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COVID-19 and antiphospholipid antibodies

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ABSTRACT

Antiphospholipid syndrome and the coagulopathy of COVID-19 share many pathophysiologic features, including endotheliopathy, hypercoagulability, and activation of platelets, complement pathways, and neutrophil extracellular traps, all acting in concert via a model of immunothrombosis. Antiphospholipid antibody production in COVID-19 is common, with 50% of COVID-19 patients being positive for lupus anticoagulant in some studies, and with non-Sapporo criteria antiphospholipid antibodies being prevalent as well. The biological significance of antiphospholipid antibodies in COVID-19 is uncertain, as such antibodies are usually transient, and studies examining clinical outcomes in COVID-19 patients with and without antiphospholipid antibodies have yielded conflicting results. In this review, we explore the biology of antiphospholipid antibodies in COVID-19 and other infections and discuss mechanisms of thrombogenesis in antiphospholipid syndrome and parallels with COVID-19 coagulopathy. In addition, we review the existing literature on safety of COVID-19 vaccination in patients with antiphospholipid antibodies and antiphospholipid syndrome.

1. Introduction

One of the major mediators of morbidity and mortality in coronavirus disease 2019 (COVID-19) is a coagulopathy characterized by increased risks of arterial, venous, and microvascular thrombosis [1,2]. A multitude of pathophysiologic processes drive this hypercoagulable state, including endotheliopathy, cellular activation and inflammation, complement activation, autoantibody generation, cytokine dysregulation, and fibrinolytic derangements, all supporting a model of immunothrombosis as observed in other microvascular inflammatory diseases [3–15].

Antiphospholipid syndrome (APS) is an autoimmune, thromboinflammatory disease characterized by thrombosis and/or pregnancy loss in the presence of one or more antiphospholipid antibodies (aPL) [16]. APS can occur as a primary disorder or concomitantly with another underlying autoimmune disease such as systemic lupus erythematosus [17]. A diagnosis of APS may be established on the basis of the revised Sapporo criteria, which require thrombotic or obstetrical complications and persistent positivity for lupus anticoagulant (LA) or high-titre anti-cardiolipin (aCL) or anti-beta-2 glycoprotein I (aβ2GPI) IgG or IgM antibodies [18]. The primary pathogenic antibodies in APS are aβ2GPI, which activate endothelial cells, leading to a hypercoagulable state. Other “non-Sapporo” criteria aPL such as antiphosphatidylserine and prothrombin antibodies (aPS/PT) have also been described in APS, but their clinical significance is uncertain [19].

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LA testing is a complex, multi-step process [20]. The first test, a screening test, measures clotting times in the presence of a reagent exquisitely sensitive to the presence of phospholipids (e.g., Russell's viper venom) [20]. If the clotting time as measured in the screening test is prolonged, a mixing study is done utilizing an equal volume of the patient's plasma with normal pooled plasma; failure of the mixing study to correct the prolonged clotting time is suggestive of the presence of an inhibitor. The final confirmatory test involves the addition of excess phospholipid to shorten or correct the prolonged coagulation test; correction of a prolonged clotting time with added phospholipid and not with control plasma is characteristic of LA. A number of factors may lead to false positive LA testing, most commonly anticoagulant medications that prolong clotting time measurements.

The presence of aPL in COVID-19 was first reported early in the pandemic by investigators in Beijing, who identified three patients with COVID-19, multiple cerebral infarctions, and, in one case, limb ischemia, who tested positive for aCL IgA and aβ2GPI IgA and IgG antibodies [21]. Several subsequent studies followed exploring potential links between APS and COVID-19 based on similar immunothrombotic features of both diseases [22]. In this review, we explore the prevalence and significance of aPL in COVID-19, the shared mechanisms of thrombosis in APS and COVID-19 coagulopathy, and the implications of COVID vaccination in APS patients.

2. Mechanisms of thrombogenesis in APS

aPL are not thrombogenic on their own, and a multiple-hit model is believed to explain the progression from aPL to thrombotic or obstetrical sequelae. Binding of aPL to endothelial cells and monocytes induces expression of cellular adhesion molecules and tissue factor, triggering activation of endothelial cells and of the coagulation cascade [23–25]. aPL also cause production of inflammatory cytokines such as interleukin-6, interleukin-8, and vascular endothelial growth factor [26]. aPL binding to β2GPI activates apolipoprotein E receptor 2, leading to upregulation of protein phosphatase 2A and down regulation of Akt and endothelial nitrous oxide synthase, reducing levels of nitric oxide, an anti-inflammatory and vasodilatory substance [27]. Together, these factors all lead to increased oxidant injury, activating the endothelium for thrombus generation [28,29]. Binding and endosomal uptake of aPL by monocytes and dendritic cells activates NADPH oxidase, producing superoxide and upregulating expression of Toll-like receptors 7 and 8, amplifying oxidative stress and inflammation and further driving thrombosis in APS [30]. aβ2GPI disrupt annexin A5, an anticoagulant protein found in placental and vascular endothelium, augmenting the risks of thrombosis and miscarriage in APS [31,32].

Platelets are also a major mediator thrombosis in APS [33]. aβ2GPI bind to multiple receptors on platelet surfaces, including platelet glycoprotein (GP) Ibα, GP IIb/IIIa (integrin $a_{IIb}\beta_3$), and apolipoprotein E receptor 2, with p38MAPK phosphorylation and release of multiple procoagulant molecules including thromboxane A2 and platelet factor 4, all leading to platelet activation [34]. In murine models, infusion of aβ2GPI leads to activation of endothelial cells, platelets, and monocytes [35]; aβ2GPI-β2GPI complexes selectively bind the platelet thrombus rather than the endothelium, amplifying platelet activation, leading to enhanced endothelial activation and fibrin generation [36]. P-selectin on platelets and endothelial cells as well as endothelial cell surface markers such as intercellular cell adhesion molecule-1 and vascular endothelial cell adhesion molecule-1 recruit leukocytes to platelet thrombi and endothelial cells in the presence of aPL [34,37].

In addition, aPL may activate the complement system, particularly the alternative complement pathway [38]. In murine models, complement deficient-mice are resistant to aPL-induced thrombosis or fetal loss [39–41]. APS patients near the time of a thrombotic event demonstrate increased complement activation as measured via a modified Ham assay and cell surface deposition of terminal complement C5b-9, while germline mutations can be identified in patients with catastrophic APS [42]. aβ2GPI complexes trigger the classical complement pathway by binding to C1q, activating C3b and engaging the alternative pathway [43]. A role for complement activation is further underscored by the successful use of eculizumab, a terminal complement inhibitor, in treating some patients with obstetrical or catastrophic APS [38].

The production of extracellular webs of chromatin by neutrophils, a.k.a. neutrophil extracellular traps (NETs), is an emerging hallmark of APS. NETs are complexes of decondensed chromatin with histones and neutrophil granule proteins released by neutrophils in response to various infectious and non-infectious stimuli. This process of NET production and release, known as NETosis, leads to activation of platelets, endothelial cells, and complement proteins [44]. Under normal conditions, NETs physically immobilize microbes and release antimicrobial substances such as antimicrobial peptides, histones and proteases [44]. When dysregulated, NETs may precipitate endothelial damage and thrombosis, contributing to the microvascular complications seen in numerous autoimmune diseases. Mice treated with IgG fractions from APS patients have higher circulating levels of cell-free DNA compared to controls, while thrombi from APS mice are enriched for citrullinated histone H3, a NET marker [45]; moreover, selective agonism of the adenosine A_{2A} receptor in a mouse APS model suppresses aPL-mediated NETosis and reduces thrombosis [46]. These studies highlight a potential role for NETosis in the pathogenesis of thrombosis in APS.

3. aPL and infections

aPL are known to develop transiently in the setting of numerous types of infections. Syphilis was the first infection to be linked with aPL [47,48]; historically, a falsely positive Rapid Plasma Reagin test was a hallmark of the presence of LA and aCL antibodies due to the presence of cardiolipin in the reagent. In one systematic review and meta-analysis, human immunodeficiency virus (HIV) and hepatitis C virus (HCV) were the two most frequent viruses reported to be involved in aPL generation, with HIV, hepatitis B virus (HBV), HCV, and Epstein-Barr virus (EBV) associated with the development of aCL antibodies and HCV and EBV additionally associated with aβ2-GPI antibody formation [47]. The prevalence of aCL in HIV, EBV, and HCV appears to be much higher than LA [49–51].

Among bacterial infections, Hansen's disease, Staphylococci, Streptococci, tuberculosis, Coxiella, Mycoplasma, Salmonella, Lyme disease, leptospirosis, and various forms of bacterial endocarditis have also been implicated in aPL production [47]. Parasitic

infections like malaria, kala azar, and toxoplasmosis also lead to aPL production [47].

One mechanism for production of aPL in infections may be molecular mimicry due to antigenic similarity and cross-reacting antibodies between the infectious agent and β2GPI in host tissue [48]. *Haemophilus influenzae*, *Neisseria gonorrhoea*, and *Clostridium tetani* share epitope homology with the β2GPI molecule, which may explain production of aβ2GPI antibodies in these and other bacterial infections [47]. However, the breadth of microbial agents associated with aPL generation is striking, and additional processes may account for aPL production across a range of different infections.

In most instances, aPL that arise in the setting of infection are transient phenomena restricted to active infection, while chronic infections such as HIV and HCV may demonstrate persistence of aPL whose clinical significance is unknown [48]. Some studies of aPL report increased rates of thromboembolic events with HBV or HCV and increased pregnancy-related events with parvovirus [48], while most other studies suggest that aPL in the setting of infection are clinically quiescent [47].

4. aPL in COVID-19

Numerous studies in the literature have described high rates of aPL in hospitalized patients with COVID-19 [52–60]. The rates of aPL in these studies are higher than those reported in other viral infections, but the analyses are all potentially confounded by reporting bias and the use of anticoagulation at the time that LA testing was performed, leading to the potential for falsely positive LA results [61]. In addition, acute phase reactants such as C-reactive protein may increase the risk of a false-positive LA result [60].

In the largest meta-analysis of aPL in COVID-19, which analyzed 1159 hospitalized patients with COVID-19 and at least one aPL across 21 different studies, the pooled prevalence rate of one or more aPL (aCL IgM or IgG, aβ2GPI, LA, or aPS/PT) was 46.8% [49]. The pooled prevalences for each of LA, aCL IgM or IgG, and aβ2GPI IgM or IgG were 50.7%, 13.9%, and 6.7% respectively. Of the total study population, 14.3% of patients were double positive for two Sapporo criteria aPL tests while 6.1% were triple positive for all three. The prevalence of aCL (28.8 versus 7.1%) and aβ2GPI (12.0 versus 5.8%) was significantly higher in critically ill versus non-critically ill patients, mirroring other analyses of aPL in critical illness outside of COVID-19 [62]. Another systematic review observed a wide range of prevalence of aPL in COVID-19 patients across different studies in the literature, with LA positivity reported in 35–90% of COVID-19 patients in the intensive care unit (ICU) and 20–66% for ICU and medical ward patients combined, and with 1–12% of patients being triple positive [22]. In this study, a high prevalence of non-Sapporo criteria antibodies was also observed (aCL IgA, 20% to more than 90% of patients; aβ2GPI IgA, 0–86%; aPS/PT, 0–24%; anti-annexin V antibodies, 3–19%) [21].

While most studies of aPL in COVID-19 have focused on hospitalized patients, one retrospective multicenter study examining both hospitalized and ambulatory COVID-19 patients found no significant difference in prevalence of aPL between these two populations (50% versus 43.3%, respectively) [49–51,63–65].

A few mechanisms have been proposed to explain the development of aPL in COVID-19: molecular mimicry, neoepitope formation, and phosphatidylserine exposure [31,66]. Coronaviruses are structurally comprised of four proteins: spike (S), membrane, envelope, and nucleocapsid [67]. The S glycoprotein, containing two subunits (S1 and S2), determines antigenic diversity of the virus and host tropism [68]. The S1 subunit allows the virus to attach to the host cell receptor while S2 mediates fusion of the viral capsid with the host cell membrane [31]. In molecular mimicry, the S1 and S2 glycoprotein subunits of the SARS-CoV-2 viral S protein form a phospholipid-like epitope that induces formation of aPL, which can trigger an autoimmune response if the antigenic determinants are similar to host human tissue [69]. The neoepitope model postulates that oxidative stress in COVID-19 causes a change in confirmation of β2GPI, a plasma protein involved in hemostasis and immunity, creating a neoepitope for the generation of aβ2GPI [70]. During pathogenesis of APS, oxidative stress leads to a thiol exchange reaction and formation of disulfide bonds in domains I and V of the β2GPI protein, leading to a conformational change that renders β2GPI immunogenic [71,72]. It is possible that oxidative stress from COVID-19 may induce similar conformational changes in β2GPI and consequent generation of aPL. Phosphatidylserine, located on the inner surface of the lipid bilayer, may become exposed during infection with COVID-19 or other viruses through the action of phospholipid scramblase, which may trigger aPL production as well as inflammatory and thrombogenic responses [66].

In the above studies, the ~50% reported prevalence of LA in COVID-19 is much higher than in other viral infections [49–51]. At first glance, this difference appears intriguing based on the increased association of LA with thrombosis compared to aCL or aβ2-GPI in APS, but reporting bias confounds any direct comparisons [63].

aPL generated during COVID-19 infection tend to demonstrate only transient elevation. One study of 31 ICU patients with COVID-19 found 23 (74.2%) with at least one aPL, but on repeat testing 1 month later, only one of the 10 patients retested had persistent aPL [73]. Another study of 79 hospitalized COVID-19 patients (mostly in the ICU) with an initially positive LA found that none of 42 who were retested between 3 and 6 months later had a positive LA, while 10 patients (23.8%) remained positive for other aPL [74]. Another study of critically ill COVID-19 patients examined aPL at multiple time points in six patients and observed distinct patterns of aPL positivity over time [75]; in some patients, aPL peaked around 30–50 days after disease onset, then declined over subsequent days, while other patients demonstrated more transient aPL positivity [75].

Compared to APS, aPL titres generated in COVID-19 are generally lower, with a preponderance of weakly reactive antibodies against domains 1 and domains 4–5 of β2-GPI, in contrast to strong reactivity against β2GPI domain 1 as seen in APS [76]. In studies of APS, aβ2GPI with strong reactivity against domain 1 are believed to be thrombogenic, while aβ2GPI with reactivity to domains 4–5 are generally not thrombogenic [76–78]. In light of this and the transient nature of aPL in COVID-19, the thrombogenicity of these antibodies is uncertain.

Table 1
Summary of studies of antiphospholipid antibodies in patients with COVID-19. Abbreviations: aPL, antiphospholipid antibodies; CVC, central venous catheter; DVT, deep venous thrombosis; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; MI, myocardial infarction; PE, pulmonary embolism.

Study [reference]	Study location	Setting	Number of patients	aPL tests performed	Number of patients with positive aPL, n	aPL persistent, type (ratio)	Thrombotic Events, n
Zhang et al. [21]	China	ICU	3	• LA • aCL IgA • aβ2-GPI IgG, IgA	0 3 3; 3	N/a	Strokes, MI, LI
Helms et al. [52]	France	ICU	57	• LA	50	N/a	N/a
Pineton de Chambrum et al. [115]	France	ICU	25	• LA • aCL IgA, IgG, IgM • aβ2-GPI IgA, IgG, IgM • aPS/PT IgG, IgM	23 7; 13; 5 3; 1;0 15; 14	n/a	6 PE
Fan et al. [93]	China	ICU	86	• aPL: LA or aCL or aβ2-GPI	12	n/a	6 strokes
Amezcua-Guerra et al [116].	Mexico	ICU	21	• aCL IgG, IgM • aβ2-GPI IgG, IgM • aPS/PT IgG, IgM • aPI IgG, IgM • aAV IgG, IgM	2; 3 1; 0 2; 4 0; 0 1; 4	n/a	2 PE
Devreese et al. [117]	Belgium	ICU	31	• LA • aCL IgA • aCL IgG, IgM • aβ2-GPI IgA • aβ2-GPI IgG, IgM • aPS/PT IgG, IgM	21 3 6; 1 3 3; 1 3; 4	At 1 month: 1/10 LA 0/4 aCL 1/2 aβ2-GPI tested again	4 CVC thrombosis, 2 Clotting of dialysis circuit, 3 Clotting ofECMO circuit, 2 DVT 1 Stroke
Borghi et al. [118]	France	ICU	122	• aCL IgG, IgM • aβ2-GPI IgG, IgM • aβ2-GPI IgA	7; 8 19; 11 8	n/a	N/a
Zhang et al. [119]	China	ICU	19	• LA • aCL IgA • aCL IgG, IgM • aβ2-GPI IgA aβ2-GPI IgG, IgM	16 2; 1 7 6; 0	n/a	4 ATE 1 VTE 7 micro-thrombi
Fan et al. [120]	Singapore	ICU	12 for LA, 4 for others aPL among 12 patients	• LA • aCL IgG, IgM • aβ2-GPI	6 1; 2 2	n/a	n/a
Alharthy et al. [121]	Saudi Arabia	ICU	3	• aCL • aβ2-GPI IgG, IgM	3 3; 3	n/a	1 DVT
Siguret et al. [122]	France	ICU	74	• LA • aCL or aβ2-GPI	63 9	n/a	26 DVT, 4 PE, 1 stroke, 1 CV thrombosis
Frapard et al. [123]	France	ICU	37	• aβ2-GPI or aCL IgA	7 6	n/a	21 VTE 11 circuit thrombosis

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Table 1 (*continued*)

Study [reference]	Study location	Setting	Number of patients	aPL tests performed	Number of patients with positive aPL, n	aPL persistent, type (ratio)	Thrombotic Events, n
				• aβ2-GPI or aCL, IgG or IgM			
Van der Linden et al. [124]	Sweden	ICU	23	• aCL IgA • aCL IgG, IgM • aβ2-GPI IgA • aβ2-GPI IgG, IgM	19 7; 9 20 7; 8	n/a	9 PE 3 DVT
Vlachoyiannopoulos et al. [125]	Greece	ICU	29	• aCL IgG, IgM • aβ2-GPI IgG, IgM	7; 3 5; 7	n/a	n/a
Karahan et al. [126]	Turkey	ICU	26 for LA, 31 for other aPL,among 31 patients	• LA • aCL IgG, IgM • aβ2-GPI IgA • aβ2-GPI IgG, IgM	6 0; 2 2 0; 0	n/a	1 stroke 1 MI 2 others thrombotic events
Mullaguri et al. [127]	USA	ICU	2	• aCL IgM, IgA	2,1	n/a	2 strokes, 2 PE
Trahtemberg et al. [128]	Canada	ICU	22	• aCL IgG, IgM • aβ2-GPI IgG, IgM • aβ2-GPI-DI IgG • aPS/PT IgG, IgM	13; 7 0; 0 0 0; 1	n/a	n/a
Najim et al. [129]	Qatar	ICU	60	• LA • aCL IgG, IgM • aβ2-GPI IgG, IgM	21 0; 0 1; 1	NA	1 VTE 2 ATE
Harzallah et al. [130]	France	NA	56	• LA • aCL or aβ2-GPI	25 5	n/a	n/a
Bowles et al. [131]	UK	NA	34	• LA	31	n/a	1 VTE
Gazzaruso et al. [82]	Italy	MW	45	• LA • aCL IgG, IgM • aβ2-GPI IgG, IgM	21 1; 1 2; 3	n/a	n/a
Popovic et al. [132]	France	NA	11	• aCL • aβ2-GPI	3 1	n/a	11 MI
Galeano-Valle et al. [133]	Spain	MW	24	• aCL IgG, IgM • aβ2-GPI IgG, IgM	0; 2 0; 2	n/a	24 VTE
Gatto et al. [65]	Italy	NA	72 for LA 121 for IgA 112 for other isotype, among 122 patients	• LA • aCL IgA • aCL IgG, IgM • aβ2-GPI IgA • aβ2-GPI IgG, IgM	16 2 15; 3 4 7; 8	n/a	17 VTE 1 stroke
Reyes et al. [91]	USA	NA	68	• LA • aCL IgG, IgM • aβ2-GPI IgG, IgM	38 0; 1 0; 1	n/a	17 DVT, 7 PE 6 ATE 2 strokes
Rothstein et al. [94]	USA	NA	9	• aPL	9	NA	strokes
Hossri et al. [134]	USA	NA	2	• LA	0 2	NA	Stroke, LI, SI

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Table 1 (*continued*)

Study [reference]	Study location	Setting	Number of patients	aPL tests performed	Number of patients with positive aPL, n	aPL persistent, type (ratio)	Thrombotic Events, n
				• aCL IgG, IgM			
				• aβ2-GPI	0		
Previtali et al. [135]	Italy	NA	35	• aCL IgA	0	Autopsy series	10 thromboembolic events 4 PE 2 strokes
				• aCL IgG, IgM	1; 2		
				• aβ2-GPI	0		
				• aPS/PT IgG, IgM	1; 2		
Gazzaruso et al. [58]	Italy	NA	192	• LA	95	NA	
Kanso et al. [136]	France	MW	2	• LA	1	NA	1 PE
Guillet et al. [137]	France	NA	4	• LA	1	NA	4 ATE (MI, LI,aortic thrombosis)
				• aCL IgG, IgM	0; 1		
Cristiano et al. [138]	Italy	MW	92	• aCL IgG, IgM	3; 1	NA	NA
				• aβ2-GPI IgG, IgM	0; 2		
				• aPS/PT IgG, IgM	2; 3		
				• aAV IgG, IgM	4; 3		
Balanchivadze et al. [139]	USA	NA	2	• aCL IgG, IgM	2; 2	At 3 months: 0/2 tested again	2 PE
				• aβ2-GPI IgA	2		
Le Joncour et al. [54]	France	MW	53 for LA 104 for other aPL,among 104 patients	• LA	21	NA	9 PE 1 DVT 1 aortic thrombus
				• aCL IgA	31		
				• aCL IgG, IgM	8; 8		
				• aβ2-GPI IgA	6		
				• aβ2-GPI IgG, IgM	5; 3		
Anaya et al. [140]	Colombia	NA	120	• aCL IgG, IgM	2; 22	NA	NA
				• aβ2-GPI IgG, IgM	0; 17		
Beyrouti et al. [141]	UK	Mixed	6	• LA	5	NA	6 strokes
				• aCL IgG, IgM	0; 1		
				• aβ2-GPI IgG, IgM	1; 1		
Pascolini et al. [142]	Italy	Mixed	33	• aCL IgG, IgM	3; 5	NA	NA
				• aβ2-GPI IgG, IgM	2; 2		
Bertin et al. [80]	France	Mixed	56	• aCL, IgG, IgM	16; 3 1; 4	NA	Strokes
				• aβ2-GPI IgG, IgM			
Zuo et al. [98]	USA	Mixed	172	• aCL IgA	6	NA	NA
				• aCL IgG, IgM	8; 39		
				• aβ2-GPI IgA	7		
				• aβ2-GPI IgG, IgM	5; 9		
				• aPS/PT IgG, IgM	42; 31		
Lerma et al. [143]	USA	Mixed	64	• aCL IgG, IgM	1; 1	NA	NA
				• aβ2-GPI IgG, IgM	1; 2		
				• aPS/PT IgG, IgM	1; 3		
Ferrari et al. [83]	France	Mixed	89	• LA	59	NA	14 VTE

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Table 1 (*continued*)

Study [reference]	Study location	Setting	Number of patients	aPL tests performed	Number of patients with positive aPL, n	aPL persistent, type (ratio)	Thrombotic Events, n
				• aCL	7		
				• aβ2-GPI	6		
Gutiérrez et al. [144]	Spain	Mixed	27	• LA	6	NA	2 LI
				• aCL (IgG or IgM)	0		6 DVT
							10 PE
				• aβ2-GPI IgA	1		2 strokes
				• aβ2-GPI (IgG or IgM)	1		
Xiao et al. [57]	China	Mixed	79	• LA	2	NA	19 DVT
				• IgA aCL, aβ2-GPI	17; 19		5 strokes
							1 MI
				• aCL IgG, IgM	4; 2		
				• aβ2-GPI IgG, IgM	12; 1		
				• aβ2-GPI-DI IgG	2		
				• aPS/PT IgG, IgM	0; 7		
Tvito et al. [145]	Israel	Mixed	43	• LA	16	NA	3 thrombotic events
				• aCL or aβ2-GPI	0		
Bauer et al. [146]	Germany	Mixed	17	• LA	3	NA	NA
Serrano et al. [59]	Spanish	Mixed	474	• aCL and/or aβ2-GPI IgG, IgM	28	NA	9 thrombotic events
				• aβ2-GPI IgA	71		
				• aPS/PT IgG or IgM	22		
Vollmer et al. [74]	France	Mixed	79 patients withLA positivity	• LA	79		30 VTE, 27 PE
			56 for aCL andaβ2-GPI,	• aCL IgG, IgM	1; 13	At 3 months: 0/42 LA	5 DTP or superficial VT
			53 for other aPL	• aβ2-GPI IgG, IgM	0; 3	tested again	10 ATE, 9 strokes, 0 MI, 1 mesenteric infarction
				• aPE	1		5 CT,
				• aPS	1		5 ECMO or RRT circuit
				• aPT	10		Clotting
				• aAV	1		
Gendron et al. [87]	France	Mixed	115 for LA, 97 for aCL IgA,	• LA	70	NA	Only for LA positivity:
				• aCL IgA	3		19 VTE
			98 for aβ2-GPI IgA,	• aCL IgG, IgM	9; 2		15 symptomatic PE
			109 for aPT				6 symptomatic DVT
			148 for other aPL among 154 patients	• aβ2-GPI IgG, IgM	5; 3		
				• aβ2-GPI IgA	2		
				• aPS/PT IgG, IgM	0; 7		
				• aPT IgG, IgM	11; 10		
Benjamin et al. [147]	UK	Mixed	77	• aCL IgG, IgM	11; 41	NA	12 VTE
				• aβ2-GPI IgG, IgM	6; 10		
				• aPS/PT IgG, IgM	3; 8		
				• aβ2-GPI-DI IgG	10		
Hollerbach et al. [148]	Germany	Mixed	174 for aCL and aβ2-GPI 53/174 had aPS/PT IgG, IgM	• aCL IgG, IgM	11; 0	NA	NA
				• aβ2-GPI IgG, IgM	1; 0		
				• aPS/PT IgG, IgM	0; 4		

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Table 1 (*continued*)

Study [reference]	Study location	Setting	Number of patients	aPL tests performed	Number of patients with positive aPL, n	aPL persistent, type (ratio)	Thrombotic Events, n
Lee et al. [149]	Korea	Mixed	105	• aCL IgG, IgM • aβ2-GPI IgG, IgM • aPS/PT IgG, IgM	2; 29 4; 4 0; 3		2 in hospital thrombosis
Gil-Etayo et al. [96]	Spain	Mixed	390	• aCL IgG, IgM • aβ2-GPI IgG, IgM • aPS/PT IgG, IgM	8; 10 4; 10 7; 9	5; 11 12; 16 8; 9	24 PE, 8 thrombotic stroke, 4 DVT and 1 arterial thrombosis
Constans et al. [85]	Spain	Mixed	211	• LA	128	NA	2 PE, 2 MI, 2 ischemic stroke
Emmenegger et al. [150]	Germany	Mixed	95	• aCL IgG, IgM • aβ2-GPI IgG, IgM • aPS/PT IgG, IgM • aAV IgG, IgM	0,12% 2.04,42.67% 0,28% 2.04,29.33%	NA	NA
Shi et al. [151]	USA	Mixed	118	• aCL IgG, IgM • aβ2-GPI IgG, IgM • aPS/PT IgG, IgM	4.29 2,5 28,18	NA	NA
Atalar et al. [152]	Turkey	Mixed	73	• aCL IgG, IgM • aβ2-GPI IgG, IgM • LA	0,3 0,7 12		3 thrombosis
Shah et al. [153]	USA	Mixed	20 (Hospitalized COVID-19 patients with a thromboembolic event)	• aCL IgG, IgM • LA	1,10 1	NA	
Bertin et al. [154]	France	Mixed	157	• aCL IgG, IgM • aβ2-GPI IgG, IgM • aPE IgG, IgM • aPT IgG, IgM	41,13 6,10 25,6 1,17	NA	8 Thromboembolic events
Espinosa et al. [155]	Spain	Mixed	158 for first sample,58 for second sample	• aCL IgG, IgM • aβ2-GPI IgG, IgM • LA • aPS/PT IgG, IgM	11,5 6,2 24 3,9	5,10 5,4 17 1,7	27 PE, 1 CVA
Rosales-Castillo et al. [156]	Granada	Mixed	189 for first sample,69 for second sample	• aCL IgG, IgM • aβ2-GPI IgG, IgM • LA	3,7 6,9 24	2,6 4,6 10	No thromboembolic event

5. aPL and clinical outcomes in COVID-19

Individual studies have drawn a diverse range of conclusions about correlations between aPL in COVID-19 and clinical outcomes such as disease severity, laboratory markers, thromboembolic complications, and mortality (Table 1). Some studies have described either a strong and statistically significant association between aPL and disease severity or mortality, or an enrichment of aPL positivity among hospitalized COVID-19 patients as a function of disease severity, while others have not [74,79–86]. Elevated levels of acute phase reactants such as C-reactive protein and fibrinogen have been observed in COVID-19 patients with a positive LA test in a couple prospective studies [82,87]. Other studies, however, have not observed differences in these parameters [42,71,83,88,89].

In the largest meta-analysis of aPL in COVID-19, no association between aPL positivity and mortality was found [49]. A number of

studies have described either an association between aPL and thrombosis in COVID-19, or an increased representation of aPL in COVID-19 patients with thrombotic complications including deep venous thrombosis, pulmonary embolism, stroke, or myocardial infarction [54,90–96]. By contrast, other studies, including the largest meta-analysis of aPL in COVID-19, have found no association with thrombosis [49,97]. Differences in aPL titres, persistence, and structural biology in COVID-19 compared to APS as described earlier may contribute to some of this variation.

One study found elevated markers of neutrophil function and NET formation in sera from 172 hospitalized patients with COVID-19 and high aPL titres [98]. In this study, IgG antibodies purified from COVID-1 patients with high aPL titres triggered NETosis in vitro, suggesting that aPL in some patients with COVID-19 may display biological activity, although their clinical relevance remains uncertain [86].

6. Pathophysiologic similarities between APS and COVID-19

APS and the coagulopathy of COVID-19 share many similar mechanisms that are believed to drive microvascular injury and thrombosis [99] (Fig. 1). In both APS and COVID-19, the production of nitric oxide is reduced due to inhibition of endothelial nitric oxide synthase, predisposing the endothelium to injury [99]. Markers of endothelial activation and damage including von Willebrand factor, tissue-type plasminogen activator, and soluble thrombomodulin correlate with disease severity in COVID-19, with upregulated expression of angiogenesis genes in lung tissue, underscoring the importance of the endothelium in COVID-19, similar to APS [88,99,100]. Complement activation has a significant role in both APS and COVID-19. SARS-CoV-2 activates all three complement pathways; viral antigens form immune complexes that activate the classical pathway while the spike protein of SARS-CoV-2 binds mannose-binding lectin, activating the lectin pathway [99]. The alternative complement pathway on cell surfaces is triggered by F-spike proteins (subunit 1 and 2), a mechanism that can be blocked using a Factor D inhibitor [43]. C3 convertase production by binding of the pathogen to a component of the alternative pathway can also activate the alternative pathway [43]. Skin and lung samples as well as elevated membrane attack complex levels in sera of patients, delineate the activation of these pathways in COVID-19, similar to thrombotic APS [43,89,101].

NETosis may be a central part of the pathogenesis of both APS and COVID-19 coagulopathy. In COVID-19, hyperstimulation of the immune system leads to NET production and microvascular occlusion as evidenced by myeloperoxidase-DNA and citrullinated histone H3 complexes, similar to APS [102]. NETosis may also function in mediating acute lung injury in COVID-19 [103].

Platelet activation is a hallmark of both APS and COVID-19 thrombosis. COVID-19 infection alters platelet transcriptosomes and leads to aggregate complexes of platelets with neutrophils, monocytes, and lymphocytes and platelet-monocyte aggregates in severe COVID-19 express tissue factor [5,104]. Moreover, sera from COVID-19 patients has been shown to lead to increased platelet apoptosis via IgG-mediated mechanisms [105]. Activated platelets in COVID-19 also express S100A8/S100A9 (MRP8/MRP14, calprotectin), correlating with markers of endothelial cell activation [106]. Hence, through various mechanisms platelet activation leads to increased thrombosis in COVID-19, similar to APS.

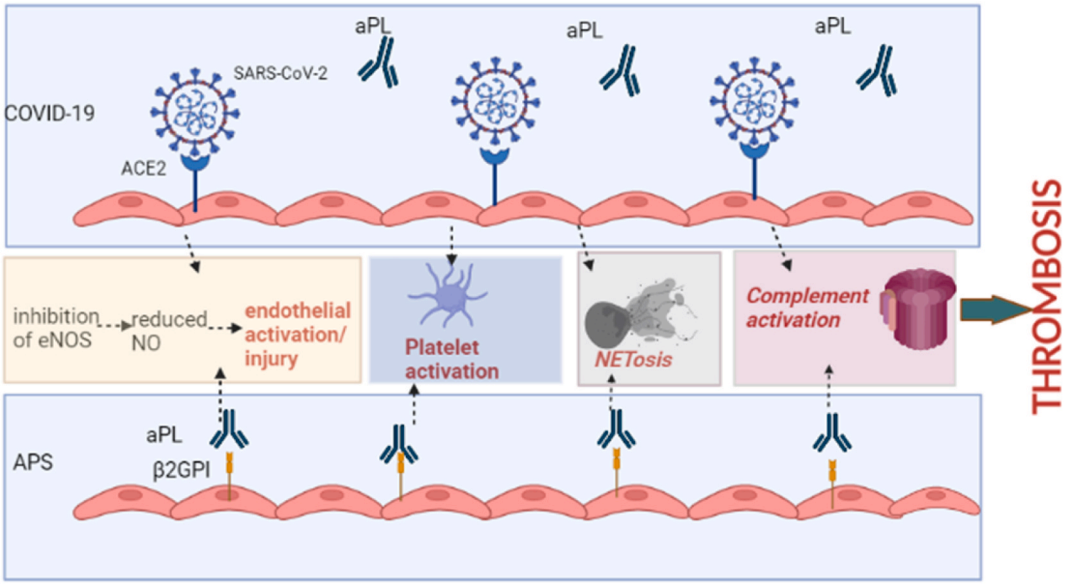

Fig. 1. Common mechanisms of thrombosis shared by antiphospholipid syndrome and COVID-19. Abbreviations: ACE2, angiotensin converting enzyme-2; aPL, antiphospholipid antibodye; β2GPI, beta-2 glycoprotein-I; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; NETosis, neutrophil extracellular trap formation and release. (Figure created using BioRender.com.)

7. COVID-19 vaccination in APS

Questions regarding the safety and efficacy of COVID vaccines in patients with aPL or APS have been frequently been raised, with a few studies reporting overall favorable tolerance and minimal complications [107]. One multicenter Italian survey study evaluated 161 patients with triple positive APS who received either the Moderna or the Pfizer-BioNTech COVID-19 vaccine [107]. Following the first vaccine dose, 83% experienced either no adverse reaction or minimal local signs/symptoms at the site of injection, while 12% had flu-like symptoms for less than 1 day and 4% for more than 1 day; 1% sought medical care, and no patients required hospitalization. Following the second dose, 68% had a minimal local reaction at the injection site; 22% had flu-like symptoms for less than 1 day and 8% for more than 1 day, while 2% sought medical care. One patient developed deep venous thrombosis 39 days after receiving the second dose. No patients required hospitalization or developed a severe allergic reaction after either dose [107].

A separate single-institution Italian survey study evaluated 102 patients who received either the Moderna or Pfizer-BioNTech COVID-19 vaccine, included 52 patients with APS and 50 with aPL and no clinical APS features [108]. Of the total study patients, 76% experienced injection-site pain, fatigue, or headache; all reported symptoms were transient and resolved within 10 days. Overall, 71% of patients classified their symptoms as mild and 29% as moderate. One patient with thrombotic APS and chronic thrombocytopenia on long-term vitamin K antagonist therapy experienced self-limiting purpuric lesions on her calves 10 days after the second vaccine dose. Together, these two studies suggest that adverse events following COVID-19 vaccination with either the Moderna or Pfizer-BioNTech vaccine in patients with aPL or APS are mostly mild and self-limited [108].

A rare complication of COVID-19 vaccination is vaccine-induced thrombotic thrombocytopenia (VITT), which may arise within several weeks following vaccination with adenovirus vector-based formulations such as ChAdOx1 nCoV-19 (AstraZeneca) or Ad26. COV2.S (Johnson & Johnson/Janssen) [109]. VITT arises as a result of antibodies against platelet factor 4 (PF4), similar to heparin-induced thrombocytopenia (HIT). Parallels among VITT, HIT, and APS have often been described, as all three are antibody-mediated processes associated with thromboembolic manifestations. Patients with VITT or HIT may be positive for aPL, although the clinical significance of aPL in these conditions is uncertain [110–113]. One study of 126 aPL-positive patients (89 with APS, 37 with asymptomatic aPL) who mostly received the Pfizer-BioNTech COVID-19 vaccine found anti-PF4 antibodies in 9 patients, with no significant change in anti-PF4 antibody titres before or after vaccination in either APS or asymptomatic aPL-positive patients [114]. Sera from patients with high-titre anti-PF4 antibodies did not alter in vitro platelet aggregation, and no cases of VITT were observed, even in the few study patients who received an adenovirus vector-based COVID-19 vaccine [114].

8. Conclusions and summary

APS and COVID-19 share many pathophysiologic features common in microvascular and immunothrombotic diseases, including endotheliopathy, platelet activation, complement activation, and NETosis, among others. Despite these shared features, a role for aPL in pathogenesis of COVID-19 remains uncertain. aPL occur at high prevalence in patients with COVID-19, with LA reported in ~50% of patients with COVID-19 and non-Sapporo criteria aPL being common; however, studies suggest that aPL titres in COVID-19 are usually only transiently elevated, and overall aPL titres in COVID-19 appear to be lower than those reported in APS. Biological differences in aβ2GPI antibody epitopes in APS compared to COVID-19 may underlie some of the differences in pathogenicity of aPL in these two conditions. A correlation between aPL positivity and disease outcomes in COVID-19 such as thrombosis or mortality remains unclear with different studies reporting varying results. Further investigation is required to delineate the significance of aPLs in mediating disease severity, thrombosis, and other outcomes in COVID-19. COVID-19 vaccination has been established to be generally safe in APS patients.

Practice points

- Antiphospholipid syndrome and COVID-19 share many pathophysiologic features common in immunothrombotic diseases
- Antiphospholipid antibodies are common in COVID-19, yet their clinical relevance is uncertain
- COVID-19 vaccination is generally safe in patients with antiphospholipid syndrome or antiphospholipid antibodies.

Research agenda

- Further studies are needed to explore the biological similarities and differences of antiphospholipid antibodies in COVID-19 and antiphospholipid syndrome and to understand the clinical implications of antiphospholipid antibodies in COVID-19

Declaration of competing interest

None of the authors report any conflicts of interest.

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