Authors: Doruk Erkan, MD, MPH, Thomas L Ortel, MD, PhD
Section Editor: David S Pisetsky, MD, PhD
Deputy Editors: Monica Ramirez Curtis, MD, MPH, Jennifer S Tirnauer, MD

Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Apr 2020. | **This topic last updated:** Feb 10, 2020.

INTRODUCTION

Antiphospholipid syndrome (APS) is characterized by venous or arterial thrombosis and/or an adverse pregnancy outcome in the presence of persistent laboratory evidence of antiphospholipid antibodies (aPL). APS occurs either as a primary condition or in the setting of an underlying disease, usually systemic lupus erythematosus (SLE).

The diagnosis of APS will be reviewed here. The clinical manifestations and treatment of this disorder are presented separately. (See "Pathogenesis of antiphospholipid syndrome" and "Clinical manifestations of antiphospholipid syndrome" and "Treatment of antiphospholipid syndrome" and "Antiphospholipid syndrome: Pregnancy implications and management in pregnant women".)

The effect of aPL on coagulation tests is also discussed separately. (See "Clinical use of coagulation tests".)

TERMINOLOGY

- **Antiphospholipid syndrome** – Antiphospholipid syndrome (APS) describes a clinical autoimmune syndrome characterized by venous or arterial thrombosis and/or pregnancy morbidity in the presence of persistent laboratory evidence of antiphospholipid antibodies (aPL) [1].

  APS can occur as a primary condition or in the setting of systemic lupus erythematosus (SLE) or another systemic autoimmune disease.

  APS can be further classified according to the type of clinical manifestation (thrombotic or obstetric; in some cases, both may be present) and whether there is life-threatening multiorgan involvement:

- **Thrombotic APS** – Thrombotic APS is used to describe patients diagnosed with APS based on venous or arterial thrombosis and persistent laboratory criteria for aPL.

- **Obstetric APS** – Obstetric APS is used to describe patients diagnosed with APS based on an APS-defining pregnancy morbidity (including fetal death after 10 weeks gestation, premature birth due to severe preeclampsia or placental insufficiency, or multiple embryonic losses [before 10 weeks gestation]) and persistent laboratory criteria for aPL.

  Individuals with both an APS-defining pregnancy morbidity and thromboembolic complications are referred to as having both thrombotic and obstetric APS.

- **Catastrophic APS** – Catastrophic APS (CAPS) is a rare, severe (life-threatening) form of APS characterized by thrombotic complications, usually microvascular, affecting multiple organs that develop simultaneously or over a short period of time. (See "Clinical manifestations of antiphospholipid syndrome", section on 'Catastrophic APS'.)

Implications of these sub-classifications for management are discussed separately.

- **Antiphospholipid antibodies** – aPL are a laboratory finding. When persistent, they are a component of the clinical syndrome of APS. They can also be seen as a transient finding following infection or other acute illness.

  aPL are a heterogeneous group of antibodies directed against phospholipid-binding proteins [2]. The aPL detection tests included in APS classification criteria are anticardiolipin (aCL) antibody (immunoglobulin G [IgG] or IgM) enzyme-linked immunosorbent assay (ELISA), anti-beta2-glycoprotein (GP) I antibody (IgG or IgM) ELISA, and lupus anticoagulant (LA) assay. Although cardiolipin is a phospholipid, most of the clinically relevant antibodies detected in this assay are actually binding to phospholipid-binding protein(s), frequently beta2-GP I, that bind to the cardiolipin in the assay. There are other aPL that are not included in APS classification criteria (eg, antibodies directed against prothrombin, phosphatidylserine, or phosphatidylinositol), which are not routinely obtained because of lack of standardized testing and uncertainty about their clinical significance. (See 'Antiphospholipid antibody testing' below.)

WHEN TO SUSPECT THE DIAGNOSIS

The two clinical scenarios that should raise clinical suspicion for antiphospholipid syndrome (APS) are the following:

- Occurrence of one or more otherwise unexplained venous or arterial thrombotic events, especially in young patients. (See "Clinical manifestations of antiphospholipid syndrome",

section on 'Clinical manifestations'.)

- One or more specific adverse outcomes related to pregnancy, including fetal death after 10 weeks gestation, premature birth due to severe preeclampsia or placental insufficiency, or multiple embryonic losses (<10 weeks gestation).

If either of the above scenarios occur in a patient who also manifests livedo reticularis, valvular heart disease, and/or neurologic findings such as cognitive deficits and white matter lesions, then the diagnostic suspicion for APS should be further increased. A systemic autoimmune disease diagnosis, especially systemic lupus erythematosus (SLE), should also increase the suspicion for APS in the setting of appropriate clinical symptoms.

In addition, other laboratory abnormalities that also raise the potential diagnostic significance of the above scenarios (ie, thrombosis or specific adverse pregnancy outcome) include an otherwise unexplained mild thrombocytopenia, the prolongation of a blood coagulation test (eg, activated partial thromboplastin time [aPTT]), or a history of a false positive serologic test for syphilis. The latter laboratory abnormality occurs because the antigen used in the Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin (RPR) tests contains cardiolipin. (See "Syphilis: Screening and diagnostic testing", section on 'Positive nontreponemal/negative treponemal'.)

We generally do not test for aPL in patients at low risk of APS, such as older adult patients who present with venous thromboembolism or stroke and/or individuals who have other risk factors for thromboembolism [3].

DIAGNOSTIC EVALUATION

In patients suspected of having antiphospholipid syndrome (APS), we perform a thorough medical history, physical examination, and laboratory testing for antiphospholipid antibodies (aPL) [4].

History — The history should be focused on the nature and frequency of thrombotic events, the outcomes of pregnancies in female patients, thrombocytopenia, and other risk factors for thrombosis, which may include immobility, contraceptive use, and/or family history of thrombophilia. A history of heparin exposure may be relevant in patients with possible heparin-induced thrombocytopenia (HIT). The history should also include inquiries about symptoms associated with systemic lupus erythematosus (SLE) such as photosensitivity, oral ulcers, patchy hair loss, and Raynaud phenomenon. (See "Clinical manifestations and diagnosis of systemic lupus erythematosus in adults", section on 'History and physical examination'.)

Physical examination — There are no pathognomonic physical findings of APS; however, abnormal features may be found on examination that are related to ischemia or infarction of the

skin, viscera, or the central nervous system. The physical examination may reveal findings consistent with livedo reticularis (and particularly livedo racemosa) (picture 1), digital ischemia, gangrene, deep vein thrombosis, a heart murmur, or neurological abnormalities suggestive of a stroke. (See "Clinical manifestations of antiphospholipid syndrome".)

Antiphospholipid antibody testing — Antibody testing in patients with suspected APS involves immunoassays for IgG and IgM antibodies to cardiolipin and beta2-glycoprotein (GP) I and a functional assay for the lupus anticoagulant (LA) phenomenon [5]:

- Anticardiolipin antibodies (aCL); IgG and IgM by enzyme-linked immunosorbent assay (ELISA).
- Anti-beta2-GP I antibodies; IgG and IgM by ELISA.
- LA testing is a three-step procedure:
  - Demonstration of a prolonged phospholipid-dependent screening test of hemostasis. Commonly used screening tests include the dilute Russell viper venom time (dRVVT) and an activated partial thromboplastin time (aPTT) that has been optimized for this purpose (aPTT or lupus aPTT).
  - Mixing patient plasma with normal plasma fails to correct the prolonged screening test(s). This eliminates the possibility that prolongation of the screening test is due to a coagulation factor deficiency. If the coagulation test remains prolonged after the addition of normal plasma, an inhibitor is present.
  - Addition of excess phospholipid shortens or corrects the prolonged coagulation test (demonstration of phospholipid-dependence).

  LA are characterized by correction of the prolonged clotting time with added phospholipid but not with control plasma, confirming that the coagulation inhibitor is phospholipid-dependent [3]. (See "Clinical use of coagulation tests", section on 'Use of mixing studies'.)

The above aPL testing is consistent with recommendations from the revised Sapporo classification criteria described below. (See 'Classification criteria' below.)

In contrast to IgG and IgM isotypes of aCL and anti-beta2-GP I, the association of the IgA isotypes with clinical thrombosis remains controversial [6]. We generally do not test for the IgA isotypes when evaluating for APS, and we generally do not consider these antibodies as supportive evidence for the diagnosis of APS if they are reported. However, many laboratories routinely test for IgA isotypes, given that rarely patients present with persistent isolated moderate-high titer IgA aCL or anti-beta2-GP I in the setting of aPL-related clinical events. The Laboratory Diagnostics and Trends APS Task Force of the 14th International Congress on aPL concluded that low-quality evidence

exists to include IgA isotype as part of the APS Classification Criteria, especially since these isotypes are usually associated with other aPL, making it difficult to understand the role of IgA alone [7]. Thus, the utility of the IgA isotypes is generally restricted to those patients with a strong clinical suspicion for APS but who have tested negative for other tests for aPL [8]. Additional prospective studies are needed to better understand the role of IgA aCL antibody as a thrombosis risk factor.

The Systemic Lupus International Collaborating Clinics (SLICC) revised classification criteria for SLE (table 1) include IgA isotype of aCL and anti-beta2-GP I as part of the definition of aPL positivity; IgA isotype may have implications for SLE classification given that it is more common in SLE patients, compared with aPL-positive patients without other autoimmune diseases [9]. (See "Clinical manifestations and diagnosis of systemic lupus erythematosus in adults", section on 'Classification criteria'.)

We do **not** routinely perform laboratory testing for other antibodies such as antiprothrombin antibodies, anti-annexin V, anti-phosphatidylserine, and anti-phosphatidylinositol antibodies, given the lack of standardized testing and uncertainty about their clinical significance [7].

Timing of testing — Initial testing is usually done shortly after a clinical event, followed by confirmatory testing at least 12 weeks later.

- **Initial aPL testing** – Typically, initial aPL testing is performed at the time of the thrombosis or adverse pregnancy outcome. While we obtain all of the tests listed above, it is worth noting that the presence of a large thrombosis may falsely normalize the result for aPTT testing (table 2). Thus, a normal aPTT or other LA screening test in the acute setting may be inaccurate and need repeating. The immunoassays (ELISA assays for aCL or beta-2-GP I) are not affected by acute thrombosis or anticoagulant administration. (See 'Patients on an anticoagulant' below.)

- **Confirmatory aPL testing** – In patients with initial positive testing for aPL, testing should be repeated after at least 12 weeks to confirm persistence of the aCL, anti-beta2-GPI, or LA test. Transiently elevated levels of IgG or IgM aCL, as well as a positive LA test, can occur in the setting of some infections or drug exposures. (See 'Other conditions associated with aPL' below.)

Positive results from aPL testing on two tests ≥12 weeks apart satisfies the laboratory criteria for the classification of APS (see 'Classification criteria' below). For the majority of patients who do not have laboratory evidence of APS from this testing, we do not perform additional antibody testing. However, repeat testing may be appropriate in selected cases in which the clinical suspicion for APS is especially high.

The need for confirmatory testing due to the transient nature of aPL was illustrated in a study including randomly selected blood donors who were tested for the presence aCL and LA [10]. On initial testing, 28 of 503 (5.6 percent) were positive for IgG aCL, 38 of 457 (8.3 percent) were positive for IgM aCL, and an additional 5 (0.9 percent) were positive for both. The number who remained positive for aCL upon repeat testing declined progressively at 3, 6, 9, and 12 months; at one year, only four were positive for IgG aCL (0.8 percent), one for IgM aCL (0.2 percent), and none for both isotypes. There were no positive tests for LA in any patient at any point, and none of the individuals had clinical evidence of APS.

Patients on an anticoagulant — In patients who are receiving an anticoagulant, we test for aCL and anti-beta2-GP I antibodies because the results are unaffected by the presence of an anticoagulant. As noted above, anticoagulants can prolong the aPTT and make interpretation of the aPTT or other LA screening test more challenging (table 2). Communication with the consulting specialist and laboratory personnel is advised prior to LA testing in a patient receiving an anticoagulant. This subject is discussed in more detail separately. (See "Clinical use of coagulation tests", section on 'Patient on anticoagulant'.)

Interpretation of positive results — Not every positive aPL test result is clinically significant. The interpretation of "clinically significant aPL positivity" should take into account the type, isotype, titer, persistency, and the number of positive aPL tests.

- We define a clinically significant aPL profile as the presence of one or more of the following aPLs on two or more occasions at least 12 weeks apart:
    - A positive LA test, based on the guidelines of International Society of Thrombosis and Haemostasis [3]
    - aCL IgG or IgM, with a titer >40 units
    - anti-beta2-GP I IgG or IgM, with a titer >40 units

  This approach is mostly consistent with the laboratory criteria described in the revised Sapporo APS Classification Criteria. (See 'Classification criteria' below.)

- In selected patients with an especially high clinical suspicion of APS, it may be appropriate to consider the following findings to be clinically significant:
    - aCL or anti-beta2-GP I IgG or IgM, with a titer of 20 to 39 units
    - aCL or anti-beta2-GP I IgA

Of note, aPL may also be present in other settings besides APS, either transiently or persistently. This is discussed in more detail below. (See 'Other conditions associated with aPL' below.)

Evaluation for other conditions — The diagnosis of APS requires several months given the need for confirmatory laboratory testing, and in the interim it may be appropriate to pursue additional laboratory testing or to evaluate patients for other possible causes of thromboembolism and/or adverse pregnancy outcomes.

Such additional testing may include the following:

- **Thrombophilia testing** – Thrombophilia testing may be appropriate in selected patients, particularly if the findings would be expected to alter management. The utility of this testing is questionable in cases in which indefinite anticoagulation is planned because the results of testing may not alter management; however, there may be implications for the testing of first-degree relatives in families with inherited thrombophilias. Thrombophilia testing may include evaluation for inherited thrombophilias such as the factor V Leiden mutation, prothrombin G20210A mutation; deficiency of protein S, protein C, and antithrombin; myeloproliferative neoplasms (MPN); or paroxysmal nocturnal hemoglobinuria (PNH). This subject is discussed in more detail separately. (See "Evaluating adult patients with established venous thromboembolism for acquired and inherited risk factors".)

- **Evaluation of unexplained cytopenias** – Patients with unexplained thrombocytopenia or anemia should be evaluated for other potential causes of these abnormalities. (See "Approach to the adult with unexplained thrombocytopenia" and "Approach to the adult with anemia".)

- **Evaluation for systemic lupus erythematosus** – Patients with other clinical features suggestive of SLE should also undergo the appropriate workup for SLE. In a cohort of 1000 individuals with APS, 36 percent had SLE, and an additional 5 percent had a lupus-like syndrome [11]. (See "Clinical manifestations and diagnosis of systemic lupus erythematosus in adults", section on 'Laboratory testing'.)

- **Evaluation for heparin-induced thrombocytopenia** – Patients with clinical features suggestive of HIT should undergo an appropriate evaluation for HIT. (See "Clinical presentation and diagnosis of heparin-induced thrombocytopenia".)

CLASSIFICATION CRITERIA

Classification criteria for antiphospholipid syndrome (APS) have been developed to select patients for clinical and laboratory research purposes [12,13]. Although classification criteria should not be used for diagnostic purposes, they can be useful to guide clinicians in diagnosing patients and

documenting key disease features [14,15]. However, the use of these criteria should not substitute for clinical judgment when diagnosing APS. (See 'Diagnosis' below.)

According to the revised Sapporo APS Classification Criteria (also called the Sydney criteria) (table 3), APS is present in patients who meet at least one of the following clinical criteria **and** at least one of the following laboratory criteria:

- **Clinical criteria** – One or more of the following is present:
  - **Vascular thrombosis** – One or more episodes of venous, arterial, or small vessel thrombosis in any tissue or organ, with unequivocal imaging or histologic evidence of thrombosis. Superficial venous thrombosis does **not** satisfy the criteria for thrombosis for APS.
  - **Pregnancy morbidity** – One or more unexplained deaths of a morphologically normal fetus at ≥10 weeks gestation, **or** one or more premature births of a morphologically normal neonate before 34 weeks gestation because of eclampsia, preeclampsia, or placental insufficiency, **or** three or more consecutive spontaneous pregnancy losses at <10 weeks gestation, unexplained by chromosomal abnormalities or by maternal anatomic or hormonal causes.
- **Laboratory criteria** – The presence of one or more of the following antiphospholipid antibodies (aPL) on two or more occasions at least 12 weeks apart:
  - IgG and/or IgM anticardiolipin antibodies (aCL) in moderate or high titer (>40 GPL or MPL units, respectively, or a titer >99th percentile for the testing laboratory), measured by a standardized enzyme-linked immunosorbent assay (ELISA).
  - IgG and/or IgM anti-beta2-glycoprotein (GP) I >40 GPL or MPL units, respectively, or a titer >99th percentile for the testing laboratory, measured by a standardized ELISA according to recommended procedures [5,16].
  - Lupus anticoagulant (LA) activity detected according to published guidelines [3,17,18].

The revised Sapporo criteria also indicate that the presence or absence of additional risk factors for thrombosis should be recognized among patients. Such patient stratification provides additional information that may be useful for research and for treatment, but does not alter the diagnosis.

DIAGNOSIS

The diagnosis of antiphospholipid syndrome (APS) is based on a combination of clinical features and laboratory findings. Although the classification criteria were designed for research purposes, many clinicians refer to these criteria when making the diagnosis of APS in adults. Although these criteria have also been shown to be specific for the diagnosis of APS in children, they may lack sensitivity in this age group [19]. We describe our general approach to the diagnosis below.

Patients who meet classification criteria — We diagnose APS in patients who meet the revised Sapporo classification criteria (table 3) with definite APS, as long as there is no alternative diagnosis to explain the clinical findings [12] (see 'Differential diagnosis' below). As mentioned above, the revised Sapporo criteria requires that a patient satisfy at least one clinical criterion related to either a vascular thrombosis or an adverse pregnancy outcome, as well as the presence of one or more specified antiphospholipid antibodies (aPL) on two or more occasions at least 12 weeks apart. The revised Sapporo criteria are considered useful in clinical practice to avoid “over-diagnosis” of APS. (See 'Classification criteria' above.)

Patients who do not meet classification criteria — Occasionally, we diagnose APS in patients who do not fulfill the revised Sapporo criteria. Examples include individuals with otherwise unexplained thrombocytopenia, heart valve disease, renal thrombotic microangiopathy (aPL nephropathy), or those with aPL-related clinical events and borderline aPL testing [20]. Consultation with a clinician with expertise in the diagnosis of APS is advised.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of antiphospholipid syndrome (APS) is broad and includes other causes of arterial and venous thrombosis and recurrent pregnancy loss.

Other causes of thrombosis — Other causes of thrombosis include inherited and acquired thrombophilias, anatomical vascular obstruction, paroxysmal nocturnal hemoglobinuria (PNH), heparin-induced thrombocytopenia (HIT), and myeloproliferative neoplasms (MPN). Like APS, these conditions may be associated with arterial or venous thromboembolism, with or without cytopenias. Unlike APS, these conditions are not associated with laboratory evidence of antiphospholipid antibodies (aPL). (See "Overview of the causes of venous thrombosis" and "Clinical manifestations and diagnosis of paroxysmal nocturnal hemoglobinuria" and "Clinical presentation and diagnosis of heparin-induced thrombocytopenia" and "Overview of the myeloproliferative neoplasms".)

On the other hand, patients with APS may have coexisting risk factors for thrombotic events, including acquired risk factors for venous thromboembolism (eg, immobility, estrogen-containing oral contraceptives) as well as cardiovascular risk factors. (See "Overview of established risk factors for cardiovascular disease".)

Other causes of recurrent pregnancy loss — Other causes of recurrent pregnancy loss include chromosomal abnormalities, anatomical abnormalities of the uterus, and endocrine disorders such as hypothyroidism. Like APS, individuals with these abnormalities may have early or late pregnancy loss. Unlike APS, these conditions generally are not associated with an increased risk of thromboembolism or the presence of aPL. (See "Recurrent pregnancy loss: Evaluation".)

Asymptomatic individuals with aPL

Transient aPL — A minority of healthy individuals have transient aPL but do not have clinical thrombosis or other features of APS. The clinical significance is unclear, but follow-up testing to assess the persistence of an aPL in selected individuals may be helpful. The clinical impact of repeat testing in asymptomatic individuals with aPL depends on how the results will be incorporated into patient management. For patients with multiple strongly positive tests, repeat testing provides information about potential risk assessment; by contrast, for patients with a single borderline positive test, repeat testing can be used to confirm that the result is likely to be clinically irrelevant. However, in some individuals, particularly those with other thrombosis risk factors, the presence of aPL is associated with an increased risk of developing APS. (See 'Antiphospholipid antibody testing' above.)

Persistent medium or high titer aPL — Occasionally individuals are identified who have persistent medium or high titer aPL (possibly meeting the revised Sapporo laboratory criteria) but no clinical manifestations of APS. The two most common scenarios in which this occurs are patients with SLE who are routinely screened for aPL and patients undergoing coagulation screening for an unrelated indication who are found to have a lupus anticoagulant (LA). While these patients do not have APS, they are at risk for clinical manifestations of APS as noted above. It is reasonable to assume that all patients with APS were, for some period of time in the past, asymptomatic individuals with significant levels of aPL. The level of risk and the role of prophylaxis in such patients is controversial and discussed elsewhere. (See "Treatment of antiphospholipid syndrome", section on 'Primary thrombosis prevention'.)

Other conditions associated with aPL — In addition to their occurrence in primary APS, aPL may be present in some people who are otherwise healthy, have an autoimmune or rheumatic disease, and have been exposed to certain drugs or infectious agents. The presence of aPL alone, in the absence of a thrombotic event or pregnancy morbidity, is insufficient for diagnosis of the clinical syndrome of APS, as detailed above (see 'Diagnosis' above). The evaluation of a patient with a positive aPL for these conditions depends on the presentation and clinical setting. In general, we limit our evaluation to a thorough history and physical examination and testing appropriate to evaluate clinical findings. We do not perform extensive laboratory testing or other studies to evaluate for these conditions in the absence of other clinical findings suggestive of APS.

- **Autoimmune and rheumatic diseases** – The most frequent rheumatic disease associated with aPL is systemic lupus erythematosus (SLE). A clinically significant aPL profile has been detected in approximately 30 percent of patients with SLE [21]:

  - Approximately 31 percent of patients have LA [22]
  - 23 to 47 percent have an anticardiolipin antibody (aCL) [6,22,23]
  - 20 percent have antibodies to beta2-glycoprotein (GP) I [6]

  Conversely, in a cohort of 1000 APS patients, APS was associated with SLE in 36 percent of patients, and with a lupus-like syndrome in an additional 5 percent [11].

  Both LAs and aCL have also been found in patients with a variety of other autoimmune and rheumatic diseases (eg, scleroderma, psoriatic arthritis) but, in the absence of clinical events associated with the APS, their significance is not clear [24,25].

- **Infections** – aPL have also been noted in patients with infections. These are usually IgM aCL, which may rarely result in thrombotic events [24,26]. Furthermore, these antibodies usually do not have anti-beta2-GP I antibody activity [27,28]. The infections that have been associated with aPLs include [25,27-35]:

  - Bacterial infections – Bacterial septicemia, leptospirosis, syphilis, Lyme disease (borreliosis), tuberculosis, leprosy, infective endocarditis, post-streptococcal rheumatic fever, and Klebsiella infections.
  - Viral infections – Hepatitis A, B, and C, mumps, human immunodeficiency virus (HIV), human T-lymphotropic virus type 1 (HTLV-I), cytomegalovirus, varicella-zoster, Epstein-Barr virus (EBV), adenovirus parvovirus, and rubella. Several earlier studies had reported an association between infection with hepatitis C virus (HCV) and aPL [30-32]. However, subsequent studies suggest no link between the two disorders [33]. As a result, the correlation between HCV infection and aPL, if present, is weak and may not have underlying pathogenic significance.
  - Parasitic infections – Malaria, *Pneumocystis jirovecii*, and visceral leishmaniasis (also known as kala-azar).

- **Medications** – A number of medications have been associated with aPL. These include phenothiazines (chlorpromazine), phenytoin, hydralazine, procainamide, quinidine, quinine, ethosuximide, alpha interferon, amoxicillin, chlorothiazide, oral contraceptives, and propranolol [25,26,36,37]. The aPL are usually transient, often of the IgM isotype, and rarely associated with thrombosis. The mechanism of drug-induced aPL is not known.

- **Malignancy** – Reports of aPL in the setting of malignancy include solid tumors of the lung, colon, cervix, prostate, kidney, ovary, breast, and bone; Hodgkin disease and non-Hodgkin lymphoma; MPN (eg, primary myelofibrosis, polycythemia vera); and myeloid and lymphocytic leukemias [25,38].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Antiphospholipid syndrome".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topics (see "Patient education: The antiphospholipid syndrome (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Clinical suspicion for antiphospholipid syndrome (APS) should be raised in the following settings (see 'When to suspect the diagnosis' above):
    - Occurrence of one or more otherwise unexplained venous or arterial thrombotic events, especially in young patients.
    - One or more specific adverse outcomes related to pregnancy, including fetal death after 10 weeks gestation, premature birth due to severe preeclampsia or placental insufficiency, or multiple embryonic losses (<10 weeks gestation).

If either of the above scenarios occur in a patient who also manifests livedo reticularis/racemosa, valvular heart disease, and/or neurologic findings such as cognitive deficits and white matter lesions, then the diagnostic suspicion for APS should be further increased. A systemic autoimmune disease diagnosis, especially systemic lupus erythematosus (SLE), should also increase the suspicion for APS in the setting of appropriate clinical symptoms.

Other laboratory abnormalities that also raise the potential diagnostic significance of the above scenarios (ie, thrombosis or specific adverse pregnancy outcome) include an otherwise unexplained mild thrombocytopenia, the prolongation of a blood coagulation test (eg, activated partial thromboplastin time [aPTT]), or a history of a false positive serologic test for syphilis.

- In patients suspected of having APS, we perform a thorough medical history, physical examination, and antibody testing for antiphospholipid antibodies (aPL) (see 'Diagnostic evaluation' above). We generally perform initial antibody testing around the time of a clinical event, followed by confirmatory testing at least 12 weeks later. Antibody testing in patients with suspected APS includes the following (see 'Antiphospholipid antibody testing' above):
  - Anticardiolipin antibodies (aCL); immunoglobulin G (IgG) and IgM by enzyme-linked immunosorbent assay (ELISA).
  - Anti-beta2-glycoprotein (GP) I antibodies; IgG and IgM by ELISA.
  - Lupus anticoagulant (LA) testing with dilute Russell viper venom time (dRVVT) and/or aPTT, or another combination as the initial screening tests.
- It may be appropriate to pursue additional laboratory testing or evaluate patients for other possible causes of thromboembolism and/or adverse pregnancy outcomes. This may include testing for other causes of thromboembolism and unexplained cytopenias and evaluation for SLE. (See 'Evaluation for other conditions' above.)
- The diagnosis of APS is based on a combination of clinical features and the aPL profile. Risk factors for thrombosis other than aPL should also be evaluated during the diagnostic assessment. Although the APS classification criteria (table 3) were designed for research purposes, they can be useful to guide clinicians in diagnosing patients. However, the use of these criteria should not substitute for clinical judgment when diagnosing APS. (See 'Diagnosis' above and 'Classification criteria' above.)
- Occasionally, we diagnose APS in patients who do not fulfill the revised Sapporo criteria. Examples include individuals with otherwise unexplained thrombocytopenia, heart valve disease, or renal thrombotic microangiopathy (aPL nephropathy), or those with aPL-related

clinical events and borderline aPL testing. Consultation with a clinician with expertise in the diagnosis of APS is advised. (See 'Patients who do not meet classification criteria' above.)

- The differential diagnosis of APS is broad and includes other causes of arterial and venous thrombosis and recurrent pregnancy loss. It should also be noted that aPL may be present in some people who are otherwise healthy, have an autoimmune or rheumatic disease, have a malignancy, and have been exposed to certain drugs or infectious agents. (See 'Other causes of thrombosis' above and 'Other causes of recurrent pregnancy loss' above and 'Other conditions associated with aPL' above.)

- The clinical manifestations and management of APS are presented separately. (See "Clinical manifestations of antiphospholipid syndrome" and "Treatment of antiphospholipid syndrome" and "Antiphospholipid syndrome: Pregnancy implications and management in pregnant women".)

ACKNOWLEDGMENTS

The editorial staff at UpToDate would like to acknowledge Peter Schur, MD, and Bonnie Bermas, MD, who contributed to an earlier version of this topic review.

REFERENCES

1. Lim W. Antiphospholipid syndrome. Hematology Am Soc Hematol Educ Program 2013; 2013:675.

2. Khamashta MA, Amigo MC. Antiphospholipid syndorme: overview of pathogenesis, diagnosis, and management. In: Rheumatology, 6, Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH (Eds), Elsevier, Philadelphia 2015. Vol 2, p.1144.

3. Pengo V, Tripodi A, Reber G, et al. Update of the guidelines for lupus anticoagulant detection. Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. J Thromb Haemost 2009; 7:1737.

4. Ruiz-Irastorza G, Crowther M, Branch W, Khamashta MA. Antiphospholipid syndrome. Lancet 2010; 376:1498.

5. Giannakopoulos B, Passam F, Ioannou Y, Krilis SA. How we diagnose the antiphospholipid syndrome. Blood 2009; 113:985.

6. Sebastiani GD, Galeazzi M, Tincani A, et al. Anticardiolipin and anti-beta2GPI antibodies in a large series of European patients with systemic lupus erythematosus. Prevalence and clinical associations. European Concerted Action on the Immunogenetics of SLE. Scand J Rheumatol 1999; 28:344.

7. Bertolaccini ML, Amengual O, Andreoli L, et al. 14th International Congress on Antiphospholipid Antibodies Task Force. Report on antiphospholipid syndrome laboratory diagnostics and trends. Autoimmun Rev 2014; 13:917.

8. Bertolaccini ML, Amengual O, Artim-Eser B, et al. Clinical and prognostic significance of non-c riteria antiphospholipid antibody tests. In: Antiphospholipid Syndrome: Current Research Highl ights and Clinical Insights, Erkan D, Lockshin MD (Eds), Springer International Publishing, 201 7. p.171.

9. Petri M, Orbai AM, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012; 64:2677.

10. Vila P, Hernández MC, López-Fernández MF, Batlle J. Prevalence, follow-up and clinical significance of the anticardiolipin antibodies in normal subjects. Thromb Haemost 1994; 72:209.

11. 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 2002; 46:1019.

12. 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 2006; 4:295.

13. 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.

14. Kaul M, Erkan D, Sammaritano L, Lockshin MD. Assessment of the 2006 revised antiphospholipid syndrome classification criteria. Ann Rheum Dis 2007; 66:927.

15. Bobba RS, Johnson SR, Davis AM. A review of the sapporo and revised Sapporo criteria for the classification of antiphospholipid syndrome. Where do the revised sapporo criteria add value? J Rheumatol 2007; 34:1522.

16. Reber G, Tincani A, Sanmarco M, et al. Proposals for the measurement of anti-beta2-glycoprotein I antibodies. Standardization group of the European Forum on Antiphospholipid Antibodies. J Thromb Haemost 2004; 2:1860.

17. Clinical and Laboratory Standards Institute (CLSI). Laboratory Testing for the Lupus Anticoagulant; Approved Guideline. CLSI document H60-A. Wayne, PA. Clinical and Laboratory Standards Institute, 2014.

18. http://shop.clsi.org/c.1253739/site/Sample_pdf/H60A_sample.pdf (Accessed on February 17, 2016).

19. Groot N, de Graeff N, Avcin T, et al. European evidence-based recommendations for diagnosis and treatment of paediatric antiphospholipid syndrome: the SHARE initiative. Ann Rheum Dis 2017; 76:1637.

20. Abreu MM, Danowski A, Wahl DG, et al. The relevance of "non-criteria" clinical manifestations of antiphospholipid syndrome: 14th International Congress on Antiphospholipid Antibodies Technical Task Force Report on Antiphospholipid Syndrome Clinical Features. Autoimmun Rev 2015; 14:401.

21. Taraborelli M, Leuenberger L, Lazzaroni MG, et al. The contribution of antiphospholipid antibodies to organ damage in systemic lupus erythematosus. Lupus 2016; 25:1365.

22. Love PE, Santoro SA. Antiphospholipid antibodies: anticardiolipin and the lupus anticoagulant in systemic lupus erythematosus (SLE) and in non-SLE disorders. Prevalence and clinical significance. Ann Intern Med 1990; 112:682.

23. 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.

24. McNeil HP, Chesterman CN, Krilis SA. Immunology and clinical importance of antiphospholipid antibodies. Adv Immunol 1991; 49:193.

25. Cervera R, Asherson RA. Clinical and epidemiological aspects in the antiphospholipid syndrome. Immunobiology 2003; 207:5.

26. Triplett DA. Many faces of lupus anticoagulants. Lupus 1998; 7 Suppl 2:S18.

27. McNally T, Purdy G, Mackie IJ, et al. The use of an anti-beta 2-glycoprotein-I assay for discrimination between anticardiolipin antibodies associated with infection and increased risk of thrombosis. Br J Haematol 1995; 91:471.

28. Santiago M, Martinelli R, Ko A, et al. Anti-beta2 glycoprotein I and anticardiolipin antibodies in leptospirosis, syphilis and Kala-azar. Clin Exp Rheumatol 2001; 19:425.

29. García Moncó JC, Wheeler CM, Benach JL, et al. Reactivity of neuroborreliosis patients (Lyme disease) to cardiolipin and gangliosides. J Neurol Sci 1993; 117:206.

30. Prieto J, Yuste JR, Beloqui O, et al. Anticardiolipin antibodies in chronic hepatitis C: implication of hepatitis C virus as the cause of the antiphospholipid syndrome. Hepatology 1996; 23:199.

31. Matsuda J, Saitoh N, Gotoh M, et al. High prevalence of anti-phospholipid antibodies and anti-thyroglobulin antibody in patients with hepatitis C virus infection treated with interferon-alpha. Am J Gastroenterol 1995; 90:1138.

32. Leroy V, Arvieux J, Jacob MC, et al. Prevalence and significance of anticardiolipin, anti-beta2 glycoprotein I and anti-prothrombin antibodies in chronic hepatitis C. Br J Haematol 1998; 101:468.

33. Muñoz-Rodríguez FJ, Tàssies D, Font J, et al. Prevalence of hepatitis C virus infection in patients with antiphospholipid syndrome. J Hepatol 1999; 30:770.

34. Uthman IW, Gharavi AE. Viral infections and antiphospholipid antibodies. Semin Arthritis Rheum 2002; 31:256.

35. Von Landenberg P, Lehmann HW, Knöll A, et al. Antiphospholipid antibodies in pediatric and adult patients with rheumatic disease are associated with parvovirus B19 infection. Arthritis Rheum 2003; 48:1939.

36. Merrill JT, Shen C, Gugnani M, et al. High prevalence of antiphospholipid antibodies in patients taking procainamide. J Rheumatol 1997; 24:1083.

37. Dlott JS, Roubey RA. Drug-induced lupus anticoagulants and antiphospholipid antibodies. Curr Rheumatol Rep 2012; 14:71.

38. Vassalo J, Spector N, de Meis E, et al. Antiphospholipid antibodies in critically ill patients with cancer: a prospective cohort study. J Crit Care 2014; 29:533.

Topic 4678 Version 30.0