LEADING ARTICLE

Managing Antiphospholipid Syndrome in Children and Adolescents: Current and Future Prospects

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Abstract

Pediatric antiphospholipid syndrome (APS) is a rare acquired multisystem autoimmune thromboinflammatory condition characterized by thrombotic and non-thrombotic clinical manifestations. APS in children and adolescents typically presents with large-vessel thrombosis, thrombotic microangiopathy, and, rarely, obstetric morbidity. Non-thrombotic clinical manifestations are frequently seen in pediatric APS and may be present even before the vascular thrombotic events occur. We review insights into the pathogenesis of APS and discuss potential targets for therapy. The identification of multiple immunologic abnormalities in patients with APS reveals molecular targets for current or future treatment. Management strategies, especially for APS in adolescents, require screening for additional prothrombotic risk factors and consideration of counseling regarding contraceptive strategies, lifestyle recommendations, treatment adherence, and mental health issues associated with this autoimmune thrombophilia. The main goal of therapy in pediatric APS is the prevention of thrombosis. The management of acute thrombosis events in children and adolescents is the same as for primary APS, which involves isolated occurrences, and secondary APS, which is seen in association with another autoimmune disease, e.g., systemic lupus erythematosus. A pediatric hematologist should be consulted so other differential thrombophilic conditions can be eliminated. Therapy includes unfractionated heparin or low-molecular-weight heparin followed by vitamin K antagonists. Treatment of catastrophic APS involves triple therapy (anticoagulation, intravenous corticosteroid pulse therapy, and plasma exchange) and may include intravenous immunoglobulin for children and adolescents with this condition. New drugs such as eculizumab and sirolimus seem to be promising drugs for APS.

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Key Points

Management strategies, especially for antiphospholipid syndrome (APS) in adolescents, should include screening for additional prothrombotic risk factors and consideration of contraceptive strategies, lifestyle recommendations, treatment adherence, and mental health issues associated with this autoimmune disorder.

The management of acute thrombotic events is the same for primary and secondary APS in children and adolescents and includes unfractionated heparin or low-molecular-weight heparin followed by long-term vitamin K antagonists. The numerous immunologic abnormalities that occur in patients with APS reveal other potential molecular approaches for current and future treatment.

1 Introduction

Pediatric antiphospholipid syndrome (APS) is a rare acquired multisystem autoimmune thrombo-inflammatory condition characterized by venous and arterial thrombo-embolic events and, rarely, pregnancy morbidity in adolescents [1–10]. Despite its rarity in childhood and adolescence, it is one of the main non-congenital causes of symptomatic thromboembolism in the pediatric population [11]. The laboratory hallmark of APS is the persistent ($\geq$ 12 weeks) presence of elevated titers of pathogenic antiphospholipid antibodies (aPL), including lupus anti-coagulant (LA), anticardiolipin antibodies (aCL), and anti-β2-glycoprotein I antibodies (anti-β2GPI) [1–10].

Compared with adults, children and adolescents generally have fewer concomitant prothrombotic risk factors such as arterial hypertension, smoking, dyslipidemia, atherosclerosis, and use of estrogen-containing oral contraceptives [9]. In addition, non-thrombotic clinical manifestations are frequently reported in pediatric APS and may be present even before the vascular thrombotic events [2]. The most common non-thrombotic manifestations in children and adolescents with APS are hematological (immune thrombocytopenia [ITP], autoimmune hemolytic anemia [AIHA], and Evans syndrome [characterized by the concomitant or sequential appearance of ITP and AIHA]), dermatological (livedo reticularis), and neurological (epilepsy, migraine, chorea) [12–17].

Pediatric APS occurs in neonates through to adolescents and can be classified as primary APS (PAPS), without any associated disease, or secondary APS (SAPS), when associated with another underlying illness [6], mainly autoimmune conditions such as childhood-onset systemic lupus erythematosus (cSLE) [8, 12–14]. A more aggressive APS subset is named pediatric catastrophic antiphospholipid syndrome (CAPS). It is a life-threatening condition characterized by multiple thromboses and micro-thrombosis in a short period of time. Prior infections are relevant precipitating factors for this devastating event in children and adolescents [18].

The updated Sapporo criteria are used for research purposes. However, these criteria were developed for adult APS [19] and did not include non-thrombotic features, a well-known clinical and laboratory spectrum of pediatric APS. Pregnancy morbidity alone is also very rare in pediatric populations with APS [1]. Data on therapy for pediatric APS are sparse, but the increased understanding of the underlying APS pathophysiology has led to emerging treatment options.

Our objective was to review the recent publications for pediatric APS, particularly focusing on new findings relevant to the pathogenesis, diagnosis, and clinical studies of pediatric APS; management and pharmacological therapy; and prognosis in children and adolescents. This narrative review does not cover neonatal APS and infants born to mothers with APS.

2 Pathogenesis

Multiple immunologic abnormalities that occur in patients with APS have potential as molecular targets for current or future treatment. In lower-level organisms, one single cell is capable of performing both hemostatic and inflammatory functions. Evolutionarily, more complex mechanisms with more cells and cytokines have developed to perform these functions, maintaining a strong interaction between the coagulation and inflammatory pathways [20, 21]. A disturbance in this interdependent and delicate system can lead to an inflammation-related thrombosis, contributing to APS pathogenesis [3, 22].

2.1 β2 Glycoprotein I

The protein β2GPI is a five-domain lipid-binding molecule with a high serum concentration. It is present in both open and closed (circular) forms and plays a central role in APS pathophysiology. The J-shaped open form exposes the N-terminal Domain I (DI), the main target of pathogenic antibodies in APS [23]. A recent study proposed that this open form is more frequent under physiological conditions [24] than previously reported [25]. In fact, in sera collected from patients with APS, antibodies to the DI of β2GPI were present more frequently and had significantly higher titers in those with thrombotic complications than in those without these conditions [26]. The structural changes between the β2GPI forms are determined by glycosylation, pH, salt concentrations, and oxidative state and may also affect β2GPI physiological functioning [23, 27, 28]. Indeed, in coagulation assays, the open form of β2GPI had a significant prolonging effect on fibrin formation in a dilute prothrombin time (PT) test and dilute activated partial thromboplastin time (aPTT) test [27], and the oxidized and more immunogenic β2GPI [29] is present in higher levels in patients with APS [30].

β2GPI also participates in a variety of physiological processes with the ability to regulate the complement and coagulation systems with procoagulant and anticoagulant effects. The procoagulant effects include thrombomodulin complex and protein C inhibition and impaired annexin V binding. On the other hand, β2GPI inhibits thrombin activation, prevents generation of factor Xa, and impairs platelet aggregation [23, 31, 32]. β2GPI also interferes in innate immunity via complement inhibition and is involved in the clearance of lipopolysaccharides [23, 33].

aPL mainly target β2GPI, promoting an imbalance in its functions towards a pro-inflammatory and prothrombotic status. Anti-β2GPI antibodies disturb neutrophils, monocytes, platelets, trophoblasts, and endothelial cell activation pathways through cell-surface proteins, such as low-density lipoprotein receptor-related protein 8, also known as apolipoprotein E receptor 2 (apoER2), annexin A2, and toll-like receptor (TLR)-4 and -2 [34]. A variety of in vitro and animal models have shown the impact of these receptors in thrombosis and fetal loss [35] (Fig. 1).

2.2 Anti-β2GPI Antibodies: Endothelial Cells and Platelets

Endothelial cells produce nitric oxide (NO) via endothelial NO synthase (eNOS). NO is a powerful vasodilator with antithrombotic effects. In response to anti-β2GPI antibodies via apoER2 receptors, eNOS activity is inhibited, reducing bioavailable NO levels and thereby blocking vasodilation [36, 37]. In the same way, patients with PAPS showed a decreased level of nitrite, a NO metabolite, and this has been associated with vascular occlusion [38]. Moreover, the eNOS antagonism induced by aPL and apoER2 receptors promoted leukocyte–endothelial cell adhesion and increased thrombus formation in animal models [39]. Interestingly, a recent in vitro study suggested that phosphatidylserine/prothrombin antibodies exerted similar prothrombotic effects in endothelial cells [40].

The chronic state of vascular cell activation produced by anti-β2GPI upregulates the expression of monocyte chemoattractant protein 1, promoting tissue factor (TF) production by monocytes, the main factor of the extrinsic pathway of coagulation, and stimulates the release of microparticles containing TF and other procoagulant and pro-inflammatory
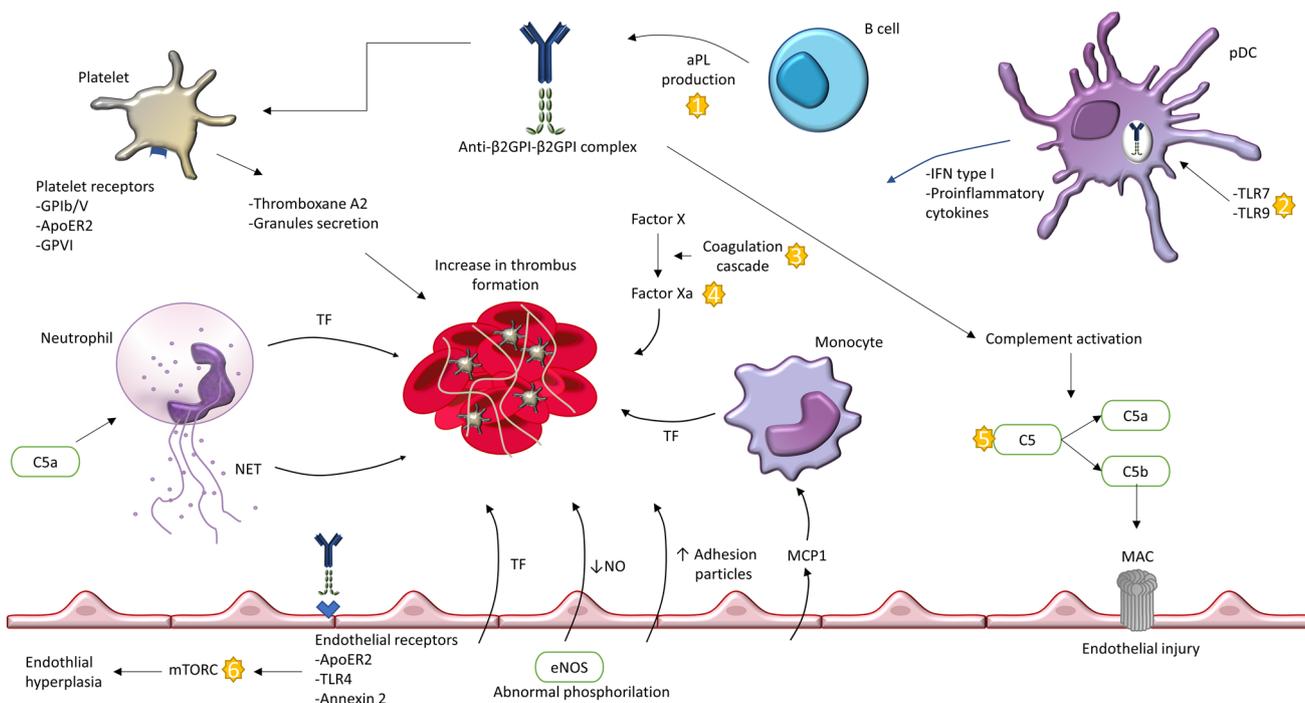

Fig. 1 Pathophysiological mechanisms of thrombus formation and sites of action of therapeutic interventions, starting from the top center and moving roughly counterclockwise. The B cells mature to plasma cells that produce aPL. aPL bind their relevant phospholipid/protein complexes. The anti-β2GPI-β2GPI complex activates platelets, increasing the secretion of granules and the synthesis of thromboxane A2, and induces the release of neutrophil extracellular traps. aPL immune complexes activate complement, producing C5a, a potent chemoattractant and activator of inflammatory cells such as neutrophils. Endothelial cells are activated, increasing the production of TF, adhesion particles, and monocyte chemoattractant protein 1. The mammalian target of rapamycin complex pathway induces endothelial hyperplasia. Endothelial NO synthase activity is impaired, reducing NO levels, inhibiting vascular relaxation and flow. Activated monocytes express TF on the cell surface. Complement activation releases anaphylatoxin and leads to membrane attack complex deposition on the cell surface. The anti-β2GPI-β2GPI complexes promote interferon type I and other proinflammatory cytokines by plasmacytoid dendritic cells via TLR7 and TLR9. Numbers indicate sites of action of the following therapeutic interventions: (**1**) rituximab; (**2**) hydroxychloroquine; (**3**) vitamin K antagonists—reduce biological activity of factors VII, IX, and X and thrombin; (**4**) direct oral anticoagulants and low-molecular-weight heparin; (**5**) eculizumab; (**6**) sirolimus, *aPL* antiphospholipid antibodies, *apoER2* apolipoprotein E receptor 2, *eNOS* endothelial NO synthase, *GPIb/V* glycoprotein Ib/V, *GPVI* glycoprotein VI, *IFN* interferon, *MAC* membrane attack complex, *MCP1* monocyte chemoattractant protein 1, *mTORC* mammalian target of rapamycin complex, *NET* neutrophil extracellular traps, *NO* nitric oxide, *pDC* plasmacytoid dendritic cells, *TF* tissue factor, *TLR* toll-like receptor, *β2GPI* β2-glycoprotein I

proteins from endothelial cells. Interestingly, endothelial cells exposed to aPL increased the expression of TF and adhesion molecules such as vascular cell adhesion molecule-1 [41]. In addition, patients with APS can present with a vasculopathy associated with severe endothelial cell proliferation and intimal hyperplasia induced by the activation of the mammalian target of rapamycin complex (mTORC) pathway. There is a correlation between aPL titers and the degree of mTORC activation [42–44], and blocking this pathway seems to be a potential therapy for a subset of patients with APS [44]; however, more studies are necessary to clarify whether this pathological mechanism of aPL is associated with the clinical characteristics of APS. Finally, endothelial cell dysfunction and interaction between aPL and oxidized low-density lipoprotein facilitate the development of atherosclerotic lesions [42, 45]. The anti-β2GPI–β2GPI complex can also activate platelet receptors such as apoER2 and glycoprotein Ib and VI, increasing the secretion of granules and the synthesis of thromboxane A2 [28, 42].

2.3 Immune Cells, Complement, and Interferon in Antiphospholipid Syndrome (APS)

Monocytes in patients with APS are in an activated state expressing TF on the cell surface, probably induced by intracellular signals via mitogen-activated protein kinase and nuclear factor (NF)-κB activation [46, 47], thereby promoting intravascular thrombosis. Neutrophil extracellular traps (NETs) are tangles of chromatin and antimicrobial proteins released by activated neutrophils containing DNA, histones, and proteins. NETs participate in host defense, inducing cell death. NETs injure the endothelium and activate the coagulation cascade. In vitro, anti-β2GPI–β2GPI immune complex induced NET formation more efficiently than anti-β2GPI or β2GPI alone [48]. β2GPI-reactive T cells are also involved in the APS pathogenesis, and the contribution of this process to clinical outcomes remains a field for investigation [49].

Evidence supports that anti-β2GPI antibodies are capable of activating the complement system [50]. Complement activation assessed via complement-mediated killing of nucleated cells was more frequently observed in patients with APS than in patients with systemic lupus erythematosus (SLE) and was related to thrombotic events [51]. Salmon and Girardi [52] demonstrated that the blockade of complement activation, via C3 convertase inhibitor or genetic deletion of C3, protected murine models from pregnancy complications induced by aPL antibodies. A recent systematic review demonstrated favorable results with an anti-C5 monoclonal antibody in CAPS treatment [53].

Increased expression of genes related to type I interferon (IFN), called the IFN signature, are associated with a variety of autoimmune diseases [54, 55]. Type I IFN can stimulate several different cell types through the Janus kinase pathway

and contribute to a disruption in the immune system. Plasmacytoid dendritic cells (pDC) are the main producers of type I IFN after endosomal TLR7 and -9 detection of nucleic acid containing immune complexes [54]. MicroRNAs are regulators of pDC activation. They are downregulated in patients with APS, and TLR7 stimulation induces this downregulation [56]. Recent studies showed that the type I IFN signature score was higher in adult patients with PAPS than in healthy controls [57, 58] and was positively correlated with anti-β2GPI antibodies [58]. This IFN signature score was lower in patients with PAPS using hydroxychloroquine [58]. Therefore, therapy targeting type I IFN production and signaling pathway components seems to be a potential approach for APS.

2.4 Infection

Via molecular mimicry, viral infections may also trigger aPL production, especially after chronic viral infections such as HIV and hepatitis C [59]. A systematic review and meta-analysis of viral infections and the risk of developing aPL and related thrombosis showed that these antibodies are not always transient and can be associated with thromboembolic events [60]. Recently, other studies reported thrombosis related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the presence of aPL, mainly LA, suggesting the presence of transiently positive aPL after infection [61, 62]. Further follow-up studies are necessary to confirm this association with APS disease.

2.5 Second Hit

Although the evidence supports a role for aPL in the pathophysiology of thromboembolic events, aPL antibodies are not in themselves sufficient to cause APS. The antibodies can be present in up to 11% of healthy children [63], indicating the need for a "second hit" endothelial injury, such as infection, trauma, neoplasia, smoking, and dyslipidemia, or an inherited prothrombotic risk factor to initiate thrombus formation.

3 Diagnosis of Pediatric APS

According to the 2006 updated APS classification criteria (Sapporo criteria), a patient is classified as having APS if at least one of the clinical criteria (vascular thrombosis or pregnancy morbidity) and at least one of the laboratory criteria (LA, aCL immunoglobulin M [IgM] and/or IgG, and anti-β2GPI IgM and/or IgG) are present [19]. An adaptation of these criteria was suggested for pediatric APS, excluding pregnancy morbidity as one of the clinical criteria, and has been used in the clinical practice of pediatric

rheumatologists [64]. However, there are no validated clinical and laboratory criteria for pediatric APS, leading to missed or delayed diagnosis in children and adolescents, especially for those with non-thrombotic manifestations [1, 2, 4, 22].

Importantly, the Single Hub and Access point for Pediatric Rheumatology in Europe (SHARE) provides evidence-based recommendations for the diagnosis and treatment of pediatric APS. The SHARE initiative suggested that the aPL profile (including LA, aCL IgG and IgM, and anti-β2GPI IgG and IgM) should be considered for all children and adolescents with suspicion of autoimmune thrombophilia [1].

Other points are relevant for the diagnosis of pediatric APS. High titers and persistent aPL positivity are important to meet the laboratory criteria and should be tested on two or more occasions at least 12 weeks apart [19], especially in children, since transient aPL related to infections and vaccines has been described [2]. LA-positive tests are associated with a higher risk of thrombosis [65, 66]. aCL and LA have demonstrated more sensitivity and specificity, respectively [22]. Inherited thrombophilia can provide the "second hit" in a child with aPL [15], so hereditary thrombophilia should be systematically investigated in pediatric patients with APS.

aPL are a heterogeneous group. Non-conventional aPL have been studied in clinical practice as a tool to optimize the diagnosis of APS, particularly in seronegative patients. In a recent study involving adolescent and adult patients, anti-β2GPI IgA, anti-β2GPI DI, and antibody against anti-phosphatidylserine/prothrombin (aPS/PT) demonstrated excellent specificity and positive predictive value without any additional benefit for the seronegative APS group. Another prospective cohort evaluated the clinical significance of IgG and IgM aPS/PT antibodies in 191 adult patients with APS and showed that the cumulative incidence rate of thrombotic events was significantly higher in the IgG aPS/PT-positive patients [67].

Recently, the first two development phases of new international APS classification criteria based on a weighted scoring system were concluded and proposed 27 candidate criteria divided into six domains (laboratory, macrovascular, microvascular, obstetric, cardiac, and hematologic). This project involved a multidisciplinary team of approximately 80 physicians, including pediatric rheumatologists [68]. To standardize laboratory diagnosis, APS ACTION, a multicenter prospective longitudinal APS study, provides proper aPL validation tests in all core laboratories worldwide [69].

CAPS is a rare and drastic manifestation of APS that affects less than 1% of cases. Interestingly, CAPS differs from APS with marked microvascular involvement and systemic inflammatory response. This diagnosis remains challenging, even for experienced professionals [70]. CAPS is diagnosed by the presence of aPL and vascular manifestations in at least three organs/tissues, confirmed by radiographic or histopathologic evidence of small-vessel occlusion. These manifestations occur simultaneously or in less than a week [70, 71]. A multicenter study showed that infections as precipitating factors and peripheral vessel thrombosis were more frequent in pediatric than in adult CAPS [18].

4 Clinical Studies of APS

The Ped-APS registry is the first relevant multicenter case series to describe clinical and laboratory characteristics in pediatric APS [12]. The authors evaluated 121 patients from 14 different countries. The mean age of APS onset was 10.7 years, with a slight predominance of female patients (54%). Deep vein thrombosis in the lower extremities, cerebral ischemic stroke, and cerebral sinus vein thrombosis were the most common first thrombotic events. The most important non-thrombotic clinical manifestations were Evans syndrome (12%), thrombocytopenia (8%), livedo reticularis (6%), and migraine (7%). PAPS occurred mainly in young patients, with a high frequency of arterial involvement and recurrence of thrombosis. Almost one-third of patients developed cSLE during follow-up [12]. Two other studies from Mexico and China, with small pediatric APS populations, also demonstrated similar characteristics [13, 14]. Interestingly, although heart valve vegetations were described as a non-thrombotic manifestation in children and adolescents [13, 14], the frequency of this manifestation was significantly lower than in adults [72].

The Childhood Arthritis and Rheumatology Research Alliance registry demonstrated that a history of vasculitis or avascular necrosis and the presence of circulating aPL were associated with increased odds of thrombosis in 979 patients with cSLE [73].

Regarding SAPS, a recent large Brazilian cohort study including 1519 patients with cSLE demonstrated that APS-related cSLE (cSLE-APS) was uncommon (4%), with a median age at diagnosis of 12 years. The main thrombotic event was deep vein thrombosis. Non-thrombotic symptoms were present in one-third of patients with cSLE-APS, especially livedo reticularis (21%) and cardiac abnormalities, such as sterile valve vegetations (6%) and valve thickening (3%). This study reinforced the finding that stroke is an important clinical manifestation, seen in 40% of cSLE-APS and 1% of all cSLE populations. Pregnancy morbidity (unexplained death of a morphologically normal fetus at 8 weeks' gestation) was observed in only 1% [8].

Other clinical studies related to APS and aPL have been recently reported. Pulmonary hypertension is a life-threatening condition that may affect outcomes in adults and patients with cSLE with APS and aPL [74, 75]. A systematic review and meta-analysis showed that the prevalence

of pulmonary hypertension in adult patients with SLE was higher in those with (12.3%) than without aPL (7.3%). The risk of pulmonary hypertension was significantly associated with LA and IgG aCL [74]. In contrast, pulmonary hypertension was a rare manifestation in 852 patients with cSLE (2%) and was generally asymptomatic and associated with mild lupus manifestations. Importantly, none of the children with pulmonary hypertension had pulmonary thromboembolism as a manifestation of pediatric APS [75]. Therefore, a transthoracic echocardiogram with pulmonary pressure measurements and valve assessment should be a routine exam in cSLE-APS and pediatric patients with PAPS [76–78]. Another study evaluated right ventricle dysfunction using the two-dimensional speckle-tracking-derived strain, an echocardiographic assessment of longitudinal myocardial deformation, in patients with cSLE and identified subclinical right ventricle systolic dysfunction in these patients. This finding was significantly associated with neuropsychiatric manifestations and the presence of aPL [79].

Furthermore, reduced penile dimensions were observed in patients with cSLE and in adult patients with SLE, with no deleterious effect in erectile function. Disease onset before first ejaculation in cSLE seems to affect penis development in the prepubertal period [80]. Interestingly, reduced penile size with erectile dysfunction and previous arterial thrombosis was reported in adolescents and adults with SLE-APS [81] as well as in young patients with PAPS [82], indicating a possible chronic subclinical endothelial dysfunction involving the corpus cavernosum. This sexual dysfunction and the penis morphofunctional abnormalities may induce psychological distress for adolescents with APS, and a multidisciplinary approach is necessary for these patients. Table 1 presents the thrombotic and non-thrombotic major clinical manifestations of pediatric APS.

Another significant aspect related to aPL positivity is the LA-hypoprothrombinemia syndrome (LA-HPS). LA-HPS is a rare condition described as bleeding symptoms associated with the prolongation of PT and aPTT because of anti-prothrombin antibodies in association with the LA. The prompt clearance of prothrombin–anti-prothrombin antibody complexes from the circulation results in hypoprothrombinemia and leads to hemorrhage [83]. A systematic review of LA-HPS associated with cSLE identified 32 cases with a median age of 12 years, the majority (70%) of whom were girls. Skin bleeding and epistaxis were the most common clinical presentation, and thrombotic manifestations were present in 12% of the patients [84]. Another study reported 54 LA-HPS cases that were commonly associated with viral infections, cSLE, and other autoimmune conditions. The mean age of diagnosis was 8 years, the female:male ratio was 2:1, and one-third presented major bleeding symptoms, including gross hematuria and gynecologic and gastrointestinal bleeding [85]. Currently, there are no uniform management recommendations for LA-HPS, and immunosuppressive drugs—such as corticosteroids, cyclophosphamide, and rituximab—have been used [83–85].

5 Management of Pediatric APS

5.1 General Management

The main goal of therapy in pediatric APS is the prevention of re-thrombosis, so treatment studies and recommendations are primarily focused on secondary thromboprophylaxis [1]. Given that most pediatric patients with APS are adolescents [12–14], management strategies should include other relevant aspects such as screening for additional prothrombotic risk factors, contraceptive strategies, lifestyle recommendations, treatment adherence, and mental health issues associated with this autoimmune thrombosis [9, 86–88].

Vaccination is a safe and powerful tool to reduce the burden of infectious diseases in clinical practice and should be recommended for patients with pediatric APS. Additional suggestions are required for cSLE-APS. Indeed, routine non-live vaccinations are strongly recommended for all patients with cSLE, whereas live attenuated immunizations are generally not indicated for immunosuppressed patients with cSLE [89]. A prospective pandemic influenza vaccine in patients with PAPS showed that this immunization was well-tolerated and did not trigger short- or long-term thrombosis or significant production of aPL-related antibodies (IgG/IgM aCL, anti-β2GPI, anti-annexin V, aPS/PT) [90]. Recently, aPL and thrombosis were reported after SARS-CoV-2

Table 1 Thrombotic and non-thrombotic major clinical manifestations of pediatric antiphospholipid syndrome

Manifestation	Major clinical presentation
Thrombotic	Arterial, venous, mixed and small vessels thrombosis
Non-thrombotic	
Cardiac	Valvular vegetation, valvular thickening
Neuropsychiatric	Chorea, epilepsy, migraine, mood disorder, cognitive disorder, transverse myelitis
Cutaneous	Livedo reticularis, Raynaud phenomenon, skin ulcers, purpura fulminans
Hematologic	Thrombocytopenia, autoimmune hemolytic anemia, Evans syndrome, bleeding disorders

infection. aPL may also induce thrombotic events following coronavirus disease 2019 (COVID-19) vaccination [91], but further prospective studies will be necessary to clarify these reports.

The general management of children and adolescents with APS includes prevention and treatment of risk factors for thrombosis, especially obesity/overweight, arterial hypertension, smoking, dyslipidemia, and avoidance of estrogen-containing oral contraceptives [88]. A study in patients with cSLE demonstrated that approximately one-third of adolescents reported alcohol use, despite a possible low risk for substance abuse/dependence [87]. These findings are particularly relevant in adolescent APS, since alcohol may interact with warfarin [5, 92].

Contraceptive counseling should be included in all medical visits for adolescents and young patients with APS, since APS in pregnancy has high maternal and fetal morbidities [9, 93, 94]. Estrogen-containing oral contraceptives increase the risk of thrombosis and are strictly prohibited for adolescents and adults with APS [9]. Recent guidelines and recommendations by the American College of Rheumatology strongly recommended intrauterine devices (levonorgestrel or copper) or the progestin-only pill in women with positive aPL. However, the copper intrauterine device may induce menstrual bleeding and cramping months after insertion, whereas progestin intrauterine devices reduce these manifestations [95].

Patients with APS using anticoagulants should also be advised to avoid contact sports because of the high risk of localized or systemic acute bleeding. However, exercise training has therapeutic potential in patients with pediatric rheumatic diseases, such as cSLE and pediatric APS [96–98]. Indeed, a 12-week supervised aerobic training program can be safe and effective in improving aerobic conditioning and physical function in patients with cSLE with APS [98].

Long-term anticoagulation requires appropriate routine monitoring of bone status for patients with pediatric APS. Unfractionated heparin, low-molecular-weight heparin (LMWH), and vitamin K antagonists (VKA) have a negative impact on bone mineral density and metabolism [99, 100]. Thus, children and adolescents with APS should be encouraged to maintain adequate calcium and vitamin D intake and to participate in regular physical activity.

5.2 Secondary Prophylaxis

The management of acute thrombotic events is the same for PAPS and SAPS in children and adolescents [101]. A pediatric hematologist should be consulted. Therapy includes unfractionated heparin or LMWH followed by VKA [101]. LMWH, mainly enoxaparin, is the primary choice for pediatric patients because of its stable pharmacokinetics and greater bioavailability [102]. A pharmacokinetic study of enoxaparin in children and adolescents proposed an initial dose of 1.0 mg/kg subcutaneously and every 12 h thereafter [103]. Although the recommendation for LMWH drug monitoring is the target anti-Xa activity [101, 104], a recent retrospective cohort study showed that the proposed guidelines did not consistently lead to therapeutic anti-Xa levels [105].

If thrombosis is associated with persistent aPL positivity, long-term anticoagulation should be indicated in pediatric PAPS and SAPS. VKA, such as warfarin, are the standard treatment, targeting an international normalized ratio (INR) of 2.0–3.0 for venous events [1, 106]. Evidence for recurrent venous thrombosis despite adequate treatment is limited.

For recurrent thrombosis, medication adherence must be systematically assessed at all appointments, and a new INR target of 3.0–4.0 or alternative therapies, such as an extended therapeutic dose of LMWH, could be considered [1]. European Alliance of Associations for Rheumatology (EULAR) recommendations also suggest adding low-dose aspirin with VKA, as an alternative to a higher INR [88]. Similarly, in cases of arterial involvement, the combination of antiplatelet agents and anticoagulation is also indicated [1], and the target INR could be 3.0–4.0 [88, 107, 108]. In adults, hydroxychloroquine should be considered as adjunctive therapy for anticoagulant-refractory thrombotic APS [106].

5.3 Direct Oral Anticoagulants

Direct oral anticoagulants (DOACs) selectively target factors in the coagulation pathway, mainly factor Xa and thrombin, and are widely used in adult patients for the prevention and treatment of thrombosis in several contexts [109]. They have advantages over other anticoagulant options, particularly for children and adolescents, and they do not require laboratory monitoring, can be administered orally, have a short half-life, and have little interaction with other drugs and food [110–112]. However, some drugs, such as anticonvulsants, immunosuppressants (cyclosporin and tacrolimus), and non-steroidal anti-inflammatory drugs, may reduce the efficacy of DOACs or increase bleeding episodes [113, 114].

Recently, clinical trials have been carried out in pediatric populations to assess the safety and efficacy of DOACs. Dabigatran etexilate, a direct thrombin inhibitor, is an alternative for the treatment of venous thromboembolism in children and adolescents [115–118]. Pharmacokinetic and pharmacodynamic studies showed adequate safety and tolerability with these drugs, and an oral liquid formulation for infants is available [115–117]. A randomized, controlled, multicenter trial evaluated dabigatran versus standard of care in treating acute venous thromboembolism in subjects aged < 18 years initially treated with parenteral anticoagulation. Dabigatran was noninferior to the standard of care for thrombus resolution and recurrence of thrombotic events, with comparable bleeding rates [118]. In 2020,

Brandão et al. [119] studied the effect of dabigatran in secondary prophylaxis of venous thromboembolism in patients aged between 3 months and 18 years. Dabigatran showed a favorable safety profile for the prevention of secondary venous thromboembolism. Although the study included pediatric APS, no specific analyses of these patients were carried out [119].

Another recent randomized trial compared rivaroxaban, a factor Xa inhibitor, with standard anticoagulation in children and adolescents (aged 0–17 years) with acute venous thromboembolism. This study demonstrated a similarly low recurrence risk and reduced thrombotic event risk without increased bleeding in both groups [120]. Another trial assessed the safety and efficacy of rivaroxaban in central venous thrombosis compared with standard of care, and no differences were evident between the two treatments in recurrences and bleeding risks [121]. Trials in pediatric populations evaluating the safety and efficacy of other factor Xa inhibitors (edoxaban and apixaban) are also ongoing [122–125].

Although the use of DOACs represents a potential advance for the treatment and prophylaxis of thrombus in children and adolescents [126–131], guidance from professional organizations recommends strictly avoiding the use of DOACs in patients with APS with arterial, small vessel, and recurrent thrombosis or cardiac valvular disease and in those with triple aPL positivity [88, 106, 112]. This recommendation was based on clinical trials with negative outcomes for DOAC-treated patients. A trial comparing rivaroxaban versus warfarin in high-risk patients (triple positivity and a history of thrombosis) was terminated prematurely because of an excess of thromboembolic and major bleeding events among patients in the rivaroxaban arm. The study concluded no benefit and an excess of risk associated with rivaroxaban in this subgroup of patients [130]. Another study assessing whether rivaroxaban was noninferior to VKAs for thrombotic APS indicated an improved risk for recurrent thrombosis in rivaroxaban-treated patients with previous arterial thrombosis, livedo racemosa, or APS-related cardiac valvular disease [126].

5.4 Catastrophic Antiphospholipid Syndrome

CAPS has an unquestionably high mortality rate [18, 132], necessitating prompt diagnosis and treatment. Supportive management and therapy for precipitating factors, mostly infection [18], are also essential in CAPS management. Given the characteristics of CAPS as a multiorgan thrombotic microangiopathy and cytokine storm [70, 133], treatment involves triple therapy (anticoagulation, intravenous corticosteroid pulse therapy, and plasma exchange), including intravenous immunoglobulin for children and adolescents with this condition [1]. In the pediatric and adult

CAPS registry, patients who received this combination had higher recovery rates [18, 134].

5.5 Immunosuppressants/Adjunctive Therapy

The role of hydroxychloroquine in inflammatory conditions is well-established for patients with cSLE [135]. It has an immune-modulating mechanism of action in that it may block intracellular TLR7 and TLR9 activation and inhibit pDC activation, thus reducing production of type I IFN [136, 137]. In vitro studies demonstrated that this drug reversed aPL-mediated disruption of annexin A5 and reduced the formation of aPL-β2GPI complexes on phospholipid bilayers and on trophoblast cells [138, 139]. A recent randomized prospective study evaluated the efficacy of hydroxychloroquine plus standard of care as thromboprophylaxis compared with standard of care alone in adult patients with PAPS. Hydroxychloroquine decreased the incidence of thrombosis and was associated with reductions in aPL titers [140]. No robust evidence for the use of hydroxychloroquine in pediatric patients is available, but its use is recommended for patients with cSLE-APS in addition to antiplatelet agents as primary prophylaxis [1].

Likewise, the safety and efficacy of specific anti-IFN monoclonal antibodies is not yet well demonstrated in APS [55]. However, anifrolumab, a fully human monoclonal antibody that blocks the type I IFN receptor, is currently in clinical development for the treatment of SLE and lupus nephritis [141], and a phase III clinical trial showed a higher percentage of patients with SLE with a response at week 52 compared with placebo [142].

Complement activation by aPL is clearly implicated in APS pathogenesis, as reported previously [50]. A systematic review based on case reports assessed the use of eculizumab, an anti-C5 humanized monoclonal antibody, in refractory CAPS. Although data were limited, the authors demonstrated clinical and laboratory improvement after the administration of eculizumab [53]. Therefore, the *Antiphospholipid Antibodies Task Force Report on Antiphospholipid Syndrome* and the EULAR recommendations consider complement inhibition therapy with eculizumab for adult patients with refractory CAPS and microangiopathic renal lesions refractory to conventional treatment [88, 106]. Of note, evidence in the pediatric population is lacking, and there is no statement regarding eculizumab in SHARE recommendations for pediatric APS [1].

Rituximab, a B-cell-targeted therapy, is a chimeric monoclonal antibody agent against the CD20 receptor. This drug may be useful in APS, since B lymphocytes play an important part in aPL production. For adult patients, current data indicate that rituximab could be an alternative therapy in CAPS or APS with microthrombotic and hematological manifestations [143–146]. SHARE recommendations also

included rituximab as a treatment option for CAPS in children and adolescents [1].

Interestingly, the endothelial proliferation in APS is associated with activation of the mTORC pathway. Sirolimus, an mTORC inhibitor, was studied in kidney transplant recipients with APS and associated nephropathy. Sirolimus treatment seems to protect kidney transplants from recurrence of vascular lesions and loss of function [44] (Fig. 1).

5.6 Primary Prophylaxis

Most treatment recommendations for pediatric APS are based on modified recommendations for adult APS or consensus guidelines. Considering primary thromboprophylaxis, the approach for asymptomatic children and adolescents with the persistence of aPL is still controversial. A clinical trial addressing the efficacy of aspirin in persistently aPL-positive subjects aged ≥ 18 years suggested no benefit from this medication in primary thrombosis prophylaxis [147]. On the other hand, a meta-analysis of five international cohorts assessing the efficacy of aspirin as a prophylactic agent for primary prevention of thrombosis, including in children, showed a decreased risk of first thrombosis in aPL-positive patients treated with low-dose aspirin [148]. Finally, a systematic review demonstrated that data were insufficient to support the use of aspirin in subjects with aPL [149]. In 2019, the EULAR developed recommendations for adult patients with APS and advised low-dose aspirin for asymptomatic subjects classified as having a high-risk aPL profile (persistent presence of LA or double or triple aPL positivity) [88].

The annual risk of first thrombosis among asymptomatic patients with persistent aPL is probably low [150], and the use of aspirin should be balanced with the potential risk of bleeding [151]. This risk could be even higher in children and adolescents, particularly during outdoor activities and play. Therefore, the use of antiplatelet drugs for primary prophylaxis in asymptomatic children and adolescents should be individualized. LMWH may be an option to prevent thrombosis in high-risk circumstances, such as surgery or long-term immobilization [107].

cSLE is a chronic severe autoimmune condition in which inflammation and thrombosis are tightly related. Indeed, thrombosis occurs more frequently in patients with SLE than in healthy controls [152]. Additionally, proteinuria is the hallmark of lupus nephritis and may deplete endogenous anticoagulants. Venous thromboembolism was one of the most common reasons for healthcare appointments by patients in the year before cSLE diagnosis [153]. Furthermore, in a cohort involving adults with cSLE, the presence of aPL was significantly associated with damage accrual. These results reinforce the SHARE recommendation to consider antiplatelet agents in addition to hydroxychloroquine for primary thromboprophylaxis in all patients with cSLE with the presence of aPL [1].

6 Prognosis of Pediatric APS

Pediatric APS is a potentially life-threatening disease with high morbidity and mortality rates and reduced health-related quality of life in patients and caregivers. Pediatric APS outcome data are restricted to rare multicenter studies [8, 12] and reports with limited sample sizes [14, 154]. Epidemiologic studies in pediatric APS are scarce and have not mirrored geographic and racial differences.

The multicenter Ped-APS registry showed that almost 20% of the patients (23/121) presented with recurrent thrombosis after the initial event, typically occurring in the same blood vessel type. Recurrence of thrombosis tended to be more common in pediatric PAPS than in pediatric SAPS. The frequencies of arterial thrombosis and ischemic stroke were also significantly higher in pediatric patients with PAPS. The cause of death for seven patients with APS was related to thrombotic events [12].

More recently, a Chinese group retrospectively assessed 58 pediatric patients with APS from a single center. Seven cases (13%) showed recurrence of thrombosis during follow-up. One patient with CAPS died. This patient had ecchymosis and thrombocytopenia during warfarin and aspirin treatment and needed to discontinue these medications. However, thrombosis of the central nervous system occurred 10 days after therapy withdrawal. At disease onset, patients simultaneously tested for all three aPL subtypes: 52% (33/42) were triple positive, but this multiple positivity did not increase the frequency of thrombotic events compared with other immunologic profiles [14].

A Brazilian cSLE Registry Group study observed recurrent thrombosis in 18/67 (27%) of patients with cSLE-APS. Further comparisons between patients with cSLE-APS (n = 67) and those with cSLE without APS (n = 1452) showed that the median lupus damage score was significantly higher in the former group. Likewise, higher frequencies of cumulative cerebrovascular disease, polyneuropathy, and intravenous cyclophosphamide use were reported in patients with cSLE-APS. Rates of death were similar in both groups (9 vs. 5%) [8].

Prognosis may also be related to specific cumulative manifestations and multiple comorbidities that may induce permanent damage in patients with APS [155, 156]. The Damage Index for thrombotic APS (DIAPS) is a specific instrument that evaluates irreversible damage in adults with thrombotic APS [155]. Recently, a distinct pattern of damage was observed in Brazilian adult patients with PAPS and SLE-APS. Damage in PAPS was an early event, whereas SLE-APS was associated with higher rates of long-term

damage, with a relevant increment of accumulated damage at disease follow-up [157]. Further studies will be necessary to assess specific damage tools in pediatric populations, including pediatric-specific domains of growth and puberty development for children and adolescents.

Another important challenge in pediatric APS management is to identify patients at risk of recurrent thromboembolic events. Indeed, the rate of recurrence seems to be higher than in adult APS [5]. The Global Antiphospholipid Syndrome Score (GAPSS) is based on aPL profile and conventional cardiovascular risk factors (hyperlipidemia and arterial hypertension) and was initially validated in a cohort of adult patients with SLE to measure the risk of recurrence of thromboembolic events [158]. Lately, it has been validated as a surrogate marker for predicting thrombotic risk in different international APS cohorts, retrospectively and prospectively [159].

A prospective study demonstrated that the positivity of antibodies to the domain I of β2GPI was associated with higher GAPSS scores [160]. Nevertheless, no risk score has been validated in pediatric APS to evaluate thromboprophylaxis management.

7 Conclusions

Pediatric APS is a rare acquired multisystem autoimmune thromboinflammatory condition characterized by thrombotic and non-thrombotic clinical manifestations. APS classically manifests in children and adolescents with large-vessel thrombosis, thrombotic microangiopathy, and, rarely, obstetric morbidity. Non-thrombotic clinical manifestations are frequently reported in pediatric APS and may be present even before the vascular thrombosis events. New International Antiphospholipid Syndrome Classification Criteria phase I/II have been reported. A recent large cSLE Registry Group study demonstrated that APS-related cSLE occurred in 4% of 1519 patients.

The main goal of therapy in pediatric APS is the prevention of thrombosis. Management strategies should include screening for additional prothrombotic risk factors, avoiding estrogen-containing contraceptives, implementing lifestyle changes, reinforcing adherence, and addressing mental health issues associated with this autoimmune thrombophilia. The management of acute thrombotic events is the same for both primary and secondary APS in children and adolescents. A pediatric hematologist should be consulted, and therapy includes unfractionated heparin or LMWH followed by VKA. CAPS treatment requires triple therapy (anticoagulation, intravenous corticosteroid pulse therapy, and plasma exchange) and may include intravenous immunoglobulin and rituximab for children and adolescents with this condition. New drugs such as eculizumab and sirolimus

hold particular promise for APS, although data in children remain sparse.

Declarations

Conflict of interest Aline Garcia Islabão, Vitor Cavalcanti Trindade, Licia Maria Henrique da Mota, Danieli Castro Oliveira Andrade, and Clovis Artur Silva have no conflicts of interest that are directly relevant to the content of this article.

Ethics approval Not applicable.

Consent to participate Not applicable.

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Author contributions All authors performed the literature search, had full access to all of the data, take responsibility for the integrity of the data and the accuracy and interpretation of the data analysis, and prepared the manuscript.

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