The Catastrophic Antiphospholipid Syndrome

20

Ignasi Rodríguez-Pintó, Gerard Espinosa, and Ricard Cervera

20.1 Introduction

The addition of the word "catastrophic" to the term antiphospholipid syndrome (APS) was proposed 20 years ago by Ronald Asherson when he published an editorial in The Journal of Rheumatology describing a group of patients who develop multiple thrombosis in a short period of time and with a much worse prognosis than that attributed to patients with classic APS [1]. Since then, many cases have been published reporting patients with this devastating variant of the APS.

The catastrophic APS (CAPS) is a rare disease that affects around 1 % (0.4–1.6 %) of patients with APS [2] but is associated with a high rate of mortality [3]. The majority of the knowledge on this disease has been provided by studying the cases included in the CAPS Registry. This is a database in a web-based format that includes all patients published or reported directly to the CAPS Registry Project Group with this condition. This registry was created in 2000 by the European Forum on Antiphospholipid Antibodies, a group of experts devoted to perform international collaborative studies on antiphospholipid antibodies (aPLs) [4]. The results are freely available in its web site (https://ontocrf.costaisa.com/en/web/caps). The CAPS Registry includes nowadays more than 500 cases from almost 200 published papers and 100 cases directly reported to the CAPS Registry Project Group.

According to the CAPS Registry, this syndrome affects mainly women with a female to male ratio of 3:1 and involves patients in their fourth decade of life, although cases in newborns and elderly patients have been reported [5]. CAPS is the first manifestation of APS in 56.4 % of patients, and most of them do not present any associated autoimmune disease. In the remaining patients, systemic lupus

I. Rodríguez-Pintó • G. Espinosa • R. Cervera (✉)
Department of Autoimmune Diseases, Hospital Clinic, Villarroel 170, Barcelona, Catalonia 08036, Spain
e-mail: ignasirodriguezpinto@gmail.com; gespino@clinic.cat; RCERVERA@clinic.cat

P.L. Meroni (ed.), *Antiphospholipid Antibody Syndrome: From Bench to Bedside*, Rare Diseases of the Immune System, DOI 10.1007/978-3-319-11044-8_20

erythematosus (SLE) is the autoimmune disease more frequently associated with CAPS, followed by rheumatoid arthritis, dermatomyositis, Behçet disease, or Crohns' disease [5].

20.2 Pathophysiology

The pathological mechanisms involving CAPS are not yet clearly understood [6]. The rarity of this syndrome hindered any effort to perform mechanistic studies, and CAPS is considered to have a multifactorial etiology, including a genetic background and environmental factors. In this sense, an association has been found between several polymorphisms of HLA class II genes and the development of aPLs. However, its role in APS pathogenesis and, especially, in CAPS has not been elucidated.

The role of aPLs in endothelial cell (EC) activation as a pathogenic mechanism of thrombosis in APS was first proposed by Meroni et al. [7]. Rashi et al. [8] later suggested that anti-β2-glycoprotein I (GPI) antibodies might mediate the activation of EC leading to an alteration in the endothelial phenotype and a switch to a procoagulant microenvironment.

Several explanations of these events have been proposed. Asherson and Shoenfeld [9] postulated the molecular mimicry hypothesis, suggesting that some peptides derived from β2-GPI recognized by aPLs might share some amino acid sequences with those found in several microorganisms. The aPLs were found to activate EC and monocytes when they are bound to β2-GPI. The activation of EC and monocytes upregulates the production of tissue factor leading to a procoagulant state [10].

However, no more than 15 % of general population patients with aPLs develop thrombosis [6]. Indeed, β2-GPI does not bind to unstimulated endothelium in vivo [11]. This observation lead to propose the "two-hit" hypothesis to explain the only occasionally clinical observation of thrombotic events in spite of the persistent presence of aPLs in these patients [12]. In this hypothesis, a "first hit" would induce a thrombophilic state but clotting would take place only in the presence of a "second hit." This "second hit" would be another thrombophilic condition that increases the risk for clot formation. The presence of an environmental trigger as a "second hit" has been reported in more than half of cases with CAPS [5]. The most frequent precipitating factor reported are infections, especially in the pediatric age [3, 13]. In this regard, both human monoclonal IgM and polyclonal IgG anti-β2-GPI antibodies were found to induce an endothelial signal similar to that induced through toll-like receptor 4 (TLR-4) activation. The TLR are a type of pattern recognition receptors. These are transmembrane receptors that recognize molecules that are broadly shared by pathogens but different from host molecules, collectively referred as pathogen-associated molecular patterns [14]. TLR4 is known to be essential for innate immune response to components of bacteria, mycobacteria, yeast, and virus [15]. It is expressed in the innate immune system cells surface and EC [16] and is known to be the main receptor in lipopolysaccharide (LPS) signal transduction [17]. Ligand binding to TLR4 triggers the MyD88-dependent pathway finally leading to

NF-κB and AP-1 [8] activation and resulting in transcription of inflammatory genes [18]. On the other hand, virtually all patients with sepsis have coagulation abnormalities [19]. These abnormalities range from subtle activation of coagulation only detectable by sensitive techniques through somewhat subclinical stronger coagulation activation evident by a small decrease in platelet count and prolongation of global clotting times to fulminant disseminated intravascular coagulation, characterized by widespread microthrombosis and profuse bleeding [20]. At the same time, proinflammatory cytokines are important in inducing a procoagulant effect by inducing tissue factor expression on mononuclear cells and EC, probably playing their role in increasing the risk for new thrombosis.

In 1998, Kitchens [21] proposed that intravascular coagulation itself could increase the risk to develop another thrombosis. In this theory, the blood clot would promote thrombin formation and fibrinolysis would become impaired by an increase of plasminogen activator inhibitor (PAI) type I. This would determine the consumption of natural anticoagulant proteins, such as protein C and antithrombin.

However, it is still unclear why some patients with aPLs develop thrombosis affecting large vessels, while others develop this catastrophic situation with simultaneous multiple vascular occlusions that affects predominantly small vessels. In CAPS, probably all these factors are interplaying in a procoagulant milieu that leads to this multiorgan thrombosis in small vessels observed in clinical practice. Some clinical manifestations 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. This, probably, at the same time closes the circle that leads to this devastating situation.

20.3 Precipitating Factors

As previously explained, in the two-hit hypothesis, the presence of a second thrombophilic state has been proposed to explain the observation of thrombosis in patients with circulating aPLs. Different triggers have been reported in as much as 2/3 of CAPS cases. The most common precipitating factors described are infections, followed by neoplasms, surgical procedures, and anticoagulation withdrawal or low international normalized ratio (INR) [3, 5, 22].

Different infectious agents are associated with CAPS. Among them, the most frequent reported are bacteria such as *Escherichia coli, Shigella sp., Salmonella, Streptococcus, Staphylococcus aureus, Klebsiella*, and herpes virus, affecting mainly the lungs and kidneys. Most of them are gram-negative bacteria, and, thus, these infectious agents might act co-signaling with aPLs the TLR signal that leads to the prothrombotic state and, finally, to CAPS.

Not surprisingly, neoplasms are the second most frequent precipitating factor in CAPS. Hematological malignancies are the oncological diseases more frequently associated with CAPS and, among them, Hodgkin's lymphoma. However, CAPS has been reported to be associated with carcinomas and sarcomas [23]. Malignancies have been linked to the development of circulating aPLs [24], and the increased risk

of cancer patients to develop thrombosis is well known since last century when Trousseau described the development of thrombophlebitis in these patients [25]. Several reasons have been proposed to explain the increased risk of thrombosis in cancer patients. For instance, blood flow stasis due to vascular invasion, immobilization, upregulation of thrombophilic substances by both tumor and endothelial cells, chemotherapy, and central venous devices have been proposed as conditions that might explain the increased frequency of thrombosis in these patients.

Surgery and trauma are found often associated with the development of CAPS in patients with APS. The increased postoperative risk of thrombosis after major general surgery or multiple trauma has been extensively documented [26, 27]. The inflammatory response to the surgery wound is thought to explain the increased risk described in these patients. Interestingly, pre-surgery measurement such as plasma exchange have been proposed in order to decrease aPL levels and, thus, reduce the thrombotic risk [22].

Other precipitating factors such as anticoagulation withdrawn, pregnancy, and postpartum period have been reported to be linked to a CAPS episode, but in lower frequency.

20.4 Clinical Manifestations

The development of multiple microvascular thrombotic occlusions with microangiopathic anemia and thrombocytopenia is a characteristic finding of patients with CAPS. As a systemic disease, CAPS can affect any organ or system. Clinical manifestations have been classically classified into those attributed to thrombosis itself and those attributable to the cytokine storm [28]. However, sometimes it is difficult to differentiate if a clinical manifestation is attributable to one or the other cause and many times both pathways may work together.

CAPS patients present frequently with renal failure and variable degrees of hypertension, although hypotension does not exclude the diagnosis. Some patients present with proteinuria and sometimes with hematuria [3, 5, 22, 29].

Pulmonary manifestations are reported in 2/3 of cases, classically characterized by acute respiratory distress syndrome (ARDS) attributed typically to the cytokines storm. Pulmonary emboli are associated with dyspnea, and, sometimes, the clinical picture is associated with pulmonary hemorrhage [3, 22, 29, 30].

Almost half of patients with CAPS present with consciousness deterioration manifested as encephalopathy. Many times, it is not clear if this manifestation could be ascribed to general hypoperfusion because of microthrombosis, to generalized shock, or to intracranial large vessel thrombosis. Nevertheless, some patients present with classical neurological deficits with motor or sensitive symptoms and an established stroke. Less often is the report of seizures, and, when present, many times they are associated with other manifestations [3, 22, 29].

Heart failure due to myocardium infarction, angina, or cardiac valvulopathy (Libman-Sacks endocarditis) is described in 50 % of cases, sometimes with

cardiogenic shock as part of multiorganic failure, with hypotension, tachycardia, and oliguria. The main valves affected are the mitral and the aortic valves. This condition is mainly reported as valvular insufficiency, and, sometimes, it leads to the requirement of valvular replacement. Intracavitary thrombosis has been seldom reported in patients with CAPS.

Skin complications in a form of livedo reticularis are very often reported; however, few of these cases develop skin necrosis with ulcers and digital ischemia [5, 22, 29].

Other organs affected are the peripheral vessels, the intestine, the spleen, the adrenal glands, the pancreas, the retina, and the bone marrow. Anecdotally, testicular/ovarian infarction, necrosis of the prostate, and acalculous cholecystitis have been reported [5, 22, 29].

20.5 Diagnosis

The differential diagnosis of patients with multiple thrombosis is not easy. Indeed, many times, several thrombophilic situations interplay together, leading to thrombosis in multiple sites throughout the organism.

Most cases of CAPS present as microangiopathic storm rather than large-vessel occlusion, although cases with large-vessel involvement have been reported. The presence of multiple occlusions should always rise the suspicion of a thrombophilic state. However, when this thrombosis presents in large vessels, the search for classical well-known risk factors for thrombosis should be performed. Typical risk factors for thrombosis include malignancy, surgery, obesity, immobility, pregnancy and oral contraception, and hereditary and acquired thrombophilias (i.e., aPLs, antithrombin, protein C and protein S deficiency, factor V Leiden and prothrombin G20210A mutations, and increased levels of several coagulation factors such as factor VIII, IV, or XI). Nevertheless, the microangiopathic storm that is common in CAPS leads to a deferent differential diagnosis that includes diseases characteristically associated with microangiopathy. Classically, the differential diagnosis of patients with CAPS includes severe infections, with or without disseminated intravascular coagulation (DIC), noninfectious-related DIC, thrombotic thrombocytopenic purpura (TTP) or hemolytic uremic syndrome, heparin-induced thrombocytopenia, HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, and scleroderma renal crisis.

Even when the presence of aPLs in patients with multiple thrombosis gives habitually the clue for the differential diagnosis of patients with this microangiopathic picture, the presence of aPLs is not pathognomonic of CAPS and have been reported in several other situations. However, when aPLs are found in other settings, they are almost always reported at lower levels [22, 31], but the clinical situation should always guide decision making.

Systemic severe infections may recall the clinical picture of CAPS, and sometimes both situations take place together: the first acting as a trigger of the second.

There is evidence that the activation of inflammation and coagulation in the context of severe sepsis can lead to thrombosis [32], and, at the same time, infections have proved to be able to lead to the development of aPLs [24]. However, although transient aPLs positivity at low levels can be found in severe infections, they have no clinical significance. Thus, the presence of high levels of aPLs should be taken as a highly specific finding for CAPS helping in the differential diagnosis between these two clinical situations [22].

DIC is not a disease entity itself but a complication of several disorders. The most commons disorders associated with DIC are infections, severe trauma, malignancy, and obstetric complications [33, 34]. DIC is characterized clinically by thrombosis and bleeding with coagulation factor consumption leading to coagulation times prolongation and fibrinogen consumption [35]. However, clinical and laboratory features of DIC have been observed in patients with CAPS [36]. Thus, it may not be possible to differentiate between these two clinical situations, and both situations might take place together.

Nevertheless, TTP represents the most difficult differential diagnosis of patients with CAPS. Renal and neurological clinical manifestations with anemia, thrombocytopenia, and the presence of schistocytes in peripheral blood smear can be found in both TTP and CAPS. However, even when the specificity of the ADAMTS-13 activity has been long debated in the literature [37], the presence of low levels of ADAMTS-13 activity might give the clue for the diagnosis of a TTP, while high levels of aPL should favor the diagnosis of CAPS.

Heparin-induced thrombocytopenia (HIT) is a rare but sometimes severe complication of heparin treatment that occurs 4–10 days after the initiation of a therapy with heparin. The severe form (type II) is a disorder characterized by the formation of autoantibodies against the heparin-platelet factor 4 (PF4) complex that binds to platelets leading to cell aggregation and activation [38]. The history of heparin administration and the presence of PF4 antibodies may let physicians to distinguish between these clinical situations [22].

HELLP syndrome is an endothelium disease that affects small vessels of hepatic circulation. It normally takes place at the end of the pregnancy, and sometimes it has been considered an expression of CAPS. However, the small number of patients with CAPS in the obstetric period makes it difficult to differentiate this clinical situation from the CAPS, and probably both clinical situations might favor each other.

Even when scleroderma renal crisis has been proposed as a possible differential diagnosis for patients with CAPS, the presence of classical sclerodermic cutaneous findings, of classical autoantibodies or, at least, the previous history of Raynaud's phenomenon in patients with systemic sclerosis, should differentiate these situations. Nevertheless, although rarely, the development of CAPS in patients with systemic sclerosis has been reported. In these patients, the determination of aPL levels and a renal biopsy are warranted in order to establish the diagnosis.

In this sense, in order to help physicians facing this difficult differential diagnosis, a set of diagnostic criteria for CAPS has been proposed during the 14th

Table 20.1 Diagnostic criteria for CAPS

1. Evidence of involvement of 3 organs, systems, and/or tissues
2. Development of manifestations simultaneously or in less than 1 week
3. Laboratory confirmation of the presence of aPL (LAC and/or aCL and/or anti-2GPI antibodies) in titers higher than 40 UI/l
4. Exclude other diagnosis
Definite CAPS:
All 4 criteria
Probable CAPS:
All 4 criteria, except for involvement of only 2 organs, system, and/or tissues
All 4 criteria, except for the absence of laboratory confirmation at least 12 weeks apart associable to the early death of a patient never tested for aPL before onset of CAPS
1, 2, and 4
1, 3, and 4 and the development of a third event in >1 week but <1 month, despite anticoagulation treatment

International Congress on Antiphospholipid Antibodies (Table 20.1). These criteria take into account the difficulty of performing biopsy in critical care settings, and thus, they do not require the biopsy for the diagnosis although it is highly recommended (Table 20.2).

20.6 Treatment

Due to its bad prognosis, when CAPS is suspected, an aggressive treatment is justified. However, there are no randomized controlled trials to guide the efficacy of the therapies, and data is based on the reported cases and the analysis of the CAPS Registry [39]. Classically, three aspects have been claimed as the basis to treat this situation. First, the so-called supportive general measures; second, the aggressive treatment of any identifiable trigger; and, finally, the specific treatment [39].

The general measures treatment refers to supportive care. It often includes intensive care unit (ICU) admission. Sometimes, intubation is necessary but, mostly, only ICU admission and tight control are necessary. Whenever possible, classical thrombotic risk factors should be avoided, and external pneumatic compression devices might be used when immobility is a concern. When major surgery aim is not taking out necrotic tissue to control the cytokine storm, surgery procedures should be postponed. Additionally, CAPS patients may benefit from glycemic control, stress ulcer prophylaxis, and blood pressure control [39].

Treatment of any precipitating factor is mandatory. When an infection is suspected, an adequately chosen antibiotic treatment should be started, taking into account the infection site, pharmacokinetics, and organism pharmacodynamics. At the same time, amputation and debridation of necrotic tissue might help in controlling the systemic inflammatory response [39–41].

Table 20.2 Differential diagnosis

	CAPS	TTP	HELLP	Sepsis	DIC	HIT
Previous history	Previous APS/SLE/malignancy/ pregnancy	Malignancy/non	Pregnancy	Infection	Infection/malignancy	Heparin exposure
Thrombosis	Large/small vessels	Small vessels	Small vessels	Large/small vessels	Small vessels	Large/small vessels
Typical antibodies	aPL	Anti-ADAMS-13	None	None	None	Anti-HP4
Schizocytes	Present	Present	Scanty	Scanty	Scanty	Scanty
Fibrinogen	Normal/high	Normal/high	Normal/high	Normal/low	Normal/low	Normal/high

Abbreviations: *TTP* thrombotic thrombocytopenic purpura, *HELLP* hemolysis, elevated liver enzymes, low platelet count, *DIC* disseminated intravascular coagulation, *HIT* heparin-induced thrombocytopenia, *aPL* antiphospholipid antibodies, *SLE* systemic lupus erythematosus

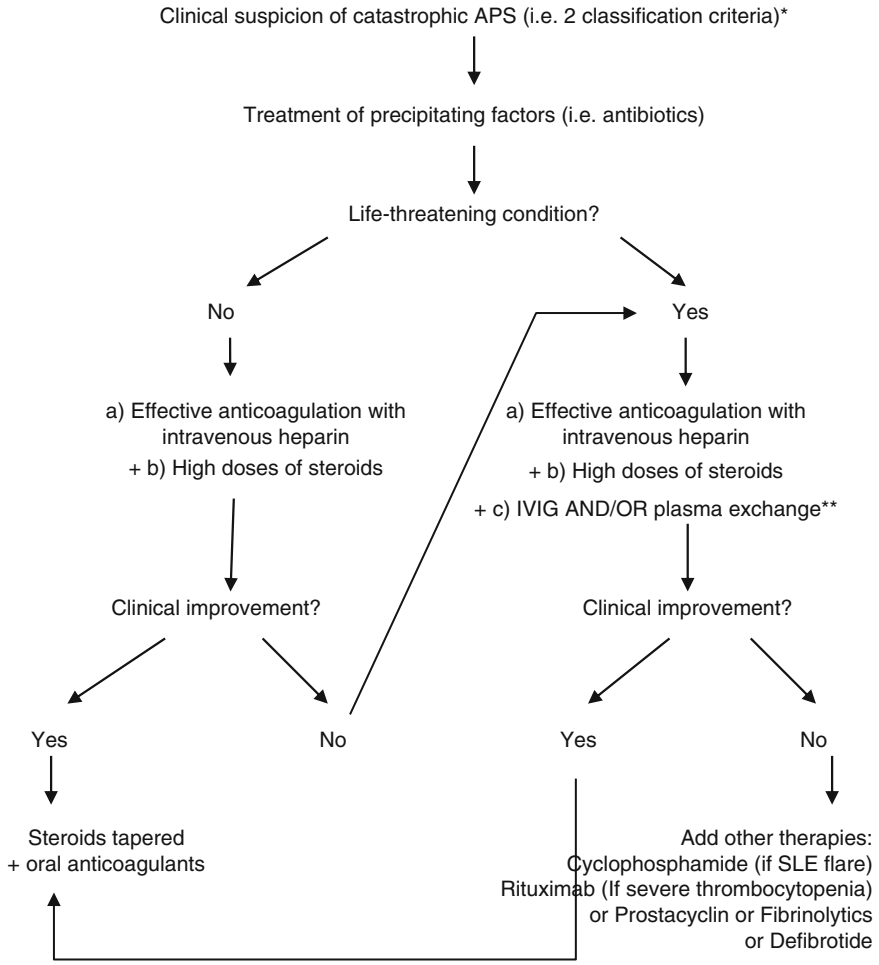
Since no randomized controlled trials have been conducted in CAPS, the specific treatment of this situation is based on the information provided by the analysis of the CAPS Registry and expert opinion. However, these data permitted the establishment of recommendations and the publication of a treatment algorithm [42].

Heparin is the mainstay of treatment in CAPS patients as it inhibits clot formation and lyses existing clots [22, 28, 30, 39, 43, 44]. Non-fractionated intravenous heparin is often chosen when the patient is in the ICU. Heparin does not only inhibit clot generation but also promotes clot fibrinolysis [45]. Additionally, heparin seems to inhibit aPL binding to their target on the cell surface [46]. Moreover, non-fractionated heparin enables throwback of its effect in case of necessity and it has an antidote. Thus, heparin is always the first line of treatment for thrombosis. Later, non-fractionated heparin can be switched to low molecular weight heparin (LMWH) and finally to oral anticoagulation. Nevertheless, physician should try to keep patients time long enough with heparin to favor clot fibrinolysis.

The combination of corticosteroids with anticoagulant therapy is the standard of care in CAPS treatment.

Many similarities have been observed between the clinical manifestations of patients with CAPS and systemic inflammatory response syndrome (SIRS). Since corticosteroids inhibit the nuclear factor (NF)-κB pathway and aPLs seem to signal NF-κB upregulation, beneficial effects of corticosteroids treatment have been invocated. However, in severe infections and in CAPS, no strong evidence has been found supporting corticosteroid use unless patients develop adrenal insufficiency [47, 48]. Until more studies analyzing the use of corticosteroids can be driven, the consensus treatment guidelines [22] should be followed [44], although there is no clear evidence on the route, dose, and duration of this treatment.

Only recently, the beneficial effects of intravenous immunoglobulins (IVIG) in primary APS have been proved. IVIG proved to decrease aPL titers and therefore, the thrombotic risk of these patients [49, 50]. However, IVIG and plasma exchanges were found few years ago to be a useful complementary tool for the treatment of patients with CAPS [51]. Their high economic cost and low availability may limit their use in patients with CAPS [52]. In this sense, an algorithm for the treatment of CAPS was published in order to guide physician facing these patients and establish treatment priorities [53]. This algorithm proposed to start specific treatment by handling independently each one of the main pathologic pathways. The authors recommended starting on anticoagulation and steroids as soon as the catastrophic situation is suspected. The former is given in order to stop the thrombophilic state and promote clot lysis and the later to downregulate the cytokine storm thought to be the one responsible for SIRS. When the patient is thought to be in a life-threatening condition, the authors suggested adding treatment with IVIG and/or plasma exchanges [53]. In case of active lupus manifestations, treatment with cyclophosphamide should be considered due to the better prognosis of these when they are treated with this drug. Cyclophosphamide is a nitrogen mustard-alkylating agent that binds to deoxyribonucleic acid in immune cells leading to cell death. Cyclophosphamide, probably, promotes the proliferation of T cells, suppression of helper Th1 activity, and enhances Th2 response (Fig. 20.1) [54].



*Consider exclusion of other microangiopathic syndromes (mainly thrombotic thrombocytopenic purpura and heparin-induced thrombosis/thrombocytopenia)
**With fresh frozen plasma, specially indicated if schistocytes are present

Fig. 20.1 Treatment algorithm of catastrophic APS. Abbreviations: *IVIG* intravenous immunoglobulins, *SLE* systemic lupus erythematosus

Rituximab is a chimeric monoclonal antibody against CD20, a surface protein expressed on the cytoplasmic membrane of B cells. Rituximab is approved for the treatment of B-cell non-Hodgkin lymphoma and rheumatoid arthritis [55]. However, it has been used extensively for the treatment of several other autoimmune diseases [56–58]. Although two randomized controlled trials failed to demonstrate its effectiveness in SLE, it seems to be safe for the treatment of APS. Rituximab has been

proposed as a second-line therapy when facing refractory CAPS cases with a relapsing course [59]. The analysis of 18 cases from the CAPS Registry showed that 80 % of them recovered from the CAPS episode in front of the 20 % who did not [22, 59]. Nevertheless, the small number of patients treated with rituximab makes difficult to propose definitive conclusions, but in light of these good results, rituximab has been also proposed as first-line therapy.

20.7 Prognostic

Despite aggressive treatment, mortality in patients with CAPS continues to be high [48]. It accounts for almost 30 % of cases according to the CAPS Registry data [3, 48, 60]. This disease normally have monophasic course, and most patients surviving a CAPS remain symptom free with anticoagulation, although some develop further APS-related events [61]. However, although rare, cases with a recurrent course have been reported. Of note, they present high prevalence of microangiopathic hemolytic anemia laboratory features [51, 62].

References

1. Asherson RA (1992) The catastrophic antiphospholipid syndrome. J Rheumatol 19:508–512
2. Cervera R, Piette J-C, Font J, Khamashta MA, Shoenfeld Y, Camps MT et al (2002) Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum 46:1019–1027
3. Cervera R, Rodríguez-Pintó I, Espinosa G (2014) On behalf of the Task Force on Catastrophic Antiphospholipid Syndrome. Catastrophic antiphospholipid syndrome: task force report summary. Lupus 23:1283–1285
4. Cervera R (2012) CAPS registry. Lupus 21:755–757
5. Cervera R, Bucciarelli S, Plasín MA, Gómez-Puerta JA, Plaza J, Pons-Estel G et al (2009) Catastrophic antiphospholipid syndrome (CAPS): descriptive analysis of a series of 280 patients from the "CAPS Registry". J Autoimmun 32:240–245
6. Ortega-Hernandez O-D, Agmon-Levin N, Blank M, Asherson RA, Shoenfeld Y (2009) The physiopathology of the catastrophic antiphospholipid (Asherson's) syndrome: compelling evidence. J Autoimmun 32:1–6
7. Meroni PL, Raschi E, Camera M, Testoni C, Nicoletti F, Tincani A et al (2000) Endothelial activation by aPL: a potential pathogenetic mechanism for the clinical manifestations of the syndrome. J Autoimmun 15:237–240
8. Raschi E, Testoni C, Bosisio D, Borghi MO, Koike T, Mantovani A et al (2003) Role of the MyD88 transduction signaling pathway in endothelial activation by antiphospholipid antibodies. Blood 101:3495–3500
9. Asherson RA, Shoenfeld Y (2000) The role of infection in the pathogenesis of catastrophic antiphospholipid syndrome–molecular mimicry? J Rheumatol 27:12–14
10. Vega-Ostertag M, Casper K, Swerlick R, Ferrara D, Harris EN, Pierangeli SS (2005) Involvement of p38 MAPK in the up-regulation of tissue factor on endothelial cells by antiphospholipid antibodies. Arthritis Rheum 52:1545–1554
11. Agostinis C, Biffi S, Garrovo C, Durigutto P, Lorenzon A, Bek A et al (2011) In vivo distribution of β2 glycoprotein I under various pathophysiologic conditions. Blood 118:4231–4238

12. Shoenfeld Y, Meroni PL, Toubi E (2009) Antiphospholipid syndrome and systemic lupus erythematosus: are they separate entities or just clinical presentations on the same scale? Curr Opin Rheumatol 21:495–500
13. Berman H, Rodríguez-Pintó I, Cervera R, Gregory S, de Meis E, Rodrigues CEM et al (2014) Pediatric catastrophic antiphospholipid syndrome: descriptive analysis of 45 patients from the "caps registry.". Autoimmun Rev 13:157–162
14. Janeway CA, Medzhitov R (2002) Innate immune recognition. Annu Rev Immunol 20:197–216
15. Kurt-Jones EA, Popova L, Kwinn L, Haynes LM, Jones LP, Tripp RA et al (2000) Pattern recognition receptors TLR4 and CD14 mediate response to respiratory syncytial virus. Nat Immunol 1:398–401
16. Allen KL, Fonseca FV, Betapudi V, Willard B, Zhang J, McCrae KR (2012) A novel pathway for human endothelial cell activation by antiphospholipid/anti-β2 glycoprotein I antibodies. Blood 119:884–893
17. Chow JC, Young DW, Golenbock DT, Christ WJ, Gusovsky F (1999) Toll-like receptor-4 mediates lipopolysaccharide-induced signal transduction. J Biol Chem 274:10689–10692
18. Xie H, Sheng L, Zhou H, Yan J (2014) The role of TLR4 in pathophysiology of antiphospholipid syndrome-associated thrombosis and pregnancy morbidity. Br J Haematol 164:165–176
19. Levi M, Schultz M, van der Poll T (2013) Sepsis and thrombosis. Semin Thromb Hemost 39:559–566
20. Levi M (2008) The coagulant response in sepsis. Clin Chest Med 29:627–642, viii
21. Kitchens CS (1998) Thrombotic storm: when thrombosis begets thrombosis. Am J Med 104: 381–385
22. Cervera R, Rodríguez-Pintó I, Colafrancesco S, Conti F, Valesini G, Rosário C et al (2014) 14th international congress on antiphospholipid antibodies task force report on catastrophic antiphospholipid syndrome. Autoimmun Rev 13:699–707
23. Miesbach W, Asherson RA, Cervera R, Shoenfeld Y, Gomez Puerta J, Bucciarelli S et al (2006) The catastrophic antiphospholipid (Asherson's) syndrome and malignancies. Autoimmun Rev 6:94–97
24. Cervera R, Asherson RA, Acevedo ML, Gómez-Puerta JA, Espinosa G, De La Red G et al (2004) Antiphospholipid syndrome associated with infections: clinical and microbiological characteristics of 100 patients. Ann Rheum Dis 63:1312–1317
25. Trousseau A (1865) Phlegmasia alba dolens. Lectures on clinical medicine, delivered at the Hotel-Dieu, Paris, pp 281–332
26. Anderson FA, Spencer FA (2003) Risk factors for venous thromboembolism. Circulation 107:I9–I16
27. Reed RL, Ericsson CD, Wu A, Miller-Crotchett P, Fischer RP (1992) The pharmacokinetics of prophylactic antibiotics in trauma. J Trauma 32:21–27
28. Rodríguez-pintó I, Espinosa G, Cervera R (2013) Catastrophic antiphospholipid syndrome – 20 years later. Curr Rheumatol Rev 9:73–80
29. Asherson RA, Cervera R, Piette JC, Font J, Lie JT, Burcoglu A et al (1998) Catastrophic antiphospholipid syndrome. Clinical and laboratory features of 50 patients. Medicine (Baltimore) 77:195–207
30. Cervera R, Espinosa G (2012) Update on the catastrophic antiphospholipid syndrome and the "CAPS Registry". Semin Thromb Hemost 38:333–338
31. Gruel Y, Rupin A, Watier H, Vigier S, Bardos P, Leroy J (1992) Anticardiolipin antibodies in heparin-associated thrombocytopenia. Thromb Res 67:601–606
32. Levi M, Keller TT, van Gorp E, ten Cate H (2003) Infection and inflammation and the coagulation system. Cardiovasc Res 60:26–39
33. Spero JA, Lewis JH, Hasiba U (1980) Disseminated intravascular coagulation. Findings in 346 patients. Thromb Haemost 43:28–33
34. Siegal T, Seligsohn U, Aghai E, Modan M (1978) Clinical and laboratory aspects of disseminated intravascular coagulation (DIC): a study of 118 cases. Thromb Haemost 39:122–134

35. Taylor FB Jr, Toh C, Hoots WK, Wada H, Levi M, Scientific and Standardization Committee Communications, *On behalf of the Scientific Subcommittee on Disseminated Intravascular Coagulation (2001) Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost 86:1327–1330
36. Asherson RA, Espinosa G, Cervera R, Gómez-Puerta JA, Musuruana J, Bucciarelli S et al (2005) Disseminated intravascular coagulation in catastrophic antiphospholipid syndrome: clinical and haematological characteristics of 23 patients. Ann Rheum Dis 64:943–946
37. George JN, Charania RS (2013) Evaluation of patients with microangiopathic hemolytic anemia and thrombocytopenia. Semin Thromb Hemost 39:153–160
38. Arepally GM, Ortel TL (2006) Clinical practice. Heparin-induced thrombocytopenia. N Engl J Med 355:809–817
39. Cervera R (2010) Catastrophic antiphospholipid syndrome (CAPS): update from the "CAPS Registry". Lupus 19:412–418
40. Amital H, Levy Y, Davidson C, Lundberg I, Harju A, Kosach Y et al (2001) Catastrophic antiphospholipid syndrome: remission following leg amputation in 2 cases. Semin Arthritis Rheum 31:127–132
41. Sacks S, Finn J, Sanna G, Khamashta MA, Chowdhury F, Hunt BJ et al (2013) N2010 adult-onset Still's disease complicated by hemophagocytic syndrome and catastrophic antiphospholipid syndrome resulting in four limb amputation. Isr Med Assoc J 15:192–194
42. Asherson RA, Espinosa G, Cervera R, Font J, Reverter JC (2002) Catastrophic antiphospholipid syndrome: proposed guidelines for diagnosis and treatment. J Clin Rheumatol 8:157–165
43. Cervera R, Tektonidou MG, Espinosa G, Cabral AR, González EB, Erkan D et al (2011) Task Force on Catastrophic Antiphospholipid Syndrome (APS) and Non-criteria APS Manifestations (II): thrombocytopenia and skin manifestations. Lupus 20:174–181
44. Erkan D (2006) Therapeutic and prognostic considerations in catastrophic antiphospholipid syndrome. Autoimmun Rev 6:98–103
45. Weitz JI, Hirsh J, Samama MM (2004) New anticoagulant drugs: the Seventh ACCP Conference on antithrombotic and thrombolytic therapy. Chest 126:265S–286S
46. Franklin RD, Kutteh WH (2003) Effects of unfractionated and low molecular weight heparin on antiphospholipid antibody binding in vitro. Obstet Gynecol 101:455–462
47. Manoach S (2008) Corticosteroids for septic shock. N Engl J Med 358:2070; author reply 2070–2071
48. Bucciarelli S, Espinosa G, Cervera R, Erkan D, Gómez-Puerta JA, Ramos-Casals M et al (2006) Mortality in the catastrophic antiphospholipid syndrome: causes of death and prognostic factors in a series of 250 patients. Arthritis Rheum 54:2268–2576
49. Sciascia S, Giachino O, Roccatello D (2012) Prevention of thrombosis relapse in antiphospholipid syndrome patients refractory to conventional therapy using intravenous immunoglobulin. Clin Exp Rheumatol 30:409–413
50. Tenti S, Guidelli GM, Bellisai F, Galeazzi M, Fioravanti A (2013) Long-term treatment of antiphospholipid syndrome with intravenous immunoglobulin in addition to conventional therapy. Clin Exp Rheumatol 31:877–882
51. Bucciarelli S, Erkan D, Espinosa G, Cervera R (2009) Catastrophic antiphospholipid syndrome: treatment, prognosis, and the risk of relapse. Clin Rev Allergy Immunol 36:80–84
52. Erkan D, Espinosa G, Cervera R (2010) Catastrophic antiphospholipid syndrome: updated diagnostic algorithms. Autoimmun Rev 10:74–79
53. Asherson R, Cervera R, de Groot PG, Erkan D, Boffa M-CC, Piette J-CC et al (2003) Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. Lupus 12:530–534
54. Matar P, Rozados VR, Gervasoni SI, Scharovsky GO (2002) Th2/Th1 switch induced by a single low dose of cyclophosphamide in a rat metastatic lymphoma model. Cancer Immunol Immunother 50:588–596

55. Buch MH, Smolen JS, Betteridge N, Breedveld FC, Burmester G, Dörner T et al (2011) Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. Ann Rheum Dis 70:909–920
56. Ramos-Casals M, Soto MJ, Cuadrado MJ, Khamashta MA (2009) Rituximab in systemic lupus erythematosus: a systematic review of off-label use in 188 cases. Lupus 18:767–776
57. Calich AL, Puéchal X, Pugnet G, London J, Terrier B, Charles P et al (2014) Rituximab for induction and maintenance therapy in granulomatosis with polyangiitis (Wegener's). Results of a single-center cohort study on 66 patients. J Autoimmun 50:135–141
58. Devauchelle-Pensec V, Mariette X, Jousse-Joulin S, Berthelot J-M, Perdriger A, Puéchal X et al (2014) Treatment of primary Sjögren syndrome with rituximab: a randomized trial. Ann Intern Med 160:233–242
59. Berman H, Rodríguez-Pintó I, Cervera R, Morel N, Costedoat-Chalumeau N, Erkan D et al (2013) Rituximab use in the catastrophic antiphospholipid syndrome: descriptive analysis of the CAPS registry patients receiving rituximab. Autoimmun Rev 12:1085–1090
60. Espinosa G, Bucciarelli S, Asherson RA, Cervera R (2008) Morbidity and mortality in the catastrophic antiphospholipid syndrome: pathophysiology, causes of death, and prognostic factors. Semin Thromb Hemost 34:290–294
61. Erkan D, Asherson RA, Espinosa G, Cervera R, Font J, Piette J-C et al (2003) Long term outcome of catastrophic antiphospholipid syndrome survivors. Ann Rheum Dis 62:530–533
62. Espinosa G, Rodríguez-Pintó I, Gomez-Puerta JA, Pons-Estel G, Cervera R (2012) Relapsing catastrophic antiphospholipid syndrome potential role of microangiopathic hemolytic anemia in disease relapses. Semin Arthritis Rheum 42:417–423