognition of antinuclear antibodies in sera presenting a typical chromatin fluorescence pattern.

HMG Antibodies

Autoantigens

Chromosomal **h**igh **m**obility **g**roup (HMG) proteins. The proteins HMG-1, -2, -14 and -17 have been described as target proteins of autoantibodies involved in systemic autoimmune diseases. Furthermore, antigens with HMG motifs (HMG-box proteins such as Sp100, SOX13) can be targeted by antibodies from autoimmune patients (Fida etal., 2002).

Detection Methods

- WB using cell extracts or HMG preparations.
- EIA using biochemically purified HMG.

Part 2

Systemic Autoimmune Diseases — Syndromes, Diagnostic Criteria, Symptoms

Abortion, spontaneous

Recurrent spontaneous abortions that generally occur after the 10th week of gestation (caused by thrombotic events in the placenta) are a characteristic sign of ➢ antiphospholipid syndrome.

Acidosis, renal-tubular

Renal manifestation of ➢ Sjögren's syndrome.

Acro-Osteolysis

Occurs as a typical feature of ➢ systemic sclerosis and is a reflection of a severe acral microcirculatory disorder.

Addison's disease

May be due to thrombosis of the blood vessels of the adrenal glands as a rare complication (<1%) of ➢ antiphospholipid syndrome.

Adrenocortical failure

➢ Addison's disease

Aldolase, elevated in plasma

➢ Polymyositis/dermatomyositis

➢ Mixed connective tissue disease (MCTD)

Alopecia

Diffuse (alopecia diffusa) or localized alopecia (alopecia areata) may occur in cutaneous lupus erythematosus (ANA negative!) or ➤ systemic lupus erythematosus.

Alveolitis

Interstitial lung involvement occurs in:

- ➤ Systemic lupus erythematosus,
- ➤ Sjögren's syndrome,
- ➤ Polymyositis/dermatomyositis,
- ➤ Systemic sclerosis,
- ➤ Scleroderma/myositis overlap syndrome,
- ➤ Microscopic polyangiitis (hemorrhagic alveolitis is a feared complication!).

Typical feature of:

- ➤ Anti-Jo-1 syndrome or anti-synthetase syndrome.

See also ➤ hemorrhagic alveolitis.

Amaurosis fugax

Reversible, mostly unilateral blindness due to retinal circulatory disorder. Rare ophthalmologic manifestation of ➤ antiphospholipid syndrome (in 5 %). Also symptom of ➤ giant cell arteritis (temporal arteritis).

ANCA-associated vasculitis

Group of primary systemic vasculitides associated with ANCA (➤ cANCA/proteinase 3 antibodies, ➤ pANCA/myeloperoxidase antibodies):

- ➤ Wegener's granulomatosis (WG),
- ➤ Microscopic polyangiitis (MPA),
- ➤ Churg-Strauss syndrome (CSS).

Anemia

Anemia may occur in all inflammatory diseases and is associated with the degree of inflammatory activity. Coombs-positive autoimmune hemolytic anemia may occur in ➢ systemic lupus erythematosus and rarely in other ➢ connective tissue diseases. Coombs-positive hemolytic anemia occurs in about 9 % of patients with ➢ antiphospholipid syndrome.

Anti-Jo-1 syndrome

Original name for ➢ anti-synthetase syndrome.

Antiphospholipid syndrome (APS)

Synonyms: Hughes syndrome, anticardiolipin syndrome, phospholipid antibody syndrome, cardiolipin antibody syndrome

APS is one of the most common autoimmune diseases. Its clinical picture is extremely variable, and the complications arising from the disease may be minimal to life-threatening. The features of APS include venous and arterial thrombosis, recurrent spontaneous abortions, neurological complications and phospholipid antibody expression. APS may occur as an isolated disease entity (formerly primary antiphospholipid syndrome) or in combination with another autoimmune disease, especially systemic lupus erythematosus (formerly secondary antiphospholipid syndrome).

➢ **Sneddon's syndrome** and ➢ **Budd-Chiari syndrome** are partially attributable to APS. The ➢ **catastrophic antiphospholipid syndrome** is a rare form of APS characterized by extensive vascular occlusions in multiple organ systems, leading to renal failure and malignant arterial hypertension, severe CNS manifestations, acrocyanosis and gangrene.

A workshop, preceding the Eleventh International Congress on antiphospholipid antibodies (aPL) in Sydney, Australia, considered revisions to the international classification criteria for APS.

Revised classification criteria for the APS
[according to Miyakis et al., 2006]

Clinical criteria

1. **Vascular thrombosis***
   One or more clinical episodes of arterial, venous, or small vessel thrombosis. Thrombosis must be confirmed by objective validated criteria (i. e. unequivocal findings of appropriate imaging studies or histopathology). 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 10^{th} 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 before the 34th week of gestation because of (i) eclampsia or severe preeclampsia defined according to standard definitions, or (ii) recognized features of placental insufficiency, 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 one type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to a, b, or c above.

Laboratory criteria**

1. Lupus anticoagulant (LA) present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on LAs/phospholipid-dependent antibodies) (Brandt et al., 1995, Wisloff et al., 2002). See ➢ Lupus anticoagulant.
2. Anticardiolipin (aCL) antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (i. e. > 40 GPL or MPL, or > the 99^{th} percentile), on two or more occasions, at least l2 weeks apart, measured by a standardized EIA (Tincani et al., 2001; Harris et al., 2002; Wong et al., 2004). See ➢ Cardiolipin antibodies.

3. Anti-β 2 glycoprotein I antibody of IgG and/or IgM isotype in serum or plasma (in titer > the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardized EIA, according to recommended procedures (Reber et al., 2004). See ➢ β2 glycoprotein I antibodies.

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

It must be pointed out that the classification of APS should be avoided if less than 12 weeks or more than 5 years separate the positive aPL test and the clinical manifestation.

* Coexisting inherited or acquired factors for thrombosis are not reasons for excluding patients from APS trials. However, two subgroups of APS patients should be recognized, according to: (a) the presence, and (b) the absence of additional risk factors for thrombosis. Indicative (but not exhaustive) such cases include: age (> 55 in men, and > 65 in women), and the presence of any of the established risk factors for cardiovascular disease (hypertension, diabetes mellitus, elevated LDL or low HDL cholesterol, cigarette smoking, family history of premature cardiovascular disease, body mass index $\geq 30\ kg\ m^{-2}$, microalbuminuria, estimated CFR $< 60\ m\ell\ min^{-1}$), inherited thrombophilias, oral contraceptives, nephrotic syndrome, malignancy, immobilization, and surgery. Thus, patients who fulfil criteria should be stratified according to contributing causes of thrombosis.

** Investigators are strongly advised to classify APS patients in studies into one of the following categories: I, more than one laboratory criteria present (any combination); IIa, LA present alone; IIb, aCL antibody present alone; IIc, anti-β 2 glycoprotein I antibody present alone.

Features associated with APS but not included in the revised criteria:

- heart valve disease (Libman-Sacks endocarditis; rheumatic fever and septic endocarditis have to be excluded)
- livedo reticularis
- thrombocytopenia
- nephropathy
- neurological manifestations (cognitive dysfunction, transient cerebral ischemia and stroke, dementia, transverse myelopathy, seizure)
- IgA ➢ aCL
- IgA ➢ anti-β 2GPI
- antibodies against ➢ phosphatidylserine
- antibodies against ➢ phosphatidylethanolamine

- antibodies against ➢ prothrombin alone
- antibodies to the ➢ phophatidylserine-prothrombin complex

Autoantibodies:
➢ Phospholipid antibodies (see also appendix VI)

Anti-SRP syndrome

A subtype of idiopathic myositis (see ➢ Polymyositis).

Characteristic features:

- Predominantly occurs in women of black African descent
- Acute/subacute onset with severe polymyositis
- Cardiac involvement frequently occurs
- Severe myonecrosis with only minimal inflammation
- Responds poorly to immunosuppressive therapy; very poor prognosis (5-year mortality of 75 %!)

Comment: In rare cases atypical clinical manifestations may occur in the presence of necrotizing myopathy (Dimitri et al., 2007).

Autoantibodies: ➢ SRP antibodies serve as diagnostic marker. ➢ Ro52 antibodies can be found but did not have any diagnostic or prognostic relevance.

Anti-Synthetase syndrome

Synonym: Anti-Jo-1 syndrome.

Subtype of idiopathic myositis (see ➢ **Polymyositis**) characterized by the additional occurrence of arthralgia/arthritis and interstitial lung involvement (alveolitis, pulmonary fibrosis) and the detection of autoantibodies that react with tRNA synthetases (especially Jo-1).

Major criteria of the anti-synthetase syndrome

1. Polymyositis
2. Polysynovitis (arthralgia, arthritis, tenosynovitis)

3. Interstitial lung disease (fibrosing alveolitis)
4. Aminoacyl-tRNA synthetase antibodies

Additional associations

- Rhagades and keratoses of the hands ("mechanic's hands")
- Raynaud's phenomenon
- Acrosclerosis
- Sicca symptoms
- Dermatomyositis-like skin manifestations

Autoantibodies: ➢ Aminoacyl-tRNA synthetase antibodies are diagnostic markers. Among these, ➢ Jo-1 antibody is the most common detectable biomarker. ➢ Ro52 antibodies are found at high frequencies but without aid in diagnosing this type of autoimmune myositis.

Arthralgia

Common feature of all degenerative and inflammatory rheumatic diseases; frequently occurs as a manifestation of systemic and organ-specific autoimmune diseases.

Autoantibodies: Patients suspicious for inflammatory rheumatic disease should be screened for ➢ antinuclear antibodies (ANA), ➢ antineutrophil cytoplasmic antibodies (ANCA), ➢ CCP/citrullinated protein/peptide antibodies and ➢ rheumatoid factor (RF).

Arthritis

Characteristic feature of inflammatory joint diseases: HLA-B27 associated spondylarthropathia, ➢ juvenile chronic arthritis (JIA), ➢ rheumatoid arthritis (RA).

Common symptom of systemic autoimmune diseases: ➢ Connective tissue diseases, ➢ systemic vasculitides, ➢ relapsing polychondritis, ➢ hypocomplementemic urticarial vasculitis syndrome.

Autoantibodies: Patients suspicious for inflammatory rheumatic diseases should be screened for ➢ antinuclear antibodies (ANA), ➢ antineutrophil cytoplasmic