Antiphospholipid antibodies in critical illness

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The antiphospholipid syndrome is defined by the presence of antiphospholipid antibodies in patients with recurrent venous or arterial thromboembolism or pregnancy morbidity. Antithrombotic therapies are the mainstay of treatment to reduce the risk of recurrent thromboembolism. Among patients with antiphospholipid antibodies, the absolute risk of new thrombosis developing is low in healthy patients without previous thrombotic events. However, the risk of recurrent thrombosis appears to be high in patients with a history of arterial or venous thrombosis. Compared with placebo or untreated control, anticoagulation with warfarin administered to achieve an international normalized ratio of 2.0 to 3.0 probably reduces the risk of recurrence of thrombotic events. Aspirin and moderate-intensity warfarin appear equally effective for preventing recurrent stroke in patients with a single positive antiphospholipid antibody test result and previous stroke. It is unknown how best to prevent first stroke in patients found to be persistently positive for the antiphospholipid syndrome. The catastrophic variant of the antiphospholipid syndrome is a condition characterized by multiple vascular occlusive events, usually affecting small vessels and evolving over a short period of time. This condition has a very high mortality rate. First-line treatment with therapeutic anticoagulation, corticosteroids, plasma exchange, and intravenous immunoglobulin seems to be effective in reducing mortality and risk of catastrophic thrombotic events in these patients. In conclusion, moderate-intensity warfarin is effective for preventing recurrent thrombotic events in patients with venous thrombosis. Aspirin appears to be as effective as moderate-intensity warfarin for preventing recurrent stroke in patients with previous stroke and a single positive test result for antiphospholipid antibody. The optimal treatment of other clinical manifestations of antiphospholipid syndrome needs to be addressed in well-designed prospective studies. (Crit Care Med 2010; 38[Suppl.]:S51–S56)

Key Words: antiphospholipid syndrome; anticoagulation; thrombosis; risk

The antiphospholipid syndrome (APS) is the association of thrombosis or recurrent pregnancy loss with persistent antiphospholipid antibodies (APLA). The spectrum of thrombosis in APS includes venous, arterial, and microvascular events. This syndrome is referred to as *primary APS* when it occurs alone and as *secondary APS* when it occurs in association with other conditions, such as systemic lupus erythematosus (SLE).

APLA Are a Heterogeneous Group of Autoantibodies Directed Against Phospholipid Binding Proteins

International consensus criteria for the classification of definite APS were initially published in 1999 (1) and updated in 2006 (2). The presence of persistent APLA, including lupus anticoagulants (LAC), anticardiolipin antibodies, and anti-β2-glycoprotein I (anti-β2-GPI) antibodies, in patients with arterial or venous thromboembolism or pregnancy morbidity defines APS. The criteria do not include a number of clinical manifestations commonly associated with APLA, including thrombocytopenia, livedo reticularis, valvular heart disease, nephropathy, and ischemic neurologic abnormalities (1).

Given the high risk of first and recurrent thromboembolism that characterizes this condition, the mainstay of APS treatment is antithrombotic therapy. However, the optimal antithrombotic management of patients with APS is challenging because of a lack of standardized laboratory tests to confirm the diagnosis, limited data on its natural history, and a paucity of randomized treatment trials.

Diagnosis of Antiphospholipid Syndrome

The diagnosis of APS can be made only when a characteristic clinical presentation is combined with objective laboratory abnormalities (2). The clinical criteria include objectively confirmed arterial, venous, or small-vessel thrombosis, or pregnancy morbidity consisting of recurrent (≥3) fetal losses before the 10th week of gestation, one or more unexplained fetal deaths at or beyond the 10th week of gestation, or premature birth caused by placental insufficiency, eclampsia, or preeclampsia. Laboratory testing requires a positive test for at least one of the following: LAC, medium-titer or high-titer immunoglobin (Ig) and/or IgM anticardiolipin antibodies (>40 GPL or MPL1 or above the 99th percentile), or IgG and/or IgM anti-β2-GPI at titers above the 99th percentile. APLA have to be present on two or more occasions measured at least 12 wks apart. Interestingly, the use of 99th percentile cut-off level of anticardiolipin antibodies seems more sensitive than >40 GPL values in the classification of APS in recent studies (3). Other antiphospholipid antibodies, such as antiphosphatidylserine antibodies, antiphosphatidylethanolamine antibodies, antibodies against prothrombin alone, and antibodies to the phosphatidylserine–prothrombin complex, were frequent in patients with APS. However, these features were not included in the diagnostic criteria of this syndrome because of their low specificity (1).

Lupus anticoagulants (nonspecific inhibitors) are antibodies that block phospholipid surfaces and reduce the coagulant potential of plasma, thus prolonging the clotting time in coagulation tests

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based on the activated partial thromboplastin time (4). Failure to correct the prolonged clotting time after a 1:1 mix with normal platelet-free plasma and correction after addition of excess phospholipids confirms the presence of a LAC. Consensus guidelines recommend screening for LAC with at least two phospholipid-dependent coagulation tests (5). LAC detection can be problematic in patients receiving anticoagulant therapy because clotting times will be prolonged but usually can be overcome by mixing patient and normal plasma before LAC measurement (6).

Anticardiolipin antibodies do not prolong coagulation assays and are detected using enzyme-linked immunosorbent assay techniques. In the diagnosis of APS, IgG and IgM isotypes may be considered, although the IgG isotype seems to have the strongest association with thrombosis (7).

Because the accuracy and reliability of assays for anticardiolipin antibodies are limited, consensus guidelines recommend semiquantitative reporting of results as low, medium, or high titers (8).

β_2-GPI is a glycoprotein that circulates in high concentration in the plasma and that has an unknown function. β_2-GP1 is the likely antigenic target for some forms of APLA. Like anticardiolipin antibodies, anti-β_2-GPI antibodies may be of the IgG, IgM, or IgA isotype, and are detected using enzyme-linked immunosorbent assay. Anticardiolipin and anti-β_2-GPI antibody testing must be interpreted with knowledge that many commercial and locally developed assays suffer from both a lack of standardization and significant batch-to-batch variability (9, 10).

APLA may be found in patients with SLE and can be induced by infections and drugs (11, 12). Antibodies found in the setting of infection or drugs are often transient, and their clinical importance is uncertain.

How APLA cause thrombosis is not known. The effects of APLA on various coagulation and hemostatic pathways have been studied, and numerous mechanisms of APLA-mediated thrombosis have been suggested. Most APLA are directed against phospholipid-binding plasma proteins (13). The two best characterized antigens are β_2-GPI and prothrombin. Many physiologic roles for β_2-GPI have been suggested, including apoptotic cell clearance (14), binding to oxidized low-density lipoproteins (15), and an interaction with coagulation factor XI (16). It is postulated that APLA-associated thrombosis occurs when anti-β_2-GPI antibodies bind and induce dimerization of β_2-GPI, which increases its binding affinity for cell-surface phospholipids and induces endothelial, monocyte, platelet, and complement activation (17).

Consistent data suggest that APLA have a procoagulant effect by inhibiting the anticoagulant protein C pathway (18–20). In the presence of an anti-β_2-GPI antibody, β_2-GPI seems to be concentrated and stabilized on the anionic surface of the cells in an active conformation, which allows binding to anticoagulant protein C and thereby decreases the activity of anticoagulant protein C (18).

Furthermore, APLA also may act by up-regulating the expression of tissue factor (21). Tissue factor, a high-affinity receptor and cofactor for factor VII/VIIa, is the physiologic trigger of normal blood coagulation and, in many cases, of thrombosis (22). Tissue factor expression is increased on monocytes from APS patients (23–25), particularly in patients with SLE (26). In some studies, anti-β_2-GPI antibodies have been specifically implicated in tissue factor induction (25). APS patient sera and purified IgG have also been shown to up-regulate tissue factor on normal human neutrophils (27).

Association Between Antiphospholipid Antibodies and Thrombosis

Depending on the assay and cut-off values used, APLA may be found in 5% to 10% of healthy blood donors (28). However, only a few healthy individuals have persistently positive APLA at follow-up (28). The prevalence of APLA appears to be higher among patients presenting with thrombosis (4–21%) (29, 30). APLA are present in 30% to 50% of patients with SLE (31, 32).

In a recent meta-analysis of 25 studies involving >7000 patients, the mean odds ratio (OR) for thrombosis was 11.0 for LAC, and a weaker association was found for anticardiolipin antibodies (≈1.6), for which half of the studies reviewed did not reach statistical significance (10). This difference may be explained by different anticardiolipin antibodies being assayed, assay methodology, quantitation, and cut-off values. Another meta-analysis of the risk of venous thrombosis in patients with APLA without other autoimmune diseases found an overall OR of 11.1 for LAC (33). In the latter study, the OR was approximately 1.6 for anticardiolipin antibodies of any titer, and 3.2 for high-titer anticardiolipin antibodies. These data suggest an association between APLA and thrombosis, and the increasing risk of thrombosis among those patients with increasing antibody titer further strengthens the evidence that the association is causal. Meta-analyses of the clinical implications of APLA are limited by the quality of the included studies; there are no large prospective studies of unselected patients whose antiphospholipid antibody status was determined before objective documentation of their thrombotic complications.

In the Framingham Heart Study cohort, increased anticardiolipin antibodies were independently associated with an increased risk of ischemic stroke or transient ischemic attack in women (hazard ratio [HR], 2.6; absolute risk, 3.2%) but not in men (HR, 1.3; absolute risk, 4.5%) (34). Ginsburg et al (35) investigated the association between venous thrombosis and ACA in a cohort from the Physicians' Health Study and found a relative risk of approximately eight for medium-titer to high-titer IgG anticardiolipin antibodies. In contrast, in the HUNT 2 study, no statistically significant association between anticardiolipin antibodies levels and venous thrombosis was observed (36). This discrepancy may, in part, be explained by the age difference of the patients in the two studies because in the Physicians Health Study article, the average age of patients with venous thrombosis was 58 yrs. However, half of the patients with venous thrombosis in the HUNT 2 study were age 70 yrs or older.

Finally, thrombosis is presumed to cause many of the pregnancy complications associated with APS. In women without SLE, a retrospective review of >13,000 patients found a 20% prevalence of APLA among women with recurrent fetal loss compared with 5% in healthy women (37). The association between APLA and fetal loss is strongest for loss occurring after 10 wks (38). However, the association between APS and the risk of premature birth attributable to eclampsia or preeclampsia and intrauterine growth restriction is less well-established and studies have yielded conflicting results (39, 40).

Interestingly, approximately 50% of APLA-positive patients with thrombosis have coincident non-APLA risk factors at the time of thrombosis (41), including oral contraceptives, hormone re-

placement therapy, cigarette smoking, and inherited thrombophilia (e.g., factor V Leiden or the prothrombin 20210A mutation). The combination of APLA with one or more inherited risk factors significantly increased the risk of venous thrombosis (42, 43).

Determining Thrombosis Risk in APS

The optimal treatment of thrombosis risk in patients with APS requires assessment of thrombosis risk associated with APLA and the potential benefits and risks of antithrombotic therapies. The risk of thrombosis among healthy patients who are incidentally found to have APLA seems to be low: among 552 randomly selected blood donors, no thrombotic events were observed after 12 mos of follow-up among patients found to have anticardiolipin antibodies (28).

However, in patients with SLE, the incidence of thrombosis was not negligible: in a prospective cohort of 551 patients, of whom 49% had either LAC or anticardiolipin antibodies, the annual incidence of thrombosis was 2% (44). The OR of thrombosis was 3.20 for LAC and 6.80 for high-titer anticardiolipin antibodies. However, patients with SLE have a high prevalence of thrombosis even in the absence of APLA (31).

Information on the risk of recurrent thrombosis among patients with APLA is based on retrospective studies of untreated patients or prospective studies in which anticoagulants have been discontinued (45). Three prospective studies showed a high risk of recurrence, ranging from 10% to 67% per year (46–48). In a study on 412 patients with a first episode of venous thromboembolism who completed 6 mos of anticoagulation, presence of anticardiolipin antibodies was associated with an increased risk of recurrence after anticoagulant discontinuation (incidence at 4 yrs: 29% vs. 14%; risk ratio, 2.1; 95% confidence interval [CI], 1.3–3.3) (46).

In retrospective studies, recurrent thrombosis was observed in 52% to 69% of patients during 5 to 6 yrs of follow-up, regardless of the type of antithrombotic therapy (49, 50), and the incidence of thrombosis was highest during the first 6 mos after discontinuation of warfarin therapy. Interestingly, recurrent thrombosis tends to occur in the same vascular distribution as the original event. Patients with venous thrombosis generally have recurrent venous events and patients with arterial thrombosis have recurrent arterial events (49, 51).

Management of Antithrombotic Therapy in Patients With Antiphospholipid Antibodies

Venous thromboembolism is the most common initial clinical manifestation of APLA, occurring in 32% of patients with APS (52). Initial treatment of venous thromboembolism in patients with APS should consist of unfractionated or low-molecular-weight heparin for at least 4 to 5 days, overlapped with warfarin administered to achieve an international normalized ratio (INR) of 2.0 to 3.0 if baseline INR is not elevated (53). Management of anticoagulation may be complicated in patients with APLA by artifactual elevation of the INR. This effect is dependent on the type of instrument and thromboplastin that are used to measure the INR and can be avoided in most patients by simply selecting an INR reagent that is insensitive to the effect of the APLA (54). Alternatively, functional factor II or X levels may be used to monitor the degree of oral anticoagulant-associated suppression of the coagulation cascade (54).

Similarly, monitoring of unfractionated heparin intensity in patients with LAC may be misleading because the activated partial thromboplastin time may be elevated at the baseline control in many patients (55). However, there are some studies that suggest a heparin resistance in some patients with LAC (56). Two randomized trials (57, 58) have shown that high-intensity warfarin (INR, 3.0–4.0) is not better than moderate-intensity warfarin (INR, 2.0–3.0) in preventing recurrent thrombosis. In the first trial (57), in 114 patients with APS, the incidence of recurrent thrombosis was 10.7% among patients who received high-intensity warfarin and 3.4% among those who received moderate-intensity warfarin after a mean follow-up of 2.7 yrs (HR, 3.1; 95% CI, 0.6–15.0). Major bleeding rates were not different in the two groups, occurring in 5.4% and 6.9%, respectively (HR, 1.0; 95% CI, 0.2–4.8). In the other trial, which included 109 patients with APS (54), the incidence of recurrent thrombosis after a median follow-up of 3.6 yrs was 11.1% among patients who received high-intensity warfarin and 5.5% among those who received moderate-intensity warfarin (HR, 1.97; 95% CI, 0.49–7.89). Bleeding rates were not significantly different in the two groups (27.8% vs. 14.6%; HR, 2.18; 95% CI, 0.92–5.15) (58). Combining these studies, a significant excess of minor bleeding was evident in patients allocated to high-intensity warfarin therapy (OR, 2.30; 95% CI, 1.16–4.58; $p = .02$), whereas incidence of recurrent thrombosis (high-intensity vs. moderate-intensity: OR, 2.49; 95% CI, 0.93–6.67), total bleeding (OR, 1.73; 95% CI, 0.93–3.31), or major bleeding (OR, 0.73; 95% CI, 0.23–2.31) were not different between the two groups.

The optimal duration of anticoagulation for prevention of recurrent thrombosis in patients with APS is unknown. The risk of recurrence is highest during the first 6 mos after discontinuation of warfarin therapy, but it is unknown whether the absolute risk of recurrence decreases with increasing duration of anticoagulation (50). In a prospective study, 211 patients with a single positive test result for anticardiolipin antibodies were randomly assigned to stop warfarin after 6 mos or to receive indefinite anticoagulation (46). In this study there were 23 recurrent events in patients who stopped anticoagulation compared with three recurrences in patients receiving indefinite anticoagulation (HR, 7.7; 95% CI, 2.4–25.0). Furthermore, all recurrent events in the indefinite treatment group occurred after patients discontinued warfarin. Interestingly, preliminary data suggest that anticoagulation may be discontinued in those patients with primary APS and persistent negative APA, especially if the thrombotic event was venous and occurred in association with a transient risk factor, such as immobilization or pregnancy (59). However, other studies are required to confirm these results.

Prospective studies of patients with APS receiving antithrombotic therapy report an incidence of recurrent thrombosis ranging from 3% to 24% per year (51, 57, 58, 60). Retrospective studies report higher recurrence rates, ranging from 53% to 69% (49, 50).

In summary, although the optimal duration of anticoagulation is uncertain, indefinite anticoagulation is recommended because prospective data suggest a high rate of recurrence after warfarin discontinuation.

Decisions regarding duration of anticoagulation may also be influenced by the type of APLA (LAC vs. anticardiolipin antibodies or both) and whether the antibody is persistently present. It is un-

known whether anticoagulation can be discontinued in patients whose LAC testing result becomes negative or if the only laboratory finding is a persistent low-titer anticardiolipin antibody.

Arterial events in APS most commonly involve the cerebral circulation, with stroke being the initial clinical manifestation in 13% and transient ischemic attack in 7% of patients with APS (52). The association between APS and other arterial thrombosis, including myocardial infarction, is less well-established (61).

APLA and Stroke

The Antiphospholipid Antibodies and Stroke Study (APASS) (60) is a subanalysis of a randomized, double-blind study (62) in which 1770 patients with APLA were included. In this prospective cohort study, use of warfarin (INR, 1.4–2.8) and aspirin (325 mg/d) was compared in the secondary prevention of stroke. Interestingly, there was no difference in the risk of thrombosis, death, or bleeding in patients treated with warfarin compared with aspirin. Furthermore, the presence of either LAC or anticardiolipin antibodies was not predictive of recurrent thrombotic events at 2 yrs (adjusted risk ratio, 0.98; 95% CI, 0.80–1.20). Warfarin and aspirin appeared to be equivalent for the prevention of thromboembolic complications in these patients. Thus, patients with first ischemic stroke and a single positive APLA test result who do not have another indication for anticoagulation may be treated with aspirin (325 mg/d) or moderate-intensity warfarin (INR, 1.4–2.8) (63), although aspirin is likely to be preferred for reasons of simplicity.

The management of patients who are incidentally found to have an APLA and have no previous thrombosis has not been adequately studied, except in patients with SLE. Consensus opinion suggests no treatment or low-dose aspirin (81 mg/day) for asymptomatic, nonpregnant patients (64). In a recent randomized, controlled trial, low-dose aspirin was not effective in preventing thrombosis in asymptomatic individuals with APLA (65). Patients with SLE and an antifactor II antibody usually present with hemorrhagic complication (66). Thus, in these patients, use of warfarin or aspirin does not appear to be indicated because of the risk of bleeding.

Catastrophic Antiphospholipid Syndrome

The catastrophic variant of the APS was defined in 1992 as a condition characterized by multiple vascular occlusive events, usually affecting small vessels, presenting over a short period of time, with laboratory confirmation of the presence of APLA (67). The catastrophic APS is characterized predominately by a diffuse thrombotic microvasculopathy, with a predilection for lung, brain, heart, kidney, skin, and gastrointestinal tract (68).

Catastrophic APS is an unusual presentation that represents <1% of APS cases (52). In the earliest published series (69), the mortality rate was approximately 50%; however, in the recent report from Bucciarelli et al (68), the mortality rate was slightly reduced. This appears to be attributable to the use of full anticoagulation, corticosteroids, plasma exchanges, and intravenous immunoglobulins as first-line therapies (68). In catastrophic APS, 60% of patients appear to have a triggering factor, especially infections (68). Multiple triggering factors may be present in the same patient (e.g., infection, anticoagulation withdrawal followed by a surgical procedure, or biopsy in patients with neoplasia and APLA). The presence of thrombotic microangiopathic anemia is a hallmark of catastrophic APS. Differential diagnosis of catastrophic APS includes several entities that share the same pathologic process, such as thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, acute disseminated intravascular coagulation, and hemolytic anemia, elevated liver enzyme, and low platelets syndrome.

The pathogenesis of catastrophic APS is not clear. In these patients, microvascular occlusions might be responsible for propagation of thrombosis as clots continue to generate thrombin. Fibrinolysis may be decreased by increased circulating plasminogen activator inhibitor type-1, and there is consumption of the natural anticoagulant proteins such as protein C and antithrombin (70). Thrombotic manifestations may also be attributable to the systemic inflammatory response syndrome, possibly caused by excessive cytokine release from affected and necrotic tissues. In a recent multicenter study of 250 patients with catastrophic APS, cerebrovascular and cardiovascular diseases were the most frequent cause of death (27.2% and 19.8%, respectively) (68). Infection was described as the main cause of death in 19.8% of patients. The presence of SLE was associated with a higher mortality in patients with catastrophic APS (59% vs. 37.9%; $p = .003$). Anticoagulation was associated with a lower mortality (36.9% vs. 77.8%; $p < .0001$), and the higher recovery rate was achieved by the combination of anticoagulants, corticosteroids, and plasma exchange, whereas concomitant treatment with cyclophosphamide did not appear to add benefit (68). A few studies have evaluated the long-term outcome of catastrophic APS survivors (71). In a study of 73 patients over an average follow-up of 67.2 mos, 19% patients had further APS-related events and 16% patients died (71). Furthermore, 15% of patients were functionally impaired as a consequence of catastrophic APS.

CONCLUSION

APS is a complex disorder with evolving diagnostic criteria. Patients with persistent APLA and venous thromboembolic events should be treated indefinitely with warfarin administered at moderate intensity (INR, 2.0–3.0). Aspirin seems to be equally effective compared to warfarin in the secondary prevention of ischemic stroke in patients with a single positive test for APLA. Low-dose aspirin does not seem to be effective in the primary prevention of cardiovascular events in asymptomatic patients with APLA.

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