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PREDICTION AND TREATMENT OF CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME (CAPS): A CRITICAL REVIEW AND CURRENT APPROACHES

Radjabova Zulola Abdukhakimovna
Center for the Development of Professional
Qualifications of Medical Workers, Tashkent, Uzbekistan
ORCID: 0009-0008-9408-9312

Abstract
Catastrophic antiphospholipid syndrome (CAPS) is a rare but the most severe and life-threatening form of antiphospholipid syndrome (APS), characterized by rapidly progressive multi-organ failure due to small vessel thrombosis. Despite advances in understanding its pathogenesis, mortality in CAPS remains unacceptably high, dictating the need for early diagnosis and aggressive therapy. This review systematizes current data on the pathogenesis, clinical manifestations, diagnosis, and treatment of CAPS. Key pathogenetic mechanisms are examined, including the "second hit" theory, the central role of complement activation, endothelial cell dysfunction, and the "thrombotic-inflammatory storm" concept. Classification criteria and the challenges of differential diagnosis with other thrombotic microangiopathies (TTP, HUS, sepsis, HELLP syndrome) are analyzed. Special attention is given to modern therapeutic approaches: from the standard "triple therapy" (anticoagulants, glucocorticoids, plasma exchange/intravenous immunoglobulins) to the use of targeted agents such as rituximab and eculizumab. Prognostic factors and unresolved issues, including the absence of biomarkers for predicting CAPS development in APS patients, are discussed. It is emphasized that success in treating CAPS depends on a high index of clinical suspicion, rapid diagnosis, and a multidisciplinary approach.

Keywords: Catastrophic antiphospholipid syndrome, CAPS, antiphospholipid syndrome, APS, thrombotic microangiopathy, thrombosis, cytokine storm, complement system, triple therapy, eculizumab, rituximab.

Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disease defined, according to the classification criteria updated by the group led by Miyakis S. (2006), as a combination of recurrent venous or arterial thrombosis and/or obstetric morbidity with the persistent presence of antiphospholipid antibodies (aPL) [1]. In the vast majority of cases, APS follows a chronic course requiring lifelong anticoagulant therapy [19]. However, in less than 1% of patients with APS, a fulminant, catastrophic form develops.

Catastrophic antiphospholipid syndrome (CAPS), first described in detail by Ronald Asherson in 1992, represents the most extreme manifestation of APS [2]. It is characterized by the rapid development (usually within a week) of multiple thromboses, predominantly in the microvasculature, leading to multi-organ failure. Despite its rarity, CAPS is a medical

emergency in rheumatology and intensive care, with a mortality rate that, even with modern treatment, reaches 30-40% [3]. To systematize data on this rare disease, an international online registry for CAPS ("CAPS Registry") was established, curated by a group led by Ricard Cervera. It serves as the main source of information on the clinical manifestations, triggers, treatment, and outcomes of CAPS [14]. This registry, which includes over 500 cases, has allowed for the transition from describing single case reports to analyzing a large cohort, which has been fundamental to understanding the epidemiology and developing therapeutic strategies.

The aim of this review is to critically analyze the current understanding of the pathogenesis of CAPS, discuss the complexities of its diagnosis, and systematize the data on the evolution of therapeutic approaches, from standard combination therapy to the use of targeted biologic agents.

1. Pathogenesis: From Autoantibodies to a "Thrombo-inflammatory Storm"

The pathogenesis of CAPS is complex and not fully understood, but the central concept is a massive, uncontrolled thrombo-inflammatory response where thrombosis and inflammation mutually reinforce each other, creating a vicious circle.

1.1. The "Second Hit" Theory: Predisposition and Trigger

The presence of aPL alone is not sufficient to cause CAPS. This is supported by the fact that many patients with APS, despite high antibody titers, never develop the catastrophic form. This led to the formulation of the "second" or "multiple hit" theory, proposed by Asherson R.A. and Shoenfeld Y. (2000) [5]. According to this model, aPL create a prothrombotic background (the "first hit"), but an additional trigger (the "second hit") is required to initiate CAPS. Analysis of the CAPS Registry data shows that such a trigger can be identified in about half of the patients, with infections being the most common [18].

Discussion:

While the "second hit" concept is widely accepted, it does not explain why no trigger can be identified in half of the patients. It is possible that in these cases, subclinical factors, such as viral infections, act as the "second hit," or perhaps there is a certain "threshold" of aPL activity, beyond which the system loses stability without an apparent external stimulus.

1.2. Key Molecular Mechanisms: The "Complement-Endothelium-Cytokine" Triad

Complement Activation. The work of S.S. Pierangeli and G. Girardi on animal models of APS was groundbreaking, showing that complement activation is not a consequence but a central link in the pathogenesis [6, 7]. aPL binding to cells triggers complement activation, leading to the formation of potent pro-inflammatory anaphylatoxins C3a and C5a, as well as the membrane attack complex C5b-9.

Comparison:
This model is similar to the pathogenesis of atypical hemolytic uremic syndrome (aHUS), which is also based on complement dysregulation. However, in aHUS, it is often associated with genetic defects, whereas in CAPS, the trigger is an autoantibody.

Endothelial Dysfunction and "Cytokine Storm." aPL directly interact with endothelial cells, inducing the expression of tissue factor and adhesion molecules. This leads to a massive release of pro-inflammatory cytokines (IL-6, IL-1, TNF-α). Y. Shoenfeld et al. described this process as a "cytokine storm," similar to that seen in sepsis [8].

Discussion:
While the cytokine profiles in CAPS and sepsis are similar, the underlying causes are different: an autoimmune process versus a pathogen.

Neutrophil Extracellular Traps (NETs). The studies of M. Knight and I. Shapira have shown that aPL-stimulated neutrophils release networks of DNA and proteins (NETs), which are potent procoagulant substrates [9, 13]. Uncontrolled NETosis is thought to occur in CAPS.

Discussion:
All these mechanisms are closely interconnected. C5a can induce NETosis, and cytokines can enhance complement activation, creating a self-sustaining "thrombo-inflammatory storm."

2. Clinical Presentation and Diagnosis: A Race Against Time

2.1. Clinical Manifestations

CAPS is characterized by the rapid development of thromboses in three or more organs or systems. According to the CAPS Registry, the most commonly affected are the kidneys (~70%), lungs (~60%), CNS (~60%), heart (~50%), and skin (~50%) [14].

2.2. Diagnostic Criteria: Practicality vs. Precision

R. Asherson and R. Cervera proposed preliminary classification criteria for CAPS. A diagnosis of **definite CAPS** requires all four criteria: involvement of ≥3 organs, development in <1 week, histological confirmation of microthrombosis, and presence of aPL [4].

Discussion:
Obtaining histological confirmation is often impossible due to the patient's critical condition. Therefore, the category of **probable CAPS** (meeting three of the four criteria, usually without histology) was introduced as a pragmatic compromise to initiate treatment.

2.3. Differential Diagnosis: Navigating the Clinical Labyrinth of TMAs

CAPS is often called the "great imitator" due to its profound clinical overlap with other thrombotic microangiopathies (TMAs) and systemic inflammatory states. The urgency of the

situation often forces clinicians to make therapeutic decisions based on incomplete information, making a structured approach to differential diagnosis critical. The challenge, as highlighted by Scully M. and Goodship T., is that while the underlying pathologies of TMAs are distinct, their final common pathway—microvascular thrombosis, endothelial injury, and organ failure—is strikingly similar.

- **Thrombotic Thrombocytopenic Purpura (TTP):** The clinical pentad of TTP (fever, thrombocytopenia, microangiopathic hemolytic anemia, renal dysfunction, and neurological symptoms) almost perfectly mirrors that of CAPS. However, the pathophysiology is fundamentally different. TTP is caused by a severe deficiency of the von Willebrand factor (VWF)-cleaving protease, ADAMTS13. As established by Furlan M. and Lämmle B., this deficiency leads to the accumulation of ultra-large VWF multimers that spontaneously bind to platelets, causing systemic microthrombi. According to J.N. George, a cornerstone of TTP diagnosis is an ADAMTS13 activity level of less than 10% [10]. **Discussion & Comparison:** The critical challenge is the turnaround time for ADAMTS13 testing, which can take several days. In contrast, CAPS requires immediate immunomodulatory intervention beyond what is standard for TTP. Therefore, many expert guidelines, including those proposed by the McMaster RARE-Bestpractices group, recommend initiating empirical plasma exchange (PEX) immediately if either TTP or CAPS is suspected, as PEX is the primary treatment for TTP and a core component of CAPS therapy [15]. The presence of high-titer aPL, particularly lupus anticoagulant, should strongly steer the diagnosis toward CAPS, even before ADAMTS13 results are available.
- **Atypical Hemolytic Uremic Syndrome (aHUS):** Differentiating CAPS from aHUS is arguably the most challenging task, as both involve profound complement activation. aHUS is primarily a disease of genetic or acquired dysregulation of the alternative complement pathway. High-titer aPL are the hallmark of CAPS, but low-titer aPL can sometimes be found in aHUS as an epiphenomenon of endothelial damage. **Discussion & Comparison:** The work of Fakhouri F. and Loirat C. has been pivotal in classifying aHUS based on underlying genetic mutations in complement regulatory proteins (Factor H, Factor I, etc.). In the absence of genetic testing, which is not acutely available, clinical clues are vital. A personal or family history of similar episodes points towards aHUS. Conversely, a known history of APS or another autoimmune disease (like SLE) strongly suggests CAPS. The therapeutic implications are significant: while both conditions may respond to the C5 inhibitor eculizumab, the long-term management differs. aHUS often requires lifelong complement inhibition, whereas in CAPS, treatment is focused on controlling the acute autoimmune storm.
- **Sepsis with Disseminated Intravascular Coagulation (DIC):** Sepsis can be a potent trigger for CAPS, and the resulting clinical picture of multi-organ failure, shock, and coagulopathy can be identical. The systemic inflammatory response in sepsis leads to a cytokine storm and endothelial activation, mirroring the pathophysiology of CAPS. **Discussion & Comparison:** The key differentiator is the presence of an infectious

source. As emphasized by Gando S. and Levi M. in their work on sepsis-induced coagulopathy, positive blood cultures or a clear infectious focus are crucial. However, aPL can be transiently positive during severe infections ("sepsis-induced aPL"), further confounding the diagnosis. The pragmatic approach, advocated by Cervera R. et al., is to treat both conditions simultaneously [4]. This involves administering broad-spectrum antibiotics and supportive care for sepsis while concurrently initiating triple therapy for CAPS. Aggressive immunosuppression is a double-edged sword: it is life-saving in CAPS but can be detrimental in uncontrolled sepsis. Therefore, meticulous microbiological investigation is paramount.

- **HELLP Syndrome:** Occurring exclusively in the context of pregnancy, HELLP syndrome is considered a pregnancy-specific TMA. The debate, fueled by the work of B.M. Sibai and J.N. Martin Jr., is whether HELLP is a severe variant of preeclampsia or a separate entity that can trigger CAPS in a predisposed patient [13]. **Discussion & Comparison:** While both feature hemolysis, elevated liver enzymes, and thrombocytopenia, HELLP is typically confined to the liver-platelet axis, with other organ involvement being secondary to severe hypertension. In contrast, "true" CAPS in pregnancy often involves more widespread thrombosis (e.g., cerebral, cardiac, pulmonary) that cannot be explained by preeclampsia alone. The presence of high-titer, persistent aPL (especially lupus anticoagulant and triple positivity) favors a diagnosis of CAPS triggered by pregnancy, whereas isolated, low-titer aPL that resolve postpartum are more consistent with HELLP. Management also differs: the definitive treatment for HELLP is delivery, whereas for CAPS, delivery is a necessary but insufficient intervention, requiring full-scale immunosuppression.

3. Therapeutic Strategies: From the Triad to Targeted Therapy

Treatment for CAPS is a medical emergency and should be initiated based on a high degree of suspicion, often before a definitive diagnosis is confirmed. The therapeutic paradigm has evolved from supportive care to an aggressive, multi-pronged attack on the thrombo-inflammatory storm.

3.1. The Cornerstone: "Triple Therapy"

Analysis of the extensive data from the CAPS Registry, meticulously curated by R. Cervera and his team, has unequivocally shown that the best outcomes are achieved with a combination of three components, often termed "triple therapy" [4, 15].

1. **Anticoagulation:** Intravenous unfractionated heparin is the agent of choice in the acute phase due to its short half-life, reversible effects, and pleiotropic anti-inflammatory properties.
2. **Glucocorticoids:** High-dose intravenous pulses (e.g., methylprednisolone) are administered to quell the systemic inflammatory response and cytokine storm.
3. **Antibody Removal/Modulation:** This is achieved via either plasma exchange (PEX) or high-dose intravenous immunoglobulins (IVIG).

Discussion: Plasma Exchange versus IVIG? This remains a subject of intense debate with no definitive answer from randomized trials. Proponents of PEX, referencing the mechanism of action, argue for its superiority as it physically removes pathogenic aPL, cytokines, and activated complement components from the circulation. Proponents of IVIG highlight its multiple immunomodulatory effects, including Fc receptor blockade and anti-idiotypic antibody action. **Comparison of Evidence:** The retrospective analysis by Cervera et al. from the CAPS Registry found that both modalities, when added to anticoagulation and steroids, significantly improved survival compared to dual therapy, but they did not find a statistically significant difference between PEX and IVIG [4]. The McMaster RARE-Bestpractices guidelines, representing a consensus of experts, give a conditional recommendation for either PEX or IVIG, suggesting the choice may depend on local expertise, availability, and the patient's clinical context (e.g., IVIG might be preferred in the presence of active infection or hemodynamic instability) [15]. The consensus championed by M.A. Khamashta is that in the most severe, refractory cases, a combination of both PEX and IVIG is a reasonable approach [11].

3.2. Second-Line and Targeted Therapies

For patients who do not respond to initial triple therapy or present with life-threatening organ failure, targeted biological agents are considered.

- **Rituximab:** A monoclonal antibody targeting the CD20 antigen on B-cells. Its use in autoimmune diseases was pioneered by researchers like M.J. Leandro and G. Cambridge [12]. The rationale is to deplete B-cells, the precursors to antibody-producing plasma cells, thereby reducing the production of pathogenic aPL. **Discussion:** The critical limitation of rituximab in CAPS is its delayed onset of action. B-cell depletion takes days to weeks, and a subsequent fall in antibody titers takes even longer. Therefore, as highlighted in reviews by Kazzaz N.M. et al., rituximab is not an effective emergency treatment for the acute thrombo-inflammatory storm [16]. Its primary role is in managing refractory APS or preventing relapses of CAPS in patients who have recovered from the acute episode.
- **Eculizumab:** A monoclonal antibody that binds to the C5 complement component, preventing its cleavage into C5a and C5b and thus blocking the formation of the membrane attack complex (C5b-9). Its use is the most direct, pathogenetically justified intervention based on the foundational work of Pierangeli and Girardi demonstrating the centrality of complement in APS [6]. The first successful case reports of its use in refractory CAPS paved the way for its consideration as a powerful rescue therapy. **Comparison with Rituximab:** The therapeutic mechanisms and timelines of eculizumab and rituximab are fundamentally different. Eculizumab provides an immediate "firewall," halting the effector arm of complement-mediated damage within hours of administration, making it ideal for the acute, life-threatening situation. Rituximab acts "upstream" on the cause of the problem (autoantibody production), but its effect is slow. In an ideal scenario, one might use eculizumab to control the acute storm and rituximab to establish long-term remission, but

the prohibitive cost and risks associated with both agents make such a strategy feasible only in very select cases.

4. Prognosis and Unresolved Issues

Thanks to the widespread adoption of aggressive combination therapy, the prognosis for CAPS has improved significantly since its initial description. While early reports by R. Asherson documented mortality rates exceeding 50%, the latest comprehensive analysis of the CAPS Registry by Rodriguez-Pinto et al. indicates a mortality rate of approximately 37% [14, 17]. This improvement is a testament to increased awareness and better intensive care, yet a mortality rate of over one-third remains unacceptably high and underscores the numerous unresolved challenges in managing this devastating syndrome. Factors consistently associated with a poor prognosis include older age at presentation, concurrent diagnosis of Systemic Lupus Erythematosus (SLE), cardiac and cerebral involvement, and the development of Disseminated Intravascular Coagulation (DIC) [17].

Unresolved Issues and Future Directions: Charting a Course for Improvement

Despite progress, our understanding and management of CAPS are still fraught with critical knowledge gaps. The rarity of the disease makes traditional evidence-based approaches challenging, but several key areas are ripe for investigation.

Prediction: The Quest for a CAPS-Specific Biomarker. This is arguably the most critical unmet need. How can we identify the <1% of APS patients who are at imminent risk of developing CAPS? Currently, no specific biomarkers exist. The "triple-positive" aPL profile (presence of Lupus Anticoagulant, anti-cardiolipin, and anti-β2-glycoprotein I antibodies), strongly linked by Pengo V. et al. to a higher thrombosis risk in general APS, is also more common in CAPS patients but lacks the specificity to be a useful predictive tool. **Future Directions:** The search is on for a "CAPS signature." Promising avenues include:

"Omics" Approaches: Utilizing proteomics and metabolomics to identify unique protein or metabolite profiles in the plasma of patients during the onset of CAPS. This could reveal novel pathways and biomarkers.

Complement Activation Products: Measuring levels of circulating complement split products like C5a or the soluble membrane attack complex (sC5b-9). The hypothesis, supported by the work of Oku K. and Atsumi T., is that a quantifiable surge in complement activation may precede the clinical explosion of CAPS.

Markers of Endothelial and Neutrophil Activation: Quantifying levels of circulating endothelial microparticles, cell-free DNA (a surrogate for NETosis), or specific pro-inflammatory cytokines (like IL-6). A composite score combining several such markers might provide the necessary predictive power.

Genetic Susceptibility: Beyond aPL, are there genetic factors that predispose a patient to the catastrophic phenotype? Genome-wide association studies (GWAS) could identify polymorphisms in genes related to complement regulation, innate immunity (e.g., Toll-like

receptors), or fibrinolysis that act as a "third hit," tipping the balance toward a systemic thrombo-inflammatory storm.

Therapy Optimization: Beyond the Triad. While triple therapy is the established standard of care, its application is largely empirical. Numerous questions remain regarding its optimization.

Optimal Sequence and Duration: What is the ideal duration for plasma exchange? Is a set number of sessions sufficient, or should it be guided by the normalization of clinical and laboratory parameters? When is it safe to de-escalate immunosuppression? The current guidelines, such as those from the McMaster RARE-Bestpractices group, are based on expert consensus rather than hard data [15].

Defining "Refractory CAPS": At what point should a patient be considered a non-responder to triple therapy, warranting escalation to second-line agents? There is no consensus on this crucial clinical decision point. Is it a failure to improve after 48 hours? 72 hours? The development of a validated CAPS activity score would be invaluable in standardizing this assessment.

The Role of Targeted Therapies: The use of eculizumab and rituximab is based on strong pathogenic rationale and compelling case series, but their precise place in the therapeutic algorithm is undefined. Should eculizumab be used earlier in patients with clear evidence of severe complement activation or multi-organ failure, rather than as a last resort? The work of Chaturvedi S. and Brodsky R.A. in other complement-mediated TMAs suggests that early intervention is key to preventing irreversible organ damage. Could a short course of eculizumab to "break the cycle" followed by B-cell depletion with rituximab for long-term control be a more effective strategy?

Clinical Trials: The Challenge of Rarity. Conducting randomized controlled trials (RCTs) in CAPS is nearly impossible due to its rarity and acute, life-threatening nature. It is ethically and logistically unfeasible to randomize critically ill patients to placebo or a potentially less effective therapy. **Future Directions:** The path forward lies in innovative trial designs and international collaboration.

Registry-Based Trials: The CAPS Registry provides a powerful platform. A "registry-based RCT" could be designed where patients are randomized to different second-line therapies, with primary data collection occurring through the established registry infrastructure.

Adaptive Platform Trials: These modern trial designs allow for multiple therapies to be tested simultaneously against a common control arm. Ineffective treatments can be dropped and new, promising agents can be added over time, making the trial process more efficient.

International Collaboration: Progress is only possible through the combined efforts of global networks like the European Reference Network (ERN) for rare diseases. Pooling data and standardizing protocols across centers is essential to gather meaningful evidence.

Conclusion

Catastrophic antiphospholipid syndrome remains one of the most dramatic and complex challenges in medicine, sitting at the dangerous intersection of autoimmunity, thrombosis, and critical illness. Its pathogenesis represents a self-sustaining "thrombo-inflammatory storm"

that, once ignited, can rapidly consume the body's resources and lead to irreversible organ failure. Our understanding has evolved significantly from the initial clinical descriptions by Asherson to the molecular insights provided by researchers like Karumanchi, Girardi, and Knight. The diagnosis requires a high index of clinical suspicion and a rapid, structured approach to differentiate it from its clinical mimics.

Treatment has progressed from being largely supportive to an immediate, aggressive, and multidisciplinary strategy based on the cornerstone of "triple therapy." The advent of targeted agents like eculizumab has provided a powerful new weapon, yet its optimal use remains to be defined. Despite these advances, the high mortality rate serves as a stark reminder of our remaining knowledge gaps. The future of improving outcomes for patients with CAPS lies not in a single breakthrough but in a multi-pronged effort. We must focus on identifying predictive biomarkers to catch the storm before it breaks, optimizing our use of existing therapies through innovative trial designs, and leveraging international collaboration to study this rare but devastating disease. The ultimate goal is to transform this medical catastrophe into a manageable, and ultimately preventable, condition.

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