

# KLINIČKE MANIFESTACIJE UDRUŽENE SA PRISUSTVOM ANTIFOSFOLIPIDNIH ANTITELA

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REVIEW ARTICLE

## CLINICAL MANIFESTATIONS ASSOCIATED WITH THE PRESENCE OF ANTIPHOSPHOLIPID ANTIBODIES

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### SAŽETAK

Antifosfolipidna antitela (aPL antitela; engl. *antiphospholipid antibodies*) su heterogena grupa autoantitela koja su usmerena na anjonske fosfolipide ili proteine koji se vezuju za fosfolipide. Mogu biti udružena sa brojnim kliničkim manifestacijama u gotovo svim oblastima medicine, ali je antifosfolipidni sindrom (engl. *antiphospholipid syndrome* – APS) najpreciznije definisani entitet koji se karakteriše prisustvom ovih antitela. Najčešće kliničke manifestacije prisustva aPL antitela su tromboze, u bilo kom delu cirkulacije, kao i komplikacije trudnoće, u formi spontanog gubitka ploda ili prevremenog porođaja usled preeklampsije, eklampsije ili placentalne insuficijencije. Prema modifikovanoj Sapporo klasifikaciji iz 2006. godine, ove manifestacije predstavljaju jedini klinički kriterijum za dijagnozu APS-a. Međutim, kod približno četvrtine bolesnika sa APS-om, prisutne su i druge patološke promene, koje su često udružene sa aPL antitelima, ali koje ne ulaze u zvanične kriterijume za klasifikaciju ove bolesti. Značajno je da ove manifestacije mogu biti udružene sa aPL antitelima i u odsustvu tromboze ili patologije trudnoće, dakle bez zadovoljenih kriterijuma za APS. Prepoznavanje ne-kriterijumskih manifestacija je od velikog značaja pošto bi njihov nalaz trebalo da skrene pažnju na moguće prisustvo aPL antitela i ukaže na postojanje APS-a ili na rizik od njegove pojave. Najnovija klasifikacija, objavljena 2023. godine, od strane Američkog koledža za reumatologiju/Evropske alijanse udruženja za reumatologiju (engl. *American College of Rheumatology/European Alliance of Associations for Rheumatology* – ACR/EULAR), proširila je spisak kliničkih kriterijuma za prepoznavanje antifosfolipidnog sindroma. Ova klasifikacija ima veću specifičnost ali manju senzitivnost u prepoznavanju APS-a u odnosu na ranije kriterijume. Za sada su ACR/EULAR kriterijumi prevashodno namenjeni za odabir bolesnika u kliničkim studijama, a ne za dijagnostikovanje APS-a u svakodnevnoj kliničkoj praksi.

**Ključne reči:** antifosfolipidna antitela, tromboza, antifosfolipidni sindrom, komplikacije trudnoće, klasifikacija

### ABSTRACT

Antiphospholipid antibodies (aPL antibodies) are a heterogeneous group of autoantibodies that target anionic phospholipids or phospholipid-binding proteins. They can be associated with numerous clinical manifestations in almost all areas of clinical medicine, but antiphospholipid syndrome (APS) is the most precisely defined entity. The most common clinical manifestations of aPL are thrombosis in any part of the circulation, as well as pregnancy complications in the form of miscarriage or premature birth due to preeclampsia, eclampsia, or placental insufficiency. According to the modified Sapporo classification of 2006, thrombosis and/or pregnancy complications represent the clinical criteria for diagnosing APS. However, in approximately a quarter of patients with APS, additional clinical manifestations are present, which are not accepted as criteria for APS. Interestingly, these manifestations can be associated with aPL antibodies even in the absence of thrombosis or pregnancy morbidity, i.e., without the presence of the criteria for definitive APS. Recognizing non-criteria manifestations is highly significant because it can draw attention to the possible presence of aPL antibodies and indicate the presence of APS or the risk of its occurrence. The latest classification was published in 2023 by the American College of Rheumatology/European Alliance of Rheumatology Associations (ACR/EULAR). It expanded the list of clinical criteria for the recognition of antiphospholipid syndrome. This classification demonstrates higher specificity but lesser sensitivity in recognizing APS than earlier criteria. At present, the application of the ACR/EULAR criteria is primarily intended for research purposes, i.e., selecting study subjects, rather than for diagnosing APS in everyday clinical practice.

**Keywords:** antiphospholipid antibodies, thrombosis, antiphospholipid syndrome, pregnancy complications, classification

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## UVOD

Poremećaji u regulaciji imunološkog sistema i abnormalna produkcija autoantitela mogu uzrokovati veći broj autoimunih bolesti. Autoantitela koja su usmerena ka specifičnim antigenima obično su udružena sa tipičnom kliničkom slikom kao što je slučaj sa reumatoidnim faktorom kod reumatoidnog artritisa. S druge strane, prisustvo antifosfolipidnih antitela ispoljava se putem brojnih i heterogenih kliničkih manifestacija. Najsnažnija povezanost aPL antitela je dokazana sa pojavom tromboze ili razvojem komplikacija u trudnoći, ali se ova antitela mogu naći i kod čitavog niza drugih oboljenja u čijoj patogenezi ova antitela imaju manje jasnu ulogu [1]. Gotovo da nema oblasti kliničke medicine u kojoj ne postoji neka bolest ili poremećaj koji predstavljaju manifestaciju prisustva aPL antitela. Međutim, i pored uloge u patogenezi nekih od najčešćih bolesti, značaj aPL antitela je u svakodnevnoj praksi prilično potcenjen. Na primer, iako se ova antitela mogu naći kod 10% bolesnika sa infarktom srca, njihovo određivanje često nije deo rutinske prakse čak ni kod mlađih osoba sa trombozom koronarnih arterija [2].

Od posebnog značaja je napomenuti da aPL antitela najčešće predstavljaju perzistentni rizik za pojavu ili progresiju oboljenja sa kojima su udružena. Zbog toga je važno poznavati kliničke manifestacije aPL antitela kako bi se što ranije moglo dijagnostikovati njihovo prisustvo i preduzeti lečenje oboljenja do kojeg dovode.

## ANTIFOSFOLIPIDNA ANTITELA

Termin *antifosfolipidna antitela* predstavlja zajednički naziv za heterogenu grupu autoantitela usmerenih ka anjonskim fosfolipidima ili proteinima koji se vezuju za fosfolipide [3]. Mogu biti tranzitorna (prolazna) i perzistentna. Tranzitorna antitela se najčešće javljaju u okviru akutnih virusnih infekcija i iščezavaju u roku od nekoliko nedelja, pri čemu uglavnom ne dovode do kliničkih manifestacija [4]. S druge strane, perzistentna aPL antitela koja su udružena sa kliničkim manifestacijama mogu se javiti kao samostalni (primarni) fenomen ili mogu pratiti autoimune ili neke druge hronične bolesti.

Brojne studije su uverljivo dokumentovale da je nalaz antikardiolipinskih antitela (aCL antitela; engl. *anticardiolipin antibodies*) IgG i IgM klase, anti beta 2 glikoprotein I antitela (anti  $\beta$ 2GPI antitela) IgG i IgM klase i lupusnog antikoagulansa (engl. *lupus anticoagulant* – LAC) značajno povezan sa većim rizikom od nastanka tromboze ili komplikacija u toku trudnoće. Zbog toga je prisustvo bar jednog od ovih antitela neophodan laboratorijski kriterijum za dijagnozu antifosfolipidnog sindroma [5]. Antifosfolipidna antitela mogu biti usmerena i na najmanje 20-tak drugih fosfolipida ili fosfolipid-vezujućih proteina, kao što su fosfatidilserin, protein C,

## INTRODUCTION

Disruption in the immune system regulation and abnormal production of autoantibodies can cause many autoimmune diseases. Autoantibodies directed against specific antigens are usually associated with a typical clinical presentation such as the rheumatoid factor in rheumatoid arthritis. On the other hand, the presence of antiphospholipid antibodies is expressed through numerous and heterogeneous clinical manifestations. The strongest association of aPL antibodies has been proven with the occurrence of thrombosis or the development of complications in pregnancy, but these antibodies can also be found in a whole series of other diseases in whose pathogenesis these antibodies have a less clear role [1]. There is almost no area of clinical medicine without any diseases or disorders that are manifestations of the presence of aPL antibodies. However, despite their role in the pathogenesis of some of the most common diseases, the importance of aPL antibodies is rather underestimated in everyday practice. For example, although these antibodies can be found in 10% of heart attack patients, testing for aPL antibodies is often not included in routine practice even in younger patients with coronary artery thrombosis [2].

It is particularly important to note that aPL antibodies most often present a persistent risk for the occurrence or progression of the diseases with which they are associated. Therefore, it is important to understand the clinical manifestations of aPL antibodies in order to diagnose their presence as early as possible and treat the disease they cause.

## ANTIPHOSPHOLIPID ANTIBODIES

*Antiphospholipid antibodies* is an umbrella term for a heterogeneous group of autoantibodies that target anionic phospholipids or phospholipid-binding proteins [3]. They can be transient and persistent. Transient antibodies most often appear in acute viral infections disappearing within several weeks, and they generally do not lead to clinical manifestations [4]. On the other hand, persistent aPL antibodies associated with clinical manifestations may occur as an independent (primary) phenomenon or may accompany autoimmune or other chronic diseases.

Numerous studies have definitively documented that the presence of anticardiolipin antibodies (aCL antibodies) – class IgG and class IgM, anti-beta 2 glycoprotein I antibodies (anti- $\beta$ 2GPI antibodies) – class IgG and class IgM, and the lupus anticoagulant (LAC) was significantly associated with a higher risk of thrombosis or complications during pregnancy. Therefore, the presence of at least one of these antibodies is a necessary laboratory criterion for the diagnosis of an-

protein S, aneksin II, aneksin V, trombomodulin i drugi. Za ova aPL antitela nije dokazana definitivna povezanost sa kliničkim manifestacijama pa se njihovo određivanje ne preporučuje u redovnoj kliničkoj praksi [5].

Laboratorijska metodologija za dokazivanje antifosfolipidnih antitela obuhvata dve osnovne grupe testova: prisustvo LAC-a se dokazuje koagulacionim metodom dok se aCL antitela i anti  $\beta_2$ GPI antitela detektuju enzimskim imunosorbentnim esejom (*enzyme-linked immunosorbent assay* – ELISA) ili drugim imunoesejima baziranim na principu vezivanja antitela za kardiolipin ili  $\beta_2$ GPI u čvrstoj fazi. Ove metode detektuju heterogene populacije aPL antitela koja mogu biti usmerena ka različitim antigenima – u imunoesejima to su kardiolipin ili  $\beta_2$ GPI, a u slučaju lupusnog antikoagulansa antigeni su fosfolipid-vezujući proteini kao što su  $\beta_2$ GPI ili protrombin [6]. Novije studije su pokazale da kliničko ispoljavanje prisustva aPL antitela u značajnoj meri zavisi od njihovog profila. Pojava tromboze ili komplikacija trudnoće najsnažnije korelira sa istovremenim postojanjem aCL antitela, anti  $\beta_2$ GPI antitela i LAC-a (tzv. trostruka pozitivnost) [7]. Pokazano je da antitela usmerena na domen D1 u  $\beta_2$ GPI molekulu imaju najveći potencijal da dovedu do kliničkih manifestacija antifosfolipidnog sindroma [8].

Prisustvo aPL antitela se može ispoljiti na četiri osnovna načina: kao prisustvo asimptomatskih antitela, kao APS, kao katastrofični APS i putem kliničkih manifestacija koje nisu obuhvaćene kriterijumima za klasifikaciju antifosfolipidnog sindroma.

## ASIMPTOMATSKO PRISUSTVO APL ANTITELA

Interesantno je da se prisustvo aPL antitela može dokazati kod približno 1% – 5% osoba u opštoj populaciji, pri čemu učestalost pozitivnog nalaza raste kod starijih osoba, te osoba sa autoimunim bolestima, hroničnim infekcijama i malignitetima [9]. Nije zapažena povezanost između titra i vrste antifosfolipidnih antitela i pojave kliničkih manifestacija kod asimptomatskih osoba [10].

## ANTIFOSFOLIPIDNI SINDROM

Antifosfolipidni sindrom je sistemska autoimuna bolest koju karakteriše perzistentno prisustvo aPL antitela sa jedne strane, odnosno dokazana tromboza u bilo kojem delu cirkulatornog sistema i/ili patologija trudnoće, sa druge strane. Prvi, tzv. *Sapporo* kriterijumi za klasifikaciju antifosfolipidnog sindroma publikovani su 1999., a revidirani su 2006. godine (tzv. *Sydney* kriterijumi) [11,5]. Interesantno je da, prema revidiranoj klasifikaciji, brojne kliničke manifestacije za koje se zna da često mogu biti udružene sa prisustvom aPL antitela nisu uvrštene u kriterijume za prepoznavanje definitivnog APS-a. Međutim, klasifikacioni kriterijumi nedavno

tiposfolipid syndrome [5]. Antiphospholipid antibodies can also target at least 20 other phospholipids or phospholipid-binding proteins, such as phosphatidylserine, protein C, protein S, annexin II, annexin V, thrombomodulin, and other. For these aPL antibodies, no definitive association with clinical manifestations has been proven, therefore it is not recommended to test for them in regular clinical practice [5].

The laboratory methodology for proving antiphospholipid antibodies includes two basic groups of tests: LAC detection is based on functional coagulation assays, while aCL antibodies and anti- $\beta_2$ GPI antibodies are detected with the enzyme-linked immunosorbent assay (ELISA) or other immunoassays based on the principle of antibodies binding to cardiolipin or  $\beta_2$ GPI, in the solid phase. These methods detect heterogeneous populations of aPL antibodies targeting different antigens – in immunoassays, these are cardiolipin or  $\beta_2$ GPI, and in the case of the lupus anticoagulant, the antigens are phospholipid-binding proteins such as  $\beta_2$ GPI or prothrombin [6]. Recent studies have shown that the clinical manifestation of the presence of aPL antibodies significantly depends on their profile. The development of thrombosis or pregnancy complications correlates most strongly with the concurrent presence of aCL antibodies, anti  $\beta_2$ GPI antibodies and LAC (so-called triple positivity) [7]. It has been shown that antibodies targeting the D1 domain in the  $\beta_2$ GPI molecule have the greatest potential to lead to clinical manifestations of the antiphospholipid syndrome [8].

The presence of aPL antibodies can manifest in four basic ways: as the presence of asymptomatic antibodies, as APS, as catastrophic APS, as well as in the form of clinical manifestations that are not covered by the criteria for the classification of the antiphospholipid syndrome.

## ASYMPTOMATIC PRESENCE OF APL ANTIBODIES

Interestingly, the presence of aPL antibodies can be proven in approximately 1% – 5% of people in the general population, with the frequency of positive findings increasing among the elderly, as well as in people with autoimmune diseases, chronic infections, and malignancies [9]. No correlation was observed between the titer and type of antiphospholipid antibodies and the presence of clinical manifestations in asymptomatic individuals [10].

## ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome is a systemic autoimmune disease characterized by the persistent presence of aPL antibodies, on the one hand, or proven thrombosis in any part of the circulatory system and/or pregnancy

publikovani od strane ACR/EULAR proširuju spektar kliničkih manifestacija koje se smatraju ispoljavanjem antifosfolipidnog sindroma [12].

Prema ACR/EULAR kriterijumima, boduje se šest kliničkih domena (tromboza vena, tromboza arterija, tromboza u mikrocirkulaciji, obstetričke komplikacije, promene na srčanim zaliscima i hematološke manifestacije) kao i dva laboratorijska domena. U odnosu na modifikovanu Sapporo klasifikaciju u kojoj su svi kriterijumi imali istu težinu, u ACR/EULAR klasifikaciji je izvršeno rangiranje kriterijuma prema važnosti zasnovanoj na specifičnosti za prisustvo APS-a. Tako, na primer, u

pathology, on the other. The first criteria for the classification of the antiphospholipid syndrome, i.e., the Sapporo criteria, were published in 1999. They were revised in 2006 (the Sydney criteria) [11,5]. Interestingly, according to the revised classification, numerous clinical manifestations that are known to be often associated with the presence of aPL antibodies are not included in the criteria for the recognition of definite APS. However, the classification criteria recently published by the ACR/EULAR expand the spectrum of clinical manifestations that are considered to be manifestations of the antiphospholipid syndrome [12].

**Tabela 1.** Poređenje kriterijuma za antifosfolipidni sindrom po modifikovanoj Sapporo i ACR/EULAR klasifikaciji

| Modifikovani Sapporo kriterijumi (2006.)                                                                                                                                                                                                                                                                                                                                                                                                                              | ACR/EULAR kriterijumi (2023.)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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| <b>Klinički kriterijumi</b><br>1. Tromboze (bilo koji organ ili tkivo)<br>a. Arterija<br>b. Vena<br>c. Mikrocirkulacija<br>2. Patologija trudnoće<br>a. Tri ili više spontanih gubitaka ploda pre desete nedelje trudnoće<br>b. Spontani gubitak morfološki normalnog fetusa nakon 10-te nedelje trudnoće<br>c. Jedan ili više prevremenih porođaja normalnog neonatusa pre 34. nedelje trudnoće zbog teške preeklampsije, eklampsije ili placentalne insuficijencije | <b>Klinički kriterijumi</b><br>1. Tromboze vena – makrovaskularne<br>a. Sa drugim faktorima rizika za trombozu vena: 1 bod<br>b. Bez drugih faktora rizika: 3 boda<br>2. Tromboze arterija – makrovaskularne<br>a. Sa drugim faktorima rizika za kardiovaskularne bolesti: 2 boda<br>b. Bez drugih faktora rizika: 3 boda<br>3. Mikrovaskularne tromboze<br>a. <i>Livedo racemoso</i> , livedoidna vaskulopatija, aPL nefropatija, pulmonalna hemoragija (sumnja: 2 boda; potvrđena: 5 bodova)<br>b. Potvrđena adrenalna hemoragija/miokardna bolest: 5 bodova<br>4. Obstetričke manifestacije<br>a. Tri i više konsektivnih gubitaka ploda pre desete nedelje i/ili smrt fetusa u dobu 10 – 15 nedelja gestacije + 6 dana: 1 bod<br>b. Smrt fetusa u dobu od 16 – 33 nedelja gestacije + 6 dana, u odsustvu teške preeklampsije ili teške placentalne insuficijencije: 1 bod<br>c. Teška preeklampsija ili teška placentalna insuficijencija pre 34. nedelje gestacije, sa ili bez smrti fetusa: 3 boda<br>d. Teška preeklampsija i teška placentalna insuficijencija pre 34. nedelje gestacije, sa ili bez smrti fetusa: 4 boda<br>5. Srčani zalisci<br>a. Zadebljanje: 2 boda<br>b. Vegetacija: 4 boda<br>6. Hematološki kriterijumi<br>a. Trombocitopenija: 2 boda |
| <b>Laboratorijski kriterijumi</b><br>1. Perzistentno pozitivan test na LAC i/ili<br>2. Perzistentno pozitivna antikardiolipinska antitela IgG ili IgM izotipa (u srednjem ili visokom titru, odnosno > 40 GPL ili MPL, odnosno veća od 99. percentila za opštu populaciju) i/ili<br>3. Perzistentno pozitivna anti $\beta_2$ GPI antitela IgG ili IgM izotipa u titru većem od 99. percentila za opštu populaciju                                                     | <b>Laboratorijski kriterijumi</b><br>1. Pozitivan test na LAC<br>a. Jednom: 1 bod<br>b. Perzistentno: 5 bodova<br>2. Perzistentno pozitivna aCL i/ili anti $\beta_2$ GPI antitela<br>a. Srednje visok ili visok titar IgM aCL i/ili anti $\beta_2$ GPI antitela: 1 bod<br>b. Srednje povećan titar (40 – 79 U/ml) IgG aCL i/ili anti $\beta_2$ GPI antitela: 4 boda<br>c. Visok titar (> 80 U/ml) IgG aCL ili anti $\beta_2$ GPI antitela: 5 bodova<br>d. Visok titar (> 80 U/ml) IgG aCL i anti $\beta_2$ GPI antitela: 7 bodova                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>Dijagnoza:</b> Najmanje jedan klinički i jedan laboratorijski kriterijum unutar pet godina jedan od drugog.                                                                                                                                                                                                                                                                                                                                                        | <b>Dijagnoza:</b> Sabira se po jedna karakteristika sa najvišim brojem bodova iz svakog domena. Za dijagnostikovanje APS-a potrebno je najmanje po tri boda u kliničkim i u laboratorijskim domenima. Klinički i laboratorijski kriterijumi moraju biti ustanovljeni unutar tri godine jedan od drugog.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

obstetričkim kriterijumima, postojanje  $\geq 3$  konsekutivna gubitka ploda pre desete nedelje trudnoće se vrednuje jednim bodom i ima manju važnost u odnosu na tešku placentalnu insuficijenciju pre 34. nedelje trudnoće, koja se ocenjuje sa četiri boda. Definitivna dijagnoza se dobija zbirom bodova pojedinačnih kliničkih i laboratorijskih kriterijuma, pri čemu je za definitivnu dijagnozu APS-a neophodno najmanje tri klinička i tri laboratorijska boda. Osnovni cilj ACR/EULAR klasifikacije je da se unapredi specifičnost u prepoznavanju APS-a, kako bi se formirale što homogenije grupe bolesnika za kliničke studije. Međutim, na taj način se zna-

According to the ACR/EULAR criteria, six clinical domains (vein thrombosis, arterial thrombosis, thrombosis in the microcirculation, obstetric complications, heart valve changes, and hematological manifestations) and two laboratory domains are scored. As compared to the modified Sapporo classification, wherein all criteria carry the same weight, in the ACR/EULAR classification, the criteria are ranked according to significance based on specificity for the presence of APS. Thus, for example, in the obstetric criteria, the occurrence of  $\geq 3$  consecutive pregnancy losses before week 10 of gestation is scored with one point and is

**Table 1.** Comparison of criteria for antiphospholipid syndrome according to the modified Sapporo and ACR/EULAR classifications

| Modified Sapporo criteria (2006)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | ACR/EULAR criteria (2023)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Clinical criteria</p> <ol style="list-style-type: none"> <li>Thrombosis (any organ or tissue) <ol style="list-style-type: none"> <li>Arterial</li> <li>Venous</li> <li>Small vessels</li> </ol> </li> <li>Pregnancy morbidity <ol style="list-style-type: none"> <li><math>\geq 3</math> miscarriages before week 10 of gestation</li> <li>Unexplained death of a morphologically normal fetus at <math>\geq 10</math> weeks of gestation</li> <li><math>\geq 1</math> birth of a morphologically normal neonate <math>&lt; 34</math> weeks of gestation, due to: (i) eclampsia or severe preeclampsia or (ii) placental insufficiency</li> </ol> </li> </ol> | <p>Clinical criteria</p> <ol style="list-style-type: none"> <li>Macrovascular venous thromboembolism (VTE) <ol style="list-style-type: none"> <li>VTE with other high-risk VTE profile: 1 point</li> <li>VTE without other high-risk VTE profile: 3 points</li> </ol> </li> <li>Macrovascular arterial thrombosis <ol style="list-style-type: none"> <li>Arterial thrombosis with high-risk CVD profile: 2 points</li> <li>Arterial thrombosis without high-risk CVD profile: 4 points</li> </ol> </li> <li>Microvascular thrombosis <ol style="list-style-type: none"> <li>Livedo racemosa, livedoid vasculopathy, aPL nephropathy, pulmonary hemorrhage (suspected: 2 points; confirmed: 5 points)</li> <li>Confirmed adrenal hemorrhage/microvascular myocardial disease: 5 points</li> </ol> </li> <li>Obstetric complications <ol style="list-style-type: none"> <li><math>\geq 3</math> consecutive prefetal (<math>&lt; 10</math> weeks of gestation) and/or early fetal death (10 – 15 weeks + 6 days of gestation): 1 point</li> <li>Fetal death (16 – 33 weeks + 6 d of gestation) in the absence of severe preeclampsia or severe placental insufficiency: 1 point</li> <li>Severe preeclampsia (<math>&lt; 34</math> weeks of gestation) or severe placental insufficiency (<math>&lt; 34</math> weeks of gestation) with/without fetal death: 3 points</li> <li>Severe preeclampsia (<math>&lt; 34</math> weeks of gestation) and severe placental insufficiency (<math>&lt; 34</math> weeks of gestation) with/without fetal death: 4 points</li> </ol> </li> <li>Cardiac valves <ol style="list-style-type: none"> <li>Thickening: 2 points</li> <li>Vegetation: 4 points</li> </ol> </li> <li>Hematological criteria <ol style="list-style-type: none"> <li>Thrombocytopenia: 2 points</li> </ol> </li> </ol> |
| <p>Laboratory criteria</p> <ol style="list-style-type: none"> <li>Persistently positive LAC test and/or</li> <li>Persistently positive IgG/IgM aCL antibodies (at medium or high ELISA titer, i.e., <math>&gt; 40</math> GPL or MPL, i.e., higher than the 99<sup>th</sup> percentile for the general population) and/or</li> <li>Persistently positive IgG or IgM isotype anti-<math>\beta_2</math> GPI antibodies in a titer higher than the 99<sup>th</sup> percentile for the general population</li> </ol>                                                                                                                                                  | <p>Laboratory criteria</p> <ol style="list-style-type: none"> <li>Positive LAC test: <ol style="list-style-type: none"> <li>On one occasion: 1 point</li> <li>Persistently: 5 points</li> </ol> </li> <li>Persistently positive aCL and/or a<math>\beta_2</math>GPI antibodies <ol style="list-style-type: none"> <li>Moderate or high titer of IgM aCL and/or a<math>\beta_2</math>GPI: 1 point</li> <li>Moderately elevated titer (40 – 79 U/ml) of IgG aCL and/or a<math>\beta_2</math>GPI antibodies: 4 points</li> <li>High titer (<math>\geq 80</math> U/ml) of IgG aCL or a<math>\beta_2</math>GPI antibodies: 5 points</li> <li>High titer (<math>\geq 80</math> U/ml) of IgG aCL and a<math>\beta_2</math>GPI antibodies: 7 points</li> </ol> </li> </ol>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <p><b>Diagnosis:</b> At least one clinical criterion and at least one laboratory criterion.<br/>Clinical and laboratory criteria must be detected within five years of each other</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | <p><b>Diagnosis:</b> The single highest-scoring feature from each domain is added up. APS is classified as <math>\geq 3</math> points in clinical domains and <math>\geq 3</math> points in laboratory domains.<br/>Clinical and laboratory criteria must be detected within three years of each other.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

čajno smanjuje senzitivnost u prepoznavanju APS-a, odnosno povećava verovatnoća neprepoznavanja bolesti kod pojedinačnog bolesnika. U **Tabeli 1** su uporedno prikazani kriterijumi za prepoznavanje APS-a po revidiranoj Sapporo i novoj ACR/EULAR klasifikaciji.

## TROMBOZA VELIKIH KRVNIH SUDOVA

Za razliku od urođene trombofilije, tromboze udružene sa aPL antitelima se mogu javiti u bilo kom delu cirkulatornog sistema, odnosno u venama, arterijama i mikrocirkulaciji. Tromboze dubokih vena donjih ekstremiteta, sa ili bez trombozne embolije pluća, predstavljaju najtipičniju kliničku manifestaciju antifosfolipidnog sindroma. U jednoj meta-analizi je pokazano da se kod približno 10% bolesnika sa trombozom dubokih vena može dokazati prisustvo aPL antitela [13]. Bolesnici sa trombozom i aPL antitelima su u visokom riziku od recidiva tromboze nakon obustavljanja antikoagulantne terapije, a mortalitet kod ovih osoba u toku četvorogodišnjeg praćenja je bio značajno veći u odnosu na osobe sa trombozom ali bez aPL antitela [14].

Infarkt mozga i tranzitorni ishemični atak (TIA) predstavljaju najčešće manifestacije tromboze arterija kod bolesnika sa APS-om [15]. Veza između infarkta mozga i prisustva aPL antitela je snažnija kod mlađih nego kod starijih osoba, a moguće je da i etnički faktori imaju važnu ulogu, pri čemu je infarkt mozga posebno čest kod bolesnika azijskog porekla. U jednoj japanskoj studiji, 61% bolesnika sa APL sindromom prezentovalo je infarktom mozga. Treba imati na umu da infarkt mozga ili tranzitorni ishemični atak može biti i posledica embolizacije sa izmenjenih aortalnih ili mitralnih ventila, što nije redak nalaz kod bolesnika sa aPL antitelima.

Infarkt srca nije česta manifestacija antifosfolipidnog sindroma. U jednoj novijoj studiji, prisustvo aPL antitela je nađeno kod 11% od ukupno 805 konsekutivnih bolesnika sa prvim infarktom srca mlađih od 75 godina i kod 1% od ukupno 805 zdravih osoba [16]. Pored toga, pokazano je da prisustvo antifosfolipidnih antitela povećava rizik od rekurentnog ishemijskog događaja kod bolesnika koji imaju koronarnu bolest [17].

## PATOLOGIJA TRUDNOĆE

Komplikacije u trudnoći su česta manifestacija prisustva aPL antitela kod žena u reproduktivnom dobu. Najčešće ali najmanje specifične obstetričke manifestacije su ponavljani gubici ploda pre desete nedelje gestacije. Kasniji gubici ploda kao i insuficijencija posteljice koja uzrokuje porođaj pre 34. nedelje trudnoće znatno snažnije sugerišu prisustvo aPL antitela. Kod žena sa aPL antitelima povećan je rizik abrupcije posteljice i pojave sindroma karakterisanog hemolizom,

less significant than severe placental insufficiency before week 34 of gestation, which is scored with four points. A definitive diagnosis is obtained by summing up the points of individual clinical and laboratory criteria, whereby at least three clinical and three laboratory points are necessary for a definitive diagnosis of APS. The primary goal of the ACR/EULAR classification is to improve the specificity in detecting APS, in order to form more homogeneous groups of patients for clinical studies. However, in this way, the sensitivity in recognizing APS is significantly reduced, i.e., the probability of not recognizing the disease in an individual patient increases. **Table 1** compares the criteria for detecting APS according to the revised Sapporo and the new ACR/EULAR classification.

## THROMBOSIS OF LARGE BLOOD VESSELS

Unlike congenital thrombophilia, thrombosis associated with aPL antibodies can occur in any part of the circulatory system, i.e., in the veins and arteries, and as microvascular thrombosis. Deep vein thrombosis of the lower extremities, with or without pulmonary embolism, is the most typical clinical manifestation of the antiphospholipid syndrome. In one meta-analysis, it was shown that the presence of aPL antibodies can be detected in approximately 10% of patients with deep vein thrombosis [13]. Patients with thrombosis and aPL antibodies are at high risk of thrombosis recurrence after anticoagulant therapy is discontinued. The mortality in such patients was shown to be significantly higher, as compared to people with thrombosis but without aPL antibodies, during a four-year follow-up [14].

Cerebral infarction and transient ischemic attack (TIA) are the most common manifestations of arterial thrombosis in patients with APS [15]. The association between cerebral infarction and the presence of aPL antibodies is stronger in younger people than in older people, and it is possible that ethnic factors also play an important role, whereby cerebral infarction is especially common in patients of Asian descent. In a Japanese study, 61% of patients with APL syndrome presented with cerebral infarction. It should be noted that cerebral infarction or transient ischemic attack can also be the consequence of embolization originating from malformed aortic or mitral valves, which is not a rare finding in patients with aPL antibodies.

Myocardial infarction is not a common manifestation of the antiphospholipid syndrome. In a recent study, the presence of aPL antibodies was found in 11% of a total of 805 consecutive patients younger than 75 years who had suffered their first myocardial infarction and in 1% of a total of 805 healthy individuals [16]. In addition, it has been shown that the presence of anti-

porastom jetrenih enzima i trombocitopenijom odnosno HELLP sindroma (*Hemolysis, Elevated Liver enzyme levels, and Low Platelet levels – HELLP syndrome*).

Interesantno je da značajan broj žena sa aPL antitelima pokazuje izrazitu sklonost ka obstetričnim komplikacijama bez ispoljavanja sklonosti ka trombozi pa neki autori koriste termine „obstetrični APL sindrom“ i „trombotični APL sindrom“, ali još uvek nema jasnih patofizioloških kriterijuma za ovakvu podelu [18].

## TROMBOZA U MIKROCIRKULACIJI

Tromboza sitnih krvnih sudova u različitim organima se javlja kod približno 12% bolesnika sa APS-om i ređa je u odnosu na trombozu arterija i vena [19]. Najčešće se dokazuje patohistološkim pregledom i dominantan je nalaz kod bolesnika sa katastrofičnim antifosfolipidnim sindromom. Može se ispoljiti u velikom broju organa ali su najčešće zahvaćeni koža i bubrezi. U koži se mikrotromboze mogu javiti kao livedoidna vaskulopatija, superficijalna gangrena, subakutni nodusi ili ekhimoza. U srcu i mozgu mikrotromboze mogu rezultovati mikrotrombima i mikroinfarktima dok u plućima mogu rezultovati alveolarnom hemoragijom ili akutnim respiratornim distres sindromom. Mikrotromboze u bubrezima se ispoljavaju kao akutna bubrežna insuficijencija, hipertenzija ili trombotična mikroangiopatija. Infarkti creva, jetre, slezine ili pankreasa mogu biti manifestacije tromboze sitnih krvnih sudova u ovim organima. Do formiranja tromba može doći i u sitnim sudovima retine sa znacima retinalne vaskulopatije.

## KOŽNE LEZIJE KOD BOLESNIKA SA APL ANTITELIMA

Koža je često zahvaćena kod bolesnika sa prisutnim aPL antitelima. *Livedo reticularis* je načešća kožna promena kod bolesnika sa APS-om i prisutan je kod približno 24% bolesnika sa ovom bolešću. Njegovo prisustvo bi trebalo redovno da pobudi sumnju na APS, mada zbog male specifičnosti, *livedo reticularis* nije uvršten u kliničke kriterijume APS-a prema novoj ACR/EULAR klasifikaciji [15]. Kod nekih bolesnika, aPL antitela su udružena sa ulceracijama na potkolenicama, gangrenom distalnih delova prstiju i pseudovaskulitisom. Interesantno je da se prisustvo aPL antitela može naći kod približno 50% bolesnika sa tzv. Snedonovim sindromom koji podrazumeva postojanje promena na koži po tipu *livedo racemosa* i ponavljanih TIA ili infarkta mozga. *Livedo racemosa* je po morfološkim karakteristikama sličan *livedo reticularis*-u i predstavlja ljubičastu, simetričnu, mrežastu šaru na koži trupa koja ne iščezava pri zagrevanju kože. Kod značajnog procenta bolesnika sa Snedonovim sindromom, prisutni su i arterijska hipertenzija i valvularne mane srca [20].

phospholipid antibodies increases the risk of recurrent ischemic events in patients with coronary disease [17].

## PREGNANCY PATHOLOGY

Complications in pregnancy are a frequent manifestation of the presence of aPL antibodies in women of reproductive age. The most common but least specific obstetric manifestation is repeated pregnancy loss before week ten of gestation. Later fetal losses as well as placental insufficiency causing delivery before week 34 of pregnancy strongly indicate the presence of aPL antibodies. In women with aPL antibodies, there is an increased risk of placental abruption and the development of HELLP syndrome (*Hemolysis, Elevated Liver enzyme levels, and Low Platelet levels*).

Interestingly, a significant number of women with aPL antibodies show a marked tendency towards obstetric complications without manifesting a tendency to thrombosis, so some authors use the terms “obstetric APL syndrome” and “thrombotic APL syndrome”, but there are still no clear pathophysiological criteria for this categorization [18].

## THROMBOSIS IN THE MICROCIRCULATION

Small blood vessel thrombosis in various organs occurs in approximately 12% of patients with APS and is less common than arterial and venous thrombosis [19]. It is most often proven with pathohistological examination and is the dominant finding in patients with catastrophic antiphospholipid syndrome. It can manifest in many organs, but the skin and kidneys are most often affected. In the skin, microthrombosis can occur as livedoid vasculopathy, superficial gangrene, subacute nodules, or ecchymosis. In the heart and brain, microthrombosis can result in microthrombi and microinfarcts, while, in the lungs, it can result in alveolar hemorrhage or acute respiratory distress syndrome. Microthrombosis in the kidneys manifests as acute renal failure, hypertension, or thrombotic microangiopathy. Infarctions of the intestine, liver, spleen, or pancreas can be manifestations of small blood vessel thrombosis in these organs. Thrombus formation can also occur in the small vessels of the retina with signs of retinal vasculopathy.

## SKIN LESIONS IN PATIENTS WITH APL ANTIBODIES

In patients with aPL antibodies, the skin is often affected. *Livedo reticularis* is the most common skin change in patients with APS and is present in approximately 24% of patients with this disease. This is why its presence should always raise suspicion of APS. However, due to low specificity, *livedo reticularis* is not included in the clinical criteria of APS according to the new ACR/

## KARDIOLOŠKE MANIFESTACIJE

Promene na srčanim zaliscima, u smislu zadebljanja valvula, disfunkcije zaliska ili prisustva vegetacija mogu se naći kod približno 14% bolesnika sa APS-om [15]. Kod bolesnika sa sistemskim eritemskim lupusom (SEL) i antifosfolipidnim antitelima, promene na valvulama su češće nego kod bolesnika bez SEL-a. U najnovijoj ACR/EULAR klasifikaciji, promene na srčanim zaliscima su uvrštene kao klinički kriterijum u prepoznavanju APS-a.

## HEMATOLOŠKE MANIFESTACIJE

Trombocitopenija je najčešći hematološki nalaz kod bolesnika sa APS-om, koji zbog svoje nespecifičnosti nije bio prepoznat kao kriterijum u revidiranoj Sapporo klasifikaciji. Broj trombocita ispod  $100 \times 10^9/L$  je prisutan kod približno 30% bolesnika sa APS-om, pri čemu je veća učestalost trombocitopenije kod bolesnika sa sekundarnim APS-om nego kod onih sa primarnim APS-om. Trombocitopenija je najčešće umerenog stepena sa brojem trombocita  $50 - 100 \times 10^9/L$ . Interesantno je da se prisustvo aPL antitela može dokazati kod približno 40% bolesnika sa primarnom imunološkom trombocitopenijom, bez drugih kriterijuma za APS [15]. Autoimuna hemolizna anemija se može naći kod oko 10% bolesnika sa APS-om. Nalaz neimunološke hemolizne anemije kod bolesnika sa APS-om može ukazivati na mehaničku hemolizu u okviru katastrofičnog antifosfolipidnog sindroma.

## BUBREŽNE MANIFESTACIJE

Bubrežne manifestacije, u formi nefropatije koja prati APS, uglavnom su posledica trombotične mikroangiopatije. Najčešće se ispoljavaju u vidu arterijske hipertenzije, nefrotskog sindroma ili češće subnephrotske proteinurije i bubrežne insuficijencije. Pri patohistološkom pregledu se uočavaju hiperplazija i fibroza intime, fokalna kortikalna atrofija i okluzije sitnih arterija [21].

## MANIFESTACIJE CENTRALNOG NERVNOG SISTEMA

Pored tranzitornog ishemičnog ataka, infarkta mozga i tromboze venskih sudova mozga, koji ulaze u klasifikacione kriterijume i po revidiranoj Sapporo i po ACR/EULAR klasifikaciji, prisustvo antifosfolipidnih antitela može biti udruženo sa epilepsijom, migrenom i horeom. U retke manifestacije spadaju i amaurosis fugax i transverzni mijelitis [12].

## KATASTROFIČNI ANTIFOSFOLIPIDNI SINDROM

Akutna egzacerbacija protrombogenog stanja u krvi sa pojavom mikrotromboza u većem broju organa kod bolesnika sa aPL antitelima naziva se katastrofični APS.

EULAR klasifikacija [15]. In some patients, aPL antibodies are associated with leg ulcers, gangrene of the distal parts of the fingers, and pseudovasculitis. Interestingly, the presence of aPL antibodies can be found in approximately 50% of patients with the so-called Sneddon syndrome, which implies the existence of livedo racemosa-type skin changes and repeated TIA or brain infarction. Livedo racemosa is morphologically similar to livedo reticularis and is a purple, symmetrical, net pattern on the skin of the trunk that does not disappear when the skin is warmed up. In a significant percentage of patients with the Sneddon syndrome, arterial hypertension and valvular heart defects are also present [20].

## CARDIOLOGICAL MANIFESTATIONS

Malformations of heart valves, in terms of valve thickening, valve dysfunction, or the presence of vegetation can be found in approximately 14% of patients with APS [15]. In patients with systemic lupus erythematosus (SEL) and antiphospholipid antibodies, valve pathology is more common than in patients without SEL. In the latest ACR/EULAR classification, heart valve malformations are included as clinical criteria for recognizing APS.

## HEMATOLOGICAL MANIFESTATIONS

Thrombocytopenia is the most common hematological finding in patients with APS, which, due to its non-specificity, was not recognized as a criterion in the revised Sapporo classification. A platelet count below  $100 \times 10^9/L$  is present in approximately 30% of patients with APS, with a higher frequency of thrombocytopenia in patients with secondary APS than in those with primary APS. Thrombocytopenia is most often moderate with a platelet count of  $50 - 100 \times 10^9/L$ . Interestingly, the presence of aPL antibodies can be demonstrated in approximately 40% of patients with primary immune thrombocytopenia, without other criteria for APS [15]. Autoimmune hemolytic anemia can be found in about 10% of patients with APS. The finding of non-immunological hemolytic anemia in patients with APS may indicate mechanical hemolysis as a part of catastrophic antiphospholipid syndrome.

## RENAL MANIFESTATIONS

Renal manifestations, in the form of nephropathy accompanying APS, are mainly the result of thrombotic microangiopathy. They most often manifest as arterial hypertension, nephrotic syndrome, or, more commonly, subnephrotic proteinuria and renal insufficiency. Hyperplasia and fibrosis of the intima, focal cortical atrophy, and occlusion of small arteries are observed during pathohistological examination [21].

Javlja se kod približno 1% bolesnika sa APS-om i najčešće ga pokreću pojava infekcije, hirurške ili druge invazivne procedure ili prekid u primeni antikoagulantne terapije. Katastrofični APS karakteriše brzo nastupajuća insuficijencija većeg broja organa, pri čemu je najčešće kompromitovana funkcija pluća (24% bolesnika), centralnog nervnog sistema (18% bolesnika) i bubrega (18% bolesnika) [22]. Katastrofični APS predstavlja životno ugrožavajuće stanje i, uprkos primeni terapije, smrtnost kod ove bolesti je još uvek oko 30%.

## ZAKLJUČAK

Antifosfolipidna antitela su udružena sa širokim spektrom kliničkih manifestacija u gotovo svim medicinskim oblastima. Različite forme tromboze i pojava komplikacija u trudnoći su najtipičnije manifestacije i predstavljaju kliničke kriterijume za utvrđivanje postojanja antifosfolipidnog sindroma kod osoba sa aPL antitelima. S druge strane, povezanost aPL antitela i brojnih drugih kliničkih manifestacija koje ne predstavljaju zvanične kriterijume u klasifikaciji APS-a nije uvek jasna i konzistentna. Međutim, prepoznavanje ovih manifestacija ipak ima veliki značaj jer skreće pažnju na moguće prisustvo aPL antitela i daje povod za temeljno ispitivanje prisustva drugih laboratorijskih i kliničkih kriterijuma za postojanje antifosfolipidnog sindroma. Iako je najnovija klasifikacija APS-a preporučena od strane ACR/EULAR usvojila dodatne kliničke kriterijume koji nisu postojali u prethodnoj klasifikaciji, treba imati u vidu da su sve trenutno važeće preporuke za lečenje APS-a donete na osnovu prethodnih, tzv. revidiranih Sapporo kriterijuma. Zbog toga, klasifikacione ACR/EULAR kriterijume, koji su prevashodno namenjeni za selekciju bolesnika u kliničkim studijama, za sada ne treba koristiti pri postavljanju dijagnoze antifosfolipidnog sindroma kod pojedinačnih bolesnika u svakodnevnoj praksi.

## SKRAĆENICE:

aPL antitela – antifosfolipidna antitela (engl. *antiphospholipid antibodies*)  
APS – antifosfolipidni sindrom (engl. *antiphospholipid syndrome*)  
ACR/EULAR – engl. *American College of Rheumatology/European Alliance of Associations for Rheumatology*  
SEL – sistemski eritemski lupus  
LAC – engl. *lupus anticoagulant*  
ELISA – enzimski imunosorbentni esej (*enzyme-linked immunosorbent assay*)  
aCL antitela – antikardiolipinska antitela (aCL antitela; engl. *anticardiolipin antibodies*)  
β2GPI – beta 2 glikoprotein I  
HELLP sindrom – sindrom karakterisan hemolizom, porastom jetrenih enzima i trombocitopenijom (*Hemolysis, Elevated Liver enzyme levels, and Low Platelet levels – HELLP syndrome*)  
TIA – tranzitorni ishemični atak

**Sukob interesa:** Nije prijavljen.

## CENTRAL NERVOUS SYSTEM MANIFESTATIONS

In addition to transient ischemic attack, cerebral infarction, and cerebral venous thrombosis, which are included in the classification criteria of both the revised Sapporo and ACR/EULAR classifications, the presence of antiphospholipid antibodies may be associated with epilepsy, migraine, and chorea. Rare manifestations include amaurosis fugax and transverse myelitis [12].

## CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME

Acute exacerbation of the prothrombotic state in the blood with the appearance of microthrombosis in multiple organs in patients with aPL antibodies is called catastrophic APS. It occurs in approximately 1% of patients with APS and is most often triggered by an infection, surgical or other invasive procedures, or discontinuation of anticoagulant therapy. Catastrophic APS is characterized by rapidly occurring failure of multiple organs, with the lung function being the one most commonly compromised (24% of patients), followed by the central nervous system (18% of patients), and the kidneys (18% of patients) [22]. Catastrophic APS is a life-threatening condition and, despite the administration of therapy, mortality in this disease is still around 30%.

## CONCLUSION

Antiphospholipid antibodies are associated with a wide range of clinical manifestations in almost all medical fields. Various forms of thrombosis and the development of complications in pregnancy are the most typical manifestations and represent clinical criteria for determining the presence of antiphospholipid syndrome in persons with aPL antibodies. On the other hand, the association of aPL antibodies with numerous other clinical manifestations that do not represent official criteria in the classification of APS is not always clear and consistent. However, recognizing these manifestations is still of great significance because it draws attention to the possible presence of aPL antibodies and indicates the need for a detailed analysis of the presence of other laboratory and clinical criteria proving the existence of antiphospholipid syndrome. Although the latest classification of APS recommended by ACR/EULAR adopted additional clinical criteria that did not exist in the previous classification, it should be noted that all currently valid recommendations for the treatment of APS were made based on the previous criteria, i.e., the revised Sapporo criteria. Therefore, the ACR/EULAR classification criteria, which are primarily intended for the selection of patients in clinical stud-

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ies, should not as yet be used in the diagnosis of antiphospholipid syndrome in individual patients in daily practice.

## ABBREVIATIONS AND ACRONYMS:

aPL antibodies – antiphospholipid antibodies  
 APS – antiphospholipid syndrome  
 ACR/EULAR – American College of Rheumatology/European Alliance of Associations for Rheumatology  
 SEL – systemic lupus erythematosus  
 LAC – lupus anticoagulant  
 ELISA – enzyme-linked immunosorbent assay  
 aCL antibodies – anticardiolipin antibodies  
 $\beta_2$ GPI – beta 2 glycoprotein I  
 HELLP syndrome – Hemolysis, Elevated Liver enzyme levels, and Low Platelet levels  
 TIA – transient ischemic attack

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