

Antiphospholipid Syndrome - APS

Diagnosis

Indications for Testing

- Recurrent vascular thromboses, recurrent pregnancy loss, unexplained prolonged PTT in an asymptomatic patient (indication for lupus anticoagulant testing)
- Additional indications for testing may also include the presence of endocarditis, livedo reticularis, thrombocytopenia, hemolytic anemia, and thrombotic microangiopathy

Criteria for Diagnosis

Revised classification criteria for the antiphospholipid antibody syndrome

Revised Classification Criteria for the Antiphospholipid Antibody Syndrome	
<i>(At least 1 clinical and 1 laboratory criterion must be met)</i>	
<p style="text-align: center;">Clinical criteria</p> <p><i>Vascular thrombosis</i> – One or more clinical episodes of arterial, venous, or small-vessel thrombosis in any tissue or organ validated by imaging studies or histopathology</p> <p><i>Pregnancy morbidity</i></p> <ul style="list-style-type: none"> • One or more unexplained deaths of a morphologically normal fetus after 10th week of gestation • One or more premature births of a morphologically normal neonate before the 34th week of gestation due to preeclampsia, eclampsia, or placental insufficiency • Three or more unexplained, consecutive, spontaneous abortions before 10th week of gestation, and with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded 	<p style="text-align: center;">Laboratory criteria</p> <p>Positive test on 2 or more occasions at least 12 weeks apart</p> <ul style="list-style-type: none"> • <i>Lupus anticoagulant</i> – detected in plasma according to the guidelines of the International Society on Thrombosis and Hemostasis • <i>aCL antibody</i> – IgG and/or IgM isotype present in a medium or high titer (>40 GPL or MPL or >99th percentile), measured by standardized ELISA • <i>Anti-β2GP1 antibody</i> – IgG and/or IgM isotype in high titer (>99th percentile), measured by standardized ELISA
<p>GPL – IgG phospholipid antibody; MPL – IgM phospholipid antibody; ELISA – enzyme-linked immunosorbent assay</p>	

Laboratory Testing

- Current recommendations for first-line laboratory testing should include the following
 - LA activity
 - At least 2 phospholipid-dependent clotting assays, based on different principles, should be performed to identify LA activity
 - aCL IgG and IgM antibodies
 - β2GP1 IgG and IgM antibodies
 - Combination of all three tests reduces rate of false-positive results
 - Repeat positive laboratory tests after 12 weeks to confirm persistent positivity
 - Repeat testing if a strong clinical suspicion exists for APS but criteria laboratory tests are negative (seronegative APS)
- Also consider the following non-criteria tests for patients with repeatedly negative results from criteria tests
 - aCL antibody, IgA
 - β2GP1 antibody, IgA

- Phosphatidylserine antibodies, IgG, IgM, & IgA
- Prothrombin antibodies, IgG and IgM

Differential Diagnosis

- Inherited thrombophilia
- Connective tissue disease
 - SLE
- Malignancy

Screening

- Not recommended for patients with single deep vein thrombosis unless a risk factor is present
- Test for antibodies in the following situations
 - Thrombosis
 - Arterial thrombosis <50 years
 - Unprovoked venous thrombosis <50 years
 - Recurrent thrombosis
 - Thrombosis at unusual site
 - Patients with both arterial and venous thrombotic events
 - Patients admitted with thrombotic microangiopathy of unknown etiology
 - Obstetric manifestations
 - ≥1 unexplained fetal loss after 10th week of gestation
 - Unexplained severe intrauterine growth restriction
 - Early or severe preeclampsia
 - ≥3 spontaneous miscarriages before 10th week of gestation
 - Patients with SLE
 - Perform baseline test
 - Repeat testing
 - Before pregnancy, surgery, transplantation, and use of estrogen-containing treatments
 - New neurologic, vascular or obstetric event present

Clinical Background

Antiphospholipid syndrome (APS) is an autoimmune disorder in which autoantibodies are directed against phospholipid-protein complexes. APS is characterized by thrombosis (arterial, venous, or small vessel) and/or pregnancy complications and persistently positive tests for antiphospholipid-protein (aPL) antibodies.

Epidemiology

- Prevalence
 - Present in a small percentage of young healthy subjects (1-5%) and in up to 10% of patients with venous thrombosis
 - Estimates of prevalence are hampered by the variety of testing systems available for diagnosis
 - Higher prevalence in patients with connective tissue disease, but most patients with aPL antibodies do not have an underlying autoimmune disease

Risk Factors

- Connective tissue disease
 - Systemic lupus erythematosus – up to 50% of patients
- Infections – no increase in thrombotic risk
- Malignancy

- Liver disease
- Vascular disease
- Medications – increased thrombotic risk

Pathophysiology and Basis for Laboratory Tests

- Proposed mechanisms for thrombosis include endothelial cell damage or activation, platelet activation, and interference with the function of anticoagulant protein function
- LAs are autoantibodies that target complexes of phospholipids with either β 2GP1 or another plasma protein such as prothrombin
 - LAs usually demonstrate an inhibitor effect in laboratory clotting tests by interfering with phospholipid-dependent clotting reactions
 - Prolongation of clotting times (apparent anticoagulation) is an in vitro laboratory phenomenon; in vivo thrombosis is much more common than bleeding
- aPL antibodies are often classified as either lupus anticoagulant (LA), or anticardiolipin (aCL) antibodies, or anti-beta-2 glycoprotein 1 (β 2GP1) antibodies
 - Thrombosis appears to be more common in patients with LA activity
 - Positivity for all 3 (LA activity, aCL and β 2GP1 antibodies) is a strong independent risk factor for thrombosis
- Transient aPL antibodies may occur in association with infections and with certain medications (procainamide, hydralazine, quinidine, chlorpromazine, penicillin)

Clinical Presentation

- Venous, arterial, or small vessel thrombosis, and/or obstetric complications
- Other potential abnormalities include cytopenias or other hematologic disorders, and neurologic, dermatologic, or cardiopulmonary abnormalities
- Catastrophic APS is a multi-organ illness caused by diffuse small vessel thrombosis and tissue ischemia

Treatment

- Treatment decisions depend on the extent of clinical symptoms and may range from no treatment to long-term anticoagulation therapy

Lab Tests

Indications for Laboratory Testing

Tests generally appear in the order most useful for common clinical situations. For test-specific information, refer to the test number in the ARUP Laboratory Test Directory on the ARUP Web site at www.aruplab.com.

Test Name and Number	Recommended Use	Limitations	Follow Up
Antiphospholipid Syndrome Reflexive Panel 2003222 Method: Clotting/Semi-Quantitative Enzyme-Linked Immunosorbent Assay	Recommended laboratory testing for APS Components include β 2GP1 antibodies, IgG & IgM; aCL antibodies, IgG & IgM; and LA reflexive panel	Refer to individual components	Positive results – confirm at least 12 weeks apart

<p>Lupus Anticoagulant Reflexive Panel 0030181</p> <p>Method: Clotting</p>	<p>Identify LA activity in patient with clinical features of APS or unexpected prolonged partial thromboplastin time results</p> <p>Not recommended as stand-alone test for APS; for suspected APS, order along with</p> <ul style="list-style-type: none"> • aCL antibodies, IgG & IgM • β2GP1 antibodies, IgG & IgM <p>Panel includes LA-sensitive PTT and dilute Russell Viper Venom (dRVVT) for screening, followed by mixing studies and confirmatory assays if indicated</p>	<p>No single testing system will identify 100% of LA activity</p> <p>Anticoagulant therapy may interfere with test results</p>	<p>Negative results – consider repeat testing if clinical suspicion is high</p> <p>Positive results – confirm at least 12 weeks apart</p>
<p>Cardiolipin Antibodies, IgG and IgM 0099344</p> <p>Method: Semi-Quantitative Enzyme-Linked Immunosorbent Assay</p>	<p>Diagnose APS</p> <p>Not recommended as stand-alone test; order along with</p> <ul style="list-style-type: none"> • LA reflexive panel • β2GP1 antibodies, IgG & IgM 	<p>False-positive results may occur with infectious and autoimmune diseases</p>	<p>Inconclusive results – consider repeat testing</p> <p>Positive results – confirm at least 12 weeks apart</p>
<p>Beta-2 Glycoprotein 1 Antibodies, IgG & IgM 0050321</p> <p>Method: Semi-Quantitative Enzyme-Linked Immunosorbent Assay</p>	<p>Diagnose APS</p> <p>Not recommended as stand-alone test; order along with</p> <ul style="list-style-type: none"> • LA reflexive panel • aCL antibodies, IgG & IgM 		<p>Inconclusive results – consider repeat testing</p> <p>Positive results – confirm at least 12 weeks apart</p>
<p>High-Specificity <TestName>Antiphospholipid Antibodies, IgG and IgM 2005457</p> <p>Method: Semi-Quantitative Enzyme-Linked Immunosorbent Assay</p>	<p>Use to diagnose APS</p> <p>More specific than cardiolipin IgG and IgM antibodies in diagnosis of APS</p>		

Non-Criteria Antiphospholipid Syndrome (APS) Antibody Panel 2005386 Method: Semi-Quantitative Enzyme-Linked Immunosorbent Assay	Use only for selected cases of strongly suspected APS with negative initial testing		
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Additional Tests Available

Test Name and Number	Comments
Beta-2 Glycoprotein 1 Antibody, IgA 0050324 Method: Semi-Quantitative Enzyme-Linked Immunosorbent Assay	Not recommended
Cardioliipin Antibodies, IgG, IgM, and IgA 0051162 Method: Semi-Quantitative Enzyme-Linked Immunosorbent Assay	IgG and IgM panel test preferred
Cardioliipin Antibody, IgG 0050901 Method: Semi-Quantitative Enzyme-Linked Immunosorbent Assay	IgG and IgM panel test preferred
Cardioliipin Antibody, IgM 0050902 Method: Semi-Quantitative Enzyme-Linked Immunosorbent Assay	IgG and IgM panel test preferred
Cardioliipin Antibody, IgA 0098358 Method: Semi-Quantitative Enzyme-Linked Immunosorbent Assay	Not recommended
Phosphatidylcholine Antibodies, IgG, IgM & IgA 0051590 Method: Semi-Quantitative Enzyme-Linked Immunosorbent Assay	Not recommended
Phosphatidylethanolamine Antibodies, IgG, IgM and IgA 0051622 Method: Semi-Quantitative Enzyme-Linked Immunosorbent Assay	Not recommended
Phosphatidylinositol Antibodies, IgG, IgM and IgA 0051624 Method: Semi-Quantitative Enzyme-Linked Immunosorbent Assay	Not recommended

Phosphatidylglycerol Antibodies, IgG, IgM and IgA 0051623 Method: Semi-Quantitative Enzyme-Linked Immunosorbent Assay	Not recommended
Phosphatidylserine Antibodies, IgG, IgM, and IgA 0050905 Method: Semi-Quantitative Enzyme-Linked Immunosorbent Assay	Not recommended
Prothrombin Antibody, IgG 0051302 Method: Semi-Quantitative Enzyme-Linked Immunosorbent Assay	Not recommended
Prothrombin Antibody, IgM 0051303 Method: Semi-Quantitative Enzyme-Linked Immunosorbent Assay	Not recommended
Prothrombin Antibodies, IgG & IgM 2004411 Method: Semi-Quantitative Enzyme-Linked Immunosorbent Assay	Not recommended
Dilute Russell Viper Venom Time (dRVVT) with Reflex to dRVVT 1:1 Mix & Confirmation 0030461 Method: Clotting	Preferred test is the LA reflexive panel
Thrombotic Risk (Acquired) Reflexive Panel 0030268 Method: Electromagnetic Clot Detection/Semi-Quantitative Enzyme-Linked Immunosorbent Assay/Immunturbidimetry/Quantitative Enzymatic	
Hexagonal Phospholipid Neutralization 0030064 Method: Qualitative Clotting	Preferred test is the LA reflexive panel

Guidelines

Antiphospholipid syndrome. American College of Obstetricians and Gynecologists - Medical Specialty Society. 2005 November (Revised 2011 January).

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General References

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References from the ARUP Institute for Clinical and Experimental Pathology®

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Reviewed by

- Rodgers, III, George M., MD, PhD. Medical Director, Hemostasis/Thrombosis at ARUP Laboratories; Professor of Medicine and Pathology, University of Utah
- Smock, Kristi J., MD. Assistant Medical Director, Hemostasis/Thrombosis at ARUP Laboratories; Assistant Professor of Pathology (Clinical), University of Utah
- Tebo, Anne E., PhD. Assistant Medical Director, Immunology at ARUP Laboratories; Assistant Professor of Pathology (Clinical), University of Utah

Diagnostic Algorithm(s)

PDF algorithm(s) available at www.arupconsult.com.

Antiphospholipid Syndrome Testing Algorithm

Related Content

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Systemic Lupus Erythematosus - SLE

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Venous Thromboembolism

Comprehensive Review: January 2012

Last Update: January 2012