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Antiphospholipıd Syndrome and Venous Thrombosis

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1. Introductıon

Antiphospholipid syndrome(APLS) is a prothrombotic state characterized by recurrent venous thrombotic events including deep venous thrombosis, as well as pulmonary embolism, arterial thrombosis, recurrent fatal loss due to placental thrombosis and the presence of circulating antiphospholipid antibodies(APA) (Roubey RAS, 2001). As both thrombosis and pregnancy morbidity have a large number of other origins, the diagnosis of APLS relies on the quality and reliability of the laboratory investigations, on the persistent positivity of the APA assays, and sometimes on the lack of any other cause. Although a broad spectrum of APA exists, the universally accepted diagnostic APA tests are lupus anticoagulant(LA) functional coagulation assay; anticardiolipin antibody(ACA) enzyme-linked immunosorbent assay(ELISA); and anti-β_2-glycoprotein I antibody(aβ_2GPI) ELISA.

Antiphospholipid antibodies were first described in 1906 in patients with syphilis. These complement-fixing antibodies reacting with extracts from bovine hearts(mitochondrial phospholipid cardiolipin) formed the basis for the serologic syphilis test(Venereal Disease Research Laboratory-VDRL assay). Mass population screening for syphilis demonstrated that patients with systemic lupus erythematosus(SLE) without clinical syphilis had persistently false-positive VDRL tests(Haserick J,et al 1952, Baker WF, et al 2008). As false-positive VDRL tests in patients with SLE were also found to be associated with prolonged in vitro coagulation, the term 'lupus anticoagulant' was introduced.

The lupus anticoagulant is an antibody that prolongs phospholipid dependent coagulation tests in vitro. It was given this name in 1972 because clear proof of its site of action was lacking, and because the anticoagulant had been recognized in patients with systemic lupus erythematosus(Donald I Feinstein 2009). It is a misnomer because the lupus anticoagulant is more frequently encountered in patients without lupus and is associated with thrombosis rather than with bleeding. Immunoglobulins reacting with other hemostatic factors, such as von Willebrand factor (VWF), factor VIII, factor IX, and factor XI, inhibitors of thrombin and fibrin polymerization, and factor XIII have also been described in patients with SLE(Donald I Feinstein 2009), but they are rare compared with the lupus anticoagulant.

Patients with the lupus anticoagulant who do not have established SLE fall into several different categories: (1) patients with "lupus-like"chronic autoimmune disorders but without findings that fit the criteria for the diagnosis of SLE; (2) patients with other chronic systemic autoimmune disorders; (3) patients presenting with a venous or arterial thrombotic

event for which no underlying cause may be apparent; (4) patients receiving certain drugs, including procainamide and phenothiazines(a high prevalence of the lupus anticoagulant and a positive antinuclear antibody test are observed in psychotic patients receiving long-term chlorpromazine therapy); other drugs or biologics that can induce the lupus anticoagulant include hydralazine, quinidine, and possibly α-interferon; (5) patients with a recent acute viral infection, in whom the antibody is usually transient; (6) patients with human immunodeficiency virus infection; (7) women with recurrent fetal wastage;(8) occasionally in older patients with malignancies and (9) patients seeking medical attention for a variety of disorders in whom the lupus anticoagulant is discovered as an incidental finding, usually discovered because of a prolonged partial thromboplastin time (PTT) performed as a routine preoperative evaluation.

2. Epidemiology

APA can be detected in the absence of thrombosis or pregnancy morbidity or other systemic autoimmune diseases. During ongoing infectious disease, during treatments with a variety of drugs and even in healthy individuals, APA positivity may occur. The prevalence of APA ranges from 1% to 10% in the general population, 16% in patients with rheumatoid arthritis, and 30% to 40% in patients with SLE(Petri M 2000, Lim W et al 2006). The prevalence of positive tests for lupus anticoagulant and anticardiolipin antibody in a normal population has been reported in several studies. Because of the non-Gaussian distribution of anticardiolipin antibody levels in normal subjects, the cut-off points between normal and abnormal results is difficult to determine. One study reported IgG and IgM anticardiolipin antibodies in approximately 5% of normal individuals, although only 2% had persistently elevated levels on repeat testing. Shi and colleagues detected anticardiolipin antibodies in 6% of normal blood donors, respectively, and detected lupus anticoagulant activity by kaolin clotting time in 4%Shi W 1993). The prevalence of anticardiolipin antibody appears to increase with age.

The prevalences of elevated levels of IgG and IgM anticardiolipin antibody in healthy pregnant women were 2% to 3% and 4%, respectively(Harris EN 1991, Aoki K 1994, Lockshin MD 1997). Most of these were low titer; only 0.2% were high titer. In other studies, the incidence of anticardiolipin antibodies in pregnant individuals ranged from 1% to 2% and lupus anticoagulant 1% to 4%(Petri M 2000).

When the patient does not exhibit any other symptom that would allow the diagnosis of another associated autoimmune disease, the antiphospholipid syndrome is considered primary, or isolated. The term 'secondary' APLS is sometimes used for patients suffering from another autoimmune or inflammatory disease.

3. Etiopathogenesis

Lupus anticoagulants and anticardiolipin antibodies are immunoglobulins that were originally thought to react only with phospholipid. However, it is now well established that these antibodies react directly with epitopes on β2-GPI(McNeil HP 1990, Galli M 1990) or prothrombin(Rao LVM 1996, Bevers EM 1991), that subsequently bind to anionic phospholipid. Anticardiolipin antibodies are low-affinity monovalent antibodies to β2-GPI when in solution, and the monovalent complexes bind weakly to anionic phospholipids. However, when the antigen density is high, bivalent complexes are formed that have a high affinity for phospholipid surfaces. The fact that β2-GPI antibodies are polyclonal reacting

with different epitopes on the β2-GPI molecule and the increased affinity of the divalent antigen-antibody complexes for phospholipid surfaces explains why some anticardiolipin antibodies have anticoagulant activity and some do not(Arnout J 2003). This anticoagulant activity correlates best with the incidence of thrombosis(Galli M 2003), and a subset of lupus anticoagulants caused by anti–β2-GPI antibodies with specificity for an epitope on domain I. In some patients the anticardiolipin antibody will react with immobilized cardiolipin in vitro but not prolong phospholipid-dependent coagulation tests. Similarly, some of the antiprothrombin antibodies can prolong coagulation tests and some will not.

As with most autoimmune conditions, the etiology of APLS is not understood. It has been demonstrated that normal healthy individuals without APS have memory B cells that produce aPL antibodies; in a study of patients with infectious mononucleosis, 10 to 60 percent of immunoglobulin M aCL-producing cells expressed CD 27, the marker of memory B cells(Lieby P 2003).

Although antibodies against anionic phospholipid moieties arise during the course of infections such as syphilis and lyme disease, those are distinct from antibodies generated by patients with the syndrome because they generally recognize phospholipid epitopes directly and are not associated with the clinical manifestations of the syndrome.

Reports of familial clustering of raised aPL antibody levels indicate that genetic susceptibility can play a role in their development(Donald I. Feinstein 2007). In one study of 84 APLS patients, more than 35% had at least one relative, and more than 20% had two or more relatives, with evidence of at least one clinical feature of APS, such as thrombosis or recurrent fetal loss(Weber M 2000).

Many different mechanisms have been described for thrombosis during APLS, mainly after in-vitro experiments: (1) activation of endothelial cells by complexes of β2 GPI and anti-β2 GPI, these complexes could bind to annexin 2 or even Toll-like receptors on the surface of endothelial cells(Zhang J 2005, Fischetti F 2005); (2) platelet activation after direct binding of the β2 GPI, which targets the autoantibodies on the surface of these cells, the β2 GPI is selectively bound by the activator receptor apo ER 2(Lutters BC 2003); (3) functional dysregulation of hemostasis by the presence of autoantibodies against natural anticoagulant proteins like annexin 5 and activated protein C; (4) abnormal fibrinolysis directly linked to the presence of APL(Cesarman-Maus G 2006).

APL can stimulate platelet aggregation(Lin YL 1992), an effect that might be promoted via signalling through apolipoprotein E receptor 2(apoER2) receptors; the beta2GPI binding site for apo ER2 on platelets was localized to its domain V. Beta2GPI also has a dampening effect on platelet adhesion by interfering with the platelet-von Willebrand factor interaction, and consequently aPL antibodies, by interfering with this dampening, can increase platelet adhesion in flow systems(Hullstein JJ 2007).

Normal endothelial function includes control over thrombosis and thrombolysis, platelets and leukocyte interaction with the vessel wall, and regulation of vascular tone and smooth muscle proliferation. Several in vitro studies and studies on animal models have shown that incubation of endothelial cells with aPL from APLS patients generates different effects on endothelial function via β2 GPI. As a whole this might cooperate in sustaining endothelial perturbation that has been suggested to have a pivotal pathogenetic role in APS associated thrombosis(Stalc M 2006).

Because high-level aPLs may persist for years in asymptomatic persons, it is likely that vascular injury, endothelial cell activation, or both immediately precede the occurrence of thrombosis in those bearing the antibody (second-hit hypothesis). Of note, at least 50% of

APLS patients with vascular factors possess other acquired thrombosis risk factors at the time of their events(Kaul M 2006, Erkan D 2002).

Both persons congenitally lacking ß2GPI39 and ß2GPI knockout mice appear normal(Sheng Y 2001). ß2GPI polymorphisms influence the generation of aPLs in individuals, but they have only a weak relationship to the occurrence of APLS. A cluster of 50 upregulated genes may have an effect on the occurrence of thrombosis in aPL-positive individuals(Potti A 2006).

4. Diagnostic criteria of the antiphospholipid syndrome

The international preliminary classification criteria for APLS was published in 1999 after a workshop in Sapporo, Japan(Wilson WA 1999)-the so-called Sapporo criteria-. It was updated in 2006 after another workshop in Sydney, Australia(Miyakis S 2006). (table 1).

Clinical criteria

1.   Vascular thrombosis
One or more clinical episodes of arterial,venous or small vessel thrombosis, in any tissue or organ.
2.   Pregnancy morbidity
    a.   One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, or
    b.   One or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia, severe preeclampsia, or recognized features of placental insufficiency, or
    c.   Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

Laboratory criteria

1.   Lupus anticoagulant present in plasma, on 2 or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis
2.   Anticardiolipin antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer(ie, >40 GPL or MPL, or greater than the 99th percentile),on 2 or more occasions at least 12 week apart, measured by a standardized ELISA.
3.   Anti-β_2-glycoprotein I antibody of IgG and/or IgM isotype in serum or plasma(in titer greater than the 99th percentile) present one or more occasions, at least 12 week apart, measured by a standardized ELISA.

***Definite APLS is present if at least one of the clinical criteria and one of the laboratory criteria are met. Classification of APLS should be avoided if less than 12 weeks or more than 5 years seperate the positive APL test and the clinical manifestation.

Table 1. Updated Sapporo classification criteria for the antiphospholipid syndrome

The first clinical aspect of the APLS is thrombosis, which can affect arterial or venous vessels, as well as small vessels, and must be confirmed by means of imaging studies and/or histopathology. Arterial thrombosis mainly occurs in the central nervous system. But all arteries can be effected and myocardial infarction, peripheral gangrene, aseptic osteonecrosis and adrenal insufficency can develop with respect to effected arterial site. The venous thrombosis commonly localizes to the deep veins of the limbs and can be complicated by pulmonary embolism. As in arterial thrombosis, any segment of the venous vasculature can be effected, which will induce different manifestations.

A definitive diagnosis of APLS is based on fulfilling at least one of the Updated Sapporo Clinical criteria(vascular thrombotic event or pregnancy morbidity) and at least one of the laboratory criteria(Table 1). In general, medium titer aCL is considered 40 U or more and high titer, more than 80 U; titers between 20 and 40 U should be evaluated cautiously. Transient APL positivity is common during infections; thus documentation of the persistence(at least 12 weeks apart) of autoimmune APL is crucial for both diagnostic and therapeutic purposes.

The choice of initial APL tests remains a subject of debate. In general, the LA test is more specific for APL-related clinical events. The specificity of aCL for APL-related clinical events increases with higher titers. The IgG isotype is more strongly associated with APL-related clinical events than the IgM isotype. In a patient with suspected APS, testing for LA and IgG/IgM aCL should be ordered initially. If these tests are negative or low-titer and there is still a high level of suspicion for APS, then testing for antiβ_2GPI antibodies and IgA aCL/antiβ_2GPI can be pursued(George D 2009). Antiphospholipid antibody tests developed based on other phospholipids such as phosphatidylserine, phosphatidylinositol, or phosphatidylethanolamine or phospholipid-binding plasma proteins(such as prothrombin) are not yet well standardized and accepted.

5. Clinical features

Although any vasculature can be affected by thrombosis, stroke and transient ischemic attack are the most common presentations of arterial thrombosis, whereas deep vein thrombosis with or without pulmonary embolism is the most common presentation of venous thrombosis in APLS(George D 2009). Antiphospholipid antibodies can cause both arterial and venous thrombosis in the same patient. Reccurent thromboses tend to occur in the same vascular distribution(venous followed by venous and arterial followed by arterial). in some studies the incidence of venous thrombosis (70%) is greater than the incidence of arterial thrombosis.(Galli M 1997, Triplett DA 1995).

Superficial thrombophlebitis, superior vena cava syndrome, renal vein thrombosis, Budd Chiari syndrome, central retinal vein occlusion, pulmonary hypertension due to recurrent pulmonary embolism, and diffuse pulmonary hemorrhage due to microthrombosis are some of the thrombotic manifestations of APLS.

Of unselected patients with antiphospholipid antibody, 1% to 2.5% per year will develop thromboembolism(Galli M 2003, Finazzi G 1996),and 10% to 25% of patients with deep venous thrombosis will be found to have antiphospholipid antibodies(Ginsburg KS 1992).However, in a prospective population based study of 66140 individuals in Norway(Naess IA 2005), elevated anticardiolipin antibody levels were not a risk factor for

predicting an initial venous thrombosis. Thrombosis is more frequent as the level of anticardiolipin antibody increases, and medium and high titers (>40 GPL and/or MPL units) are more frequently associated with thrombotic events. Although some investigators believe that elevated levels of IgG or IgA isotypes are more common than IgM in patients with thrombotic complications, this has not been clearly established. The lupus anticoagulant or increased levels of anticardiolipin antibody must be persistently present on more than one occasion at least 12 weeks apart because the incidence of thrombotic complications is almost the same in patients with transiently positive tests as in patients with negative tests at two different time intervals. The persistent presence of elevated levels of anticardiolipin antibody has been shown to be associated with indices of in-vivo coagulation activation. In a study of patients with SLE(Ginsberg JS 1993) who were persistently anticardiolipin antibody– positive versus patients who were transiently positive or persistently negative, anticardiolipin antibody–positive patients had a higher mean level of F1+2 and fibrinopeptide A than patients who were transiently positive, persistently negative, or on warfarin therapy. The differences remained significant even if patients with prior thromboembolism were excluded from the analysis. These results suggest that the presence of persistently elevated levels of anticardiolipin antibody in SLE patients is associated with an ongoing prothrombotic state.

Patients who are persistently positive for the lupus anticoagulant or who have persistently elevated levels of anticardiolipin antibody and suffer a thromboembolic event have a recurrence rate of approximately 50% within 2 years(Rosove MH 1992, Khamashta MA 1995). Recurrences tend to occur in most of the patients on the same side of the circulation as the initial event—venous recurrences after an initial venous event and arterial recurrences after an initial arterial event.

6. Treatment of venous thrombosis in APLS

6.1 General treatment

The standard of care for venous thromboembolism is continous infusion of intravenously delivered unfractionated heparin(UFH) and, more recently, subcutaneous low-molecular weight heparins(LMWH). DVT is associated with several possible complications, including recurrent nonfatal venous thromboembolism, postthrombotic chronic venous insufficiency, and nonfatal/fatal pulmonary embolism. The goals of therapy for DVT include the prevention of thrombus propagation, embolization, and early and late thrombus recurrence. Proper anticoagulation is the first critical step in the effective treatment of DVT. Complications can develop soon after thrombus detection, presenting a narrow window of opportunity for a safe and effective intervention. The secondary stage of treatment involves the maintenance of adequate anticoagulation to prevent the development of recurrent thromboembolism.

LMWH or fondaparinux is preferred for the initial anticoagulation of patients with deep vein thrombosis(Table 2). LMWH and fondaparinux are as safe and as effective as continuous unfractionated heparin (UFH). Suitable patients can be safely treated with LMWH and fondaparinux in the outpatient setting. Heparin/fondaparinux should be continued for at least five days after the initiation of warfarin therapy and until International Normalized Ratio (INR) is > 2.0 for two consecutive days. Warfarin should be initiated 5 mg on day 1.

Treatment for venous thromboembolism with LMWH provides reliable anticoagulation levels when given subcutaneously on a weight-based dosing schedule. No laboratory monitoring of the intensity of anticoagulation is required for LMWH, except in special circumstances. Recent randomized controlled trials of the treatment of pulmonary embolism (PE) have shown LMWH to be as effective and safe as UFH. One randomized controlled trial of the treatment of venous thromboembolism (VTE) in 1,021 patients included 271 patients presenting with PE. In this study, there were no significant differences in outcomes following treatment with UFH versus LMWH. These studies used reviparin and tinzaparin. Two reviews agreed that LMWH may be efficacious in the treatment of PE, but cautioned that the LMWH products may not be equivalent to each other (Raskob 1999 ; Charland, 1998; Columbus Investigators, 1997; Simonneau, 1997).

LMWH may not be appropriate for patients with renal insufficiency (creatinine clearance less than 30 mL/min). Studies have shown modestly delayed clearance in patients with chronic renal failure. The clinician should weigh this evidence when considering outpatient therapy.

A high-loading dose of warfarin (greater than 10 mg) is of no clinical use and should be discouraged. A 10 mg initial dose of warfarin has been associated with early over-anticoagulation and, when compared to a 5 mg initial dose, was no more effective in achieving a therapeutic international normalized ratio (INR) by day four or five of therapy. A therapeutic range of anticoagulation to keep the INR at 2.5 (range 2.0-3.0) is recommended for patients with venous thromboembolism. Heparin and warfarin may be started at the same time. The anticoagulant effect of warfarin is delayed until clotting factors already circulating are cleared. Although Factor VII has a shorter half-life in the blood (six to seven hours), peak anticoagulant activity is delayed for up to 96 hours until factors with longer plasma half-lives (II, IX and X) have cleared . Heparin (UFH or LMWH) and warfarin may be started at the same time. Heparin (UFH or LMWH) and/or fondaparinux should be given for a minimum of five days. Patient should continue heparin until INR >=2.0 for two consecutive days. In patients with suspected hypercoagulable state (Protein C or Protein S deficiency), the patient should be adequately anticoagulated with heparin (UFH or LMWH) and/or fondaparinux before warfarin is started at a low dose (2-5 mg). This is to avoid warfarin-induced skin necrosis or other transient hypercoagulable complications.

Recommendations for the management of thrombosis in the APLS have been based largely on retrospective case series. Recently, several clinical trials have been published on the management of thrombosis in APLS.These new clinical trials have challenged the previous dogma of a target INR of 3 to 4(high-intensity warfarin).

6.2 Primary prophylaxis of thrombosis in patients with APL antibodies

The therapeutic approach in asymptomatic carriers of APL without prior thrombotic events is still controversial. Present evidence-based knowledge does not support the widespread use of aspirin in all these aPL-positive patients. Annual thrombosis risk in asymptomatic APL-positive patients range from 0% to 3.8%(Finazzi G 1996, Shah NM 1998), being equivalent to that of major bleeding associated with the use of aspirin. The only randomized clinical trial (APLASA study) in which 98 asymptomatic persistently APL-positive individuals were randomized to recieve a daily dose of 81 mg of aspirin or placebo showed that these patients have a low overall annual incidence rate of acute

thrombosis, and develop vascular events when additional risk factors are present(Erkan D 2007). Therefore, according to the results of this trial, asymptomatic, persistently APL-positive individuals seem not to benefit from low-dose aspirin for primary thromboprophylaxis.

However, a more realistic approach with a lower degree of evidence would be to stratify these individuals according to some clinical features such as the presence of traditional congenital or acquired procoagulant risk factors, the APL profile(persistently positive aCL and or anti-β_2GPI antibodies at moderate/high titers), and the coexistence of an underlying autoimmune disease, to consider primary prophylactic therapy with low-dose 75-100 mg aspirin daily. It is known that SLE represents a prothrombotic condition and acts as strong thrombophilic risk factor, primarily related to the chronic systemic inflammation and renal involvement. Furthermore, one study has shown that prophylactic aspirin should be given to all patients with SLE to prevent both arterial and venous thrombotic manifestations, especially in patients with APL(Wahl DG 2000). In the same study, the authors suggested that in selected patients with LA and a low bleeding risk, prophylactic oral anticoagulant therapy may provide higher utility. Therefore, there is currently consensus for primary thromboprophylaxis in these patients, mainly with low-dose aspirin.

An alternative to aspirin in SLE patients may be hydroxychloroquine. There are many evidences for the protective role of this old drug against the development of both venous and arterial thrombosis(Ruiz-Irastorza G 2006, Erkan D 2002).

All nonthrombotic APL-positive subjects should be encouraged to stop smoking. Cessation of oestrogen –containg oral contraceptive use and treatment of other vascular risk factors if present are additional recommended therapeutic measures.

At least half of patients with APLS with vascular events also have another reversible risk factors which are not related to APLS at time of thrombosis(Erkan D 2002). Therefore, identification and elimination of these risk factors and agressive prophylaxis during high-risk periods, are crucial for the primary thrombosis prevention in asymptomatic persistently APL-positive individuals. Serious perioperative complications including catastrophic antiphospholipid syndrome(CAPS) may occur despite prophylaxis in APL-positive individuals as they are at additional risk for thrombosis when undergoing surgical procedures. Therefore, perioperative strategies should be clearly identified before any surgical procedure, pharmacological, and physical antithrombosis interventions should be vigorously used; periods without anticoagulation should be kept to an absolute minimum(George D 2009).

6.3 Therapy for acute thrombosis and secondary propylaxis of thrombosis in patients with antiphospholipid syndrome

Therapy for thrombosis associated with the APLS should be guided by the knowledge that recurrence is common. In one study, patients who had discontinued oral anticoagulation had a 50% probability of recurrence in 2 years and a 78% recurrence in 8 years(Derksen RHWM 1993). Similar results have been published by others with a recurrence rate of 10% to 30% per year(Galli M 2003, Rosove MH 1992, Khamashta MA 1995). Three prospective studies reported that there was an increased risk of recurrence that varied from 10% to 67% per year(Lim W 2006, Schulman S 1998, Kearon C 1999, Kearon C 2003, Ortel TL

2005). In most reports the incidence of recurrence is highest in the first 6 months after discontinuing anticoagulant therapy. Although it was initially thought that prevention of venous recurrence required high-intensity warfarin with a target INR of 3.5, evidence has been accumulating from recent studies that standard intensity warfarin (INR 2 to 3) can almost completely abrogate recurrence of venous thromboembolic disease(Crowther MA 2003, Finazzi G 2005). The pooled data from these two studies revealed no difference in recurrent thrombosis between moderate-intensity warfarin (INR 2 to 3) and high-intensity (INR 3 to 4), nor was there a greater bleeding risk. As the data from several studies have demonstrated that patients with antiphospholipid syndrome have a high risk for recurrent venous thromboembolic disease after anticoagulation is discontinued, many feel that anticoagulation should be continued indefinitely. The American College of Chest Physicians recommends treatment for 12 months and consideration of indefinite therapy after an initial event(Ortel TL 2005, Buller HR 2004). Because of the efficacy of warfarin therapy in preventing recurrences, the use of corticosteroids and other immunosuppressive agents to suppress antibody production in the absence of autoimmune disease is not recommended.

- Objectively confirm DVT; provide short-term treatment with SC LMWH or IV UFH or SC UFH(1A)
- High clinical suspicion for DVT: treat until diagnosis is confirmed(1C)
- Initial treatment LMWH or UFH for ≥5 days
- Warfarin should be started on the first day of treatment
- IV UFH by weight based or standard dosing to achieve and maintain an aPTT prolongation that corresponds to plasma heparin levels of 0.3 to 0.7 IU/mL anti-Xa activity(1C)
- UFH with large doses:measure anti-Xa to adjust dose(1B)
- SC UFH at a dose of 17500 U,SC, Q 12 hours or 250 U/kg, sc, Q 12 hours with adjustment to achieve a therapeutic aPTT(1C).
- SC fixed dose UFH at a dose of 333 U/kg, sc, Q 12 hours without monitoring for adjustment of dose(1C).
- SC LMWH once or twice daily over UFH as an outpatient if possible(1C) or as an inpatient(1A).
- Reccomend against monitoring with anti-Xa levels(1A).
- Severe renal failure: suggest IV UFH over LMWH(2C).

Table 2. Venous thromboembolism(VTE) treatment guidelines adapted from the American College of Chest Physicians Evidence –based clinical practice guidelines-8th edition

Monitoring anticoagulant therapy may be difficult in patients with lupus anticoagulants and a prolonged PTT. It is mandatory when using unfractionated heparin to monitor therapy using a specific heparin assay, such as the one dependent on factor Xa inhibition (therapeutic range, 0.3 to 0.7). In most instances, it is preferable to use low-molecular-weight heparin in therapeutic doses, which usually eliminates the need for monitoring. When using warfarin, the optimal INR for patients with lupus anticoagulants is controversial, because patients with lupus anticogulants may have a variably prolonged prothrombin time,and various thromboplastins have a different sensitivity in the presence of a lupus

anticoagulant.Therefore, it is possible that in various studies of therapy in patients with lupus anticoagulants that the degree of anticoagulation is overestimated, and the target INR of 3.0 noted earlier might be an overestimate because of the presence of the lupus anticoagulant(Donald I. Feinstein 2007). Rarely, patients may continue to have recurrent venous thromboembolic events despite INR values in the therapeutic range. Recurrent thrombotic events despite therapeutic anticoagulation require evaluation and modification of all non-APL thrombosis risk factors. Warfarin therapy is generally increased to high-intensity(INR, 3.0-4.0). Other options include adding low-dose aspirin, hydroxychloroquine, and/or statins to warfarin or switching to low-molecular weight heparin. There are no randomized controlled studies investigating the effectiveness of any of these approaches.

Based on many cohort studies ,subgroup analysis and two randomized controlled studies, a recent review(Ruiz-Irastorza G 2007) suggests that patients with definite APLS with a first venous thrombosis should be treated with prolonged oral anticoagulation at a target INR of 2.0-3.0 and those with an arterial event at an 3.0-4.0.

So, the best secondary thromboprophylaxis in patients with definite APLS is long-term anticoagulation at a target INR of 2.0-3.0. Patients with recurrent venous thrombotic events despite optimal anticoagulation should be treated with warfarin at an INR of 3.0-4.0.

7. References

Roubey RAS. Antiphospholipid antibody syndrome. In:Koopman WJ, editor. Arthritis and allied conditions, 14th edition, vol2;2001.p.1446-61.

Haserick J, Long R: Systemic lupus erythematosus preceded by false positive serologic tests for syphillis, presentation of five cases. Ann Intern Med 37:559-565, 1952.

Baker WF, Bick RL, Fareed J: Controversies and unresolved issues in antiphospholipid syndrome pathogenesis and management. Hematology/Oncology Clinics of North America 22:155-174, 2008.

Donald I. Feinstein: Inhibitors of blood coagulation. Hematology Basic Principles Chapter 131-4th edition 2009.

Petri M. Epidemiology of the antiphospholipid antibody syndrome. J Autoimmun 15:145-151, 2000.

Lim W, Crowther MA, Eikelboom JW: Manegement of antiphospholipid antibody syndrome- a systematic review.JAMA 295:1050-1057,2006.

Shi, W., Chong, B. H., Hogg, P. J. & Chesterman, C. N. (1993) Thromb. Haemostasis 70, 342-345.

Harris EN, Spinnato JA: Should anticardiolipin tests be performed in otherwise healthy pregnant women?. Am J Obstet Gynecol 1991; 165:1272.

Aoki K, Matsuura E, Sasa H, et al: Beta2-glycoprotein I-dependent and independent anticardiolipin antibodies in healthy pregnant women. Hum Reprod 1994; 9:1849.

Lockshin MD: Antiphospholipid antibody: Babies, blood clots, biology. JAMA 1997; 277:1549.

McNeil HP, Simpson RJ, Chesterman CN, Krilis SA: Antiphospholipid antibodies are directed against a complex antigen that includes a lipid-binding inhibitor of

coagulation: b2-glycoprotein I (apolipoprotein H). Proc Natl Acad Sci U S A 1990; 87:4120.

Galli M, Comfurius P, Maasen C, et al: Anticardiolipin antibodies (ACA) directed not to cardiolipin but to a plasma protein cofactor. Lancet 1990; 335:1544.

Rao LVM, Hoang AD, Rapaport SI: Mechanism and effects of lupus anticoagulant IgG and prothrombin to surface phospholipid. Blood 1996; 11:4173.

Bevers EM, Galli M, Barbui T, et al: Lupus anticoagulant IgG's (LA) are not directed to phospholipid only, but to a complex of lipid-bound human prothrombin. Thromb Haemost 1991; 66:629.

Arnout J, Vermylen J: Current status and implications of autoimmune antiphospholipid antibodies in relation to thrombotic disease. Thromb Haemost 2003; 1:931.

Galli M, Luciani D, Bertolini G, et al: Lupus anticoagulants are stronger risk factors for thrombosis than anticardiolipin antibodies in the antiphospholipid syndrome: A systematic review of the literature. Blood 2003; 101(5):1827.

Lieby P, Soley A, Knapp AM, et al: Memory B cells producing somatically mutated antiphospholipid antibodies are present in healthy individuals. Blood 102;2459:2003.

Donald I. Feinstein. Lupus anticoagulant and acquired inhibitors of blood coagulation. Book chapter 131. Williams Hematology 2007, 5th edition.

Weber M, Hayem G, DeBandt M, et al: The family history of patients with primary or secondary antiphospholipid syndrome(APS). Lupus 9:258, 2000.

Zhang J, McCrae KR. Annexin A2 mediates endothelial cell activation by antiphospholipid/anti-beta2 glycoprotein I antibodies. Blood 2005;105:1964-1969.

Fischetti F, Durigutto P, Pellis V et al. Thrombus formation induced by antibodies to beta 2-glycoprotein I is complement dependent and requires a priming factor. Blood 2005;106:2340-2346.

Lutters BC, Derksen RH, Tekelenburg WL et al. Dimers of beta 2-glycoprotein I increase platelet deposition to collagen via interaction with phospholipids and the apolipoprotein E receptor 2. The journal of Biological Chemistry 2003;278:33831-33838.

Cesarman-Maus G, Rios-Luna N, Deora AB et al. Autoantibodies against the fibrinolytic receptor, annexin 2, in antiphospholipid syndrome. Blood 2006;107.4375-4382.

Lin YL, Wang CT: Activation of human platelets by the rabbit anticardiolipin antibodies. Blood 80:3135, 1992.

Hulstein JJ, Lenting PJ, de LB, et al: Beta2-glycoprotein I inhibits von Willebrand factor dependent platelet adhesion and aggregation. Blood 110:1483, 2007.

Stalc M, Poredos P, Peternel P, et al. Endothelial function is impaired in patients with primary antiphospholipid syndrome. Thrombosis Research 2006;118, 455-461.

Kaul M, Erkan D, Sammaritano L, et al: Assessment of the 2006 revised antiphospholipid syndrome (APS) classification criteria [abstract]. Arthritis Rheum 54:S796, 2006.

Erkan D, Yazici Y, Peterson MG, et al: A cross-sectional study of clinical thrombotic risk factors and preventive treatments in antiphospholipid syndrome. Rheumatology (Oxford) 41:924-929, 2002.

Sheng Y, Reddel SW, Herzog H, et al: Impaired thrombin generation in beta 2-glycoprotein I null mice. J Biol Chem 276:13817-13821, 2001.

Potti A, Bild A, Dressman HK, et al: Gene-expression patterns predict phenotypes of immune-mediated thrombosis. 107:1391-1396, 2006.

Wilson WA, Gharavi AE, Koike T, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum 42:1309-1311,1999.

Miyakis S, Lockshin MD, Atsumi T, et al: International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome. J Thromb Haemost 4:295-306, 2006.

George D, Erkan D. Antiphospholipid syndrome. Progress in Cardiovascular Diseases 52(2009):115-125.

Galli M, Finazzi G, Barbui T: Antiphospholipid antibodies: Predictive value of laboratory tests. Thromb Haemost 1997; 78:75.

Triplett DA: Protean clinical presentation of antiphospholipid-protein antibodies (APA). Thromb Haemost 1995; 74:329.

Galli M, Barbui T: Antiphospholipid antibodies and thrombosis: Strength of association. Hematol J 2003; 4:180.

Finazzi G, Brancaccio V, Moia M, et al: Natural history and risk factors for thrombosis in 360 patients with antiphospholipid antibodies: A four-year prospective study from the Italian Registry. Am J Med 1996; 100:530.

Ginsburg KS, Liang MH, Newcomer L, et al: Anticardiolipin antibodies and the risk for ischemic stroke and venous thrombosis. Ann Intern Med 1992; 117:997.

Naess IA, Christiansen SC, Cannegieter SC, et al: A prospective study of anticardiolipin antibodies as a risk factor for venous thrombosis in a general population (the HUNT study). Thromb Haemost 2005; 4:44-49.

Ginsberg JS, Demeers C, Brill-Edwards P, et al: Increased thrombin generation and activity in patients with systemic lupus erythematosus and anticardiolipin antibodies: Evidence for a prothrombotic state. Blood 1993; 81:2958.

Rosove MH, Brewer PM: Antiphospholipid thrombosis: Clinical course after the first thrombotic event in 70 patients. Ann Intern Med 1992; 117:303.

Khamashta MA, Cuadrado MJ, Mujic F, et al: The management of thrombosis in antiphospholipid-antibody syndrome. N Engl J Med 1995; 332:993.

Raskob GE. Heparin and low molecular weight heparin for treatment of acute pulmonary embolism. Curr Opin Pulm Med. 1999 Jul;5(4):216-21. Review.

Charland SL, Klinter DE. Low-molecular-weight heparins in the treatment of pulmonary embolism. Ann Pharmacother. 1998 Feb;32(2):258-64. Review.

The Columbus Investigators. Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. N Engl J Med. 1997 Sep 4;337(10):657-62.

Simonneau G, Sors H, Charbonnier B, Page Y, Laaban JP, Azarian R, Laurent M, Hirsch JL, Ferrari E, Bosson JL, Mottier D, Beau B. A comparison of low-molecular-weight

heparin with unfractionated heparin for acute pulmonary embolism. The THESEE Study Group. Tinzaparine ou Heparine Standard: Evaluations dans l'Embolie Pulmonaire. N Engl J Med. 1997 Sep 4;337(10):663-9.

Shah NM, Khamashta MA, Atsumi T et al. Outcome of patients with anticardiolipin antibodies: a 10 year follow-up of 52 patients. Lupus 1998 7:3-6

Erkan D, Harrison MJ, Levy R et al. Aspirin for primary thrombosis prevention in the antiphospholipid syndrome: a randomized, double-blind, placebo-controlled trial in asymptomatic antiphospholipid antibody-positive individuals. Arthritis Rheum 2007;56:2382-2391.

Wahl DG, Bounameaux H, de Moerloose P et al. Prophylactic antithrombotic therapy for patients with systemic lupus erythematosus with or without antiphospholipid antibodies: do the benefits outweigh the risks? A decision analysis. Arch Intern Med 2000;160:2042-2048.

Ruiz-Irastorza G, Egurbide MV, Pijoan JI et al(2006) Effect of antimalarials on thrombosis and survival in patients with systemic lupus erythematosus. Lupus 2006;15:577-583.

Derksen RHWM, DeGroot PG, Kateer L, Nieuweahuis HK: Patients with antiphospholipid antibodies and venous thrombosis should receive long-term anticoagulant treatment. Ann Rheum Dis 1993; 52:689.

Khamashta MA, Cuadrado MJ, Mujic F, et al: The management of thrombosis in antiphospholipid-antibody syndrome. N Engl J Med 1995; 332:993.

Lim W, Crowther MA, Eikelboom JW: Management of antiphospholipid antibody syndrome. JAMA 2006; 295(9):1050.

Schulman S, Svenungsson E, Granqvist S: Duration of anticoagulation study group. Anticardiolipin antibodies predict early recurrence of thromboembolism and death among patients with venous thromboembolism following anticoagulant therapy. Am J Med 1998; 104:332.

Kearon C, Gent M, Hirsh J, et al: A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med 1999; 340:901.

Kearon C, Ginsberg JS, Kovacs MJ, et al: Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. N Engl J Med 2003; 349:631.

Ortel TL: Thrombosis and the antiphospholipid syndrome. Hematology Am Soc Hematol Educ Program 2005; 462:

Crowther MA, Ginsberg JS, Julian J, et al: A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. N Engl J Med 2003; 349:1133.

Finazzi G, Marchioli R, Brancaccio V, et al: A randomized clinical trial of high-tensity warfarin vs. conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS). Thromb Haemost 2005; 3:848.

Buller HR, Agnelli G, Hull RD, et al: Antithrombotic therapy for venous thromboembolic disease. The seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest 2004; 126(Suppl):401S.

Ruiz-Irastorza G, Hunt BJ, Khamashta MA. A systematic review of secondary thromboprophylaxis in patients with antiphospholipid antibodies. Arthritis Rheum 2007;57:1487-1495.
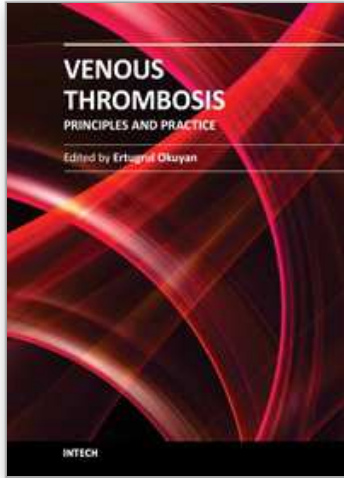
Venous Thrombosis - Principles and Practice

Edited by Dr. Ertugrul Okuyan

According to Virchow's triad, venous thrombosis can occur as a result of one or more of three factors: changes in the dynamics of the blood flow, endothelial injury/dysfunction of the blood vessel and hypercoagulability. The blood in the veins is constantly forming microscopic thrombi that are routinely broken down by the body, and significant clotting can occur only when the balance of thrombus formation and resolution is altered. This book is a fresh synthesis of venous thromboembolism care and considers the opinions and studies from different fields of medicine. As venous thrombosis spectrum is wide and can affect many organ systems, from deep veins of the leg to the cerebral venous system, our intent is for this to be a comprehensive, up-to-date and readable book. We tried to present a synthesis of existing material infused with new ideas and perspectives and authors own clinical studies and even case-reports.

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