

develop the current and future research in rheumatology and areas closely linked to rheumatology.

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focus on educational articles. One of the challenges for researchers and clinicians today is to select articles among the increasing flow of information within a short period of time. I hope we may find solutions to make it possible for readers to easily capture the main “take home messages” from the published articles in ARD. An additional challenge is to find the optimal balance between material published in paper format and electronically.

I look forward to future collaborations with colleagues; the members of the editorial boards and reviewers are essential for the success of the journal. Finally, I will welcome any advice or proposals from the readership that can contribute to further improve the quality of the journal.

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# Antiphospholipid syndrome dilemmas still to be solved: 2008 status

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Extensive investigation of antiphospholipid syndrome (APS) has improved our knowledge of the disease, but raised new questions. Although the pathogenic role of antiphospholipid antibodies (aPL) is widely accepted, the fact that aPL induces thrombotic events only occasionally suggests the need for a “second hit” to display the thrombogenic effect. Infectious agents are thought to trigger autoantibody production through a molecular mimicry mechanism, but may also induce an inflammatory process that eventually favours clotting. The involvement of complement and cytokines in the pathogenesis further supports the role of inflammation in APS as well as the possibility for new therapeutic approaches. The question of whether other environmental triggers or a genetic individual susceptibility can behave as a second hit is still open. The clinical

involvement of different organs and systems poses the question of whether the syndrome should be considered a true systemic autoimmune disease, rather than an acquired autoimmune coagulopathy. A positivity for more than one laboratory test displays a higher predictive value for clinical events, but it is still not known which other parameters are useful in clinical practice to identify all the aPL positive subjects at risk for manifestation. In particular, there is no clear evidence when a more aggressive treatment must be used in primary prophylaxis. The standard anticoagulant therapy has dramatically changed the prognosis of APS; however, the vascular and/or obstetrical recurrences in spite of the treatment pose the question whether additional therapeutic strategies (ie, immunosuppression) should be used, or whether alternative therapies (ie, inhibitory/tolerogenic peptides) should be sought.

Antiphospholipid syndrome (APS) was first described in 1983.<sup>1</sup> Extensive investigations and several congresses have addressed the basic and the clinical aspects of APS.<sup>2–8</sup> Consequently, 25 years later a large knowledge base has been built up on the aetiology, the pathogenesis and the therapy of APS in a relatively short period of time compared to other systemic autoimmune diseases.

In spite of such progress, however, there are still dilemmas to be solved.

The disease was first defined as a triad of thrombosis, abortions and thrombocytopenia,<sup>1</sup> but quickly the definition evolved into that of a systemic condition that may be even more systemic than lupus.<sup>9</sup> This review will focus on some unanswered issues surrounding APS that will require future research, classifying them into the domains of aetiology, pathogenic mechanisms, diagnostics and therapy (table 1).

## AETIOLOGY

The primary unsolved question remains whether the aetiology is single or multiple? A two-hit hypothesis has been

**Table 1** Future directions for antiphospholipid syndrome (APS) research

Category	Outstanding issues
Aetiology	Role of infection, drugs, tumours Activation of complement cascade Additional genetic markers
Mechanisms	Complement role Cytokines/chemokines role Non-ischaemic CNS, heart, skin involvement
Diagnostics	Additional autoantibodies (Multiplex) <i>Livedo reticularis</i> Seizures/cognitive abnormalities and autoantibodies Libman–Sacks endocarditis Nephropathy
Therapy	Optimal INR Anticoagulation resistant cases Primary prophylaxis (asymptomatic aPL positive cases) CNS, heart, skin involvements Peptide therapy

aPL, antiphospholipid antibodies; CNS, central nervous system; INR, international normalised ratio.

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suggested to explain the clinical observation that thrombotic events occur only occasionally in spite of the persistent presence of antiphospholipid antibodies (aPL). The aPL ("first hit") increases the thrombophilic risk and the clotting takes place in the presence of another thrombophilic condition ("second hit").<sup>10</sup> It has been suggested that infectious processes may be the second hit since they frequently precede the full-blown state of the syndrome and may be the initiator of the catastrophic subtype.<sup>10</sup> Innate immunity receptors (ie, toll-like receptors (TLR)) and mediators (complement) involved in sensing microbial agents might synergise and contribute to the triggering the clotting event.<sup>10-11</sup> However, the infectious aetiology of APS is not limited to the triggering effect of infectious processes. In fact, it has been shown that antibodies against the main aPL antigenic target, ie,  $\beta$ 2 glycoprotein I ( $\beta$ 2GPI), may be synthesised by B-cell clones cross-reacting with epitopes expressed on infectious agents as the result of a molecular mimicry between exogenous molecules and  $\beta$ 2GPI.<sup>12-13</sup> Whether an individual will develop APS will depend mainly on his/her genetic predisposition that may or may not favour the production of the cross-reacting autoantibodies.<sup>10</sup>

Therefore, if there are additional aetiological factors for APS, the questions remain: (1) are there other environmental factors that are responsible for inducing APS, ie, drugs, tumours? And (2) Are there other stimulants of the innate immune system driving it toward an overt APS, ie, redox effect?

If persistent positivity for aPL represents a condition necessary but not sufficient by itself to induce the clinical manifestations of the syndrome, is there a genetic background for explaining why a positive aPL carrier develops thrombotic events or remains asymptomatic? Could the same genetic background explain why the catastrophic variant does occur but only in some cases?

The presence of aPL, but not the clinical manifestations of the disease, has been associated with major histocompatibility complex (MHC) genes,<sup>14</sup> while concomitant genetic thrombophilic conditions were reported to increase the ultimate risk of thrombotic events.<sup>15</sup>

More recently, polymorphism of genes encoding for signalling pathways of pro-inflammatory mediators (ie, the *tlr4* gene) was suggested to represent a protective factor for thrombosis.<sup>11</sup> A reduced inflammatory response could, in fact, protect

against the thrombogenic effect of aPL, while a prompt inflammatory response would favour it. Additionally, polymorphisms of other genes encoding for platelet glycoproteins have been found to increase the risk of thrombosis in patients with APS.<sup>15</sup> Larger studies may address the question of whether or not polymorphisms of other candidate gene mechanisms may help in defining the susceptibility for developing the full-blown clinical manifestations of APS.

Conversely, it seems that sex hormones are less important in APS than in some other autoimmune diseases, such as systemic lupus erythematosus (SLE), because the female/male ratio is not as high (5/1 in APS and 9/1 in SLE).<sup>6</sup> However, other factors, such as trauma, arterial hypertension, smoking, high cholesterol levels, etc, could increase the risk for thrombosis.

### PATHOGENIC MECHANISMS

The hypercoagulable environment in APS is relatively well known. The key role of the up-regulated expression of tissue factor (TF) on the cell surface of endothelial cells and peripheral blood monocytes represents a relatively new aspect.<sup>16-18</sup> However, the revelation of complement involvement in experimental placental pathology as well as in thrombosis models<sup>19-21</sup> has been a finding that may facilitate the pursuit of new therapeutic agents, such as complement activation inhibitors. At the present time there is no data for APS patients regarding the involvement of complement in the vascular manifestation, and there are contrasting findings in human placentas.<sup>22-23</sup> Hence, the questions remaining here are: (1) is complement activation really instrumental in human APS? (2) Which aspects of the syndrome (venous/arterial/microcirculation thrombosis) are involved? And (3) if the APS clinical manifestations are closely associated to a strong pro-inflammatory mediator such as complement, what kind of cytokines/chemokines are involved in the pathogenesis of APS lesions?

There is evidence for the importance of tumour necrosis factor (TNF)  $\alpha$  in the experimental models of aPL-mediated foetal loss.<sup>24</sup> Will anti-TNF $\alpha$  agents be incorporated as therapeutic tools? There is no clear answer at the moment, but it is intriguing that treatment of pregnant mice with polyethylene glycol-conjugated soluble TNF-R type I,<sup>24</sup> or vaccination with TNF $\alpha$ ,<sup>25</sup> protected them from the foetal loss induced by aPL.

The redundancy of the cytokine system raises the question of whether or not additional cytokines or chemokines may be involved. This is apparently the case since chemokines are important in mediating the aPL foetal loss in the murine model.<sup>26</sup>

Do these findings support the presence of an inflammatory process in APS? This is still an open question, since there is no sound evidence for a systemic inflammation in patients to date. This is true for vascular events in particular rather than for the placental involvement.

Other enigmas to be solved relate to the involvement of the central nervous system (CNS) not due to ischaemic processes and heart valve afflictions (Libman-Sacks endocarditis).<sup>27-29</sup> The CNS involvement entails seizures, cognitive impairments, migraine, etc.<sup>7</sup> The experimental models allude to hyperactive behaviour of mice with induced APS.<sup>30</sup> There are additional studies alluding to some mechanisms such as synaptosomal destruction and direct aPL binding to neuronal cells.<sup>31-32</sup> However, the precise mechanisms by which aPL effects the brain are still not understood. A possible relationship with the anti-NR2 antibodies, whose presence has been related with cognitive dysfunction in SLE patients,<sup>33</sup> should be verified. This may lead to a better understanding of the mechanisms of cognitive impairment or memory loss in general.

Similarly, deciphering the mechanism of Libman-Sacks endocarditis may prevent many valve replacements, as well as some of the cerebrovascular accidents closely associated with the valve involvement.

### DIAGNOSTIC CRITERIA

The detection of aPL is a milestone in the diagnosis of APS, but frequently the answer from the laboratory is not clear enough. Despite the fact that the diagnosis of APS so far is based on a panel of serological and functional assays (ie, anticardiolipin (aCL), anti- $\beta$ 2GPI antibodies or lupus anticoagulant (LA)), there are cases negative for these autoantibodies but with clinical manifestations comparable to the classical examples.<sup>34</sup>

The most recent consensus paper stated that the positivity for more than one laboratory test displays a higher predictive value for clinical events, the highest risk being a positivity for all three assays.<sup>5</sup> However, it is not known whether there are combinations of other autoantibodies that carry a more deleterious prognosis.

For example, what is the significance of antibodies against the chromatin antigens (in particular nucleosomes) frequently detected in patients with primary APS?<sup>25</sup> Do they represent a signature for developing a systemic lupus disease in the future?

So far, more than 25 different autoantibodies have been reported in relation to APS;<sup>36</sup> are all of them pathogenic, synergistic, or are some of them just an epiphenomenon?

Are better still classification criteria needed? The recently updated classification criteria for APS state that seizures, *livedo reticularis*, Libman–Sacks endocarditis and nephropathy are features undoubtedly frequent in patients with APS. However, their adoption as independent criteria for definite APS was suggested to decrease the diagnostic specificity.<sup>5</sup> Should the possibility of combining standard manifestations with the new suggested ones be taken into consideration in order to improve the sensitivity of our classification guidelines? Should definite as well as possible/probable APS diagnosis be proposed in cases that are negative for the classic, but positive for the newly-mentioned clinical features?

### THERAPEUTICAL DILEMMA

There is no question that despite the very effective therapies achieved during the last decade,<sup>1</sup> the optimum therapy has not yet been reached. Questions such as the following are yet to be answered.

Regarding the obstetrical aspects of the syndrome, low dose aspirin (LDASA) plus unfractionated or low molecular weight heparin (LMWH) are effective in the majority of the cases, but recurrent miscarriages in spite of the therapy are not rare. What is the alternative therapy in such refractory cases? Should intravenous immunoglobulins (IVIG) be used in addition to LDASA and heparin? Should corticosteroids be added in line with evidence of a local inflammation from animal studies as well as from histological analysis of placental tissues from APS women?<sup>11–37</sup> Should the pharmacological activity of heparin be re-evaluated according to its inhibitory effect on complement and/or chemokines? Keeping in mind the new findings from the experimental aPL-mediated foetal loss models, should the pharmacological activity of heparin be reconsidered? In fact, it is widely accepted that heparin displays a strong binding activity to  $\beta$ 2GPI, and it is potentially able to compete with the binding of  $\beta$ 2GPI to placental structures. In addition, heparin also displays an inhibitory activity against

the new pro-inflammatory pathogenic players in aPL-mediated foetal loss: ie, complement and chemokines.

Regarding the vascular aspects of the syndrome, several additional questions arise: (1) what is the ideal INR to be achieved? Although several studies favour a target of 2.5,<sup>2</sup> it is possible that specific situations (ie, recurrence of thrombosis, catastrophic APS, arterial events, etc) may require a higher target. (2) Should a more aggressive treatment (ie, higher international normalisation ratio (INR)) be used in the management of CNS ischaemic involvement, particularly in APS secondary to systemic autoimmune disease?<sup>2–7</sup> (3) Should INR be measured/monitored by the patients? (4) What should be done with anticoagulant resistant cases? Should pharmacogenetic studies be performed? Should the use of immunosuppressive therapy (ie, anti-CD20 agents) be taken into account to modulate the B-cell compartment and to down-regulate the production of pathogenic autoantibodies? Would heparin be the ideal agent due to its  $\beta$ 2GPI displacing and anti-complement/chemokine characteristics, or should other anticoagulants be used? (5) What is the best therapy for catastrophic APS (plasma exchange, IVIG, LDASA, anticoagulants, antibiotics, anticytokines etc)? (6) Given the efficacy of hydroxychloroquine and statins in experimental models of APS, what should their role be in treating the clinical manifestations of the syndrome?

Special concerns may be raised regarding prevention and attitude towards “grey zone” cases. There are several questions depending on different conditions. In the case of asymptomatic aPL clearly-positive subjects (medium/high aCL/anti- $\beta$ 2GPI antibody titres and/or LA), should further traditional risk factors just be avoided and the patients treated for primary prophylaxis with LDASA? Should new risk factors (such as a pro-inflammatory susceptibility profile) be looked for? Should a more aggressive treatment be used in managing transient risk conditions (prolonged venous stasis)?

By contrast, in the case of asymptomatic subjects that are aPL “grey zone” positive (low aCL/anti- $\beta$ 2GPI antibody titres and negative LA), is a prophylactic regimen with LDASA really needed keeping in mind the low rate of thrombotic events and the apparently low protective role of such a therapy?<sup>37</sup> Should just a simple follow-up be performed?

More importantly, is there any predictive marker for the development of the clinical manifestations in asymptomatic

aPL positive subjects? Can APS be predicted years in advance (family history, autoantibodies) and can it be predicted whom to offer preventative treatment to? And how should these patients be treated: full anticoagulation therapy or only LDASA?

If the infectious aetiology of APS is true, and infectious episodes represents trigger hits for clotting, should antibiotics and vaccines be involved in the preventive therapy of APS?<sup>10</sup>

Finally, it is also useful to speculate on future therapeutical approaches based on the information from experimental studies: (1) should complement component inhibitors be added to the treatment regime? (2) What could be the role of peptide-specific therapy be? (3) Could treatment aimed at modulating the signalling pathways triggered by aPL complexed with  $\beta$ 2GPI on the cell membrane offer an additional future approach?

Regarding the first question, there is experimental evidence that peptides displaying  $\beta$ 2GPI epitopes recognised by aPL may inhibit the autoantibody binding and the aPL-associated manifestations in *in vivo* experimental animal models.<sup>39</sup> A comparable protective effect was also related to the ability of another peptide to displace  $\beta$ 2GPI from the cell membrane of endothelial cells and monocytes, making the molecule no longer available for the autoantibodies and eventually inhibiting cell activation.<sup>40</sup> By contrast, antagonists of the putative receptor(s) for  $\beta$ 2GPI (such as blocking antibodies) might be used to inhibit/reduce the binding of  $\beta$ 2GPI to target cell membranes. Moreover, inhibitors of intracellular signalling triggered by aPL (ie, nuclear factor (NF)- $\kappa$ B or p38 mitogen-activating protein kinase (p38MAPK) inhibitors) have been shown to be effective *in vitro* and *in vivo* experimental models and can theoretically be used in patients.<sup>41–43</sup>

### IS ATHEROSCLEROSIS ASSOCIATED WITH APL?

aPL have been associated with accelerated atherosclerosis mainly on the basis of *in vivo* experimental models where passive infusion of aPL or active induction of antibodies cross-reacting with murine  $\beta$ 2GPI showed an enhanced formation of atherosclerotic plaques.<sup>45</sup> Additional *in vitro* findings suggested a potential role for aPL in atherosclerosis. In particular,  $\beta$ 2GPI-dependent aPL are associated with endothelial perturbation, with the induction of a pro-inflammatory and pro-coagulant phenotype and cross-reaction with oxidised low density lipoproteins

(ox-LDL).<sup>44-46</sup> These events may play a role in the inflammatory process localised in the atherosclerotic plaque. However, a few clinical studies with small series of patients did show clear evidence of accelerated atherosclerosis in patients with primary APS in the absence of any underlying systemic autoimmune disease.<sup>47-49</sup> Furthermore, large studies in SLE patients found no association between aPL and the accelerated atherosclerotic process characteristic of this disease.<sup>49-53</sup> Hence, the issue of aPL association with atherosclerosis is still unresolved and large multicentre studies in patients with primary APS are necessary to reach definite answers.<sup>54</sup>

In conclusion, from the above list of questions and dilemmas it seems that an optimal regime toward APS is approaching, yet there is still some distance to go.

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