The Antiphospholipid Syndrome: Cases and Conundrums

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Disclosure

None

Brief Review of the Antiphospholipid Syndrome (APS)

Major clinical manifestions

- Venous thrombosis (any vessel, DVT most common)
- Arterial thrombosis (any vessel, stroke most common)
- Pregnancy loss
  - late 1st trimester/early 2nd trimester most characteristic
- Other pregnancy morbidity
  - premature birth due to eclampsia
  - severe preeclampsia
  - placental insufficiency

Non-Criteria Clinical Manifestations Probably or Possibly Associated with aPL

Cutaneous Manifestations
- Livedo reticularis
- Cutaneous ulcers

Hematologic Manifestations
- Thrombocytopenia
- Hemolytic anemia

Cardiac Manifestations
- Valve vegetation/thickening

Renal Manifestations
- Antiphospholipid antibody-associated nephropathy

Nonstroke Neurological Manifestations (controversial)
- Chorea
- Cognitive dysfunction
- Headache
- Multiple sclerosis–like syndromes

Libman-Sachs Endocarditis

Forms of Livedo

Reticularis

Racemosa

Catastrophic APS

- acute onset of multiple organ thromboses

May be associated with -

- thrombotic angiopathy
- microangiopathic hemolytic anemia
- thombocytopenia

Antiphospholipid antibodies (aPL)

Routine tests

- Lupus anticoagulant
- Anticardiolipin (aCL) (IgG, IgM)
- Anti-β_2-glycoprotein I (anti-β_2GPI) (IgG, IgM)

Other autoantibodies (probably or possibly associated)

- IgA aCL, anti-β_2GPI
- Antiphosphatidylserine
- Antiphosphatidylethanolamine
- Anti-prothrombin, anti-phosphatidylserine/prothrombin
- Anti-β_2GPI (domain 1)
- Panels of antibodies to multiple phospholipids

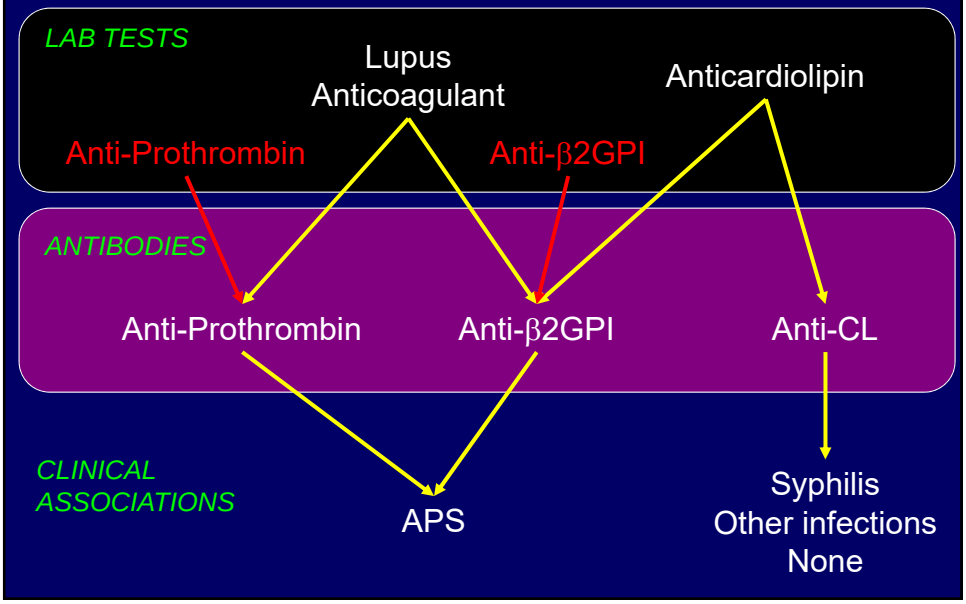
Principles of Lupus Anticoagulant Testing

1. Demonstration of a prolonged phospholipid-dependent screening test of hemostasis (*e.g.*, aPTT, dRVVT, KCT, dPT, textarin time, Taipan time)
2. Mixing patient plasma with normal plasma fails to correct the prolonged screening coagulation tests (rules out factor deficiencies)
3. Addition of excess phospholipids or hexagonal phase phospholipids shortens or corrects the prolonged screening tests (demonstrates phospholipid-dependence)

Mixing and Confirmatory Studies in the Diagnosis of Lupus Anticoagulants

	dRVVT Screen		dRVVT Confirm	
Diagnosis	Patient Plasma (Unmixed)	Patient and Normal Plasma Mixed	Patient Plasma (Unmixed)	Patient and Normal Plasma Mixed
Normal	N	N	N	N
LA	ABN	ABN	N	N
Factor Deficiency	ABN	N	ABN	N
LA and Factor Deficiency	ABN	ABN	ABN	N
Other Inhibitor	ABN	ABN	ABN	ABN

Antiphospholipid Antibodies and Tests



Antiphospholipid Antibodies and the Antiphospholipid Syndrome: Misnomers

> Her name was McGill
> And she called herself Lil
> But everyone knew her as Nancy
>
> *Lennon, McCartney*

Lupus anticoagulants
- occur in many patients without SLE
- anticoagulant *in vitro* but procoagulant *in vivo*

Anticardiolipin antibodies
- not directed against cardiolipin

Antiphospholipid antibodies
- not directed against phospholipids

Is APS a rare condition?

Prevalence of aPL and APS

Patients with SLE
- anticardiolipin antibodies in ~ 40%
- lupus anticoagulant in ~ 30%
- clinical manifestations in one third of patients with antibodies, or 10 - 15% of SLE patients

Primary APS
- aPL in 7 - 30% of patients with a history of thrombosis
- up to 20% of DVT/PE
- one third of new strokes, age < 50
- 5 - 15% of recurrent fetal loss

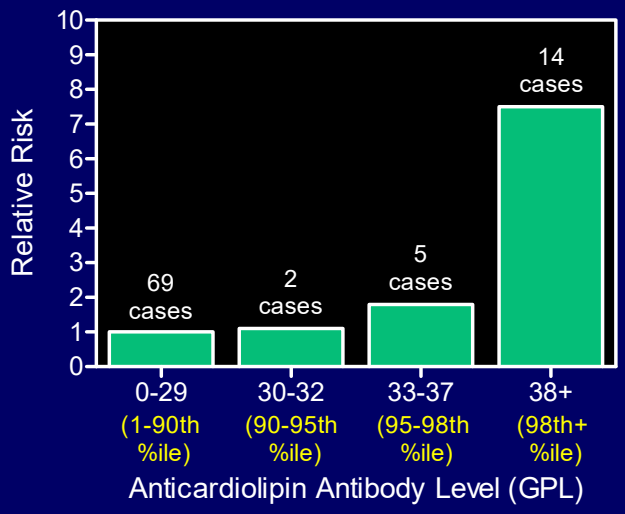
Anticardiolipin Antibodies and the Risk for Ischemic Stroke and Venous Thrombosis

Ginsburg KS et al. Ann Int Med 1992; 117:997-1002

- Nested, case-control study from the Physicians' Health Study
- 15,008 males (age 40-84)
  - blood samples at enrollment
  - followed prospectively for 37 months
- 100 cases with ischemic stroke
- 90 with DVT or PE
- Controls matched for age, smoking, length of follow-up

Results
- No association of anticardiolipin antibodies with ischemic stroke
- Of 90 DVT/PE cases, 19 (21%) were associated with elevated IgG anticardiolipin antibodies (≥ 33 GPL)

Risk of Deep Vein Thrombosis or Pulmonary Embolus is Associated with Anticardiolipin Antibody Level



Ginsburg et al., Ann Int Med, 1992

Antiphospholipid Antibodies in the Leiden Thrombophilia Study

De Groot, et al. *J Thromb Haemost* 2005; 3:1993

- Population based case-control study
- Unselected patients with a first venous thrombosis
- 473 patients, 472 controls

Odds Ratios (OR) and 95% CI for Thrombosis

Assay	OR (95% CI)
Lupus anticoagulant	3.6 (1.2-10.9)
Anti-β_2GPI	2.4 (1.3-4.2)
Anti-prothrombin	1.4 (1.0-2.1)
LA+ alone	1.3 (0.3-6.0)
LA+ and anti-β_2GPI or anti-prothrombin +	10.1 (1.3-79.8)

Antiphospholipid Antibodies in the RATIO Study

(**R**isk of **A**rterial **T**hrombosis **I**n relation to **O**ral contraceptives)
Urbanus, et al. *Lancet Neurol* 2009; 8:998

- Population based case-control study
- Women under the age of 50 with first ischemic stroke or MI
- 175 patients with stroke, 203 patients with MI
- 628 healthy controls

Odds Ratios (OR) and 95% CI for Stroke or MI

Assay	Stroke	MI
Lupus anticoagulant	43.1 (12.2-152.0)	5.3 (2.4-20.8)
Anti-β_2GPI	2.3 (1.4-3.7)	ns
Anticardiolipin	ns	ns
Oral contraceptives, LA -	2.9 (1.8-4.6)	2.3 (1.6-3.4)
Oral contraceptives, LA +	201.0 (22.1-1828.0)	21.6 (1.9-242.0)
Smoking, LA -	2.2 (1.5-3.4)	6.4 (4.2-9.7)
Smoking, LA +	87.0 (14.5-523.0)	33.7 (6.0-189.0)

Interpretation of aPL Tests

Antiphospholipid Antibodies: Diagnostic Tests vs. Risk Factors

- aPL are a necessary inclusion criterion for APS
- aPL are not true diagnostic tests
  - no independent "gold standard" or "truth"
  - ? meaning of "false positive" and "false negative"
    - someone with + aPL but no clinical manifestations is still at risk
    - someone without aPL can still have clinical manifestations of APS
- Risk is associated with antibody level
  - Low levels may be abnormal, but carry little risk

"The patient has antiphospholipid antibodies but doesn't have the antiphospholipid syndrome."

Why don't we talk this way about other thrombophilic conditions or other risk factors?

"The patient has factor V Leiden but doesn't have the factor V Leiden-thrombosis syndrome."

"The patient has a high LDL but doesn't have the high LDL-myocardial infarction syndrome."

Interpretation of aPL Tests

- Consider aPL as risk factors rather than diagnostic tests
- Factors associated with increased risk of clinical manifestations:
  - Moderate to high titer, *e.g.*, aCL ≥ 40 GPL
  - Persistence
  - Lupus anticoagulant positivity
  - Multiple aPL positivity
  - Isotype (IgG > IgM > IgA) – *but* isolated IgM or IgA may occur
- Classification criteria for definite APS are not particularly useful for clinical decisions

Cases

CASE STUDY 1

History: 34 year-old woman with acute onset of shortness of breath and right-sided pleuritic chest pain

- Previously in good health, physically active
- One pregnancy, live term birth
- Medication: oral contraceptive (estrogen-containing)
- Review of systems negative

Physical Exam: Mild tachypnea, rales, accentuated S2, otherwise normal

Diagnostic studies:

- Elevated d-dimer
- Chest x-ray and ECG normal
- Chest CT scan - pulmonary embolus

Hospital course:

- Treated with LMWH, converted to warfarin

CASE STUDY 1

Additional laboratory data:

- Normal CBC, comprehensive metabolic panel, urinalysis
- Normal cardiac enzymes
- Antiphospholipid antibodies (aPL)
  - IgG aCL - 34 GPL (nl 0-23)
  - IgM aCL - 29 MPL (nl 0-11)
  - Lupus anticoagulant negative
- Remainder of hypercoagulable work-up normal

Plan:

- Discharged on warfarin (INR 2.3)
- Oral contraceptive discontinued
- Referred to rheumatologist for further evaluation of the positive aPL tests

CASE STUDY 1

Rheumatology consultation (6 weeks after event):

- Feeling well, no chest pain or shortness of breath
- On a stable dose of warfarin, recent INR 2.5
- No symptoms to suggest SLE
- Physical exam normal

Antiphospholipid antibodies:

- Anticardiolipin antibodies
  - 55 GPL (nl 0-23)
  - 12 MPL (nl 0-11)
- Anti-β_2-glycoprotein I antibodies
  - IgG 90 u/L (nl < 15)
  - IgM 4 (nl < 15)
- Lupus anticoagulant not tested

Question #1

Does this patient have the antiphospholipid syndrome?

a) Yes

b) No

c) Maybe

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a) Yes
b) No
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Classification Criteria for Definite APS

Clinical criteria

1. Vascular thrombosis – one or more episodes of arterial, venous, or small vessel thrombosis in any tissue/organ, confirmed by objective criteria
2. Pregnancy morbidity
   a) One or more unexplained fetal deaths (≥ 10 wk gestation) with normal fetal morphology, or
   b) One or more premature births (< 34 wk) of morphologically normal neonate due to eclampsia/pre-eclampsia or placental insufficiency, or
   c) Three or more unexplained consecutive spontaneous abortions (< 10 wk)

J Thromb Haemost 2006; 4: 295–306

Classification Criteria for Definite APS

Laboratory criteria

1. LA present in plasma, on 2 or more occasions at least 12 weeks apart, detected according to the guidelines of the ISTH SSC, and/or
2. aCL of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (i.e. > 40 GPL or MPL, or > 99th percentile), on 2 or more occasions, at least 12 weeks apart, measured by a standardized ELISA, and/or
3. Anti-β_2GPI antibody of IgG and/or IgM isotype in serum or plasma (titer > 99th percentile), present on 2 or more occasions, at least 12 weeks apart, measured by a standardized ELISA.

J Thromb Haemost 2006; 4: 295–306

CASE STUDY 1

Based on criteria, does this patient have APS?

Clinical Criteria

Yes, confirmed pulmonary embolus

Laboratory Criteria

No

Lab Test	At Event	6 weeks later
aCL IgG (0-23)	34	55
aCL IgM (0-11)	29	12
Anti-β_2GPI IgG (< 15)	Not done	90
Anti-β_2GPI IgM (< 15)	Not done	4
Lupus anticoagulant	Negative	Not done

Does this patient have APS?

- This patient doesn't meet classification criteria for definite APS at this point in time.
- The more important clinical question – *Is this patient at risk for further thrombosis and does she require long-term anticoagulation?*
- In general, patients meeting the classification criteria for definite APS are at risk, however, some patients not meeting criteria may also be at risk.

Question #2

Given the available lab data, what would you recommend about the patient's anticoagulation?

a) Start hydroxychloroquine and discontinue warfarin after 3 months of treatment

b) Discontinue warfarin after 3 months of treatment, then start low-dose aspirin

c) Reassess and repeat aPL tests in 3-4 months, continue warfarin at least until that time

d) Continue warfarin indefinitely

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Question #3

The rheumatologist in this case didn't order a lupus anticoagulant test because the patient was on warfarin. Is it possible to accurately test for a lupus anticoagulant in someone on warfarin?

a) Yes
b) No

Question #3

The rheumatologist in this case didn't order a lupus anticoagulant test because the patient was on warfarin. Is it possible to accurately test for a lupus anticoagulant in someone on warfarin?

a) Yes*

b) No

* in a good coagulation lab, if INR is not above 3.0

Difficulty in Managing Warfarin in APS Patients

- aPL may interfere with the prothrombin time assay, causing an unreliable INR
  - 6.5% to 10% of patients with positive LA tests
  - often seen in LA+ patients with prolonged PT pre-treatment
- Not all vitamin K-dependent proteins affect the INR equally
  - general issue using INR to guide warfarin therapy
  - INR affected by levels of factor II (prothrombin), factor VII, and factor X
  - factor VII has the greatest impact on INR
  - prothrombin the most important determinant of the therapeutic effect

Suggested Approach to Managing Warfarin in APS Patients

Kasthuri & Roubey, *Arthritis Rheum* (2007)

APS patient started on warfarin, INR stable in 2.0-3.0 range

- Check INR and factor II activity assay simultaneously
- If INR in target range and factor II therapeutic (15%–25%):
  - patient is adequately anticoagulated
  - INR is reliable for monitoring
- If INR in target range but factor II > 30%:
  - patient is not adequately anticoagulated
  - INR not reliable
  - For subsequent monitoring:
    - Establish INR range corresponding to therapeutic factor II level, or
    - follow factor II level in lieu of INR (alternative chromogenic factor X)
- Approach is rational but no RCT data

CASE STUDY 2

- 28-year-old man found to have an elevated aPTT during an ED evaluation of minor trauma after a motor vehicle accident
- Further testing demonstrated a positive LA
  - LA persistently positive for the last year
  - aCL and anti-β_2GPI antibodies negative
- No thrombosis or other significant medical history
- Smokes cigarettes, ½ pack per day × 7 yr
- Review of systems negative
- Physical examination normal
- Other laboratory studies (CBC, CMP, U/A) normal

Question #4

What treatment do you recommend for this patient?

a) Aspirin, 75 or 81 mg daily
b) Hydroxychloroquine, 200 mg twice daily
c) Warfarin, target INR 1.5
d) Warfarin, target INR 2.0 - 3.0
e) No treatment

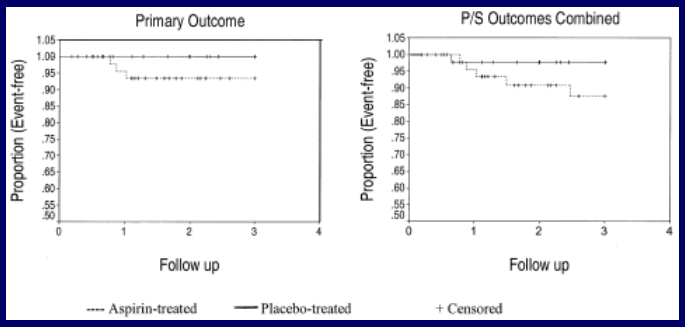
Question #4

What treatment do you recommend for this patient?

a) Aspirin, 75 or 81 mg daily
b) Hydroxychloroquine, 200 mg twice daily
c) Warfarin, target INR 1.5
d) Warfarin, target INR 2.0 - 3.0
e) No treatment

Aspirin for Primary Thrombosis Prevention in the Antiphospholipid Syndrome

Erkan, et al. Arthritis Rheum 2007; 56:2382-2391



Primary outcome – thrombosis
Secondary outcome - TIA

- Low incidence of thrombotic events (~ 2.7/100 pt-yr)
- Significantly under-powered

Question #5

What's the most important advice you should give to this patient?

a) Stop smoking
b) Stop smoking
c) Stop smoking
d) All of the above

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a) Stop smoking
b) Stop smoking
c) Stop smoking
d) All of the above

Primary Prevention of Thrombosis in aPL+ Patients

- At least 50% of APS patients with thrombotic events have one or more non-aPL reversible risk factors at time of thrombosis.
- Identification and elimination of these risk factors, and aggressive prophylaxis during high-risk periods (*e.g.*, post-surgical procedures), are crucial for primary thrombosis prevention.

CASE STUDY 3

- 43 year-old woman is planning to become pregnant
- Found to have false positive syphilis serology 15 years ago while in the military; +IgG aCL on further testing
- No prior pregnancies, no history of thrombosis.
- No medications

Test	2 Years Ago	1 year ago	3 months ago
IgG aCL (0-23)	75	60	83
IgM aCL (0-11)	17	10	2
IgG anti-β_2GPI (< 15)	nd	68	75
IgM anti-β_2GPI (< 15)	nd	5	3
LA	Negative	Negative	Negative

Question #6

What treatment would you recommend for this patient?

a) Start low-dose aspirin; add prednisone, 40 mg daily, when pregnancy is confirmed.

b) Start low-dose aspirin; add prophylactic dose LMWH when pregnancy is confirmed.

c) Start low-dose aspirin and continue through pregnancy.

d) Start hydroxychloroquine, 200 mg twice daily, and continue through pregnancy.

e) No treatment

Question #6

What treatment would you recommend for this patient?

a) Start low-dose aspirin; add prednisone, 40 mg daily, when pregnancy is confirmed.

b) Start low-dose aspirin; add prophylactic dose LMWH when pregnancy is confirmed.

c) Start low-dose aspirin and continue through pregnancy.

d) Start hydroxychloroquine, 200 mg twice daily, and continue through pregnancy.

e) No treatment

CASE STUDY 4

- 24 year-old woman is planning a second pregnancy. Her first pregnancy, 8 months ago, was an early miscarriage at about 6 weeks gestation.
- Found to have a low level of aCL
- No history of thrombosis.
- No medications except prenatal vitamins

Test	7 months ago	1 month ago
IgG aCL (0-23)	28	25
IgM aCL (0-11)	14	3
IgG anti-β_2GPI (< 15)	nd	10
IgM anti-β_2GPI (< 15)	nd	6
LA	Negative	Negative

Question #7

What treatment would you recommend for this patient?

a) Start low-dose aspirin; add prednisone, 40 mg daily, when pregnancy is confirmed.
b) Start low-dose aspirin; add prophylactic dose LMWH when pregnancy is confirmed.
c) Start low-dose aspirin and continue through pregnancy.
d) Start hydroxychloroquine, 200 mg twice daily, and continue through pregnancy.
e) No treatment

Question #7

What treatment would you recommend for this patient?

a) Start low-dose aspirin; add prednisone, 40 mg daily, when pregnancy is confirmed.
b) Start low-dose aspirin; add prophylactic dose LMWH when pregnancy is confirmed.
c) Start low-dose aspirin and continue through pregnancy.
d) Start hydroxychloroquine, 200 mg twice daily, and continue through pregnancy.
e) No treatment

Summary

- Be cautious using the Classification Criteria for Definite APS to exclude the diagnosis of APS.
- Use the principles of the laboratory criteria to assess an individual patient's level of risk.
- Consider aPL as risk factors.
- In patients with aPL, eliminate or aggressively treat non-aPL risk factors for thrombosis.
- Be aware of the possible "over-diagnosis" of APS in women with early pregnancy losses and low-risk aPL profiles.

Contact

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