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Diagnosis and Management of the Antiphospholipid Syndrome

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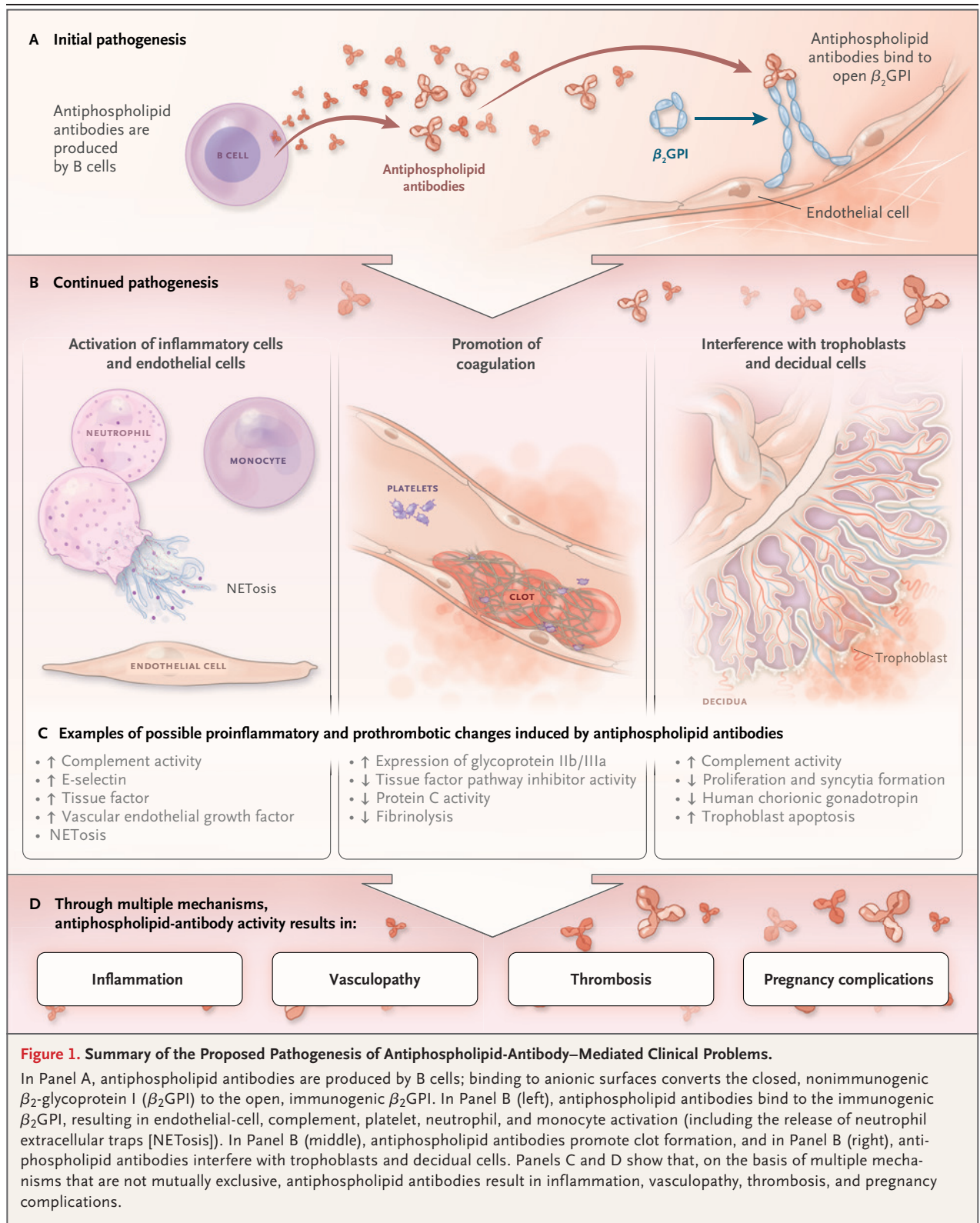
THE ANTIPHOSPHOLIPID SYNDROME IS A SYSTEMIC AUTOIMMUNE DISEASE defined by thrombotic or obstetrical events that occur in patients with persistent antiphospholipid antibodies.[1] Thrombotic antiphospholipid syndrome is characterized by venous, arterial, or microvascular thrombosis. Patients with catastrophic antiphospholipid syndrome present with thrombosis involving multiple organs.[2] Obstetrical antiphospholipid syndrome is characterized by fetal loss after the 10th week of gestation, recurrent early miscarriages, intrauterine growth restriction, or severe preeclampsia.[1] The major nonthrombotic manifestations of antiphospholipid-antibody positivity include valvular heart disease, livedo, antiphospholipid-antibody–related nephropathy, thrombocytopenia, hemolytic anemia, and cognitive dysfunction. The antiphospholipid syndrome is often associated with other systemic autoimmune diseases such as systemic lupus erythematosus (SLE); however, it commonly occurs without other autoimmune manifestations (primary antiphospholipid syndrome).

Although criteria for classification of the antiphospholipid syndrome have been proposed,[1] the definition of clinically significant antiphospholipid-antibody positivity is not well established, and thrombosis is generally multifactorial. Our objectives are to help both general practitioners and specialty-based physicians recognize and accurately diagnose the antiphospholipid syndrome, as well as to provide basic recommendations for the treatment of patients who are persistently positive for antiphospholipid antibodies. Given the limited number of well-designed, randomized, controlled trials, our recommendations are evidence-based whenever possible but often reflect expert opinion.

PATHOGENESIS OF ANTIPHOSPHOLIPID-ANTIBODY–MEDIATED CLINICAL EVENTS

The pathogenesis of the antiphospholipid syndrome has been reviewed elsewhere.[3] A brief summary of the proposed mechanisms by which antiphospholipid antibodies cause clinical symptoms (Fig. 1) provides the rationale for some new treatment strategies currently being investigated.

In the antiphospholipid syndrome, the major target of antiphospholipid antibodies is β_2-glycoprotein I (β_2GPI), a plasma protein that binds avidly to phospholipid surfaces, even more so when dimerized by binding to an anti-β_2GPI antibody. Congenital deficiency of β_2GPI is not associated with an increased risk of thrombosis,[4] but the binding of antiphospholipid antibodies to β_2GPI on cellular surfaces up-regulates the expression of prothrombotic cellular adhesion molecules such as E-selectin and tissue factor. Furthermore, the binding of antiphospholipid antibody to β_2GPI suppresses the activity of the tissue factor pathway inhibitor,[5]

A Initial pathogenesis

Antiphospholipid
antibodies are
produced
by B cells

B CELL

Antiphospholipid
antibodies

β_2GPI

Antiphospholipid
antibodies bind to
open β_2GPI

Endothelial cell

B Continued pathogenesis

Activation of inflammatory cells
and endothelial cells

NEUTROPHIL

MONOCYTE

NETosis

ENDOTHELIAL CELL

Promotion of
coagulation

PLATELETS

CLOT

Interference with trophoblasts
and decidual cells

Trophoblast

DECIDUA

C Examples of possible proinflammatory and prothrombotic changes induced by antiphospholipid antibodies

- ↑ Complement activity
- ↑ E-selectin
- ↑ Tissue factor
- ↑ Vascular endothelial growth factor
- NETosis

- ↑ Expression of glycoprotein IIb/IIIa
- ↓ Tissue factor pathway inhibitor activity
- ↓ Protein C activity
- ↓ Fibrinolysis

- ↑ Complement activity
- ↓ Proliferation and syncytia formation
- ↓ Human chorionic gonadotropin
- ↑ Trophoblast apoptosis

**D Through multiple mechanisms,
antiphospholipid-antibody activity results in:**

| Inflammation | Vasculopathy | Thrombosis | Pregnancy complications |

Figure 1. Summary of the Proposed Pathogenesis of Antiphospholipid-Antibody–Mediated Clinical Problems.

In Panel A, antiphospholipid antibodies are produced by B cells; binding to anionic surfaces converts the closed, nonimmunogenic β_2-glycoprotein I (β_2GPI) to the open, immunogenic β_2GPI. In Panel B (left), antiphospholipid antibodies bind to the immunogenic β_2GPI, resulting in endothelial-cell, complement, platelet, neutrophil, and monocyte activation (including the release of neutrophil extracellular traps [NETosis]). In Panel B (middle), antiphospholipid antibodies promote clot formation, and in Panel B (right), antiphospholipid antibodies interfere with trophoblasts and decidual cells. Panels C and D show that, on the basis of multiple mechanisms that are not mutually exclusive, antiphospholipid antibodies result in inflammation, vasculopathy, thrombosis, and pregnancy complications.

reduces activated protein C activity,[6] and activates complement.[7,8] A knockout mouse model suggests that annexin A2, a tissue plasminogen activator receptor, may be an important intermediary.[9]

Exposing platelets from healthy donors to antiphospholipid antibodies in vitro increases the expression of glycoprotein IIb/IIIa (the receptor for fibrinogen),[10] and platelets may play a key role in the prothrombotic interactions between antiphospholipid antibodies and endothelial cells.[11] Neutrophil activation, including the expression of tissue factor and the release of neutrophil extracellular traps (NETosis) and interleukin-8, may also be an important element of antiphospholipid-antibody–associated thrombosis.[12-14] In addition, monocytes and monocyte-derived microparticles from patients with the antiphospholipid syndrome express high levels of tissue factor.[15] Microthrombotic antiphospholipid syndrome may be explained in part by antiphospholipid-antibody–induced upregulation of the mechanistic target of rapamycin (mTOR) complex on endothelial cells, leading to antiphospholipid-antibody–related vasculopathy.[16]

Complement-mediated disruption of endothelial and trophoblast function[17] partly explains pregnancy complications and microthrombosis associated with antiphospholipid antibodies. Placental thrombosis and antiphospholipid-antibody interactions with decidual cells may also contribute to pregnancy complications.

PREVALENCE OF ANTIPHOSPHOLIPID ANTIBODIES

Given the absence of population-based studies, the true prevalence of antiphospholipid-antibody positivity in the general population is not known. Ten percent of healthy blood donors are positive for anticardiolipin antibodies, and 1% are positive for lupus anticoagulant. However, after 1 year, less than 1% are still positive for these tests.[18] In our experience, it is rare to identify a high-risk antiphospholipid-antibody profile (Table 1) in a healthy person.

Between 20% and 30% of patients with SLE have persistent moderate-to-high-risk antiphospholipid-antibody profiles that are associated with an increased risk of clinical sequelae.[28] Among patients without autoimmune disease, the prevalence of antiphospholipid-antibody positivity is 6% among women with pregnancy complications, 10% among patients with venous thrombosis, 11% among patients with myocardial infarction, and 17% among patients with stroke who are younger than 50 years of age.[29] However, these prevalence estimates were derived mostly from studies that included patients who underwent antiphospholipid-antibody testing only once, those in whom test results were borderline positive, or both. Large studies that use rigorous definitions of clinical events and strict criteria for antiphospholipid-antibody positivity are needed.

CLINICAL PRESENTATIONS OF ANTIPHOSPHOLIPID-ANTIBODY–POSITIVE PATIENTS

Patients who are positive for antiphospholipid antibodies may present with no related symptoms. Such patients are usually identified during an evaluation for systemic autoimmune diseases, early miscarriages, an elevated activated partial-thromboplastin time (aPTT), or a false positive result of a syphilis test. Symptomatic patients seek medical attention for thrombotic, obstetrical, or other clinical sequelae of antiphospholipid antibodies.

Stroke and transient ischemic attack are the most common arterial events in patients with the antiphospholipid syndrome. Patients with venous thromboembolism most commonly present with lower-extremity deep-vein thrombosis, pulmonary embolism, or both. Antiphospholipid-antibody–related complications of pregnancy generally develop after 10 weeks of gestation; losses before 10 weeks, especially if not recurrent, would more commonly be attributed to chromosomal defects. Although not part of the classification criteria, additional clinical manifestations of the antiphospholipid syndrome are listed in Table 2. Among patients with SLE, the prevalence of thrombosis, pregnancy complications, valve disease, pulmonary hypertension, livedo reticularis, thrombocytopenia, hemolytic anemia, acute or chronic renal vascular lesions, and moderate or severe cognitive impairment is higher among patients with antiphospholipid antibodies than among patients who are negative for such antibodies.[28]

DIAGNOSIS OF THE ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid-antibody positivity should be included in the differential diagnosis if a patient presents with thrombosis at a young age, with

Table 1. Key Concepts for Clinicians Evaluating the Results of Antiphospholipid-Antibody Testing.*

Key Concepts	Comments
Step 1: Understanding the basics	Antiphospholipid antibodies (aPL) are not only a diagnostic marker for APS but also a risk factor for thrombosis and pregnancy complications, which are commonly multifactorial. Thus, consideration of non-aPL thrombotic risk factors is critical in evaluating patients who are positive for aPL. Transient aPL positivity is common during infections.
Step 2: Assessing individual aPL tests	Not every positive aPL test is clinically significant.
LA testing	LA testing is a three-step functional coagulation assay to detect aPL.[19] The LA test correlates better with clinical events than do aCL and anti-β_2GPI tests.[20]† False positive LA results may occur in patients treated with warfarin, heparin, or direct oral anticoagulants; thus the LA test should not be ordered for such patients (or should be interpreted with caution if performed). Given the lack of accuracy in LA determination and nonstandardized reporting of the results, the LA test report should be discussed with an experienced laboratory specialist or a clinician when the interpretation is difficult.
ELISA	The aCL and anti-β_2GPI antibodies (IgG, IgM, or IgA) are most commonly detected by ELISA; they should be tested by experienced laboratory specialists, given the relatively high variability among commercially available assays.[26] Moderate to high titers (40 GPL or MPL or 99th percentile) of aCL or anti-β_2GPI IgG or IgM (99th percentile) correlate better with aPL-related clinical events than do lower titers; IgG is more strongly associated with clinical events than is IgM.[27] Isolated moderate-to-high-titer aCL or anti-β_2GPI IgA is rare and of unknown clinical significance.
Step 3: Assessing the aPL profile	Assessment of the aPL profile has diagnostic implications and helps risk-stratify patients who are persistently positive for aPL. "Persistent" is defined as tested "on two or more occasions at least 12 weeks apart" based on the revised Sapporo classification criteria[1]; a high-risk aPL profile is more likely to remain positive when repeated, independent of the timing. For diagnostic purposes, both high- and moderate-risk aPL profiles are important; a high-risk profile provides more confidence in the diagnosis.
High risk†	A high-risk profile is defined as a positive LA test with or without a moderate-to-high-titer‡ of aCL or anti-β_2GPI IgG or IgM.
Moderate risk	A moderate-risk profile is defined as a negative LA test with a moderate-to-high titer‡ of aCL or anti-β_2GPI IgG or IgM.
Low risk	A low-risk profile is defined as a negative LA test with a low titer‡ of aCL or anti-β_2GPI IgG or IgM.
Clinical judgment	Clinical judgment is important if the LA test is performed on an anticoagulated patient, if the aPL profile is low-risk, if the aPL result for only a single time point is available, or if aCL or anti-β_2GPI IgA is the only positive aPL test.
Step 4: Understanding the future	Although LA, aCL, and anti-β_2GPI tests are the mainstay of APS diagnosis, several additional aPL tests have been developed recently; the clinical significance of other proposed aPL tests must be established with additional outcome-based studies.

* The abbreviation aCL denotes anticardiolipin antibody, anti-β_2GPI anti-β_2-glycoprotein I antibody, APS antiphospholipid syndrome, ELISA enzyme-linked immunosorbent assay, GPL IgG phospholipid, LA lupus anticoagulant, and MPL IgM phospholipid.

† Studies are conflicting on the question of whether triple aPL (LA, aCL, and anti-β_2GPI) positivity confers a higher risk of clinical events[21-23] than LA positivity alone.[20,24,25] From a diagnostic point of view, we believe that they are equally important.

‡ In clinical practice, our definition of a moderate-to-high titer of aCL or anti-β_2GPI is 40 or more GPL or MPL units, and a low titer is 20 to 39 GPL or MPL units.

Table 2. Major Clinical Manifestations of the Antiphospholipid Syndrome That Are Not Included in the Revised Sapporo Classification Criteria.

Hematologic

Thrombocytopenia

    More common: mild (platelet count, 50,000–150,000 per mm^3), asymptomatic

    Less common: severe (platelet count, <20,000 per mm^3), with or without thrombotic microangiopathy

Hemolytic anemia

    Without schistocytes, suggesting immune-mediated hemolytic anemia

    With schistocytes, suggesting thrombotic microangiopathy

Renal

Acute thrombotic microangiopathy

Chronic vaso-occlusive lesions (cortical ischemia or infarction with arteriosclerosis, arteriolosclerosis, arterial fibrous intimal hyperplasia, glomerular ischemia, interstitial fibrosis, tubular thyroidization, tubular atrophy, organized thrombi with or without recanalization, or a combination of such lesions)

Cardiac

Valve vegetations or thickening (valve thickness >3 mm, thickening of the proximal or middle portion of the leaflet, or irregular nodules on the atrial face of the edge of the mitral valve, the vascular face of the aortic valve, or both)

Dermatologic

Livedo reticularis or racemosa

Livedoid vasculopathy (recurrent, painful skin ulcerations)

Neurologic

Cognitive dysfunction (in the absence of stroke)

Subcortical white-matter changes

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antibodies).[1] Since the current classification criteria do not incorporate the full spectrum of clinical findings for the antiphospholipid syndrome, an international effort is under way to develop a more comprehensive classification, with the use of the same methods that were used to develop the most recent classification criteria for rheumatoid arthritis and SLE.[30-32] Classification criteria are used to identify homogeneous cohorts for clinical or translational research purposes, whereas diagnostic criteria are intended to capture all patients with a given disorder, including those with unusual clinical presentations.[33] Pending the development and widespread acceptance of a newer, more comprehensive approach, we use the revised Sapporo criteria for classification of the antiphospholipid syndrome as a guide, rather than as a rigid formula. The diagnosis should be considered in patients with persistent, moderate-to-high-risk antiphospholipid-antibody profiles (tested with validated methods) and in patients with any antiphospholipid-antibody–related finding. Table 1 and Figure 2 show key principles for interpreting the results of antiphospholipid-antibody testing that may be useful in diagnosing or ruling out the antiphospholipid syndrome.

PREVENTION AND TREATMENT OF THROMBOTIC ANTIPHOSPHOLIPID SYNDROME

The first step in the treatment of patients who have antiphospholipid antibodies in the absence of thrombosis is risk stratification based on age, antiphospholipid-antibody profile, concomitant risk factors for thrombosis, and other systemic autoimmune diseases. While thrombotic risk calculators for antiphospholipid-antibody–positive patients are under development,[34,35] it is important that traditional risk factors for cardiovascular disease, such as smoking, hypertension, diabetes, and hypercholesterolemia, as well as active systemic autoimmune diseases, are properly addressed. A moderate-to-high-risk antiphospholipid-antibody profile warrants avoidance of estrogen supplements when possible and aggressive postoperative prophylaxis against thrombosis if feasible.

PRIMARY THROMBOSIS PREVENTION

Given the low background risk of thrombosis in the general population, the absolute risk of a first

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an unusual site of or recurrent thrombosis, with late pregnancy loss, with early or severe preeclampsia, or with the HELLP syndrome (characterized by hemolysis, elevated liver-enzyme levels, and low platelet counts). When combined with thrombosis or obstetrical complications, the following clinical findings may be a clue that a patient has the antiphospholipid syndrome: livedo, signs or symptoms of another systemic autoimmune disease, unexplained prolongation of the aPTT, or mild thrombocytopenia. Severe thrombocytopenia (platelet count, <20,000 per cubic millimeter) is rare and should prompt the clinician to consider other causes of a low platelet count.

According to the revised Sapporo criteria for classification of the antiphospholipid syndrome, the disease is characterized by thrombosis, pregnancy complications, or both in patients with persistent antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, or anti-β_2GPI
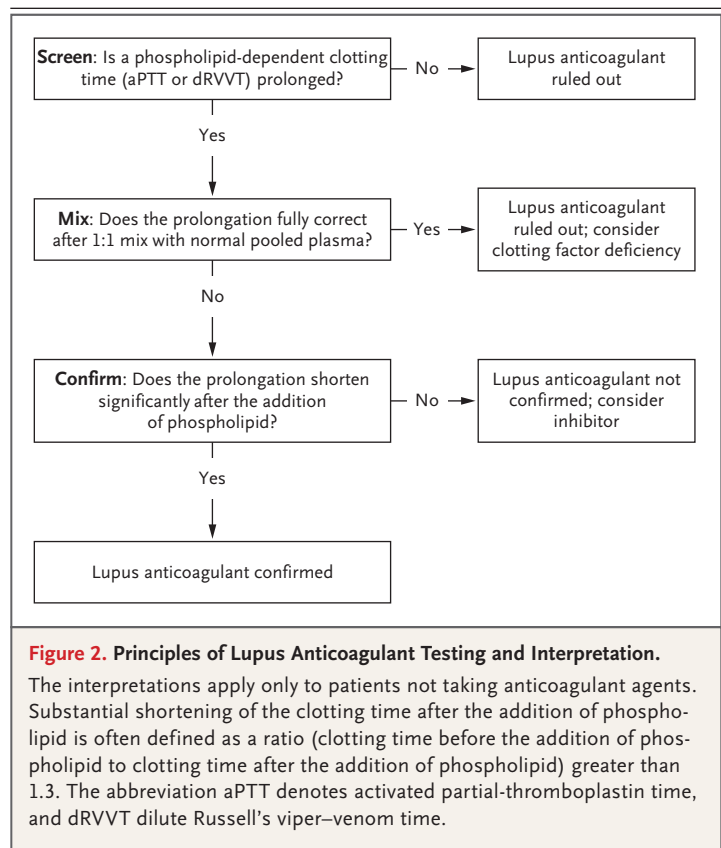
thrombosis in antiphospholipid-antibody–positive patients who do not have other risk factors is probably less than 1% per year.[36,37] As in the general population, arterial and venous thrombotic events in antiphospholipid-antibody–positive patients are often multicausal.[38-41] A substantial proportion of patients with the antiphospholipid syndrome who present with thrombosis have one other thrombotic risk factor at the time of the event.[39] The annual risk of a first thrombosis in patients with persistently moderate-to-high-risk antiphospholipid-antibody profiles and a systemic autoimmune disease or additional thrombotic risk factors may be as high as 5%.[22]

The use of low-dose aspirin for primary thrombosis prevention is still controversial, given the low quality of evidence and lack of prospective data documenting that this strategy is effective.[42] Our approach is to follow the guidelines for prevention of cardiovascular disease in the general population when weighing the pros and cons of low-dose aspirin as primary prophylaxis in an antiphospholipid-antibody–positive patient.

Although there is experimental and clinical evidence that hydroxychloroquine may reduce the risk of thrombosis in patients with SLE,[43,44] additional controlled studies are needed to determine the effectiveness of hydroxychloroquine for primary prophylaxis in antiphospholipid-antibody–positive patients who do not have other systemic autoimmune diseases. We do not prescribe hydroxychloroquine for primary thrombosis prevention.

SECONDARY VENOUS THROMBOSIS PREVENTION

For patients with the antiphospholipid syndrome defined by venous thrombosis, initial therapy with unfractionated or low-molecular-weight heparin, followed by long-term anticoagulant therapy with a vitamin K antagonist such as warfarin (target international normalized ratio [INR], 2 to 3), is recommended. Higher-intensity warfarin therapy (target INR, 3 to 4), though associated with fewer thrombotic events in two retrospective studies,[45,46] does not further reduce the risk of recurrent thrombosis, on the basis of two randomized, controlled trials.[47,48] Although the proportion of patients with therapeutic INRs was less than ideal in the prospective trials, the mean achieved INRs were significantly increased in the groups that received higher-intensity warfarin therapy as compared with the groups that received lower-inten-

Figure 2. Principles of Lupus Anticoagulant Testing and Interpretation.
The interpretations apply only to patients not taking anticoagulant agents. Substantial shortening of the clotting time after the addition of phospholipid is often defined as a ratio (clotting time before the addition of phospholipid to clotting time after the addition of phospholipid) greater than 1.3. The abbreviation aPTT denotes activated partial-thromboplastin time, and dRVVT dilute Russell's viper–venom time.

sity therapy. For most patients with persistent antiphospholipid antibodies and otherwise unprovoked venous thromboembolism, discontinuation of anticoagulant therapy would be associated with an unacceptably high risk of recurrent thrombosis.[49] However, the benefit of prolonged anticoagulation is less certain in patients who are positive for antiphospholipid antibodies and in whom thrombosis was provoked — for example, by a surgical procedure — and in patients with laboratory tests for antiphospholipid antibodies that become negative over time.

SECONDARY ARTERIAL THROMBOSIS PREVENTION

Many experts recommend warfarin or another vitamin K antagonist for arterial thrombosis outside the cerebral vasculature. For older patients with stroke and a single test showing a low titer of anticardiolipin antibodies, aspirin alone may be as effective as warfarin[50,51]; however, patients with moderate-to-high-risk antiphospholipid-antibody profiles are often treated with warfarin (target INR, 2 to 3), with or without low-dose aspirin.[52,53] Although there is a biologic rationale

for adding aspirin to anticoagulant therapy, dual antithrombotic therapy — because it increases the risk of major hemorrhage — is often reserved for patients with clinically significant risk factors for cardiovascular disease and patients in whom a single antithrombotic agent has failed to prevent recurrence. Higher-intensity warfarin therapy (target INR, 3 to 4) is preferred for arterial thrombosis at some centers because relatively few patients with arterial thrombosis were enrolled in the randomized, controlled trials that compared different intensities of warfarin therapy.[47,48] Validated risk-stratification models are needed to identify those patients with arterial (or venous) thrombosis who would benefit from more aggressive antithrombotic strategies.

SECONDARY VENOUS AND ARTERIAL THROMBOSIS PREVENTION IN PATIENTS IN WHOM WARFARIN FAILS

Recurrent venous thrombosis despite warfarin use is a well-recognized complication of the antiphospholipid syndrome.[54] There is no high-quality evidence to support any particular management strategy when warfarin therapy fails despite a therapeutic INR, but options include higher-intensity warfarin therapy (target INR, 3 to 4); the addition of low-dose aspirin, hydroxychloroquine, or a statin; use of a different anticoagulant, such as low-molecular-weight heparin; and a combination of these approaches.

In addition, antiphospholipid antibodies can cause artifactual prolongation of the prothrombin time, leading to falsely elevated INR results and a subtherapeutic warfarin dose. This phenomenon is most common with point-of-care devices; laboratory instruments are usually accurate, depending on the sensitivity of the thromboplastin used.[55] Confirming that factor X activity, measured with the use of a chromogenic assay, is concordant with the INR (as measured by the device that will be used to adjust the warfarin dose) may reduce the likelihood of inadequate anticoagulation.[56]

DIRECT ORAL ANTICOAGULANTS

Since 2010, five direct oral anticoagulants have been approved for use in many countries. Although most of these medications have compared favor-

ably with warfarin for the prevention of stroke in patients with atrial fibrillation and for the treatment of venous thromboembolism, published data on direct oral anticoagulants for highly prothrombotic states such as the antiphospholipid syndrome and heparin-induced thrombocytopenia are quite limited. One randomized, open-label study compared rivaroxaban with warfarin (target INR, 2 to 3) for secondary prevention of venous thromboembolism in 116 patients with the antiphospholipid syndrome. This study used a surrogate end point (the percentage change in endogenous thrombin potential in the two groups from randomization to day 42), and the clinical implications of the findings are not known. No patient in either group had bleeding or thrombosis during the 6-month follow-up period.[57] Other trials of direct oral anticoagulants for patients with the antiphospholipid syndrome are ongoing. For now, there is insufficient evidence to determine the relative efficacy and safety of such agents in this patient population.[58]

TREATMENT OF CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME

Acute renal failure and the respiratory distress syndrome, diffuse alveolar hemorrhage, encephalopathy, and adrenal hemorrhage are common in patients with catastrophic antiphospholipid syndrome. The diagnosis can be challenging, especially if there is no history of antiphospholipid-antibody positivity. Proposed classification criteria for definite and probable catastrophic antiphospholipid syndrome have been published.[2] The disorder is classified as definite in a patient with multiple (three or more) organ thromboses (with microthrombotic involvement of at least one organ) developing within 7 days in a patient with persistently positive test results for antiphospholipid antibodies. At the bedside, catastrophic antiphospholipid syndrome is difficult to distinguish from other thrombotic microangiopathies. A detailed discussion of the differential diagnosis can be found elsewhere.[59]

Early treatment is critical in patients with catastrophic antiphospholipid syndrome, usually with a combination of anticoagulants, glucocorticoids, intravenous immune globulin, and plasma exchange. Possible therapies beyond antithrom-

Table 3. Our Treatment Strategies for Antiphospholipid-Antibody (aPL)–Positive Patients.*

Treatment	Use
Low-dose aspirin (<100 mg per day)	Primary thrombosis prevention, if indicated, based on guidelines for cardiovascular disease prevention in the general population; secondary arterial thrombosis prevention, if patient has other risk factors for cardiovascular disease; prevention of pregnancy complications in pregnant patients with obstetrical or thrombotic APS or both; potential add-on treatment for recurrent thrombosis despite therapeutic-dose anticoagulant therapy
Hydroxychloroquine (200–400 mg per day)	Potential add-on treatment for recurrent thrombosis despite therapeutic-dose anticoagulant therapy
Statins	Potential add-on treatment for recurrent thrombosis despite therapeutic-dose anticoagulant therapy
Warfarin	Secondary thrombosis prevention (INR, 2–3); target INR of 3–4 is a possible strategy for recurrent thrombosis despite therapeutic-dose anticoagulant therapy
Low-molecular-weight heparin	Thrombosis prevention during high-risk periods (e.g., perioperative or postpartum period); prevention of thrombosis and pregnancy complications in pregnant patients with obstetrical APS (e.g., enoxaparin, 40 mg daily) and thrombotic APS (e.g., enoxaparin, 1.5 mg/kg of body weight daily or 1 mg/kg twice daily); potential alternative treatment for recurrent thrombosis despite therapeutic-dose warfarin (e.g., enoxaparin, 1.5 mg/kg daily or 1 mg/kg twice daily)
Unfractionated heparin	Part of first-line combination treatment for catastrophic APS; prevention of thrombosis and pregnancy complications in pregnant patients with obstetrical APS (5000 units subcutaneously twice daily) and thrombotic APS (e.g., 250 units/kg subcutaneously twice daily)
Direct oral anticoagulants	More data needed
Glucocorticoids (e.g., intravenous methylprednisolone, 250–1000 mg for 3 days)	Part of first-line combination treatment for catastrophic APS; first-line treatment for severe thrombocytopenia, hemolytic anemia, or both
Intravenous immune globulin	Part of first- or second-line combination treatment for catastrophic APS (1–2 g/kg, given over a period of 3–5 days); first- or second-line treatment for severe thrombocytopenia (1 g/kg; can repeat once, usually 1–2 days after first dose)
Plasma exchange	Part of first- or second-line combination treatment for catastrophic APS; for acute thrombotic microangiopathy in patients with aPL-related nephropathy
Traditional immunomodulatory agents (e.g., azathioprine, 100–150 mg per day, or mycophenolate mofetil, 1000–3000 mg per day)†	An option for severe thrombocytopenia, hemolytic anemia, or both; an option for aPL nephropathy
Sirolimus†	More data needed
Rituximab (e.g., 1000 mg on days 0 and 15, repeated every 6 mo)†	An option for thrombocytopenia, hemolytic anemia, livedoid vasculopathy, and aPL nephropathy; an option for catastrophic APS that is refractory to standard treatment
Eculizumab†	An option for catastrophic APS that is refractory to standard treatment; an option for acute thrombotic microangiopathy in patients with aPL-related nephropathy
Defibrotide†	More data needed

* INR denotes international normalized ratio.
† The only clinical information about the use of this immunosuppressive agent or class of agents in patients with APS comes from case reports of hematologic or microthrombotic manifestations of APS or both.

botic agents are discussed below and shown in Table 3. Given the rarity of the syndrome, no controlled studies have been done, and the proposed therapies are based on low-quality evidence (e.g., case reports). Nonthrombotic complications such as bleeding or infections often affect risk–benefit calculations related to anticoagulation or immunosuppression.

PREVENTION AND TREATMENT OF OBSTETRICAL ANTIPHOSPHOLIPID SYNDROME

The current strategy for the prevention of pregnancy complications in patients with obstetrical antiphospholipid syndrome, based on low-quality evidence, is use of low-dose aspirin and a prophylactic dose of unfractionated or low-molecular-weight heparin.[60] Low-dose aspirin and therapeutic-dose heparin should be used in pregnant women with thrombotic antiphospholipid syndrome, regardless of the pregnancy history. Low-dose aspirin during pregnancy is often suggested for antiphospholipid-antibody–positive patients who have no history of thrombosis or pregnancy complications; however, no data support this strategy. We suggest that antiphospholipid-antibody–positive patients without a history of thrombosis receive a prophylactic dose of low-molecular-weight heparin for at least 6 weeks post partum, given the increased risk of thrombosis during this period.[61]

The long-term risk of thrombosis for women with obstetrical antiphospholipid syndrome is lower than the risk for women whose syndrome-defining event was thrombotic[62,63] and higher than the risk for women with pregnancy complications due to factors other than antiphospholipid antibodies.[64] We generally do not recommend long-term antithrombotic therapy for women who have a history of obstetrical antiphospholipid syndrome but no other risk factors for thrombosis.

PHARMACOLOGIC MANAGEMENT BEYOND ANTITHROMBOTIC AGENTS

Anticoagulation is usually not effective for nonthrombotic manifestations of antiphospholipid antibodies, nephropathy, and microthrombosis. In fact, some nonthrombotic manifestations may develop despite (or be a contraindication for) full-dose anticoagulant therapy. Thus, treatment strategies beyond antiplatelet and anticoagulant agents have been used and increasingly investigated. Table 3 lists many of the treatments that have been used (or are being investigated) for thrombotic or nonthrombotic manifestations of the antiphospholipid syndrome.

Although patients with platelet counts greater than 50,000 per cubic millimeter usually require no therapy, glucocorticoids with or without intravenous immune globulin are the first-line treatment for patients with platelet counts below 20,000 per cubic millimeter. Splenectomy is not a first-line treatment because of the increased risk of thrombosis for patients with the antiphospholipid syndrome who undergo surgery. Warm-antibody–mediated hemolytic anemia is initially treated with glucocorticoids. Second-line therapies for immune-mediated thrombocytopenia and hemolytic anemia include mycophenolate mofetil, cyclophosphamide, and azathioprine. Antiphospholipid-antibody–related nephropathy is usually slowly progressive, with no proven treatment; acute renal failure due to thrombotic microangiopathy is often treated with plasma exchange. Antithrombotic agents do not stop the progression of valve disease; however, aspirin or warfarin can be used for vegetations associated with a high thromboembolic risk. Livedoid vasculopathy is usually refractory to glucocorticoids; low-dose aspirin, dipyridamole, clopidogrel, pentoxifylline, sildenafil, intravenous immune globulin, tissue plasminogen activator, hyperbaric oxygen therapy, or a combination of these interventions, with or without anticoagulant therapy, have been used.

Although traditional immunomodulatory agents (e.g., azathioprine and mycophenolate mofetil) have been used for some of the nonthrombotic or microthrombotic manifestations of antiphospholipid antibodies discussed above, the risk–benefit tradeoffs associated with these agents do not always favor their use. On the basis of newly understood mechanisms, immunomodulatory approaches targeting mTOR, B cells, and complement have been proposed. Statins and adenosine receptor agonists have also been investigated. Further studies are needed to determine whether, how much, and in which specific clinical situations any of these strategies will benefit patients with the antiphospholipid syndrome.

Inhibition of the mTOR pathway blocks antiphospholipid-antibody–mediated endothelial proliferation, prevents the accumulation of vascular

cellular infiltrates, and reduces fibrosis of the vascular intima and media. In a small cohort of antiphospholipid-antibody–positive renal transplant recipients, those treated with sirolimus had significantly less vascular proliferation in post-transplantation biopsy samples and a significantly higher rate of functioning allograft than those who did not receive sirolimus.[16]

Mouse models suggest that B-cell inhibition could have a role in management of the antiphospholipid syndrome[65]; case reports describe rituximab for patients who have the antiphospholipid syndrome with thrombocytopenia, hemolytic anemia, livedoid vasculopathy, antiphospholipid-antibody–related nephropathy, and catastrophic antiphospholipid syndrome, with variable responses. A pilot study involving 19 patients showed that despite the absence of a change in antiphospholipid-antibody profiles, rituximab may control some of the manifestations of antiphospholipid syndrome that are not part of the current classification criteria.[66]

Anti-C5 monoclonal antibodies and C5aR antagonist peptides prevent antiphospholipid-antibody–mediated pregnancy loss and thrombosis in preclinical models.[67] Case reports have been published on the use of eculizumab, an anti-C5 monoclonal antibody, in patients with either acute thrombotic microangiopathy after kidney transplantation or catastrophic antiphospholipid syndrome.[68,69]

In vitro, in vivo, and clinical studies (using surrogate markers) indicate that statins reduce antiphospholipid-antibody–induced endothelial-cell activation and tissue factor expression. These observations, along with the finding that statins significantly decrease inflammatory and pro-thrombotic biomarkers such as interleukin-6 and soluble tissue factor in antiphospholipid-antibody–positive patients, have generated the hypothesis that statins may reduce the risk of thrombosis in the antiphospholipid syndrome.[70,71]

Adenosine 2A receptor agonism, by triggering cyclic AMP formation in neutrophils, may lower thrombotic risk by reducing antiphospholipid-antibody–mediated NETosis.[72] Defibrotide, an adenosine receptor agonist, is approved for hepatic veno-occlusive disease (also known as the sinusoidal obstruction syndrome) after hematopoietic stem-cell transplantation. The use of defibrotide in one patient with catastrophic antiphospholipid syndrome who had had a limited response to heparin, aspirin, and dipyridamole resulted in a complete remission.[73]

CONCLUSIONS

The antiphospholipid syndrome has a broad spectrum of thrombotic and nonthrombotic clinical manifestations. The diagnosis requires positive antiphospholipid-antibody tests; however, not every positive test has diagnostic importance. Thus, both misdiagnosis due to underrecognition of signs or symptoms and overdiagnosis due to overinterpretation of antiphospholipid-antibody tests are common. Although antithrombotic medications are still the cornerstone of treatment, advances in our understanding of the mechanisms by which antiphospholipid antibodies cause disease have revealed additional targets that may lead to immunomodulatory treatment options.

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