Antiphospholipid Antibody Syndrome (APS)

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ISTH Workshop Bangkok 2017
APS is…
a syndrome of (unprovoked) venous, arterial and microvascular thrombosis rarely associated with other (non-ischaemic) conditions
Antiphospholipid antibodies - what are they?

Lupus Anticoagulant (LA)

Anticardiolipin antibodies (ACL)

Anti-β2 GPI

Heterogeneous antibodies against phospholipid-binding proteins (β2 GPI, prothrombin, others…)

Common in healthy populations - prevalence of LA 1-3.6%
prevalence of ACL 1-5.6%

Even higher in the elderly, often transient - not useful in population screening

Minority of APL positive cases develop symptoms

Stronger association of LA with thrombosis than ACL - role of specific antibodies (β2 GPI) still under debate

Rand Hematology 2007
What we know about APS...

- Autoantibodies to phospholipid-binding proteins...
- VTE
- ATE
- Atypical thrombosis
- Fetal loss
- Other...

are more common in clinical scenarios.
What we don’t know about APS...

- Cause of immune dysfunction
  - autoantibodies to phospholipid-binding proteins...

- Mechanism or trigger
  - VTE
  - ATE
  - Fetal loss
  - Other...

- Optimal therapy?
  - are more common in clinical scenarios
Antiphospholipid (antibody) syndrome (APS)

Venous thrombosis
Arterial thrombosis (esp stroke/TIA)
Microvascular thrombosis
Pregnancy loss, other obstetric complications
Livedo reticularis
Cardiac valvular disease (mitral > aortic)
Renal thrombotic microangiopathy
Thrombocytopenia
Haemolytic anaemia
Cognitive impairment, other non-ischaemic changes

Ruiz-Irastorza et al The Lancet 2010
Which APL are pathogenic?

**Lupus anticoagulant** – strongest predictor of thrombosis

- 40x increase stroke risk, 5x MI risk in women <50
- Strong assocn with recurrent miscarriage <24 weeks

**Anticardiolipin** – persistent ACL+LA- showed more thrombosis than ACL-LA- lupus patients

- Both IgG and IgM ACL associated with miscarriage risk

**β2-GPI antibodies**

- Not associated with thrombosis, miscarriage in 3 reviews
- Highest risk in “triple positive” (LA+ACL+GPI+)
- Improved specificity if anti-domain 1 of β2-GPI

*Ruiz-Irastorza et al The Lancet 2010*
Rheumatologists
Female predominant
SLE and CT disorders
Younger

Autoimmune diseases

Thrombo-embolism

...are these patient groups comparable?

Obstetricians
Females only!
Minimal risk of thrombosis

Haematologists/Vascular Physicians
Males + Females
Broad age range
Uncommon to get CT symptoms

Adverse Pregnancy
Antiphospholipid antibodies activate

Endothelium
- Adhesion molecules expressed
- Tissue factor upregulated
  - Interaction with Protein C, prothrombin, plasmin

Monocytes
- Tissue factor upregulated
  - Prothrombotic state
  - Secondary triggers: inflammation, oestrogen, smoking

Platelets
- TxA₂ upregulated
  - GPIIb-IIIa expression
  - Complement activation

Thrombosis
(Microvascular) thrombosis
Thrombocytopenia
Endothelial inflammation
Ischaemic organ failure
Systemic inflammation

Endothelial damage
Complement activation
Coagulation activation

“Endotheliopathy” or TMAs

APS syndrome
Heparin-induced Thrombocytopenia
HELLP
Atypical HUS
Drug-induced TTP
Transplant-associated TTP
International Consensus Criteria for Antiphospholipid Syndrome

APL requires at least one clinical and laboratory criteria:

**Clinical**

- **Vascular thrombosis** - arterial, venous or small vessel in any tissue, without inflammation

- **Pregnancy morbidity** - unexplained fetal loss >10 weeks, premature birth w eclampsia or placental insufficiency, recurrent early fetal losses <10 weeks

**Laboratory**

- **Lupus anticoagulant** positive

- **Anticardiolipin antibody** (mod-high titre)

- **Anti-β2GPI antibody**

APL must be detected on 2 or more occasions, at least 12 weeks apart

(The Sydney Criteria for APS)  
*Miyakis J Thromb Haem 2006*
When should we test for APL?

Samples can be negative when presenting with an acute VTE and serial samples may show a positive APL.

NOACs (rivaroxaban and apixaban) will give false positive LAC results – if essential, retest after NOAC ceased or transition to LMWH for several weeks.

Must repeat after 12 weeks to meet criteria.

Consider APL testing in: atypical sites of VTE (e.g. cerebral sinus) recurrent VTE without a family history younger patients with arterial events combined arterial and venous thrombi unexplained multiorgan failure and likely microvascular ischaemia.
Aspirin for primary thrombosis prevention in APL patients

**APLASA study**: 98 asymptomatic, persistently APL+ subjects randomised to 81mg aspirin or placebo - prospective follow-up

Incidence of acute thrombosis

- **2.75/100 pt-years in ASA-treated**
- **0/100 pt-years in placebo-treated**

Similar outcomes in observational cohort of 74 nonrandomised individuals - 61 on ASA (2.7/100 pt-years) and 13 not (0/100 pt-years)

9/10 patients with events had systemic autoimmune disease or thrombotic risk factors - thrombosis risk also higher (11%) in those with high titre APL and/or LA positive

Asymptomatic APL+ individuals have a low risk of acute thrombosis do not benefit from aspirin

*Erkan Arthritis Rheum 2007*
What is the significance of a positive APL test?

Not much in the absence of a vascular event or recurrent miscarriage...

Take care not to diagnose APL without confirming persistence (testing at least 12 weeks apart) of antibodies, transient APL antibodies are common and of uncertain significance

Anticardiolipin antibody titre and lupus anticoagulant ratios do not correlate with clinical events – is a second “hit” needed?

APL may persist despite immunosuppression/plasmapheresis

Beta-2 GPI antibody assays are highly variable in performance – this assay is not suitable to replace standard testing – but “triple positive” cases may be at higher risk of thrombosis

Overall, clinical history guides therapy rather than assay results...
How much warfarin do APL patients need after VTE?

114 APS patients - low risk, ~75% with VTE, randomised to either high-intensity (INR 3.5) or moderate-intensity (INR 2.5) recurrence rates (3.4% mod, 10.7% high intensity) major bleeding (2.2% mod, 3.6% high intensity)

Excluded pts with high bleeding risk, those with events on warfarin Inadequate numbers with arterial TE Crowther NEJM 2003

Similar study of 109 patients, with equivalent recurrence and bleeding rates at standard and high-intensity warfarin Finazzi JTH 2005
What is the risk of a first TE event in APLA-positive individuals?

*no prospective data*

What is the risk of recurrent VTE in APLA-positive individuals?

after 6 months Rx

<table>
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<tr>
<th>Status</th>
<th>Recurrence Rate</th>
<th>Duration</th>
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<tbody>
<tr>
<td>APLA positive</td>
<td>29% recurrence</td>
<td>over 4 years</td>
</tr>
<tr>
<td>APLA negative</td>
<td>14% recurrence</td>
<td>over 4 years</td>
</tr>
<tr>
<td>RR 2.1</td>
<td></td>
<td><em>Schulman Am J Med 1998</em></td>
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after 3 months Rx for first idiopathic VTE:

<table>
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<tr>
<th>Status</th>
<th>Recurrence Rate</th>
<th>CI</th>
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</thead>
<tbody>
<tr>
<td>APLA positive</td>
<td>4/16 recurrence</td>
<td>(HR 4.0, CI 1.2-13)</td>
</tr>
<tr>
<td>APLA negative</td>
<td>2/61</td>
<td><em>Kearon N Engl J Med 1999</em></td>
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No data regarding risk of recurrent arterial events in APLA
APL and recurrent thromboembolism:

Evidence for increased risk is weak. Ruiz-Astoria 2007

Most studies retrospective, combine ATE and VTE, inconsistent definitions of APL, single test

Recurrence rates high (19-29%) in untreated patients (cohort studies), much less on warfarin

DURAC subgroup analysis: recurrence in 29% with first VTE and anticardiolipin antibodies cf 14% without (p <0.01)

Lower risk recurrence in APL patients after VTE than ATE. Eichinger and Kyrle, ISTH 2009

Systematic analysis of 8 prospective but poor-quality studies of patients with a first APL-related thrombotic event: 40% higher risk of recurrence off AC in APL+ (n=588) compared to APL- (n=1914) (RR 1.4, 95%CI 0.99-2.36)

Garcia, Blood 2013
Hydroxychloroquine plus AC in primary APS

Primary APS patients with 1 or 2 prior episodes of VTE on VKA (2 w stroke, no obstetric events)

Prospective, but non-randomised study

VKA only (n=20) 6 venous events (30%) despite therapeutic INRs (TTR claimed 98% incl 30d before recurrence)

VKA + HCQ (n=20) 0 events over 6 and 36 months

VTE events – 3 femoral, 3 tibial DVTs at 12-18 months, 50% recurred at site of prior thrombus

Minor bleeding rates equal (10% in both groups)

Small numbers, short follow-up, but suggests addition of HCQ warrants further investigation – is recommended in SLE patients as “prophylaxis”

Schmidt-Tanguy et al J Thromb Haemost 2014
Use of warfarin in APS

Warfarin remains the “standard of care” for APS patients with venous thromboembolism

In typical VTE, an INR range of 2.0-3.0 is sufficient

Use warfarin rather than NOACs for atypical VTE (cerebral sinus or mesenteric/portal vein thrombi) – no evidence yet

Consider higher INR range for arterial events (and add aspirin if possible)

If patients progress on warfarin, or need temporary interruption of VKA, switch to twice daily LMWH

When using LMWH, aim for an anti-Xa peak of 1.0U/mL

LMWH may be preferable to warfarin in “unstable” patients
Cqn we use NOACs in APL patients?

Remember that patients with “strong” antibodies can be resistant to warfarin and other anticoagulants...

Patients with a typical presentation of VTE (leg vein DVT or small-volume PE) may respond normally to NOACs.

NOACs can be used for secondary prevention after an initial period of "stabilisation” with warfarin or LMWH.

LMWH (twice daily) is a preferred option in unstable or unwell patients, can monitor anti-Xa to ensure levels high (>1U/mL).

Insufficient evidence to use NOACs in atypical VTE sites, patients with arterial events (warfarin plus aspirin preferred) and in catastrophic APL.

Would a b.d. dosed NOAC be preferable to once daily?

Would APL patients benefit from a higher dose-intensity?
116 patients w previous VTE, confirmed APL on standard-intensity warfarin, randomised to continue or rivaroxaban (n=56)

Primary outcome – laboratory assay of thrombin generation differed between anticoagulants, no difference in activation markers (D-dimer, TAT, P1+2)

Serious AEs in 4 of each group, no thrombosis or major bleeding seen in either group. Study suggests rivaroxaban is a suitable alternative in this type of APL patient

Cohen et al Lancet Haematol 2016
Higher endogenous thrombin potential (AUC) but lower and delayed peak thrombin on rivaroxaban – does this matter?
Arterial thromboembolism and APL ...

A probable risk factor in early stroke/MI, etc

Minimal evidence for altered management - not listed in ACCP guidelines

Patients will often receive combined antiplatelet and anticoagulant therapy, at least initially

Tend to have indefinite prophylaxis cf. VTE cases

Consider **combined** antiplatelet/anticoagulant therapy - role of higher intensity warfarin uncertain, likely to increase bleeding risk...
Intensity of anticoagulation in APL?

Venous thrombosis
Warfarin INR 2.0-3.0

Arterial (non-cerebral) thrombosis
Warfarin INR 2.0-3.0

Stroke
ASA or Warfarin (INR 1.4-2.8)

*Lim* et al *JAMA* 2006
(only 3 studies eligible, few stroke pts, most low-titre ACL)

Venous thrombosis (first)
Warfarin INR 2.0-3.0

Arterial or recurrent events
Warfarin INR 3.0-4.0
(high risk of recurrence at std INR)

*Ruiz-Irastorza* et al *Arth Rheum* 2007
(incl observational studies, 16 studies, 1740 patients)

*Ruiz-Irastorza* et al *The Lancet* 2010
Prevention of recurrent miscarriage for APL+ women

Metanalysis of 13 studies (women with prior miscarriage and APL: n=849) - poor quality studies (50% with allocation concealment):

**UFH plus aspirin** (n=140, 2 trials) reduced pregnancy loss compared to **aspirin** alone (RR 0.46, 95% CI 0.29-0.71)

**LMWH plus aspirin** (n=98, 1 trial) equivalent to **aspirin** (RR 0.78, 95% CI 0.39-1.57)

**Aspirin alone** (n=286, 3 trials) did not significantly reduce pregnancy loss (RR 1.05 95% CI 0.66-1.68)

**Combined UFH and aspirin may reduce pregnancy loss by 54%** - further randomised controlled studies needed to establish effects of LMWH

**ACCP 2012 Guidelines** – recommend UFH or prophylactic LMWH plus low-dose aspirin in those with confirmed APL and 3 or more early pregnancy losses over no treatment (Grade 1B)

*Cochrane Database Empson et al 2008*
Catastrophic Antiphospholipid Syndrome (CAPS)

Proposed Diagnostic Criteria

1. Involvement of 3 or more organs, systems, tissues
2. Simultaneous onset symptoms or within 1 week
3. Small vessel occlusion (histologically confirmed)
4. APL positive (LA or ACL)

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<thead>
<tr>
<th>Definite CAPS</th>
<th>All four criteria</th>
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<tr>
<td>Probably CAPS</td>
<td>Other combinations, no biopsy, etc</td>
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Cervera et al  (CAPS Registry Project Group) Ann Rheum Dis 2005
Managing refractory thrombosis/catastrophic APL

Anticoagulation alone can be insufficient to control progressive thromboembolism, with any agent.

Monitored heparin or LMWH is a good baseline.

Targeting the pathogenic antibody is critical in severe cases:

- Plasmapheresis (daily)
- Immunosuppression with steroids, cyclophosphamide
- Rituximab (can be given after daily plasmapheresis)

Case series and anecdotal cases only to guide treatment.

Platelet count can be a useful marker, rises as microvascular events come under control...

Observational data supports use of plasmapheresis, rituximab, eculizumab and defibrotide...
Potential new therapies in APL

N-acetyl cysteine – scavenge oxygen radicals

Statins – upregulate endothelial NO synthase

Hydroxychloroquine - antiplatelet and prevents disruption of Annexin A5 matrix on endothelium by APL

Inhibitors of PDI – higher ratio of oxidised β2GPI in APS, TF

Eculizimab – inhibits complement C5

Inhibitors of B-cell activating factor (BAFF) – belimumab approved in SLE, prevented thrombosis in mouse model

Inhibitors of FXIa – dysregulated in APS

Giannakopoulos and Krilis NEJM 2013
Antiphospholipid antibody syndrome

How I treat....

Asymptomatic APL+ individuals - nothing...

**APL+ VTE** - standard VKA, LMWH if refractory, extended duration, not always indefinite

**APL+ ATE** - VKA and/or ASA, indefinite

**APL+ obstet** - prophyl LMWH ?plus ASA

**Catastrophic APL** – anticoagulation must be combined with strategies to remove Ab (Pex, steroids, rituximab)