2 Antiphospholipid Syndrome: General Features

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Introduction

The first papers on the antiphospholipid syndrome (APS) described recurrent arterial and venous thromboses and fetal losses. These remain the characteristic clinical features of this syndrome although the spectrum of associated symptoms and signs has broadened considerably over the last 15 years. The aim of this chapter is to give a clinical overview and preliminary classification criteria for the APS by way of introduction to the more detailed chapters that follow.

Demographics

APS has been recognized largely as a disease of young women due to the association with systemic lupus erythematosus (SLE), and pregnancy loss. In our experience approximately 50% of patients with APS do not have an underlying systemic disease and are labeled primary APS (PAPS). The age of first thrombosis in PAPS has been shown to range between 32 and 45 years [1]. There are problems with reporting bias, with young patients with thrombosis, and pregnancy loss more likely to be investigated, hence skewing the results. However, antiphospholipid antibodies (aPL) are being increasingly recognized in a diverse number of conditions and in older subjects.

The prevalence of APS in SLE increases with duration of follow up and on the number of samples tested for aPL. In a cohort of 667 patients with SLE (15% definite APS and 21% probable APS), with a mean follow up of 3.1 years, the prevalence of definite APS increased from 5 to 15% as the number of samples tested increased from 1–3 to 7–10 [2].

Racial differences have been noted with immunoglobulin A (IgA) anticardiolipin antibodies (aCL) more common in Afro-Caribbeans [3]. Histocompatibility genes associated with APS also show genetic differences. HLA-DR4 seems more important in Anglo-Saxons, whereas DR7 emerges in populations of Latin origin [4].

Definition and Classification of APS

An international consensus statement on classification criteria for definite antiphospholipid syndrome was published after a workshop in 1998 (Table 2.1) [5].

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Table 2.1. Preliminary criteria for the classification of the antiphospholipid syndrome.

Clinical criteria

1. Vascular thrombosis:
   One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by imaging or Doppler studies or histopathology, with the exception of superficial venous thrombosis. For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.
2. Pregnancy morbidity
   a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th weeks of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or
   b) One or more premature births of a morphologically normal neonate at or before the 34th week of gestation because of severe pre-eclampsia or eclampsia, or severe placental insufficiency or
   c) Three more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic, or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

Laboratory criteria

1. Anticardiolipin antibody of IgG and/ or IgM isotype in blood, present in medium or high titre, on two or more occasions, at least 6 weeks apart, measured by a standard enzyme linked immunosorbent assay for β_2-glycoprotein 1-dependent anticardiolipin antibodies.
2. Lupus anticoagulant present in plasma on two or more occasions at least 6 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis.

Definite APS is considered to be present if at least one of the clinical and one of the laboratory criteria are met.

The purpose of the classification criteria was to facilitate studies of treatment and causation, and focused on defining a category of "definite" APS. Probable or possible categories were excluded due to lack of supportive prospective studies or experimental evidence. The workshop acknowledged that thrombosis may be multifactorial and other contributing factors and comorbidities should be identified.

Other features of APS such as thrombocytopenia, hemolytic anemia, transient cerebral ischaemia, transverse myelopathy or myelitis, livedo reticularis, cardiac valve disease, multiple sclerosis-like syndrome, chorea, and migraine were felt by the workshop to not have as strong an association and were excluded as classification criteria. This should not deter the practicing clinician from making the diagnosis or administering therapy if other causes of such features have been excluded.

Piette has urged clinicians to be aware of suspicious symptoms. Fever and weight loss are unusual in APS and suggest infection or malignancy. Splenomegaly is not a feature of PAPS unless complicated [6]. Human immunodeficiency virus (HIV) infection is the syphilis of the late 20th century and can be a great mimicker, including the production of aPL, although thrombosis associated with aPL in these patients is rare.

When Should aPL Be Measured?

In the past 15 years it has become increasingly recognized that hereditary or acquired defects in anticoagulant mechanisms may predispose to thrombosis. The requirement for thrombophilia screening in patients who develop a thrombotic event must be assessed on an individual patient basis. Indications for screening are

Table 2.2. Indications for the measurement of aPL.

- Connective tissue disease especially SLE
- Venous/arterial thrombosis before the age of 45 years
- Thrombosis after trivial provocation
- Association of arterial and venous thrombosis
- Association of thrombosis and fetal loss
- Recurrent events
- Family history
- Thrombosis in an unusual site: retinal vein, portal, cerebral venous, renal vein
- Recurrent superficial thromophlebitis
- Recurrent miscarriage
- Coumarin-induced skin necrosis

listed in Table 2.2. The prevalence of aPL in SLE ranges between 30 and 50%; therefore a search for these antibodies is mandatory [7, 8]. aPL have also been found in a variety of other systemic autoimmune disorders including Sjögren's syndrome, myositis, vasculitis and rheumatoid arthritis [9].

The timing of measurement may be important. It has been suggested that aPL may be consumed during a thrombotic episode, or alternatively due to endothelial activation and exposure of cryptic antigens they may become positive after thrombosis: "epiphenomenon" [10]. For these reasons aPL should be measured between 6 weeks and 3 months post-thrombosis to confirm results. Steroid therapy and the development of the nephrotic syndrome may also be associated with a falsely negative result [11–13].

What Should Be Measured?

It is generally agreed that both IgG and IgM aCL isotypes should be tested in addition to lupus anticoagulant (LA). The significance of IgA aCL antibodies is however debated. Several studies have found an increased prevalence in Afro-Caribbean or Afro-American patients with SLE [14]. However the thrombotic risk is unclear. In contrast, in Spanish patients a very low prevalence was found, 2% in SLE patients and no cases of PAPS were positive [15]. A London-based study found a low frequency in a SLE population (13%) and in only 3/18 of these was IgA the only aCL isotype [16]. Molina et al found a correlation with hemolytic anemia, but not with thrombosis, in Hispanics [3]. Lopez, however, found a significant association of IgA aCL with thrombosis and thrombocytopenia in SLE patients that was more significant than IgM or IgG [17]. McCarty found IgA aCL to be the only isotype in 28 patients with APS [18].

IgA aCL has been associated with infection including human T-cell lymphotrophic virus (HTLV-1). An elevated total IgA level in sera of patients with HTLV-1 suggests that the IgA aCL in this population may represent polyclonal B-cell activation [19]. Tsutsumi measured IgA anti-β_2-glycoprotein I (anti-β_2GPI) in 124 SLE patients, and found 25% were positive and a significant relationship to thrombosis was observed [20].

Anti-β_2-glycoprotein I assays have shown a higher specificity for APS than aCL in 120 patients with PAPS, SLE with APS and SLE without APS. Anti-β_2GPI were detected in 53.5% of APS patients but only 4.1% of SLE patients [21].

Prevalence of aPL

General Population

What is the prevalence of aPL in the general population? Nencini et al in 1993 studied 55 healthy volunteers with a mean age of 40 years; only one patient had a positive aCL or LA [22]. In 543 blood donors under 65 years Fields et al found a prevalence of 2% for aCL [23]. The Antiphospholipid Antibodies in Stroke Study (APASS) Group also found a prevalence of aCL in 4.3% of 257 hospitalized patients (non stroke) with mean age 66, which was similar to the prevalence in 1014 inpatients studied by Schved et al with a mean age of 66.7 years with the most frequent association carcinoma or alcohol abuse [24, 25]. Ginsberg in a population of 179 patients, mean age 55 years in whom DVT had been excluded found a prevalence of aCL in 18% and LA in 2% [26].

Venous Thromboembolism

In patients with venous thromboembolism(VTE): the prevalence of aCL varies from 3% to 17% and LA 3–14%. The lowest rates were found by Kearon et al in a study of "idiopathic" VTE. The highest figures were found by Schulman et al who examined 897 patients with VTE, with a follow up of 4 years, in whom aCL were tested 6 months post-deep vein thromboembolism (DVT). Interestingly, of 20 recurrent episodes aCL was negative in 14 at the time of the recurrent episode [26–29].

Systemic Lupus Erythematosus

The highest prevalence of aPL occurs in patients with SLE, with estimates varying between 30 and 63%. Ghirardello et al found 51.4% of SLE patients were positive for aCL and 8.6% for LA, whilst in Horbach's retrospective study IgG aCL were found in 64% of patients with a history of thrombosis and 41% in those without thrombosis; LA were found in 25.1% [30, 31].

Arterial Thrombosis

In the situation of stroke Nencini et al found 18% of young patients, mean age 38 years, were positive for aPL (LA and aCL) whereas APASS found 9.7% of first stroke patients had a positive aCL. In myocardial infarction the prevalence of aCL is between 5 and 15% [22, 24, 32].

Elderly

Many autoantibodies become more prevalent with increasing age and aPL is no exception. Fields found that 12% of 300 healthy elderly, those older than 65, had IgG or IgM aCL antibodies and that there was an association with positive antinuclear antibodies (ANA) but not rheumatoid factor [23]. Schved found a prevalence of 7% [25]. However, it is unclear whether this is a result of the increasing

prevalence of associated conditions in the elderly such as malignancy, and drug treatment. The significance of such antibodies in the elderly remains unclear although they have been found to be a risk factor for ischemic stroke in both the young and elderly.

Risk of Positive aPL Tests

What is the risk of having these antibodies in the above groups of patients? In VTE Bongard compared 107 patients with DVT to 186 without DVT and found no association with aCL [33]. Ginsberg, in 1995, studied patients with a first episode of venous thromboembolism. A strong association with LA was found with an odds ratio of 9.4 but no significant association was found with aCL, even when only those patients with high levels (greater than 50 G phospholipid (GPL) units) were studied [26]. Simioni also found a significant association with the LA with an odds ratio of 10.7 [29]. Schulman in 1998 examined the incidence of recurrent DVT in patients who were aCL positive. The risk ratio for further venous thrombosis was 2.1 [28]. A similar risk was found by Kearon in 1999 who looked at recurrence rates in 162 patients with "idiopathic" DVT where the risk was 2.3 for aCL and 6.8 for LA [27]. In a meta-analysis Wahl in 1998 examined the risk of venous thromboembolism in aPL positive patients without autoimmune disease or previous thrombosis. The odds ratio was 11.1 for LA and 1.6 for aCL. However, that risk rose to 3.21 if higher titers of aCL were examined [34]. There were 90 DVTs in the American Physicians Health Study and aCL levels greater than the 95th percentile (greater than 33 GPL units) had a relative risk of venous thromboembolism of 5.3 [35].

In terms of arterial disease the American Physicians Study did not find a significant association of aCL with CVA. A study of community-dwelling elderly by Schmidt, found no association between MRI findings and aCL status but there was an association with neuropsychological performance [36]. Nencini and coworkers in 1993 found 18% of young strokes were positive for aPL tested at 99 days post-CVA compared to 2% of controls. They also found that the recurrence rate for stroke was higher in the aPL group compared to a group of stroke patients that were negative [22]. The APASS group compared first stroke to a control population of non-stroke hospitalized patients. ACL were studied and were positive in 24 of 248 of the stroke patients compared to 11 of 257 control patients. The odds ratio for stroke in patients who were aCL positive was calculated at 2.33. There was no correlation between time of blood drawn after first stroke and aCL status. In addition they found that the prevalence of aCL was only slightly higher in patients with prior stroke compared with those with first stroke. They concluded that it was unlikely that stroke causes a positive aCL status i.e. is an epiphenomenon [24]. This was supported in a study by Chakravarty et al who found that none of initial antibody-negative stroke patients became positive when sera were retested after 6 months [37]. The APASS group concluded that aCL were a risk factor for first ischemic stroke and the extent of association was comparable to that between stroke and hypertension. Kittner, who reviewed several epidemiological studies concluded that the strength of association between aCL and stroke, in patients over 50 years, was comparable to hypertension with an odds ratio of 2.2. In a young population < 50 years the odds ratio may rise to 8.3 [38].

Further information on arterial disease is obtained from the Helsinki heart study. In this study healthy men with a low-density lipoprotein (LDL) cholesterol greater than 5.2 mmol/l, with a mean age of 49 years, were studied for cardiac end points. In the highest quartile of aCL patients, the odds ratio for myocardial infarct was significant at 2.0. In multivariate analysis the risk was independent of other risk factors and interestingly aCL levels were higher in smokers [32].

In SLE, Ghirardello et al found that thrombosis was associated with LA and to a lesser extent with IgG aCL [30]. Horbach et al found that LA was a significant risk factor for both VTE and arterial events (odds ratio 6.55 and 9.77, respectively) but only IgM aCL greater than 20 M phospholipid (MPL) units were associated with venous events (odds ratio 3.90). There was no association of aCL with arterial disease [31]. Abu Shakra et al studied 390 lupus patients and found no association of aCL with thrombosis, but there was an association with Coombs positive status and thrombocytopenia. LA was associated with thrombosis with odds ratio of 7.9 [39]. Wahl performed a meta-analysis of the risk of venous thromboembolism and examined 26 studies comprising 2249 patients. The odds ratio for LA and venous events was 6.32 and 2.17 for aCL. When recurrent venous events were examined these ratios increased to 11.6 and 3.91, respectively [40].

A significant impact on survival has also been noted by several authors. In a retrospective study of 52 patients with aCL followed over 10 years, 29% of APS patients (31 patients) had recurrent events and in the asymptomatic group (21 patients) half developed APS. Mortality was 10% [41]. The negative impact on survival of aCL has been reported by several authors. Jouhikainen et al compared 37 SLE patients, LA positive, with 37 age and sex matched SLE patients without LA. During a median follow up of 22 years, 30% in the LA group died in contrast to 14% in the control group [42]. Among patients with VTE (major associated disease excluded) the mortality in Swedish patients was 15% at 4 years in those with aCL and 6% in those without antibodies ($P = 0.01$) [28].

In summary, the following observations can be made. aPL are present in approximately 2–4% of the normal population and the prevalence increases with age. A high prevalence amongst SLE patients is seen. There is an association with both venous and arterial thrombosis but the strength of association varies amongst studies. This probably reflects on different population groups, study designs i.e. retrospective versus prospective, different assays used and definitions of thrombosis. In several studies the risk of thrombosis appears to be higher with LA and the data suggests a true association rather than epiphenomenon. In a given patient, both aCL and LA should be measured. A significant impact on long-term survival has been noted. The positive predictive value of individual tests will need to be evaluated in future studies.

Risk Factors for Thrombosis in APS

In a cohort of 360 patients in the Italian aPL Registry (patients identified by either previous thrombosis, abnormal coagulation study suggestive of LA, or suffering with a disease known to be associated with aPL) followed prospectively for a median of 3.9 years, with either a positive LA or aCL, 34 patients developed a thrombotic event (26 spontaneously). This was a total incidence of 2.5%/patient-year, with a rate of 5.4%/patient-year in those with a previous thrombosis and 0.95%/patient-year in

asymptomatic subjects [43]. Clearly the mere presence of aPL is not sufficient for an event. Patients with aCL > 40 units and previous thrombosis were important risk factors for future events. The importance of previous thrombosis as a risk factor was highlighted by the recurrence rate in our patients at St. Thomas' Hospital, where those with APS and previous thrombosis, had a recurrence rate of 20%/patient-year of follow-up [44]. In pregnancy, patients with a prior history of miscarriages or vascular occlusions have a significantly higher rate of adverse pregnancy outcome [43].

Emlen was also concerned about the low positive predictive value of current aPL assays and reminded us of the many risk factors for thrombosis in lupus patients [45]. Most centers dealing with large numbers of SLE patients are now focussing on the increased prevalence of arterial disease and aiming to correct risk factors in individual patients including hypertension, lipids and homocysteinemia in the hope of preventing late morbidity, which is often vascular in origin.

Several studies have shown that risk factors can be additive. In venous thrombosis in the young, Rosendaal found that the risk of thrombosis rose sharply with the number of risk factors and that fewer factors were required for thrombosis in older subjects (greater than 55 years) [46]. The coincidental presence of other coagulation abnormalities such as factor V Leiden in patients with APS has been reported by several groups. Factor V Leiden and aCL can both cause the activated protein C resistance phenotype and not surprisingly the combination has been associated with severe thrombosis [47–50]. Methylenetetrahydrofolate reductase $C^{677} \rightarrow T$ substitution (increased homocystinuria) may also have an effect on age at first occlusive event [49]. Furthermore, Peddi reported the development of catastrophic APS in a patient with SLE, aCL and antithrombin III deficiency [51].

Conditions Associated with Secondary APS

It has been estimated that up to one half of patients with APS do not have an associated systemic disease [52]. A large number of conditions have however been reported in association with aPL. These are listed in Table 2.3. In most of these conditions apart from SLE, thrombosis i.e. APS is unusual. In a prospective study Merkel found 16% of rheumatoid arthritis and SLE patients had either IgG or IgM aCL compared with 4.0% of blood donors. Patients with scleroderma, myositis, undifferentiated connective tissue disease and systemic vasculitis did not differ in prevalence from the control blood donors [9].

Table 2.3. aPL in other conditions.

- Connective tissue disorders
- Systemic vasculitis
- Malignancy
- Crohn's disease
- Infection
  - Syphilis/Lyme
  - Human immunodeficiency virus
  - Hepatitis C
  - Cytomegalovirus
  - Mycoplasma
- Drugs
  - Chlorpromazine
  - Quinine/quinidine
  - Hydralazine
  - Procainamide
  - Phenytoin
  - Interferon-α

The manifestations of APS are not usually seen in infection- or drug-associated aCL although occasional reports of the development of thrombosis in infections such as acquired immune deficiency syndrome (AIDS) and cytomegalovirus (CMV) has prompted people to recommend searching for infections in patients developing manifestations of APS [53, 54]. Procainamide has been shown to produce β_2-glycoprotein 1-dependent antibodies that are potentially pathogenic [55].

Differences Between Primary and Secondary APS

Vianna et al found that PAPS and APS secondary to SLE had similar clinical features, but heart valve disease, autoimmune hemolytic anemia, lymphopenia, neutropenia, and low C4 levels were more common in patients with SLE [56]. Anti-dsDNA or antibodies to extractable nuclear antigens were not found in PAPS and their presence should suggest a secondary cause. The distinction between PAPS and APS due to SLE can sometimes be difficult. Features such as thrombocytopenia, anemia, renal, and central nervous system (CNS) disease may be seen in both conditions. Piette has been a strong advocate of exclusion criteria for PAPS and these are listed in Table 2.4 [57].

There do not appear to be any differences in rates of arterial or venous thrombosis, or fetal loss [43, 56, 58]. Shah et al found IgM aCL more commonly in SLE than PAPS (22/42 versus 1/10) but no difference in thrombotic rates [41].

Descriptions of families with multiple family members affected have suggested a familial association. Not all studies in SLE have found an association with HLA class 2 alleles though several studies have shown an association with HLA DR4, HLA-DR7 and HLA-DRw53. There appear to be ethnic differences with HLA-DR4 more important in Anglo-Saxons and HLA DR7 in populations of Latin extraction. At this stage no clear pattern of differences between PAPS and secondary APS has emerged [4, 50, 59].

The number of cases reported in the literature of patients with PAPS evolving into SLE is small. Silver et al and Mujic et al have reported the evolution in small numbers (7/71 and 3/80, respectively) but Asherson et al and Vianna et al did not find any [52, 56, 60, 61]. The short period of follow-up may have been responsible for the latter result (5 and 2 years, respectively) as several patients have developed the syndrome after 10 years. The presence of high titer of ANA (> 1:320) and lymphopenia may be predictive [62].

Table 2.4. Exclusion criteria to distinguish SLE associated APS from PAPS.

- Malar or discoid rash
- Oral, pharyngeal, or nasal ulceration
- Frank arthritis
- Pleurisy/pericarditis
- Persistent proteinuria > 0.5 g/day, due to biopsy proven immune complex related glomerulonephritis
- Lymphopenia < 1000 cells/μl
- Antibodies to dsDNA (crithidia or radioimmunoassay), or ENA
- ANA > 1:320
- Treatment with drugs known to produce aPL
- Follow up < 5 years from the initial clinical manifestation.

Clinical Features

Clinical features will be covered extensively in following chapters. The definite associations are with arterial and venous thrombosis, recurrent miscarriage and thrombocytopenia. The latter is generally mild and occurs in 20–40% of patients with APS. Severe thrombocytopenia is unusual [63]. Cardiac valve abnormality is also seen in up to 35% of patients, usually regurgitation and the mitral valve is affected more often than the aortic. Valve thrombi, subendothelial deposits of immunoglobulins, including aCL have been noted in deformed valves [64]. Diastolic dysfunction and cardiomyopathy perhaps related to subclinical myocardial damage has also been reported [65]. Avascular necrosis is of interest to rheumatologists and most cases

Table 2.5. Clinical associations.

CNS	**Bone**
Chorea	Avascular necrosis
Migraine	Bone marrow necrosis
Psychosis	
Epilepsy	**Obstetric**
CVA/TIA	Recurrent miscarriage
Hypoperfusion on SPECT scanning	Pre-eclampsia
Sensorineural hearing loss	Growth retardation
Transverse myelopathy	HELLP syndrome
Cognitive impairment	
Pseudotumor cerebri	**Renal**
Cerebral vein/artery thrombosis	Glomerular thrombosis
Retinal venous thrombosis	Renal artery stenosis
Multiple sclerosis like syndrome	Renal insufficiency
	Renal artery thrombosis
Gastrointestinal	Renal vein thrombosis
Hepatic necrosis	
Acalculous cholecystitis	**Pulmonary**
Budd–Chiari	Pulmonary embolism
Intestinal ischemia	Pulmonary hypertension
	ARDS
Vascular disease	
Atherosclerosis	**Endocrine**
Cardiac valvular disease	Adrenal failure
Acute myocardial infarction	Hypopituitarism
Failed angioplasty	
Diastolic dysfunction	**Hematological**
Intracardiac thrombosis	Thrombocytopenia
Cardiomyopathy	Autoimmune hemolytic anemia
Buerger's disease	
Skin	
Livedo reticularis	
Cutaneous ulcers	
Dego's Disease	
Splinter hemorrhages	
Superficial thrombophlebitis	
Distal cutaneous ischemia	

CVA, cerebrovascular accident; TIA, transient ischemic attack; SPECT, single position emission computerized tomography; HELLP, hemolytic anaemia, elevated liver function tests and low platelets; ARDS, adult respiratory distress syndrome.

are seen in patients taking steroids. However, although avascular necrosis has been reported in small number of patients with PAPS, studies in patients with SLE have not shown a definite association with aPL. Numerous other associations have been reported and these manifestations are listed in Table 2.5. Whether these will all stand the test of time remains to be determined.

Conclusion

The APS has been clearly defined with distinct clinical and serological features. Early recognition of this syndrome by clinicians in a variety of specialties is crucial in improving the risk of morbidity and mortality in these patient populations.

References

1. Piette JC, Cacoub P. Antiphospholipid syndrome in the elderly: caution. Circulation 1998;97:2195–2196.
2. Perez-Vazquez ME, Villa A, Drenkard C, Cabiedes J, Alarcon-Segovia D: Influence of disease duration, continued follow up and further antiphopholipid testing on the frequency and classification category of antiphospholipid syndrome in a cohort of patients with SLE. J Rheumatol 1993;20:437–42.
3. Molina JF, Gutierrez-Urena S, Molina J et al. Variability of anticardiolipin antibody isotype distribution in 3 geographic populations of patients with systemic lupus erythematosus. J Rheumatol 1997; 1997;24:291–296.
4. Sebastiani GD, Galeazzi M, Morozzi G, Marcolongo R: The immunogenetics of the antiphospholipid syndrome, anticardiolipin antibodies,and lupus anticoagulant. Semin Arthritis Rheum 1996;25:414–420.
5. Wilson WA, Gharavi AE, Koike T et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome. Report of an International Workshop. Arthritis Rheum 1999;42:1309–1311.
6. Piette JC: Criteria for the antiphospholpid syndrome. Lupus 1998;7(Suppl 2):S149–S157.
7. Cervera R, Font J, Lopez-Soto A et al. Isotype distribution of anticardiolipin antibodies in SLE, prospective analysis of 100 patients. Ann Rheum Dis 1990;49:109–113.
8. Alarcon-Segovia D, Deleze M, Oria CV et al. Antiphospholipid antibodies and the antiphospholipid syndrome in SLE. A prospective analysis of 500 consecutive patients. Medicine 1989;68:353–365.
9. Merkel P, Chang Y, Pierangeli S, Convery K, Harris N, Polisson R. The prevalence and clinical associations of anticardiolipin antibodies in a large inception cohort of patients with connective tissue diseases. Am J Med; 1996; 101: 576–583.
10. Petri M. Update on antiphospholipid antibodies. Curr Opin Rheumatol 1998;10:426–430.
11. Perez-Vazquez ME, Cabiedes J, Cabral AR, Alarcon-Segovia D. Decrease in serum antiphospholipid antibodies upon development of the nephrotic syndrome in patients with SLE: relationship to urinary losses of IgG and other factors. Am J Med 1992;92:357–363.
12. Silveira LH, Jara LJ, Espinoza LR. Transient disappearance of serum antiphospholipid antibodies can also be due to prednisolone therapy. Clin Exp Rheumatol 1996; 14: 217–226.
13. Drenkard C, Sanchez-Guerrero J, Alarcon-Segovia D. Fall in antiphospholipid antibody at time of thromboocclusive episodes in SLE. J Rheumatol 1989;16:614–617.
14. Faghiri Z, Taheri F, Wilson WA et al. IgA is the most prevalent isotype of anticardiolipin and anti-β_2 glycoprotein-1 antibodies in Jamaican and African–American SLE patients. Lupus 1998; 7(Suppl 2):S185.
15. Selva-O'Callaghan A, Ordi-Ros J, Monegal-Ferran F, Martinez N, Cortes-Hernandez F, Vilardell-Tarres M. IgA anticardiolipin antibodies – relation with other antiphospholipid antibodies and clinical significance. Thromb Haemost 1998;79:282–285.
16. Bertolaccini ML, Atsumi T, Amengual O, Katsumata K, Khamashta MA, Hughes GRV. IgA anticardiolipin antibody testing does not contribute to the diagnosis of antiphospholipid syndrome in patients with SLE. Lupus 1998;7(Suppl 2): S184.
17. Lopez LR, Santos ME, Espinoza LR, La Rosa FG. Clinical significance of IgA versus IgG and M anticardiolipin antibodies in patients with SLE. Am J Clin Pathol 1992;98:449–454.

18. McCarty GA, Freeland E,Wagenknecht DR, McIntyre JA. Antiphospholipid antibody syndrome in 28 patients with IgA as the sole antibody isotype. Lupus 1998;7(Suppl 2):S186.
19. Wilson WA, Morgan OC, Barton EN et al. IgA antiphospholipid antibodies in HTLV1 associated tropical spastic paraparesis. Lupus 1995;4:138–141.
20. Tsutsumi A, Matsuura E, Ichikawa K et al. Ig A class anti β_2 glycoprotein 1 in patients with SLE. J Rheumatol 1998;25:74–78.
21. Amengual O, Atsumi T, Khamashta MA, Koike T, Hughes GR. Specificity of ELISA for antibody to beta 2 glycoprotein 1 in patients with antiphospholipid syndrome. Br J Rheumatol 1996;35:1239–1243.
22. Nencini P, Baruffi M, Abbate R, Massai G, Amaducci L, Inzitari D. Lupus anticoagulant and anticardiolipin antibodies in young adults with cerebral ischaemia. Stroke 1992;23:189–193.
23. Fields R, Toubbeh H, Searles R, Bankhurst A. The prevalence of anticardiolipin antibodies in a healthy elderly population and its association with antinuclear antibodies. J Rheumatol 1989;16:623–625.
24. Antiphospholipid Antibodies in Stroke Study Group. Clinical, radiological, and pathological aspects of cerebrovascular disease associated with antiphospholipid antibodies. Stroke 1993;24(Suppl 1):S1–123.
25. Schved JF, Dupuy-Fons C, Biron C, Quere I, Janbon C. A prospective epidemiological study on the occurrence of antiphospholipid antibody: the Montpellier Antiphospholipid (MAP) Study. Haemostasis 1994;24:175–182.
26. Ginsberg J, Wells P, Brill-Edwards P et al. Antiphospholipid antibodies and venous thromboembolism. Blood 1995;86:3685–3691.
27. Kearon C, Gent M, Hirsh J, Weitz J et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med 1999;340:901–907.
28. Schulman S, Svenungsson E, Granqvist S and the Duration of Anticoagulation Study Group. Anticardiolipin antibodies predict early recurrence of thromboembolism and death among patients with venous thromboembolism following anticoagulant therapy. Am J Med 1998;104:332–338.
29. Simioni P, Prandoni P, Zanon E et al. Deep venous thrombosis and lupus anticoagulant. A case–control study. Thromb Haemost 1996;76:187–189.
30. Ghirardello A, Doria A, Ruffatti A et al. Antiphospholipid antibodies (aPL) in systemic lupus erythematosus. Are they specific tools for the diagnosis of aPL syndrome. Ann Rheum Dis 1994;53:140–142.
31. Horbach DA, van Oort E, Donders RC et al. Lupus anticoagulant is the strongest risk factor for both venous and arterial thrombosis in patients with systemic lupus erythematosus – comparison between different assays for the detection of antiphospholipid antibodies, Thromb Haemost 1996;76:916–924.
32. Vaarala O, Puurunen M, Manttari M et al. Anticardiolipin antibodies and risk of myocardial infarction in a prospective cohort of middle-aged men. Circulation 1995;91:23–27.
33. Bongard O, Reber G, Bounameaux H, deMoerloose P. Anticardiolipin in acute venous thromboembolism. Thromb Haemost 1992;67:724.
34. Wahl DG, Guillemin F, de Maistre E, Perret-Guillaume C, Lecompte T, Thibaut G. Meta-analysis of the risk of venous thrombosis in individuals with antiphospholipid antibodies without underlying autoimmune disease or previous thrombosis. Lupus 1998;7:15–22.
35. Ginsburg K, Liang M, Newcomer L et al. Anticardiolipin antibodies and the risk for ischemic stroke and venous thrombosis. Ann Intern Med 1992;117:997–1002.
36. Schmidt R, Auer-Grumbach P, Fazekas F, Offenbacher H, Kapeller P. Anticardiolipin antibodies in normal subjects. Neuropsychological correlates and MRI findings. Stroke 1995;26:749–754.
37. Chakravaty KK, Byron MA, Webley M et al. Antibodies to cardiolipin in stroke: Association with mortality and functional recovery in patients without systemic lupus erythematosus. Q J Med 1991;79:397–405.
38. Kittner S, Gorelick P. Antiphospholipid antibodies and stroke: an epidemiological perspective. Stoke 1992;23(Suppl 1):1–19, 1–22.
39. Abu-Shakra M, Gladman DD, Urowitz MB, Farewell V. Anticardiolipin antibodies in systemic lupus erythematosus: clinical and laboratory correlations. Am J Med 1995;99:624–628.
40. Wahl DG, Guillemin F, de Maistre E, Perret C, Lecompte T, Thibaut G. Risk for venous thrombosis related to antiphospholipid antibodies in systemic lupus erythematosus. A meta-analysis. Lupus 1997;6:467–473.
41. Shah NM, Khamashta MA, Atsumi T, Hughes GRV. Outcome of patients with anticardiolipin antibodies: a 10 year follow up of 52 patients. Lupus 1998;7:3–6.
42. Jouhikainen T, Stephansson E, Leirisalo-Repo M. Lupus anticoagulant as a prognostic marker in systemic lupus erythematosus. Br J Rheumatol 1993;32:568–573.

43. Finazzi G, Brancaccio V, Moia M et al. Natural history and risk factors for thrombosis in 360 patients with antiphospholipid antibodies. A four year prospective study from the Italian Registry. Am J Med. 1996;100:530–536.
44. Khamashta M, Cuadrado M, Mujic F, Taub N, Hunt B, Hughes GRV. The management of thrombosis in the antiphospholipid–antibody syndrome. N Engl J Med 1995;332:993–997.
45. Emlen W. Antiphospholipid antibodies: new complexities and new assays. Arthritis Rheum 1996;39:1441–1443.
46. Rosendaal F. Thrombosis in the young: epidemiology and risk factors. A focus on venous thrombosis. Thromb Haemost 1997;78:1–6.
47. Brenner B, Vulfsons SL, Lanir N, Nahir M. Coexistence of familial antiphospholipid syndrome and factor V Leiden: impact on thrombotic diathesis. Br J Haematol 1996;94:166–167.
48. Alarcon-Segovia D, Ruiz-Arguelles GJ, Garces-Eisele J, Ruiz-Arguelles. Inherited activated protein C resistance in a patient with familial primary antiphospholipid syndrome. J Rheumatol 1996;23:2162–2165.
49. Ames P, Tommasino C, D'Andrea G, Iannaccone L, Brancaccio V, Margaglione M. Thrombophilic genotypes in subjects with idiopathic antiphospholpid antibodies – prevalence and significance. Thromb Haemost 1998;79:46–49.
50. Schutt M, Kluter H, Hagedorn-Greiwe M, Fehm HL, Wiedemann GJ. Familial coexistence of primary antiphospholipid syndrome and factor V Leiden. Lupus 1998;7:176–82.
51. Peddi VR, Kant KS. Catastrophic secondary antiphospholipid syndrome with concomitant antithrombin III deficiency. J Am Soc Nephrol 1995;5:1882–1887.
52. Asherson RA, Khamashta MA, Ordi-Ros J et al. The primary antiphospholipid syndrome: major clinical and serological features. Medicine 1989;68:366–374.
53. Soweid AM, Hajjar RR, Hewan-Lowe KO, Gonzalez EB. Skin necrosis indicating antiphospholipid syndrome in patient with AIDS. S Med J 1995;88:786–778.
54. Labarca J, Rabaggliati R, Radrigan F et al Antiphospholipid syndrome associated with cytomegalovirus infection: case report and review. Clin Infect Dis 1997;24:197–200.
55. Merrill JT, Shen C, Gugnani M, Lahita RG, Mongey AB. High prevalence of antiphospholipid antibodies in patients taking procainamide. J Rheumatol 1997;24:1083–1088.
56. Vianna JL, Khamashta MA, Ordi-Ros J et al. Comparison of the primary and secondary antiphospholipid syndrome: a European multicenter study of 114 patients. Am J Med 1994;96:3–9.
57. Piette JC, Weschler B, Frances C, Papo T, Godeau P. Exclusion criteria for primary antiphospholipid syndrome. J Rheumatol 1993;20:1802–1804.
58. Krnic-Barrie S, O'Connor CR, Looney S, Pierangeli S, Harris N, Phil M. A retrospective review of 61 patients with antiphospholipid syndrome. Analysis of factors influencing recurrent thrombosis. Arch Intern Med 1997;157:2101–2108.
59. Granados J, Vargas-Alarcon G, Drenkard C et al. Relationship of anticardiolipin antibodies and antiphopholipid syndrome to HLA-DR7 in Mexican patients with SLE. Lupus 1997;6:57–62.
60. Silver RM, Draper MJ, Scott JR, Lyon JL, Reading J, Branch DW. Clinical consequences of antiphospholipid antibodies. An historic cohort study. Obstet Gynecol 1994;83:372–377.
61. Mujic F, Cuadrado MJ, Lloyd M et al. Primary antiphospholipid syndrome evolving into SLE. J Rheumatol 1995;22:1589–1592.
62. Seisdedos L, Munoz-Rodriguez F J, Cervera R, Font J, Ingelmo M. Primary antiphospholipid syndrome evolving into SLE. Lupus 1997;6:285–286.
63. Galli M, Finazzi G, Barbui T. Thrombocytopenia in the antiphospholipid syndrome: pathophysiology, clinical relevance and treatment. Ann Med Interne 1996;147(Suppl 1):24–27.
64. Hojnik M ,George J, Ziporen L, Schonfeld Y. Heart valve involvement in the antiphopsholipid sydrome. Circulation 1996;93:1579–1587.
65. Coudray N, de Zuttere D, Bletry O et al. M mode and Doppler echocardiographic assessment of left ventricular diastolic function in primary antiphospholipid syndrome. Br Heart J 1995;74:531–535.