Pediatric Antiphospholipid Syndrome
– from Bench to Bedside

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Beograd, 21.5.2010
1. Antiphospholipid antibodies (aPL)
   - Mechanisms of action

2. Antiphospholipid syndrome (APS)
   - Clinical manifestations

3. Specific features of aPL in pediatric population

4. Treatment
Phospholipids and Protein Targets of Antiphospholipid Antibodies

Anionic phospholipids
- Cardiolipin
- Phosphatidylserine
- Phosphatidylinositol
- Phosphatidylglycerol
- Phosphatidylethanolamine

Phospholipid binding proteins
- β2 glycoprotein I
- Prothrombin
- Protein C
- Protein S
- Annexin V
- Low & high MW kininogen
Why study the role of aPL in children?

- Evidence that aPL can be pathogenic rather than a simple serological marker for APS:
  
  
  - antigens recognized by aPL are accessible to circulating antibodies
  - some aPL target molecules are involved in hemostasis
  - passive transfer of aPL in naïve animals can reproduce APS manifestations
  - prospective studies report a close association between aPL and clinical manifestations
Mechanism of action of aPL

- Platelet activation
- Endothelial activation
- Impaired function of activated protein C
- Complement activation
- Promote clot formation
- Impair thrombolysis
Platelets in APS
aPL and the Endothelial Cell
Two-hit hypothesis in APS

- aPL are necessary but not sufficient for inducing the clot - 1st hit

- Thrombus would be triggered by a 2nd hit
  - Infection
  - Immobilization
  - Surgery
  - Systemic autoimmune disease
Injection of aPL+ve IgG does not induce any significant effect in the rat mesenteric microcirculation w/o LPS pre-treatment

(Fischetti et al. *Blood* 2005)
3 hours after i.p.
LPS 2.5 mg/Kg

30-45 min after IgG aPL infusion

(Fischetti et al. *Blood* 2005)
# Antiphospholipid syndrome (APS)

## Classification criteria


| Clinical criteria | 1. Vascular thrombosis  
<table>
<thead>
<tr>
<th></th>
<th>2. Pregnancy morbidity</th>
</tr>
</thead>
</table>

| Laboratory criteria | 1. Lupus anticoagulant in plasma, detected according to the guidelines of the ISTH  
|                    | 2. Anticardiolipin antibody of IgG/IgM isotype in serum or plasma, present in medium or high titer, measured by a standardized ELISA  
|                    | 3. Anti-ß2GPI antibody of IgG/IgM isotype in serum or plasma (in titer > the 99th percentile), measured by a standardized ELISA |

(present on 2 or more occasions at least 12 weeks apart)
Pediatric APS

- Important differences in the clinical spectrum of the APS related to the age at onset of the disease

- Issues unique to the pediatric population
  - absence of common acquired risk factors for thrombosis
  - pregnancy related morbidity not a pediatric problem
  - prevalence of particular disease manifestations
  - differences in cut-off values for determination of aPL
  - increased incidence of infection-induced antibodies
  - specific factors regarding long-term therapy
Antiphospholipid Syndrome

Epidemiology

- Euro APS cohort study of 1,000 consecutive patients with APS
  - 85% of patients diagnosed between ages 15 and 50 years
  - 2.8% of APS cases younger than 15 years

- Cohort studies of unselected children with thrombosis
  - APS considered the most common acquired hypercoagulation state of autoimmune etiology
  - aPL found in 12-25% of unselected children with thrombosis
Pediatric APS Register

- A collaborative project of the:
  - European Forum on Antiphospholipid Antibodies (Euro aPL Forum)
  - Lupus Working Group of Paediatric Rheumatology European Society (PReS)

- An internet-based register that allows multicenter data collection

  http://www.med.ub.es/MIMMUN/FORUM/PEDIATRIC.HTM

Objectives:
- to obtain data on association of aPL with clinical manifestations in childhood
- enable future studies to determine impact of treatment and long-term outcome of pediatric APS
**Inclusion criteria**

- Onset of APS must have occurred prior to the patient’s 18th birthday
- Patient must meet the preliminary criteria for the classification of pediatric APS *(Adapted from: Miyakis S et al. J Thromb Haemost 2006;4:295-306)*

<table>
<thead>
<tr>
<th>Clinical criteria</th>
<th>1. Vascular thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory criteria</td>
<td>1. Lupus anticoagulant in plasma</td>
</tr>
<tr>
<td>(present on 2 or more occasions at least 12 weeks apart)</td>
<td>2. Anticardiolipin antibody of IgG/IgM isotype in blood</td>
</tr>
<tr>
<td></td>
<td>3. Anti-ß2GPI antibody of IgG/IgM isotype in blood</td>
</tr>
</tbody>
</table>

**Exclusion criteria**

- Infants born to mothers with APS
- Infants with congenital thrombophilia
Pediatric Antiphospholipid Syndrome: Clinical and Immunologic Features of 121 Patients in an International Registry


- 121 confirmed pediatric APS cases from 14 countries
  - Argentina, Brazil, Canada, Denmark, Estonia, France, Germany, Israel, Italy, Macedonia, Serbia, Slovenia, Turkey, and United States
- 56 male, 65 female (mean age at diagnosis 10.7 yrs)
- 60 (49.5%) patients with underlying autoimmune disease
<table>
<thead>
<tr>
<th>Thrombotic Event</th>
<th>No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous thrombosis</td>
<td>72 (60)</td>
</tr>
<tr>
<td>DVT in the lower extremities</td>
<td>49 (40)</td>
</tr>
<tr>
<td>Cerebral sinus vein thrombosis</td>
<td>8 (7)</td>
</tr>
<tr>
<td>Portal vein thrombosis</td>
<td>4 (3)</td>
</tr>
<tr>
<td>DVT in the upper extremities</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Superficial vein thrombosis</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Thrombosis in the left atrium</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Jugular vein thrombosis</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Inferior vena cava thrombosis</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Renal vein thrombosis</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Retinal vein thrombosis</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Arterial thrombosis</td>
<td>39 (32)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>31 (26)</td>
</tr>
<tr>
<td>Peripheral arterial thrombosis</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Retinal artery thrombosis</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Renal artery thrombosis</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Splenic infarction</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Small-vessel thrombosis</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Digital ischemia</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Renal thrombotic microangiopathy</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Mixed arterial and venous thrombosis</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Ischemic stroke and portal vein thrombosis</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Mesenteric artery and venous thrombosis</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Renal artery and venous thrombosis</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>
### Associated Nothrombotic Clinical manifestations at the Time of the Initial Thrombotic Event


<table>
<thead>
<tr>
<th>Clinical Manifestation</th>
<th>No. (%) of Patients</th>
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</thead>
<tbody>
<tr>
<td>Hematologic disorders</td>
<td>46 (38)</td>
</tr>
<tr>
<td>Evans syndrome</td>
<td>15 (12)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10 (8)</td>
</tr>
<tr>
<td>Leucopenia/lymphopenia</td>
<td>10 (8)</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Bleeding disorder</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Skin disorders</td>
<td>22 (18)</td>
</tr>
<tr>
<td>Livedo reticularis</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Raynaud phenomenon</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Skin ulcers</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Pseudovasculitic lesions</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Chronic urticaria</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Nonthrombotic neurologic disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Migraine headache</td>
<td>8 (7)</td>
</tr>
<tr>
<td>Chorea/athetosis</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Pseudotumor cerebri</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Mood disorder</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>
Pediatric Antiphospholipid Syndrome: Clinical and Immunologic Features of 121 Patients in an International Registry


<table>
<thead>
<tr>
<th></th>
<th>Primary APS</th>
<th>APS associated with autoimmune disease</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>60</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Age at onset (yrs)</td>
<td>8.7 ± 5.3</td>
<td>12.7 ± 3.5*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Female/male</td>
<td>29:31</td>
<td>36:24</td>
<td>0.02</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>31</td>
<td>41*</td>
<td>0.047</td>
</tr>
<tr>
<td>Arterial thrombosis</td>
<td>27*</td>
<td>11</td>
<td>0.0002</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>23*</td>
<td>7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hematologic disorders</td>
<td>9</td>
<td>37*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Skin disorders</td>
<td>9</td>
<td>19*</td>
<td>0.049</td>
</tr>
<tr>
<td>Neurologic disorders</td>
<td>6</td>
<td>13</td>
<td>0.07</td>
</tr>
</tbody>
</table>
Multiple positivity of aPL in pediatric APS patients

Pediatric Antiphospholipid Syndrome: Clinical and Immunologic Features of 121 Patients in an International Registry


**Treatment**

- **Venous thrombosis:** all patients received long-term anticoagulation therapy

- **Arterial thrombosis:**
  - (a.) no treatment (25%)
  - (b.) antiaggregation therapy (35%)
  - (c.) anticoagulation with or without antiaggregation therapy (40%)

**Outcome** (mean F/u time 6.1 yrs)

- 23 (19%) patients had recurrent thrombosis
- 9 (7%) patients died
- 30% of patients with SLE developed APS before SLE diagnosis (mean interval 1.2 yrs)
## Prevalence of aPL in pediatric SLE

<table>
<thead>
<tr>
<th>Authors</th>
<th>No.</th>
<th>aCL (%)</th>
<th>Anti-β2GPI (%)</th>
<th>LA (%)</th>
<th>Clinical associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shery (1988)</td>
<td>32</td>
<td>50</td>
<td>-</td>
<td>-</td>
<td>CNS disease</td>
</tr>
<tr>
<td>Montes de Oca (1991)</td>
<td>111</td>
<td>-</td>
<td>-</td>
<td>19</td>
<td>Thrombosis</td>
</tr>
<tr>
<td>Molta (1993)</td>
<td>37</td>
<td>19</td>
<td>-</td>
<td>11</td>
<td>Thrombosis</td>
</tr>
<tr>
<td>Ravelli (1994)</td>
<td>30</td>
<td>87</td>
<td>-</td>
<td>20</td>
<td>CNS disease, cytopenia</td>
</tr>
<tr>
<td>Gattorno (1995)</td>
<td>19</td>
<td>79</td>
<td>-</td>
<td>42</td>
<td>Thrombosis, CNS disease, AHA</td>
</tr>
<tr>
<td>Messengill (1997)</td>
<td>36</td>
<td>50</td>
<td>-</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>Gedalia (1998)</td>
<td>36</td>
<td>36</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Avčin (2002)</td>
<td>11</td>
<td>55</td>
<td>46</td>
<td>-</td>
<td>N/A</td>
</tr>
<tr>
<td>Von Scheven (2002)</td>
<td>57</td>
<td>53</td>
<td>48</td>
<td>23</td>
<td>CNS thrombosis</td>
</tr>
<tr>
<td>Campos (2003)</td>
<td>57</td>
<td>70</td>
<td>-</td>
<td>29</td>
<td>-</td>
</tr>
<tr>
<td>Male (2005)</td>
<td>58</td>
<td>21</td>
<td>31</td>
<td>26</td>
<td>Thrombosis</td>
</tr>
<tr>
<td><strong>Meta-analysis</strong></td>
<td><strong>719</strong></td>
<td><strong>44%</strong></td>
<td><strong>40%</strong></td>
<td><strong>22%</strong></td>
<td></td>
</tr>
</tbody>
</table>
Non-thrombotic manifestations

- Non-thrombotic clinical findings reported in aPL positive SLE patients
  - chorea
  - migraine headache
  - neuropsychiatric manifestations
  - thrombocytopenia
  - hemolytic anemia
  - livedo reticularis, skin ulcerations
  - APS nephropathy (thrombotic microangiopathy)

- ‘Non-classical’ manifestations less strongly associated with aPL
aPL and associated neuropsychiatric manifestations in pediatric SLE


• Study design
  - A retrospective cohort study with longitudinal follow-up
  - aPL determined at the time of diagnosis and then at a minimum of yearly intervals as part of routine clinical care

• Patients
  - 137 children with SLE (diagnosed between 1995 and 2005 at SickKids, Toronto)
    25 boys and 112 girls
  - Mean age at diagnosis 13.0 years (range 3.1-17.7 yrs)
  - Mean follow-up period 31 months (range 1-118 mo)
Results – *follow-up*


- During the study period neuropsychiatric manifestations occurred in 35/137 (26%) children with SLE

<table>
<thead>
<tr>
<th></th>
<th>At presentation n (%)</th>
<th>Study period n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>13 (10)</td>
<td>22 (16)</td>
</tr>
<tr>
<td>Psychosis</td>
<td>8 (6)</td>
<td>13 (10)</td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td>7 (5)</td>
<td>12 (9)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>6 (4)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Seizures</td>
<td>3 (2)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Mood disorder</td>
<td>2 (2)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Chorea</td>
<td>2 (2)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Transverse myelitis</td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>23 (17)</strong></td>
<td><strong>35 (26)</strong></td>
</tr>
</tbody>
</table>
Comparison between the presence of aPL and individual NP manifestations

- **At the time of diagnosis:**
  - statistically significant association between **positive LA and cerebrovascular disease** (5 patients; p=0.015)

- **During the study period:**
  - statistically significant association between **persistently positive LA and chorea** (2 patients; p=0.02)
Specific features of aPL in pediatric population

- Neonatal/perinatal antiphospholipid syndrome
- Infection and vaccination-induced aPL
  - increased incidence of infections
  - routine immunizations
- Alternative responses of the developing immune system
  - transitory production of anti-β2GPI antibodies in infants
• 16 case reports describing neonates who have suffered from aPL-associated thrombosis in the perinatal period
  – Cerebral ischaemia
  – Aortic thrombosis
  – Renal vein thrombosis
  – Mesenteric thrombosis
  → arterial thromboses in 80% of cases
  → additional thrombophilic risk factor identified in >60% of cases
    - arterial or venous catheters, sepsis, asphyxia, congenital thrombophilia

• Established European register of babies born to mothers with APS (Boffa MC et al. Lupus 2004;13:713-7)
20 days old girl with ischemic stroke

- heterozygous genotype C677T for MTHF reductase and prothrombin G20210A mutation

- high-positive aCL in mother and child
aPL associated with infections


- **Viral**
  - EBV, VZV, CMV, adenovirus, parvo B19, hepatitis C, HIV, mumps, rubella
- **Bacterial**
  - staphylococci, streptococci, *M. pneumoniae*, Salmonella, Tuberculosis, Leprosy
- **Spirochaetal**
  - B. burgdorferi, Leptospirosis, Syphilis
- **Parasitic**
  - Toxoplasmosis, Malaria
aPL associated with infections


- Post-infectious aPL usually transient
  - aPL positivity should be verified on two or more occasions at least twelve weeks apart
- The majority of post-infectious aPL seems to be non-pathogenic
  - A few reports of children who suffered from clinical symptoms due to the presence of post-infectious aPL (Campanelli et al. *Dermatology* 2004)
    → all had acquired protein S deficiency and clinically presented with purpura fulminans after varicella
aPL following vaccination with hepatitis B vaccine


**Case 1**

**Case 2**

**Case 3**

**Case 4**

Fig. 1. Subjects with evident anti-cardiolipin antibodies (aCL) (■) and/or anti-β2GPI (▲) fluctuation after vaccination (cut-off for aCL = 7 GPL, cut-off for anti-β2GPI = 7.2 mg/l). T0 = time of vaccination, T1 = 1 month after vaccination, T2 = 6 months after vaccination.
Autoimmune response following annual influenza vaccination in 92 apparently healthy adults


<table>
<thead>
<tr>
<th></th>
<th>Before vaccination</th>
<th>1 month after vaccination</th>
<th>6 months after vaccination</th>
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<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
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<tr>
<td>ANA</td>
<td>24 (26)</td>
<td>24 (26)</td>
<td>24 (26)</td>
</tr>
<tr>
<td>aCL</td>
<td>15 (16)</td>
<td>12 (13)</td>
<td>14 (15)</td>
</tr>
<tr>
<td>Anti-β2-GPI</td>
<td>6 (7)</td>
<td>8 (9)</td>
<td>8 (9)</td>
</tr>
<tr>
<td>LA</td>
<td>2 (2)</td>
<td>4 (4)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Anti-ENA</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
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Anti-β₂GPI in healthy populations


**IgG**

<table>
<thead>
<tr>
<th>mOD</th>
<th>5.0 y</th>
<th>13.5 y</th>
<th>34.0 y</th>
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<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>80</td>
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**IgM**

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<th>13.5 y</th>
<th>34.0 y</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td>20</td>
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<tr>
<td>80</td>
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</tbody>
</table>
Frequency of aPL in infants with atopic dermatitis (AD)

Whole molecule recombinant $\beta_2$GPI (WM) and various domain deleted mutants of $\beta_2$GPI (DM)

(kindly provided by Prof. Takao Koike, Sapporo, Japan)
Binding to purified human β₂GPI, whole molecule recombinant β₂GPI (WM) and various domain deleted mutants of β₂GPI (DMs)

In every child with positive aPL:

- avoidance of additional risk factors for thrombosis such as smoking, hypertension, obesity and hypercholesterolemia

- use of estrogen-containing oral contraceptives is not allowed in adolescent girls with aPL
Primary thromboprophylaxis in asymptomatic children

- low-dose aspirin (80-100 mg daily) recommended for prevention of thrombosis in asymptomatic adult patients with persistently positive aPL
- the decision on the use of specific prophylactic therapy in children should be individualized and based on the presence of additional congenital or acquired prothrombotic risk factors and the aPL profile (multiple aPL antibodies, high titers of aCL and/or anti-β2GPI, presence of LA)
- Prophylaxis with LMWH s.c. should be considered during high-risk situations (prolonged immobilization, surgery)
Primary thromboprophylaxis in children with SLE

- Low-dose aspirin (3-5 mg/kg/day) recommended as thromboprophylaxis in all pediatric SLE patients with persistently positive aPL.

- An additional protection may be provided by hydroxychloroquine, which has modest anticoagulant properties.

- Prophylactic oral anticoagulant therapy may provide further advantage in selected SLE patients with a low bleeding risk and a high thrombotic tendency (i.e. young SLE patients with positive LA).
Prevention of recurrent thrombosis

- Adult APS patients with venous or non-cerebral arterial thromboembolism treated with oral anticoagulation at a target INR of 2.0-3.0

- London protocol advises life-long anticoagulation at a target INR of 2.0-3.0 in patients with first venous events and above 3.0 for those with recurrent and/or arterial events

- Given the higher recurrence rate of thrombosis, reasonable to consider anticoagulation in all pediatric patients with definite APS at least at a target INR suggested for adult population
Conclusions


- **aPL pathogenic autoantibodies with multiple mechanisms of action**
- **Clinical manifestations associated with aPL:**
  - Venous and arterial thrombosis of small and large vessels
  - Nonthrombotic clinical manifestations:
    » hematological (thrombocytopenia, hemolytic anemia)
    » dermatological (livedo reticularis, Raynaud phenomenon)
    » neurological (chorea, migrain headache, epilepsy)
- **Specific features of aPL should be considered in childhood**
  » Infection/vaccination induced aPL
  » Alternative immune responses due to immaturity of the immune system
Acknowledgements

Univ. Medical Center Ljubljana, Slovenia

The Hospital for Sick Children, Toronto, Canada

University of Milan, Italy

Ped-APS Project coordinators:

- Rolando Cimaz, Florence, Italy
- Ricard Cervera, Barcelona, Spain
- Angelo Ravelli & Alberto Martini Genoa, Italy
- Blaž Rozman, Ljubljana, Slovenia
- PierLuigi Meroni, Milan, Italy

Supported by grants L3-0624 and P3-0314 from
The Slovenian Research Agency.

Participating physicians:

- Stella Garay, La Plata, Argentina
- Flavio Sztajnbok, Rio de Janeiro, Brasil
- Sheila Oliveira, Brasil
- Clovis Silva & Lucia Campos, Sao Paulo, Brasil
- Claudia S Magalhaes, Botucatu, Brasil
- Earl D Silverman, Toronto, Canada
- E. Descloux, Lyon, France
- Susan Nielsen, Copenhagen, Danemark
- Chris Pruunsild, Tartu, Estonia
- Frank Dressler, Hannover, Germany
- Yackov Berkun, Israel
- Marco Gattorno, Genoa, Italy
- Fernanda Falcini, Florence, Italy
- Donato Rigante, Rome, Italy
- Dafina B. Kuzmanovska, Skopje, Macedonia
- Gordana Susic, Belgrade, Serbia
- Atilla Buyukgebiz, Izmir, Turkey
- Kanat Ozisik, Ankara, Turkey
- Sevgi Gozdasoglu Ankara, Turkey
Ongoing and future projects of the Ped-APS Registry


- Prospective enrollment of new patients with aPL-related thrombosis
- Differences between the pediatric and adult APS
- Evaluation of pro-inflammatory genotype as a risk factor for APS manifestations
- Evaluation of patients with isolated nonthrombotic aPL-related manifestations
- Immunological aspects of the pediatric APS