

## What is the best strategy in treating catastrophic antiphospholipid syndrome?

The current recommendation for specific therapy of catastrophic antiphospholipid syndrome (CAPS) is the triple therapy with anticoagulation, glucocorticoids, plasma exchange and/or intravenous immunoglobulins. Of note, only anticoagulation had a significant effect improving the vital prognosis of these patients. From the experimental point of view, there is only indirect evidence to advocate the use of these immunomodulatory therapies in CAPS. Recently, two monoclonal antibodies, rituximab and eculizumab, have been successfully used in some cases of severe or refractory CAPS. The first decreases the generation of pathogenic autoantibodies such as antiphospholipid. The second prevents the generation of C5b-C9 complex. The current review describes the conventional and recent modalities of CAPS treatment, discussing the rationale for each one.

**Keywords:** anticoagulation • catastrophic antiphospholipid syndrome • corticoids • eculizumab therapeutics • plasma exchange • review • rituximab • sirolimus

Catastrophic antiphospholipid syndrome (CAPS), the most severe manifestation of antiphospholipid syndrome (APS), is a multisystemic autoimmune life-threatening condition characterized by multiple organ thrombosis [1]. These patients classically present circulating antiphospholipid antibodies (aPL), usually in high titer, and developing multiple organ involvement with histopathological evidence of small vessel occlusion over a short period of time. Typically, this clinical picture unlike classical manifestations of APS is preceded by an identifiable precipitating factor, mainly infections although others are often described such as cancer, drugs, surgery or anticoagulation withdrawal [2].

Due to its rarity, the analysis of this condition in formal prospective studies is not easy to design appropriate clinical trials. Thus, in order to improve the knowledge about CAPS, the European Forum on Antiphospholipid Antibodies created in 2000 the CAPS Registry, an international registry where all cases from anywhere in the world published or communicated to the group

are included. The analysis of hundreds of patients with this condition included in this registry has allowed to evaluate the best management strategy and, especially, to assess its therapeutic options [3].

Actually, the recommendation in front of a patient with the clinical suspicion of CAPS is the identification and treatment of the precipitating factor together with the supportive measures if they are needed. Regarding specific therapy, the combination of high doses of glucocorticoids (GC) and anticoagulation (AC) with heparin is the cornerstone of the treatment. In cases with associated life-threatening situation, the addition of plasma exchange (PE) and intravenous immunoglobulins (IVIG) should be considered. In patients with associated systemic lupus erythematosus (SLE), IV cyclophosphamide has improved their prognosis [4].

Recently, rituximab has been used in patients with severe forms of CAPS as first line of treatment together with conventional therapy or as a second-third line in refractory cases to conventional treatment [5]. Another

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drug that has been successfully used in CAPS is eculizumab. In fact, some authors have reported its use in patients with refractory or recurrent episodes of CAPS [6,7]. The introduction of these two monoclonal antibodies in the therapeutic armamentarium of CAPS is very important because they are directed against specific molecules that have a potential role in the pathogenic mechanism of this condition. In other words, AC prevents the consequence of aPL, the thrombosis and PE and IVIG removes and blocks aPL, respectively. Rituximab, blocking CD20, a surface protein expressed on the cytoplasmic membrane of B cells, decreases the generation of pathogenic autoantibodies such as aPL. Eculizumab binds with high affinity to C5 complement protein inhibiting its cleavage and, thus, preventing the generation of C5b-C9 complex generation.

Management of CAPS has been a challenge for the attending physicians since its description. Indeed, the optimal management of CAPS is still not known. Nowadays, CAPS mortality continues to be extremely high (around 30%) despite therapy. Due to this high mortality rate, early diagnosis and aggressive treatment are essential key points in its management.

### Current approach

The literature describing treatment of CAPS is confusing since no prospective trial can be conducted. Classically, three aspects have been claimed as the backbone to treat this situation. First, the so-called supportive general measures; second, the aggressive treatment of any identifiable trigger, and, finally, the specific treatment.

Current treatment guidelines for CAPS were established more than 10 years ago based on the analysis of the first 130 patients with this condition that had been treated according the criteria of their physicians [8]. Of note, when each treatment was analyzed individually, only AC had a significant effect improving the vital prognosis of these patients. It is important to keep in mind that when the combination regimens were analyzed, the highest survival rate (70%) was achieved with the combination of AC + GC + PE and/or IVIG. However, this result was only statistically significant in the first 50 patients with CAPS [9] but it was not confirmed in the first 80 patients [10].

In 2006, our group published the results of the mortality analysis of the first 250 patients included in the CAPS Registry [11]. Death occurred in 44% of patients and cerebral involvement, consisting mainly of stroke, cerebral hemorrhage and encephalopathy, was the main cause of death, being present in 27% of patients, followed by cardiac involvement (20%) and infection (20%), respectively. Regarding the prognostic factors,

patients with associated-SLE presented with a higher mortality rate compared with those with primary APS (59 vs 38%;  $p < 0.003$ ). We confirmed that AC was the only treatment associated with high recovery rate (63% in CAPS episodes treated with AC vs 22% in episodes not treated with AC;  $p < 0.0001$ ).

Considering the combined therapy, the highest survival rate was achieved by the combination of AC + GC + PE (78% in 18 treated episodes) and AC + GC + PE and/or IVIG (69% in 42 treated episodes), but there was no statistical difference between them. Moreover, when we considered the presence and absence of a specific combination of treatments, there were no differences in the recovery rate. However, in the case of AC + GC + PE and/or IVIG and AC + GC + PE, there was a trend toward a higher rate of recovery for episodes that were treated with this combination versus those that were not (69 vs 54.4% [ $p = 0.089$ ], and 77.8 vs 55.4% [ $p = 0.083$ ], respectively). The other important result was that mortality rate decreased over time, from 53% in patients diagnosed before 2001 to 33% in those diagnosed between 2001 and February 2005 ( $p < 0.005$ ). The most important differences between these two periods were the higher number of precipitating factors in the second period and the fact that combined therapy of AC + GC + PE and/or IVIG was used most often for CAPS episodes diagnosed in the second period. Despite evident methodological limitations, these data reinforced the initial recommendation of the combined therapy (AC + GC + PE and/or IVIG) as the first line of treatment in front of a patient with the clinical suspicion of CAPS.

Finally, on the occasion of last 14th International Congress on Antiphospholipid Antibodies, a Task Force on CAPS collected and summarized all these evidences and developed a set of recommendations regarding the diagnosis and treatment of this devastating complication [12]. In the field of therapeutic strategy, the Task Force recommended the triple therapy (AC + GC + PE and/or IVIG) with a grade of recommendation B. In addition, for patients with SLE or another autoimmune disease, tetra therapy (AC + GC + PE and/or IVIG + cyclophosphamide) may be beneficial with a grade of recommendation D [13].

### The rationale for the use of immunomodulatory therapies in CAPS

Up to now, AC has been the only single treatment associated with high recovery rate in patients with CAPS. Its use is based on the thrombotic nature of CAPS. Regarding the immunomodulatory therapies such as GC, PE and IVIG, which would be the rationale for this usefulness in CAPS? From the clinical point of

view, some of the clinical manifestations characteristics of CAPS such as encephalopathy, acute respiratory distress syndrome or circulatory failure do not seem to be related with vascular thrombosis but due to systemic inflammatory response syndrome (SIRS). In these cases, similar to those with severe sepsis, a pro-inflammatory microenvironment associated to high levels of cytokines may be the cause of these organ involvements [14].

However, is there any experimental or basic evidence of the existence of this SIRS to advocate the use of immunomodulatory therapies in CAPS? Unfortunately, the answer is that only indirect evidence does exist. The only evidence is the fact that CAPS is one of the so-called 'thrombotic storm' conditions. This concept defines an extreme prothrombotic phenotype, characterized by multiple thrombotic events affecting diverse vascular beds occurring over a brief period of time, and includes patients with CAPS [15] but also patients with *purpura fulminans* or hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome [16]. Kitchens hypothesized that newly formed clots in patients with preexisting hypercoagulability (aPL in cases of CAPS), continue to promote thrombin formation. In addition, fibrinolysis is not able to prevent this process due to increase in plasminogen activation inhibitors [15]. Some patients with thrombotic storm exhibit laboratory evidence for an acute inflammatory state represented by an elevated erythrocyte sedimentation rate, C-reactive protein, fibrinogen and/or factor VIII levels on initial presentation [17]. Moreover, high levels of ferritin, an iron storage protein considered also an acute phase reactant, has recently been described in patients with APS. Interestingly, hyperferritinemia was present in 71% of CAPS patients, and ferritin levels among this subgroup were significantly higher compared with classic APS [18]. In fact, CAPS has recently been included in the definition of the hyperferritinemic syndrome together with adult-onset Still disease, macrophage activation syndrome and severe sepsis that are characterized by high levels of proinflammatory cytokines [19].

Finally, Bontadi *et al.* [20], demonstrated that anti- $\beta$ 2GPI antibodies isolated from an APS patient during the catastrophic phase enhanced the expression of platelet P-selectin more than antibodies isolated from the same patient in the quiescent stage of disease. Of note, soluble P-selectin and von Willebrand factor activity were significantly higher during catastrophic than in quiescent phase.

Given all these data, it seems possible that an inflammatory state promoted by a 'cytokine storm' would be present in patients with CAPS, and that immunomod-

ulatory therapies neutralizing it, would have a theoretical role in the treatment of these patients.

### Supportive general measures

Many patients with CAPS end up in intensive care units because of multiorgan failure [21]. Accordingly, appropriate supportive care according to the patient medical condition is mandatory. Thus, hemodialysis in cases of renal insufficiency is sometimes required. Mechanical ventilation for respiratory failure may be indicated when SIRS affects the lungs, especially when the patients develop acute respiratory distress syndrome. Sometimes inotropic drugs due to cardiovascular system failure need to be administered.

Another supportive measure may be the amputation and debridement of any necrotic tissue. Asherson *et al.* [22], described the remission of CAPS in two patients after the amputation of the suppurative leg ulcers due to vascular thrombosis. The hypothesis is that necrotic tissues are a source of proinflammatory cytokines and may become infected. Both facts may perpetuate the SIRS.

### Trigger-guided therapy

As this condition is classically preceded by a precipitant factor, the early identification and treatment of any possible trigger is recommended. In the last review of 280 patients with CAPS, a precipitating factor was reported in 53% of them [11]. By order of frequency, infections were the most common precipitating condition present in 22% of patients followed by surgical procedures (10%), anticoagulation withdrawal or low international normalized ratio (INR) (8%), medications (7%), obstetric complications (7%), neoplasia (5%) and SLE flares (3%).

Regarding infections, the most common site of infection was the respiratory airway (33%), followed by urinary tract, (19%), skin (13%) and gastrointestinal tract (8%). The microorganism isolated more frequently was *Escherichia coli* (13%), followed by *Streptococcus pyogenes* (6%), *Staphylococcus aureus* (4%), *Pseudomonas aeruginosa* (4%) and *Candida* sp. (3%; data unpublished). When an infection is suspected, adequately chosen antibiotic treatment should be started, taking into account the infection site, pharmacokinetics and organism pharmacodynamics when it is identified.

The perioperative management of patients with APS or aPL carriers is very important given the high risk to thrombotic recurrence or, more importantly, the development of a catastrophic episode. In this situation, the substitution of heparin in place of oral anticoagulation, the so-called bridging therapy, is mandatory. However, a multidisciplinary analysis of each case is necessary evaluating the risk of thrombosis but also the bleeding risk [23].

### Specific therapies

As we mentioned before, therapeutic approach to CAPS is based on the physiopathology events though to take place during the catastrophic episode. However, pathological ways evolving CAPS are not yet clearly understood because the exceptionality of this condition hindered any effort to perform mechanistic studies [12]. Applying results from studies performed on classic APS, CAPS is now considered to arise as a result of a prothrombotic microvascular environment that ensue after antibody deposition, endothelial cell and complement cascade activation leading to a prothrombotic milieu. Clinical manifestations are ascribed to the thrombotic obstruction of blood flow taking place in the affected organs and to the SIRS attributed to excessive cytokine release from affected and necrotic tissues.

### Anticoagulation

Anticoagulation with heparin is the mainstay of treatment for CAPS. The main rationale for its use is the inhibition of ongoing clotting and the lysis of existing clots that may contribute to the ongoing thrombosis. However, given the evidence of a link between coagulation and inflammation [24], heparin also possesses anti-inflammatory activity that may explain its usefulness in CAPS. Few clinical studies have shown the beneficial effects of heparin in patients with bronchial asthma [25], ulcerative colitis [26] and burns [27]. However, the mechanisms underlying its anti-inflammatory activity are not well understood. Some of the potential involved mechanisms are the capacity of heparin to bind acute phase and complement proteins [28], the inhibition of neutrophil adherence to activated endothelial cells by binding to P-selectin, and blocking of NF- $\kappa$ B, that can potentially reduce inflammatory gene activation and regulate the gene expression and production of proinflammatory cytokines, chemokines and adhesion molecules [29].

The majority of patients were treated initially with unfractionated heparin (61%) followed by low molecular weight heparin (13%). If the clinical course is satisfactory, heparin must be maintained for 7 to 10 days and then it should be replaced by oral anticoagulant therapy (warfarin or coumadin). Of note, heparin should not be withdrawn before achieving a correct international normalized ratio (INR) with oral anticoagulants. The optimal intensity of oral anticoagulation for patients with classic APS and venous thrombosis is between two and three. In patients with arterial events, the intensity of oral anticoagulation (INR 2–3 or >3) is still a matter of discussion [30]. It is unknown the recommended INR for patients with CAPS. Erkan *et al.* [31] described the long-term follow-

up of a series of patients with CAPS. 15 of 58 (26%) developed further APS related thrombosis after the initial CAPS event and only one had recurrence with a subtherapeutic INR (<2). A range of INR between two and three could be effective, with low risk of hemorrhagic events.

### Steroids

Proinflammatory cytokines may be important leading to a procoagulant effect by inducing tissue factor expression on mononuclear cells and endothelial cells. In addition, some clinical manifestations of CAPS are not directly related to the blood flow occlusion but to the cytokine overexpression in the ischemic necrotic tissue, leading to the so-called cytokine storm. Glucocorticoids would be necessary on the one hand to overcome the excessive cytokine response in these patients, and in the other hand to decrease the production of aPL. However, the initial dose, the route of administration, and the tapering dose are unanswered questions. Data from CAPS Registry revealed that GC were given as intravenous pulses (500–1000 mg/day for 1–3 days) in 34% of episodes and as oral or intravenous dosages of 1–2 mg/kg/day in 34% of them.

### Plasma exchange

Plasma exchange is a technique designed to remove large quantities of plasma (usually 2 to 5 liters) and to replace by either fresh-frozen or stored plasma. Conversely, plasmapheresis is the technique when a solution other than plasma such as isotonic saline or albumin is used as replacement fluid. The rationale of this modality of therapy is based on the fact that this is the treatment of choice in patients with a classical microangiopathic condition, thrombotic thrombocytopenic purpura. On the one hand, PE removes aPL and possibly proinflammatory cytokines, and in the other hand, fresh frozen plasma contains the natural anticoagulants.

The grade of evidence of the recommendation use of therapeutic PE in CAPS is 2C according to the American Society for Apheresis (ASA) [32]. Of note, it would be specially indicated in those patients with CAPS who show serological features of microangiopathy (schistocytes).

Regarding the replacement fluid of choice for therapeutic PE in CAPS, there is no consensus and fresh frozen plasma, human albumin and solvent/detergent plasma have been used [11]. Following the recommendations of ASA a combination of plasma and albumin would provide the necessary benefit of therapeutic PE and minimize potentially serious and undesirable side effects from excessive exposure to plasma. Our suggestion is the use of 5% albumin solution as a choice

replacement fluid in cases of CAPS. In those patients with a lack of prompt response, consider the use of fresh frozen plasma [33]. Other European group suggested that PE should be initiated during the first 12 h of the event, sessions must be daily during the first 3 days and then tapered, and 4% human albumin solution should be the replacement fluid [34].

Finally, there is no recommendation about the duration of this procedure. In general, it should be continued for a minimum of 3 to 5 days and clinical response is the main parameter that dictates the discontinuation of the therapy.

### Intravenous immunoglobulins

The mechanisms of action by which IVIG exert its immunomodulatory and anti-inflammatory effects remain unclear. Among their pleiotropic effects and in the field of CAPS, it is important to highlight the suppression or neutralization of autoantibodies, suppression or neutralization of cytokines and blockade of leukocyte-adhesion-molecule binding [35]. Therefore, IVIG may be effective to achieve a prompt reduction of aPL titer in some patients and decrease the levels of proinflammatory cytokines.

There is no recommendation on the dose ranging from 400 mg/kg daily (~25 g/day) for 5 days or a total dose of 2 g/kg of body weight, administered over a period of 2 to 5 days on a monthly basis.

In our experience, IVIG are administered together with PE. Specifically, the day after PE session, the patients receive IVIG (200 mg/kg) in order to prevent the removal of IVIG by PE.

### Cyclophosphamide

The rationale for the use of cyclophosphamide in CAPS is the reduction of aPL production. Cyclophosphamide was used in a third of episodes of CAPS, mostly as an IV pulse but also as an oral dose. There was no statistically significant difference between patients who died and those who survived with regard to the dosages and routes of administration of this drug. Moreover, the addition of cyclophosphamide to combined therapy did not demonstrate additional benefit [11]. In other words, it seems that cyclophosphamide do not play a role in the therapy strategy of CAPS.

However, Bayraktar *et al.* [4], based on a logistic regression analysis, demonstrated that cyclophosphamide was associated with increased mortality in patients with primary CAPS but improved survival in those patients with SLE-associated CAPS.

In the light of these results, this drug might be used in cases of SLE patients with severe CAPS. Given the data in other autoimmune diseases such as renal involvement of SLE or antineutrophil cytoplasmic

antibody-associated vasculitis, the recommended regimen should be a monthly (750 mg/m<sup>2</sup>) or every 2 weeks (500 mg) intravenous pulse during 6 or 3 months, respectively.

### Future perspective

Last year an increase activity in the search for new treatment for systemic autoimmune diseases arose. Several factors may have contributed to this progress. First, advance in basic science lead to a substantial understanding on the pathogenic mechanisms of these conditions. Concurrently, basic science progress in turn generated new ideas for new biologic-based immunotherapies development, which have been included in the treatment armamentarium giving a pragmatic perspective of possible new uses. However, very few clinical trials have been driven regarding on biologic therapies use to treat or prevent the clinical manifestations associated to APS.

### Rituximab

Rituximab is a chimeric monoclonal antibody against a surface protein expressed on the cytoplasmic membrane of B cells (CD20). It is currently approved for the treatment of chronic lymphocytic leukemia, diffuse large B-cell, advanced follicular lymphoma, rheumatoid arthritis refractory to infliximab and severe vasculitis remission induction [36]. In addition, rituximab has been extensively used for the treatment of several other autoimmune diseases [37–39]. There is a widely held belief among clinicians that anti-CD20 therapy is effective in rheumatologic conditions based on personal and published experience. Although, two randomized controlled trials failed to demonstrate its effectiveness in SLE, rituximab showed to be safe in an open-label trial with APS patients and appear to add some benefit controlling noncriteria manifestations such as thrombocytopenia, skin ulcers, nephropathy and cognitive dysfunction [40]. Furthermore, rituximab seem to be able to decrease recurrence rate in patients with recurrent thrombosis or refractory thrombocytopenia due to classical APS [41]. Although some authors saw a decrease in IgG aCL antibodies titers in patients with APS who received rituximab [42], a previous study failed to show any statistically significant change in aPL profile after 12-month of follow-up [40]. Indeed, aPL titers in the former study seem to be in concentrations below the diagnosis cut off of APS.

Rituximab has been proposed as an alternative second line therapy facing refractory or recurrent cases of CAPS [5]. However, it will be difficult to prove its effectiveness because a classical randomized controlled trial can hardly ever be driven. Nevertheless, the analysis of 20 cases treated with rituximab assembled in the



CAPS Registry showed that 80% of them recovered from the CAPS [5,12]. Moreover, most of them did not present further episodes of thrombosis although their follow-up was not always available and highly variable. Even though the small number of patients treated with rituximab and the lack of a control group in the analysis hamper any definitive conclusions, a clear decrease in mortality rate published up-to-date (50%) draws a positive trend. Indeed, in light of these results, rituximab has even been proposed as first line therapy in patients with CAPS and is nowadays used in refractory cases of CAPS. Probably, future experience will allow us to proof its effectiveness in severe cases of CAPS to avoid continuous stimulation of B cells that carries on their maturation to plasmatic cell and endless aPL flood.

During the last 14th International Congress on aPL, the members of Task Force on CAPS stated that rituximab had a good safety profile in patients with CAPS with a variable effect on the aPL profile. In fact, one conclusion was that rituximab may have a role as a second-line therapy in patients refractory to standard triple therapy [12].

### Ecuzumab

The pathophysiology mechanism underlying thrombosis in APS and CAPS remains unknown. Some authors have argued that complement inhibitory properties of heparin rather than its anticoagulant effect prevent pregnancy loss in obstetric APS. Complement activation results in C3 cleavage into C3a and C3b by the C3 convertases. C3b facilitates phagocytosis and participates in the assembly of the C5 convertases which cleave C5 into C5a and C5b. C5a stimulates expression of tissue factor (monocytes, neutrophils, endothelial cells) while C5b participates in the assembly of membrane attack complex (C5b-9) on the surface of cells [43]. Sublytic concentration of membrane attack complex stimulates endothelial cells adhesion molecules expression and induces apoptosis. These events lead to endothelial cell detachment, type IV collagen exposure and subsequent triggering of the indirect clotting pathway. Additionally, complement binding to receptors on endothelial cells has been found to upregulate tissue-factor synthesis. Further, C3 knock out mice to whom aPL were administered and vein pinch injury performed showed shorter thrombi formation than the controls with normal complement [44] and a similar effect was observed in C5 null mice. Moreover, mice treated with monoclonal anti-C5 antibody seem to develop smaller thrombi [45]. Additionally, inhibition of the complement cascade at the level of C5 preserves C3b-mediated opsonization of infectious agents as well as immune complexes, thus preserving a nearly

normal immune response. Thus, a targeted therapy against complement offers an attractive therapeutic approach to APS and especially in CAPS where often an infectious trigger is found [46].

Ecuzumab is a humanized monoclonal antibody against complement protein C5 approved by the US FDA for the treatment of paroxysmal nocturnal hemoglobinuria and for atypical hemolytic uremic syndrome.

Ecuzumab binds with high affinity to C5 complement protein inhibiting its cleavage and, thus, preventing the generation of C5b-C9 complex generation. Atypical hemolytic-uremic syndrome and CAPS classically present clinically as a thrombotic storm with small vessel thrombosis and thrombotic microangiopathic anemia [47]. Renal transplant has been contraindicated in patients with end-stage renal diseases due to CAPS owing to the risk of recurrence. However, recently, Lonze *et al.* reported successful renal transplant in a patient with a previous history of CAPS using ecuzumab together with anticoagulation and standard immunosuppression as a prophylactic therapy [48]. In this regard, a Phase II open label clinical trial (NCT01029587) was approved in order to prove the efficacy and safety of ecuzumab to prevent recurrence in patients with previous history of CAPS who undergo a renal transplant. However, this trial is not recruiting patients anymore because the small incidence of this condition precludes enrollment of enough patients to conduct the trial.

Recently, some authors have reported its use in patients with refractory or recurrent episodes of CAPS with great success [6,7,48,49]. Although they are only case reports and larger experience is needed to define ecuzumab place in CAPS therapeutics it seems to be an attractive promising treatment for patients who develop a CAPS or at least to prevent its recurrence in high-risk situations. Expected future economic cost drop will increase its use in refractory catastrophic situations leading to an increased physician experience and allowing its wide use as a first line therapy for CAPS. Simultaneously, this will provide some insights on the probable role of complement in this catastrophic manifestation of APS.

### Intracellular signal modulation

Recently, the mammalian target of rapamycin (mTORC) pathway has been proposed to be a key step in the vascular stenosis that results from mechanical endothelial injury of patients with CAPS [50]. mTORC is a large protein kinase ubiquitously and constitutively expressed [51]. It associates with various proteins to generate two structurally and functionally distinct complexes termed mTOR complex 1 (mTORC1) and

mTORC2 [52]. Under high nutrient supply, mTORC1 promotes protein synthesis, lipogenesis and energy metabolism [53]. Endothelial intimal hyperplasia in kidney biopsies from patients with APS nephropathy was associated to mTORC pathway activation despite adequate anticoagulation [54]. Further, mTORC pathway activation and endothelial cell proliferation was proved in both carotid and left anterior descending arteries of patients with CAPS [54]. Hence, mTORC pathway activation by aPL seems to drive part of the vascular injury noted in patients with CAPS although the mechanism through what aPL lead to cell activations remains unknown.

Sirolimus is a macrolide antibiotic produced by *Streptomyces hygroscopicus*. Initially, it was evaluated as an antifungal, but later, it proved to be a potent immune-suppressant. In 1999, sirolimus was approved for the regulatory agencies as a treatment to prevent acute renal transplants rejection. Later, sirolimus has shown to be able to avoid restenosis in patients undergoing percutaneous coronary intervention when eluted from stent. Indeed, sirolimus-eluting stents are currently in use as a potent antiproliferative drug in patients to avoid arterial restenosis. However, some evidence points to a prothrombotic effect of mTORC inhibitors and thus its potential benefit in patients with CAPS remains as a matter of debate [55].

Simultaneously, some new pathways are being traced which point to possible new therapeutic targets. Bacterial infection and lipopolysaccharides released are known to induce intracellular signaling through Toll-like receptor 4. It leads to tissue factor and adhesion molecules upregulation, which probably accounts for some of the clinical manifestations seen in disseminated intravascular coagulation and probably in CAPS triggered by infections. Steroids are known to block nuclear translocation of NF- $\kappa$ B and although they seem to be of small benefit in sepsis [56], they proved to improve patients' outcome when they are used in patients with CAPS [11]. In this sense, an specific proteasome inhibitor MG-132 has been shown to inhibit the thrombotic properties of aPL in mice [57]. However, its usefulness in patients with APS has not yet been proved.

### New oral anticoagulants

In recent years, new oral anticoagulants such as rivaroxaban, dabigatran and apixaban have been approved. They offer several potential advantages over vitamin K antagonists because they are able to inhibit a single clotting factor either thrombin or factor Xa. They overcome some limitations of vitamin K antagonists because they have fewer interactions with food and other drugs and do not need periodic

control because they can be prescribed at fixed doses. Furthermore, there is an on-going trial evaluating the safety of these new oral anticoagulants in patients with thrombotic APS, which will give some light on its possible role in patients with APS. However, we still think that in CAPS unfractionated heparin or low molecular weight heparin should be used due to its recognized fibrinolytic effects and its recognized effects on the complement system.

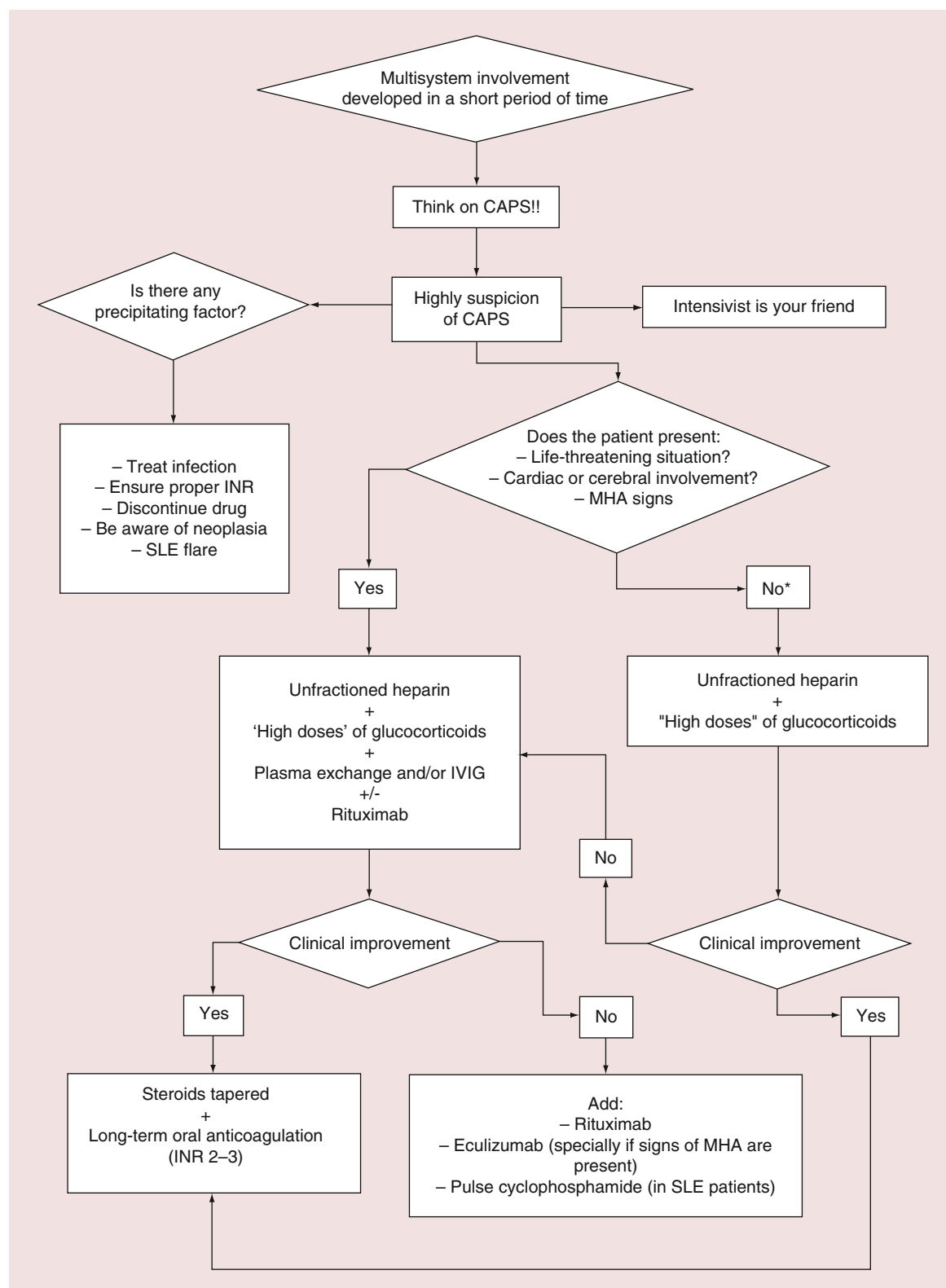
### Conclusion

What is the best strategy in treating CAPS? The first important point is to suspect this condition in front of a patient with multisystem involvement and signs of microangiopathic anemia. The second step is to identify and treat some precipitating factor, especially infection. Do not forget drugs, neoplasia or SLE flares. Be aware of bridging therapy in cases of surgery or diagnostic procedures such as renal biopsies. The third step is to decide if the patient needs supportive measures, in other words, do you need to talk with your colleague of intensive care unit?

Given the published evidence, AC is the essential treatment and the triple therapy remains the treatment strategy associated with highest survival of CAPS. The triple therapy refers to the administration of AC + GC + PE or IVIG and it would be the treatment of choice if the patient presented a life-threatening situation, severe organ involvement such as cerebral or cardiac manifestations or signs of microangiopathic hemolytic anemia (remember searching of schistocytes) (Figure 1). In those cases without these parameters, AC + GC might be sufficient. Keep in mind cyclophosphamide if the patients had associated SLE.

However, current mortality rate for CAPS is still unacceptably high and optimizing current approaches by other therapies seems mandatory. In those cases with a severe presentation in the beginning or those refractory to triple therapy, rituximab may be an add-on treatment. Eculizumab may be the chosen option if the signs of THMA are present.

New experimental treatments have shown apparent success although they have only been tested in a few cases, giving limited evidence of its effectiveness. Thus, the curative treatment for APS might still be a long time away. In the meantime, some new approaches with promising outcomes appear on the horizon giving some hope on the treatment while simultaneously providing some light on the pathways that lead to this dramatic situation. However, much work remains to be done to define the best approach to this condition and many questions need to be answered in the near future (Box 1).



**Figure 1. Current approach of patients with suspected catastrophic antiphospholipid syndrome.**  
CAPS: Catastrophic antiphospholipid syndrome; INR: International normalized ratio; MHA: Microangiopathic hemolytic anemia; SLE: Systemic lupus erythematosus.



**Box 1. Research agenda for the future.**

- Collect blood and serum during acute episodes in order to perform mechanistic studies.
- Need to identify the triggers that could be treated concurrently in order to avoid this catastrophic situation.
- Evaluate the best steroid dose and the tapering schedule in patients with catastrophic antiphospholipid syndrome (CAPS).
- Provide data on the best replacement fluid during the plasma exchange sessions in patients with CAPS.
- Assess the best therapeutic dose and moment to administrate intravenous immunoglobulins in patients with CAPS.
- Delineate the role of new anticoagulants on the treatment of patients with CAPS.
- Assess the role of rituximab on the management of patients with CAPS.
- Define the effectiveness of adding eculizumab to standard triple therapy with or without thrombotic microangiopathy.
- Need for more data on switching regimens in cases of treatment failure.
- Need to identify new specific targets on the CAPS cascade in order to design new treatments with best safety profile.

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**Executive summary****Current approach**

- Current best therapeutic approach for catastrophic antiphospholipid syndrome (CAPS) is the so-called triple therapy, which includes the administration of anticoagulation + glucocorticoids + intravenous immunoglobulins and/or plasma exchange.

**Future perspective**

- Rituximab has been proposed as first-line therapy in cases of severe CAPS and those for recurrent and refractory cases of CAPS as second-line treatment.
- Eculizumab has been used in patients with CAPS in order to prevent new events following kidney transplant and in patients with CAPS refractory to standard therapy with favorable outcomes.
- Several new intracellular pathways are being recognized to be involved in CAPS pathogenesis. Some of them might offer an opportunity to develop new therapeutic weapons against this catastrophic situation although none of them has yet been proved in patients with CAPS.

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