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European evidence-based recommendations for diagnosis and treatment of paediatric antiphospholipid syndrome: the SHARE initiative

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ABSTRACT

Antiphospholipid syndrome (APS) is rare in children, and evidence-based guidelines are sparse. Consequently, management is mostly based on observational studies and physician's experience, and treatment regimens differ widely. The Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) initiative was launched to develop diagnostic and management regimens for children and young adults with rheumatic diseases. Here, we developed evidence-based recommendations for diagnosis and treatment of paediatric APS. Evidence-based recommendations were developed using the European League Against Rheumatism standard operating procedure. Following a detailed systematic review of the literature, a committee of paediatric rheumatologists and representation of paediatric haematology with expertise in paediatric APS developed recommendations. The literature review yielded 1473 articles, of which 15 were valid and relevant. In total, four recommendations for diagnosis and eight for treatment of paediatric APS (including paediatric Catastrophic Antiphospholipid Syndrome) were accepted. Additionally, two recommendations for children born to mothers with APS were accepted. It was agreed that new classification criteria for paediatric APS are necessary, and APS in association with childhood-onset systemic lupus erythematosus should be identified by performing antiphospholipid antibody screening. Treatment recommendations included prevention of thrombotic events, and treatment recommendations for venous and/or arterial thrombotic events. Notably, due to the paucity of studies on paediatric APS, level of evidence and strength of the recommendations is relatively low. The SHARE initiative provides international, evidence-based recommendations for diagnosis and treatment for paediatric APS, facilitating improvement and uniformity of care.

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INTRODUCTION

The antiphospholipid syndrome (APS) is defined by vascular thrombosis or pregnancy morbidity (including premature births due to eclampsia, severe pre-eclampsia or unexplained fetal death), combined with persistently positive antiphospholipid antibodies (aPLs).[1] The routine tests to screen for aPL are lupus anticoagulant (LA); anticardiolipin antibodies (aCL) IgG and/or IgM; and/or anti-β2 glycoprotein-I antibodies (anti-β2GPI) IgG and/or IgM.[1] Primary APS is not as well defined in children but comprises the finding of aPL combined with thrombosis.[2] APS may occur in association with other disorders, including particularly childhood-onset systemic lupus erythematosus (cSLE). Patients with cSLE who are positive for aPL can present with aPL-related clinical manifestations.[3–6]

Although APS and SLE can share biological and clinical manifestations, immunogenetic studies in adult patients showed that the two diseases display different combinations of susceptibility genes, suggesting that they are two distinct disease entities.[7–9] In paediatric patients, APS is more commonly associated with SLE than in adults,[3] but no immunogenetic studies were performed in paediatric population.

In 2004, the international Ped-APS registry was initiated to determine the extent and characteristics of paediatric APS. This registry has identified 121 cases of paediatric APS in 14 European countries. Of these patients, 50% had primary APS and 41% had APS in association with cSLE or lupus-like disease.[2 3]

The low prevalence of APS impedes translational research, resulting in a lack of evidence to inform guidelines for disease management. Treatment approaches can differ even within centres and are mostly based on adult-derived studies, anecdotal evidence based on case series in children and clinical expertise. International collaboration is necessary: only by sharing expertise can we optimise and disseminate best practices regarding diagnosis and management of these rare diseases. For this reason, the Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) project was initiated.[10] One of the objectives of this project was to identify best practices for diagnosis and management of paediatric rheumatic diseases (PRDs), including paediatric APS. SHARE-recommendations for juvenile dermatomyositis and autoinflammatory diseases have already been published.[11–13]

METHODS

A European-wide panel of 16 paediatric rheumatologists along with representation of paediatric haematology, with expertise in paediatric APS, was established to develop evidence-based

recommendations. A project plan for the systematic literature search was written following the European League Against Rheumatism standardised operating procedure of recommendations.[10 14] In short, a systematic literature review based on specific research questions was performed in the MEDLINE, EMBASE and Cochrane databases in July 2013 (see online supplementary table 1). Relevant articles were selected by two authors (NG, NdG) based on predefined inclusion and exclusion criteria (see online supplementary table 2). All selected articles were independently reviewed by two experts (TA, MWB), who were responsible for data extraction, assessment of level of evidence and of methodological quality, according to a predefined proforma (see online supplementary table 3).[15 16] Provisional recommendations for the diagnosis and treatment of paediatric APS were based on the results of the literature review mapped against the initial research questions. The strength of the recommendations was based on the level of evidence relevant for the specific recommendation (see online supplementary table 4). Recommendations were discussed and finalised in two face-to-face consensus meetings (Genoa, March 2014, and Barcelona, March 2015), where the nominal group technique (NGT) was used to reach consensus (defined by at least 80% agreement) among the expert panel.[17]

RESULTS

A total of 1473 articles were found on paediatric primary APS or APS in association with other diseases. After screening on title and abstract and assessing the full text for relevance, 11 articles on primary paediatric APS, 9 articles regarding paediatric APS associated with cSLE and 4 articles on paediatric Catastrophic Antiphospholipid Syndrome (CAPS) fulfilled the inclusion criteria. Sixteen articles were considered to be valid (see online supplementary table 5). The consensus meetings resulted in 14 final recommendations (figure 1). Nine statements were accepted for diagnosis and management of paediatric APS, two statements for children born to mothers with APS being accepted and three statements for treatment of paediatric CAPS (table 1).

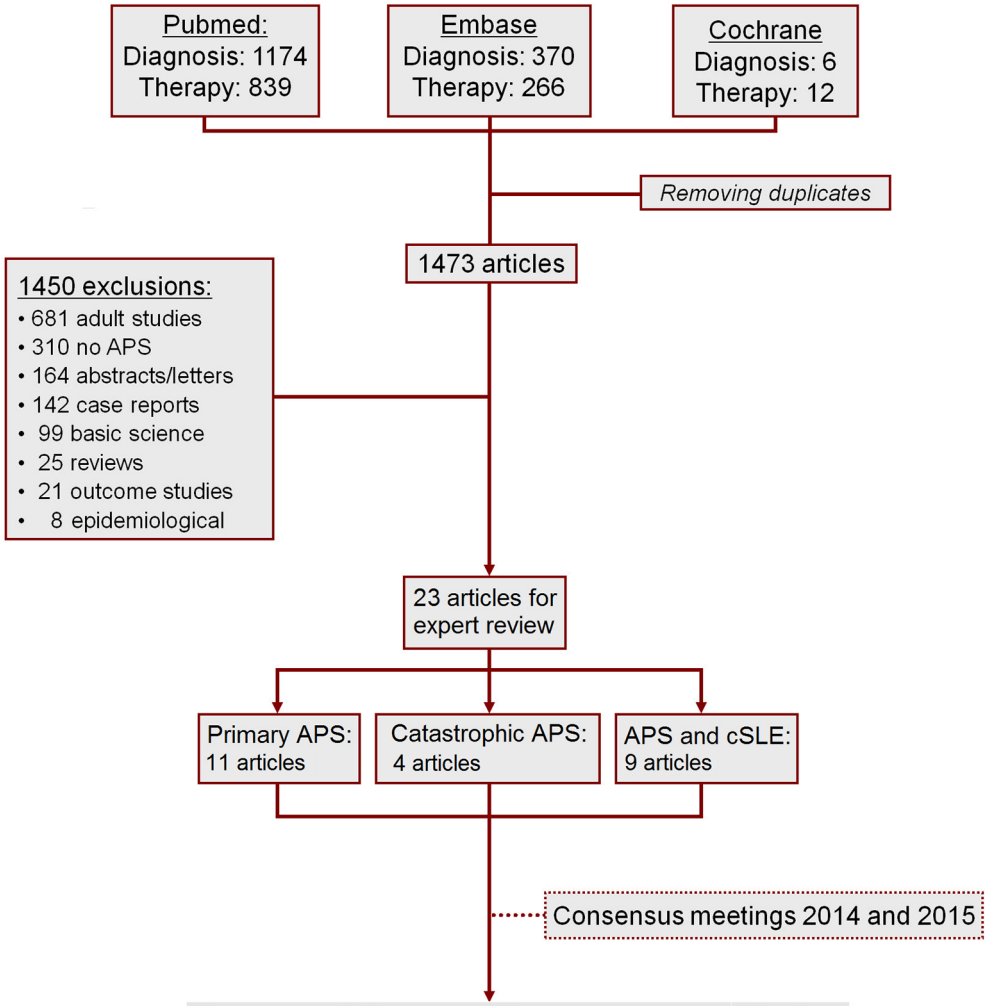

Figure 1 Summary results from the systematic literature review. APS, antiphospholipid syndrome; cSLE, childhood-onset systemic lupus erythematosus.

Table 1 Recommendations for the paediatric antiphospholipid syndrome (APS)

	Level of evidence	Strength	Agreement (%)
Diagnostic recommendations			
1. The adult criteria for APS, while specific, may lack sensitivity for paediatric APS.	3	C	100
2. New classification criteria for paediatric APS are needed that would incorporate non-thrombotic manifestations in children, in addition to thrombosis.	4	D	100
3. The following tests should be performed when suspecting paediatric APS: lupus anticoagulant, anticardiolipin IgG and IgM and anti-β2-glycoprotein-I IgG and IgM.	2A/B	B	100
4. aPL screening should be performed in all patients with cSLE.	3	C	100
Treatment recommendations			
1. In patients with cSLE and aPL, antiplatelet agents could be considered for primary prevention of thrombosis in addition to hydroxychloroquine.	3	C	100
2. When a patient has suffered a venous thrombotic event, anticoagulation therapy is indicated when manifestations are related to aPL.	3	C	100
3. When a patient has suffered a venous thrombotic event associated with persistent aPL positivity, long-term anticoagulation therapy is indicated.	3	C	100
4. When a patient has suffered an arterial thrombotic event associated with persistent aPL positivity, adequate long-term anticoagulation therapy or combined anticoagulation and antiaggregation therapy is indicated.	3	C	100
5. When a patient has suffered a recurrent thrombotic event associated with persistent aPL positivity despite oral anticoagulation with a target INR 2.0–3.0, long-term anticoagulation therapy to a target INR 3.0–4.0 or alternative therapies such as extended therapeutic dose of low-molecular- weight heparin yielding a target anti-Xa is indicated.	3	C	100
Recommendations for children born to mothers with APS			
1. Perinatal thrombosis associated with aPL is a very rare complication in infants born to mothers with positive aPL. Recurrence rates in infants with perinatal thrombosis are extremely low and there are no uniform guidelines for the therapeutic approach. In general, infants with perinatal arterial ischaemic stroke associated with aPL should not usually receive anticoagulation.	3	C	100
2. Children born to mothers with APS may exhibit a higher frequency of neurodevelopmental abnormalities; regular neurodevelopmental assessments during their long-term follow-up may be considered.	3	C	87
Recommendations for treatment of paediatric CAPS			
1. In a patient with paediatric CAPS, immediate combination treatment with anticoagulants, corticosteroids, plasma exchange with or without intravenous immunoglobulins should be considered.	3	C	100
2. In a patient with paediatric CAPS, rituximab or other immunosuppressive therapy may also be considered as a treatment option.	3	C/D	100
3. In CAPS, there are too few data to support the routine use of antiaggregation therapy.	4	D	100

Level of evidence; for diagnostic and observational studies: 1A, meta-analysis of cohort studies; 1B, meta-analysis of case–control studies; 2A, cohort studies; 2B, case–control studies; 3, non-comparative descriptive studies; 4, expert opinion; and for treatment studies: 1A, meta-analysis of randomised controlled trial; 1B, randomised controlled study; 2A, controlled study without randomisation; 2B, quasi-experimental study; 3, descriptive study; 4, expert opinion; Strength, strength of recommendation: A, based on level 1 evidence; B, based on level 2 or extrapolated from level 1; C, based on level 3 or extrapolated from level 1 or 2; D, based on level 4 or extrapolated from level 3 or 4 expert opinion,[8–10] Agreement indicates % of experts agreeing on the recommendation during the final voting round of the consensus meeting.
aPL, antiphospholipid antibodies; CAPS, Catastrophic Antiphospholipid Syndrome; cSLE, childhood-onset systemic lupus erythematosus; INR, international normalised ratio.

Recommendations on the diagnosis of paediatric primary APS and APS associated with other diseases

The current classification criteria used for APS in adults include two clinical criteria: vascular thrombosis and pregnancy morbidity.[1] Although the former is also an important feature in paediatric APS, the latter was deemed less relevant in children. However, in addition to thrombosis, other non-thrombotic features such as haematological or neurological manifestations are also frequently present in children.[3 18–25] Incorporation of these clinical features in a specific set of classification criteria for paediatric APS is therefore important.

The prognosis of APS is dependent on the number, type and titre of specific aPL (LA, aCL, anti-β2GPI) present. When APS is suspected, screening for all three aPL types should be performed. As the prevalence of aPL in patients with cSLE can range from 11% to 87% (depending on aPL subtypes present), it is important to screen for aPL in all patients with cSLE at baseline.[5 26–34] Timely diagnosis and appropriate management of paediatric APS can then be facilitated. When the presence of aPL is detected, but no thrombotic events have occurred, a diagnosis of APS cannot be made.

There is increasing evidence of differences in the cut-off threshold for detection of positive aPL between paediatric and adult population.[35 36] The majority of data pertaining to paediatric APS literature however refer to the adult cut-off values.[31 37]

Recommendations on the treatment of paediatric primary APS and APS associated with other diseases

A meta-analysis examining the preventive effect of aspirin in patients positive for aPL demonstrated a significant decrease in the risk of first thrombotic event in those taking aspirin.[38 39] Furthermore, a study of seven children with acute cerebral infarction associated with the presence of aPL indicated that aspirin may be effective in the prevention of recurrent thrombotic events.[40] Extrapolating from adult evidence, while recognising paucity of specific evidence available in children, it was concluded that addition of an antiplatelet agent (such as aspirin at an antiplatelet dose) to the therapy of patients with cSLE who are positive for aPL should be considered, in addition to the use of hydroxychloroquine.

After a thrombotic event, long-term anticoagulation therapy is indicated when manifestations are related to persistent aPL

positivity. If the thrombotic event initially seemed to be related to aPL, but persistence of aPL was not found, long-term anticoagulation therapy is not indicated. Although no specific evidence is available supporting this directly in paediatric APS, it was considered reasonable to continue anticoagulation therapy in the case of persistent aPL positivity 0.1as the patient is prone to develop a second thrombotic event when aPLs remain positive.[3] If a patient has suffered an arterial thrombotic event associated with persistent aPL positivity, adequate long-term anticoagulation therapy or combined anticoagulation and antiaggregation (such as aspirin) therapy is indicated. If recurrent thrombotic events associated with persistent aPL positivity occur despite oral anticoagulation, a higher target international normalised ratio (INR) or alternative therapies should be considered. In all instances of paediatric APS associated with other diseases, the primary disease (including cSLE and other PRDs including systemic vasculitis) should be treated appropriately.

Recommendations for children born to mothers with APS

There are few data on the outcomes of children born to mothers with APS. A European registry was set up to follow these children prospectively.[41] None of the 134 children that were included developed perinatal thrombosis, illustrating the rarity of the event. Evaluation of the management of infants with recurring perinatal thrombosis should be done on a case-by-case basis. It was agreed that in general infants with perinatal arterial ischaemic stroke associated with aPL should not usually receive anticoagulation.

From the above registry experience during the 5-year follow-up, three children had impaired neuropsychological development (axial hypotony, autism, hyperactive behaviour and a combination of feeding disorders, language delay and growth failure).[41] It was recommended that neurodevelopmental assessment should be considered to detect these problems early on.

Recommendations for treatment of paediatric CAPS

CAPS is the most severe, acutely life-threatening form of APS, characterised by multiple organ involvement and extensive small vessel thrombosis.[42] By definition, manifestations develop simultaneously or in less than a week. Histopathology of small vessel occlusion is found in at least one organ or tissue, along with the presence of aPL, according to the validated classification criteria for CAPS.[43 44]

A recent subanalysis of 45 paediatric patients included in the CAPS registry showed minimal differences in clinical and laboratory features between adult and paediatric patients with CAPS . Similar to adults, mortality in this group was high (27%). None of the patients who received only partial treatment with anticoagulants, corticosteroids, plasma exchange, with or without intravenous immunoglobulins (IVIG), survived the catastrophic event.[45] Three paediatric CAPS patients reported in a case series received combination treatment (heparinisation with high-dose corticosteroids and IVIG, in one patient additional rituximab). This led to resolution of symptoms in all three patients.[46] These results underline the importance of immediate combination treatment with anticoagulants, corticosteroids, plasma exchange with or without IVIG in paediatric CAPS, as is advised in adults with CAPS.[47]

Evidence regarding the use of biologics or other immunosuppressive drugs is very sparse in paediatric CAPS.[46] Some evidence is available in adults with CAPS. Based on an analysis of 20 adult CAPS patients who were treated with rituximab, there may be a role for rituximab in patients with haematological and/or microthrombotic manifestations.[48] Adults with CAPS associated with SLE could benefit from treatment with cyclophosphamide.[49] The use of eculizumab, a complement pathway inhibitor, has been described in several case reports and may be promising in the prevention of recurrence of CAPS.[50–54] As evidence in the paediatric population is lacking for these medications, their use should be considered carefully and with caution.

DISCUSSION

Following systematic review of the literature and international NGT consensus methodology, a total of 14 recommendations regarding paediatric APS were accepted with at least 80% agreement. These recommendations should help specialists with the diagnosis and treatment of children with APS. There is very little evidence on paediatric primary APS and APS associated with other diseases; consequently, the recommendations have a low level of evidence and strength. The collaboration already initiated with the Ped-APS registry, combined with generalised treatment for these patients and with improved classification criteria for APS in children, should result in a good documentation of treatment outcomes of this patient population. The SHARE recommendations should be updated with the evidence of future publications from this registry to keep improving diagnosis and therapeutic strategies for these patients.

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REFERENCES

1 Miyakis S, Lockshin MD, Atsumi T, *et al*. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006;4:295–306.
2 Avcin T, Cimaz R, Rozman B. Ped-APS Registry Collaborative Group. The Ped-APS registry: the antiphospholipid syndrome in childhood. *Lupus* 2009;18:894–9.
3 Avcin T, Cimaz R, Silverman ED, *et al*. Pediatric antiphospholipid syndrome: clinical and immunologic features of 121 patients in an international registry. *Pediatrics* 2008;122:e1100–7.
4 Cimaz R, Descloux E. Pediatric antiphospholipid syndrome. *Rheum Dis Clin North Am* 2006;32:553–73.

5 Descloux E, Durieu I, Cochat P, *et al*. Paediatric systemic lupus erythematosus: prognostic impact of antiphospholipid antibodies. *Rheumatology* 2008;47:183–7.
6 Ravelli A, Martini A. Antiphospholipid antibody syndrome in pediatric patients. *Rheum Dis Clin North Am* 1997;23:657–76.
7 Sebastiani GD, Iuliano A, Cantarini L, *et al*. Genetic aspects of the antiphospholipid syndrome: an update. *Autoimmun Rev* 2016;15:433–9.
8 Shoenfeld Y, Meroni PL, Toubi E. Antiphospholipid syndrome and systemic lupus erythematosus: are they separate entities or just clinical presentations on the same scale? *Curr Opin Rheumatol* 2009;21:495–500.
9 Tincani A, Andreoli L, Chighizola C, *et al*. The interplay between the antiphospholipid syndrome and systemic lupus erythematosus. *Autoimmunity* 2009;42:257–9.
10 Wulffraat NM, Vastert B, SHARE consortium. Time to share. *Pediatr Rheumatol Online J* 2013;11:5.
11 Enders FB, Bader-Meunier B, Baildam E, *et al*. Consensus-based recommendations for the management of juvenile dermatomyositis. *Ann Rheum Dis* 2017;76:329–40.
12 Giancane G, Ter Haar NM, Wulffraat N, *et al*. Evidence-based recommendations for genetic diagnosis of familial mediterranean fever. *Ann Rheum Dis* 2015;74:635–41.
13 ter Haar NM, Oswald M, Jeyaratnam J, *et al*. Recommendations for the management of autoinflammatory diseases. *Ann Rheum Dis* 2015;74:1636–44.
14 Dougados M, Betteridge N, Burmester GR, *et al*; EULAR. EULAR standardised operating procedures for the elaboration, evaluation, dissemination, and implementation of recommendations endorsed by the EULAR standing committees. *Ann Rheum Dis* 2004;63:1172–6.
15 Zhang W, Doherty M, Bardin T, *et al*; EULAR Standing Committee for International Clinical Studies Including Therapeutics. EULAR evidence based recommendations for gout. Part II: management. Report of a task force of the EULAR standing committee for international clinical studies including therapeutics (ESCISIT). *Ann Rheum Dis* 2006;65:1312–24.
16 Zhang W, Doherty M, Pascual E, *et al*; EULAR Standing Committee for International Clinical Studies Including Therapeutics. EULAR evidence based recommendations for gout. Part I: diagnosis. Report of a task force of the standing committee for international clinical studies including therapeutics (ESCISIT). *Ann Rheum Dis* 2006;65:1301–11.
17 Delbecq AL, Van de Ven AH. A group process model for problem identification and program planning. *J Appl Behav Sci* 1971;7:466–92.
18 Angelini L, Rumi V, Nardocci N, *et al*. Hemidystonia symptomatic of primary antiphospholipid syndrome in childhood. *Mov Disord* 1993;8:383–6.
19 Cervera R, Asherson RA, Font J, *et al*. Chorea in the antiphospholipid syndrome. Clinical, radiologic, and immunologic characteristics of 50 patients from our clinics and the recent literature. *Medicine* 1997;76:203–12.
20 Espinosa G, Font J, García-Pagan JC, *et al*. Budd-Chiari syndrome secondary to antiphospholipid syndrome: clinical and immunologic characteristics of 43 patients. *Medicine* 2001;80:345–54.
21 Kiechl-Kohlendorfer U, Ellemunter H, Kiechl S. Chorea as the presenting clinical feature of primary antiphospholipid syndrome in childhood. *Neuropediatrics* 1999;30:96–8.
22 Takanashi J, Sugita K, Miyazato S, *et al*. Antiphospholipid antibody syndrome in childhood strokes. *Pediatr Neurol* 1995;13:323–6.
23 Berkun Y, Padeh S, Barash J, *et al*. Antiphospholipid syndrome and recurrent thrombosis in children. *Arthritis Rheum* 2006;55:850–5.
24 Gattorno M, Falcini F, Ravelli A, *et al*. Outcome of primary antiphospholipid syndrome in childhood. *Lupus* 2003;12:449–53.
25 Zamora-Ustaran A, Escarcega-Alarcón RO, Garcia-Carrasco M, *et al*. Antiphospholipid syndrome in mexican children. *Isr Med Assoc J* 2012;14:286–9.
26 Ahluwalia J, Singh S, Naseem S, *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.
27 Berube C, Mitchell L, Silverman E, *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.
28 Campos LM, Kiss MH, D'Amico EA, *et al*. Antiphospholipid antibodies and antiphospholipid syndrome in 57 children and adolescents with systemic lupus erythematosus. *Lupus* 2003;12:820–6.
29 Male C, Mitchell L, Julian J, *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.
30 Massengill SF, Hedrick C, Ayoub EM, *et al*. Antiphospholipid antibodies in pediatric lupus nephritis. *Am J Kidney Dis* 1997;29:355–61.
31 Ravelli A, Caporali R, Di Fuccia G, *et al*. Anticardiolipin antibodies in pediatric systemic lupus erythematosus. *Arch Pediatr Adolesc Med* 1994;148:398–402.
32 Seaman DE, Londino AV, Kwoh CK, *et al*. Antiphospholipid antibodies in pediatric systemic lupus erythematosus. *Pediatrics* 1995;96:1040–5.
33 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.
34 Montes de Oca MA, Babron MC, Blétry O, *et al*. Thrombosis in systemic lupus erythematosus: a French collaborative study. *Arch Dis Child* 1991;66:713–7.
35 Avcin T, Ambrozic A, Kuhar M, *et al*. Anticardiolipin and anti-β2-glycoprotein I antibodies in sera of 61 apparently healthy children at regular preventive visits. *Rheumatology* 2001;40:565–73.
36 Andreoli L, Nalli C, Motta M, *et al*. Anti-β2-glycoprotein I IgG antibodies from 1-year-old healthy children born to mothers with systemic autoimmune diseases preferentially target domain 4/5: might it be the reason for their 'innocent' profile? *Ann Rheum Dis* 2011;70:380–3.
37 Giordano P, Tesse R, Lassandro G, *et al*. Clinical and laboratory characteristics of children positive for antiphospholipid antibodies. *Blood Transfus* 2012;10:296–301.
38 Arnaud L, Mathian A, Devilliers H, *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.
39 Arnaud L, Mathian A, Ruffatti A, *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.
40 Baca V, Garcia-Ramirez R, Ramirez-Lacayo M, *et al*. Cerebral infarction and antiphospholipid syndrome in children. *J Rheumatol* 1996;23:1428–31.
41 Mekinian A, Lachassinne E, Nicaise-Roland P, *et al*. European registry of babies born to mothers with antiphospholipid syndrome. *Ann Rheum Dis* 2013;72:217–22.
42 Erkan D, Espinosa G, Cervera R. Catastrophic antiphospholipid syndrome: updated diagnostic algorithms. *Autoimmun Rev* 2010;10:74–9.
43 Asherson RA, Cervera R, de Groot PG, *et al*; Catastrophic Antiphospholipid Syndrome Registry Project Group. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. *Lupus* 2003;12:530–4.
44 Cervera R, Font J, Gómez-Puerta JA, *et al*; Catastrophic Antiphospholipid Syndrome Registry Project Group. Validation of the preliminary criteria for the classification of catastrophic antiphospholipid syndrome. *Ann Rheum Dis* 2005;64:1205–9.
45 Berman H, Rodríguez-Pintó I, Cervera R, *et al*; Catastrophic Registry Project Group (European Forum on Antiphospholipid Antibodies). Pediatric catastrophic antiphospholipid syndrome: descriptive analysis of 45 patients from the 'CAPS Registry'. *Autoimmun Rev* 2014;13:157–62.
46 Haskin O, Amir J, Schwarz M, *et al*. Severe abdominal pain as a presenting symptom of probable catastrophic antiphospholipid syndrome. *Pediatrics* 2012;130:e230–5.
47 Cervera R, Rodríguez-Pintó I. G Espinosa on behalf of the Task Force on Catastrophic Antiphospholipid Syndrome. Catastrophic antiphospholipid syndrome: task force report summary. *Lupus* 2014;23:1283–5.
48 Berman H, Rodríguez-Pintó I, Cervera R, *et al*; Catastrophic Antiphospholipid Syndrome (CAPS) Registry Project Group (European Forum on Antiphospholipid Antibodies). Rituximab use in the catastrophic antiphospholipid syndrome: descriptive analysis of the CAPS registry patients receiving rituximab. *Autoimmun Rev* 2013;12:1085–90.
49 Bayraktar UD, Erkan D, Bucciarelli S, *et al*. Catastrophic antiphospholipid syndrome project G. The clinical spectrum of catastrophic antiphospholipid syndrome in the absence and presence of lupus. *J Rheumatol* 2007;34:346–52.
50 Zikos TA, Sokolove J, Ahuja N, *et al*. Eculizumab induces sustained remission in a patient with refractory primary catastrophic antiphospholipid syndrome. *J Clin Rheumatol* 2015;21:311–3.
51 Barratt-Due A, Fløisand Y, Orrem HL, *et al*. Complement activation is a crucial pathogenic factor in catastrophic antiphospholipid syndrome. *Rheumatology* 2016;55:1337–9.
52 Lonze BE, Zachary AA, Magro CM, *et al*. Eculizumab prevents recurrent antiphospholipid antibody syndrome and enables successful renal transplantation. *Am J Transplant* 2014;14:459–65.
53 Shapira I, Andrade D, Allen SL, *et al*. Brief report: induction of sustained remission in recurrent catastrophic antiphospholipid syndrome via inhibition of terminal complement with eculizumab. *Arthritis Rheum* 2012;64:2719–23.
54 Kronbichler A, Frank R, Kirschfink M, *et al*. Efficacy of eculizumab in a patient with immunoadsorption-dependent catastrophic antiphospholipid syndrome: a case report. *Medicine* 2014;93:e143.

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