EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2019.19160

Invited Review

# Pediatric antiphospholipid syndrome

Jacqueline A. Madison[1], Yu Zuo[2], Jason S. Knight[2]

## Abstract

Despite its potential to cause significant morbidity in children, pediatric antiphospholipid syndrome (APS) is an understudied condition. In this review, we will cover what is known about pediatric APS epidemiology and how the clinician might approach the diagnosis of pediatric APS. We will highlight similarities and differences with the adult disease, both for primary APS and in the context of lupus. Clinical manifestations beyond thrombosis, especially neurologic and hematologic in nature, will be discussed. We will also consider what unique implications antiphospholipid antibody-positivity may have for children with lupus and for neonates born to mothers with APS. The approach to treatment will be covered, including the unique impact of APS medications on children as compared with adults. Finally, the importance of future mechanistic research is emphasized as physicians endeavor to provide the personalized care that children with APS clearly deserve.

**Keywords:** Antiphospholipid syndrome, antiphospholipid antibodies, catastrophic antiphospholipid syndrome, pediatric, neonatal, lupus

## Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by an increased risk of thrombotic events and pregnancy morbidity in the setting of persistently positive antiphospholipid antibodies (aPL) (1). The concept of "pediatric APS" is typically applied when the disorder occurs in individuals under the age of 18 years, although some researchers might consider ages such as 16 and 21 as alternative cutoffs (2). For research purposes, formal classification of APS will typically utilize the updated Sapporo criteria (developed in 2006 and sometimes referred to as the Sydney criteria), which require the presence of at least one clinical event and one durably-positive (over at least 12 weeks) laboratory test (3). Clinical events that fulfill the criteria include proven vascular thrombosis in arteries, veins, or small vessels, and certain types of pregnancy morbidity. The laboratory criteria may be met by a positive lupus anticoagulant (a functional assay that screens for aPL), anticardiolipin IgG or IgM in medium or high titer (>40 GPL/MPL or >99$^{th}$ percentile), or anti-beta-2 glycoprotein I ($\beta_2$GPI) IgG or IgM in titer >99$^{th}$ percentile (Table 1).

The updated Sapporo criteria were developed with adults in mind, and there are no specific criteria for pediatric APS. As will be discussed in more detail below, potential limitations of these criteria in children include the fact that most individuals under the age of 18 will not have experienced pregnancy (and therefore have no opportunity to meet that aspect of the criteria), as well as that certain neurologic and hematologic manifestations of APS (chorea, thrombocytopenia, etc.) that are not part of the criteria may be particularly common in children.

### Pathogenesis

The pathophysiology of APS remains incompletely understood with aberrations identified in endothelial cells, platelets, monocytes, neutrophils, and the complement cascade (4). The inflammatory potential of APS is highlighted by placental pathology, which demonstrates vasculopathy, infiltration of inflammatory cells, and complement deposition (5-7). Further emphasizing the inflammatory nature of the disease, anticoagulant medications are not universally protective against additional thrombotic events, and do little to mitigate "extra-criteria" manifestations of the disease such as thrombocytopenia, heart valve dysfunction, and leg ulcers (4).

Pathogenic antibodies in APS do not typically target phospholipids themselves, but rather phospholipid-binding proteins such as $\beta_2$GPI and prothrombin—which have the potential to promote cellular activation when cross-linked by aPL (4, 8-10). Beyond these autoantigens, a number of cell-surface cofactors have been implicated in cellular activation by aPL, including annexin A2, apolipoprotein E receptor 2 (ApoER2), Toll-like receptor 2 (TLR2), and TLR4, among others (4, 11). Furthermore, myriad downstream pathways that

ORCID IDs of the authors:
Y.Z. 0000-0001-6721-7755;
J.S.K. 0000-0003-0995-9771.

**Cite this article as:** Madison JA, Zuo Y, Knight JS. Pediatric antiphospholipid syndrome. Eur J Rheumatol 2020; 7(Suppl 1): S3-S12

[1] Division of Pediatric Rheumatology, Department of Pediatrics, University of Michigan, Ann Arbor, Michigan, USA
[2] Division of Rheumatology, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, USA

*Address for Correspondence:* Jason S. Knight; Division of Rheumatology, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, USA

E-mail: jsknight@umich.edu

Submitted: August 19, 2019
Accepted: October 1, 2019
Available Online Date: December 3, 2019

**Table 1.** Classification criteria for antiphospholipid syndrome (3). APS is present if at least one of the clinical criteria and one of the laboratory criteria are met.

| | | |
|---|---|---|
| Clinical criteria | Vascular thrombosis | ≥1 clinical episode of arterial, venous, or small-vessel thrombosis |
| | Pregnancy morbidity | a) ≥1 unexplained death of a morphologically normal fetus at ≥10 weeks of gestation |
| | | b) ≥1 premature delivery of a morphologically normal fetus at <34 weeks' gestation because of: |
| | | i) Severe preeclampsia or eclampsia defined according to standard definition |
| | | ii) Recognized features of placental insufficiency |
| | | c) ≥3 unexplained consecutive miscarriages at <10 weeks gestation, with maternal and paternal factors (anatomic, hormonal or chromosomal abnormalities) excluded |
| | Laboratory criteria | The presence of antiphospholipid antibodies on ≥2 occasions ≥12 weeks apart |
| | | a) Presence of lupus anticoagulant in plasma |
| | | b) Medium- to high-titer anticardiolipin antibodies of IgG or IgM isoforms |
| | | c) Medium- to high-titer anti-beta-2 glycoprotein I (anti-β2GPI) antibodies of IgG or IgM isoforms |

## Main Points

- Antiphospholipid syndrome (APS) is an autoimmune thromboinflammatory disease that classically manifests with large-vessel thrombosis, thrombotic microangiopathy, and obstetric complications.
- APS may affect children from neonates to adolescents, and is likely underdiagnosed given that widely-used classification criteria were designed for adults.
- Beyond thrombosis, children with APS may have additional "non-criteria" manifestations of the disease including hematologic and neurologic abnormalities; at the same time, some children may have positive antibody testing but no clinical manifestations.
- Antiphospholipid antibodies may be transiently positive in children, especially in the context of infections, and so confirmatory testing should always be performed.
- Half or more of children with APS have another autoimmune condition, most often lupus.
- Treatment must take into account risk stratification based on an individual's specific antibody profile, as well as other factors such as personal behaviors and risk of bleeding.

potentially amplify inflammation and thrombosis continue to be explored in APS. Some interesting examples include TLR7-mediated paracrine signaling by endothelial cells (12), $\beta_2$GPI-specific T cells that promote cell death in atherosclerotic plaques (13), interferon-mediated dysfunction of circulating endothelial progenitors (14), exuberant endosomal reactive oxygen species formation in monocytes (4, 15), release of prothrombotic neutrophil extracellular traps (NETs) by neutrophils (16, 17), and complement activation on the surface of endothelial cells and other cell types (4).

*Are there features of pathogenesis specific to pediatric APS?* At the present time, we do not know enough about the pathophysiology of APS in children to delineate how it differs from the adult disease. We can, however, say that children with APS typically lack many thrombotic risk factors seen in adults such as hypertension, hyperlipidemia, obesity, and tobacco exposure—suggesting that the molecular drivers of APS in children may be particularly severe in order to break through natural antithrombotic mechanisms and thereby trigger events. The genetic basis of APS has been explored in familial and non-familial cases with consistent associations found with certain human leukocyte antigen (HLA) DR and DQ haplotypes, and in other genes commonly associated with autoimmunity such as STAT4 (18, 19); the extent to which pediatric APS may be associated with a higher burden of genetic risk factors than the adult disease remains unstudied. Given how much has been learned about conditions such as lupus by study of pediatric cases (20), it would seem that further characterization of the genetic and molecular signatures that define pediatric APS should be a high priority for the APS research community.

### Epidemiology and demographics

The epidemiology of APS in the pediatric population is largely undefined. While thought of as a rare diagnosis, it is certainly possible that pediatric APS is instead underdiagnosed, especially in the absence of pediatric-specific classification or diagnostic criteria. The largest reported case series is the Ped-APS Registry of 121 children from 14 countries—an ambitious international collaboration coordinated by the European Forum on Antiphospholipid Antibodies and Juvenile Systemic Lupus Erythematosus Working Group of the Paediatric Rheumatology European Society and assembled between 2004 and 2007 (21). The cohort had a mean age of APS onset of 10.7 years, and included children ranging from neonates to adolescents (21). Indeed, in other smaller case series of children with APS, the mean age has typically been similar with a range of 9 to 14 years (8, 22-26). Overall, the breakdown of children by sex is split nearly evenly between males and females at a ratio of 1:1.2 (25). That ratio is much less striking than in adults where the ratio of males to females has been estimated at 1:5—likely related to the strong female predominance of lupus-related cases (which stands in contrast to pre-adolescents with lupus where the ratio is essentially 1:1) (18, 21, 25, 27, 28).

### Primary versus secondary APS

APS can occur in isolation as so-called "primary APS" or in conjunction with another autoimmune condition, in which case it is referred to as secondary APS. While secondary APS is classically associated with lupus, other conditions may also associate with APS as discussed below. In the aforementioned Ped-APS Registry, 60 cases (49.5%) were considered primary APS, 60 (49.5%) were associated with a second autoimmune condition, and one (1.0%) was associated with malignancy (21). Of the 60 cases associated with a second autoimmune condition, there were 46 cases of lupus (76.7%), 4 of lupus-like disease (7.7%), 4 of autoimmune thyroiditis (7.7%), 2 of rheumatic fever (3.3%), and 1 each (1.7%) of immune thrombocytopenic purpura, hemolytic-uremic syndrome, pauci-immune glomerulonephritis, and Behçet's disease (21). As compared with these secondary cases, primary

**Table 2.** Potential non-thrombotic manifestations of APS reported in children

| | |
|---|---|
| Hematologic | Thrombocytopenia |
| | Autoimmune hemolytic anemia |
| | Evans syndrome |
| | Leukopenia |
| | Bleeding diathesis (e.g., lupus anticoagulant-hypoprothrombinemia syndrome) |
| Neurologic | Migraine headache |
| | Chorea/athetosis |
| | Seizures/epilepsy |
| | Pseudotumor cerebri |
| | Mood disorder |
| | Transverse myelitis |
| | Cognitive impairment |
| | Ocular ischemia |
| | Stroke/TIA |
| Dermatologic | Livedo reticularis |
| | Raynaud's phenomenon |
| | Purpura fulminans |
| | Skin ulcers |
| | Pseudovasculitic lesions |
| | Chronic urticaria |
| Cardiac | Valvular disease |
| | Myocardial infarction |
| Pulmonary | Pulmonary hypertension |
| | Interstitial fibrosis |
| Renal | Thrombotic microangiopathy |
| | Antiphospholipid nephropathy |
| Endocrine | Adrenal insufficiency (secondary to adrenal infarction) |

APS was characterized by younger age, more male predominance, more ischemic strokes, more arterial thrombosis overall, less venous thrombosis, fewer hematologic disorders, and fewer skin disorders (21). In another large case series of 58 children in China, only 24% were primary APS, and 69% of cases were secondary to lupus (8). The proportion of primary relative to secondary APS may be somewhat lower in children as compared with adults—in whom well over half of APS cases are primary in most series (18, 29). Although clearly requiring additional study, it has also been suggested that there may be a somewhat higher rate of progression from primary APS to secondary APS in children as compared with adults. For example, in one series, 3/14 (21%) children with primary APS progressed to lupus or lupus-like disease during six years of follow-up, as compared with 17/128 (13%) adults (30, 31).

### Clinical features

*What are the most common thrombotic manifestations in children with APS?* As discussed above, the cardinal feature of pediatric APS is vascular thrombosis, as pregnancy morbidity has only rarely been described for children with APS in the literature. Again referencing the Ped-APS Registry of 121 cases, the most common presenting feature was venous thrombosis in 60% of children (21). Lower-limb deep venous thrombosis (DVT) was the most common single form of thrombotic event (40%), which was also the most common event (37%) in the large case series from China (8, 21). The other venous thrombotic events that affected more than one child were cerebral venous sinus thrombosis (7%), portal vein thrombosis (3%), upper extremity DVT (2%), superficial vein thrombosis (2%), and left atrial thrombus formation (2%) (21). There were also rare forms of venous thrombosis described in just a single child including involvement of the jugular vein, inferior vena cava, renal vein, and retinal vein (21). Arterial thrombosis affected 32% of children, with ischemic stroke as by far the most common in this category (79% of arterial events) (21). Other rare forms of arterial thrombosis were peripheral artery thrombosis, retinal artery thrombosis, myocardial infarction (MI), renal artery thrombosis, and splenic infarction (21). Interestingly, just 2% of children demonstrated a mixture of arterial and venous thrombosis (21). Small-vessel thrombosis in the form of digital ischemia or renal thrombotic microangiopathy affected approximately 6% of children (21).

*What is known about catastrophic APS in children?* Catastrophic APS (CAPS) is a life-threatening complication of APS typically characterized by precipitous, widespread microvascular occlusions placing organs such as heart, lungs, and kidneys at significant risk. CAPS was fatal in 26% of the 45 children described in the largest case series to date (32). With a mean age of 11.5 years, 71% of the children with CAPS were female, while approximately two-thirds had primary APS (32). As compared with adults with CAPS in the same patient registry, the two most striking differences were an increased association with infection as the precipitator in children (60.9% versus 26.8% in adults) and the fact that for those children diagnosed with CAPS, it was the first manifestation of APS 87% of the time (versus less than half the time in adults) (32). The latter emphasizes the need for education of the general pediatrics community to consider APS when a child presents with infection and multiple-organ dysfunction.

*Are children with APS at risk for other manifestations beyond thrombosis?* APS is increasingly being recognized as a truly systemic autoimmune disease with manifestations that extend beyond the thrombotic and pregnancy-related events highlighted by the updated Sapporo criteria (3, 33). In the Ped-APS Registry, 16% of children had nonthrombotic neurologic manifestations including migraine headache, chorea/athetosis, epilepsy, pseudotumor cerebri, and mood disorder (21). Other neurologic features that have been described in children with APS include transverse myelitis and cognitive impairment (18, 26, 34, 35). Nonthrombotic hematologic abnormalities are also commonly appreciated in children with APS (38% of Ped-APS Registry cases) including Evans syndrome (typically the combination of thrombocytopenia and autoimmune hemolytic anemia), isolated thrombocytopenia, isolated autoimmune hemolytic anemia, leukopenia, and even bleeding diatheses such as the lupus anticoagulant-hypoprothrombinemia syndrome (which will be discussed in more detail in the lupus section below) (21, 36, 37). The Ped-APS Registry also reported skin disorders as occurring in 18% of cases. Some examples include livedo reticularis, Raynaud's phenomenon, skin ulcers, pseudovasculitic lesions, and chronic urticaria (21); purpura fulminans has been reported in other series (18, 24). Elsewhere in the literature, other clinical manifestations have been reported including cardiac manifestations (especially valvular disease), kidney disease including end-stage renal disease secondary to thrombotic microangiopathy, primary adrenal insufficiency secondary to adrenal infarction, and pulmonary disease (18, 38-42). One interesting series described 16 cases of pediatric APS in which bilateral adrenal infarction led to primary adrenal insufficiency (18, 38). With regards to pulmonary disease, pulmonary fibrosis has been reported, largely in children with lupus, while pulmonary hypertension may also develop secondary to chronic vaso-occlusive disease (18, 39, 43). Some examples of non-thrombotic manifestations of pediatric APS are highlighted in Table 2.

### Laboratory testing

The laboratory criteria as described in the updated Sapporo criteria are typically applied to children in the same fashion as for adults—although it is not clear that the normal ranges can be applied with the same sensitivity and

**Table 3.** Studies investigating the prevalence of antiphospholipid antibodies among children with lupus

| | | aPL prevalence | | |
|---|---|---|---|---|
| Reference, Year | Study population | anticardiolipin IgG/IgM | anti-β2GPI IgG/IgM | lupus anticoagulant |
| Ahluwalia (58), 2014 | 27 | 70.4% | 27.3% | 42.9% |
| Descloux (57), 2008 | 56 | 49% | ND | 35% |
| Berube (59), 1998 | 59 | 27% | ND | 24% |
| Campos (43), 2003 | 57 | 70.2% | ND | 29.1% |
| Ravelli (64), 1994 | 30 | 87% | ND | 20% |
| Seaman (65), 1994 | 29 | 66% | ND | 62% |
| Von Scheven (66), 2002 | 57 | 53% | 48% | 23% |
| Molta (62), 1994 | 37 | 19% | ND | 11% |
| Levy (60), 2003 | 149 | 39% | ND | 16% |

ND=not determined

**Table 4.** Studies investigating annual thrombosis incidence rate in aPL-positive children with lupus

| Reference | Study Design | Annual Thrombosis Incidence Rate (ATIR) |
|---|---|---|
| Ahluwalia (58) | Longitudinal observation of 14 children with any aPL | 3 children developed thrombosis with a mean follow up of 7 years. The estimated ATIR was 3.1%. |
| Descloux (57) | Longitudinal observation of 30 children with lupus anticoagulant and/or anticardiolipin IgG/IgM | 14 children developed thrombosis with a mean follow up of 7.1 years. The estimated ATIR was 6.6%. |
| Levy (60) | Longitudinal observation of 24 children with lupus anticoagulant and 54 children with anticardiolipin IgG/IgM | 13 of 24 lupus anticoagulant-positive and 12 of 54 anticardiolipin-positive children developed thrombosis with a follow up of 10 years. The estimated ATIR was 5.4% and 2.2%, respectively, among lupus anticoagulant-positive and anticardiolipin-positive children. |

specificity in children (18). As part of the SHARE initiative (Single Hub and Access point for paediatric Rheumatology in Europe, an effort to develop diagnostic and management regimens for children with rheumatic diseases), the recommendation regarding pediatric APS with the strongest evidence (level 2A/B) was that the following tests should be performed when considering a pediatric APS diagnosis: lupus anticoagulant, anticardiolipin IgG and IgM, and anti-$\beta_2$GPI IgG and IgM (44). In reviewing the lab tests from the Ped-APS registry, there was a higher frequency of lupus anticoagulant detection in children as compared with adults (54% versus 40%), but similar frequencies of anticardiolipin and anti-$\beta_2$GPI (21). In children, it is also important to note that there may be an especially high prevalence of transiently-positive aPL testing in the absence of any features of APS, most likely related to infectious exposures (45-48). For example, in a study of 88 children with upper airway infections, 30% had positive anticardiolipin antibodies (45). Transient aPL positivity has also been reported in the setting of varicella, Streptococcal infections, hepatitis B vaccination, and even upon exposure to nutritional antigens in children with atopic dermatitis (45, 48, 49). Additionally, up to 25% of asymptomatic, healthy children may test positive for low levels of aPL (50-54). Thus, repeat testing is always recommended to confirm durable positivity.

### What are the implications of detecting antiphospholipid antibodies in children with lupus?

***What is the prevalence of aPL among children with lupus?*** The prevalence of aPL positivity among adults with lupus has typically been described as ranging from 30% to 40% (55). The prevalence in children with lupus may be significantly higher, with a number of studies suggesting rates above 50% (43, 56-66) (Table 3). When traditional categories of aPL are investigated individually, the prevalence of positive anticardiolipin antibodies varies between 19% and 87% (62, 64), positive anti-$\beta_2$GPI between 27.3% and 48% (58, 66), and positive lupus anticoagulant between 11% and 62% (62, 65) (Table 3). Based on data available to date (which are admittedly quite limited for anti-$\beta_2$GPI) anticardiolipin antibodies appear to have the highest prevalence among children with lupus.

***Among aPL-positive children with lupus, what is the incident thrombosis rate?*** Thrombosis is multifactorial, and the mechanisms of aPL-induced thrombosis in lupus remain incompletely understood. Furthermore, long-term prospective observational studies of aPL-positive children with lupus are scarce, making the risk of thrombosis for an individual child very difficult to estimate. Here we will summarize three prospective observational studies of aPL-positive children with lupus (Table 4). One seven-year prospective study of 14 aPL-positive children with lupus demonstrated an annual risk of thrombotic events of 3.1% (58). A second larger study followed 30 children with lupus and either positive anticardiolipin IgG/IgM or lupus anticoagulant over a mean 7.1 years of follow-up and found annual thrombosis incidence to be 6.6% (57). Finally, a third study observed 24 children with lupus anticoagulant and 54 with anticardiolipin IgG/IgM (all 78 met standard criteria for pediatric lupus) over 10 years and found an annual thrombosis incidence of 5.4% for lupus anticoagulant carriers and 2.2% for anticardiolipin carriers (60). These studies were all obviously limited by their relatively small sample size, as well as heterogeneity in terms of aPL profile assessment. The studies were also not designed to account for potentially prophylactic medications (aspirin, hydroxychloroquine), lupus disease activity, or coexisting non-aPL thrombotic risk factors (such as deficiency of protein C or S, factor V Leiden, increased factor VIII level, indwelling central venous catheter, surgery, or malignancy), all of which may contribute to incident rates of thrombosis.

It should also be noted that a cross-sectional analysis of 979 children with lupus from the Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry demonstrated that apart from positive aPL, the presence of vasculitis and avascular necrosis were independent risk factors for incident thrombosis (67). In summary, the limited data available to date suggest an annual risk of thrombosis on the

order of 2 to 6% in aPL-positive children with lupus. Lupus anticoagulant-positive children may carry the highest risk, although more data are clearly needed in the area of individual risk stratification.

*How might aPL impact clinical manifestations in children with lupus?* The presence of aPL is likely the most important risk factor for arterial and venous thrombosis among children with lupus. The cross-sectional cohort study of 979 children with lupus from the CARRA registry demonstrated an overall prevalence of arterial and venous thrombosis (independent of aPL status) of 2.5% and 3.6%, respectively. Importantly, the presence of any aPL significantly heightened overall thrombosis risk (OR=2.95, 95% CI=1.38-6.28, p=0.0052) (67). Another study, a 10-year observation of 149 children with lupus, demonstrated an overall thrombosis incidence of 54% among lupus anticoagulant-positive children and 22% among anticardiolipin-positive children (60). A final noteworthy study, a cross-sectional cohort study of 58 children with lupus, found that any positive aPL [anticardiolipin IgG/IgM (OR=15.7, 95% CI=2.5-97, p=0.003), anti-$\beta_2$GPI IgG/IgM (OR=22, 95% CI=2.3-207, p=0.002), or lupus anticoagulant (OR=∞, 95% CI=6-∞, p<0.001)] was significantly associated with thrombotic events, with lupus anticoagulant as the strongest predictor (68).

Potential neurologic manifestations of lupus—including headache, psychosis, cognitive dysfunction, cerebrovascular disease, seizure, mood disorder, chorea, and transverse myelitis—have been reported as more common in children with lupus as compared with adults (potentially affecting 25% to 75% of such children) (69-72). Among those manifestations, aPL correlate most strongly with cerebrovascular disease (i.e., stroke) (66, 73-75) and chorea (76-78). For example, a relatively large prospective observation of 137 children with lupus (mean follow-up of 31 months) demonstrated that persistent presence of lupus anticoagulant was significantly associated with both cerebrovascular disease and chorea (79); anti-$\beta_2$GPI IgG/IgM was also somewhat predictive of neurologic manifestations (79). Another retrospective cohort study of 106 children with lupus showed a statistically significant, albeit modest, association between either anticardiolipin IgM or lupus anticoagulant and various neurologic manifestations (75).

It is well established that aPL-positive adults with lupus carry an elevated risk of non-thrombotic hematologic manifestations such as thrombocytopenia and autoimmune hemolytic anemia (80). The relationship between aPL and hematologic manifestations has also been suggested for children with lupus, primarily in the form of case reports and case series (43, 64, 65, 81). One unique hematologic complication of aPL-positivity that is most often seen in children is the so-called lupus anticoagulant-hypoprothrombinemia syndrome (LAHPS) (37, 82, 83). LAHPS is characterized by a positive lupus anticoagulant test and also prolongation of both prothrombin time (PT) and activated partial thromboplastin time (aPTT); the latter are attributable to depletion of factor II levels triggered by "non-criteria aPL" in the form of anti-prothrombin antibodies (37, 82, 83). Children who have lupus complicated by LAHPS are at high risk of bleeding, as well as life-threatening complications such as disseminated intravascular coagulation (37, 82).

In summary, beyond the well-established risk of thrombotic events associated with aPL, these antibodies also appear to increase risk of neurologic and hematologic complications in children with lupus.

*Does aPL positivity impact lupus disease activity and prognosis?* As compared with adults with lupus, children with lupus tend to have more active disease both at the time of diagnosis and during long-term follow-up (84). For example, one study that compared 67 children to 131 adults found the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) to be significantly higher among children with lupus as compared with adults, both at presentation (16.8 versus 9.3, p<0.0001) and on average over three years of follow-up (5.7 versus 4.6, p=0.012) (85). Furthermore, in both adults and children, aPL positivity is an important risk factor for acquiring organ damage over time (57, 85-87). For example, a prospective study of 56 children with lupus found that that aPL-positive children had a three-fold higher risk of organ damage as assessed by SLICC/ACR Damage Index (SDI) (57). Another prospective study of 67 children with lupus found that even when normalizing for cumulative disease activity over time, the presence of aPL added value in predicting children at risk for more disease-related damage (85). In summary, the presence of aPL appears to herald more aggressive forms of lupus and predicts the development of more lupus-related damage over time.

### Do maternal antiphospholipid antibodies confer increased risk of neonatal APS?

While thrombotic episodes (especially strokes) have been described in neonates born to mothers with APS, a review of 16 such cases found that the majority (9/14 that could be evaluated, or 64%) were associated with other prothrombotic risk factors beyond aPL—either prenatal (preeclampsia, intra-uterine growth retardation) or perinatal (asphyxia, sepsis, arterial or venous catheter, congenital thrombophilia) (88). When the issue has been assessed prospectively, the findings have been relatively reassuring. One study followed 134 neonates born to mothers with APS over a five-year period (89). Anticardiolipin and anti-$\beta_2$GPI were regularly detected in newborns and, when present, matched the mother's antibody profile (89). Most of these antibodies cleared within six months of birth, although some persisted to 24 months (89). Notably, of the 134 children born to mothers with APS, there were no cases of neonatal thrombosis or lupus (89). At this point, it is also worth noting that stroke has been described in neonates in whom their positive aPL showed no concordance with presence of maternal aPL. In one series of 12 such children, 10/12 had aPL levels decrease to the normal range within 2.5 years, and none of the infants showed recurrent thrombosis or any other APS manifestations, despite variable use of anticoagulation (90). The issue of neonatal stroke and its relationship to positive aPL in both mother and child is clearly an area that warrants further investigation.

Returning to the large series of 134 children born to mothers with APS, four children (3%) had impaired neuropsychological development, but only two had positive aPL (interestingly, neither had aPL at birth but instead became positive later in life, making it unclear whether these features were related to the mother's APS) (89). To address the question from a different perspective, a retrospective study compared children of women with APS to children of women with lupus. The study found no episodes of thrombosis, although 3/26 children of women with APS (11.5%) later developed autism, all of whom had persistently-positive anti-$\beta_2$GPI (91); there were no such episodes in the lupus group. The authors suggested that neurodevelopmental screening and long-term follow up may be indicated in these children and emphasized the need for further study in larger cohorts (91). Another interesting study characterized 40 children born to mothers who had positive aPL in the third trimester (a combination of women with APS, lupus, and undifferentiated connective tissue disease) with detailed neurological testing including a physical exam, cognitive testing, and behavioral questionnaires (92). While all children had normal physical exams, cognitive impairment (7%), learning disabilities (19%), and epilepsy (10%) were identified (92). The authors suggested that physicians consider

counseling their patients on these possible risks so that children can be identified and referred to specialists early. The authors also highlighted an experimental mouse model suggesting that maternal hydroxychloroquine use may prevent complement deposition in the developing neural structures of the fetus (92, 93), a concept that could be pursued in the future as part of a trial protocol.

### Approach to treatment

In general, data specific to pediatric APS are quite limited. Most concepts are derived from small observational studies, extrapolation from adult data, or expert opinion.

*Prevention of Thrombosis.* When aPL are identified prior to a thrombotic event (this is most likely to happen in the context of lupus), some would advocate for the use of low-dose aspirin as primary prevention (44, 94-96)—although acknowledging that any rule that does not consider both the specific antibody profile (for example, a single positive test versus so-called "triple positivity") and other thrombotic or bleeding risk factors is likely to be overly simplistic. In aPL-positive children with lupus, hydroxychloroquine will almost always be employed, which may provide some adjunctive properties for prevention of APS complications as well (44, 97). Overall, this is an area that clearly needs more research and no evidence-based recommendations for how to approach these children can be made at this time.

*Treatment after Thrombosis.* With venous thrombosis and persistently-positive aPL, the current recommendation is for treatment with long-term anticoagulation (44). There is no difference in the acute treatment of thrombosis attributable to APS as compared with other causes. Initial treatment in the acute setting consists of anticoagulation with either low-molecular-weight heparin (most common in current clinical practice) or unfractionated heparin. There is experience using either preparation in the treatment of acute venous thromboembolism in children (98-100). Children are most often transitioned to a vitamin K antagonist such as warfarin for long-term anticoagulation. The goal INR should typically be 2-3 following the first venous thrombotic event, as higher INR targets have not been shown to reduce recurrence and have additional bleeding risks in adult studies (101, 102). In arterial thrombosis, there may be additional benefit with regards to secondary prevention of recurrence by adding anti-aggregation therapy such as low-dose aspirin (44). For example, a small study of seven children with aPL and acute cerebral infarction with follow-up of 15.7 months demonstrated no recurrent events on aspirin (103). If there is a recurrent thrombotic event while a child is on long-term anticoagulation with a vitamin K antagonist, then additional options include changing the target INR to 3-4 or considering an alternate therapy, particularly low-molecular-weight heparin (44). It should be emphasized that such recommendations come from retrospective studies in adults and therefore may be limited in their ability to guide pediatric care.

At this time, direct oral anticoagulants (DOACs) should probably be avoided (especially as first-line therapy) pending more data. For example, a recent randomized clinical trial of rivaroxaban versus warfarin in adults with APS (all with "triple-positivity") was halted early due to excessive arterial thrombotic events in the rivaroxaban arm (104). A second randomized study of rivaroxaban versus warfarin in adults with APS focused on individuals with history of venous thrombosis only and with lower-risk aPL profiles (105). While no thrombotic events were observed over the six months of the trial, the endogenous thrombin potential in subjects treated with rivaroxaban did not reach the non-inferiority threshold, which was the primary endpoint of the study (105). Still, in the most recent EULAR recommendations regarding APS treatment in adults, a panel concluded that DOACs may be considered in non-triple-positive patients having difficulty reaching INR goals despite compliance on a vitamin K antagonist, or in those with contraindications to a vitamin K antagonist (106). The hope is that additional data will clarify this issue in the coming years. Finally, there is no evidence to support the regular use of immunomodulatory treatment in primary APS, although some ongoing protocols are prospectively assessing hydroxychloroquine in this context for adults (107).

*Treatment of CAPS.* The general approach to treatment of pediatric CAPS includes anticoagulation and immunosuppression. The CAPS task force recommends initial use of anticoagulation and corticosteroids, with strong consideration for plasmapheresis and/or intravenous immunoglobulin (IVIG) (108). The SHARE initiative recommends immediate combination therapy with anticoagulants, corticosteroids, and plasma exchange with or without IVIG (44). In analyzing 250 adult and pediatric patients in the CAPS registry for prognostic factors, a higher rate of recovery was found in individuals who used a combination of anticoagulation, corticosteroids, and plasma exchange compared to those using only anticoagulation and corticosteroids; no benefit was demonstrated by the use of cyclophosphamide (109, 110). When 45 children in the CAPS registry were analyzed separately, there was increased use of multiple treatments (anticoagulation, corticosteroids, plasma exchange and/or IVIG) in the children who survived (8/33) compared to those who died (0/12), but the difference was not statistically significant (p=0.087) (111). Other immunosuppressive therapies may be considered, especially rituximab. In the CAPS registry, 20 patients received rituximab as first or second-line therapy, and 16 survived; none had thrombosis after treatment (110, 112). In a review of pediatric CAPS cases, four children were identified who received rituximab, and all recovered (110). Eculizumab has also been reported as effective in several case reports where it was used in individuals with recurrent thrombosis despite rituximab therapy (110, 113-116). Finally, because there is so often an underlying infection in pediatric CAPS, control of the infection or other inciting event is critically important (110).

*Additional considerations in children with APS.* There are some children for whom the general recommendations may not be appropriate. For example, when considering prophylactic aspirin use in asymptomatic children, one must also weigh bleeding risks especially with childhood activities including play and outdoor activities such as contact sports; as such, some experts would not advocate for the use of aspirin in these situations at least until puberty (22, 100). In secondary prevention when on anticoagulation, additional counseling is required with children and families regarding particularly risky behaviors that would place them at high risk for bleeding. This is particularly important in adolescents who may be less adherent with treatment than adults. If considering between low-molecular-weight heparin and an oral therapy, considerations must be given to the child's ability to tolerate injections, the likelihood of a missed dose while on a mediation with a shorter half-life such as low-molecular-weight heparin, use of alcohol which could interfere with warfarin, and the ability to complete recommended lab monitoring (18). In the rare cases of neonatal APS, one must also consider that there are particular differences in the neonatal coagulation system that may play a role in the increased risk for the development of thromboembolic events; these risk factors include decreased plasminogen, decreased coagulation factors, decreased platelet aggregation, lower levels of protein C and S, and relative vitamin K deficiency (100, 116). For example, protein C and S are at levels about 35% of the adult values (117). In these especially rare cases, care should be coordinated with Neo-

natology and Hematology in tertiary centers. Along similar lines, there may be higher rates of complications with therapeutic plasma exchange in children compared to adults, and so again, treatment should ideally be delivered at specialized centers (110, 118).

### Summary

Despite its potential to drive significant morbidity in children, pediatric APS is an understudied condition. Available classification criteria have been tailored to adults, and the future development of pediatric-specific criteria is clearly indicated. Pediatric APS, probably even more commonly than for adults, regularly associates with various neurologic and hematologic manifestations (chorea, thrombocytopenia, etc.)—both in the context of lupus and in children with primary APS. Relatively unique presentations that the pediatrician should be aware of include the potential for CAPS as a first manifestation of APS (especially in the context of infection) and the bleeding diathesis known as LAHPS—an interesting condition that is rarely seen in adults with APS. Areas clearly in need of more study include how to best apply aPL-related lab testing to children with APS, an overall better understanding of the molecular signatures that define and drive the disease, and how to specifically treat children with APS or asymptomatic but persistently positive aPL. Committing a child to life-long anticoagulation is far from ideal, and more precise instruments for predicting risk and defining prognosis are clearly needed.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - J.A.M., J.S.K.; Design - J.A.M., J.S.K.; Supervision - J.S.K.; Data Collection and/or Processing - J.A.M., Y.Z.; Analysis and/or Interpretation - J.A.M., Y.Z., J.S.K.; Literature Search - J.A.M., Y.Z.; Writing Manuscript - J.A.M., Y.Z.; Critical Review - J.A.M., Y.Z., J.S.K.

**Conflict of Interest:** The authors have no conflict of interest to declare.

**Financial Disclosure:** J.A.M. was partially supported by the VA Healthcare System. J.S.K. was supported by grants from the NIH (R01HL134846), Lupus Research Alliance, and Burroughs Wellcome Fund.

## References

1. Lim W. Antiphospholipid syndrome. Hematology Am Soc Hematol Educ Program 2013; 2013: 675-80. [CrossRef]
2. Aguiar CL, Soybilgic A, Avcin T, Myones BL. Pediatric antiphospholipid syndrome. Curr Rheumatol Rep 2015; 17: 27. [CrossRef]
3. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006; 4: 295-306. [CrossRef]
4. Vreede AP, Bockenstedt PL, Knight JS. Antiphospholipid syndrome: an update for clinicians and scientists. Curr Opin Rheumatol 2017; 29: 458-66. [CrossRef]
5. Stone S, Pijnenborg R, Vercruysse L, Poston R, Khamashta MA, Hunt BJ, et al. The placental bed in pregnancies complicated by primary antiphospholipid syndrome. Placenta 2006; 27: 457-67. [CrossRef]
6. Shamonki JM, Salmon JE, Hyjek E, Baergen RN. Excessive complement activation is associated with placental injury in patients with antiphospholipid antibodies. Am J Obstet Gynecol 2007; 196: 167.e1-5. [CrossRef]
7. Marder W, Knight JS, Kaplan MJ, Somers EC, Zhang X, O'Dell AA, et al. Placental histology and neutrophil extracellular traps in lupus and pre-eclampsia pregnancies. Lupus Sci Med 2016; 3: e000134. [CrossRef]
8. Ma J, Song H, Wei M, He Y. Clinical characteristics and thrombosis outcomes of paediatric antiphospholipid syndrome: analysis of 58 patients. Clin Rheumatol 2018; 37: 1295-303. [CrossRef]
9. Allen KL, Fonseca FV, Betapudi V, Willard B, Zhang J, McCrae KR. A novel pathway for human endothelial cell activation by antiphospholipid/anti-beta2 glycoprotein I antibodies. Blood 2012; 119: 884-93. [CrossRef]
10. Sorice M, Longo A, Capozzi A, Garofalo T, Misasi R, Alessandri C, et al. Anti-beta2-glycoprotein I antibodies induce monocyte release of tumor necrosis factor alpha and tissue factor by signal transduction pathways involving lipid rafts. Arthritis Rheum 2007; 56: 2687-97. [CrossRef]
11. Muller-Calleja N, Lackner KJ. Mechanisms of Cellular Activation in the Antiphospholipid Syndrome. Semin Thromb Hemost 2018; 44: 483-92. [CrossRef]
12. Wu M, Barnard J, Kundu S, McCrae KR. A novel pathway of cellular activation mediated by antiphospholipid antibody-induced extracellular vesicles. J Thromb Haemost 2015; 13: 1928-40. [CrossRef]
13. Benagiano M, Gerosa M, Romagnoli J, Mahler M, Borghi MO, Grassi A, et al. beta2 Glycoprotein I Recognition Drives Th1 Inflammation in Atherosclerotic Plaques of Patients with Primary Antiphospholipid Syndrome. J Immunol 2017; 198: 2640-8. [CrossRef]
14. Grenn RC, Yalavarthi S, Gandhi AA, Kazzaz NM, Nunez-Alvarez C, Hernandez-Ramirez D, et al. Endothelial progenitor dysfunction associates with a type I interferon signature in primary antiphospholipid syndrome. Ann Rheum Dis 2017; 76: 450-7. [CrossRef]
15. Manukyan D, Muller-Calleja N, Jackel S, Luchmann K, Monnikes R, Kiouptsi K, et al. Cofactor-independent human antiphospholipid antibodies induce venous thrombosis in mice. J Thromb Haemost 2016; 14: 1011-20. [CrossRef]
16. Yalavarthi S, Gould TJ, Rao AN, Mazza LF, Morris AE, Nunez-Alvarez C, et al. Release of neutrophil extracellular traps by neutrophils stimulated with antiphospholipid antibodies: a newly identified mechanism of thrombosis in the antiphospholipid syndrome. Arthritis Rheumatol 2015; 67: 2990-3003. [CrossRef]
17. Meng H, Yalavarthi S, Kanthi Y, Mazza LF, Elfline MA, Luke CE, et al. In Vivo Role of Neutrophil Extracellular Traps in Antiphospholipid Antibody-Mediated Venous Thrombosis. Arthritis Rheumatol 2017; 69: 655-67. [CrossRef]
18. Wincup C, Ioannou Y. The Differences between Childhood and Adult Onset Antiphospholipid Syndrome. Front Pediatr 2018; 6: 362. [CrossRef]
19. Sebastiani GD, Iuliano A, Cantarini L, Galeazzi M. Genetic aspects of the antiphospholipid syndrome: An update. Autoimmun Rev 2016; 15: 433-9. [CrossRef]
20. Banchereau R, Hong S, Cantarel B, Baldwin N, Baisch J, Edens M, et al. Personalized Immunomonitoring Uncovers Molecular Networks that Stratify Lupus Patients. Cell 2016; 165: 551-65. [CrossRef]
21. Avcin T, Cimaz R, Silverman ED, Cervera R, Gattorno M, Garay S, et al. Pediatric antiphospholipid syndrome: clinical and immunologic features of 121 patients in an international registry. Pediatrics 2008; 122: e1100-7. [CrossRef]
22. Meroni PL, Argolini LM, Pontikaki I. What is known about pediatric antiphospholipid syndrome? Expert Rev Hematol 2016; 9: 977-85. [CrossRef]
23. Zamora-Ustaran A, Escarcega-Alarcon RO, Garcia-Carrasco M, Faugier E, Mendieta-Zeron S, Mendoza-Pinto C, et al. Antiphospholipid syndrome in Mexican children. Isr Med Assoc J 2012; 14: 286-9.
24. Tavil B, Ozyurek E, Gumruk F, Cetin M, Gurgey A. Antiphospholipid antibodies in Turkish children with thrombosis. Blood Coagul Fibrinolysis 2007; 18: 347-52. [CrossRef]
25. Berkun Y, Padeh S, Barash J, Uziel Y, Harel L, Mukamel M, et al. Antiphospholipid syndrome and recurrent thrombosis in children. Arthritis Rheum 2006; 55: 850-5. [CrossRef]
26. Ravelli A, Martini A. Antiphospholipid antibody syndrome in pediatric patients. Rheum Dis Clin North Am 1997; 23: 657-76. [CrossRef]
27. Cervera R, Piette JC, Font J, Khamashta MA, Shoenfeld Y, Camps MT, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum 2002; 46: 1019-27. [CrossRef]
28. Ambrose N, Morgan TA, Galloway J, Ionnoau Y, Beresford MW, Isenberg DA, et al. Differences in disease phenotype and severity in SLE across age groups. Lupus 2016; 25: 1542-50. [CrossRef]
29. Cervera R, Serrano R, Pons-Estel GJ, Ceberio-Hualde L, Shoenfeld Y, de Ramon E, et al. Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients. Ann Rheum Dis 2015; 74: 1011-8. [CrossRef]
30. Gomez-Puerta JA, Martin H, Amigo MC, Aguirre MA, Camps MT, Cuadrado MJ, et al. Long-term follow-up in 128 patients with primary antiphospholipid syndrome - Do they develop lupus? Medicine 2005; 84: 225-30. [CrossRef]

31. Gattorno M, Falcini F, Ravelli A, Zulian F, Buoncompagni A, Martini G, et al. Outcome of primary antiphospholipid syndrome in childhood. Lupus 2003; 12: 449-53. [CrossRef]
32. Berman H, Rodriguez-Pinto I, Cervera R, Gregory S, de Meis E, Rodrigues CEM, et al. Pediatric catastrophic antiphospholipid syndrome: Descriptive analysis of 45 patients from the "CAPS Registry". Autoimmun Rev 2014; 13: 157-62. [CrossRef]
33. Abreu MM, Danowski A, Wahl DG, Amigo MC, Tektonidou M, Pacheco MS, et al. The relevance of "non-criteria" clinical manifestations of antiphospholipid syndrome: 14th International Congress on Antiphospholipid Antibodies Technical Task Force Report on Antiphospholipid Syndrome Clinical Features. Autoimmun Rev 2015; 14: 401-14. [CrossRef]
34. Shaharao V, Bartakke S, Muranjan MN, Bavdekar MS, Bavdekar SB, Udani VP. Recurrent acute transverse myelopathy: association with antiphospholipid antibody syndrome. Indian J Pediatr 2004; 71: 559-61. [CrossRef]
35. Okun MS, Jummani RR, Carney PR. Antiphospholipid- associated recurrent chorea and ballism in a child with cerebral palsy. Pediatr Neurol 2000; 23: 62-3. [CrossRef]
36. Becton DL, Stine KC. Transient lupus anticoagulants associated with hemorrhage rather than thrombosis: the hemorrhagic lupus anticoagulant syndrome. J Pediatr 1997; 130: 998-1000. [CrossRef]
37. Yacobovich JR, Uziel Y, Friedman Z, Radnay J, Wolach B. Diffuse muscular haemorrhage as presenting sign of juvenile systemic lupus erythematosus and lupus anticoagulant hypoprothrombinaemia syndrome. Rheumatology (Oxford) 2001; 40: 585-7. [CrossRef]
38. Ramon I, Mathian A, Bachelot A, Hervier B, Haroche J, Boutin-Le Thi Huong D, et al. Primary adrenal insufficiency due to bilateral adrenal hemorrhage-adrenal infarction in the antiphospholipid syndrome: long-term outcome of 16 patients. J Clin Endocrinol Metab 2013; 98: 3179-89. [CrossRef]
39. von Scheven E, Athreya BH, Rose CD, Goldsmith DP, Morton L. Clinical characteristics of antiphospholipid antibody syndrome in children. J Pediatr 1996; 129: 339-45. [CrossRef]
40. Clauss SB, Manco-Johnson MJ, Quivers E, Takemoto C, Spevak PJ. Primary antiphospholipid antibody syndrome and cardiac involvement in a child. Pediatr Cardiol 2003; 24: 292-4. [CrossRef]
41. Butani L. End-stage renal disease from glomerulonephritis associated with anti-phospholipid syndrome. Pediatr Nephrol 2004; 19: 812-4. [CrossRef]
42. Noda S, Ogura M, Tsutsumi A, Udagawa T, Kamei K, Matsuoka K, et al. Thrombotic microangiopathy due to multiple autoantibodies related to antiphospholipid syndrome. Pediatr Nephrol 2012; 27: 681-5. [CrossRef]
43. Campos LM, Kiss MH, D'Amico EA, Silva CA. Antiphospholipid antibodies and antiphospholipid syndrome in 57 children and adolescents with systemic lupus erythematosus. Lupus 2003; 12: 820-6. [CrossRef]
44. Groot N, de Graeff N, Avcin T, Bader-Meunier B, Dolezalova P, Feldman B, et al. European evidence-based recommendations for diagnosis and treatment of paediatric antiphospholipid syndrome: the SHARE initiative. Ann Rheum Dis 2017; 76: 1637-41. [CrossRef]
45. Hunt BJ. Pediatric antiphospholipid antibodies and antiphospholipid syndrome. Semin Thromb Hemost 2008; 34: 274-81. [CrossRef]
46. Vaarala O, Palosuo T, Kleemola M, Aho K. Anticardiolipin response in acute infections. Clin Immunol Immunopathol 1986; 41: 8-15. [CrossRef]
47. Kurugol Z, Vardar F, Ozkinay F, Kavakli K, Ozkinay C. Lupus anticoagulant and protein S deficiency in otherwise healthy children with acute varicella infection. Acta Paediatr 2000; 89: 1186-9. [CrossRef]
48. Manco-Johnson MJ, Nuss R, Key N, Moertel C, Jacobson L, Meech S, et al. Lupus anticoagulant and protein S deficiency in children with postvaricella purpura fulminans or thrombosis. J Pediatr 1996; 128: 319-23. [CrossRef]
49. Ambrozic A, Avicin T, Ichikawa K, Kveder T, Matsuura E, Hojnik M, et al. Anti-beta(2)-glycoprotein I antibodies in children with atopic dermatitis. Int Immunol 2002; 14: 823-30. [CrossRef]
50. Avcin T, Ambrozic A, Kuhar M, Kveder T, Rozman B. Anticardiolipin and anti-beta(2) glycoprotein I antibodies in sera of 61 apparently healthy children at regular preventive visits. Rheumatology (Oxford) 2001; 40: 565-73. [CrossRef]
51. Male C, Lechner K, Eichinger S, Kyrle PA, Kapiotis S, Wank H, et al. Clinical significance of lupus anticoagulants in children. J Pediatr 1999; 134: 199-205. [CrossRef]
52. Siemens HJ, Gutsche S, Bruckner S, Bucsky P, Katus HA. Antiphospholipid antibodies in children without and in adults with and without thrombophilia. Thromb Res 2000; 98: 241-7. [CrossRef]
53. Rapizzi E, Ruffatti A, Tonello M, Piccoli A, Calligaro A, Sfriso P, et al. Correction for age of anticardiolipin antibodies cut-off points. J Clin Lab Anal 2000; 14: 87-90. [CrossRef]
54. Cabiedes J, Trejo-Hernandez J, Loredo-Abdala A, Castilla-Serna L, Lopez-Mendoza AT, Cordero-Esperon HA, et al. Anti-cardiolipin, anti-cardiolipin plus bovine, or human beta(2)glycoprotein-I and anti-human beta(2)glycoprotein-I antibodies in a healthy infant population. Arch Med Res 2002; 33: 175-9. [CrossRef]
55. Petri M. Epidemiology of the antiphospholipid antibody syndrome. J Autoimmun 2000; 15: 145-51. [CrossRef]
56. Groot N, de Graeff N, Avcin T, Bader-Meunier B, Brogan P, Dolezalova P, et al. European evidence-based recommendations for diagnosis and treatment of childhood-onset systemic lupus erythematosus: the SHARE initiative. Annals of the rheumatic diseases 2017; 76: 1788-96. [CrossRef]
57. Descloux E, Durieu I, Cochat P, Vital Durand D, Ninet J, Fabien N, et al. Paediatric systemic lupus erythematosus: prognostic impact of antiphospholipid antibodies. Rheumatology (Oxford) 2008; 47: 183-7. [CrossRef]
58. Ahluwalia J, Singh S, Naseem S, Suri D, Rawat A, Gupta A, et al. Antiphospholipid antibodies in children with systemic lupus erythematosus: a long-term clinical and laboratory follow-up status study from northwest India. Rheumatol Int 2014; 34: 669-73. [CrossRef]
59. Berube C, Mitchell L, Silverman E, David M, Saint Cyr C, Laxer R, et al. The relationship of antiphospholipid antibodies to thromboembolic events in pediatric patients with systemic lupus erythematosus: a cross-sectional study. Pediatr Res 1998; 44: 351-6. [CrossRef]
60. Levy DM, Massicotte MP, Harvey E, Hebert D, Silverman ED. Thromboembolism in paedia ric lupus patients. Lupus 2003; 12: 741-6. [CrossRef]
61. Male C, Mitchell L, Julian J, Vegh P, Joshua P, Adams M, et al. Acquired activated protein C resistance is associated with lupus anticoagulants and thrombotic events in pediatric patients with systemic lupus erythematosus. Blood 2001; 97: 844-9. [CrossRef]
62. Molta C, Meyer O, Dosquet C, Montes de Oca M, Babron MC, Danon F, et al. Childhood-onset systemic lupus erythematosus: antiphospholipid antibodies in 37 patients and their first-degree relatives. Pediatrics 1993; 92: 849-53.
63. Montes de Oca MA, Babron MC, Bletry O, Broyer M, Courtecuisse V, Fontaine JL, et al. Thrombosis in systemic lupus erythematosus: a French collaborative study. Arch Dis Child 1991; 66: 713-7. [CrossRef]
64. Ravelli A, Caporali R, Di Fuccia G, Zonta L, Montecucco C, Martini A. Anticardiolipin antibodies in pediatric systemic lupus erythematosus. Arch Pediatr Adolesc Med 1994; 148: 398-402. [CrossRef]
65. Seaman DE, Londino AV, Jr., Kwoh CK, Medsger TA, Jr., Manzi S. Antiphospholipid antibodies in pediatric systemic lupus erythematosus. Pediatrics 1995; 96: 1040-5.
66. von Scheven E, Glidden DV, Elder ME. Anti-beta2-glycoprotein I antibodies in pediatric systemic lupus erythematosus and antiphospholipid syndrome. Arthritis Rheum 2002; 47: 414-20. [CrossRef]
67. Driest KD, Sturm MS, O'Brien SH, Spencer CH, Stanek JR, Ardoin SP, et al. Factors associated with thrombosis in pediatric patients with systemic lupus erythematosus. Lupus 2016; 25: 749-53. [CrossRef]
68. Male C, Foulon D, Hoogendoorn H, Vegh P, Silverman E, David M, et al. Predictive value of persistent versus transient antiphospholipid antibody subtypes for the risk of thrombotic events in pediatric patients with systemic lupus erythematosus. Blood 2005; 106: 4152-8. [CrossRef]
69. Ramirez Gomez LA, Uribe Uribe O, Osio Uribe O, Grisales Romero H, Cardiel MH, Wojdyla D, et al. Childhood systemic lupus erythematosus in Latin America. The GLADEL experience in 230 children. Lupus 2008; 17: 596-604. [CrossRef]
70. Parikh S, Swaiman KF, Kim Y. Neurologic characteristics of childhood lupus erythematosus. Pediatr Neurol 1995; 13: 198-201. [CrossRef]
71. Quintero-Del-Rio AI, Van M. Neurologic symptoms in children with systemic lupus erythematosus. J Child Neurol 2000; 15: 803-7. [CrossRef]

72. Sibbitt WL, Jr., Brandt JR, Johnson CR, Maldonado ME, Patel SR, Ford CC, et al. The incidence and prevalence of neuropsychiatric syndromes in pediatric onset systemic lupus erythematosus. J Rheumatol 2002; 29: 1536-42.
73. Sanna G, Bertolaccini ML, Cuadrado MJ, Laing H, Khamashta MA, Mathieu A, et al. Neuropsychiatric manifestations in systemic lupus erythematosus: prevalence and association with antiphospholipid antibodies. J Rheumatol 2003; 30: 985-92.
74. Nojima J, Kuratsune H, Suehisa E, Kitani T, Iwatani Y, Kanakura Y. Strong correlation between the prevalence of cerebral infarction and the presence of anti-cardiolipin/beta2-glycoprotein I and anti-phosphatidylserine/prothrombin antibodies--Co-existence of these antibodies enhances ADP-induced platelet activation in vitro. Thromb Haemost 2004; 91: 967-76. [CrossRef]
75. Harel L, Sandborg C, Lee T, von Scheven E. Neuropsychiatric manifestations in pediatric systemic lupus erythematosus and association with antiphospholipid antibodies. J Rheumatol 2006; 33: 1873-7.
76. Athanasopoulos E, Kalaitzidou I, Vlachaki G, Stefanaki S, Tzagkaraki A, Niotakis G, et al. Chorea revealing systemic lupus erythematosus in a 13-year old boy: A case report and short review of the literature. Int Rev Immunol 2018; 37: 177-82. [CrossRef]
77. Besbas N, Damarguc I, Ozen S, Aysun S, Saatci U. Association of antiphospholipid antibodies with systemic lupus erythematosus in a child presenting with chorea: a case report. Eur J Pediatr 1994; 153: 891-3. [CrossRef]
78. Watanabe T, Onda H. Hemichorea with antiphospholipid antibodies in a patient with lupus nephritis. Pediatr Nephrol 2004; 19: 451-3. [CrossRef]
79. Avcin T, Benseler SM, Tyrrell PN, Cucnik S, Silverman ED. A followup study of antiphospholipid antibodies and associated neuropsychiatric manifestations in 137 children with systemic lupus erythematosus. Arthritis Rheum 2008; 59: 206-13. [CrossRef]
80. Unlu O, Zuily S, Erkan D. The clinical significance of antiphospholipid antibodies in systemic lupus erythematosus. Eur J Rheumatol 2016; 3: 75-84. [CrossRef]
81. Gattorno M, Buoncompagni A, Molinari AC, Barbano GC, Morreale G, Stalla F, et al. Antiphospholipid antibodies in paediatric systemic lupus erythematosus, juvenile chronic arthritis and overlap syndromes: SLE patients with both lupus anticoagulant and high-titre anticardiolipin antibodies are at risk for clinical manifestations related to the antiphospholipid syndrome. British journal of rheumatology 1995; 34: 873-81. [CrossRef]
82. Pilania RK, Suri D, Jindal AK, Kumar N, Sharma A, Sharma P, et al. Lupus anticoagulant hypoprothrombinemia syndrome associated with systemic lupus erythematosus in children: report of two cases and systematic review of the literature. Rheumatol Int 2018; 38: 1933-40. [CrossRef]
83. Mulliez SM, De Keyser F, Verbist C, Vantilborgh A, Wijns W, Beukinga I, et al. Lupus anticoagulant-hypoprothrombinemia syndrome: report of two cases and review of the literature. Lupus 2015; 24: 736-45. [CrossRef]
84. Mina R, Brunner HI. Pediatric lupus--are there differences in presentation, genetics, response to therapy, and damage accrual compared with adult lupus? Rheum Dis Clin North Am 2010; 36: 53-80, vii-viii. [CrossRef]
85. Brunner HI, Gladman DD, Ibanez D, Urowitz MD, Silverman ED. Difference in disease features between childhood-onset and adult-onset systemic lupus erythematosus. Arthritis Rheum 2008; 58: 556-62. [CrossRef]
86. Ruiz-Irastorza G, Egurbide MV, Ugalde J, Aguirre C. High impact of antiphospholipid syndrome on irreversible organ damage and survival of patients with systemic lupus erythematosus. Arch Intern Med 2004; 164: 77-82. [CrossRef]
87. Drenkard C, Villa AR, Alarcon-Segovia D, Perez-Vazquez ME. Influence of the antiphospholipid syndrome in the survival of patients with systemic lupus erythematosus. J Rheumatol 1994; 21: 1067-72.
88. Boffa MC, Lachassinne E. Infant perinatal thrombosis and antiphospholipid antibodies: a review. Lupus 2007; 16: 634-41. [CrossRef]
89. Mekinian A, Lachassinne E, Nicaise-Roland P, Carbillon L, Motta M, Vicaut E, et al. European registry of babies born to mothers with antiphospholipid syndrome. Ann Rheum Dis 2013; 72: 217-22. [CrossRef]
90. Berkun Y, Simchen MJ, Strauss T, Menashcu S, Padeh S, Kenet G. Antiphospholipid antibodies in neonates with stroke--a unique entity or variant of antiphospholipid syndrome? Lupus 2014; 23: 986-93. [CrossRef]
91. Abisror N, Mekinian A, Lachassinne E, Nicaise-Roland P, De Pontual L, Chollet-Martin S, et al. Autism spectrum disorders in babies born to mothers with antiphospholipid syndrome. Semin Arthritis Rheum 2013; 43: 348-51. [CrossRef]
92. Bertolaccini ML, Contento G, Lennen R, Sanna G, Blower PJ, Ma MT, et al. Complement inhibition by hydroxychloroquine prevents placental and fetal brain abnormalities in antiphospholipid syndrome. J Autoimmun 2016; 75: 30-8. [CrossRef]
93. Nalli C, Iodice A, Andreoli L, Galli J, Lojacono A, Motta M, et al. Long-term neurodevelopmental outcome of children born to prospectively followed pregnancies of women with systemic lupus erythematosus and/or antiphospholipid syndrome. Lupus 2017; 26: 552-8. [CrossRef]
94. Arnaud L, Mathian A, Ruffatti A, Erkan D, Tektonidou M, Cervera R, et al. Efficacy of aspirin for the primary prevention of thrombosis in patients with antiphospholipid antibodies: an international and collaborative meta-analysis. Autoimmun Rev 2014; 13: 281-91. [CrossRef]
95. Arnaud L, Mathian A, Devilliers H, Ruffatti A, Tektonidou M, Forastiero R, et al. Patient-level analysis of five international cohorts further confirms the efficacy of aspirin for the primary prevention of thrombosis in patients with antiphospholipid antibodies. Autoimmun Rev 2015; 14: 192-200. [CrossRef]
96. Erkan D, Aguiar CL, Andrade D, Cohen H, Cuadrado MJ, Danowski A, et al. 14th International Congress on Antiphospholipid Antibodies: task force report on antiphospholipid syndrome treatment trends. Autoimmun Rev 2014; 13: 685-96. [CrossRef]
97. Belizna C. Hydroxychloroquine as an anti-thrombotic in antiphospholipid syndrome. Autoimmun Rev 2015; 14: 358-62. [CrossRef]
98. Chaturvedi S, McCrae KR. Diagnosis and management of the antiphospholipid syndrome. Blood Rev 2017; 31: 406-17. [CrossRef]
99. Mahajerin A, Betensky M, Goldenberg NA. Thrombosis in Children: Approach to Anatomic Risks, Thrombophilia, Prevention, and Treatment. Hematol Oncol Clin North Am 2019; 33: 439-53. [CrossRef]
100. Rumsey DG, Myones B, Massicotte P. Diagnosis and treatment of antiphospholipid syndrome in childhood: A review. Blood Cells Mol Dis 2017; 67: 34-40. [CrossRef]
101. Crowther MA, Ginsberg JS, Julian J, Denburg J, Hirsh J, Douketis J, et al. A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. N Engl J Med 2003; 349: 1133-8. [CrossRef]
102. Finazzi G, Marchioli R, Brancaccio V, Schinco P, Wisloff F, Musial J, et al. A randomized clinical trial of high-intensity warfarin vs. conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS). J Thromb Haemost 2005; 3: 848-53. [CrossRef]
103. Baca V, Garcia-Ramirez R, Ramirez-Lacayo M, Marquez-Enriquez L, Martinez I, Lavalle C. Cerebral infarction and antiphospholipid syndrome in children. J Rheumatol 1996; 23: 1428-31.
104. Pengo V, Denas G, Zoppellaro G, Jose SP, Hoxha A, Ruffatti A, et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. Blood 2018; 132: 1365-71. [CrossRef]
105. Cohen H, Hunt BJ, Efthymiou M, Arachchillage DR, Mackie IJ, Clawson S, et al. Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus (RAPS): a randomised, controlled, open-label, phase 2/3, non-inferiority trial. Lancet Haematol 2016; 3: e426-36. [CrossRef]
106. Tektonidou MG, Andreoli L, Limper M, Amoura Z, Cervera R, Costedoat-Chalumeau N, et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. Ann Rheum Dis 2019. [CrossRef]
107. Belizna C, Pregnolato F, Abad S, Alijotas-Reig J, Amital H, Amoura Z, et al. HIBISCUS: Hydroxychloroquine for the secondary prevention of thrombotic and obstetrical events in primary antiphospholipid syndrome. Autoimmun Rev 2018; 17: 1153-68. [CrossRef]
108. Cervera R, Rodriguez-Pinto I, Colafrancesco S, Conti F, Valesini G, Rosario C, et al. 14th Interna-

tional Congress on Antiphospholipid Antibodies Task Force Report on Catastrophic Antiphospholipid Syndrome. Autoimmun Rev 2014; 13: 699-707. [CrossRef]
109. Bucciarelli S, Cervera R, Espinosa G, Gomez-Puerta JA, Ramos-Casals M, Font J. Mortality in the catastrophic antiphospholipid syndrome: causes of death and prognostic factors. Autoimmun Rev 2006; 6: 72-5. [CrossRef]
110. Go EJL, O'Neil KM. The catastrophic antiphospholipid syndrome in children. Curr Opin Rheumatol 2017; 29: 516-22. [CrossRef]
111. Berman H, Rodriguez-Pinto I, Cervera R, Gregory S, de Meis E, Rodrigues CE, et al. Pediatric catastrophic antiphospholipid syndrome: descriptive analysis of 45 patients from the "CAPS Registry". Autoimmun Rev 2014; 13: 157-62. [CrossRef]
112. Berman H, Rodriguez-Pinto I, Cervera R, Morel N, Costedoat-Chalumeau N, Erkan D, et al. Rituximab use in the catastrophic antiphospholipid syndrome: descriptive analysis of the CAPS registry patients receiving rituximab. Autoimmun Rev 2013; 12: 1085-90. [CrossRef]
113. Kronbichler A, Frank R, Kirschfink M, Szilagyi A, Csuka D, Prohaszka Z, et al. Efficacy of eculizumab in a patient with immunoadsorption-dependent catastrophic antiphospholipid syndrome: a case report. Medicine (Baltimore) 2014; 93: e143. [CrossRef]
114. Strakhan M, Hurtado-Sbordoni M, Galeas N, Bakirhan K, Alexis K, Elrafei T. 36-year-old female with catastrophic antiphospholipid syndrome treated with eculizumab: a case report and review of literature. Case Rep Hematol 2014; 2014: 704371. [CrossRef]
115. Wig S, Chan M, Thachil J, Bruce I, Barnes T. A case of relapsing and refractory catastrophic anti-phospholipid syndrome successfully managed with eculizumab, a complement 5 inhibitor. Rheumatology (Oxford) 2016; 55: 382-4. [CrossRef]
116. Zikos TA, Sokolove J, Ahuja N, Berube C. Eculizumab Induces Sustained Remission in a Patient With Refractory Primary Catastrophic Antiphospholipid Syndrome. J Clin Rheumatol 2015; 21: 311-3. [CrossRef]
117. Thornburg C, Pipe S. Neonatal thromboembolic emergencies. Semin Fetal Neonatal Med 2006; 11: 198-206. [CrossRef]
118. Kara A, Turgut S, Cagli A, Sahin F, Oran E, Tunc B. Complications of therapeutic apheresis in children. Transfus Apher Sci 2013; 48: 375-6. [CrossRef]