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Systematic Review of Case Reports of Antiphospholipid Syndrome Following Infection

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Abstract

Objective—To conduct a systematic review of case reports documenting the development of antiphospholipid syndrome (APS) or APS-related features after an infection.

Methods—We searched Medline, EMBASE, Web of Science, PubMed ePubs, and The Cochrane Library – CENTRAL through March 2015 without restrictions. Studies reporting cases of APS or APS-related features following an infection were included.

Results—259 publications met inclusion criteria, reporting on 293 cases. Three different groups of patients were identified; group 1 included patients who fulfilled the criteria for definitive APS (24.6%), group 2 included patients who developed transient antiphospholipid (aPL) antibodies with thromboembolic phenomena (43.7%), and group 3 included patients who developed transient aPL antibodies without thromboembolic events (31.7%). The most common preceding infection was viral (55.6%). In cases that developed thromboembolic events *Human immunodeficiency* (HIV) and *Hepatitis C* (HCV) viruses were the most frequently reported. Parvovirus B19 was the most common in cases that developed antibodies without thromboembolic events. Hematological manifestations and peripheral thrombosis were the most common clinical manifestations. Positive anticardiolipin antibodies were the most frequent antibodies reported, primarily coexisting IgG

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and IgM isotypes. Few patients in groups 1 and 2 had persistent aPL antibodies for more than 6 months. Outcome was variable with some cases reporting persistent APS features and others achieving complete resolution of clinical events.

Conclusions—Development of aPL antibodies with all traditional manifestations of APS were observed after variety of infections, most frequently after chronic viral infections with HIV and HCV. The causal relationship between infection and APS cannot be established, but the possible contribution of various infections in the pathogenesis of APS need further longitudinal and controlled studies to establish the incidence, and better quantify the risk and the outcomes of aPL-related events after infection.

Keywords

anticardiolipin antibodies; antiphospholipid antibodies; lupus anticoagulant; infection; systematic review

Antiphospholipid syndrome (APS) is a systemic autoimmune disease with persistent elevation of antiphospholipid (aPL) antibodies that can result in recurrent thromboembolic events, and pregnancy-related morbidity with recurrent fetal losses.(1) The disease may be life-threatening with multiple organ failure in about 1% of cases, who develop catastrophic antiphospholipid syndrome (CAPS).(2)

The reported prevalence of elevated aPL antibodies, mainly anticardiolipin (aCL) and lupus anticoagulant (LA), among healthy individuals is 1–5%; higher among elderly individuals with chronic diseases. It is not clear how many people with elevated aPL antibodies develop APS.(3–7) APS often occurs in association with other autoimmune diseases, most commonly systemic lupus erythematosus (SLE).(2)

The molecular pathogenesis of APS is complex, and environmental triggers may play a crucial role in genetically predisposed individuals.(8) APS may occur in association with an infection or malignancy, or may be induced by certain drugs (e.g., interferon-alpha).(9) The pathogenesis of these associations is unclear.(10) Molecular mimicry with shared genetic epitopes with infectious agents has been proposed as a possible mechanism.(11, 12) Previous studies suggested that infection may lead to the development of transiently elevated non-thrombogenic aPL antibodies lacking anti-β2 glycoprotein-I (anti-β2 GPI) activity.(13, 14) However, there are increasing case reports of patients with various types of infections who develop aPL antibodies and thromboembolic events.

We conducted a systematic review of all such reported cases in the literature to summarize existing evidence. Although a systematic review of case reports cannot support causality between infection and APS, it can identify unrecognized or rare associations, and can generate hypotheses for subsequent studies. Our objective was to identify potentially putative infections identified in the literature in association with APS, and to describe related clinical and immunologic features.

METHODS

Data sources and searches

We searched electronic databases (Medline, EMBASE, Web of Science, PubMed ePubs, and The Cochrane Library - CENTRAL) with no language restrictions, from inception through March 2015 to identify case reports of patients with elevated aPL antibodies after an infection. References of included articles were also searched manually. Search terms are provided in Appendix 1.

Study selection

The screening of eligible publications was carried out independently by two raters. First, the titles and abstracts of all citations were reviewed. Next, the full text of potentially relevant citations was reviewed. Discrepancies were resolved by consensus. Cases were only included if they reported patients with a history of infection that was diagnosed before elevated aPL antibodies were identified in those patients, whether or not they had APS-related clinical features. We considered any type of infection as long as the infectious agent was identified. To meet the definition of aPL antibodies elevation, one positive laboratory test either LA, aCL, or anti-β2 GPI antibodies after a prior diagnosis of infection was required. For the diagnosis of APS, infection must be followed by thromboembolic manifestations (arterial or venous), or pregnancy-related complications, with persistent elevation of aPL antibodies that remained positive for at least 12 weeks.(1) Diagnosis of CAPS was considered when the authors of the reported cases considered the diagnosis of CAPS, or when thromboembolic events developed in three or more organs simultaneously with persistent aPL antibodies positivity and small vessels occlusion confirmed by biopsy.(15) A time frame was not chosen between the earlier diagnosis of infection and the subsequent recognition of aPL antibodies positivity as there are no published validated criteria to define this time window. Nevertheless, studies were excluded if they reported patients with APS diagnosed before the infection was acquired, or coexisted with the diagnosis of infection. Studies were also excluded if they reported patients with a definite history of SLE diagnosed prior to APS or infection.

Data extraction and quality assessment

Data was extracted by one reviewer and crosschecked by another. Data from articles published in languages other than English were extracted by physician collaborators proficient in the original language (Chinese, Japanese, Spanish, French, and Germany). We extracted data on the potentially putative infections (whether viral, bacterial, fungal, or parasitic), clinical presentation following infection and prior comorbidities, laboratory abnormalities, aPL antibodies elevation (whether LA, aCL, or anti-β2 GPI antibodies), aPL antibodies positivity (whether persistent or transient), treatment required and patient outcomes.

We used a modified version of a tool for quality appraisal of case reports.(16) The assessment was carried out by one investigator and a random sample was crosschecked by another. For articles published in languages other than English only one reviewer performed the assessment. We used four items: i) patient was described adequately (i.e., chief

complaint, history, clinical and laboratory evaluations, treatments), ii) an accurate diagnosis was provided (i.e., valid and reliable outcome measures were utilized), iii) convincing evidence in support of the diagnosis was presented (i.e., according to the criteria for diagnosis of APS/CAPS, or describing the evidence for diagnosis), and iv) alternate explanations were considered and refuted (differential diagnosis was illustrated and scientifically excluded, or underlying possible mechanisms that could explain the finding were addressed). Possible item ratings were yes, partially, or no.

Data synthesis and analysis

Data were summarized using descriptive statistics, with means and standard deviations for continuous variables and frequencies and percentages for dichotomous variables.

RESULTS

Publication characteristics

A total of 2,510 unique citations were initially retrieved (Figure 1). We identified 358 citations as potentially relevant and reviewed the full publication. We excluded 29 publications reporting cases in which no proof that infection preceded the development of APS, 57 publications reporting cases in which diagnosis of APS preceded the infection, 9 publications were not retrievable, and 4 Russian language publications as we were unable to translate them. We included 259 publications (reporting on 293 cases where clinical description of each reported case was provided separately). Bibliographic references for the case reports are included in Appendix 2. Cases from the United States were most common (20.5%), followed by Spain (14.7%), and France (12.6%).

Quality appraisal

The overall quality of the cases was good to moderate. Most cases reported an adequate description of the chief complaint, patient past medical history, laboratory and image investigations, and treatments (87.0%). Accurate diagnosis with valid and reliable outcomes measures were reported for two thirds (65.9%). Convincing evidence of diagnosis was provided in 81.6% and an alternate explanation was reported in 73.0% (Appendix 2).

Patient characteristics

The mean age of the cases was 34.0 years (standard deviation, 19.4 years). One hundred and fifty-three patients (52.2%) were male. Patients were categorized into 1 of 3 groups according to the clinical presentation reported. Group 1 included 72 patients (24.6%) whose infection was followed by symptoms that fulfilled the classification criteria for definitive APS, including 17 patients (5.8%) who fulfilled the most up-to-date CAPS criteria.(1, 13) Group 2 included 128 patients (43.7%) who developed thromboembolic phenomena associated with elevated aPL antibodies during the course of infection, but did not fulfill APS/CAPS criteria (either transient antibodies or not enough follow-up duration). Group 3 included 93 patients (31.7%) who developed transient elevated aPL antibodies after an infection but did not develop thromboembolic manifestations or pregnancy-related complications.

Types of infections

The most common type of infection across all groups was viral (55.6%) (Table 1). In general, *Human immunodeficiency* (HIV) and *Hepatitis C* (HCV) viruses were the most frequent infections reported primarily in cases that developed thromboembolic events in group 1 (17.0%) and group 2 (9.9%). *Parvovirus B19* (PVB19) was the most frequently reported viral infection in group 3 (antibodies with no thromboembolic or pregnancy events) (16.1%).

Bacterial infections were reported in 108 patients (36.9%), most commonly secondary to *Coxiella burnetii, Mycoplasma pneumonia,* streptococci*, and Mycobacterium tuberculosis*. Most *Coxiella* cases resulted in development of antibodies without clinical manifestations, while for the other infections the majority of the cases reported had APS.

Parasitic and fungal infections were less common across all groups; only 12 patients (4.1%) had a parasitic infection and 5 patients (1.7%) had a fungal infection. Fifteen patients (5.1%) were reported to have more than one type of infection (viral, bacterial, spirochetal, parasitic, and fungal). In 22 cases (7.5%) the infectious agent was not clearly identified. These cases were reported to have gastrointestinal, urinary, upper respiratory tract infections, or other unspecified infections.

In cases that developed CAPS, HCV was the most common infection reported, although another 9 different viral and bacterial infections were also observed (Appendix 3).

Most commonly, infection alone was reported as the precipitating factor for APS or elevated aPL antibodies with no other comorbidities were identified (83.6%) (Table 2). A history of other concomitant diseases was reported in the remainder of the cases, most frequently an autoimmune or inflammatory disease (7.5%) (cases with SLE were excluded), or a previous diagnosis of cancer (2.4%). In addition, a prior history of congenital, cardiovascular, blood, or allergic diseases was reported in a few cases. For these cases, there was no evidence of the presence of aPL antibodies before the onset of infection. Viral infection was predominant in cases with a prior history of autoimmune diseases (81.8%), with PVB19 occurring in approximately one third of the cases (31.8%) (Appendix 4).

Clinical features

Table 3 shows the most common features in patients who presented with thromboembolic or pregnancy related events (with or without fulfilling APS criteria). Hematologic manifestations, were reported in 33.5% of the cases, with 5.0% developing disseminated intravascular coagulopathy (DIC). Thrombocytopenia was reported in 33.3% of cases fulfilling the diagnosis of APS or CAPS, in 21.9% of those who developed thromboembolic events with elevated aPL antibodies and in 6 out of 10 cases complicated by DIC. Peripheral thrombosis was the most commonly reported thromboembolic complication occurring in 30.0% of the cases, followed by stroke or transient ischemic attacks (23.5%) and pulmonary thromboembolism (16.5%). Obstetric complications (with up to 5 recurrent abortions) were reported among 7 patients in the group fulfilling APS criteria (9.7%). Other less frequent manifestations are shown in Table 3.

In patients with HIV, avascular necrosis was the main presentation followed by peripheral thrombosis, stroke, and cutaneous necrosis as well. Whereas in patients with HCV infection, thrombocytopenia, peripheral thrombosis, and stroke were the main clinical features similarly observed (Appendix 5).

By definition, patients in group 3 did not develop thromboembolic manifestations or pregnancy complications related to APS or CAPS. Transient thrombocytopenia after the infection was detected in 9 patients (9.7%); 4 (4.3%) of whom had platelet counts of less than 100,000/mm3, but was not associated with any clinical consequences. No other laboratory abnormalities were reported.

aPL antibody profiles

All cases were tested for at least one positive aPL antibody as per our inclusion criteria, but not all cases were tested for the same antibodies (Table 4). Positive aCL antibodies were the most frequently reported in groups 1 (89.2%) and 2 (93.3%), mainly as coexisting IgG and IgM antibodies. Positive LA was the most common in group 3 (92.3%) and anti-β2 GPI antibodies were reported in 60.6% of all cases among the three groups. Additionally, positive aPL antibodies with unspecified isotype were reported in 8.5%.

In cases that developed anti-β2 GPI antibodies, viral infections were predominant (65.0%); HCV in group 1 (40.0%), CMV in group 2 (20.0%) followed by HIV and varicella (16.0% each), and PVB19 in group 3 (45.0%).

Follow-up was reported for 168 cases, and among them 120 (71.4%) had transient aPL antibodies (in general considered for most case as less than 6 months). Persistent positive antibodies were observed in 28 patients in group 1 (84.8%) in contrast to only 11 patients in group 2 (14.3%) and 9 patients in group 3 (15.5%). Nine patients in group 1 (27.3%) and 7 patients in group 2 (9.2%) showed persistent positive aPL antibodies for more than 6 months. Follow-up data was reported in 41 cases that developed anti-β2 GPI antibodies, and revealed transient antibodies not associated with any clinical consequences in 70.7%.

Treatment

Details of treatment were available for 266 cases. All patients received antimicrobial therapy. Anticoagulation was given to most patients who develop thromboembolic events; anticoagulants and/or antiplatelet therapy (aspirin or clopidogrel) were administered to 54 patients in group 1 (88.5%) and 72 patients in group 2 (63.2%). In group 3, only 1 HIV infected case (1.1%) received anticoagulation for stroke thought to be secondary to neurosyphilis with brain vasculitis.

Outcomes

Data on patient outcomes was available in 236 cases. In group 1, 7 patients (15.2%) died (5 from CAPS, 1 from active acquired immunodeficiency, and the cause of death was not defined in 1 patient with HIV infection); 17 (37.0%) continued to have recurrent APS manifestations, and 22 (47.8%) became asymptomatic on antithrombotic therapy.

HIV and HCV were the most common infections reported in patients who died; no specific aPL antibody was identified. Two thirds of cases that developed CAPS, had persistent APS or died.

In group 2, 9 (8.1%) died from thrombotic complications and the remainder (91.9%) had complete resolution of thrombotic events with no recurrences. Four patients in group 3 (5.1%) died during the course of their infection, the rest recovered completely with no complications of APS or CAPS.

Patients with anti-β2 GPI antibodies and HCV had worse outcomes (persistent APS and death) than those with PVB19, where antibodies were transient and not associated with thromboembolic events.

Sixty-five cases were 18 years old or younger. Of these, 38 (58.5%) had viral, and 22 (33.9%) had bacterial infections (Appendix 6). Infection was the sole precipitating factor in 52 cases (80.0%), and 37 cases (56.9%) developed clinical manifestations (groups 1 and 2) mainly hematologic and cutaneous, followed by peripheral thrombosis and stroke. Non-typical presentations such as cardiac, vena cava, carotid artery, pulmonary thrombosis, and splenic infarction were also reported in the pediatric group. Three cases diagnosed were diagnosed with CAPS where the identified agents were *Escherichia coli*, *Pseudomonas aeruginosa*, and *PVB19*. Persistent APS and death were reported in 6 cases; 88.2% had complete recovery.

DISCUSSION

Since their discovery, aPL antibodies have been a subject of great interest. Cardiolipin was the major tissue extract for reactive non-treponemal tests for syphilis since 1906.(17, 18) Although cardiolipin antibodies (IgG, IgM or IgA) were considered a serological marker for syphilis, many other infections, such as hepatitis, varicella, measles, scarlet fever, or viral pneumonia, were associated with transient positive tests considered to be false positive tests for syphilis.(19–21) It was subsequently observed that patients with autoimmune diseases, primarily SLE, could develop persistent false positive tests for syphilis.(22–24) In the early 1980s, aCL antibodies cross-reacting with negatively charged phospholipids were discovered using an enzyme-linked immunosorbent assay (ELISA) and its association with APS syndrome was described.(23, 25–28) Further studies identified the role of β2 GPI, a cofactor with anticoagulant properties required to enhance aCL binding to target phospholipids.(13, 29, 30) Generally, it had been thought that aCL antibodies in patients with infection were not associated with β2 GPI.(14, 31) However, increasingly, case reports of patients have shown that aCL, LA and β2 GPI can occur after infection with clinical consequences, not just as a transient non-pathogenic process.

To our knowledge, we are reporting the largest and most comprehensive systematic review of case reports on the association of infection with subsequent APS or APS-related features. Our review identified 293 case reports with more than 50 different infections associated with subsequent development of aPL antibodies. We classified cases according to the clinical presentation reported: APS or CAPS, as per diagnostic criteria (group 1), APS events not

fulfilling criteria (group 2), and elevated aPL antibodies alone with no associated thromboembolic or pregnancy events (group 3). The most common putative infections in all three groups were viral, with HIV and HCV as the most frequent infections in patients with clinical manifestations (group 1 and 2), and PVB19 in group 3. Bacterial infections were the second most common infections in all 3 groups with *Mycoplasma pneumonia*, streptococci, and *Mycobacterium tuberculosis* being the most frequently reported in group 1 and 2, while *Coxiella* cases were more frequent in group 3. Infection alone was the sole precipitating factor in the majority of the reported cases (83.6%), with the remainder reporting primarily pre-existing autoimmune or inflammatory disorders (SLE was excluded) or cancer. In cases with pre-existing autoimmune disease, PVB19 infection was the predominant infection.

Thrombocytopenia and peripheral vascular thrombosis were the most common presenting features among patients with clinical manifestations (groups 1 and 2). Outcomes were variable and ranged from complete resolution of clinical manifestations and antibodies to persistent APS with recurrent events, and CAPS. In general, patients who fulfilled criteria for APS or CAPS were more likely to develop chronic persistent disease. HIV and HCV were the most common infections reported in those cases where persistent APS or death occurred. Non-typical presentations such as retinal, aortic, and abdominal vessel occlusion, splenic infarction, and/or adrenal crisis were also reported.

Among the included cases, 65 were children with 23 different infectious agents identified. Similar to adults, viral infection was the most common putative infection followed by bacterial. More than half of the cases developed clinical manifestations (groups 1 and 2) with occasional atypical presentations. Persistent APS and death were reported in few cases, but the majority had complete recovery.

The coexistence of infection and thromboembolic events has been previously reported in two other reviews, and in two case reports with a literature search included.(32–35) The first review of 100 patients with APS thrombotic manifestations and infection reported skin infections, HIV, pneumonia, HCV, and urinary infection as the most common infections, with pulmonary, skin, and renal thromboembolic events as the main clinical presentations. (32) In their review, cases with aPL antibodies and infection were not included unless thromboembolic events occurred. They reported a lower proportion of HIV cases compared to our findings, while the prevalence of HCV was relatively similar. Sixty eight percent of their cases had primary APS, with the reminder reporting other autoimmune diseases (27 cases had SLE). The timing of infection in relation to the diagnosis of primary APS was not clearly specified. The other comprehensive review described 82 patients with chronic HCV or HIV and reported non-typical presentations compared to patients from other case series of APS without infection.(35) Their findings, as ours, showed that avascular necrosis, followed by cutaneous necrosis and peripheral thrombosis, and neurological manifestations were most common in patients with HIV. Intra-abdominal thrombosis and myocardial infarction were more frequent in patients with HCV. Both reviews had a more limited search (only one database), and did not follow the specific steps required for systematic reviews, such as specific inclusion criteria, and quality appraisal.(32, 35, 36) Another previous review of 80 patients with CAPS pointed to infection as a possible triggering factor in 35% of the cases, but the majority of them had previous diagnosis of SLE or primary APS. Respiratory tract

infection was the most common precipitating factor.(36) Analysis of 280 patients from a CAPS Registry also showed that infection was the most common precipitating factor in 22%, but the infectious agents were not identified.(37)

With respect to the frequency of aPL antibodies, aCL antibodies were the most commonly reported in groups 1 and 2, primarily coexisting IgG and IgM isotypes, and LA was the most frequently reported antibody in group 3. Many reports however, were old and did not test for the presence of anti-β2 GPI. Genetic polymorphism of β2 GPI may be an important risk factor in susceptibility to APS. (38–42) Molecular mimicry between infectious agents and β2 GPI has been proposed as a possible etiology of APS (11, 12) but the relationship between mimicry and genetic variants is unknown. In our review, positive anti-β2 GPI antibodies were identified across all three groups. Overall, more than two thirds of anti-β2 GPI antibodies were transient and not associated with any clinical consequences. However, in HCV infections, anti-β2 GPI appeared to be associated with persistent APS and/or death. None of the previous reviews had information on anti-β2 GPI.(32, 35, 36)

Our systematic review included a comprehensive literature search without any language restrictions, with specific criteria for inclusion and quality appraisal. Our findings are limited nevertheless by the quality and breadth of the data in the reports, which was not uniform or consistent (e.g. all reported cases were not tested for all aPL antibodies). Publication bias could account for increased number of cases with HIV and HCV. Most importantly, case series and reports are uncontrolled, and while they can suggest hypotheses they cannot establish robust associations. Nevertheless, clinicians should be aware of the large number of cases reported in the literature suggesting that infection may be implicated in the pathogenesis of APS, perhaps in genetically predisposed individuals. While case reports can identify signals, they are not robust enough for statistical inference. Therefore, the evidence provided is not sufficient to recommend systematic screening in patients with infections, but should alert physician of the possible putative association in patients with both signs and symptoms of infection and clinical features of APS.

In conclusion, development of aPL antibodies with all traditional manifestations of APS was observed after a variety of infections including viruses, bacteria, fungi and parasites. Our findings warrant the need for controlled longitudinal studies to establish the incidence and outcomes of aPL-related events after infection, and to help identify if specific infections may warrant systematic screening for aPL antibodies.

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Appendix 1. MEDLINE search strategy

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to 03/2015

1	exp “BACTERIAL INFECTIONS AND MYCOSES”/
2	exp VIRUS DISEASES/
3	exp PARASITIC DISEASES/
4	exp BACTERIA/
5	exp VIRUSES/
6	PARASITES/
7	or/1–6 [pathogen or pathogen dis MeSH terms]
8	ANTIPHOSPHOLIPID SYNDROME/
9	7 and 8
10	exp ANTIBODIES, ANTIPHOSPHOLIPID/
11	BETA 2-GLYCOPROTEIN I/
12	or/10–11
13	(exp *“BACTERIAL INFECTIONS AND MYCOSES”/ or exp *VIRUS DISEASES/ or exp *PARASITIC DISEASES/) and (exp *ANTIBODIES, ANTIPHOSPHOLIPID/ or *BETA 2-GLYCOPROTEIN I/) [pathogen dis major MeSH AND antibody terms major MeSH]
14	((antiphospholipid* adj3 (syndrom* or antibod*)) or (anti phospholipid* adj3 (syndrom* or antibod*)) or “lupus anticoagula*” or “lupus anti coagula*” or “lupus coagulation inhibitor*” or anticardiolipin* or anti-cardiolipin* or “beta2 glycoprotein i” or “beta 2 glycoprotein i” or “beta2 gpi” or beta2gpi or “beta 2 gpi” or “beta 2gpi” or “apolipoprotein h” or “apo h” or apoh).ti. [antibody terms in titles]
15	(infect* or coinfect* or co-infect* or bacter* or fungus* or fungem* or fungi* or fungal* or mycoses* or mycotic* or communicable* or virus* or viral* or viremi* or viridae or parasit* or microorganism* or micro-organism* or pathogen*1 or microbe*1 or microbial* or parvovir* or ebv or “epstein barr vir*” or mononucleos* or (human adj2 herpesvirus 4) or (burkitt* adj2 herpesvirus*) or (burkitt* adj2 lymphoma adj2 virus*) or “hhv 4”).ti. [infectious disease or pathogen terms in titles]
16	14 and 15
17	(((antiphospholipid* adj3 (syndrom* or antibod*)) or (anti phospholipid* adj3 (syndrom* or antibod*)) or “lupus anticoagula*” or “lupus anti coagula*” or “lupus coagulation inhibitor*” or anticardiolipin* or anti-cardiolipin* or “beta2 glycoprotein i” or “beta 2 glycoprotein i” or “beta2 gpi” or beta2gpi or “beta 2 gpi” or “beta 2gpi” or “apolipoprotein h” or “apo h” or apoh) adj10 (infect* or coinfect* or co-infect* or bacter* or fungus* or fungem* or fungi* or fungal* or mycoses* or mycotic* or communicable* or virus* or viral* or viremi* or viridae or parasit* or microorganism* or micro-organism* or pathogen*1 or microbe*1 or microbial* or parvovir* or ebv or “epstein barr vir*” or mononucleos* or (human adj2 herpesvirus 4) or (burkitt* adj2 herpesvirus*) or (burkitt* adj2 lymphoma adj2 virus*) or “hhv 4”)).ab. [keyword phrases within 10 words of each other in an abstract]
18	7 and 14 [MeSH pathogen or dis and antibody keyword term]
19	(8 or 12) and 15 [APS MeSH term AND infect term in titles]
20	9 or 13 or 16 or 17 or 18 or 19 [all facets merged]
21	(animals not (humans and animals)).sh.
22	20 not 21

Appendix 2. Reported cases and their quality appraisal

Author	Year	Country	Adequate description	Reliable outcome	Convincing evidence	Alternate explanation
Abernethy (1)	1995	USA	Yes	Partially	Partially	Yes
Abulafia (2, 3)[a]	2004	Brazil	Partially	Partially	No	No
Aguilar (4)	2005	Spain	Yes	Yes	Yes	Yes
Akerkar (5)	2005	India	Yes	Yes	Yes	Yes
Alcock (6)	2011	Australia	Yes	Yes	Yes	Yes
Aldamiz-Echebarria (7)	1991	Spain	Yes	Partially	No	Yes
Alric (8)	1998	France	Yes	Yes	Yes	Yes
Amiral (9)	1997	Greek	Yes	Yes	Yes	Yes
Amit (10)	2012	Israel	Yes	Yes	Yes	Yes
Anton-Martinez (11)	2011	Spain	Yes	Yes	Yes	Partially
Appert-Flory (12)	2010	France	Yes	Yes	Yes	Yes
			Yes	Yes	Yes	Yes
Arnason (13)	1995	USA	Yes	Yes	Partially	Yes
Arruda (14)	1993	Brazil	Yes	Partially	Yes	Yes
Asano (15)	2006	Japan	Yes	Yes	Yes	Yes
Ascer (16)	2011	Brazil	Yes	Partially	Partially	Partially
Asherson (17)	2001	South Africa	Yes	Partially	Partially	No
			Yes	Partially	Partially	No
Ashrani (18)	2003	USA	Yes	Yes	Partially	Yes
			Yes	Yes	Partially	Yes
Aydin (19)	2006	Turkey	Yes	Partially	Yes	Yes
Baid (20)	1999	USA	Yes	Partially	Yes	Yes
			Yes	Partially	Yes	Yes
Bakos (21)	1996	Brazil	Yes	Partially	Yes	Yes
Bakshi (22)	2006	India	Yes	Yes	Yes	Yes
Balderramo (23)	2009	Spain	Yes	Yes	Yes	Yes
Barfield (24)	1997	USA	Yes	Yes	Yes	Yes
Belmonte (25)	1993	Spain	Yes	Partially	Yes	Yes
			Yes	Partially	Yes	Yes
			Yes	Partially	Yes	Yes
Ben-Chetrit (26)	2013	Israel	Partially	Partially	Partially	No
Bibler (27)	1986	USA	Yes	Partially	Yes	Yes
Bloom (28)	1986	USA	Partially	Partially	Partially	Partially
Bouchard (29)	1998	France	Partially	Partially	Yes	No
Brackett (30)	2011	USA	Yes	Yes	Yes	No
Brown (31)	2001	USA	Yes	Partially	Yes	Yes

Author	Year	Country	Adequate description	Reliable outcome	Convincing evidence	Alternate explanation
			Yes	Partially	Yes	Yes
			Yes	Partially	Yes	Yes
Brown (32)	2008	UK	Yes	Yes	Yes	Yes
Bulucu (33)	2002	Turkey	Yes	Yes	Partially	Yes
Cagatay (34)	2004	Turkey	Yes	Partially	Yes	Partially
Cailleux (35, 36)[a]	1999	France	Yes	Yes	Yes	Yes
Calvo (37)	1998	Spain	Partially	Yes	Yes	Partially
Campanelli (38)	2004	Switzerland	Yes	Yes	Yes	Yes
Campos-Alvarez (39)	1992	Spain	Yes	Partially	Yes	No
Canpolat (40)	2008	Turkey	Yes	Yes	Yes	Yes
Cappell (41)	1993	USA	Yes	Partially	Yes	Yes
Carli (42)	1993	France	Partially	Yes	Yes	No
			Partially	Yes	Yes	No
Catteau (43)	1995	France	Yes	Yes	Yes	Yes
			Yes	Yes	Yes	Yes
Charloux (44)	1993	France	Yes	Partially	Partially	Yes
Chen (45)	2005	Taiwan	Yes	Yes	Yes	Yes
Chen (46)	2006	Taiwan	Yes	Yes	Yes	Yes
Chevalier (47)	1993	France	Yes	Yes	Yes	Yes
Cho (48)	2006	Korea	Yes	Partially	Partially	Yes
Chou (49)	2000	Taiwan	Yes	Yes	Yes	Yes
			Yes	Yes	Yes	Yes
			Yes	Yes	Yes	Yes
Clark (50)	2003	UK	Yes	Yes	Yes	Yes
Collazos (51)	1994	Spain	Yes	Partially	Yes	Yes
Cooray (52)	2013	Canada	Yes	Yes	Yes	Yes
Corti (53)	2001	Spain	Yes	Yes	Yes	Yes
Cross (54)	1999	USA	Yes	Yes	Yes	Partially
Cull (55)	2012	USA	Yes	Yes	Yes	Yes
Damian (56)	2004	Romania	Yes	Partially	Yes	No
Daniels (57)	2008	USA	Yes	Partially	Yes	Yes
De Argila Fernandez-Auran (58)	1996	Spain	Yes	Partially	Partially	Partially
de, Corla-Souza André (59)	2003	USA	Yes	Partially	Yes	Yes
de, Lucas (60)	1998	Spain	Partially	Yes	Yes	No
De, Larranaga (61)	2005	Argentina	Yes	Yes	Yes	Yes
del, Arco (62)	2001	Spain	Partially	Yes	Yes	No
Del, Castillo (63)	1997	Spain	Yes	Yes	Partially	Yes

Author	Year	Country	Adequate description	Reliable outcome	Convincing evidence	Alternate explanation
Delbos (64)	2007	France	Yes	Yes	Yes	Yes
Demey (65)	1997	Belgium	Yes	Yes	Partially	No
			Yes	Yes	Partially	No
Devars (66)	1997	France	Partially	Yes	Yes	Partially
Diaz (67)	2010	Spain	Yes	Yes	Yes	Yes
Doyle (68)	1998	USA	Yes	Yes	Yes	Yes
Drulovic (69)	2000	Yugoslavia	Yes	Partially	Yes	Yes
Durkin (70)	2013	USA	Yes	Yes	Yes	Yes
Economou (71)	2003	Greece	Yes	Yes	Yes	Yes
Enomoto (72)	2010	Japan	Partially	Partially	Yes	Yes
Ergas (73)	2008	Israel	Yes	Partially	Yes	Yes
Ertem (74, 75)[a]	2001	Turkey	Yes	Yes	Yes	Yes
			Yes	Yes	Yes	Yes
Fain (76)	2009	France	Partially	Partially	Partially	No
Faller (77)	1999	France	Yes	Partially	Partially	Yes
Fanlo (78)	2010	Spain	Yes	Yes	Yes	Yes
			Yes	Yes	Yes	Yes
Faria (79)	2011	Portugal	Partially	Yes	Yes	No
Fernandez (80)	2007	Spain	Yes	Yes	Yes	Yes
			Yes	Yes	Yes	Yes
			Yes	Yes	Yes	Yes
Flateau (81)	2013	France	Yes	Yes	Yes	Yes
Freeman (82)	2014	UK	Yes	Yes	Yes	Yes
Frontino (83)	2009	Italy	Yes	Yes	Yes	Yes
Galvez (84)	1997	Spain	Partially	Yes	Partially	Yes
Garcia Rincon (85)	2014	Colombia	Yes	Yes	Yes	Yes
Germano (86)	2005	Portugal	Yes	Yes	Yes	Yes
Ghosh (87)	2008	India	Yes	Yes	Yes	Yes
Giordano (88)	2005	Italy	Yes	Yes	Yes	Yes
Girard (89)	2005	France	Yes	Partially	Yes	Yes
Gologorsky (90)	2011	USA	Yes	Partially	Yes	Yes
Gorczyca (91)	2005	Poland	Yes	Partially	Partially	Partially
Graffin (92)	2007	France	Yes	Yes	Yes	Yes
Granel (93)	1998	France	Yes	Yes	Yes	Partially
Grau (94)	1991	Spain	Partially	Yes	Yes	No
			Partially	Yes	Yes	No
			Partially	Yes	Yes	No
Graw-Panzer (95)	2009	USA	Yes	Yes	Yes	Yes
Greco (96)	2011	USA	Yes	Yes	Yes	Yes

Author	Year	Country	Adequate description	Reliable outcome	Convincing evidence	Alternate explanation
			Yes	Partially	Partially	Partially
			Yes	Partially	Partially	No
Gru (97)	2010	USA	Yes	Yes	Yes	Yes
Guedes-Barbosa (98)	2008	Brazil	Yes	Yes	Yes	Yes
Haire (99)	1986	USA	Yes	Partially	Yes	Yes
Hal Sebastiaan (100)	2005	Australia	Yes	Yes	Yes	Yes
Hamidou (101)	1993	France	Yes	Partially	No	No
Hansen (102)	1998	USA	Yes	Yes	Yes	Yes
Harada (103)	2003	Japan	Yes	Partially	Yes	Yes
Hassoun (104)	2004	USA	Yes	Partially	Partially	Yes
Hernandez (105)	2000	Spain	Yes	Partially	Yes	Yes
Herscovici (106)	2012	Israel	Yes	Partially	Partially	Yes
Hoxha (107, 108)[a]	2008	Italy	Yes	Yes	Partially	Partially
Humphries (109)	1994	USA	Yes	Yes	Partially	Yes
Ignatov (110)	2004	Bulgaria	Yes	Partially	Yes	Yes
Ihle (111)	2002	Australia	Yes	Yes	Partially	Yes
Inglot (112)	2013	Poland	Yes	Yes	Yes	Yes
Inomata (113)	2008	Japan	Yes	Partially	Yes	No
Iqbal Belkys (114)	2012	UK	Partially	Partially	Yes	Yes
Izhevsky (115)	2004	USA	Yes	Yes	Yes	Yes
Jacq (116)	1997	France	Yes	Yes	Yes	Yes
Jani (117)	1997	India	Yes	Partially	Yes	Partially
Jarrett (118)	1998	New Zealand	Yes	Partially	Yes	Yes
Jin (119)	2011	Korea	Yes	Yes	Yes	Yes
Johnston (120)	2000	UK	Yes	Yes	Yes	Yes
Kalt (121)	2001	USA	Yes	Yes	Yes	Yes
Kang (122)	2013	Korea	Yes	Yes	Yes	Yes
Karunatilaka (123)	2007	UK	Yes	Yes	Yes	Yes
Keeling (124)	1990	UK	Partially	Partially	Yes	Yes
Kida (125)	2009	Japan	Yes	Yes	Yes	Partially
Kirrstetter (126)	2004	Cameroon	Yes	Yes	Yes	Yes
Kobayashi (127)	2008	Japan	Yes	Partially	Yes	Yes
Korkmaz (128)	2001	Turkey	Yes	Yes	Yes	Yes
Ku (129)	2003	USA	Yes	Yes	Yes	No
Kurugol (130)	2001	Turkey	Yes	Yes	Yes	Yes
Labarca (131)	1997	USA	Yes	Yes	Yes	Yes
Lamaury (132)	1996	France	Partially	Yes	Yes	Yes

Author	Year	Country	Adequate description	Reliable outcome	Convincing evidence	Alternate explanation
Le Goff (133)	2004	France	Yes	Partially	Yes	Yes
Leder (134)	2001	South Africa	Yes	Partially	Yes	Partially
Lee (135)	2011	Taiwan	Yes	Yes	Yes	Yes
Lefebvre (136)	2010	France	Yes	Yes	Yes	Yes
			Yes	Yes	Yes	Yes
Lehmann (137)	2004	Germany	Yes	Partially	Yes	Yes
			Yes	Partially	Yes	Yes
			Yes	Partially	Yes	Yes
Lehmann (138)	2008	Germany	Yes	Partially	Yes	Yes
			Yes	Partially	Yes	Yes
			Yes	Partially	Yes	Yes
			Yes	Partially	Yes	Yes
Liappis (139)	2003	USA	Yes	Yes	Yes	Yes
Lijfering (140)	2007	Netherlands	Yes	Yes	Yes	Yes
Linares (141)	2006	Spain	Yes	Yes	Yes	Yes
Lioger (142)	2013	France	Yes	Yes	Yes	Yes
Lobrano (143)	2006	USA	Yes	Yes	Yes	Yes
Lydakis (144)	2005	Greece	Yes	Yes	Partially	Yes
Magdalena (145)	2006	Poland	Yes	Yes	Yes	Partially
Maldonado (146)	2004	Spain	Yes	Yes	Yes	Yes
Maldonado (147)	2014	Mexico	Yes	Yes	Yes	Yes
Malnick (148)	1997	Israel	Yes	Yes	Yes	Yes
Manas (149)	2006	Spain	Yes	Yes	Yes	Partially
Manco-Johnson (150)	1992	USA	Partially	Yes	Yes	Partially
Marruchella (151)	2010	Italy	Yes	Yes	Yes	Yes
Martin (152)	2011	USA	Yes	Yes	Yes	Yes
Martin-Aspas (153)	2006	Spain	Yes	Yes	Yes	No
Massano (154)	2008	Portugal	Yes	Yes	Yes	Yes
McKinley (155)	2010	USA	Yes	Partially	Partially	No
Medina (156)	2009	Mexico	Yes	Yes	Partially	Partially
Meissner (157)	2013	Germany	Yes	Partially	Yes	No
Merino (158)	1996	Spain	Partially	Yes	Yes	No
			Partially	Yes	Yes	No
Mizumoto (159)	2006	Japan	Yes	Yes	Yes	Yes
			Yes	Yes	Yes	Yes
			Yes	Yes	Yes	Yes
Molina-Ruiz (160)	2012	Spain	Yes	Yes	Yes	Yes
Moreira (161)	2000	Spain	Yes	Partially	No	Partially

Author	Year	Country	Adequate description	Reliable outcome	Convincing evidence	Alternate explanation
Morino (162)	2009	Japan	Yes	Yes	Yes	Yes
Muntean (163)	1980	Austria	Yes	Yes	Yes	Yes
Muwakkit (164)	2002	Lebanon	Yes	Yes	Yes	Yes
Nadir (165)	2000	USA	Partially	Partially	Partially	Yes
			Partially	Partially	Partially	Yes
			Partially	Partially	Partially	Yes
Nagashima (166)	2010	Japan	Yes	Yes	Yes	Yes
Nakayama (167)	2014	Japan	Yes	Yes	Yes	Yes
Naranjo (168)	1992	Spain	Yes	Yes	Yes	Partially
Nasilowska-Adamska (169)	2014	Poland	Yes	Yes	Yes	Yes
Ndimbie (170)	1989	Germany	Yes	Partially	Yes	Yes
Newcombe (171)	2013	Australia	Yes	Yes	Yes	Yes
Niitsuma (172)	2003	Japan	Yes	Partially	Yes	No
Nishio (173)	2013	Japan	Yes	Partially	No	Yes
Noureddine (174)	2003	Moraco	Yes	Partially	Yes	Yes
Noval (175)	1999	Spain	Yes	Partially	Yes	Yes
Novelli (176)	2011	Italy	Partially	Yes	Yes	Yes
Nunzie (177)	2014	Ecuador	Yes	Yes	Yes	Yes
Orbea (178)	1999	Spain	Yes	Partially	Yes	No
Padmakumar (179)	2004	UK	Yes	Yes	Yes	Yes
Padovan (180)	2001	Munich	Yes	Yes	Yes	Yes
Pamuk (181)	2003	Turkey	Yes	Yes	Yes	Yes
Parola (182)	1998	France	Yes	Yes	Yes	Yes
Pelletier (183)	1995	France	Partially	Yes	Yes	Yes
Pers (184)	2008	France	Yes	Yes	Yes	Yes
Peter (185)	2013	USA	Partially	Partially	Partially	Partially
Peyton (186)	1998	USA	Yes	Yes	Yes	No
			Yes	Yes	Yes	Yes
Pittschieler (187)	2011	Austria	Partially	Yes	Yes	No
Poon Michelle (188)	2012	Singapore	Yes	Yes	Yes	Yes
Pourrat (189)	2003	France	Yes	Yes	Yes	Yes
Poux (190)	1995	France	Partially	Yes	Yes	No
Puri (191)	1999	Canada	Yes	Partially	Yes	No
Reitblat (192)	2000	Israel	Yes	Partially	Partially	No
Rennke (193)	1999	USA	Yes	Yes	Partially	Yes
Rivoisy (194)	2014	France	Yes	Partially	Yes	Yes
Rizzi (195)	1994	Italy	Yes	Yes	Partially	Partially

Author	Year	Country	Adequate description	Reliable outcome	Convincing evidence	Alternate explanation
Rodriguez-Hernandez (196)	1996	Spain	Partially	Yes	Yes	Yes
Rodriguez-Quinonez (197)	2004	USA	Yes	Yes	Yes	Yes
Ronayne (198)	2013	New Zealand	Yes	Yes	Yes	Yes
Rosca (199)	2010	Romania	Yes	Partially	Yes	Yes
Rose (200)	1998	France	Yes	Yes	Yes	Partially
Saberi (201, 202)[a]	2009	USA	Yes	Partially	Yes	No
Sanchez (203)	2004	Spain	Yes	Yes	Yes	Yes
Sanli (204)	2002	Turkey	Yes	Yes	Yes	Yes
Santos (205)	2004	Spain	Yes	Partially	Yes	Yes
Schattner (206)	1994	Israel	Yes	Yes	Yes	Yes
Schmidt (207)	1990	USA	Yes	Yes	Yes	Yes
Schmugge (208)	2001	Switzerland	Yes	Yes	Partially	Yes
Scimeca (209)	1987	USA	Yes	Partially	Yes	Yes
Sedlak (210)	2008	Slovakia	Yes	Partially	Partially	Yes
Selman (211)	2011	UK	Yes	Partially	Partially	No
Senda (212)	2010	Japan	Yes	Yes	Yes	Yes
Shah (213)	2006	India	Yes	Yes	Yes	Yes
Shahnaz (214)	2004	USA	Yes	Partially	Yes	Partially
Shimizu (215)	2009	Japan	Yes	Partially	Yes	Partially
Shimizu (216)	2014	Japan	Yes	Yes	Yes	Yes
Shimura (217)	2013	Japan	Yes	Yes	Yes	Yes
Shinohara (218)	2009	USA	Yes	Partially	Yes	Partially
Shiomou (219)	2002	Greece	Yes	Yes	Yes	Yes
Shroff (220)	2011	Canada	Yes	Yes	Yes	Yes
Sinnreich (221)	2003	Switzerland	Yes	Yes	Yes	Yes
Sonoda (222)	2005	Japan	Yes	Partially	No	Yes
Soper (223)	2000	Egypt	Yes	Yes	Yes	Partially
Soweid (224)	1995	USA	Partially	Partially	Partially	Partially
Steuerwald (225)	1995	Pakistan	Partially	Yes	Yes	Yes
Suero (226)	2005	Spain	Yes	Yes	Yes	Yes
Sztajzel (227)	2000	Switzerland	Yes	Yes	Yes	Yes
Tanir (228)	2006	Turkey	Yes	Yes	Yes	Yes
Tanizawa (229)	2009	Japan	Yes	Yes	Yes	Yes
Tattevin (230)	2003	France	Yes	Yes	Yes	Yes
Tavakoli (231)	2011	Iran	Yes	Yes	Yes	Yes
Thirumalai (232)	1994	USA	Yes	Partially	Yes	Yes
Tolosa-Vilella (233)	1995	Spain	Yes	Yes	Yes	Yes

Author	Year	Country	Adequate description	Reliable outcome	Convincing evidence	Alternate explanation
Toyoshima (234)	2007	Japan	Yes	Yes	Yes	Partially
Tullett (235)	1989	UK	Yes	Partially	Yes	Yes
Tung (236)	2011	Spain	Yes	Yes	Yes	Yes
Turhal (237)	2001	Turkey	Yes	Partially	Yes	Partially
			Yes	Partially	Yes	Partially
			Yes	Partially	Yes	Partially
			Yes	Partially	Yes	Yes
Turtle (238)	1999	Australia	Yes	Yes	Yes	Yes
Ulvestad (239)	2000	Norway	Yes	Yes	Yes	Yes
Uthman (240)	1999	Lebanon	Yes	Yes	Partially	No
Uthman (241)	2001	Lebanon	Yes	Yes	Yes	No
Uthman (242)	2002	Lebanon	Yes	Yes	Partially	No
Vassalluzzo (243)	1995	USA	Partially	Yes	Yes	No
Venugopalan (244)	2001	Oman	Yes	Partially	Partially	Yes
Vidal (245)	2005	France	Yes	Yes	Yes	Yes
			Yes	Yes	Yes	Yes
Viseux (246)	2000	France	Yes	Yes	Yes	Yes
Waller Elizabeth (247)	2008	USA	Yes	Partially	Yes	Yes
Wallin (248)	2009	Brazil	Yes	Yes	Yes	Yes
Wiegering (249)	2010	Germany	Yes	Yes	Yes	Yes
Witmer (250)	2007	USA	Yes	Yes	Yes	Yes
			Yes	Yes	Yes	Yes
Witz (251)	2000	Isreal	Yes	Yes	Yes	Yes
Wong (252)	2001	Australia	Yes	Yes	Yes	Yes
			Yes	Yes	Yes	Yes
Wong (253)	2004	USA	Partially	Partially	Partially	Yes
Yamazaki (254)	1991	Japan	Yes	Yes	Yes	Partially
Yanez (255)	1999	USA	Yes	Yes	Yes	No
Yilmaz (256)	2002	Turkey	Yes	Yes	Yes	Partially
Yoo (257)	2004	Korea	Yes	Yes	Yes	Partially
Younes (258)	2002	Tunisie	Partially	Yes	Partially	Yes
Zhang (259)	2012	China	Yes	Yes	Partially	Yes

[a]Two publications for the same case reports.

Appendix 3. Infections reported in patients with catastrophic antiphospholipid syndrome

Infection	N (%)
	Catastrophic antiphospholipid syndrome, N = 17[a]
Viral	**7 (41.2)**
Hepatitis C virus	3 (17.7)
Cytomegalovirus	2 (11.8)
Parvovirus B19	1 (5.9)
Influenza A virus (subtype H1N1)	1 (5.9)
Bacterial	**7 (41.2)**
Staphylococci	2 (11.8)
Streptococci	1 (5.9)
Escherichia coli	1 (5.9)
Mycobacterium tuberculosis	1 (5.9)
Pseudomonas aeruginosa	1 (5.9)
Spirochetal	
Treponema pallidum	1 (5.9)
Unidentified organisms	**4 (23.5)**

[a]One case had both viral and bacterial infections.

Appendix 4. Infections reported in patients with a history of autoimmune or inflammatory diseases

Infection	N (%)
	Autoimmune diseases N = 22
Viral	**18 (81.8)**
Parvovirus B19	7 (31.8)
Cytomegalovirus	3 (13.6)
Human immunodeficiency virus	2 (9.1)
Hepatitis C virus	2 (9.1)
Hepatitis B virus	1 (4.6)
Herpes simplex virus	1 (4.6)
Influenza A virus (subtype H1N1)	1 (4.6)
Varicella-zoster virus	1 (4.6)
Bacterial	**4 (18.2)**
Streptococci	2 (9.1)
Listeria monocytogenes	1 (4.6)
Spirochetal	

Infection	N (%)
	Autoimmune diseases N = 22
Treponema pallidum	1 (4.6)

Appendix 5. Thromboembolic events in patients with human immunodeficiency virus and hepatitis C virus

Clinical presentation	N (%)	
	Human immunodeficiency N = 47[a]	Hepatitis C N = 29
Hematologic manifestations	**6 (12.8)**	**6 (20.7)**[b]
Thrombocytopenia and/or hemolytic anemia	4 (8.5)	6 (20.7)
Pancytopenia	2 (4.3)	0
Disseminated intravascular coagulopathy	0	1 (3.5)
Peripheral thrombosis	**8 (17.0)**	**6 (20.7)**
Vascular thrombosis in UL/LL	7 (14.9)	5 (17.2)
Jugular and/or subclavian vein thrombosis	0	1 (3.5)
Testicular thrombosis	1 (2.1)	0
Neurologic manifestations		
Stroke and/or transient ischemic attack	**8 (17.0)**	**6 (20.7)**
Cutaneous manifestations	**8 (17.0)**	**5 (17.2)**
Cutaneous necrosis and/or capillary thrombosis (livedo reticularis/ pseudovasculitis/purpura)	6 (12.8)	2 (6.9)
Digital gangrene	2 (4.3)	2 (6.9)
Penile leukocytoclastic vasculitis	0	1 (3.5)
Respiratory manifestations		
Pulmonary thromboembolism	**6 (12.8)**	**1 (3.5)**
Cardiac manifestations	**3 (6.4)**	**5 (17.2)**
Superior and/or inferior vena cava thrombosis	1 (2.1)	1 (3.5)
Intra-cardiac thrombus + aortic occlusion	0	1 (3.5)
Myocardial infarction	1 (2.1)	3 (10.3)
Valve thickening and/or vegetation	1 (2.1)	0
Renal manifestations	**0**	**5 (17.2)**
Renal vessels occlusion	0	3 (10.3)
Acute renal failure	0	1 (3.5)
End stage renal disease	0	1 (3.5)
Splenic infarction	**2 (4.3)**	**2 (6.9)**
Gastrointestinal manifestations		
Abdominal vessels (mesenteric/iliac/abdominal aorta) occlusion	**0**	**2 (6.9)**
Osteo-articular manifestations		

Clinical presentation	N (%)	
	Human immunodeficiency N = 47[a]	Hepatitis C N = 29
Avascular necrosis	**9 (19.2)**	**1 (3.5)**
Hepatic manifestations		
Portal and/or hepatic vessels thrombosis	**2 (4.3)**	**3 (10.3)**
Ophthalmologic manifestations		
Retinal thrombosis and/or optic neuropathy	**1 (2.1)**	**3 (10.3)**
Obstetric manifestations	**0**	**2 (6.9)**
Adrenal crisis	**0**	**1 (3.5)**

HIV: human immunodeficiency syndrome; HCV: hepatitis c virus.

[a]Twenty four cases have been diagnosed with acquired immune deficiency syndrome.

[b]Only 1 case was complicated by disseminated intravascular coagulopathy among the 6 cases of HCV infection who develop thrombocytopenia and/or hemolytic anemia.

Appendix 6. Infections reported in patients 18 years old or younger

Infection	N (%)
	Pediatric Cases N = 65[a]
Viral	**38 (58.5)**
Varicella-zoster virus	9 (13.9)
Parvovirus B19	7 (10.8)
Adenovirus	5 (7.7)
Epstein-Barr virus	5 (7.7)
Human immunodeficiency virus	3 (4.6)
Hepatitis A virus	3 (4.6)
Hepatitis B virus	1 (1.5)
Hepatitis C virus	1 (1.5)
Herpes simplex virus	1 (1.5)
Cytomegalovirus	1 (1.5)
Dengue virus	1 (1.5)
Measles	1 (1.5)
Bacterial	**22 (33.9)**
Mycoplasma pneumonia	8 (12.3)
Streptococci	4 (6.2)
Pseudomonas aeruginosa	2 (3.1)
Bartonella henselae	1 (1.5)
Coxiella burnetii	1 (1.5)
Escherichia coli	1 (1.5)
Mycoplasma penetrans	1 (1.5)

Infection	N (%)
	Pediatric Cases N = 65[a]
Mycobacterium tuberculosis	1 (1.5)
Rickettsia africae	1 (1.5)
Spirochetal	
Borellia burgdorferi	2 (3.1)
Parasitic	**1 (1.5)**
Malaria	
Unidentified organisms	**6 (9.2)**

[a]Two patients reported more than 1 type of infection (viral, and bacterial).

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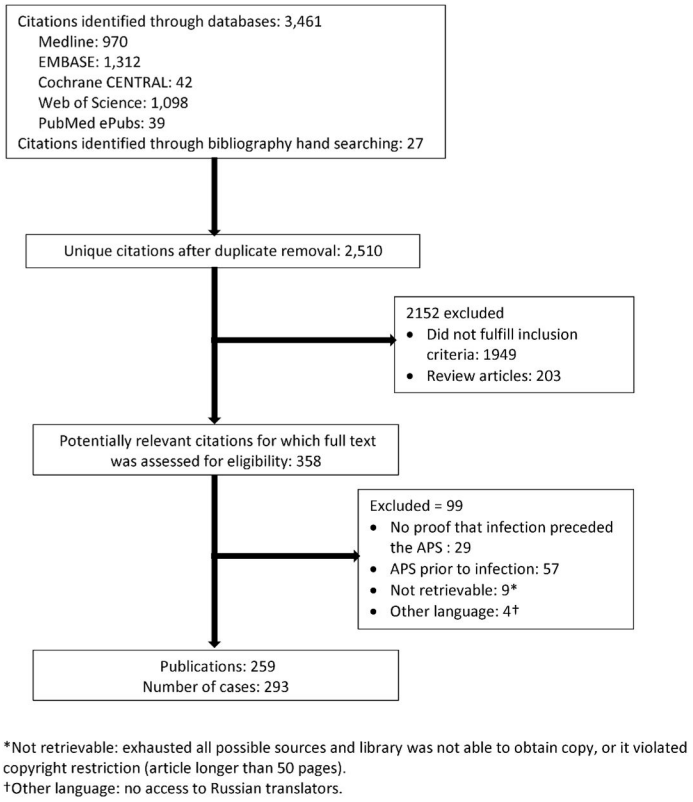

Figure 1.
Study selection flow chart.

Table 1

Types of infections reported in the 3 patient groups

Infection	N (%)[a]			
	Total, N=293	Group 1 APS/CAPS criteria N=72	Group 2 Incomplete criteria N=128	Group 3 No clinical events N=93
Viral	**163 (55.6)**	**38 (52.8)**	**78 (60.9)**	**47 (50.5)**
Human immunodeficiency virus	47 (16.0)	13 (18.1)	26 (20.3)	8 (8.6)
Human immunodeficiency virus + Hepatitis C virus	3 (1.0)	1 (1.4)	1 (0.8)	1 (1.1)
Hepatitis C virus	29 (9.9)	11 (15.3)	14 (10.9)	4 (4.3)
Hepatitis A virus	3 (1.0)	0	2 (1.6)	1 (1.1)
Hepatitis B virus	2 (0.7)	0	2 (1.6)	0
Parvovirus B19	19 (6.5)	2 (2.8)	2 (1.6)	15 (16.1)
Cytomegalovirus	17 (5.8)	4 (5.6)	9 (7.0)	4 (4.3)
Varicella-zoster virus	15 (5.1)	3 (4.2)	12 (9.4)	0
Epstein-Barr virus	9 (3.1)	1 (1.4)	6 (4.7)	2 (2.2)
Herpes simplex virus	2 (0.7)	1 (1.4)	0	1 (1.1)
Cytomegalovirus + Epstein-Barr virus	2 (0.7)	0	0	2 (2.2)
Human herpes virus 6	1 (0.3)	0	0	1 (1.1)
Adenovirus	6 (2)	0	0	6 (6.5)
Dengue virus	2 (0.7)	0	2 (1.6)	0
Influenza	3 (1.0)	2 (2.8)	1 (0.8)	0
Rubella	1 (0.3)	0	0	1 (1.1)
Measles	1 (0.3)	0	0	1 (1.1)
Japanese encephalitis	1 (0.3)	0	1 (0.8)	0
Bacterial	**108 (36.9)**	**22 (30.6)**	**48 (37.5)**	**38 (40.9)**
Coxiella burnetii	21 (7.2)	0	5 (3.9)	16 (17.2)
Coxiella burnetii + Rickettsia typhi	1 (0.3)	0	0	1 (1.1)
Coxiella burnetii + Helicobacter pylori	1 (0.3)	0	1 (0.8)	0
Coxiella burnetii + Mycoplasma pneumonia	1 (0.3)	0	0	1 (1.1)
Mycoplasma pneumonia	14 (4.8)	1 (1.4)	11 (8.6)	2 (2.2)
Streptococci	9 (3.1)	5 (6.9)	2 (1.6)	2 (2.2)
Staphylococci	5 (1.7)	3 (4.2)	2 (1.6)	0
Mycobacterium tuberculosis	8 (2.7)	1 (1.4)	5 (3.9)	2 (2.2)
Mycobacterium tuberculosis + Staphylococci	1 (0.3)	0	1 (0.8)	0
Mycobacterium lepra	6 (2.0)	3 (4.2)	2 (1.6)	1 (1.1)
Escherichia coli	4 (1.4)	1 (1.4)	2 (1.6)	1 (1.1)
Escherichia coli + Bacteroides fragilis	1 (0.3)	0	1 (0.8)	0
Escherichia coli + Bacteroides ovatus + Fusobacterium necrophorum	1 (0.3)	0	1 (0.8)	0

Infection	N (%)[a]			
	Total, N=293	Group 1 APS/CAPS criteria N=72	Group 2 Incomplete criteria N=128	Group 3 No clinical events N=93
Salmonella	3 (1.0)	1 (1.4)	2 (1.6)	0
Klebsiella	2 (0.7)	0	1 (0.8)	1 (1.1)
Bartonella henselae	2 (0.7)	0	1 (0.8)	1 (1.1)
Rickettsia africae	2 (0.7)	0	0	2 (2.2)
Pseudomonas aeruginosa	2 (0.7)	1 (1.4)	1 (0.8)	0
Mycoplasma penetrans	1 (0.3)	1 (1.4)	0	0
Proteus mirabilis	1 (0.3)	1 (1.4)	0	0
Helicobacter pylori	1 (0.3)	0	0	1 (1.1)
Chlamydia	1 (0.3)	0	0	1 (1.1)
Listeria monocytogenes	1 (0.3)	0	0	1 (1.1)
Neisseria meningitides	1 (0.3)	0	1 (0.8)	0
Bacteroides fragilis	1 (0.3)	0	1 (0.8)	0
Fusobacterium necrophorum	1 (0.3)	0	1 (0.8)	0
Campylobacter jejuni	1 (0.3)	0	1 (0.8)	0
Eubacterium Limosum	1 (0.3)	1 (1.4)	0	0
Spirochetal	13 (4.4)	3 (4.2)	6 (4.7)	4 (4.3)
Borellia burgdorferi	6 (2.0)	1 (1.4)	3 (2.3)	2 (2.2)
Syphilis	5 (1.7)	2 (2.8)	1 (0.8)	2 (2.2)
Leptospirosis	2 (0.7)	0	2 (1.6)	0
Parasitic	**12 (4.1)**	**3 (4.2)**	**4 (3.1)**	**5 (5.4)**
Malaria	5 (1.7)	0	2 (1.6)	3 (3.2)
Fasciola hepatica	2 (0.7)	0	2 (1.6)	0
Toxoplasmosis	1 (0.3)	1 (1.4)	0	0
Entamoeba histolytica	1 (0.3)	1 (1.4)	0	0
Enterobius vermicularis	1 (0.3)	1 (1.4)	0	0
Sarcoptes scabies	1 (0.3)	0	0	1 (1.1)
Trypanosoma brucei	1 (0.3)	0	0	1 (1.1)
Fungal	**5 (1.7)**	**1 (1.4)**	**2 (1.6)**	**2 (2.2)**
Candida	2 (0.7)	0	1 (0.8)	1 (1.1)
Aspergillus fumigatus	1 (0.3)	1 (1.4)	0	0
Bipolaris spicifera	1 (0.3)	0	0	1 (1.1)
Cryptococcus	1 (0.3)	0	1 (0.8)	0
Unidentified organism	**22 (7.5)**	**10 (3.9)**	**5 (3.9)**	**7 (7.5)**

[a]Fifteen patients (2 in group 1, 8 in group 2, and 5 in group 3) reported more than 1 type of infection (viral, bacterial, parasitic, and fungal).

Table 2

Possible factors precipitating APS or elevated aPL antibodies in each group

Precipitating factor	N (%)			
	Total, N=293	Group 1 APS/ CAPS criteria N=72	Group 2 Incomplete criteria N=128	Group 3 No clinical events N=93
Infection only	**245 (83.6)**	**61 (84.7)**	**113 (88.3)**	**71 (76.3)**
Infection and concomitant disease	**48 (16.4)**	**11 (15.3)**	**15 (11.7)**	**22 (23.7)**
Autoimmune diseases[a]	**22 (7.5)**	**6 (8.3)**	**3 (2.3)**	**13 (14.0)**
Acute rheumatic fever		2 (2.8)	0	0
Cutaneous sarcoidosis and leukocytoclastic vasculitis		1 (1.4)	0	0
Discoid lupus		1 (1.4)	0	0
Drug-induced SLE		0	0	1 (1.1)
Kikuchi-Fujimoto disease		1 (1.4)	0	0
Seronegative spondyloarthropathies		1 (1.4)	1 (0.8)	4 (4.3)
Polyarticular JIA		0	0	4 (4.3)
Vasculitis[b]		0	0	4 (4.3)
Sjögren syndrome		0	1 (0.8)	0
Multiple sclerosis		0	1 (0.8)	0
Tumor[a]	**7 (2.4)**	**0**	**5 (3.9)**	**2 (2.2)**
Hairy cell leukemia		0	0	1 (1.1)
Lymphoma in complete remission		0	1 (0.8)	0
Acute myeloid leukemia		0	0	1 (1.1)
Epidermoid carcinoma of the mouth in complete remission		0	1 (0.8)	0
Benign tumor near optic chiasma		0	1 (0.8)	0
Idiopathic inflammatory pseudotumor of the orbits + tolosa Hunt syndrome		0	1 (0.8)	0
Squamous cell carcinoma of the cervix incomplete remission		0	1 (0.8)	0
Congenital diseases	**6 (2.0)**	**3 (4.2)**	**2 (1.6)**	**1 (1.1)**
Cardiovascular diseases	**5 (1.7)**	**1 (1.4)**	**3 (2.3)**	**1 (1.1)**
Blood diseases	**4 (1.4)**	**0**	**1 (0.8)**	**3 (3.2)**
Congenital afibrinogenemia		0	1 (0.8)	0
Chronic hemolytic anemia		0	0	1 (1.1)
Mild hemophilia A		0	0	1 (1.1)
Factor VIII deficiency		0	0	1 (1.1)
Allergic and hypersensitivity diseases	**4 (1.4)**	**1 (1.4)**	**1 (0.8)**	**2 (2.2)**

SLE: systemic lupus erythematosus; JIA: juvenile idiopathic arthritis.

[a]Serum level of antiphospholid antibodies was not determined in patients with autoimmune diseases or patients with malignancy before the onset of infection.

[b] Four case reports with vasculitis including Wegener granulomatosis, central nervous system vasculitis secondary to neurosyphilis, and 2 cases with leukocytoclastic vasculitis secondary to infection.

Table 3

Clinical presentations of antiphospholipid syndrome in group 1 and thromboembolic phenomena associated with elevated aPL antibodies in group 2[a]

Clinical presentation	N (%)		
	Total, N = 200	Group 1 APS/CAPS criteria N=72	Group 2 Incomplete criteria N=128
Hematologic manifestations	**65 (33.5)**	**31 (43.1)**	**34 (26.6)**
Thrombocytopenia and/or hemolytic anemia	52 (26.0)	24 (33.3)	28 (21.9)
Pancytopenia	3 (1.0)	2 (2.8)	1 (0.8)
Disseminated intravascular coagulopathy	10 (5.0)	5 (6.9)	5 (3.9)
Peripheral thrombosis	**60 (30.0)**	**28 (38.9)**	**32 (25.0)**
Vascular thrombosis in UL/LL	53 (26.5)	23 (31.9)	30 (23.4)
Jugular and/or subclavian vein thrombosis	4 (2.0)	2 (2.8)	2 (1.6)
Jugular and subclavian veins thrombosis + vascular thrombosis in LL	1 (0.5)	1 (1.4)	0
Testicular thrombosis	1 (0.5)	1 (1.4)	0
Penile infarction + vascular thrombosis in UL/LL	1 (0.5)	1 (1.4)	0
Neurologic manifestations	**54 (27.0)**	**21 (29.2)**	**33 (25.8)**
Stroke and/or transient ischemic attack	47 (23.5)	17 (23.6)	30 (23.4)
Chorea	1 (0.3)	1 (1.4)	0
Seizures	3 (1.0)	1 (1.4)	2 (1.6)
Multi-infarct dementia	1 (0.3)	1 (1.4)	0
Transverse myelopathy	1 (0.3)	1 (1.4)	0
Encephalopathy	1 (0.3)	0	1 (0.8)
Cutaneous manifestations	**39 (19.5)**	**15 (20.8)**	**24 (18.7)**
Cutaneous necrosis and/or capillary thrombosis (livedo reticularis/pseudovasculitis/purpura)	22 (11.0)	10 (13.9)	12 (9.4)
Digital gangrene	14 (7.0)	5 (6.9)	9 (7.0)
Penile leukocytoclastic vasculitis	3 (1.5)	0	3 (2.3)
Respiratory manifestations	**38 (19.0)**	**14 (19.4)**	**24 (18.8)**
Pulmonary thromboembolism	33 (16.5)	12 (16.7)	21 (16.4)
Pulmonary hypertension	1 (0.5)	0	1 (0.8)
Pulmonary and diffuse alveolar hemorrhage	1 (0.5)	0	1 (0.8)
Pulmonary thromboembolism + pulmonary and diffuse alveolar hemorrhage	2 (1.0)	1 (1.4)	1 (0.8)
Acute respiratory distress syndrome	1 (0.5)	1 (1.4)	0
Cardiac manifestations	**34 (17.0)**	**17 (23.6)**	**17 (13.3)**
Intra-cardiac thrombus	7 (3.5)	5 (6.9)	2 (1.6)
Superior and/or inferior vena cava thrombosis	10 (5.0)	4 (5.6)	6 (4.7)
Internal carotid artery thrombosis	3 (1.5)	0	3 (2.3)
Aortic occlusion	2 (1.0)	0	2 (1.6)

Clinical presentation	N (%)		
	Total, N = 200	Group 1 APS/CAPS criteria N=72	Group 2 Incomplete criteria N=128
Intra-cardiac thrombus + aortic occlusion	1 (0.5)	1 (1.4)	0
Myocardial infarction	8 (4.0)	6 (8.3)	2 (1.6)
Valve thickening and/or vegetation	3 (15)	1 (1.4)	2 (1.6)
Renal manifestations	**23 (11.5)**	**13 (18.1)**	**10 (7.8)**
Renal vessels occlusion	9 (4.5)	5 (6.9)	4 (3.1)
Acute renal failure	11 (5.5)	6 (8.3)	5 (3.9)
End stage renal disease	2 (1.0)	2 (2.8)	0
Membranous/focal proliferative glomerulonephritis	1 (0.5)	0	1 (0.8)
Splenic infarction	**19 (9.5)**	**8 (11.1)**	**11 (8.6)**
Gastrointestinal manifestations	**13 (6.5)**	**5 (6.9)**	**8 (6.2)**
Abdominal vessels (mesenteric/iliac/abdominal aorta) occlusion	11 (5.5)	5 (6.9)	6 (4.7)
Gastric ulcer	2 (1.0)	0	2 (1.6)
Osteo-articular manifestations	**12 (6.0)**	**3 (4.2)**	**9 (7.0)**
Arthralgia/arthritis	2 (1.0)	2 (2.8)	0
Avascular necrosis	10 (5.0)	1 (1.4)	9 (7.0)
Hepatic manifestations			
Portal and/or hepatic vessels thrombosis	**11 (5.5)**	**4 (5.6)**	**7 (5.5)**
Ophthalmologic manifestations			
Retinal thrombosis and/or optic neuropathy	**8 (4.0)**	**2 (2.8)**	**6 (4.7)**
Obstetric manifestations	**7 (3.5)**	**7 (9.7)**	**0**
Adrenal crisis	**2 (1.0)**	**2 (2.8)**	**0**

LL: lower limb; UL: upper limb.

[a]Patients in group 3 did not show postinfectious thromboembolic complications related to antiphospholipid syndrome.

Table 4

Antiphospholipid antibody isotypes in each patient group among reported cases

Antiphospholipid antibodies	N (%)			
	Total, N=293	Group 1 APS/CAPS criteria N=72	Group 2 Incomplete criteria N=128	Group 3 No clinical events N=93
Anticardiolipin antibodies (reported data)	**n = 243**	**n = 65**	**n = 105**	**n = 73**
IgG alone	54 (22.2)	19 (29.2)	22 (21.0)	13 (17.8)
IgM alone	40 (16.5)	4 (6.2)	23 (21.9)	13 (17.8)
IgA alone	5 (2.1)	0	1 (1.0)	4 (5.5)
IgG + IgM	87 (35.8)	28 (43.1)	36 (34.3)	23 (31.5)
IgG + IgM + IgA	2 (0.8)	0	2 (1.9)	0
Unspecified	25 (10.3)	7 (10.8)	14 (13.3)	4 (5.5)
Positive for any isotype	**213 (87.7)**	**58 (89.2)**	**98 (93.3)**	**57 (78.1)**
Negative for all isotypes	30 (12.3)	7 (10.8)	7 (6.7)	16 (21.9)
Lupus anticoagulant antibodies (reported data)	**n = 170**	**n = 48**	**n = 70**	**n = 52**
Positive	**120 (70.6)**	**30 (62.5)**	**42 (60.0)**	**48 (92.3)**
Negative	50 (29.4)	18 (37.5)	28 (40.0)	4 (7.7)
Anti-β2 glycoprotein-I antibodies (reported data)	**n = 99**	**n = 20**	**n = 44**	**n = 35**
Positive	**60 (60.6)**	**15 (75.0)**	**25 (56.8)**	**20 (57.1)**
Negative	39 (39.4)	5 (25.0)	19 (43.2)	15 (42.9)
Unspecified isotype[a]	**25 (8.5)**	**5 (6.9)**	**15 (11.7)**	**5 (5.4)**

IgG: immunoglobulin G; IgM: immunoglobulin M; IGA: immunoglobulin A.

[a]Unspecified isotype: antiphospholipid antibodies without defining the isotype, antiphosphatidylserine, antiphosphatidylcholine, and antiphosphatidylserine-prothrombin complex.