

Clinical Management of Antiphospholipid Syndrome-Related Thrombosis

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Abstract: There is evidence that the presence of antiphospholipid antibodies is related with an increased risk of thrombotic events. Patients with definite antiphospholipid syndrome (APS) and a first venous event should receive long term oral anticoagulation to an international normalized ratio (INR) of 2.0-3.0. In patients with definite APS and arterial or recurrent thrombosis oral anticoagulation to an INR > 3.0 may be advisable. Catastrophic antiphospholipid syndrome is an unusual form of presentation of antiphospholipid syndrome with a mortality rate of approximately 50%. Its treatment is based on the combined use of full anticoagulation, corticosteroids, plasma exchanges, and intravenous immunoglobulins. We also summarize the evidence-based information about management of some difficult cases such as “seronegative” APS and patients who do not display formal classification criteria for APS.

Keywords: Antiphospholipid syndrome, thrombosis, oral anticoagulation, catastrophic antiphospholipid syndrome.

INTRODUCTION

The antiphospholipid syndrome (APS) is characterized by the development of venous or arterial thromboses, fetal losses and thrombocytopenia, in the presence of antiphospholipid antibodies (aPL), namely lupus anticoagulant (LA), anticardiolipin antibodies (aCL) or antibodies directed to various proteins, mainly β_2 glycoprotein I (β_2 GPI), or all three [1]. First recognized in patients with systemic lupus erythematosus (SLE) and later less frequently in other autoimmune disorders, it is now well known that the development of this syndrome may also be independent of any underlying disease, being termed “primary” APS [2].

Regarding the thrombotic clinical spectrum, APS may present with multiple faces. Any combination of vascular occlusive events may occur in the same individual and the time interval between them also varies considerably from weeks to months or even years. Data from the largest series of patients with APS (the “Euro-phospholipid project”) [3] reveal that, at the disease onset, deep vein thrombosis is the most frequently reported venous thrombotic manifestation in this syndrome (38.9%), followed by pulmonary embolism (9.0%). Cerebrovascular accidents—either stroke (19.8%) or transient ischemic attacks (11.1%)—are the most common arterial thrombotic manifestations followed by myocardial infarction (5.5%).

In 1992, Asherson [4] described the ‘catastrophic’ variant of the APS as a condition characterized by multiple vascular occlusive events, usually affecting small vessels, presenting over a short period of time, and laboratory confirmation of the presence of aPL. The hallmark of this disorder is the diffuse thrombotic microvasculopathy being microthrombosis the main finding in necropsy studies [5]. The pathogenesis of catastrophic APS is not completely understood. Catastrophic

APS represents less than 1% of the APS cases [3]. However, patients with catastrophic APS usually end-up in a life-threatening situation with a mortality rate around 50% in the largest published series [6, 7].

This review focuses on the treatment of thrombotic manifestations of APS. In addition, the evidence-based information about management of catastrophic APS is summarized. Finally, the management of some difficult cases, such as “seronegative” APS, patients who do not display formal classification criteria for APS and recurrent thrombotic events despite optimal anticoagulation is discussed.

SECONDARY THROMBOPROPHYLAXIS IN PATIENTS WITH ANTIPHOSPHOLIPID SYNDROME

There are evidences from two metaanalysis performed in patients with SLE [8] and primary APS [9], that the presence of aPL is related with an increased risk of thrombotic events. Furthermore, a systematic review of the published articles on the APS showed that LA was a clear risk factor for thrombosis, irrespective of the site and type of thrombosis, the presence of SLE and the methods used to detect them [10]. Moreover, high-level of aCL [11, 12] and concomitant positivity for anti- β_2 GPI and LA or aCL have been recognized to increase the risk of thrombosis in patients with aPL [13].

There are evidence-based data about the therapeutic management of patients with aPL and previous thrombotic event [14]. The best secondary thromboprophylaxis in patients with definite APS, that is, those who suffered from thrombosis and at least two positive determinations of aPL [1], is the long-term anticoagulation [15]. This point is very important taking into account that some studies included patients with only a single positive determination of aPL [16]. In other words, most patients included in some studies on secondary thromboprophylaxis did not have definite APS.

In accordance with a recent excellent systematic review [15], patients with definite APS with first venous thrombosis have to be treated with prolonged oral anticoagulation at a

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target INR of 2.0-3.0 and of 3.0-4.0 for those with arterial or recurrent thrombotic events. These conclusions are based on the analysis of nine cohort studies [17-25], five subgroup analysis [26-29] and two randomized controlled studies [30, 31]. The main limitation of this review is the low-quality of some of the included studies (observational, non-randomized, and retrospective cohorts). However, it is important to bore in mind that despite the potential risks of missing information and reporting bias, they offer a more realistic photography of these patients. The most recent guidelines for the treatment of venous thromboembolic disease also recommend an INR of 2.0 to 3.0 as the preferred intensity of long-term anticoagulant treatment with vitamin K antagonists in all patients with venous thromboembolism, including patients with APS [32]. One of the main conclusions of this review was that general population and subjects with only a single positive aPL determination seemed to have a similar recurrent thrombotic rate [15]. Otherwise, among patients fulfilling laboratory criteria for definite APS [1], the risk of recurrent events was lower in the patients with predominant first venous thromboses than in those patients who presented with arterial and/or recurrent events. Furthermore, standard-intensity oral anticoagulation (target INR 2.0-3.0) protected well the former from further thrombosis whereas in the latter, a better outcome was demonstrated with higher-intensity anticoagulation (INR >3.0) [15].

In this sense, the Antiphospholipid Antibody in Stroke Study (APASS) group, in collaboration with the Warfarin-Aspirin Recurrent Stroke Study (WARSS) group designed a prospective study of the role of aPL in recurrent ischemic stroke [33]. They compared the risk of recurrent stroke and other thrombo-embolic disease over a two year follow-up period in patients with ischemic stroke who were randomised to either aspirin therapy (325 mg per day) or warfarin therapy at a dose to maintain the INR between 1.4 and 2.8. Conversely to the previous review [15], in both warfarin and aspirin arms, the recurrent thrombosis rate was not different between patients who were positive for both aCL and LA, LA+/aCL-, LA-/aCL+, and those who were LA-/aCL-. However, WARSS/APASS study included patients with only a single aCL value of < or = 10 GPL at the time of an initial ischemic stroke. Therefore, this trial has not been conducted in patients with definite APS and its conclusions should not be applied to these patients.

One of the problems of the high-intensity anticoagulation may be the higher risk of secondary bleeding, a point that the clinician have to bore in mind at the time to decide the best treatment in these patients. In a study performed in 66 patients with definite APS with previous thrombosis treated with oral anticoagulation to a target INR of 3.5, the risk of intracranial and fatal bleeding was similar than in groups of patients treated to lower target ratios [23]. As a whole, the rate of major bleeding was 6 cases per 100 patient-years (95% CI 1.6-15.0). The rate of intracranial bleed was 1.5 per 100 patient-years (95% CI, 0.04-8.4) and the rate of thrombotic recurrences was 9.1 cases per 100 patient-years (95% CI, 3.3-19.6). Nevertheless, in the systematic review repeated thromboses were more frequent and associated with a higher mortality than hemorrhagic complications in patients taking warfarin [15]. On the other hand, 31 out of 420 (7.4%) patients in the prospective study of the "Europhospholipid" cohort receiving oral anticoagulants presented with

haemorrhages, 13 of them in internal organs (cerebral in seven, gastrointestinal in four and intra-abdominal in two) and in six of them, they were the main cause of death [34].

In addition to the anticoagulant therapy, it is important to take into account that, in all patients who present with persistently positive aPL, the common sense advises to avoid other vascular risk factors, such as hypertension, hypercholesterolemia, or tobacco use. Estrogen-containing oral contraceptives are forbidden in women with aPL. Prophylaxis with low molecular weight heparin administered subcutaneously should certainly be given to cover higher-risk situations, such as surgery.

As a conclusion, patients with definite APS and a first venous event should be treated with long-term oral anticoagulation to an INR of 2.0-3.0. In patients with definite APS and arterial thrombosis, oral anticoagulation to an INR > 3.0 may be advisable (Table 1).

IMPROVING THE SECONDARY THROMBOPROPHYLAXIS IN PATIENTS WITH ANTIPHOSPHOLIPID SYNDROME

One important and novel aspect of the APS is that patients should be stratified and treated according to some clinical and immunologic characteristics in addition to the aPL positivity [1].

Thrombophilic Risk Factors

It is advisable to categorize APS patients according the presence or not of classic thrombophilic risk factors, such as hypertension, diabetes mellitus, hypercholesterolemia, or tobacco use, because they may contribute to modifications in the eventual risk factor profile [17]. Close control of these factors has to be an important clue in the management of patients with APS and thrombosis.

The most recent set of classification criteria for APS [1] advise to categorize the APS patients according to the presence or the absence of additional risk factors for thrombosis including the inherited thrombophilias. The two most common genetic causes of thrombophilia are the Leiden mutation of factor V and the G20210A mutation of prothrombin. The prevalence of Factor V Leiden, varies in different populations, averaging 2% to 10% for the heterozygous form and 1.5% for the homozygous form [35]. Heterozygous factor V Leiden is present in approximately 20% of patients with a first thromboembolism and is homozygous in 2% of these patients [36]. Factor V Leiden increases the risk of an initial venous thromboembolism. For the heterozygotic and homozygotic forms of factor V Leiden, the relative risk (RR) is 3 to 10 and 79, respectively [37]. The prothrombin mutation G20210A increases the risk of an initial venous thromboembolism (RR = 2-5) [38]. Its prevalence in the general population varies in different ethnic groups, averaging 1% to 5%, but its average prevalence in multiple reports of patients with an initial venous thromboembolism is 9% [39]. However, the role of inherited thrombophilia in the thrombotic risk of patients with APS is contradictory. In general, the prevalence of factor V Leiden and prothrombin gene mutation are similar in patients with APS and healthy individuals and their presence do not increase the risk of a thrombotic event [40-47]. On the contrary, the presence of factor V Leiden has been related with an increased risk of thrombosis in patients

Table 1. Proposed Therapeutic Strategies for Secondary Thromboprophylaxis of Patients with Antiphospholipid Antibodies

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|---|--|
| GENERAL MEASURES | |
| To avoid vascular risk factors such as hypertension, hypercholesterolemia, and tobacco. | |
| Estrogen-containing contraceptives are contraindicated. | |
| Prophylaxis with LMWH in higher-risk situations (surgery, immobilization) | |
| SECONDARY THROMBOPROPHYLAXIS | |
| Patients with a single determination of aPL after several determinations and either venous or arterial thrombotic event | Same plan that the general population |
| Patients with definite APS and a first venous thrombotic event | OA (INR 2.0-3.0) |
| Patients with definite APS and a arterial thrombotic event | OA (INR >3.0) |
| Patients with definite APS and recurrent thrombotic events while on oral anticoagulation | 1. Warrant the therapeutic range of INR 2. INR>3.0 |
| Patients with definite APS and recurrent thrombotic events while on oral anticoagulation achieving a target INR >3.0 | INR>3.0 + LDA Consider hydroxychloroquine (mainly in patients with SLE) |
| Patients with seronegative APS | OA (INR depending on the type, venous or arterial, involved vessels) |
| Patients with aPL and previous thrombosis without clinical or laboratory classification criteria for APS | OA (INR >2.0) |

Abbreviations: aPL: antiphospholipid antibodies, APS: antiphospholipid syndrome, INR: international normalized ratio, LDA: low dose aspirin, LMWH: low molecular weight heparin, OA: oral anticoagulation, SLE: systemic lupus erythematosus.

with APS [48-50]. Galli *et al.* [51] suggested that factor V Leiden was associated with the thrombotic risk of patients with LA. Regarding prothrombin mutation, its presence has not been related with increased thrombotic risk in patients with APS [44, 46, 51].

No studies have evaluated if thrombophilic defects are risk factors for recurrent venous thrombosis in patients with APS under anticoagulant therapy. Data not yet published from our cohort of patients showed that patients with inherited thrombophilic defects, such as factor V Leiden or prothrombin mutation, did not show increased risk of recurrent thrombosis under anticoagulant therapy. Further studies are necessary to establish the exact role of these genetic thrombophilic defects in patients with APS.

Profile of aPL

As we mentioned before, patients with LA, IgG aCL at high titres, or anti- β_2 GPI antibodies plus LA or aCL had the highest thrombotic risk [52]. In this sense, it is well known that the combination of positive assays is a better predictor for thrombotic risk than when a single test is positive [53]. In the retrospective study performed by Pengo *et al.* [54] on 100 patients with aPL, the positivity for LA, aCL and anti- β_2 GPI conferred the highest risk for thrombosis (OR exceeding 33). Interestingly, no other assay combination was related with significant risk for thrombosis. The same results were found by Forastiero *et al.* [55]. In this study, the triple positivity for LA, IgG anti- β_2 GPI, and IgG antiprothrombin antibodies (aPT) gave the highest annual rate of thrombosis (8.4%). It is worth pointing out that any significant association for antibodies of the IgM isotype was found.

From the diagnostic point of view, this observation is important. The latest revised classification criteria recommend classifying these patients into different categories ac-

ording their aPL profile [1]. In this way, patients with positivity for multiple aPL in any combination belonged to category I and those with positivity for a single aPL to the category II (further divided based on the type of antibody). This subclassification may be especially important for patients' enrolment in clinical studies.

From the therapeutic point of view, there is no evidence about the effectiveness of more intensive therapy in these patients. However, the common sense dictates the need of closer clinical and therapeutic monitoring (to ensure a correct INR) is advisable in patients with thrombosis and any of these immunological profiles.

Persistence of aPL Positivity

Apart of the profile, another point to bore in mind is the persistence of aPL positivity over the time. At present, there is no evidence about the usefulness of repeat aPL testing on patients who meet criteria for APS. However, a recent prospective study in patients with SLE, has demonstrated that LA-positive patients had the risk of thrombosis highly increased, both at the arterial and venous level. Interestingly, LA-negative patients but with persistently positive aCL (defined as positive in more than two-thirds of the determinations) had increased the risk of thrombosis at the expense of arterial events, whereas in LA-negative and transiently aCL-positive patients (defined as positive on at least two occasions, but on less than two-thirds of the determinations), the risk of thrombosis – both arterial and venous – was no different from that in aPL-negative SLE patients.[56] Similar results were obtained by our group in patients with APS [57]. Adjusted risk for recurrent thrombosis during follow-up was increased in persistently positive aPL patients (defined as more than 75% of the aPL determinations positive during follow-up) compared with transiently positive aPL patients.

The profile of persistently positive aPL related with the appearance of thrombosis during follow-up was the combination of IgG aCL plus LA. The role of high aCL titres (≥ 40 GPL or MPL), which are laboratory criterion for APS diagnosis, in the recurrent thrombosis risk was not performed in these two studies.

CONTROVERSIES IN THE SECONDARY THROMBOPROPHYLAXIS OF PATIENTS WITH ANTI-PHOSPHOLIPID SYNDROME

Recurrent Thrombotic Events Despite Optimal Anticoagulation

In the 5 year follow-up of the "Europhospholipid" cohort of 1000 APS patients, recurrent thrombotic events appeared in 166 (16.6%) of them and the most common were strokes (2.4%), transient ischemic attacks (2.3%), deep vein thromboses (2.1%), and pulmonary embolism (2.1%) [34]. The best evidence to make any therapeutic recommendation in this group of patients comes up of the published systematic review of literature [15]. Of the 180 recurrent thrombotic events reported, 49 (27%) occurred in patients treated with warfarin. Within this group, the actual INR at the time of the event was <3.0 in 42 cases (86%). In the "Europhospholipid" cohort study [34], the INR at the time of the recurrent thrombotic event was difficult to determine in most patients and, unfortunately, these data were not consistently obtained in this study. Interestingly, strokes and transient ischaemic attacks were the most common recurrent thrombotic events. As most of these patients were receiving oral anticoagulants at a target INR between 2 and 3, this might indicate that this treatment mainly protects against venous thrombosis but may be not sufficiently protective against arterial thrombosis. However, a sub-therapeutic INR at time of thrombosis may only represent inadequate anticoagulation and not treatment failure. Recurrences were infrequent among patients effectively receiving oral anticoagulation at an INR of 3.0-4.0. Therefore, patients with APS with recurrent venous events should be treated with warfarin at an INR >3.0 . This recommendation is based on cohort studies because randomized controlled trials included few patients with this profile. In addition, there are no evidence-based data to recommend additional antithrombotic treatment such as aspirin for patients who experience recurrent events while receiving oral anticoagulants at an INR >3.0 . However, it may be a reasonable option adding low-dose aspirin to the oral anticoagulation in these cases.

As a conclusion, in patients with definite APS and recurrent thrombotic events while on oral anticoagulants, it is mandatory to warrant that the INR was in therapeutic range. In this case, the best option is oral anticoagulation to an INR > 3.0 . In patients who have recurrent events while on oral anticoagulants achieving a target INR of > 3.0 , an option is to add low dose aspirin.

Another therapeutic option, mainly in patients with SLE, is the addition of hydroxychloroquine. Firstly, it has an excellent safety profile. Secondly, there is wide published evidence from several studies that hydroxychloroquine has a protective effect on the development of both venous and arterial thrombosis in SLE patients with aPL [58-63]. Specific studies in patients with primary APS are still lacking. However, according to these data, antimalarial treatment

may be a possible complement of the anticoagulant therapy in patients with APS.

Seronegative APS

There are a small number of patients with the classical features of APS but with aPL persistently negative, leading to the concept of "seronegative APS". First of all, careful differential diagnosis with other causes of thrombophilia and repeat testing are mandatory before this diagnosis can be made. Antibodies may be directed against other phospholipids such as phosphatidylethanolamine, phosphatidylinositol, or against components of the protein C pathway or annexin V (see below). It may be also a "technical" problem due to the conventional tests were not able to detect aPL. In this sense, in the sera of 10 patients with signs of APS but aPL negative, a study detected aPL by immunostaining on thin layer chromatography [64].

Patients which Their aPL Test Turns Negative

Few patients with APS and previously positive aPL may become negative over time. Erkan *et al.* [65] demonstrated that aPL remained stable for at least three quarters of subsequent tests, regardless of the laboratory performing the test. At present, the factors related with the "disappearance" of aPL are completely unknown.

One important question is whether these patients do really suffered from APS. Recently, in a series of 10 patients with primary APS according to the Sapporo criteria [66] who become negative over time, 4 presented with another known precipitating factor for venous thrombosis [67]. In addition, some of these patients had low titres (<40 GPL/MPL units) of aCL. Therefore, it is difficult to confirm the exact pathogenic role of these aCL in these patients.

There are no evidences about the increased thrombotic risk and the role of prophylactic treatment in this group of patients. Also, the question whether or not treatment should be stopped after (spontaneous) disappearance of aPL needs further study. However, from clinical practice point of view, in patients with seronegative APS and previous thrombotic events, the common sense recommends the need of long-term anticoagulation. Although the anticoagulation withdrawal may be safe in APS patients when aPL become negative [67], further evidence describing the clinical importance of a disappearance of aPL is needed to recommend this approach. A therapeutic option may be to switch anticoagulation by antiaggregation and in the case that aPL persist negative over time, to stop any treatment with a strict control of classic thrombotic risk factors.

Patients with "Probable APS"

We refer in this section to patients with aPL but who do not display formal laboratory or clinical classification criteria for APS [1]. Examples of this group are patients with thrombosis and repeated low titres of aCL (below 40 GPL/MPL units or 99th percentile) or anti- β_2 GPI antibodies (below 99th percentile) and negative LA or patients with aPL and clinical features not included as clinical criteria such as non-bacterial thrombotic endocarditis, seizures or nephropathy. In the first example, the diagnostic problem is due to the absence of data to establish the threshold between moderate-high levels from low levels. Unfortunately, gold standards

for aPL ELISAs are still lacking, which makes standardization very difficult. In addition, the interlaboratory reproducibility of aCL and anti- β_2 GPI measurement is unacceptably poor. Specifically, for β_2 GPI assays, no accepted common calibrator is available, and therefore the comparison of the numerical results obtained with different assays is not possible. As a consequence, interpretation of the degree of positivity shows important discrepancies between laboratories [68]. Therefore, the status of medium and high positive samples as defined in the laboratory criteria of APS currently has no relevance for anti- β_2 GPI results.

In the second case, the recently updated classification criteria for APS indicate that these "atypical" clinical characteristics are frequently related with aPL and try to define the characteristics of these clinical pictures. However, their inclusion as classification criteria for definite APS may decrease the diagnostic specificity [1]. It is imperative to remember that these set of criteria have only a classificatory purpose and their usefulness is directed to include patients in clinical or therapeutic studies. Therefore, in the daily clinical practice, in these two cases, the therapeutic approach is similar: long-term anticoagulation in a similar manner than in a patient who fulfils the laboratory and clinical criteria of APS.

The Role of Other Antiphospholipid Antibodies Other than LA, aCL or Anti- β_2 GPI

The family of aPL includes a number of antibodies with specificities other than that for β_2 GPI. Among them, the antibodies directed against prothrombin (aPT) have been extensively studied. Studies *in vitro* have demonstrated the ability of IgG aPT to interfere with the anticoagulant protein C pathway [69] and to promote thrombin generation [70]. However, their clinical significance is still under debate. In the one hand, no consensus exists regarding which is the best test to perform aPT measurement. In the other hand, a systematic review of the literature did not show any consistent association between aPT and thrombosis [10]. More recent studies suggest that IgG against human PT or the PT/phosphatidylserine complex may represent a risk factor for venous thrombosis [52].

Protein S (PS) is another target for aPL. Antibodies to PS are reported in children during or after infections (mainly viral) [71], but they are commonly transient, and their routine detection could be of little use in adult patients suspected of suffering from APS.

Antibodies directed against phosphatidylethanolamine (aPE), a zwitterionic phospholipid, deserve particular attention because of their relationship with the thrombotic events of APS as reported in several studies [72, 73]. Specifically, in the later study, aPE and the conventional aPL were measured in a large cohort of thrombotic patients with or without the main known clinical and biological risk factors for thrombosis. Most of the subjects were suffering from venous thrombosis. Interestingly, aPE were present in 15% of the thrombotic patients versus 3% of the controls ($p < 0.001$) and mostly alone (62%). Moreover, aPE were found to be an independent risk factor for venous thrombosis with an odds ratio of 6.

From the clinical practice point of view, in some patients with high clinical degree of suspicion of APS, but without

aPL (the so-called "seronegative APS"), the detection of these antibodies with specificities other than that for β_2 GPI should not be neglected. In case of positive result, long-term anticoagulation could be assessed.

Another difficult case is the existence of the IgA isotype of aCL and anti- β_2 GPI. Their exact role in the pathogenesis of APS is unknown because the paucity of data and the contradictory results concerning their clinical relevance. One reason may be the lack of standardized assays and cut off values accounting for the variability in the data. In addition, in some studies, the prevalence of both IgA aCL and anti- β_2 GPI IgA may possibly depend on the ethnicity of the study population [74-76]. On the contrary, several recent reports support the clinical utility of the IgA isotype, especially anti- β_2 GPI IgA [77]. In a prospective study of patients with known aCL-associated illnesses, IgA was the most common isotype in both aCL and anti- β_2 GPI, and anti- β_2 GPI was superior to aCL for the diagnosis of APS [78]. In a retrospective study, a strong relationship between elevated titres of IgA anti- β_2 GPI and a history of venous thrombosis, thrombocytopenia, valvular heart disease, livedo reticularis and epilepsy were found [79]. Recently, Shen *et al.* [80] found that elevated titres of the IgA isotype of any ELISA-based aPL appeared to be an independent risk factor for thromboses even in the absence of LA in 472 patients with thrombosis. Given these data, in patients with high degree of suspicion of APS and aPL negative, the detection of IgA aCL and anti- β_2 GPI may be performed. In case of positivity, long-term anticoagulation may be assessed.

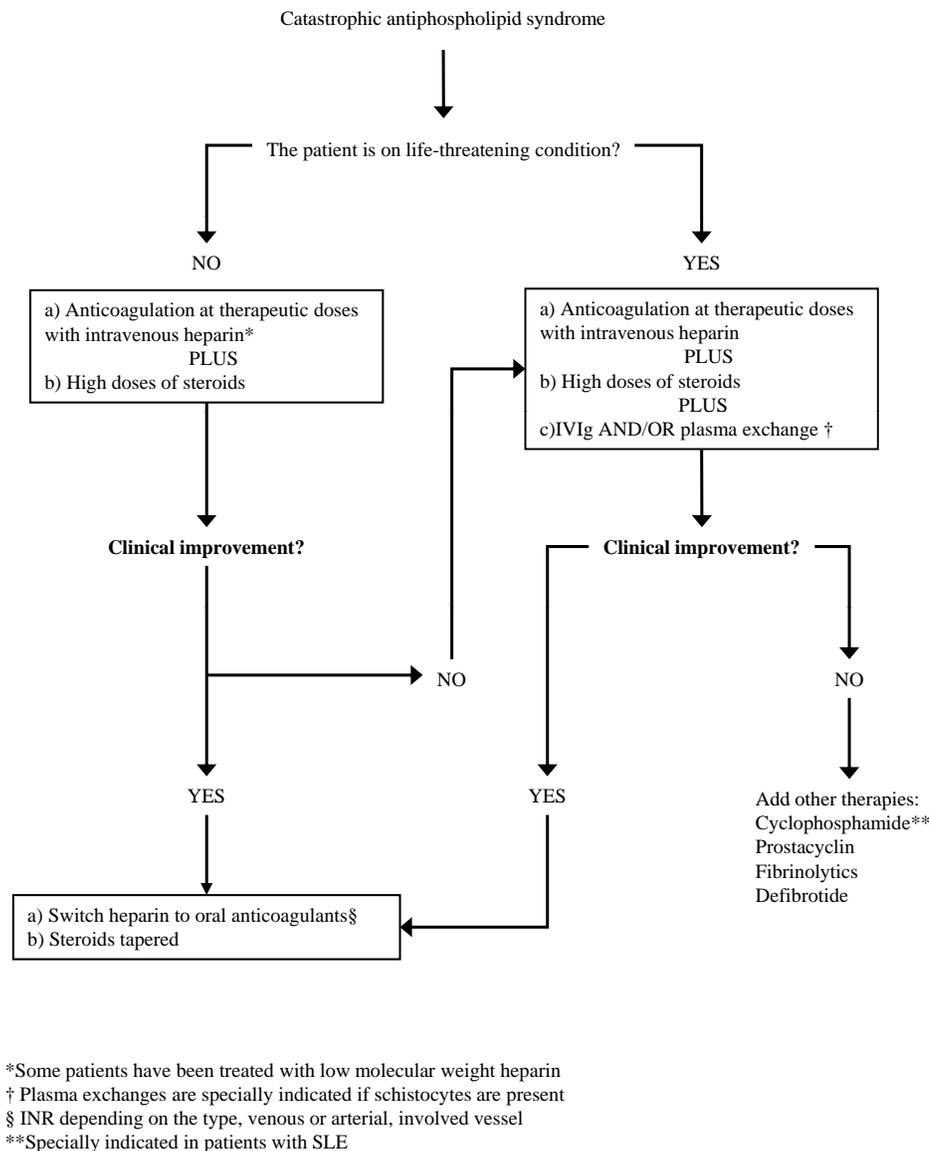
CATASTROPHIC APS

Catastrophic APS is an unusual form of presentation of APS that represents less than 1% of APS cases reported [81]. In the earliest published series, the mortality rate was approximately 50% [6, 7]. However, our group described that the mortality rate had clearly fallen by some 20% [82]. This is clearly due to the use, as first line therapies, of full anticoagulation (AC), corticosteroids (CS), plasma exchanges (PE), and intravenous immunoglobulins (IVIG).

The mechanisms of causation and pathogenesis of catastrophic APS are not completely understood. It is still unclear as to why some patients will develop recurrent thromboses, mainly affecting large vessels, while others develop rapidly recurring vascular occlusions, predominantly affecting small vessels. A possible mechanism of the catastrophic APS is the systemic inflammatory response syndrome (SIRS), which are presumed to be due to excessive cytokine release from affected and necrotic tissues [83].

As we mentioned previously, the higher recovery rate was achieved by the combination of AC+CS+PE (77.8%), followed by AC+CS+PE and/or IVIG (69%). In contrast, concomitant treatment with cyclophosphamide did not demonstrate additional benefit [82]. However, Bayraktar *et al.* [84] demonstrated that cyclophosphamide use improved survival in SLE-associated patients.

When the patients were divided according to their year of diagnosis and treatment, the mortality rate decreased from 53% in the patients diagnosed before 2000 to 33.3% in those diagnosed from 2001 to February 2005 ($p = 0.005$; OR 2.25



Abbreviation: IVIg: intravenous immunoglobulins

Fig. (1). Treatment algorithm of catastrophic APS.

95% CI 1.27-3.99) [82]. Patients in the second period were younger than those in the first (34.4 ± 11.8 and 39.4 ± 14.8 years, $p=0.016$) and a higher number of precipitating factors for catastrophic APS episodes was identified in the second period. In addition, in the episodes of catastrophic APS diagnosed after 2001, treatments including AC+CS+PE and/or IVIG were more frequently administered compared with the previous period (28.6% vs 13.3%). We consider that the difference, although statistically significant, in the mean age at the time of catastrophic APS between patients in the first and the second period was not high enough to explain the decrease of mortality rate in the second period. The higher number of identifiable precipitating factors in the second period may indicate that physicians are increasingly recognizing catastrophic APS and, therefore, earlier and more spe-

cific therapies for both precipitating factors as well as for catastrophic event is prescribed. However, we consider that the main explanation for this significant reduction of mortality was the more frequent use of treatment with AC+CS+PE and/or IVIG. According to the results of this study, we therefore strongly advocate the use of a combined treatment of AC+CS+PE as first line of therapy for patients with catastrophic APS [82]. This is in accordance with the international consensus on guidelines for the management of catastrophic APS [85] (Fig. 1).

THE FUTURE

From the diagnostic point of view, it is imperative to improve the methods to detect the presence of aPL in the sera of patients with thrombosis. In this sense, it is important to

implement strict guidelines for the performance of the LA assay, to define the real significance of the aCL compared to anti- β_2 GPI and the relationship between aPL with non- β_2 GPI specificity and thrombotic events [53]. Regarding the clinical manifestations, it would be interesting to know the pathogenic role of aPL in some clinical features not included as "formal" clinical criteria, such as non-bacterial thrombotic endocarditis or nephropathy [86]. In this sense, it is possible that aPL have inflammatory properties to explain some of these clinical features [87]. This information may lead to design an alternative therapeutic approach for these manifestations (immunosuppressants versus anticoagulation) [88]. At present, the therapeutic management of these atypical manifestations is unknown.

Finally, the extensive knowledge of new pathogenic mechanisms of aPL allows the identification of potential therapeutic targets in APS patients [89]. Statins that have shown anti-inflammatory properties inhibiting the aPL-mediated increase of tissue factor in cultured human endothelial cells and angiotensin-converting enzyme inhibitors that inhibit the monocyte tissue factor expression might have a role in the armamentarium of APS in the future. The inhibition of complement, nuclear factor- κ B, and p38 mitogen-activated protein kinase will probably open new therapeutic possibilities in these patients. The molecular mimicry between bacterial or viral antigens and certain regions of the β_2 GPI structure to explain the induction of aPL from infectious agents is the basis for using synthetic peptides to inhibit the thrombogenic properties of aPL [90]. A similar method is performed by β_2 GPI toleragen. In this case, a polyvalent conjugate of recombinant domain I of human β_2 GPI cross-links with specific surface immunoglobulins to target and induce tolerance in B cells to β_2 GPI. CD20+ B cells produce aPL and also interact with other immune cells to increase the risk of thrombosis. This is the theoretical prospect that rituximab could reduce aPL titres, prevent thrombosis and avoid the need for anticoagulant treatment in APS. At present, only one recent case report suggested that rituximab could improve several thrombotic symptoms of APS including headaches, reduce the need for analgesia and stabilise the dose of warfarin and the INR [91]. Of note, an ongoing randomised, placebo-controlled proof-of-concept study aims to ascertain whether rituximab influences the coagulation cascade with a aim of eliminating the need for long-term anti-coagulation during a 2-year follow up [92].

ABBREVIATIONS

| | | |
|---------------|---|---|
| AC | = | anticoagulation |
| aCL | = | anticardiolipin antibodies |
| APASS | = | antiphospholipid antibody in stroke study |
| aPL | = | antiphospholipid antibodies |
| APS | = | antiphospholipid syndrome |
| β_2 GPI | = | beta-2-glycoprotein I |
| CI | = | confidence interval |
| CS | = | corticosteroids |
| HDX | = | hydroxichloroquine |
| INR | = | international normalized ratio |

| | | |
|-------|---|---|
| IVIG | = | intravenous immunoglobulin |
| LA | = | lupus anticoagulant |
| LDA | = | low dose aspirin |
| LMWH | = | low molecular weight heparin |
| OA | = | oral anticoagulation |
| PE | = | plasma exchanges |
| SIRS | = | systemic inflammatory response syndrome |
| SLE | = | systemic lupus erythematosus |
| WARSS | = | warfarin-aspirin recurrent stroke study |

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