

Antiphospholipid Antibodies

Compiled by Dr. Nigel Harris

Updated 2002 by Lisa Sammartino, MD and Elena Flagg, MD

Updated 2003 by Amy Evangelisto, MD and Joan Von Feldt, MD

Updated 2006 by Kara Prescott, MD and David Karp, MD/PhD

Clinical Diagnosis

Non-Obstetric

1. [Cervera R, Font J, Gomez-Puerta JA, Espinosa G, et al.](#) Validation of the preliminary criteria for the classification of catastrophic antiphospholipid syndrome. *Ann Rheum Dis* 64(8):1205-9, 2005.

A confirmation of the utility in epidemiologic studies of the preliminary classification criteria for APS.

2. [Cervera R, Piette JC, Font J, et al.](#) Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. *Arthritis Rheum* 46:1019-27, 2002.

A large cohort study (1000 patients) helping to further define the implications and manifestations of antiphospholipid antibody syndrome.

3. [Sammaritano LR.](#) Antiphospholipid syndrome:review. *South Med J* 98(6):617-25, 2005.

A review of the clinical manifestations, complications and treatment recommendations.

4. [Silver RM, Porter TF, et al.](#) Anticardiolipin antibodies: Clinical consequences of "low titers". *Obstet Gynecol* 87:494-500, 1996.

Four groups of women ranging from 93-153 women in each group underwent testing for antiphospholipid antibodies. Patients with IgM or low titer IgG antiphospholipid antibodies are not at risk of an antiphospholipid associated event as opposed to those patients with lupus anticoagulant or mid to high level IgG APL levels. The latter are key risk factors for thrombosis.

5. [Tanne D, Hassin-Baer S.](#) Neurologic manifestations of antiphospholipid syndrome. *Curr Rheum Reports* 3:286-292, 2001.

A review of neurologic manifestations.

6. [Triplet DA](#). Antiphospholipid antibodies. *Clin Adv Hematol Oncol*. 1(12):726-30, 2003.

A review of the different types of APS antibodies.

7. [Vianna JL](#), [Khamshita MA](#), [Ordi-Ros J](#), et al. Comparison of the primary and secondary antiphospholipid syndrome. A European multi-center of 114 patients. *Am J Med* 96:3-9, 1994.

A large study that compares primary and secondary antiphospholipid antibody syndrome: the features of the syndrome are similar, but associated diseases modify symptoms and outcomes.

8. [Miyakis S](#), [Lockshin MD](#), [Atsumi T](#), et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 4(2):295-306, 2006.

Proposed amendments to the Sapporo criteria after the Eleventh International Congress.

9. [Wisloff F](#), [Jacobsen EM](#), [Liestol S](#). Laboratory diagnosis of the antiphospholipid syndrome. *Thrombosis Res* 108:263-71, 2003.

A detailed recent update on the various tests available for diagnosis of antiphospholipid syndrome.

Obstetric

10. [Branch DW](#), [Silver RM](#). Criteria for antiphospholipid syndrome: early pregnancy loss, fetal loss, or recurrent pregnancy loss? *Lupus* 5:409-413, 1996.

A thoughtful, critical and imaginative analysis of criteria used to define pregnancy loss. The criteria change how we think about the illness.

11. [Oshiro BT](#), [Silver RM](#), [Scott JR](#), et al. Antiphospholipid antibodies and fetal death. *Obstet Gynecol* 87:489-493, 1996.

This paper documents that second trimester fetal loss is more characteristic of antiphospholipid antibody pregnancies than is early abortion.

Pediatrics

12. [Quintero-Del-Rio AI](#). Antiphospholipid antibodies in pediatrics. *Curr Rheumatol Rep* 4(5):387-91, 2002.

Concise overview of APS in association with pediatrics.

13. [von Scheven E](#), [Glidden DV](#), [Elder ME](#). Anti-beta2-glycoprotein I antibodies in pediatric systemic lupus erythematosus and antiphospholipid antibody syndrome. *Arthritis Rheum* 47(4):414-20, 2002.

In this pediatric population the investigators found anti-B2-glycoprotein I antibodies to be rare in pediatric APS.

Disease Pathophysiology

14. [Asherson RA](#), [Cervera R](#), [Piette JC](#), [Shoenfeld Y](#), [Espinosa G](#), [Petri MA](#), [Lim E](#), [Lau TC](#), [Gurjal A](#), et al. Catastrophic antiphospholipid syndrome: clues to the pathogenesis from a series of 80 patients. *Medicine* 80(6):355-7, 2001.

A summary of the world's literature to date of this rare but devastating complication.

15. [Hattori N](#), [Kuwana M](#), [Kaburaki J](#), et al. T cells that are autoreactive to B2-glycoprotein I in patients with Antiphospholipid Syndrome and healthy individuals. *Arthritis and Rheum* 43:65-75, 2000.

T cells that respond to B2-glycoprotein I and mediate antiphospholipid antibody production were studied. Blood samples from 12 patients with APS were compared to that of 12 healthy controls and 13 patients with SLE but no APS. B2-glycoprotein I antibodies appear to be responsible for APS via pathogenic B2-glycoprotein reactive CD4+ T cells, a HLA-driven response (HLA-DR53). Eliminating or suppressing these T cells may be useful in treating patients with APS.

16. [Roubey RA](#). Antiphospholipid antibodies: immunological aspects. *Clin Immunol.* 112(2):127-8, 2004.

Editorial which gives an overview of current immunological aspects of APS.

17. [Yasuda S](#), [Bohgaki M](#), [Atsumi T](#), [Koike T](#). Pathogenesis of antiphospholipid antibodies: impairment of fibrinolysis and monocyte activation via the p38 mitogen-activated protein kinase pathway. *Immunobiology* 210(10):775-80, 2005.

Demonstration of aCL and B2GPI playing a dual role in the pathogenesis of APL.

Historical/Landmark

18. [Harris EN, Gharavi AE, Boey ML, et al.](#) Anticardiolipin antibodies: detection by radioimmunoassay and association with thrombosis in systemic lupus erythematosus. *Lancet* 2:1211-1214, 1983.

First description of the assay whose simplicity made possible the first widespread generation of studies on the antiphospholipid antibody.

19. [Hughes GR.](#) Thrombosis, abortion, cerebral disease and lupus anticoagulant. *BR Med J* 187:1088-1089, 1983.

Early description of the complex clinical syndrome of antiphospholipid syndrome.

20. [Hughes GR.](#) Hughes' syndrome: The antiphospholipid syndrome. A historical view. *Lupus* 7(2):S1-S4, 1998.

A concise historical review.

21. [Lockshin MD, Druzin ML, Goei S, et al.](#) Antibody to cardiolipin as a predictor of fetal distress or death in pregnant patients with systemic lupus erythematosus. *N Engl J Med* 313:152-156, 1985.

This paper is one of several that quickly capitalized on the new Harris assay, applied it to pregnant patients, and pointed out the role of antiphospholipid antibody in predicting intrauterine growth restriction or fetal death in patients with systemic lupus erythematosus.

Clinical Treatment

Non-Obstetric

22. [Asherson RA.](#) Multiorgan failure and antiphospholipid antibodies: the catastrophic antiphospholipid (Asherson's) syndrome. *Immunobiology* 210(10):727-33, 2005.

A review of 250 patients with CAPS and a discussion of pathogenesis, clinical presentation and treatment.

23. [Crowther MA, Wisloff F.](#) Evidence based treatment of the antiphospholipid syndrome II. Optimal anticoagulant therapy for thrombosis. *Thromb Res* 115(1-2):3-8, 2005.

MEDLINE search and review to determine "best practice" for the prevention of thromboembolism in patients with antiphospholipids and thromboembolism.

24. [Finazzi G, Marchioli R, Barbui T, et al.](#) A randomized clinical trial of high intensity warfarin vs conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with antiphospholipid syndrome (WAPS). *J Thromb Haemost* 3:848-853, 2005.

A randomized trial demonstrating high intensity warfarin was not superior to conventional treatment for prevention for recurrent thromboembolic events.

25. [Levine SR, Brey RL, Tilley BC et al.](#) Antiphospholipid antibodies and subsequent thrombo-occlusive events in patients with ischemic stroke. *JAMA* 291(5):576-584, 2004.

Prospective cohort study looking at warfarin vs aspirin in association with aPL antibodies and recurrent stroke.

26. [Lockshin MD.](#) Which patients with antiphospholipid antibody should be treated and how? *Rheum Dis Clin N Am* 19:235-247, 1993.

A discussion of the controversies.

27. [Moll S, Ortel TL.](#) Monitoring Warfarin Therapy in Patients with Lupus Anticoagulants. *Ann Intern Med* 127:177-185, 1997.

The validity of monitoring the INR in patients with positive lupus anticoagulant, on warfarin therapy was assessed. In a group of 34 patients, the INR did not accurately reflect the true level of anticoagulation..

28. [Turiel M, Sarzi-Puttini P, Peretti R, Bonniato S, et al.](#) Five year follow-up by transesophageal echocardiographic studies in primary antiphospholipid syndrome. *Am J Cardiol* 96(4):574-9, 2005.

Prospective study finding abnormalities of the mitral valve in association with APS. Also discussed are treatment and association with aCL titers.

Obstetric

29. [Erkan D, Merrill JT, Yazici Y, Sammaritano L, Buyon JP, Lockshin MD.](#) High thrombosis rate after fetal loss in antiphospholipid syndrome: effective prophylaxis with aspirin. *Arthritis Rheum* 44:1466-1467, 2001.

Although retrospective, this is the first study to define risk of subsequent thrombosis in women with APS and pregnancy complications. Risk of thrombosis over the long term is significantly decreased in patients who are treated with daily low dose aspirin.

30. Girardi G, Redecha P, Salmon JE. Heparin prevents antiphospholipid antibody induced fetal loss by inhibiting complement activation. *Nat Med* 10:1222-1226, 2004.

Describes the role of heparin as an anti-complementary factor.

31. Noble LS, Kutteh WH, Lashey, et al. Antiphospholipid antibodies associated with recurrent pregnancy loss: prospective, multi-center controlled pilot study comparing treatment with low-molecular-weight heparin vs. unfractionated heparin. *Fertil Steril* 83:684-690, 2005.

Trial to ascertain effectiveness of LMWH.

32. Rai R, Cohen H, Dave M, et al. Randomized controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with antiphospholipid antibodies. *BMJ* 314: 253-257, 1997.

A group of 90 patients with history of recurrent miscarriages and persistently positive antiphospholipid antibodies were randomized to either a low dose aspirin (75mg daily) or low dose aspirin with low dose heparin group at the start of the pregnancy. The combination of low dose aspirin with low dose heparin led to a significantly higher rate of live births.

33. Wu S, Stephenson MD. Obstetrical Antiphospholipid Syndrome. *Semin Rep Med* 24(1):40-53, 2006.

Overview of APS in relation to obstetrics.

Cutting Edge Research/Discoveries

34. Berman J, Girardi G, Salmon JE. TNF-alpha is a critical effector and a target for therapy in antiphospholipid antibody induced pregnancy loss. *J Immunol* 174(1):485-90, 2005.

When looking at murine models, the investigators found that aPL abs can cause an increase in TNF-alpha levels, suggesting this may be a link to fetal damage, as well as a potential target.

35. Meroni P, Ronda N, Raschi E, Borghi MO. Humoral autoimmunity against endothelium: theory or reality? *Trends Immunol* 26(5):275-81, 2005.

The suggestion in this paper is made that the thrombophilic state of APS may be related to antibodies to beta2 glycoprotein I which is adhered to endothelium.

36. [Thurman JM, Kraus DM, Girardi G, et al.](#) A novel inhibitor of the alternative complement pathway prevents antiphospholipid antibody-induced pregnancy loss in mice. *Mol Immun* 42:87-97.

A confirmation of the role of complement in APS.