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Antiphospholipid syndrome (APS) is characterised by arterial and venous thromboembolic events and pregnancy morbidity (mainly, recurrent foetal losses), in the presence of antiphospholipid antibodies. Diagnosis is based on the presence of at least one laboratory and at least one clinical manifestation of antiphospholipid syndrome. There are also so-called “non-criteria” clinical features, and thrombocytopenia is one of the most important among them. Thrombocytopenia has been reported with a prevalence between 30 and 46% among patients with antiphospholipid syndrome. The pathogenesis of thrombocytopenia related to antiphospholipid antibodies is not absolutely clear. Binding of antiphospholipid antibodies to platelets and the promotion of platelet activation and aggregation thus thrombus formation must be an important mechanism as well as the immune-mediated clearance of platelets. Thrombocytopenia in antiphospholipid syndrome is usually mild and does not require clinical intervention. The presence of thrombocytopenia in patients with antiphospholipid syndrome is typically associated not with haemorrhagic complications, rather it can trigger thrombotic events. Other causes of thrombocytopenia, such as TTP, SLE, MDS, and ITP should be excluded. As thrombocytopenia is usually mild and it predicts later thrombosis, patients may be given platelet aggregation inhibitors and/or anticoagulant therapy. Anti-thrombotic treatment should be stopped only in case of severe thrombocytopenia.

Keywords: antiphospholipid syndrome, APS, antiphospholipid antibody, thrombocytopenia, thrombosis, SLE, pregnancy
are generated against different epitopes of the participant of the coagulation system (mainly against phospholipid-binding proteins) that result in thrombosis. These antiphospholipid antibodies are a heterogeneous group of autoantibodies. Lupus anticoagulant (LA), anti-cardiolipin antibodies (ACA) and anti-β2 glycoprotein 1 (β2GPI) are the most important among them [2].

APS may be a secondary disease, as it frequently associates to systemic autoimmune diseases such as SLE and also to malignant lymphoproliferative diseases and chronic hepatic disorders [3]. On the contrary, APS can appear without any underlying disease, and in this case, it is called primary antiphospholipid syndrome.

Neurologic involvement in APS is common and can be manifested by headaches, memory impairment, dizziness, epilepsy and blurred vision, but the most common presentations are transient ischaemic attacks and ischaemic strokes. Some of them are not thrombotic manifestations but are generated by connection of aPL antibodies and an antigen in the nervous system [4].

There is a special form of APS: the obstetric antiphospholipid syndrome (OAPS). It is characterised clinically only by obstetrical morbidity: at least two unexplained miscarriages, three non-consecutive miscarriages, preeclampsia, placental abruption, foetal growth restriction, stillbirth, premature birth, or two or more unexplained in vitro fertilisation failures [5, 6].

Catastrophic antiphospholipid syndrome (CAPS) is rare, but very serious form of APS. The mortality rate is very high. CAPS is characterised by thromboses generating in two or more organs in a few days. That leads to infarction and necrosis of the affected tissues causing multiple organ failures [7].

Standard care for thrombotic APS is indefinite anticoagulation with a vitamin K antagonist [8]. There is currently insufficient evidence to recommend the routine use of direct oral anticoagulants (DOAC) in thrombotic APS [9].

The 13th Task Force recommendation for primary thromboprophylaxis in APS supports the use of aspirin [10]. A recent meta-analysis conducted on a total of 1208 asymptomatic patients with persistently positive aPL has shown that low-dose aspirin (LDA) is associated with significant risk reduction in arterial but not in venous thrombosis when compared to placebo [11]. Aspirin with low molecular weight or unfractionated heparin may reduce the incidence of pregnancy loss in obstetric APS [12]. Aspirin alone is advised for treating patients with aPL-associated stroke or acute myocardial infarction [13].

Treatment regimens of APS further include hydroxychloroquine, statins, B-cell inhibitors, complement inhibitors, blocking of aPL/B2 GPI receptors on target cells and tissue factor inhibitors [14].

A combined therapy of anticoagulation, glucocorticoids, plasma exchange and intravenous immunoglobulin (especially in the presence of infection) can be used in complicated cases of multiorgan failure due to thrombosis as in CAPS. Cyclophosphamide can also be used in CAPS in the presence of secondary autoimmune disease such as SLE [15]. Rituximab can also be used in refractory cases after failure or inability to take the above-mentioned combined therapies or in the presence of micro-angiopathic haemolytic anaemia [16].

However, the majority of aPL-positive patients do not have thrombosis. That is why the stereotypical treatment for APS patients should be avoided and stratification of the thrombotic
risks is important as aPLs are prevalently observed in various diseases or elderly population. Current risk-stratification tools are largely limited to the antiphospholipid antibody profile and traditional thrombotic risk factors.

Novel biomarkers that correlate with disease activity and potentially provide insight into future clinical events include domain 1 specific anti-β2GPI antibodies, antibodies to other phospholipids, or phospholipid-protein complexes (such as antiphosphatidylserine/prothrombin antibodies (aPS/PT)), and functional/biological assays such as thrombin generation, complement activation, levels of circulating microparticles, and annexin A5 resistance [17].

Clinical risk scores (antiphospholipid score (aPL-S) and the Global Anti-phospholipid Syndrome Score [GAPSS]) may also have value in predicting clinical events [18].

2. Diagnosis of APS

Diagnosis of APS is based on the Sapporo criteria (proposed in 1999 and updated in 2006 after a conference in Sydney, Australia) [19].

These include at least one clinical and at least one laboratory manifestation of APS. Clinical criteria include objectively confirmed venous, arterial, or small vessel thrombosis, and/or obstetric morbidity including recurrent miscarriage, stillbirth, or intrauterine growth retardation.

The laboratory criteria require demonstration of a persistent presence of lupus anticoagulant (LA), anti-cardiolipin (ACA) or anti-2GPI antibody (IgG or IgM). Antiphospholipid antibody positivity can be stated if at least one of these antibodies could be detected twice, 12 weeks apart. LA is measured by the help of coagulation tests, while ACA and anti-β2glycoprotein 1 (aβ2GPI) are determined by means of ELISA. LA results are expressed as qualitative data and only strong positivity carries clinical significance. In case of ACA and aβ2GPI, antibody medium/high titres of IgM and/or IgG subtype have important clinical value (Table 1).

Clinical symptoms of APS include thrombosis in any blood vessel of any organ. Typically, thrombosis may recur and can present both in arteries and in veins. Anti-phospholipid antibodies represent the strongest thrombophilic factors, mainly LA.

Although thrombosis due to APS does not differ from thrombosis caused by any other factors, some other symptoms and signs may accompany to the elevated blood clotting: for example, if a patient presents with thrombosis and also has livedo reticularis, it is very likely that thrombosis is a manifestation of APS.

Besides, there are only a few situations when arterious and venous thrombosis present on the same patient. This and the recurrence of the thrombotic event is very likely refers to APS.

There are the so-called “non-criteria” clinical features of APS, such as livedo reticularis, cardiac valve disease, haematological manifestations (thrombocytopenia and haemolytic anaemia), nephropathy and neurological manifestations (migraine, chorea and epilepsy).

Non-criteria manifestations mean that the presence of these characteristic features of the disease is not a requisite of the diagnosis, or with other words, they are not the sine qua non of the diagnosis.
Thrombocytopenia is the most relevant non-criteria manifestation of APS. However, despite the pro-thrombotic nature of APS, thrombocytopenia is one of the most common non-criteria findings of the disease. Recently, thrombocytopenia is proposed to be a diagnostic clinical criterion of APS.

In case of OAPS several disease processes may occur in the placentae of women with antiphospholipid syndrome due to the antiphospholipid autoantibodies, not only thrombosis and infarction, but also inflammatory events, mediated by cytokine release, complement activation, angiogenic imbalance and activation of immune cells [20].

### 3. Epidemiology of APS

Presence of aPL Abs per se does not guarantee a patient will develop APS as only 8.1% of patients with aPL antibodies without a history of clinical thrombosis developed thrombosis during a 5-year follow-up period, suggesting that a patient needs an additional insult to develop the clinical disease [21, 22]. The prevalence of the antibodies increases with age [23].

Forty percent of patients with APS have SLE. The prevalence of ACA in SLE is from 12 to 30%, and LA is found in 5–34%. From the patients with SLE and aPL antibodies 50–70% progress to APS.

The incidence of the APS is around five new cases per 100,000 persons per year, and the prevalence is around 40–50 cases per 100,000 persons [24].

The aPLs are positive in approximately 13% of patients with stroke, 11% with myocardial infarction, 9.5% of patients with deep vein thrombosis and 6% of patients with pregnancy morbidity [16]. These data can underline the significance of APS.

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**Table 1. Revised classification criteria for antiphospholipid syndrome [19].**

<table>
<thead>
<tr>
<th>Vascular thrombosis</th>
<th>≥1 clinical episode of arterial, venous or small vessel thrombosis. Thrombosis must be objectively confirmed. For histopathological confirmation, thrombosis must be present without inflammation of the vessel wall.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy morbidity</td>
<td>≥1 unexplained death of a morphologically normal foetus ≥10 weeks of gestation ≥1 premature delivery of a morphologically normal foetus &lt;34 weeks of gestation because of:</td>
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<tr>
<td>▪ severe preeclampsia or eclampsia defined according to standard definition; ▪ recognised features of placental insufficiency, ≥3 unexplained consecutive miscarriages &lt;10 weeks of gestation, with maternal and paternal factors (anatomic, hormonal or chromosomal abnormalities) excluded</td>
<td></td>
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Laboratory criteria: Presence of antiphospholipid antibodies (aPLs), on two or more occasions at least 12 weeks apart and no more than 5 years prior to clinical manifestations, as demonstrated by ≥1 of the following:

- Lupus anticoagulant.
- Medium to high-titre (>40 GPL or MPL, or >99th percentile) anticardiolipin IgG or IgM.
- Anti-β2 glycoprotein-I (anti-β2GPI) IgG or IgM >99th percentile.
According to another study, patients with cerebrovascular events who are less than 50 years old have shown 17.4% prevalence of positive aPL with five times increase in the risk of ischaemic stroke [25].

Thrombocytopenia is the most common non-criteria hematologic manifestation of APS. It has been reported with prevalence between 30 and 46% among APS patients [26].

There is a difference between primary and secondary APS patients in respect of the frequency of thrombocytopenia: in Euro-Phospholipid project, the frequency of thrombocytopenia in patients with PAPS was 21%, while it was 41.9% in patients with secondary APS [27].

4. Role of platelets in APS

Platelets play a key role in APS-related thrombosis due to the presence of multiple receptors that can interact with anti-β2-GPI antibodies (especially apolipoprotein E receptor 2' (apoER2') and glycoprotein Ibα (GPIbα)) with consequent release of different pro-coagulant mediators such as thromboxane B2, platelet factor 4 (PF4) and platelet factor 4 variant (CXCL4L1) [28].

In case of APS, thrombosis results from a hypercoagulable state caused by activation of endothelial cells, monocytes and platelets. It has been demonstrated that platelets are required for enhanced activation of the endothelium and fibrin generation by the anti-β2GP1 autoantibody/β2GP1 complex. Thus, the first event is the activation of thrombocytes, endothelial cells are activated indirectly [29].

Platelet activation, a major contributing factor of arterial thrombosis in APS, might play a role in APS-related thrombosis in at least two ways:

First, due to the presence of multiple receptors that can interact with antibodies, platelets can facilitate the dimerisation of β2-GPI enhancing the coagulation response.

Second, platelets provide a surface for coagulation reactions [30].

The role of thrombocytes in the pathogenesis of APS is supported by the fact that circulating platelet- and endothelial-derived microparticle level are elevated in patients with primary APS [31].

Mouse models of APS have shown that platelets are the first target for circulating anti-β2-GPI-β2-GPI complexes, and the enhancement of endothelium activation is also platelet thrombus-dependent [29].

5. About thrombocytopenia in general

The normal value of platelet count is between 150 and 300 × 10^9/L. Platelet number between 100 and 150 × 10^9/L is considered as normal in some studies. That may be the cause of some controversial research data. Decreased thrombocyte number might be present because of
several reasons. The two main categories are the decreased thrombopoiesis in the bone marrow and the increased destruction of platelets in the peripheral blood [32].

Consequences depend on the degree of thrombocytopenia: under 20 \( \times 10^9/L \) it is considered severe, between 20 and 50 \( \times 10^9/L \) moderate and above 50 \( \times 10^9/L \) mild thrombocytopenia [33].

It is not only the number but also the thrombocyte function has a great importance in respect of consequences of thrombocytopenia: even a few thrombocytes can provide a satisfactory performance if the underlying disease does not diminish thrombocyte function. For example, in case of acute leukaemia patient may have bleeding even with a higher platelet number than that patient with immune thrombocytopenic purpura (ITP) who will be fine with a much lower thrombocyte count.

In case of the so-called consumptive thrombocytopenia, the basic phenomenon is the activation of platelets. Activation leads to thrombosis generation, factors of blood coagulation such as platelets are utilised and the thrombocyte number will decrease. As a secondary process bleeding occurs (Table 2).

### 6. Thrombocytopenia in APS

Thrombocytopenia is frequently found in patients with the APS and is usually mild (70–120 \( \times 10^9/L \)) and benign, with no intervention required. In a few cases it can be severe and aggressive treatment may be required. Low platelet counts usually appear associated with other APS manifestations, but sometimes it may be the only sign of APS [35].

The same working group has compared the frequency of thrombocytopenia in different subgroups of APS. They found no differences in the occurrence of low platelet number in patients with primary or secondary APS [35].

Thrombocytopenia is a frequent phenomenon of SLE. Increased concentrations of aPL antibodies have been found to be common in patients not only with SLE, but also with immune

<table>
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<tr>
<th>Table 2. Mechanisms of thrombocytopenia in antiphospholipid antibody (aPL)-positive patients [34].</th>
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<tr>
<td><strong>Increased platelet activation and destruction</strong></td>
</tr>
<tr>
<td>Immune-mediated (aPL-related, secondary ITP)</td>
</tr>
<tr>
<td>Thrombotic microangiopathy (CAPS, HELLP syndrome, HUS, TTP)</td>
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<tr>
<td>Drug-induced (e.g., heparin)</td>
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<td><strong>Decreased platelet production</strong></td>
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<td>Haemophagocytic syndrome</td>
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<td>Bone marrow necrosis</td>
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<tr>
<td>Increased platelet pooling</td>
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<tr>
<td>Pseudothrombocytopenia</td>
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</table>

CAPS: catastrophic antiphospholipid syndrome; HELLP: hemolysis, elevated liver enzymes, and low platelet count; aHUS: atypical hemolytic uremic syndrome; TTP: thrombotic thrombocytopenic purpura.
thrombocytopenic purpura (ITP). No clinical significance or role in mechanisms of thrombocytopenia of aPL antibodies was found [36]. In an earlier study, about 30% of ITP patients had a positive aCL test at the time of diagnosis [37]. In case of Evans syndrome (thrombocytopenia and haemolytic anaemia) aPL autoantibodies are also frequently present.

7. Pathogenesis of thrombocytopenia in APS

The pathogenesis of thrombocytopenia related to aPL antibodies is still unclear. It is possibly caused by direct binding of anti-β2-GPI antibodies or anti-β2-GPI-β2-GPI complexes on activated platelets and promotes their aggregation and thrombus formation, so thrombocytopenia is a consequence of consumption of platelets.

On the other hand, thrombocytopenia in APS may be due to immune-mediated clearance of platelets, as in case of ITP [38].

8. Characterisation of thrombocytopenia in APS

Thrombocytopenia in APS is usually mild (70–120 × 10^9/L) and does not require clinical intervention. In most of the cases, the main significance of thrombocytopenia is that it can be a sign, and when noticed it, the presence of aPL antibodies can be found. Severe thrombocytopenia (platelet count <50 × 10^9/L) may be seen in 5–10% of patients [37].

9. Clinical significance of thrombocytopenia in APS

Interestingly, the presence of thrombocytopenia in patients with APS is not typically associated with haemorrhagic complications; rather it can trigger thrombotic events. Even more, it has been proven that the more severe the thrombocytopenia, the higher the probability of future thrombosis.

In a retrospective study 138 patients were enrolled with positive aPL without fulfilling clinical criteria for APS, after a mean follow-up of 146 ± 60.3 months, 29.4% with thrombocytopenia developed thrombosis. They concluded that aPL-positive patients who develop thrombocytopenia have a potential risk of developing thrombosis [39].

Platelet activation plays an essential role in the development of atherosclerosis. In case of arterial thrombosis, the role of platelets is also essential. Continuous platelet activation in patients with APS may be involved, among other factors, in accelerated atherosclerosis. Moreover, atherosclerosis and its thrombotic complications may be mediated by local secretion of molecular effectors embedded or packed into microvesicles from the platelet surface [40].

A fundamental role of platelets and platelet activation in the process of thrombosis generation of APS patients has been supported by several data. These data suggest that aPL antibodies do not interact with circulating platelets in these patients. Instead, anti-β2-GPI-β2-GPI complexes bind exclusively to the platelet thrombus and not to the endothelium, a phenomenon leading
to the amplification of platelet activation [29]. A possible explanation might be that aCL antibodies are able to bind the lipid component of platelet membrane only after platelet activation. In fact, major binding targets are the anionic phospholipids phosphatidyl-serine (PS), phosphatidylinositol (PI), and phosphatidyl-ethanolamine (PE), located in the inner surface of the platelet lipid membrane that becomes exposed and accessible to anti-β2-GPI antibodies after platelet activation.

10. Thrombocytopenia and risk stratification

Among aPL-positive patients, those with a low platelet count developed thrombosis more frequently than those without. Among aPL-negative patients, no difference was found in the predictive value of thrombosis regardless of platelet count [29].

11. Mean platelet volume (MPV) in APS

Beside thrombocytopenia, MCV alterations may have significant importance in APS. Though conformation of data is still lacking, there are evidences that platelets with increased MPV are more active than smaller platelets, with a greater pro-thrombotic potential because of higher levels of intracellular TXA2 and an increased pro-coagulant surface [41]. MPV is largely regarded as a useful surrogate marker of platelet activation [42].

MPV was found to be significantly higher in APS patients, especially in triple positive patients, as compared to controls. Moreover, the level of MPV above 7.4 fl was found to be an independent predictor of thrombosis recurrence in patients with APS [43].

12. Differential diagnosis of thrombocytopenia in APS

Pseudo-thrombocytopenia should be excluded. Presence of fragmentocytes can refer to TTP. The observation of the characteristic “pentad” (fever, microangiopathic anaemia, thrombocytopenia, neurologic abnormalities and renal involvement) may strengthen the diagnosis. Bone marrow examination can show out malignant haematological diseases such as multiple myeloma, or different kind of leukaemia, when there is no place for normal thrombopoiesis.

In case of myelodysplastic syndrome (MDS), there are dysplastic features of the cells of megakaryocytic cell line and also morphological abnormalities of thrombocytes can be observed in the peripheral smear.

Haemolytic anaemia is indicative of secondary APS due to SLE, or Evans syndrome. Otherwise, in case of SLE, not only haemolytic anaemia and thrombocytopenia may be found, but also aPL antibodies, without any clinical symptoms of APS. Other clinical symptoms of the systemic autoimmune disease or a history of thrombosis can help to differentiate, but it is not always an easy task.
Immune-thrombocytopenic purpura (ITP) is the most frequent cause of “megakaryocytic” thrombocytopenia. It is typically an exclusion diagnosis: when we cannot find any other reason of decreased platelet number, and there are megakaryocytes in the bone marrow we consider ITP.

Thrombocytopenia is often experienced in pregnancy, affecting up to 10% of all pregnancies [44]. The causes of pregnancy-specific thrombocytopenia are gestational thrombocytopenia, pre-eclampsia, HELLP syndrome and acute fatty liver of pregnancy. The most common cause of thrombocytopenia in pregnancy is gestational thrombocytopenia (75% of all cases) [45]. It may be difficult to differentiate from ITP, which also presents frequently during pregnancy, mainly in the first and second trimester. However, gestational thrombocytopenia generally causes mild thrombocytopenia, usually >70 × 10^9/L, from the mid-second or third trimester, and is not related to adverse events for the mother and new-born. In some cases, pregnancy might lead to worsening of thrombocytopenia in patients with ITP [46]. This may be caused by the effects of the hormonal milieu of pregnancy on the reticuloendothelial system.

Thrombocytopenia is usually mild during pregnancy and is caused mainly by haemodilution. However, ITP, or SLE, even APS can start during pregnancy. Therefore complete examination of the patient, thorough laboratory checking, detailed medical history and careful follow-up is crucial.

13. How to treat thrombocytopenia in APS?

The first task is to exclude concomitant SLE, or ITP, and ascertain whether thrombocytopenia refers to an increased activation of the coagulation system or an elevated tendency of bleeding. If it has been proven that thrombocytopenia is the manifestation of APS, it might have great importance: it can predict later thrombosis.

As thrombocytopenia is usually mild and if it predicts later thrombosis, usually APS can be treated by standard therapy. Patients can be given platelet aggregation inhibitors and/or anticoagulant therapy. Anti-thrombotic treatment should be stopped only in case of severe thrombocytopenia or bleeding [34].

In the presence of severe thrombocytopenia, rituximab represents a unique drug which can balance the effect of bleeding and thrombosis. By reducing the production of autoantibodies, rituximab can simultaneously raise the platelets and reduce the chance of thrombosis. Rituximab can supersede splenectomy as a second-line therapy in this group of patients [47].

In case of SLE-associated APS, when severe thrombocytopenia is generated by disease activation SLE should be treated with high-dose glucocorticoids, IVIG, immunosuppressive agents and plasma exchange [48, 49].

CAPS is a life-threatening disease that requires very aggressive treatment. The treatment strategy is based on the combination of anticoagulation, glucocorticoids, plasma exchange and/or intravenous immunoglobulin, the so-called triple therapy. In refractory cases or in those with initial life-threatening situation, rituximab may be an effective option [15]. Recently, some cases of CAPS have been effectively treated with the addition of eculizumab to the triple therapy [50].
In case of pregnancy-associated APS, the health of the mother is considered always the more important. If there is a life-threatening situation, the pregnancy must be terminated. Pregnancy itself represents a higher thrombotic risk, so careful anticoagulation is extremely important. On the other hand, bleeding during delivery also should be avoided.

14. Conclusion

Thrombocytopenia may be a symptom of APS. Paradoxically, it refers to an elevated thrombotic tendency, not bleeding risk. The causes of decreased platelet number are complex: antiphospholipid antibodies that bind to platelets activate them and induce thrombosis. Thrombocytes are consumed during this process. On the other hand, thrombocytopenia is the consequence of destruction by immune mechanisms, like in the case of ITP. Sometimes, it might be the only sign of APS.

Diagnosis is not easy; other causes of thrombocytopenia must be excluded by careful examinations. Thrombocytopenia in APS is usually mild and per se does not require any treatment. Patients with or without thrombocytopenia require anticoagulant medication in case of venous thrombotic event while low-dose aspirin or clopidogrel is recommended after arterial thrombosis. For OAPS, the combination of anticoagulant and thrombocyte aggregation inhibitor therapy is advised. CAPS is a life-threatening disease with a rapid progression of multiorgan failure. Even application of high-dose corticosteroids, plasma exchange, intravenous immunoglobulin and complement inhibitor agent mortality is very high.

Abbreviations

- APS antiphospholipid syndrome
- aPL antiphospholipid antibody
- aβ2GPI anti-β2 glycoprotein 1
- ACA anti-cardiolipin antibody
- CAPS catastrophic antiphospholipid syndrome
- DOAC direct oral anticoagulants
- ITP immune thrombocytopenic purpura
- LA lupus anticoagulant
- MDS myelodysplastic syndrome
- OAPS obstetric antiphospholipid syndrome
- SLE systemic lupus erythematoses
- TTP thrombotic thrombocytopenic purpura
Conflict of interest

There is no conflict of interest.

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