Current management of catastrophic antiphospholipid syndrome

The catastrophic variant of the antiphospholipid syndrome (APS) is the most severe form of APS with acute multiple organ involvement and small vessel thrombosis. At present, there are no studies on the pathophysiological mechanisms of catastrophic APS. The two theoretical explanations for the clinical manifestations of catastrophic APS are the development of thrombosis and the systemic inflammatory response syndrome (SIRS). From retrospective study data, first-line therapies should always include the combination of anticoagulation against thrombosis plus glucocorticoids against manifestations of SIRS plus plasma exchange and/or intravenous immunoglobulins to remove or block the antiphospholipid antibodies and cytokines involved in the SIRS. This review is focused on current management of catastrophic APS and some of the potential new therapeutic approaches.

**KEYWORDS:** anticoagulants catastrophic antiphospholipid syndrome future perspectives intravenous immunoglobulins plasma exchange treatment

The catastrophic variant of the antiphospholipid syndrome (APS) is the most severe form and is characterized by clinical evidence of multiple organ involvement developing over a short period of time, histopathological evidence of small vessel occlusions and laboratory confirmation of antiphospholipid antibodies (aPL) as assessed in 2003 in the international consensus statement on the classification criteria for this condition [1].

Recently, our group has updated the diagnostic algorithms of catastrophic APS in a step-by-step approach [2]. Data such as previous history of APS or persistent aPL positivity, the number of organs involved by thrombosis developing in less than a week, the biopsy diagnosis of microthrombosis, and finally, other explanations for multiple organ thromboses and/or microthrombosis should be considered in the diagnostic approach.

From the pathophysiologic point of view, catastrophic APS is a thrombotic microangiopathic condition, characterized by a diffuse thrombotic microvasculopathy with a predilection for the lungs, brain, heart, kidneys, skin and GI tract [3]. Another specific characteristic of catastrophic APS is that 60% of patients appear to have a triggering factor, especially infections (present in up to 25% of cases), anticoagulation withdrawal or following a surgical procedure, a biopsy in patients with neoplasia or immunizations [3].

However, the reasons as to why a minority of patients with aPL develop a multiorgan failure syndrome are unknown. At present, there are no studies on the pathophysiological mechanisms of catastrophic APS. Theoretically, there are two possible explanations of the clinical manifestations of catastrophic APS: first, the vascular occlusions in these patients might be themselves responsible for the ongoing thrombosis, as clots continue to generate thrombin, fibrinolysis is depressed and there is consumption of the natural anticoagulant proteins [4]; second, the manifestations of the systemic inflammatory response syndrome (SIRS), which are presumed to be due to excessive cytokine release from affected and necrotic tissues [5].

Which are the main causes of mortality of patients with catastrophic APS? Among the first 250 patients included in the website-based international registry of patients with catastrophic APS (CAPS Registry; freely accessed at [10]), 114 (46%) died at the time of the catastrophic APS event, which was identified as the cause of death in 80 of them. Cerebral involvement was the most frequent cause of death (27.2%), followed by cardiac involvement (19.8%), infection (19.8%) and multiorgan failure (17.3%) (Table 1) [6]. In other words, almost half of the patients died due to thrombotic events such as stroke or to SIRS such as acute respiratory distress syndrome or encephalopathy [7].

The current treatment of catastrophic APS is based on this empirical pathogenic basis. Besides identification and treatment of any precipitating factor, first-line therapies should always include the combination of anticoagulation against thrombosis plus glucocorticoids against manifestations of SIRS plus plasma exchange and/or intravenous immunoglobulins to remove or block the antiphospholipid antibodies and cytokines involved in the SIRS.
Table 1. Major cause of death of patients with catastrophic antiphospholipid syndrome.

<table>
<thead>
<tr>
<th>Major cause of death</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Cerebral involvement</td>
<td>22 (27.2)</td>
</tr>
<tr>
<td>- Stroke</td>
<td>15 (18.5)</td>
</tr>
<tr>
<td>- Cerebral hemorrhage</td>
<td>4 (4.9)</td>
</tr>
<tr>
<td>- Encephalopathy</td>
<td>3 (3.7)</td>
</tr>
<tr>
<td>Cardiac involvement</td>
<td>16 (19.8)</td>
</tr>
<tr>
<td>- Cardiac failure</td>
<td>14 (17.3)</td>
</tr>
<tr>
<td>- Arrhythmias</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Infection</td>
<td>16 (19.8)</td>
</tr>
<tr>
<td>- Bacterial sepsis</td>
<td>10 (12.3)</td>
</tr>
<tr>
<td>- Fungal sepsis</td>
<td>3 (3.7)</td>
</tr>
<tr>
<td>- Pneumocystis jiroveci pneumonia</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>- Suppurative peritonitis</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Multorgan failure</td>
<td>14 (17.3)</td>
</tr>
<tr>
<td>Pulmonary involvement</td>
<td>8 (9.8)</td>
</tr>
<tr>
<td>- Acute respiratory distress syndrome</td>
<td>6 (7.4)</td>
</tr>
<tr>
<td>- Pulmonary embolism</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>- Pulmonary hemorrhage</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Abdominal involvement</td>
<td>4 (4.9)</td>
</tr>
<tr>
<td>- Liver failure</td>
<td>3 (3.7)</td>
</tr>
<tr>
<td>- Acute abdomen</td>
<td>1 (1.2)</td>
</tr>
</tbody>
</table>

was related to a lower rate of recovery (18.2 vs 58.1% of episodes not treated with glucocorticoids; p = 0.01); more interestingly, 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; odds ratio [OR]: 2.25; 95% CI: 1.27–3.99) and the main explanation for this significant reduction of mortality was the more frequent use of combined treatment with anticoagulation plus glucocorticoids plus plasma exchange and/or IVIG. Therefore, our study was in accordance with and confirmed the international consensus on guidelines for the management of catastrophic APS.

At this point, we could question the rationale for the use of the above agents in patients suffering catastrophic APS. In addition, due to the absence of controlled studies, some recommendations based on the experience and personal opinion of the authors are presented.

Anticoagulation
Anticoagulant treatment was the most frequent treatment, being used in 85% of episodes of catastrophic APS [6]. Recovery occurred in 63.1% of the catastrophic APS episodes treated with anticoagulation versus 22.2% in episodes not treated with anticoagulation (p < 0.0001; OR: 5.98; 95% CI: 2.84–13.80). There was no statistically significant difference between those patients who died and those who survived depending on the types of anticoagulation received (unfractioned heparin in 61% of episodes, oral anticoagulation in 42% and low-molecular-weight heparin in 13%).

Obviously, the rationale of the anticoagulation use in catastrophic APS is the same as in classic APS: the inhibition of clot formation and, mainly, lysis of existing clots. In the acute phase of catastrophic APS, the recommendation is for use of unfractioned or low-molecular-weight heparin. After the acute phase, patients with catastrophic APS should be maintained under oral anticoagulation for the long term in order to avoid recurrent thrombosis. In this sense, our group demonstrated that 66% of patients who survive an initial catastrophic APS event remained symptom free with anticoagulation during an average follow-up of 67.2 months [12]. The best target international normalized ratio (INR) is unknown but a minimum of 2.0 may be advisable.

Glucocorticoids
Glucocorticoids were used in 79% of episodes of catastrophic APS (in form of intravenous pulses of 500–1000 mg/day for 1–3 days in 34% and intravenous immunoglobulins (IVIG) to remove or block the aPL and the cytokines involved in the SIRS (Figure 1) [8].

The purpose of this evidence-based review is to focus on current management of catastrophic APS. In addition, we will discuss some of the potential new therapeutic approaches.

Current management of catastrophic APS: lights & shadows
Until now, there is an absence of prospective and randomized therapeutic studies in catastrophic APS. In fact, the evidence-based information about the current treatment of patients with catastrophic APS comes from three retrospective studies [6,9,10]. From the information extracted from the first two studies involving 130 patients, an international consensus on guidelines for the management of catastrophic APS was proposed [1,11]. Our group also analyzed the 250 patients included in the CAPS registry from January 2000 to February 2005 [6]. The main results were the following: the higher recovery rate was achieved by the combination of anticoagulation plus glucocorticoids plus plasma exchange (77.8 vs 55.4% in the remaining patients, p = 0.083), followed by anticoagulation plus glucocorticoids plus plasma exchange and/or IVIG (69 vs 54.4% in the remaining patients, p = 0.089); treatment with cyclophosphamide did not demonstrate an additional benefit; isolated use of glucocorticoids
as oral or intravenous dosages of 1–2 mg/kg/day in 34% of episodes, respectively). There was no statistically significant difference regarding the range of glucocorticoid doses [6].

The rationale for the use of glucocorticoids is based on their anti-inflammatory properties inhibiting the theoretical excessive cytokine response related to SIRS via reduction of the transcription of pro-inflammatory genes by inhibiting the NF-kB [13]. In fact, NF-kB is recognized as the principal driver of the inflammatory response and is responsible for the transcription of more than 100 genes, including TNF-α, IL-1β, and IL-6 [14].

Early use of glucocorticoids is recommended but the initial dose is unknown. Possibly, if a patient presents with obvious clinical manifestations of SIRS, such as acute respiratory distress syndrome or encephalopathy, daily intravenous pulses of methylprednisolone for 3 or 5 days are advised, followed by prednisone at doses of 1 mg/kg/day. The best practice for tapering of glucocorticoids is unknown and common sense should guide the rate of glucocorticoid decrease. Possibly, a dose of 7.5–10 mg/day of prednisone at 6 months after acute episode of catastrophic APS would be appropriate to avoid the adverse effects of glucocorticoids. In addition, in patients with primary APS, the cessation of glucocorticoid treatment should be the rule.

**Plasma exchange**

Therapeutic plasma exchange was used as treatment in 73 of the 242 episodes of catastrophic APS (30%) [6]. The usefulness of plasma exchange is based on the removal of pathological aPL and mediators of SIRS development such as cytokines, TNF-α and complement activation products [15].

The recommendation is to start plasma exchange as soon as possible. In fact, the recently published guidelines on the use of therapeutic apheresis in clinical practice evidence-based approach from the American Society for Apheresis suggests plasma exchange as a treatment of catastrophic APS with a category II (that is, as disorder for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment) [16]. However, the grade of this recommendation is low (2C, based only on observational studies or case series).

Which is the best plasma exchange protocol? Regarding the literature, there have been several different types published. Marson et al. obtained good results in two patients with a daily session frequency in the first 3 days, tapered until three sessions weekly, according to clinical condition, and finally stopped when remission of thrombotic-embolic disorder is obtained [17]. Specifically, one patient received six plasma exchange sessions in a 10-day period and the other received five sessions in 8 days. The same group added two more patients 1 year later with similar satisfactory results. Interestingly, one patient received 86 sessions in an 18-month period and the remaining 33 sessions in a 5-month period [18].

Which is the best replacement fluid for plasma exchange? Based on CAPS registry data, the majority of the studies that specified the type of replacement fluid used fresh frozen plasma (FFP), while few studies used albumin solution [15]. In fact, the 2003 international consensus statement on catastrophic APS [11] and the American Society for Apheresis 2010 guidelines [16] recommended FFP as a replacement fluid for plasma exchange in patients with catastrophic APS. However, these indications were designed taking into account the microangiopathic involvement overlapping with other microangiopathic conditions such as thrombotic thrombocytopenic purpura (TTP). In fact, plasma exchange with FFP as replacement fluid is indicated for all patients with suspected TTP, and is the most important component of treatment. However, in contrast with TTP, where the infusion of healthy plasma, in addition to the removal of the patient’s plasma, is very important for recovery, in the case of catastrophic APS...
removal of the plasma containing aPL may be enough to establish remission without the need for the infusion of healthy plasma. Moreover, FFP contains clotting factors that could counteract the anticoagulant treatment. Conversely, albumin solution is almost free of side effects and therefore may also minimize potentially serious and undesirable transfusion reactions from multiple units of plasma. In light of these data, it might be advisable to begin treatment of a catastrophic APS with plasma exchange using 5% albumin as a replacement fluid and only when there is a lack of prompt response or in the presence of schistocytes (that is, in the presence of microangiopathic hemolytic anemia) consider the use of FFP [19].

**Intravenous immunoglobulins**

Intravenous immunoglobulins were used in 21% of episodes of catastrophic APS. They have pleiotropic and beneficial effects such as the blockade of autoantibodies, the increased clearance of pathologic IgG and the modulation of complement. Additionally, they protect against autoantibody-mediated pathology by upregulating an inhibitory Fcγ receptor on macrophages and suppress pathogenic cytokines [20,21].

In our therapeutic protocol, plasma exchange are started as early as possible and performed every other day with a minimum of six sessions. The day after each plasma exchange session, we administer IVIG (200 mg/kg/day) in order to prevent the removal of IVIG by plasma exchange.

**Cyclophosphamide**

Cyclophosphamide was used in 31% of episodes (30.9%) and was given as an intravenous pulse in 40 episodes (53.3%) and as an oral dose (50–100 mg/day) in ten (13.3%). Route of administration was not specified in the remaining 25 episodes. There was no statistically significant difference between patients who died and those who survived with regard to the administration of cyclophosphamide, either in its dosages or routes of administration. Moreover, the addition of cyclophosphamide to the combined treatment showed no benefit [6].

However, Bayraktar et al. demonstrated that cyclophosphamide use was associated with increased mortality in patients with primary catastrophic APS but improved survival in those with systemic lupus erythematosus (SLE) [22]. Therefore, cyclophosphamide may play a role in SLE patients with catastrophic APS as an immunosuppressant reducing the titer of pathogenic aPL. In the light of results from studies that compare the two methods of cyclophosphamide administration (oral and intravenous) in patients with lupus nephropathy [23] and systemic vasculitis [24], the recommendation is the use of intravenous pulses of cyclophosphamide. This modality of treatment has the same efficacy with fewer adverse events.

**Identification & treatment of precipitating factors**

The most frequent precipitating factor in patients with catastrophic APS is infection, present in 22% [25]. Therefore, the recommendation in patients with a suspected episode of catastrophic APS is to look for the existence of a septic process and use antibiotic therapy if appropriate. However, the diagnosis of infection may be difficult. Frequently, fever and acute phase reactants, such erythrocyte sedimentation rate or leucocytosis, may be present in both catastrophic APS and infection. Elevated C-reactive protein and procalcitonin may be useful to diagnose an infection in these patients. The etiology of infection may be diverse and includes viral infections of upper respiratory tract, bacterial infections such as typhoid fever, urinary infections, malaria, dengue and sepsis [25].

In the context of patients with catastrophic APS, another point of controversy is the high risk of infection associated with immunosuppressive treatment and the role of prophylactic antibiotic therapy. At present, there are no evidence-based data to recommend this prophylactic therapy in all patients with catastrophic APS. Some authors recommend to individualize the antibiotic use in the presence of neutropenia, keeping in mind the development of microbial resistance or pseudomembranous diarrhea [26].

In patients with known thrombotic APS, anticoagulant treatment as secondary thromboprophylaxis should be maintained under an adequate INR (>2.0). Moreover, this is very important because in the last review, anticoagulation withdrawal or low INR were the precipitating factors in 8% of catastrophic episode of APS [25]. Therefore, physicians treating patients with known APS should bear in mind clinical situations in which anticoagulant treatment should be stopped, such as surgery, biopsy or dental extractions [27].

**Future perspective**

The future management of catastrophic APS is based on two points: to improve the knowledge of pathologic processes leading to multiple thrombosis in patients carriers of aPL, but also to improve...
the knowledge of intracellular mechanisms of aPL-mediated thrombosis. Better understanding of how aPL promotes thrombosis will help us to design more specifically targeted antithrombotic or immunomodulatory therapies.

Regarding the second point, some of these new proposed potential therapies are statins (fluvastatin diminished thrombus size in aPL-treated mice [28] and was able to reverse the expression of inflammatory proteins in a pilot proteomics analysis of 25 APS patients [29]), rituximab (effective for treating thrombocytopenia, hemolytic anemia, and recurrent thrombosis in aPL-positive patients [30]), antagonists of IIb/IIIa platelet membrane glycoproteins, p38 mitogen-activated protein kinase inhibitors, and anticytokine agents. However, no human data are available yet to support these three last therapeutic modalities.

There are few data on new therapeutic approaches from case reports. At present, nine patients with catastrophic APS have been treated with rituximab [31–38]. Specifically, they were six women and three men with a range of age between 3 months and 69 years. Only two of them had SLE and APS previously. Rituximab was used in a different fashion, including 375 mg/m² once weekly for 4 weeks or two infusions of 500–1000 mg 1 or 2 weeks apart, and all of them in different combination with anticoagulation, high doses of glucocorticoids, plasma exchange and IVIG. Only two of them died.

Recently, Lonze et al. reported a case of a 51-year-old man with end-stage renal disease due to catastrophic APS who received a live-donor renal transplantation [39]. In order to prevent a catastrophic episode of APS, he was enrolled in a protocol including prophylactic administration of eculizumab together with continuous systemic anticoagulation and standard immunosuppression.

Eculizumab is a humanized monoclonal antibody against complement protein C5 that binds to the C5 protein with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of membrane attack complex [40]. Eculizumab is approved by the US FDA and has been used extensively for the chronic treatment of paroxysmal nocturnal hemoglobinuria. Combined with plasma exchange, IVIG and rituximab, eculizumab inhibited the formation of the membrane attack complex and was useful as rescue therapy for a patient experiencing severe antibody-mediated renal rejection [41]. The pathogenic basis of eculizumab use in catastrophic APS would be to achieve complement blockade at the level of end-organ parenchymal microvasculature.

Based on this previous observation, the induction phase in the patient with catastrophic APS consisted of a preoperative loading dose of 1200 mg and weekly doses of 900 mg of eculizumab. Maintenance-phase administration of 1200 mg of eculizumab every 2 weeks was begun on day 21. Levels of aPL remained moderately elevated, and the patient continued to receive twice-monthly infusions of eculizumab [39].

Interestingly, eculizumab is being tested for its ability to prevent catastrophic APS after kidney transplantation in patients with a prior history of catastrophic APS in a clinical trial (NCT01029587) [102]. The investigators hypothesize that, by blocking the complement cascade using eculizumab, in conjunction with blocking the coagulation system, kidney transplantation can be safely and successfully performed in patients with a history of catastrophic APS.

**Financial & competing interests disclosure**

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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### Executive summary

- The catastrophic variant of the antiphospholipid syndrome (APS) is the most severe form of APS with acute multiple organ involvement and small vessel thrombosis.
- At present, there are no studies on the pathophysiological mechanisms of catastrophic APS.
- Almost half of patients with catastrophic APS died due to thrombotic events or systemic inflammatory response syndrome (SIRS) manifestations.
- Based on these data from the catastrophic antiphospholipid syndrome (CAPS) Registry, first-line therapies should always include the combination of anticoagulation against thrombosis plus glucocorticoids against manifestations of SIRS plus plasma exchange and/or intravenous immunoglobulins to remove or block the antiphospholipid antibodies and cytokines involved in SIRS.
- Novel therapies directed against antiphospholipid antibodies or some of the pathogenic processes involved in the development of thrombosis in APS are needed.
This consensus statement contains the requirements for the diagnosis and classification of catastrophic antiphospholipid syndrome (APS).


6. Original article reporting the outcomes of patients with catastrophic APS depending on the treatment that was used.


10. First large reported series of patients with catastrophic APS.


12. Second large reported series of patients with catastrophic APS.


Current management of catastrophic antiphospholipid syndrome


**Websites**

CAPS Registry
www.med.ub.es/MIMMUN/Forum/CAPS.HTM

Eculizumab to Enable Renal Transplantation in Patients With History of Catastrophic Antiphospholipid Antibody Syndrome
http://clinicaltrials.gov/ct2/show/NCT01029587