Clinical Summary

Antiphospholipid syndrome

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ICD codes
ICD-9:
Coagulation defects, other: 286.9

ICD-10:
Other specified coagulation defects: D68.8

OMIM
Antiphospholipid syndrome: 107320

Synonyms
APS; Hughes syndrome

Historical note and nomenclature

Antiphospholipid (aPL) antibodies were first detected in 1907 by a complement-fixation test developed to diagnose syphilis (Pangborn 1941). This serologic test for syphilis used phospholipid antigens called "reagins" from saline liver extracts of fetuses with congenital syphilis (Moore and Mohr 1952; Vlachoyiannopoulos et al 2007). In 1941, scientists recognized "reagins" as a type of anionic phospholipid and were able to isolate them from bovine heart muscle (Moore and Mohr 1952). After isolation from heart tissues, "reagins" were referred to as "cardiolipins" (Moore and Mohr 1952). With the increased demand for syphilis screening that heralded the turn of the century came a commensurate increase in the use of the syphilis serological tests. Screening large numbers of patients for syphilis in the 1950s revealed a significant number of individuals with positive serological tests for syphilis but no clinical signs of the disease (Vlachoyiannopoulos et al 2007). This phenomenon, referred to as biologically false-positive serological tests for syphilis (BFP-STS), catalyzed research that led to the discovery of the coagulative effects of aPL antibodies (Vlachoyiannopoulos et al 2007). In 1974, the association between aPL and thromboses and recurrent abortions was demonstrated through a

series of separate studies designed to test aPL in vivo and in vitro (Lechner 1974; Vlachoyiannopoulos et al 2007).

Throughout the 1970s and 1980s, Dr. Hughes and his colleagues collected data on large numbers of patients whom they described as having "anticardiolipin syndrome," or patients who exhibited elevated antiphospholipids in the absence of classic lupus features. Hughes's characterization reflected a clinical spectrum that included thrombosis, neurologic disease, and elevated antiphospholipid antibodies. Antiphospholipid syndrome (APS) was first described in full detail in 1983 by Dr. Graham R V Hughes of St. Thomas's Hospital in London, England. Initially, clinicians viewed antiphospholipid syndrome as a variation of systemic lupus erythematous (SLE); however, the research conducted by Hughes and colleagues offered sufficient evidence demonstrating the distinct nature and presentation of the 2 disorders (Hughes 1998; Khamashta 2006). Dr. Hughes and colleagues would go on to publish many descriptions of the disorder. In 1982, Dr. Hughes presented detailed findings on antiphospholipid syndrome to the British Society of Rheumatology and again at the 7th International Symposium of antiphospholipid antibodies in New Orleans (Hughes 1998; Khamashta 2006).

Primary antiphospholipid syndrome (PAPS). Primary antiphospholipid syndrome refers to the type of antiphospholipid syndrome that is not secondary to systemic lupus erythematosus or other rheumatologic conditions (Black 2006; Sivaprasad and Gregor 2007).

Secondary antiphospholipid syndrome (SAPS). Secondary antiphospholipid syndrome refers to antiphospholipid syndromes occurring secondary to SLE or other rheumatologic conditions (Black 2006; Sivaprasad and Gregor 2007).

Catastrophic antiphospholipid syndrome (CAPS). Catastrophic antiphospholipid syndrome (CAPS), also known as "Asherson syndrome," is considered an extreme variant of antiphospholipid syndrome and is associated with elevated mortality (Berkelhammer et al 2007; Cervera et al 2007). It is an acute process that occurs in patients with antiphospholipid syndrome as a result of widespread microthrombi in numerous vascular beds, often leading to systemic tissue necrosis, multiple organ failure, and thrombotic microangiopathy (Gezer 2003; Cervera et al 2007). Individuals with CAPS often develop respiratory failure, stroke, adrenal insufficiency, and widespread cutaneous infarction (Gezer 2003).

Antiphospholipid Lung Syndrome (APLS). Pulmonary manifestations of antiphospholipid syndrome are rather rare but can lead to antiphospholipid lung syndrome (APLS), which describes the spectrum of pulmonary disorders in patients with elevated antiphospholipid antibodies (Asherson and Cervera 1995; Stojanovich 2006). The existence of microthromboses throughout the pulmonary vasculature in patients with antiphospholipid syndrome can lead to pleuropulmonary complications such as pleuritis, pleural effusions, pneumonitis, interstitial lung disease, atelectasis, and bronchiolitis obliterans (Asherson and Cervera 1995; Stojanovich 2006). Thromboembolism of pulmonary arteries can also result in pulmonary hypertension, adult respiratory distress syndrome, intra-alveolar pulmonary hemorrhage, and postpartum syndrome (Stojanovich 2006).

Miscellaneous hypotheses related to nomenclature of antiphospholipid syndrome. Although not widely accepted, it has

been proposed that antiphospholipid syndrome manifests in 2 other forms: pre-antiphospholipid syndrome and microangiopathic antiphospholipid syndrome (MAPS). Pre-antiphospholipid syndrome has been described as a subset of antiphospholipid syndrome that is associated with small vessel occlusion in at least 1 organ or tissue along with involvement of 2 or more organs or systems (Asherson 2006). Pre-antiphospholipid syndrome, also referred to as "probable antiphospholipid syndrome," is a condition thought to mimic several conditions that may presage the development of antiphospholipid syndrome and often presents with livedo reticularis, thrombocytopenia, fetal loss, and valve lesions in patients who often develop diagnosable antiphospholipid syndrome years later (Asherson 2006). Notwithstanding, many asymptomatic individuals with aPL and some with aPL and nonthrombotic problems never develop antiphospholipid syndrome, underscoring the tenuous relationship this supposed entity has in relation to antiphospholipid syndrome.

MAPS describes those patients with microvascular occlusions along with demonstrable antiphospholipid antibodies (Asherson 2006; Asherson et al 2007). Given the widespread thrombotic microangiopathy that characterizes MAPS, patients often exhibit severe thrombocytopenia, hemolytic anemia, thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), and the HELLP syndrome (Asherson et al 2007). Like pre-antiphospholipid syndrome, the view that MAPS represents a distinct subset of antiphospholipid syndrome has gained little currency amongst experts.

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Clinical manifestations

Antiphospholipid syndrome is a potentially fatal autoimmune disorder capable of affecting any organ system or blood vessel in the body (Table 1) (Vasoo et al 2005; Black 2006; Sivaprasad and Gregor 2007). It is among the most frequently acquired thrombophilias (Ruiz-Irastorza and Khamashta 2005). Antiphospholipid syndrome arises when the body produces antibodies that react against phospholipids and phospholipid-binding proteins on cell membranes (Black 2006; Sivaprasad and Gregor 2007). The disease is defined by the development of thrombosis or obstetric complications occurring in the setting of elevated antiphospholipid antibodies (aPL) (Wilson et al 1999). Targeted action against intrinsic phospholipids undermines the body's homeostatic regulation of blood coagulation, resulting in the increased coagulability that characterizes the disorder (Black 2006; Sivaprasad and Gregor 2007). Although antiphospholipid syndrome can occur in patients without preexisting diseases, it does have an increased incidence in individuals with systemic lupus erythematous or other autoimmune disorders (Tarr et al 2007). Antiphospholipid syndrome exists in 4 distinct but related subsets: (1) primary antiphospholipid syndrome (PAPS), (2) secondary antiphospholipid syndrome (SAPS), or (3) catastrophic antiphospholipid syndrome (CAPS). PAPS refers to instances in which the disease exists in the absence of other autoimmune or rheumatologic conditions. SAPS describes antiphospholipid syndrome occurring in patients with underlying rheumatologic or autoimmune conditions such as SLE (Tarr et al 2007). Catastrophic antiphospholipid syndrome describes the severest variety of the disorder and is associated with a mortality rate as high as 50% (Merrill and Asherson 2006).

The predilection for causing blood clots in antiphospholipid syndrome affects both arterial and venous systems. Thus, patients with deep venous thrombosis in the lower extremities may be at increased risk of developing stroke due to the increased coagulability of the blood (Sanna et al 2006; Hughes 2007; Martinez-Berriotxoa et al 2007; Roldan and Brey 2007). Furthermore, given the fact that aPL antibodies have been implicated in the pathogenesis of coronary artery disease (CAD), patients with antiphospholipid syndrome are at increased risk for the development of cardiovascular compromise with advanced age (Greco et al 2007).

Other common findings of the condition include involvement of visceral organs such as the liver, kidneys, heart, and adrenal glands (D'Cruz 2005; Sangle et al 2005; Hughes 2007). Neurologic impairment can also arise secondary to thrombotic events in the setting of antiphospholipid syndrome (Sanna et al 2006; Hughes 2007; Roldan and Brey 2007). The presence of migraine headaches, memory loss, difficulty maintaining balance, as well as hearing loss and otorrhea have all been documented in patients with antiphospholipid syndrome (Hughes 2007; Jovanovic-Bateman and Warrington 2007). Transient ischemic attacks (TIA), seizures, and amaurosis fugax have also been described in patients with antiphospholipid syndrome (Cimaz et al 2006; Sanna et al 2006; Jovanovic-Bateman and Warrington 2007). Common cutaneous findings in antiphospholipid syndrome include livedo reticularis, skin ulcerations, superficial cutaneous necrosis, painful purpura, leg ulcers, superficial thrombophlebitis, and splinter hemorrhages (Diogenes et al 2004; Garcia-Carrasco et al 2007; Hughes 2007). Livedo reticularis describes the net-like, violaceous discoloration of the skin that often occurs on the lower extremities in pre-antiphospholipid syndrome and primary antiphospholipid syndrome (Hughes 2007). Other less frequent signs of antiphospholipid syndrome include renal and celiac artery stenosis, ischemic bone fractures, nasal septal perforation, and retinal vein occlusion (Maaroufi et al 2004; Banerjee et al 2007; Hughes 2007).

Table 1. Clinical Manifestations of Antiphospholipid Syndrome

System	Clinical Findings
Central nervous system (CNS)	Stroke, migraine headaches, seizures, myelopathy, chorea, hearing loss, TIA
Cardiovascular system	Pulmonary hypertension, diseases of myocardial valves, myocardial infarction, valvulopathy including vegetations, leaflet thickening, regurgitation, and stenosis
Pulmonary system	Dyspnea, respiratory distress syndrome, antiphospholipid lung syndrome
Digestive system	Hematemesis, intestinal infarction, Budd-Chiari syndrome

Renal system	Malignant hypertension, nephropathy, renal vein thrombosis, thrombotic microangiopathy
Endocrine system	Adrenal insufficiency from adrenal thrombosis (Addison disease)
Rheumatologic system	Sjogren syndrome, vasculitis, arthritis, polymyositis, systemic lupus erythematosus (SLE), discoid lupus
Skin	Skin ulceration, Sneddon syndrome, livedo reticularis
Hematology	Thrombocytopenia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia
Obstetrics and gynecology	Recurrent spontaneous miscarriages
Ophthalmologic	Retinal vein occlusion, amaurosis fugax, photopsia, diplopia, blurry vision

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Clinical vignette

Clinical vignette #1: primary antiphospholipid syndrome. A 24-year old African-American female with a past medical history of hypertension presented to her primary care physician with complaints of pain in her left calf. The pain began 2 weeks prior and had been associated with swelling of the left calf and ankle. Physician exam revealed erythema and increased warmth in the area in question. The left calf was tender to palpation. The patient denied any recent changes in diet or weight loss but did admit to having recently returned from a trip to Asia that included a 14-hour nonstop airplane ride. She denied being on any medications but admitted to regular use of oral contraceptives for the previous 4 years. Laboratory examination revealed normal levels of protein C, protein S, and antithrombin, and activated protein C resistance was within normal limits. Initial anticardiolipin test was positive for the antibodies. Elevated levels of IgM and IgG were also noted.

Clinical vignette #2: catastrophic antiphospholipid syndrome. A 32-year-old mother of 4 who was at 20 weeks' gestation was brought to the emergency department by her husband. The patient had difficulty breathing and appeared confused. Her husband reported a 3-hour history in which his wife appeared "very confused" and unable to walk or stand up alone. The patient was unable to answer questions but her husband stated that his wife complained to him earlier that morning that she was unable to urinate for the past 2 days and was worried about it. He also described her being "short of breath" and "pale

looking" for the past 2 days culminating in the period just before admission where the patient's shortness of breath became labored breathing. Physical examination of the patient revealed diffuse purplish spots on the skin of her trunk and bilateral lower extremities. Initial laboratory evaluation including CBC, PTT, PT/INR, ESR, Hepatitis B and C serologies, RPR, lupus anticoagulant, anticardiolipin, cryoglobulins, SPEP, complement levels, p- and c-ANCA, ANA, and RF were ordered. Laboratory evaluation revealed a lupus anticoagulant and elevated anticardiolipin antibody levels.

Clinical vignette #3: secondary antiphospholipid syndrome. A 47-year-old man with a past medical history of rheumatoid arthritis presented to the emergency department with shortness of breath, left-sided pain and "tightness" in the chest, and pain in the left jaw and arm. He also complained of pain in the lower right calf that had been constant in intensity for the past 4 weeks. Laboratory values revealed markedly elevated troponins and LDH, and subsequent Doppler studies confirmed the presence of a thrombosis in the vasculature of the lower right calf. IgG anticardiolipin antibodies were found to be 176 (normal less than 14-15) and the IgM anticardiolipin antibody was 54 (normal less than 20). Further testing also revealed the presence of Lupus anticoagulant.

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Etiology

No information was provided by the author.

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Pathogenesis and pathophysiology

The exact mechanism by which antiphospholipid antibodies occur in the body remains unclear (Gezer 2003). Antiphospholipid antibodies constitute a diverse group of autoantibodies that are capable of binding to phospholipids (PL) alone, protein-PL complexes, or PL-binding proteins (Vlachoyiannopoulos et al 2007). They can be detected in isolation, in association with autoimmune diseases such as SLE, and during the course of different infections (Black 2006; Vlachoyiannopoulos et al 2007). Although antiphospholipid (aPL) antibodies are linked to the onset of antiphospholipid syndrome, their role in the pathogenesis of the disorder remain unclear (Black 2006; Hughes 2007). Recent studies have examined the mechanisms by which aPL antibodies contribute to the development of thrombosis in patients with antiphospholipid syndrome (Amengual et al 2003). Although it was initially believed that aPL antibodies were the only autoantibodies that targeted phospholipid-binding plasma proteins, the contribution of other antibodies in undermining the function of these proteins has recently been established (Ieko et al 1999; Amengual et al 2003). Although not definitive, the plasma protein beta-2-glycoprotein (B2GPI) may affect hemostasis in patients with antiphospholipid syndrome by binding to apoptotic cells and facilitating clearing (Ieko et al 1999; d'Angeac et al 2005). Autoantibodies found in association with antiphospholipid syndrome may target specific phospholipid-binding plasma proteins including beta-2-glycoprotein (B2GPI), which binds to apoptotic blebs to facilitate clearing (Ieko et al 1999; Gezer 2003). These autoantibodies also target phospholipid-binding plasma proteins located on the surface of vascular endothelial cells, platelets, or other circulating cells (Ieko et al 1999). It is via this interaction between

autoantibodies and plasma proteins that B2GPI leads to the suppression of the thrombomodulin-protein C system, thus favoring a prothrombotic state (Ieko et al 1999; Amengual et al 2003).

Various hypotheses have been set forth to explain the cellular and molecular mechanisms that led to the development of antiphospholipid syndrome (Table 2). The reduction in binding ability of clotting factors accounts for the thrombocytopenia seen in many patients with antiphospholipid syndrome. Recent studies also implicate inflammatory agents and the widespread activation of the complement system that characterize antiphospholipid syndrome as playing an integral role in the development of the disease (Hughes 2007; O'Neil 2007).

Table 2. Current Hypotheses for Pathogenesis of APS

A. Activation of endothelial cells

- This hypothesis suggests that the binding of aPL antibodies to endothelial cells results in the activation of these cells. Activation of the endothelial cells causes the upregulation of adhesion molecules, secretion of cytokines, and metabolism of prostacyclines (Meroni et al 2000).

B. Oxidant-mediated injury of the endothelium

- Suggests that the development of APS leads to the circulation of autoantibodies to low-density lipoproteins (LDL) in association with anticardiolipin antibodies. According to this model, the anticardiolipin antibodies cross-react with oxidized LDL and the combination of the two is digested by macrophages, which causes activation and damage to the endothelial cells (Ames 1994; Levine et al 2002).

C. Interference of antiphospholipid antibodies with the function of phospholipid binding proteins such as B2GPI, prothrombin, protein C, and annexin V

- Describes antiphospholipid antibodies as interfering with the action of B2GPI, a natural anticoagulant that inhibits platelet activation and coagulation (Kandiah and Krilis 1994; Gezer 2003). Activated protein C is another natural anticoagulant, which downregulates coagulation factors Va and VIIIa. Protein C cannot be activated on the endothelial without the thrombin-thrombomodulin complex. This model suggests that aPL antibodies inhibit the development of this complex and, thus, prevent the activation of protein C and, ultimately, impair the ability of coagulation factors Va and VIIIa to function properly. This cascade is thought to result in the increased rate of thrombosis that characterizes the disorder (Oosting et al 1993; Kandiah and Krilis 1994).

- The elevated levels of anticardiolipin antibodies and lupus anticoagulants in patients with antiphospholipid syndrome are often seen in association with false-positive results on VDRL assay. Recent studies suggest that polymorphisms in the genes responsible for tissue factor may determine a patient's susceptibility to systemic thromboses (Lincz et al 2007). The presence of this mutation appears to be increased in patients with antiphospholipid syndrome, making them prone to hypercoagulability (Lincz et al 2007).

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Epidemiology

Because of the rarity of antiphospholipid syndrome, the actual frequency of the disorder amongst healthy populations remains undetermined (Lockshin 2006). Incidentally, up to 8% of healthy individuals in the general population demonstrate elevated aPL antibodies but no clinical signs of the disease (Schved et al 1994; Sanna et al 2006). Nonetheless, antiphospholipid syndrome is seen in approximately 10% of patients with SLE (Lockshin 2006). Antiphospholipid syndrome has also been described with increased frequency in individuals with primary systemic vasculitis (Rees et al 2006).

APS is most commonly found in young to middle-aged patients and rarely occurs in pediatric or geriatric populations (Piette and Cacoub 1998; Cimaz and Descloux 2006). Similar to other autoimmune disorders, antiphospholipid syndrome occurs more commonly in women than in men (Piette and Cacoub 1998). Although antiphospholipid syndrome has not been shown to demonstrate a predilection for certain ethnic groups, it has been documented more often in African-American and Hispanic populations, most probably as a result of the increased prevalence of SLE in these ethnic groups (Gezer 2003; Fernandez et al 2007).

Various studies suggest a familial tendency in the transmission of antiphospholipid syndrome (Elhajj et al 2004; Usugi et al 2007). The genetic predisposition of antiphospholipid syndrome is accounted for by human leukocyte antigen (HLA) alleles involved in the production aPL (Domenico Sebastini et al 2003; Namjou 2003). Specifically, the presence of the HLA-DMA*0102 allele is believed to be one of the genetic risks for the production of aPL antibodies (Sangle et al 2005). Further, certain genetic predispositions increase an individual's susceptibility to developing antiphospholipid syndrome. For instance, recent murine studies that have yet to be confirmed in humans suggest that mutations in the BXSB allele increase an individual's susceptibility of developing antiphospholipid syndrome (Shirai et al 1999). Notwithstanding, reciprocal findings have yet to be confirmed in human studies.

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Prevention

Given the increased risk of thrombotic events associated with antiphospholipid syndrome, prevention of complications associated with the disorder hinge on stabilizing the body's homeostatic coagulation mechanisms. Prophylactic therapy with pharmaceutical agents such as warfarin has shown promise, particularly after an initial event (Black 2006; Erkan et al 2007; Sivaprasad and Gregor 2007). However, warfarin's efficacy in patients with no previous event remains uncertain. Although once touted as a suitable alternative to warfarin for prophylactic treatment, aspirin is no longer recommended prophylactically in patients with antiphospholipid syndrome (Erkan et al 2007; Sivaprasad and Gregor 2007). Strict avoidance of oral contraceptives is also warranted considering the coagulating properties of such medications. Alternate methods of contraceptives should be encouraged in antiphospholipid syndrome patients with such concerns.

In addition to pharmacologic therapy, alteration in daily activities can be instrumental in preventing onset of complications in patients with antiphospholipid syndrome (Black 2006; Sivaprasad and Gregor 2007). For instance, given the increased risk of developing systemic clots,

patients with antiphospholipid syndrome are encouraged to adopt certain precautions to minimize their risk of developing deep venous thrombosis (Sivaprasad and Gregor 2007). Such patients should be encouraged to remain active, walk around every couple of hours, and wear compression stockings (Black 2006; Sivaprasad and Gregor 2007). Further, those individuals receiving warfarin should arrange for blood tests to determine INR range prior to long trips (Black 2006; Sivaprasad and Gregor 2007). Although intuitive, the efficacy of such measures for minimizing events in antiphospholipid syndrome remains unclear, given the paucity of available data analyzing the effects of such measures.

Dietary counseling that emphasizes avoidance of herbal or dietary remedies with anticoagulant properties can be instrumental in minimizing the risk of complications in patients with antiphospholipid syndrome who are on regular anticoagulant therapy such as warfarin. Finally, given the increased risk of exacerbating hypercoagulable states, smoking cessation should be promoted in such patients via counseling or therapeutic methods (Johnson et al 2005).

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Differential diagnosis

The initial diagnosis of antiphospholipid syndrome can be challenge, particularly given the many other causes of coagulopathy. Although they are distinct entities, antiphospholipid syndrome and Sneddon syndrome share many similarities in the early stages of the respective diseases (Fetoni et al 2000). Sneddon syndrome is a thrombophilia characterized by recurrent ischemic cerebrovascular episodes and livedo reticularis (Fetoni et al 2000; Kraemer et al 2005). Like antiphospholipid syndrome, Sneddon syndrome is also more commonly found in young women and is also often associated with valvulopathy, recurrent spontaneous abortions, renal involvement, and vascular dementia (Kraemer et al 2005). Although the early stages of the 2 diseases bear apparent likeness to one another, clinical manifestations that emerge in the later stages of the respective diseases make differentiating the 2 less difficult (Fetoni et al 2000). Patients with Sneddon syndrome tend to develop progressive cognitive deterioration and physical disabilities in later stages of the disorder, whereas those with antiphospholipid syndrome tend to exhibit a far more benign course (Fetoni et al 2000). Considering an appropriate differential in patients suspected of having a coagulopathy can help eliminate misdiagnosis associated with these conditions. The following conditions should be considered as possible etiologies in all patients meeting the above criteria:

(1) Multiple sclerosis
(2) Neuropsychiatric lupus
(3) Systemic lupus erythematous
(4) Human immunodeficiency virus (HIV)
(5) Hemolytic anemia
(6) Systemic sclerosis
(7) Behcet syndrome
(8) Hepatitis C
(9) Sneddon syndrome
(10) Avascular necrosis
(11) Vasculitis
(12) Cogan syndrome with hearing loss

(13) Susac syndrome with branch retinal artery occlusion

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Diagnostic workup

Given the essential role detection of aPL antibodies plays in diagnosing antiphospholipid syndrome, the role of the laboratory in the diagnostic workup of the disease is critical (Miyakis et al 2006). In addition to detecting aPL antibodies, diagnosis of antiphospholipid syndrome relies on pertinent findings that meet both clinical and laboratory criteria (Black 2006). According to the international consensus outlined in Table 3, at least 1 clinical criterion (vascular thrombosis, pregnancy complications) and 1 laboratory criterion (lupus anticoagulant, anticardiolipin antibodies) should be present for a diagnosis of antiphospholipid syndrome (Gezer 2003). The diagnosis is made after the onset of a vascular thrombosis or pregnancy followed by persistently positive aPL antibodies conducted 12 weeks apart (Table 3) (Miyakis et al 2006). aPL antibodies can be detected via immunological methods that exploit the ability of aPL to induce blood coagulation (Vlachoyiannopoulos et al 2007). Given the heterogeneous nature of aPL, a multitude of laboratory methods have been utilized for their detection (Vlachoyiannopoulos et al 2007). These assays have yet to be standardized, leading to the problem of interlaboratory variation, which is becoming relatively frequent (Vlachoyiannopoulos et al 2007). Routine screening for antiphospholipid syndrome can be achieved by enzyme-linked immunosorbent assay (ELISA) and coagulation-based tests to detect anticardiolipin antibodies or the presence of lupus anticoagulant (Bertolaccini et al 2005; Bertolaccini and Hughes 2006). Given the risk of "seronegative antiphospholipid syndrome", repeat testing is necessary to confidently rule out antiphospholipid syndrome in individuals with negative results with such tests (Bertolaccini et al 2005).

In patients with a high degree of suspicion for antiphospholipid syndrome, a thorough laboratory workup is warranted in order to rule out other sources of coagulation defects (Wunnava and Hunt 2006). Evaluation of serum levels of protein S, protein C, antithrombin III, and activated protein C resistance should be observed in patients with antiphospholipid syndrome (Wunnava and Hunt 2006). IgM and IgG levels are also expected to be elevated in such patients (Wunnava and Hunt 2006).

Table 3. Classification Criteria for Antiphospholipid Syndrome

I. Laboratory Criteria

A. Lupus anticoagulants detected in the plasma, according to the guidelines set forth by the International Society on Thrombosis and Haemostasis (Subcommittee on Lupus Anticoagulants/Antiphospholipid Antibodies).The antibodies must be detected on 2 or more occasions at least 12 weeks apart.

B. The presences of anticardiolipin antibodies of the IgG or IgM isotype in serum or plasma, present in medium or high titer (higher than 40 GPL or MPL, or greater than 99th percentile), on 2 or more occasions, at least 12 weeks apart, measured by a standardized ELISA.

C. Anti-B2GPI of IgG or IgM isotype in serum or plasma (titer greater than 99th percentile) on 2 or more occasions, at least 12 weeks apart, measured by a standardized ELISA according to recommended procedures.

II. Clinical Criteria

D. Vascular thrombosis

- One or more clinical events of arterial, venous, or small vessel thrombosis in any tissue or organ confirmed by imaging, Doppler studies, or histopathology. Superficial venous thrombosis is not considered part of these criteria.

E. Pregnancy morbidity

- One or more unexplained mortalities of morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or

- One or more premature births of a morphologically normal neonate at or before the 34th week of gestation because of severe preeclampsia or eclampsia or severe placental insufficiency, or

- Three or more unexplained consecutive spontaneous abortions prior to the 10th week of gestation in parents without anatomic, hormonal, or chromosomal abnormalities.

From: (Brandt et al 1995; Miyakis et al 2006; Vlachoyiannopoulos et al 2007)

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Prognosis and complications

Accurately assessing the prognosis of antiphospholipid syndrome relies heavily on the extent of systematic involvement and the amount of tissue damage. However, negative prognostic factors in patients with antiphospholipid syndrome include myocardial ischemia, cerebral involvement, pulmonary hypertension, and nephropathy (Bucciarelli et al 2006a; 2006b; Cheunsuchon et al 2007).

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Management

Patients with antiphospholipid syndrome are at elevated risk of developing frequent thrombosis (Khamashta et al 1995). In an effort to decrease the probability of clotting and to mitigate complications associated with such clots, patients with antiphospholipid syndrome should be encouraged to maintain a consistent, long-term, therapeutic anticoagulation regimen (Khamashta et al 1995; Wunnava and Hunt 2006; Hughes 2007). Low-dose warfarin therapy remains effective in the prevention of recurrent arterial and venous thromboses in patients with antiphospholipid syndrome (Lim et al 2006). However, prophylactic anticoagulant therapy is not recommended in patients with

high-titer anticardiolipin antibodies (more than 30 GPL U/mL) who are asymptomatic (Gezer 2003). The role of aspirin as an effective alternative remains uncertain (Lim et al 2006; Erkan et al 2007). Regular visits to a primary care physician are advisable as a means of maintaining a constant international normalized ratio (INR), which is considered crucial to minimizing complications associated with thrombosis (Wunnava and Hunt 2006; Hughes 2007). Two recent prospective studies have suggested that long-term anticoagulant therapy with an international normalized ratio (INR) of between 2 and 3 is as acceptable as an INR of greater than 3 in the prophylactic treatment of such patients (Crowther et al 2003; Finazzi et al 2005). In patients with persistently elevated aPL antibodies and a history of thrombosis, lifelong anticoagulation may be considered (Finazzi et al 1996).

An acute thrombotic event in a patient with antiphospholipid syndrome should be managed the same as acute thrombosis from any other cause (Gezer 2003). Extreme caution is advised in prescribing heparin to patients with antiphospholipid syndrome who present with a thrombotic event in association with elevated aPTT (Rosove and Brewer 1992; Gezer 2003). Such patients should have their aPTT monitored regularly to prevent unnecessary complications.

In cases of suspected catastrophic antiphospholipid syndrome, efforts to facilitate early diagnosis and institute effective treatments in a timely manner are critical to improving patient outcome (Merrill and Asherson 2006). Effective treatment options for patients with catastrophic antiphospholipid syndrome include plasmapheresis with fresh frozen plasma (Hughes 2007).

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Pregnancy

The presence of autoimmune diseases is common in women of childrearing age and may adversely impact pregnancy and neonatal health (Tincani et al 2006). Given their increased risk of causing thromboembolism, thrombophilias such as antiphospholipid syndrome predispose childbearing women to obstetric complications such as early miscarriage, fetal growth retardation, preeclampsia, pulmonary hypertension, and placental abruption (Ruiz-Irastorza and Khamashta 2007; Gumus et al 2008). Further, the risk of developing hemolysis, elevated liver enzymes, and low platelets syndrome (HELLP) is markedly increased in women with antiphospholipid syndrome (Tsirigotis et al 2007). Although the exact mechanism of pregnancy loss in patients with antiphospholipid syndrome remains unclear, it is believed to be associated with an inflammatory component (Christodoulou et al 2007; Hughes 2007). Fortunately, recurrent complications in pregnancy associated with hypercoagulable states such as antiphospholipid syndrome can be treated with minimal adverse affects (Tincani et al 2006).

Childbearing women with a past medical history of antiphospholipid syndrome or with elevated antiphospholipid antibodies on laboratory exam should be encouraged to seek preconceptual counseling that includes input from obstetricians and physicians involved in her care (Christodoulou et al 2007; Ruiz-Irastorza and Khamashta 2007). Noninvasive measures including early Doppler imaging studies of the umbilical and uterine arteries are recommended, given the important role they play in predicting antiphospholipid syndrome-associated

complications during pregnancy (Ruiz-Irastorza and Khamashta 2007; Schwartz et al 2007). Furthermore, although once widely believed to improve pregnancy outcomes, it is now believed that the administration of immunosuppressive agents such as low-dose prednisone during pregnancy may adversely impact pregnancies (Branch et al 1992; Cowchock et al 1992; Tincani et al 2006; El-Haieg et al 2007). Plasmapheresis is recommended as a method of treatment in pregnant women with antiphospholipid syndrome who do not respond to immunosuppressive agents (El-Haieg et al 2007).

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Anesthesia

Antiphospholipid syndrome is commonly encountered among hospitalized and preoperative patients (East Christopher et al 2000). The characteristic disposition of such patients has the potential to adversely impact mechanisms of anticoagulation in the preoperative setting (East Christopher et al 2000). This is believed to result from the fact that aPL antibodies interfere with in vitro tests for hemostasis by thwarting the ability of coagulation proteins to anchor onto phospholipid surfaces (Bertolaccini et al 2005). This interference often results in laboratories mistakenly describing such "artifacts" as "lupus anticoagulant" (Bertolaccini et al 2005). No consensus exists for optimal methods of perioperative anticoagulation in patients with antiphospholipid syndrome, however, meticulous, careful heparin titration maybe recommended (East Christopher et al 2000; Bertolaccini et al 2005). Notwithstanding, further studies are required to investigate the optimal management of antiphospholipid syndrome patients in the preoperative and perioperative setting.

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Associated disorders

Coronary artery disease
Deep venous thrombosis
Systemic lupus erythematous
Thrombophilias

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Related summaries

Autoantibodies
Hypercoagulable states and cerebrovascular disease
Sneddon syndrome
Systemic lupus erythematosus

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Differential diagnosis

multiple sclerosis
systemic lupus erythematous
human immunodeficiency virus
hemolytic anemia
systemic sclerosis
Behcet syndrome
hepatitis C
Sneddon syndrome
avascular necrosis

vasculitis
Cogan syndrome with hearing loss
Susac syndrome with branch retinal artery occlusion

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Demographics

For more specific demographic information, see the Epidemiology, Etiology, and Pathogenesis and pathophysiology sections of this clinical summary.

Age
0-01 month
01-23 months
02-05 years
06-12 years
13-18 years
19-44 years
45-64 years
65+ years

Population
None selectively affected.

Occupation
None selectively affected.

Sex
female>male, 1:1

Family history
family history may be obtained

Heredity
heredity may be a factor

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