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REVIEW

Infection-Triggered Antiphospholipid Syndrome: A Critical Overview

Svitlana Smiyan[1], Ganna Kuzmina[2], Olena Garmish[3], Roman Komorovsky[1]

[1]Department of Internal Medicine II, Ivan Horbachevsky Ternopil National Medical University, Ternopil, Ukraine; [2]Department of Therapy, Cardiology and Family Medicine, Faculty of Postgraduate Education, Dnipro State Medical University, Dnipro, Ukraine; [3]King's College Hospital London, Dubai, United Arab Emirates

Correspondence: Roman Komorovsky, Department of Internal Medicine II, Ivan Horbachevsky Ternopil National Medical University, 1, Maidan Voli, Ternopil, 46001, Ukraine, Email komorovsky@tdmu.edu.ua

Abstract: Antiphospholipid syndrome (APS) is a complex multisystem disorder traditionally classified into primary forms and those associated with autoimmune diseases. However, *infection-induced APS* is gaining attention as a distinct subset due to the increasing recognition of thrombotic complications occurring in the context of viral or bacterial infections. Despite its clinical relevance, this phenomenon remains poorly characterized. This narrative review synthesizes current knowledge on the pathogenesis, clinical manifestations, and diagnostic challenges of infection-induced APS. A literature search was conducted in the Medline and PubMed databases for English-language articles published between 2014 and May 2025. Of the identified publications, 35 were selected for detailed analysis. Evidence supports a multifaceted relationship between infections and APS, with proposed mechanisms including molecular mimicry, Toll-like receptor activation, generation of non-pathogenic antiphospholipid antibodies (aPL), impaired immune complex clearance, neutrophil extracellular trap formation, direct endothelial damage, and the "second hit" hypothesis. Clinical presentations are diverse, ranging from mild, transient symptoms to severe thrombotic events, and often complicate the distinction between true APS and transient aPL positivity secondary to infection. Diagnostic difficulties are compounded by the fluctuating presence of aPL and the overlap of infection-related symptoms with APS criteria. Currently, there are no standardised criteria for infection-induced APS, underscoring the need for definitions that reflect its temporal dynamics and immunological heterogeneity.

Keywords: antiphospholipid syndrome, antiphospholipid antibodies, infections, autoimmunity, diagnosis

Introduction

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by venous and arterial thrombosis, as well as pregnancy morbidity, in association with persistently elevated antiphospholipid antibodies (aPL).[1] While the classical pathogenesis of APS is well established, particularly in primary forms and in the context of systemic lupus erythematosus,[1] increasing attention has been directed toward infection-associated variants.[2] In these cases, thrombotic events arise in the setting of viral or bacterial infections, raising important questions about causality, pathophysiology, and diagnostic boundaries.

aPL in infectious diseases have been recognized since their initial discovery in patients with syphilis. More recently, the global COVID-19 pandemic has renewed interest in the potential association between infections and aPL positivity.[2] Elevated anticardiolipin antibody (aCL) levels have been observed in patients with hepatitis C virus (HCV) infection, while lupus anticoagulant (LA) and aCL positivity have also been documented in individuals infected with human immunodeficiency virus (HIV) [3]. Sporadic reports link other viral infections, including Epstein-Barr virus (EBV), varicella-zoster virus, and cytomegalovirus (CMV), to transient or persistent elevations in aPL levels.[3,4]

In a range of infectious conditions, including COVID-19, HCV, tuberculosis, syphilis, Lyme disease, and others, aPL may be detected, but their clinical significance remains debated. While infections may induce transient aPL positivity without clinical consequences, they can also, in certain instances, precipitate overt APS or its most severe form - catastrophic antiphospholipid syndrome (CAPS). This presents a diagnostic and therapeutic dilemma:

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distinguishing incidental, infection-related aPL detection from true autoimmune-mediated APS with a risk of thrombotic complications.[5] Given the fulminant nature of CAPS, which involves widespread thrombosis and consumptive coagulopathy with high mortality, early identification of at-risk patients is crucial for timely intervention.

This review aims to provide a critical synthesis of current pathogenetic hypotheses related to infection-induced antiphospholipid syndrome (APS). It summarises key clinical manifestations and immunopathogenic mechanisms with relevance to clinical practice, discusses diagnostic challenges, including the potential role of infection as a "second hit" and the clinical relevance of aPL detection in infectious contexts, and reassesses the applicability of current APS classification frameworks in light of infection-associated presentations.

Materials and Methods

This narrative review is based on an analysis of literature sourced from the Medline and PubMed databases. The search focused on English-language articles published between 2014 and May 2025, inclusive, addressing topics relevant to infection-induced antiphospholipid syndrome (APS). A limited number of earlier key publications were also included to provide essential historical context or conceptual background, particularly regarding the original description of catastrophic APS, early observations of aPL in infectious diseases, and the development of classification criteria. The search strategy incorporated the following keywords (MeSH terms): *antiphospholipid syndrome, antiphospholipid antibodies, infections*, and *diagnosis*. After screening titles, abstracts, and full texts for relevance and quality, 35 publications were selected for detailed review and analysis.

Results

Pathogenetic Hypotheses of Infection-Induced APS

Various viral infections, particularly human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis E virus (HEV), and Epstein-Barr virus (EBV), are frequently associated with the presence of aPL, occasionally accompanied by thrombotic complications.[6–8] A meta-analysis by Abdel-Wahab et al[5] identified an elevated risk of thrombosis in individuals with HCV and EBV infections. Although infrequent, HEV-associated cases of APS have also been reported, including splanchnic vein thrombosis with potentially fatal outcome.[8]

The COVID-19 pandemic has stimulated renewed interest in the role of aPL in infection-related thrombosis. Although aPL have been detected in a significant proportion of patients with COVID-19, most did not meet the clinical criteria for APS.[9] These antibodies were generally considered transient; however, in severe cases accompanied by cytokine storm, endothelial damage may have contributed to thrombotic complications. The lack of consistent association between aPL positivity and clinical features of APS could largely be explained by methodological limitations. Many studies lacked appropriate control groups, making it difficult to determine whether the prevalence of aPL was genuinely elevated in COVID-19. Where controls were included, such as patients with other infections or autoimmune diseases, differences in aPL prevalence were often minimal. Inconsistencies in the threshold values used to define aPL positivity, typically based on manufacturer cutoffs, further complicated comparisons. Moreover, the small sample sizes in many studies limited their statistical power. Notably, only larger cohort studies were able to demonstrate a clearer association between aPL and thrombosis in the context of COVID-19.[10,11] It is important to note that these prothrombotic mechanisms, including endothelial activation and cytokine-driven inflammation, are not specific to infection-induced APS and are also well recognized in primary and autoimmune-associated APS. In the setting of COVID-19, these mechanisms may either initiate aPL production or serve as a "second hit" in patients with pre-existing antibodies, contributing to thrombosis.

Interpretation of the role of aPL in COVID-19 requires caution, given the heterogeneity and contradictions within the existing literature.[2,12] Before considering routine aPL testing in COVID-19 patients, larger, well-designed studies are necessary to clarify the clinical significance of these antibodies. While the prothrombotic nature of COVID-19 is well established, other mechanisms beyond aPL involvement should continue to be explored.

Among the aPL subtypes, IgA anti-β2 glycoprotein-I (aβ2GPI) has been associated with thrombotic complications, including stroke. These antibodies are frequently found in patients with end-stage organ failure, particularly of renal or cardiac origin, and thrombotic events have been reported even after organ transplantation.[13]

Infectious triggers, particularly respiratory infections, are well recognized in the pathogenesis of catastrophic APS (CAPS). Proposed mechanisms include molecular mimicry, Toll-like receptor (TLR4) activation, complement cascade involvement, and widespread endothelial injury.[14]

Several studies have reported a high prevalence of aPL among patients with chronic Lyme disease or neuroborreliosis.[15–18] While up to 80% of patients in some cohorts tested positive for aPL, the incidence of clinically evident thrombosis remained low, around 10%.[17] Serological cross-reactivity, particularly with ganglioside antibodies, has been suggested as a confounding factor complicating diagnosis.[16,18] One case report described a patient with Lyme neuroborreliosis who developed psychosis with MRI evidence of cerebral microthrombosis in the presence of aPL, illustrating a possible link between infection, neurological symptoms, and thrombosis.[15]

Key findings from the reviewed publications are summarized in Table 1.

Based on the analysis of over 30 scientific publications and reported clinical cases, a pathogenetic and clinical association between infection and the development of antiphospholipid syndrome (APS) appears well supported.

Table 1 Summarized Findings From Selected Publications Included in the Narrative Review

Source	Year	Study Focus	Proposed Pathogenic Mechanisms	Reported APS Cases
O'Callaghan et al[18]	1990	False-positive Borrelia serology in APS patients	Cross-reactivity in serologic tests; concern for misdiagnosis	27 patients with APS; 14,2% had false-positive Lyme serology
García-Moncó et al[16]	1993	Reactivity of neuroborreliosis patients to cardiolipin and gangliosides	Cross-reactivity; ganglioside antibodies and aCL found in Lyme neuroborreliosis	About half of neuroborreliosis patients had IgG against cardiolipin, while roughly a third of them—and over half of syphilis patients—had IgM reacting to gangliosides like GM1 and GD1b
Dalekos et al[19]	2001	APS and infection with focus on HCV	aPL induction in infection; molecular mimicry; HCV linked to autoimmune phenomena	Emphasized cautious interpretation; aPL in HCV often non-pathogenic; not routinely linked to APS
Pamuk et al[7]	2003	APS and HCV – case with mitral valve and cerebral emboli	HCV and aPL coexistence; possible synergy	36-year-old woman with primary APS, HCV, recurrent miscarriages and embolic stroke
Sène et al[20]	2008	APS and infections – review	aCL common in viral infections; aβ2GPI rare; bacterial triggers possible	High aCL in HIV, HBV, HCV; some bacterial cases (leprosy, syphilis); few confirmed APS
Girschick et al[21]	2008	Bacterial infections as triggers of autoimmune rheumatic diseases	Molecular mimicry, persistent bacterial antigen stimulation, HLA-B27 association, cytokine dysregulation	Hypothesized association with APS; specific pathogens discussed include Mycobacteria, Streptococcus, Borrelia, Chlamydia
Greco et al[17]	2011	aPL in patients with chronic Lyme disease (CLD)	Frequent aPL positivity, especially IgM isotypes; unclear if pathogenic	106 patients studied; aPL in 85 (80%); aPL-related events in 17; only 12 had confirmed post-Lyme syndromes
da Silva et al[22]	2014	Systematic review of APS associated with rheumatic fever	Overlap of aβ2GPI and anti-M protein antibodies; molecular mimicry	11 cases identified; 100% carditis, 63% chorea, 64% stroke; aCL, LA, aβ2GPI found variably

(*Continued*)

Table 1 (Continued).

Source	Year	Study Focus	Proposed Pathogenic Mechanisms	Reported APS Cases
Garcia-Carrasco et al[6]	2015	Infections in CAPS	CAPS triggered by infections (especially respiratory); molecular mimicry; cytokine storm	Infections common CAPS trigger; includes multiple case descriptions
Abdel-Wahab et al[23]	2016	APS after infection	Molecular mimicry, chronic infections (HIV, HCV), genetic predisposition	293 case reports; 24,6% met criteria for APS; 5,8% CAPS; 43,7% thromboembolic with transient aPL. Most common preceding infections: HIV, HCV (with thrombotic events); Parvovirus B19 (antibodies without thrombosis); others included Coxiella burnetii, Mycoplasma pneumoniae, Streptococci, Mycobacterium tuberculosis
Neves et al[24]	2017	Case report of malaria and Borrelia coinfection causing APS	Infectious triggers (Plasmodium, Borrelia) leading to immune dysregulation	Single patient with malaria and neuroborreliosis developed APS and pulmonary embolism
Abdel-Wahab et al[5]	2018	Viral infections and aPL antibodies (meta-analysis)	HIV, HCV, EBV most linked to aPL; possible immune activation	Elevated aPL most in HIV, HCV, EBV; thrombosis in HCV/EBV; aβ2GPI in HCV significantly associated
Sciascia et al[2]	2021	aPL in COVID-19 and other infections	aPL positivity in infections is often transient; differences in aPL profiles between APS and infections	aPL detected in 53% (COVID-19) and 49% (other infections); low rate of thrombotic events; no confirmed persistent aPL
Qureshi et al[25]	2021	CAPS triggered by tuberculosis in a pediatric patient	Molecular mimicry and endothelial activation by M. tuberculosis antigens	One confirmed pediatric case of CAPS triggered by tuberculosis; aPL positivity resolved after treatment
Serrano et al[10]	2022	COVID-19 and APS	«Cytokine storm», complement activation, NETs, endothelial injury, molecular mimicry	High prevalence of aPL in COVID-19 (up to 71% in the intensive care unit); few persistent aPL or definite APS
Almeida et al[15]	2023	Psychiatric presentation in patient with APS secondary to Lyme neuroborreliosis	Recurrent cerebral microthromboses due to aPL triggered by chronic Borrelia infection	Single patient with neuropsychiatric symptoms and aβ2GPI positivity
Zekić et al[26]	2024	COVID-19, aPL and APS	Possible molecular mimicry; aPL after COVID-19; uncertain link to thrombosis	High aPL prevalence in severe COVID-19, but unclear APS diagnosis; vaccination generally well tolerated
Jin et al[9]	2025	aPL prevalence in COVID-19 patients (meta-analysis)	Immune response to infection; IgM aPL more common in early phase	aPL significantly higher in COVID-19 vs controls; especially IgM; IgG not significantly different
Karimi et al[8]	2025	HEV-induced APS exacerbation (case report)	Infection-induced worsening of APS	Young male with HEV and extensive splanchnic thrombosis; aβ2GPI and aCL positive

However, this link remains heterogeneous, depending on the nature of the infectious trigger and the isotype, avidity, and duration of antiphospholipid antibody (aPL) positivity.

Several hypotheses have been proposed to explain the mechanisms of infection-induced APS, as summarized in Table 2:

1. *Molecular mimicry.* This widely accepted hypothesis posits that microbial antigens—such as those of *Streptococcus pyogenes, Borrelia burgdorferi*, and *Mycobacterium tuberculosis*—share structural similarity

Table 2 Pathogenetic Mechanisms of Infection-Induced Antiphospholipid Syndrome

Mechanism	Pathophysiological Description (Underlying Process)
Molecular mimicry	Structural and sequence homologies between microbial proteins and host molecules (like β2-GPI) trigger an autoimmune response, leading to the production of cross-reactive antiphospholipid antibodies that contribute to thrombosis[27]
Activation of TLR4	Infections can lead to activation immune TLR4 receptors, which trigger inflammation that alters β2-GPI, promote the generation of aPL, and drive endothelial activation and thrombosis[6]
Impairment of immune complex clearance	aPL bind to β2GPI expressed on activated endothelial cells, forming immune complexes and initiating local immune activation[5,28]
Neutrophil extracellular traps (NETs)	Neutrophils release extracellular traps, while immune complexes activate complement pathways (C3a, C5a), amplifying inflammation[10]
«Second hit» theory	The "second hit" theory in APS suggests that while aPL may be present (the first hit), clinical thrombotic events typically occur only after a second trigger (eg, infection) activates immune pathways, leading to clot formation. This explains why not all individuals with aPL develop symptoms of APS[27]
β2GPI-independent pathways	Some lipid-binding aPL may promote thrombosis independently of β2GPI, via mechanisms such as TLR4 activation and endothelial stimulation. This expands upon the traditional view that non-β2GPI-dependent aPL are non-pathogenic[28]

with β2-glycoprotein I (β2GPI). The resulting cross-reactive antibodies target both microbial and self-antigens, potentially disrupting immune tolerance and triggering autoimmunity.[6,22,27]

2. *Toll-like receptor 4 (TLR4) activation*. Infectious agents can activate Toll-like receptor 4 (TLR4) both directly and indirectly. Bacterial lipopolysaccharides and viral glycoproteins can stimulate TLR4 directly on innate immune cells, initiating a cytokine storm and endothelial activation. In parallel, molecular mimicry may lead to the generation of aPL, particularly anti-β2GPI antibodies, which can form immune complexes that also activate TLR4 on monocytes and dendritic cells. Thus, both pathogens and aPL can contribute to TLR4-driven inflammation and thrombosis.[6,29]
3. *Impaired clearance of immune complexes*. APL–β2GPI complexes may deposit on endothelial surfaces, activate the complement cascade, and initiate localized inflammation and thrombosis. This mechanism appears particularly relevant in systemic infections accompanied by hypocomplementemia.[5]
4. *Neutrophil extracellular traps (NETs)*. APL have been shown to enhance the formation of NETs during infection. These structures promote platelet activation, endothelial injury, and thrombosis. This mechanism has been implicated in COVID-19–associated APS.[10]
5. "Second hit" *theory.* Circulating aPL may remain clinically silent until a secondary pro-inflammatory stimulus, such as infection, surgery, childbirth, or trauma, triggers overt thrombosis. This model suggests that the combination of pre-existing aPL and an additional stressor converts a subclinical state into active disease.[2]

To distinguish these from true pathogenic mechanisms, it should be noted that many infections, particularly HIV, HCV, syphilis, and COVID-19, are also associated with transient, low-avidity aPL, most commonly of the IgM isotype. These antibodies are generally non-pathogenic and should not be considered causative of APS. However, their presence may complicate diagnostic interpretation, especially when detected in patients with infection and thrombotic events of unrelated origin.[9,19,20,26] Besides, *c*ertain microorganisms, such as *Borrelia, Mycoplasma*, and HCV, can directly invade endothelial cells, leading to cellular activation, upregulation of adhesion molecules, and increased tissue factor expression.[7,8,17]

Table 3 Key Differences Between Primary and Infection-Induced Antiphospholipid Syndrome

Criterion	Primary APS	Infection-Induced APS
Type of aPL	Often IgG, high titer, β2GPI+	Often IgM, low titer, aCL+, β2GPI−
Persistence	≥12 weeks	Often transient
Timing of onset	Autoimmune background, without infection	During or immediately after infection
Course	Chronic, recurrent	Acute or single episode
Thrombosis	Often multiple, recurrent	Possible single, sometimes absent
Associated antibodies	Often ANA+, anti-dsDNA+ (in SLE)	Rarely, often only aPL
Antibody avidity	Generally low	Low
Autoantibody titers	Low	High
Light chains, subtype	Kappa (κ)	Lambda (λ)
Antibody isotype	IgM>IgG	IgG>IgM
Subclass IgG	IgG1, IgG3	IgG2, IgG4
Binding of antibodies to phospholipids in the presence of β2GPI	Suppressed	Enhanced

Abreviations: ANA, antinuclear antibodies; Anti-dsDNA, antibodies to double-stranded DNA; SLE, systemic lupus erythematosus.

Clinical Manifestations of Infection-Induced APS

The clinical spectrum of infection-induced antiphospholipid syndrome ranges from transient, self-limited features to severe thrombotic events, particularly when accompanied by additional proinflammatory triggers. The presentation is influenced by the nature of the infectious agent, the magnitude of the host immune response, the presence and type of cross-reactive aPL, and secondary precipitating factors. Several studies have examined viral infections in this context. One cross-sectional analysis found that APS patients co-infected with HCV and/or HIV were more likely to experience cardiovascular events and avascular necrosis, while deep vein thrombosis was reported less frequently—suggesting coexistence rather than a causal link.[7] Other studies noted thromboembolic events in aPL-positive individuals with HCV and HBV, although a definitive association with APS-related thrombosis could not be established.[19,20] Thrombotic complications have also been observed in patients following SARS-CoV-2 infection, with increased D-dimer levels and a high frequency of thromboembolic events reported in multiple cohorts.[3,11,30] Nonetheless, these findings remain heterogeneous and underscore the need for extended longitudinal follow-up.

Manifestations of infection-Induced APS include a broad spectrum of clinical features, generally less frequent or severe than in primary APS. Manifestations vary according to the infectious agent, immune response intensity, and presence of additional proinflammatory triggers.

Venous thrombosis is the most commonly reported complication, typically affecting the deep veins of the lower extremities, pulmonary arteries, or, particularly in hepatitis E virus (HEV) infection, the hepatic and splanchnic veins.[6,8] Arterial events, though less frequent, include ischemic strokes (notably in younger patients without conventional risk factors) and infarctions of the myocardium, spleen, kidneys, and brain.[7,22,23]

Obstetric complications, while less frequent than in primary APS, may involve recurrent early pregnancy loss, preeclampsia, or preterm delivery. Thrombocytopenia is observed in approximately one-third of cases and may occur in isolation or alongside thrombotic events.[22]

Neurological symptoms are heterogeneous. Stroke is most frequent, but chorea (notably in rheumatic fever), cognitive dysfunction, and organic psychosis, particularly in neuroborreliosis, have also been reported.[15,16] Cardiovascular manifestations may include valvular abnormalities such as mitral insufficiency or Libman–Sacks endocarditis; conduction disturbances are rare.[7,22]

Catastrophic APS (CAPS), although rare, represents a life-threatening form triggered by severe infections like sepsis, tuberculosis, or COVID-19. It is marked by diffuse microvascular thrombosis and multi-organ failure.[6,25]

Several cases illustrate a direct link between infection and APS. One involved a patient with chronic HCV infection who met criteria for primary APS, including recurrent thromboses, pregnancy loss, and persistent aPL positivity [7]. Another study reported thrombotic events and carditis in patients with acute rheumatic fever and detectable aPL, suggesting a pathogenetic link.[22] A fatal case of tuberculosis-associated CAPS and a case of neuroborreliosis with cerebrovascular microthrombosis and anti-β2GPI antibodies have also been documented.[15,25]

However, diagnostic certainty remains limited. In many studies, aPL positivity was transient, and clinical features did not consistently meet APS criteria. COVID-19–related studies, for example, reported high aPL prevalence (mostly IgM or isolated aCL) without thrombotic events or confirmation at 12 weeks.[9] Similarly, infections such as HIV, syphilis, and borreliosis frequently yielded false-positive aPL findings in the absence of thrombosis.[17,20] Even in chronic Lyme disease, where aPL were detected in the majority of cases, thrombotic events were uncommon.[17]

These findings underscore the importance of distinguishing infection-induced from primary APS. Key differences are summarized in Table 3.

Infection-Induced APS and the Significance of aPL Detection in Infectious Contexts

According to international classification criteria, the diagnosis of APS requires at least one clinical manifestation (such as thrombosis or obstetric pathology) in combination with one laboratory criterion, namely, the presence of antiphospholipid antibodies (aCL, LA, or aβ2GPI) at medium to high titers, confirmed on two occasions at least 12 weeks apart.[31] These criteria, however, were originally developed for primary APS or APS associated with systemic lupus erythematosus and do not account for cases arising in the context of acute infection. In such settings, aPL are often transient, typically of low avidity, and predominantly of the IgM isotype or consist of aCL antibodies that lack β2GPI-dependence. Furthermore, clinical manifestations such as stroke or thrombosis may result from multifactorial mechanisms—including complement activation, the formation of NETs, and hyperinflammatory responses such as cytokine storm—complicating the attribution of symptoms solely to APS. This diagnostic uncertainty limits the direct application of existing classification criteria to infection-associated cases.

Key Aspects and Challenges in Diagnosing Infection-Induced APS

One of the central challenges in diagnosing APS in infectious contexts lies in confirming the persistence of aPL over 12 weeks, as required by classification criteria. This is often not feasible when thrombosis occurs during the acute phase of infection, such as in COVID-19, hepatitis E, or tuberculosis.[8,9,25,32] In these situations, clinical decisions must often be made *ex juvantibus* or based on non-specific signs of coagulopathy.

The immunological profile of aPL also appears to differ in infection-induced cases. Several studies have shown that in viral and bacterial infections, aPL are commonly of the IgM-aCL isotype, lack β2GPI-dependence, and exhibit limited procoagulant potential (Table 4). In some instances, their presence likely reflects transient B-cell activation rather than an autoimmune state.[2,10]

Recent findings also shed light on the distinct immunopathogenic nature of aPL found in infectious contexts. Traditionally, antiphospholipid antibodies detected during infections, often lacking β2GPI-dependence, were considered non-pathogenic. However, Müller-Calleja et al[28] have demonstrated that certain lipid-binding aPL, which do not require β2GPI as a cofactor, may nonetheless promote thrombosis through alternative mechanisms involving endothelial activation and complement engagement. This suggests that at least a subset of infection-induced aPL may carry pathogenic potential via non-canonical pathways, distinct from those typically implicated in primary APS. These findings support the view that infection-associated APS may constitute a separate immunological entity and reinforce the need for adapted diagnostic frameworks.

The greatest diagnostic complexity arises in catastrophic APS (CAPS), where simultaneous thromboses affect multiple organs and the clinical course is often severe. Infections are implicated as a trigger in the majority of CAPS cases.[14,33] Even transient aPL may carry clinical weight in this context, calling into question the applicability of standard CAPS criteria that rely on delayed antibody confirmation.

Table 4 Variants of Antiphospholipid Antibodies and Their Impact

Antiphospholipid Antibodies (aPL)	Complications
aβ2GPI-domain I	Association with thrombosis
IgA aβ2GPI	Thrombocytopenia and livedo reticularis
Antibodies to the phosphatidylserine/prothrombin complex (Anti-PS /PT)	Strong correlation with vascular risks
Thin-layer chromatography (TLC) for aCL detection	TLC may potentially identify aPL presence
Anti-vimentin/CL	Correlation with thrombotic situations
Anti-AnnA5	Clinical correlation with morbidity
Anti-AnnA2	Changes in profibrinolytic activity
Anti-Annexin A2	Correlates with manifestations of Lyme arthritis and migrating erythema

Distinguishing APS from infection-related coagulopathies (such as those observed in sepsis, COVID-19, or HIV) is another key challenge. Certain features may assist in this differentiation: elevated D-dimer and fibrinogen in the absence of aPL are more suggestive of infectious coagulopathy, whereas the presence of aβ2GPI, persistent aPL, or a relevant clinical history (eg thrombosis or obstetric complications) supports a diagnosis of primary APS.[34–36]

A further limitation of the available literature is the frequent lack of detailed information regarding control groups and coexisting thrombotic risk factors (eg catheterisation, dehydration, sepsis). Many reports are retrospective in nature and do not consistently meet international diagnostic standards for APS, particularly regarding the requirement for repeated aPL testing. In most cases, systematic sampling was not performed, reducing the generalisability of the findings. These limitations underscore the persistent diagnostic uncertainty surrounding infection-induced APS. Taken together, the evidence suggests that infection-related APS may represent a distinct clinical entity, underscoring the need for adapted diagnostic criteria. Further clinical research is essential to validate this hypothesis, enhance diagnostic precision, and support future updates to classification criteria.

Clinical Implications

In clinical practice, transient aPL positivity may lead to uncertainty regarding the need for anticoagulation or further diagnostic work-up. However, based on current evidence, routine aPL screening in severely ill infected patients is not supported for the purpose of guiding anticoagulant therapy. Although aPL positivity has been reported in up to 50% of patients with COVID-19, these antibodies are typically transient, of low avidity, and not predictive of thrombotic events.[2,9,10] For example, Sciascia et al[2] found no thrombotic complications in aPL-positive patients with infection, while Atalar et al[36] reported no IgG aCL or anti-β2GPI positivity (markers most strongly associated with thrombotic risk in APS) in aPL-positive COVID-19 patients. Furthermore, triple aPL positivity, which is most strongly linked to thrombotic risk, was observed in only 2% of cases.[37] Still, it is important to recognize that the majority of studies have focused on COVID-19, which limits the generalizability of the findings to other infectious diseases.

These observations, together with the differing aPL profiles, lack of persistence, and absence of consistent associations with thrombosis, intensive care unit admission, or mortality, indicate that incidental aPL positivity should not serve as a basis for initiating or modifying anticoagulant therapy. While some reports have drawn attention to the potential protective role of anticoagulants in settings where APS-like features coexist with COVID-19,[38] such approaches should remain aligned with current clinical guidelines[39,40] until supported by robust prospective evidence. At the same time, clinicians should remain vigilant for true APS while avoiding overdiagnosis and overtreatment in the context of infection-induced transient aPL positivity.

Conclusions

1. The link between infection and APS is heterogeneous, varying by the type of pathogen, the profile of aPL, and their persistence over time.
2. Infections may lead to transient aPL positivity without clinical relevance or trigger autoimmune APS, particularly in catastrophic cases or when antibodies persist. Non-pathogenic or short-lived aPL should not be overinterpreted as diagnostic of APS.
3. Infection-induced APS is not well captured by current classification criteria and may represent a distinct clinical entity. The overlap of transient, non-pathogenic aPL with persistent, pathogenic forms highlights the need to re-evaluate diagnostic frameworks in infectious contexts.
4. This review underscores the need for further research to define the pathophysiology, diagnostic boundaries, and clinical implications of infection-associated APS. We hope this hypothesis-generating synthesis will encourage ongoing investigation and discussion.

Abbreviations

aβ2GPI, Anti-beta-2-glycoprotein I antibodies; aCL, Anticardiolipin antibodiesaPL, Antiphospholipid antibodies; APS, Antiphospholipid syndrome; CAPS, Catastrophic antiphospholipid syndrome; MV, Cytomegalovirus; COVID-19, Coronavirus Disease 2019; EBV, Epstein–Barr virus; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HEV, Hepatitis E virus; HIV, Human immunodeficiency virus; IL-6, Interleukin-6; LA, Lupus anticoagulant; MeSH, Medical subject headings; NETs, Neutrophil extracellular traps; TLR4, Toll-like receptor 4; TNF-α, Tumour necrosis factor-alpha.

Date and Materials Statement

This is a narrative review without statistical analysis of the raw medical record data. If necessary, more data can be provided by the corresponding author upon reasonable request.

Ethics Statement

Ethical review and approval were not required for this submission.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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