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# Catastrophic antiphospholipid syndrome: The current management approach

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A B S T R A C T

The current recommendation for catastrophic antiphospholipid syndrome (CAPS) management is the standard triple therapy with anticoagulation (AC), glucocorticoids (GCs), plasma exchange (PE), and/or intravenous immunoglobulins (IVIGs). Of note, only AC has a significant effect on the prognosis of these patients. However, from the experimental or basic point of view, there is only indirect evidence to advocate the use of these immunomodulatory therapies (GC, PE, and IVIG) in CAPS. Recently, there have been reports of severe or refractory CAPS patients treated with the monoclonal antibodies rituximab and eculizumab. The first blocks CD20, a surface protein expressed on the cytoplasmic membrane of B cells, and decreases the generation of pathogenic autoantibodies such as antiphospholipid (aPL) antibodies. The second binds with high affinity to C5 complement protein, inhibiting its cleavage and thus preventing the generation of C5b–C9 complex.



## Introduction

The descriptive adjective “catastrophic” was added to the term antiphospholipid syndrome (APS) by Ronald A. Asherson 25 years ago to highlight an accelerated form of this syndrome resulting in multiorgan failure [1,2]. Patients with catastrophic APS (CAPS) have the following in common: (a) clinical evidence of multiple organ involvement developing over a very short period of time;

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(b) histopathological evidence of multiple small-vessel occlusions; and (c) laboratory confirmation of antiphospholipid (aPL) antibodies, usually in high titer [3,4]. Therefore, the CAPS is a thrombotic microangiopathic condition, characterized by a diffuse thrombotic microvasculopathy [5].

Although <1% of patients with the APS develop this complication [6], its potentially lethal outcome emphasizes its importance in clinical medicine today. The majority of patients with CAPS end up in intensive care units (ICUs) with multiorgan failure. Unless the condition is considered in the differential diagnosis of a severe hypercoagulable state, it may be completely missed, resulting in a disastrous outcome for these patients. It is still unclear why some patients develop recurrent thromboses, mainly of large vessels (simple or classic APS), while others develop rapidly recurrent vascular occlusions, predominantly affecting small vessels (CAPS) [7–10].

Because of the rarity of this syndrome, an international registry of patients with CAPS (CAPS Registry) was created in 2000 by the *European Forum on Antiphospholipid Antibodies*, a study group devoted to the development of multicenter projects with large populations of APS patients [11]. Currently, the database documents the clinical, laboratory, and therapeutic data of >500 patients with CAPS. The periodic analysis of these data has allowed not only the description of the clinical and laboratory characteristics of this syndrome but also the elaboration of classification criteria, diagnostic algorithms, and therapeutic guidelines [7–10].

## Classification and diagnosis

The heterogeneity of the different clinical presentations of CAPS led to the development of the consensus criteria for the definition and classification of these patients. A presymposium workshop held in 2002 during the 10th International Congress on aPL in Taormina, Sicily, Italy, established preliminary criteria for the classification of CAPS [7], which were later validated [8].

However, when patients present with multiple organ thromboses in a “real-world” setting, especially in ICU, multiple factors can impede the timely diagnosis of CAPS and, at times, the differential diagnosis cannot be narrowed to a single disease. It has been suggested that a “continuum” of conditions, all demonstrating aPL, might exist comprising some patients with thrombotic thrombocytopenic purpura (TTP), HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome or CAPS, and a new term “microangiopathic” APS has been proposed to embrace this group of patients [12–15]. Certainly, patients with TTP and CAPS may share similar, but not identical, triggering factors (e.g., infections, drugs, carcinomas, occurrence during pregnancy, and the puerperium), similar clinical manifestations with predominance of small-vessel occlusions, and the presence of hemolytic anemia and thrombocytopenia (often severe), and the same therapies have been advised (e.g., plasma exchange (PE)).

To address this issue, during the 13th International Congress on aPL held in April 2010 in Galveston, Texas, USA, a “Catastrophic APS Task Force” proposed the delineation of new diagnostic algorithms to help clinicians treat patients with multiorgan thromboses in whom CAPS is suspected [9,10]. The goal of the updated CAPS diagnostic algorithms was to provide a “step-by-step” approach to clinicians and researchers while assessing patients with multiple organ thromboses.

## Clinical features

The detailed analysis of the first 280 patients included in the “CAPS Registry” [16] showed that 72% were women, with a mean age of 37 years (range 11–60). Forty-six percent suffered from primary APS, 40% from systemic lupus erythematosus (SLE), 5% from lupus-like disease, and 9% from other autoimmune diseases. Patients may develop CAPS *de novo*, without any history of thrombosis (46%).

At least 53% of patients appeared to have developed CAPS following an identifiable “trigger” factor. The most common precipitating factors were infections (22%) and surgical procedures (10%; even minor, such as dental extractions). The etiology of infection may be diverse and includes viral infections of the upper respiratory tract or dengue, bacterial infections such as typhoid fever, urinary infections or sepsis, or parasitological infections such as malaria [17]. Other less common causes were anticoagulation (AC) withdrawal or subtherapeutic (<2.0) international normalized ratio (INR; 8%), other medications (7%), obstetric complications (7%), neoplasia (5%), and SLE flares (3%).