

INTRODUCTION

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is the prototypic multisystem autoimmune disorder with a broad spectrum of clinical presentations encompassing almost all organs and tissues. The extreme heterogeneity of the disease has led some investigators to propose that SLE represents a syndrome rather than a single disease. SLE is a chronic disease of variable severity with a waxing and waning course, morbidity can be fatal—if not treated early—in some patients.⁽¹⁾

Major milestones in the history of lupus:⁽²⁻⁹⁾

The term ‘lupus’ (Latin for ‘wolf’) was first used during the Middle Ages to describe erosive skin lesions evocative of a ‘wolf’s bite’.⁽²⁾

In 1846 the Viennese physician Ferdinand von Hebra introduced the butterfly metaphor to describe the malar rash. He also used the term ‘lupus erythematosus’ and published the first illustrations in his Atlas of Skin Diseases in 1856.⁽³⁾

Lupus was first recognised as a systemic disease with visceral manifestations by Moriz Kaposi (1837–1902).⁽⁴⁾ The systemic form was further established by Osler in Baltimore and Jadassohn in Vienna.⁽⁵⁾

The description of the false positive test for syphilis in SLE by Reinhart and Hauck, Germany (1909).⁽⁶⁾ The description of the endocarditis lesions in SLE by Libman and Sacks was in New York (1923).⁽⁷⁾ The description of the glomerular changes by Baehr (1935),⁽⁸⁾ and the use of the term ‘diffuse connective tissue disease’ by Klemperer, Pollack and Baehr was in (1941).⁽⁸⁾ The discovery of the lupus erythematosus (LE) cell by Hargraves, Richmond and Morton at the Mayo Clinic was in 1948.⁽⁹⁾

Epidemiology of SLE:

Prevalence rates in lupus are estimated to be as high as 51 per 100 000 people in the USA. The incidence of lupus has nearly tripled in the last 40 years, mainly due to improved diagnosis of mild disease. Estimated incidence rates in North America, South America, and Europe range from 2 to 8 per 100 000 per year. Women are affected 9 times more frequently than men in the reproductive age. African American and Latin American mestizos are affected much more frequently than Caucasians, and have higher disease morbidity. The disease appears to be more common in urban than rural areas. 65% of patients with SLE have disease onset between the ages of 16 and 55 years, 20% present before the age of 16, and 15% after the age of 55. Men with lupus tend to have less photosensitivity, more serositis, an older age at diagnosis, and a higher 1 year mortality compared to women. SLE tends to be milder in the elderly.⁽¹⁰⁾

Aetiology and pathogenesis:

The aetiology of SLE includes both genetic and environmental components with female sex strongly influencing pathogenesis. These factors lead to an irreversible break in immunological tolerance manifested by immune responses against endogenous nuclear antigens.

Genetic factors:

Siblings of SLE patients are approximately 30 times more likely to develop SLE compared with individuals without an affected sibling. The rate of gene discovery in SLE has increased during the past few years e.g.: (HLA-DR, C2, C4, CIq), DNA repairs (repair endonuclease: TREX1), adherence of inflammatory cells to the endothelium (integrin alpha M: ITGAM), and tissue response to injury kallekrein 1, kallekrein 3 (KLK1, KLK3). These findings highlight the importance of Toll-like receptor (TLR) and type 1 interferon (IFN) signaling pathways. Some of the genetic loci may explain not only the susceptibility to disease but also its severity. For instance, signal transducer and activator of transcription 4 (STAT4), a genetic risk factor for rheumatoid arthritis and SLE, is associated with severe SLE.⁽¹¹⁾

Epigenetic effects:

Epigenetic mechanisms may represent the missing link between genetic and environmental risk factors. The risk for SLE may be influenced by epigenetic effects such as DNA methylation and post-translational modifications of histones, which can be either inherited or environmentally modified and not DNA base sequence changes. DNA methylation plays a role in a variety of human processes, such as X chromosome inactivation, certain cancers and SLE. Differences in the methylation status of genes may explain, at least in part, the discordance observed in some identical twins that are discordant for SLE.⁽¹²⁾

Environmental factors:

Candidate environmental triggers of SLE include:-

Ultraviolet light: Sunlight is the most obvious environmental factor,⁽¹³⁾

Drugs: Over 100 drugs have been reported to cause drug-induced lupus (DIL), including a number of the newer biologics and antiviral agents. Although the pathogenesis of DIL is not well understood, a genetic predisposition may play a role in the case of certain drugs, particularly those metabolized by acetylation such as procainamide and hydralazine, with disease more likely to develop in patients who are slow acetylators. These drugs may alter gene expression in CD4+ T cells by inhibiting DNA methylation. Certain drugs induce autoantibodies in a significant number of patients, most of whom do not develop signs of an autoantibody associated disease but promoting autoreactivity.⁽¹⁴⁾

Infectious or endogenous viruses or viral-like elements: Epstein-Barr virus (EBV) has been identified as a possible factor in the development of lupus. EBV may reside in and interact with B cells and promotes interferon α (IFN α) production by plasmacytoid dendritic cells (pDCs), suggesting that elevated IFN α in lupus.^(15,16)

Hormonal factors:

In murine models, addition of oestrogen or prolactin can lead to an autoimmune phenotype with an increase in mature high-affinity autoreactive B cells. Oral contraceptive use in the Nurses' Health Study was associated with a slightly increased risk of developing SLE. But the use of oral contraceptives does not increase disease flares in women with stable disease. Pregnancy may cause in some cases a lupus flare, but this is not due to an increase in oestradiol or progesterone; in fact, the levels of these hormones are lower in the second and third trimester for SLE patients in comparison with healthy pregnant women.⁽¹⁷⁾

Pathogenesis and pathophysiology:

Immune responses against endogenous nuclear antigens are characteristic for SLE (autoimmunity). Autoantigens released by apoptotic cells are presented by dendritic cells; antigen-presenting cells breaking self-tolerance; to T cells leading to their activation. Activated T cells in turn help B cells to produce antibodies to these self-constituents by secreting cytokines such as interleukin 10 (IL10) and IL23 and by cell surface molecules. In addition recent data support T cell-independent mechanisms of B cell stimulation via combined B cell antigen receptor (BCR) and TLR signaling. The pathogenesis of SLE involves a multitude of cells and molecules that participate in apoptosis, innate and adaptive immune responses (fig. 1). Once initiated, immune reactants such as immune complexes amplify and sustain the inflammatory response.⁽¹⁸⁾

- Apoptosis: a source of autoantigens and molecules with adjuvant/cytokine (interferon α (IFN α)) inducer activity. Apoptotic cell blebs are rich in lupus autoantigens. Increased spontaneous apoptosis, increased rates of ultraviolet-induced apoptosis in skin cells, or impaired clearance of apoptotic peripheral blood cells have been found in some lupus patients.⁽¹⁹⁾
- Nucleic acids (DNA and RNA): a unique target in lupus linked to apoptosis. Their recognition in healthy individuals is prohibited by a variety of barriers which are circumvented in lupus whereby alarmins released by from stressed tissues (high mobility group B1: HMGB1), antimicrobial peptides, neutrophil extracellular traps (NETs), and immune complexes facilitate their recognition and transfer to endosomal sensors.⁽¹⁸⁾

Innate immunity:

- Toll-like receptors (TLRs): conserved innate immune system receptors strategically located on cell membranes, cytosol and in endosomal compartments where they survey the extracellular and intracellular space. TLRs recognizing nucleic acids are endosomal. Autoreactive B or T lymphocytes peacefully coexisting with tissues expressing the relevant antigens may become pathogenic after engagement of TLRs. TLRs also activate APCs enhancing autoantigen presentation.⁽²⁰⁾
- Dendritic cells: Two types: plasmacytoid dendritic cells (pDCs) and myeloid (CD11c+) DC (mDCs):

- * pDCs: represent genuine 'IFN α ' factories. In lupus, exogenous factors/antigens (ie, viruses) or autoantigens recognised by the innate immune system receptors activate DCs and produce IFN α .
- * mDCs: involved in antigen presentation with immature conventional mDCs promoting tolerance while mature autoreactivity. In lupus, several factors (IFN α , immune complexes, TLRs) promote mDC maturation and thus autoreactivity. ⁽²¹⁾
- Interferon α : a pluripotent cytokine produced mainly by pDCs with potent biologic effects on DCs, B and T cells, endothelial cells, neuronal cells, renal resident cells, and other tissues. Activation of the IFN pathway has been associated with the presence of autoantibodies specific for RNA-associated proteins. RNA-mediated activation of TLR is an important mechanism contributing to production of IFN α and other proinflammatory cytokines. Activation of the IFN pathway is associated with renal disease and many measures of disease activity. ^(22,23)
- Complement: Activation of complement shapes the immune inflammatory response and facilitates clearance of apoptotic material in normal subjects. ^(19,24)
- Neutrophils: In lupus a distinct subset of proinflammatory neutrophils (low density granulocytes) induces vascular damage and produces IFN α . Pathogenic variants of ITAM (immuno-tyrosine activation motif) increase the binding to intracellular adhesion molecules (ICAM) and the adhesion leucocytes to activated endothelial cells. ⁽²³⁾
- Endothelial cells: In lupus, impaired DNA degradation as a result of a defect in repair endonucleases (TREX1) increases the accumulation of ssDNA derived from endogenous retro-elements in endothelial cells and may activate production of IFN α by them. IFN α in turn propagates endothelial damage. ⁽²⁵⁾

Adaptive immunity:

- **T and B cells:** Interactions between co-stimulatory ligands and receptors on T and B cells, including CD80 and CD86 with CD28 and CD40 ligand with CD40, contribute to B cell differentiation to antibody producing plasma cells. Autoantibodies also facilitate the delivery of stimulatory nucleic acids to TLRs. Cytokines and chemokines produced by T and B cells also shape the immune response and promote tissue damage. ⁽²⁶⁾
- **B lymphocyte stimulator (Blys):** The soluble TNF family member that helps in B cell survival and differentiation. It is increased in serum of many lupus patients; inhibition of Blys prevents lupus flares. ⁽²⁶⁾
- **Immune complexes:** In healthy individuals, immune complexes are cleared by (fragment crystallizable region: FcR) and complement receptors. In lupus, genetic variations in FcR genes and the C3bi receptor gene may impair the clearing of immune complexes which then deposit and cause tissue injury at sites such as the skin and kidney. ⁽²²⁾

Disease mechanisms and tissue damage:

Immune complexes and complement activation pathways mediate effector function and tissue injury. Failure to clear immune complexes results in tissue deposition and tissue

injury at sites. Tissue damage is mediated by recruitment of inflammatory cells, reactive oxygen intermediates, production of inflammatory cytokines, and modulation of the coagulation cascade.^(25,27)

Examples:

- * Autoantibody-mediated tissue injury has been implicated in neuropsychiatric SLE (NPSLE), where antibodies reacting with both DNA and glutamate receptors on neuronal cells can mediate excitotoxic neuronal cell death or dysfunction. Locally produced cytokines together with the cells producing them are the subject of investigation as potential therapeutic targets in lupus.⁽²⁷⁾
- * Vascular damage in SLE has received increased attention in view of its relationship with accelerated atherosclerosis. Homocysteine and proinflammatory cytokines, such as $\text{IFN}\alpha$, impair endothelial function and decrease the availability of endothelial precursor cells to repair endothelial injury. Impaired DNA degradation and increased accumulation of single stranded DNA derived from endogenous retro-elements in endothelial cells, may activate the IFN-stimulatory DNA response and direct immune-mediated injury to the vasculature. Pro-inflammatory high density lipoproteins (HDL) and a dysfunction of HDL mediated by antibodies have also been implicated in defective repair of endothelium. Moreover, pathogenic variants of ITAM alter its binding to ICAM-1 (intercellular adhesion molecule 1) and may increase the adherence of leucocytes to activated endothelial cells.⁽²⁵⁾

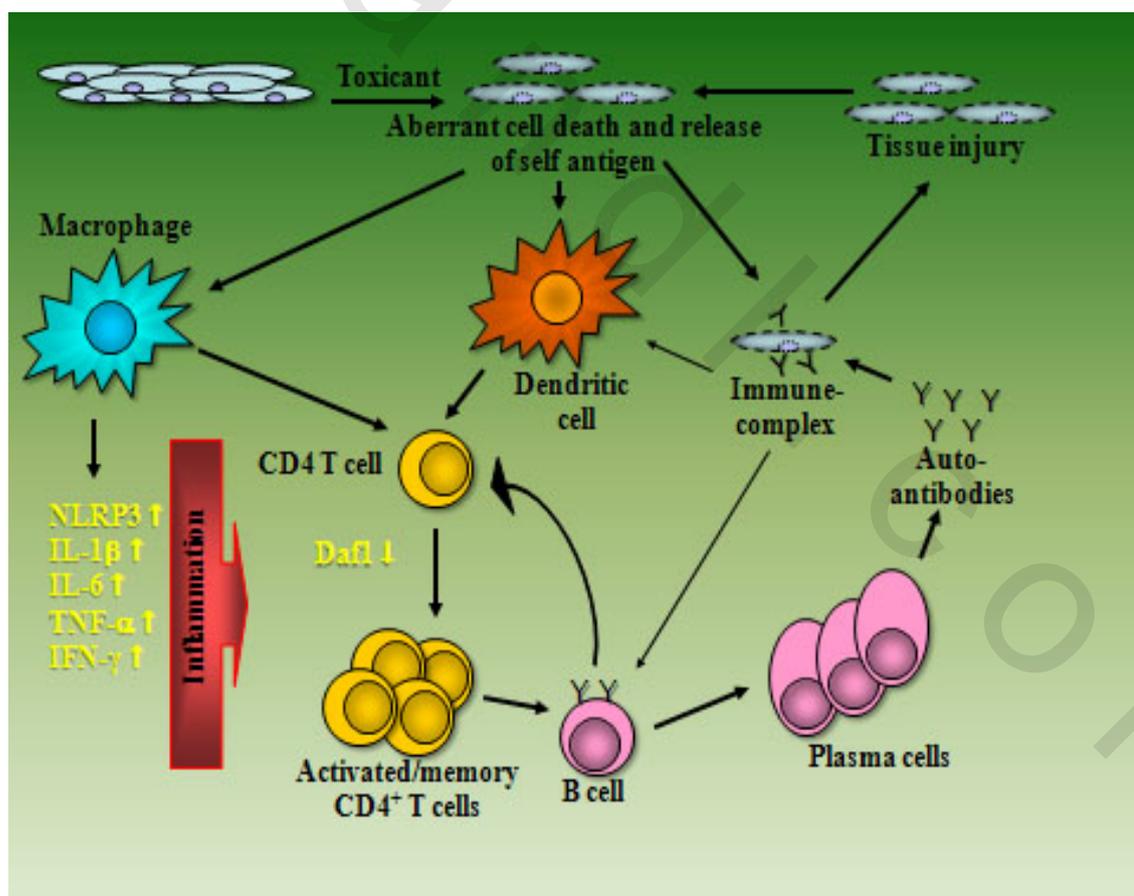


Figure (1): Pathogenesis of systemic lupus erythematosus.⁽¹¹⁻²⁷⁾

Autoantibodies in SLE:

a) ANA antibodies

Autoantibodies in SLE primary target intranuclear nucleic acids, proteins and RNP (ribonucleoprotein) complexes and are often referred to as antinuclear antibodies (ANA).

ANA is elevated in: 1/3-3/4 of subjects over age 65 (usually in low titers), systemic lupus erythematosus (98%), drug-induced lupus (100%), Sjogren's (80%), rheumatoid arthritis (30-50%), scleroderma (60%), mixed connective tissue disease (100%), Felty's syndrome, mononucleosis, hepatic or biliary cirrhosis, hepatitis, leukemia, myasthenia gravis, dermatomyositis, polymyositis, chronic renal failure. A negative ANA test does not completely rule out SLE, but alternative diagnoses should be considered.⁽²⁸⁾

b) Anti DNA

The formation of autoantibodies against chromatin is the main feature of SLE. They can be divided into three groups; antibodies reacting with DNA, antibodies reacting with histones, and antibodies that have a much higher affinity for the intact nucleosome.⁽²⁹⁾ At least three forms of DNA are antigenic in SLE; single-stranded (ss) DNA, double-stranded (ds) and left handed (z)⁽³⁰⁾ Antibodies against dsDNA are considered as a hallmark of SLE. These antibodies can be detected in 70% of SLE patients, correlate with disease activity, and an increasing titer of anti-DNA precedes exacerbations.⁽³¹⁾

c) Antihistone

Antihistone antibodies target the protein components of nucleosomes. These antibodies may be detected by Immunofloresence, ELISA, or immunoblot.

These antibodies appear uniformly in drug-induced lupus, in which they associate with anti ss-DNA antibodies. The diagnosis of drug-induced lupus should be questioned in the absence of antihistone antibodies.⁽³²⁾

d) Anti-Smith(anti-SM) antibody:

Anti-Sm is highly specific for SLE. It target a nuclear protein. Apart from its diagnostic utility, the clinical relevance of this autoantibody is controversial. Associations with renal or nervous system involvement have been reported and it has been suggested that anti-Sm levels are useful indicators of disease activity.⁽³³⁾

e) Anti-Ku (Ki/nuclear factor IV)

Ku preferentially binds to the termini of ds-DNA and has been proposed to play a role in DNA replication, recombination or repair. Anti- Ku antibodies have been detected in scleroderma-myositis overlap, scleroderma and in SLE.⁽³⁴⁾

f) Anti-RNA antibody:

Autoantibodies reactive against single - and double-stranded RNA have been reported in up to 60% of patients with SLE. No unique clinical associations with these

antibodies have been observed. Anti-RNA antibodies are also found in lower frequency in patients with other autoimmune disorders.⁽³³⁾

g) Anti-Ro (SS-A) and anti-La (SS-B)

Anti-Ro (anti rodent) is an Autoantibody against acidic nuclear ribonucleoproteins. La (lupus anticoagulant) is a nuclear phosphoprotein that binds to RNA polymerase III transcripts. Recent studies suggest that La is a transcription termination factor. The structural or functional relationships between Ro and La remain uncertain. Anti-Ro/La antibodies are important clinically since they are associated with Sjogren syndrome, subacute cutaneous lupus erythematosus (SCLE) and with neonatal lupus erythematosus (NLE). Anti-Ro/La antibodies are present in >80 % of mothers of infants with congenital heart block.⁽³⁵⁾

h) Anti-ribosomal P antibody

Anti-ribosomal P (anti-P) antibodies were first described in SLE patients in 1985 and are quite specific for SLE, 80 - 90% positive in neuropsychiatric (NP) lupus that manifests with psychosis or depression. However, the diagnostic value of the antiribosomal P antibody is yet to be determined.⁽³⁶⁾

Table (1): The structure and function of SLE antigens⁽²⁸⁻³⁶⁾

Intra cellular antigen	Structure	Function
DNA	Double helix	Template for transcription and replication
Histone	H1,H2,H3,H4.	Component of chromatin
Ro(SS-A)	Proteins	Ca binding proteins
La (SS-B)	Phospoprotein	Transcription termination factor
Sm	Proteins	Spliceosome components
RNP	Proteins	Spliceosome components
P	P0,P1,P2 ribosomal protein	Factor binding for protein synthesis
RNA	Ribosomal RNA	GTPase domain
KU	Proteins	Repair DNA terminal

Table (2): Clinical associaton of autoantibodies in SLE⁽²⁸⁻³⁶⁾

Antibody	Frequency(%)*	Specificity for SLE	Clinical subsets
Anti ds-DNA	60-90	++	Nephritis
ss-DNA	90	-	Drug induced lupus
Histones	50-70	+	Dug induced lupus
Ro (SS-A)	20-60	+	Subacute cutaneous lupus
La (SS-B)	15-40	+	Congenital heart block
Sm	10-30	++	Nephritis
RNP	10-30	+	Mixed connective tissue disease
P	10-15	++	CNS lupus
Ku	10	+	Thrombosis, foetal loss
* The frequency depends on the sensitivity of the test used to detect the antibodies. The higher frequencies are usually observed in ELISAs or radioimmunoassay.			
++ = highly specific, + = antibody present in other autoimmune disorder,			
- = antibody present in other inflammatory diseases.			

Table (3): American College of Rheumatology Revised Classification Criteria for Systemic Lupus Erythematosus (presence of ≥ 4 criteria are required for SLE diagnosis) ^(1,37)

Criteria	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring occurs in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
Serositis	<p>a. Pleuritis—convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion <i>or</i></p> <p>b. Pericarditis—documented by ECG or rub or evidence of pericardial effusion</p>
Renal disorder	<p>a. Persistent proteinuria >0.5 g/day, $>3+$ if quantitation is not performed <i>or</i></p> <p>b. Cellular casts—may be red blood cell, hemoglobin, granular tubular, or mixed</p>
Neurologic disorder	<p>a. Seizures—in the absence of offending drugs or known metabolic derangements (e.g., uremia, acidosis, or electrolyte imbalance) <i>or</i></p> <p>b. Psychosis—in the absence of offending drugs or known metabolic derangements (e.g., uremia, acidosis, or electrolyte imbalance)</p>
Hematologic disorder	<p>a. Hemolytic anemia with reticulocytosis, <i>or</i></p> <p>b. Leukopenia—$<4000/\text{mm}^3$, <i>or</i></p> <p>c. Lymphopenia—$<1500/\text{mm}^3$, <i>or</i></p> <p>d. Thrombocytopenia—$<100,000/\text{mm}^3$ in the absence of offending drugs</p>
Immunologic disorder	<p>a. Anti-DNA—antibody to native DNA in abnormal titer, <i>or</i></p> <p>b. Anti-Sm—presence of antibody to Sm nuclear antigen, <i>or</i></p> <p>c. Positive finding of antiphospholipid antibodies based on (1) abnormal serum concentration of IgG or IgM anticardiolipin antibodies, (2) positive test result for lupus anticoagulant using a standard method, or (3) false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by <i>Treponema pallidum</i> immobilization or fluorescent treponemal antibody absorption test</p>
ANA	Abnormal titer of ANA by immunofluorescence or equivalent assay at any point in time and in the absence of drugs known to be associated with drug-induced lupus syndrome

Adapted from Hochberg MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 40:1725, 1997.

ANA, antinuclear antibody; ECG, electrocardiogram.

***N.B.:** These criteria were developed and validated for the classification of patients with a longstanding established disease and may exclude patients with early disease or disease limited to a few organs. Thus, in spite of their excellent sensitivity ($>85\%$) and specificity ($>95\%$) for patients with established disease, their sensitivity for patients early in the disease may be significantly lower. Some systems are overrepresented; e.g. the mucocutaneous manifestations. All features included in the classification criteria are contributing equally without any weight based upon sensitivity and specificity for each individual criterion. Thus, studies have shown and experience supports that criteria such as objective evidence of renal disease, discoid rash, and cytopenias are more useful in establishing the diagnosis of lupus than the other criteria. Among patients referred for lupus to tertiary care centers, two thirds of patients fulfill ACR criteria, approximately 10% have clinical lupus but do not fulfill criteria, and 25% have fibromyalgia-like symptoms and positive antinuclear antibody (ANA) but never develop lupus. ^(1,37)

SLICC[†] Classification Criteria for Systemic Lupus Erythematosus

Requirements: ≥ 4 criteria (at least 1 clinical and 1 laboratory criteria)
OR biopsy-proven lupus nephritis with positive ANA or Anti-DNA

Clinical Criteria

1. Acute Cutaneous Lupus
2. Chronic Cutaneous Lupus
3. Oral or nasal ulcers
4. Non-scarring alopecia
5. Arthritis
6. Serositis
7. Renal
8. Neurologic
9. Hemolytic anemia
10. Leukopenia
11. Thrombocytopenia ($<100,000/\text{mm}^3$)

Immunologic Criteria

1. ANA
2. Anti-DNA
3. Anti-Sm
4. Antiphospholipid Ab
5. Low complement (C3, C4, CH50)
6. Direct Coombs' test (do not count in the presence of hemolytic anemia)

[†]SLICC: Systemic Lupus International Collaborating Clinics

* N.B: 2012 SLICC SLE Criteria are cumulative and need not be present concurrently. Those criteria add more help for the physician to approach the diagnosis ⁽³⁸⁾

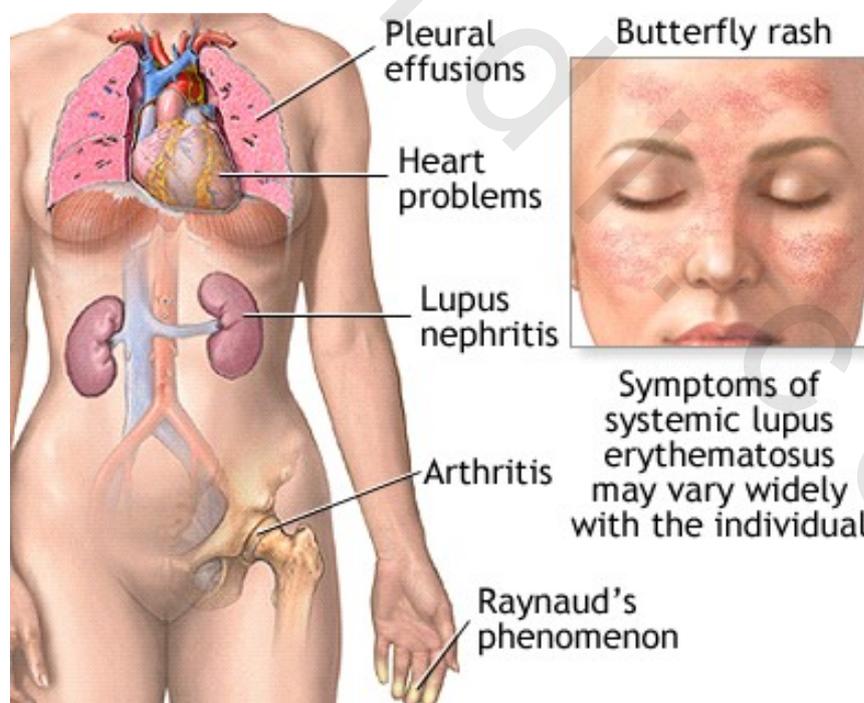


Figure (2): Some clinical features of SLE ^(1,37,38)

Lupus and pregnancy:

Pregnancy affects mothers with SLE and their offspring in several ways.

a) Mother:

- There is no significant difference in fertility in lupus patients,
- Pregnancy may increase lupus disease activity but these flares are usually mild,
- Patients with lupus nephritis and antiphospholipid antibodies are more at risk of developing pre-eclampsia and should be monitored more closely. ⁽³⁹⁾

b) Fetus:

SLE may affect the fetus in several ways, especially if the mother has a history of lupus nephritis, antiphospholipid, anti-Ro and/or anti-La antibodies. These conditions are associated with. ⁽³⁹⁻⁴¹⁾

- An increase of the risk of miscarriage, stillbirth, premature delivery, intrauterine growth restriction, and fetal heart block,
- Prednisolone, azathioprine, hydroxychloroquine and low dose aspirin may be used in lupus pregnancies. At present evidence suggests that mycophenolate mofetil, cyclophosphamide and methotrexate must be avoided.

Disease Activity indices:

Assessing disease activity in SLE is crucial to the physician as it forms the basis for prognosis and treatment decisions. Disease activity needs to be distinguished from damage. Several validated global and organ-specific activity indices are widely used in the evaluation of SLE patients (Urowitz and Gladman 1998). These include the European Consensus Lupus Activity Measure (ECLAM), the British Isles Lupus Assessment Group Scale (BILAG), the Lupus Activity Index (LAI), and the SLE Disease Activity Index (SLEDAI). These indices have been validated against each other. ⁽⁴²⁾

Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is a disorder that manifests clinically as recurrent venous or arterial thrombosis and/or fetal loss. It may be primary or secondary to other associating condition e.g. other autoimmune disease, infections, drugs and malignancies.

Characteristic laboratory abnormalities in APS include persistently elevated levels of antibodies directed against membrane anionic phospholipids (e.g. anticardiolipin [aCL] antibodies, antiphosphatidylserine aPS antibodies) or their associated plasma proteins, predominantly β -2 glycoprotein I or evidence of a circulating anticoagulant.⁽⁴³⁾

History:

Historically, antiphospholipid antibodies were first noted in patients who had positive tests for syphilis without signs of infection. Subsequently, a clotting disorder was associated with two patients with (SLE) in 1952. In 1957 a link between recurrent pregnancy loss and what is now called the lupus anticoagulant was established. In 1983, Dr. Graham Hughes described the association between antiphospholipid antibodies and arterial as well as venous thrombosis.⁽⁴⁴⁻⁴⁸⁾

Historical description of antiphospholipid:⁽⁴⁶⁾

1906	:	Wasserman reaction (regain)
1941	:	Reagin binds cardiolipin
1952	:	False-positive test for syphilis, lupus anticoagulant (LA)
1960s	:	LA: association with thrombosis
1970s	:	LA: association with fetal loss
1983	:	Anticardiolipin antibody (aCL), 1980s:Detailed description of (APS)
1990	:	Phospholipid binding proteins (b2GPI)
1999	:	Animal models for APS, classification criteria for definite APS
2006	:	Classification criteria updates

Epidemiology:

Low-titer, usually transient, anticardiolipin occurs in up to 10% of normal blood donors, and moderate- to high-titer anticardiolipin or a positive lupus anticoagulant test occurs in less than 1%. The prevalence of positive aPL tests increases with age. 10% to 40% of SLE patients and approximately 20% of rheumatoid arthritis patients have positive aPL tests.⁽⁴⁹⁾

Based on a limited number of studies, asymptomatic aPL-positive patients have a 0% to 4% annual risk of thrombosis; patients with other autoimmune diseases such as SLE are at the higher end of the range.⁽⁵⁰⁾ The aPL profile and patients' clinical characteristics (presence or absence of other acquired or genetic thrombosis risk factors) influence the individual risk of thrombosis.⁽⁵¹⁾ 10% of first-stroke victims have aPLs, especially those who are young (up to 29%), as do up to 20% of women who have suffered three or more

consecutive fetal losses. 14% of patients with recurrent venous thromboembolic disease have aPLs.⁽⁵²⁾

APS is more common in young to middle-aged adults; but also manifests in children and elderly people. Onset has been reported in children as young as 8 months. Patients without associated rheumatic disease were younger and had a higher frequency of arterial thrombotic events, whereas patients with associated rheumatic disease were older and had a higher frequency of venous thrombotic events associated with hematologic and skin manifestations.⁽⁵³⁾

Pathogenesis of APS:

Antiphospholipid antibody is most likely related to thrombosis through multiple mechanisms; a proposed pathogenesis is illustrated in (Figure 3). The process begins with activation or apoptosis of platelets, endothelial cells, or trophoblasts, during which phosphatidylserine (a negatively charged phospholipid) migrates from the inner to the normally electrically neutral outer cell membrane. Circulating β_2 GPI binds to phosphatidylserine, and then aPL binds to a β_2 GPI dimer.⁽⁵⁴⁾

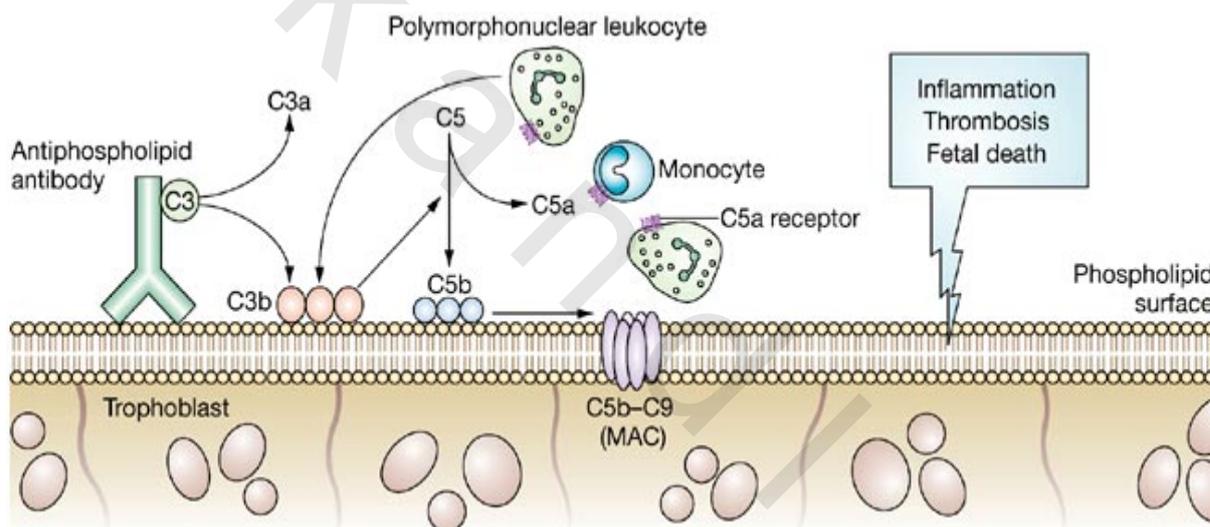


Figure (3): Pathogenesis of antiphospholipid syndrome⁽⁵⁴⁻⁶²⁾

Activation of complement cascade:

- * Antiphospholipid antibody- β_2 GPI dimer binding activates the complement cascade extracellularly; initiates an intracellular signaling cascade, probably through the C5a and β_2 GPI surface receptors; and recruits and activates inflammatory effector cells, including monocytes, neutrophils, and platelets, leading to the release of proinflammatory products (e.g., tumor necrosis factor [TNF]- α , oxidants, proteases) and the induction of a prothrombotic phenotype. The putative receptor of β_2 GPI binding protein that transduces signals from the cell membrane to the nucleus is not yet identified and may vary among cells. The following candidates have been suggested: apoER2' (a member of the low-density lipoprotein receptor superfamily), annexin A2, and a Toll-like receptor⁽⁵⁵⁻⁵⁷⁾

Inhibition of coagulation cascade:

- * Other possible contributory mechanisms of aPL-mediated thrombosis include inhibition of coagulation cascade reactions catalyzed by phospholipids (e.g., activation of circulating procoagulant proteins or inhibition of protein C and S activation), induction of tissue factor (a physiologic initiator of coagulation) expression on monocytes, reduction of fibrinolysis, and interaction with the annexin V anticoagulant shield in the placenta.⁽⁵⁸⁾

Endothelial cell activation:

- * Because high-level aPLs may persist for years in asymptomatic persons, it is likely that vascular injury, endothelial cell activation, or both immediately precede the occurrence of thrombosis in those bearing the antibody (second-hit hypothesis). Of note, at least 50% of APS patients with vascular factors possess other acquired thrombosis risk factors at the time of their events.^(57,59)

Activation of endothelial cells could be explained by two theories:

- **The first theory** depends on the antiphospholipid antibodies recognition of β 2GPI bound to endothelial cells (Ec) assessed by up-regulation of the Ec expression of adhesion molecules, the secretion of cytokines and the metabolism of prostacyclins resulting in hypercoagulation.⁽⁵⁷⁾
- **The second theory** focuses on oxidant-mediated injury of the vascular endothelium. Oxidized low-density lipoprotein (LDL) (a major contributor to atherosclerosis) is taken up by macrophages, leading to macrophage activation and subsequent damage to endothelial cells. Autoantibodies to oxidized LDL occur in association with aCL, Some aCL antibodies cross-react with oxidized LDL. Moreover, aCL antibodies bind to oxidized cardiolipin, suggesting that aCL antibodies recognize oxidized phospholipids, phospholipid-binding proteins, or both, thus contributing to hypercoagulation.⁽⁵⁷⁾
- * **N.B.:** In addition, through downregulation of the signal transducer and activator of transcription 5 (Stat5), aPLs inhibit the production of placental prolactin and insulin growth factor binding protein-1, and they adversely affect the formation of a trophoblast syncytium, placental apoptosis, and trophoblast invasion—all processes that are required for the normal establishment of placental function.⁽⁶⁰⁾
- * **N.B.:** In experimental animal models, aPLs cause fetal resorption and increase the size and duration of trauma-induced venous and arterial thrombi. Inhibiting complement activation prevents experimental aPL-induced fetal death, and C5 knockout mice carry pregnancies normally despite aPL, implying that a complement-mediated effector mechanism is an absolute requirement for fetal death to occur. Complement activation is also required for experimental thrombosis.⁽⁵⁶⁾
- * **N.B.:** Both persons congenitally lacking β 2GPI⁽⁶¹⁾ and β 2GPI knockout mice appear normal.⁽⁶²⁾

Antiphospholipids antibodies:

Phospholipids are a class of polar lipid components of cell membranes. They play an important role in the clotting cascade. ⁽⁶³⁾

Antiphospholipid antibodies are:

a) Reagin

The Wassermann reagin test was originally attributed to antibody reactivity against antigens derived from *Treponema pallidum*, until the use of normal human and animal tissues was found to give similar results (false positive). In 1941 Pangborn isolated cardiolipin from bovine heart, identifying it as the antigenic component of the reagin test. ⁽⁶⁴⁾

b) Anticardiolipin (Diphosphatidylglycerol)

Cardiolipin is a negatively charged phospholipid present mainly in the inner surface of plasma membranes, also a normal component of several plasma proteins including β 2-glycoprotein I. IgG and IgA anticardiolipin (aCL) are more related than IgM to thrombotic phenomena. IgA aCL is related to recurrent fetal loss. ⁽⁶⁵⁾

The false-positive syphilis test and the lupus anticoagulant were identified in the 1940s, the link between these entities was not investigated until the 1980s, when a researcher at the Graham Hughes laboratory in Britain named Nigel Harris began looking at antibodies to the phospholipid antigens. Harris realized that cardiolipin was a major element of the false-positive syphilis test, and he developed a more specific test for the antibody. He also determined that the presence of these anticardiolipin antibodies was associated with recurrent thromboses (blood clots) and pregnancy losses. Others in Hughes' laboratory began to publish studies showing the link between anticardiolipin antibodies and stroke, deep vein thrombosis (DVT), recurrent pregnancy loss, livedo, seizures, and other conditions. In fact, what we now know as antiphospholipid syndrome was known as the anticardiolipin syndrome even though other antiphospholipids, namely the lupus anticoagulant, were known to produce similar effects. ⁽⁶⁵⁾

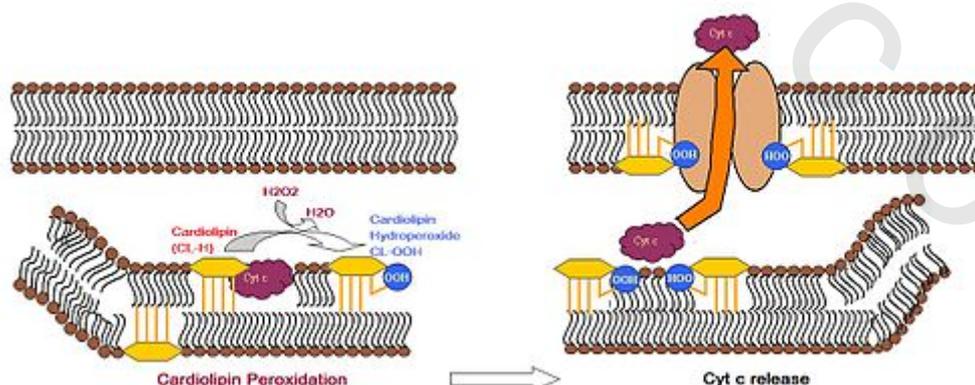


Figure (4): How cardiophilin triggers apoptosis ⁽⁶⁵⁾

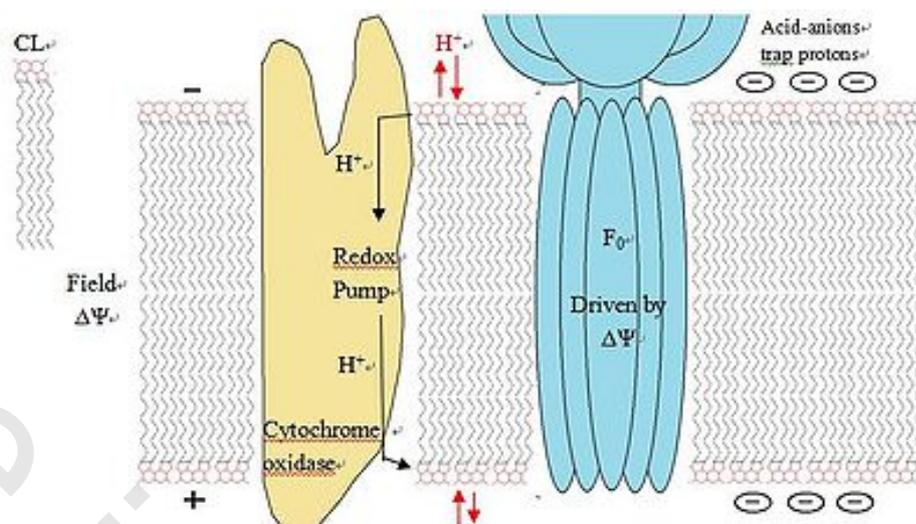


Figure (5): Cardiolipin serves as a trap in oxidative phosphorylation⁽⁶⁵⁾

c) Lupus Anticoagulant (LA)

It is a functional measurement of the capacity of heterogeneous aPL that interferes with phospholipid-dependent stages of blood coagulation in vitro and inhibits both the intrinsic and common pathways of coagulation. Paradoxically, LAs are associated with a thrombotic tendency rather than bleeding, in spite of being associated with coagulation inhibitors.⁽⁴⁶⁾

In the late 1940s, it was found that an antibody present in some lupus patients prolonged a clotting test dependent on phospholipids. For this reason, it was thought that this antibody increased the tendency to bleed, and thus it was deemed the lupus anticoagulant. However, this name is now recognized as a misnomer for two reasons. First, the term “anticoagulant” is a false label, since lupus anticoagulant actually increases the ability of the blood to clot. Second, the term “lupus” in the name of the antibody is misleading, since more than half of all people who possess this antibody do not have lupus.⁽⁴⁶⁾

Tests called coagulation tests are used to detect the lupus anticoagulant (LA). Remember that even though the lupus anticoagulant causes the blood to clot more easily in vivo (i.e., in a person’s body), they actually cause prolonged clotting times in vitro (i.e., in a test tube). Therefore, if it takes more time than normal for the blood to clot, the lupus anticoagulant is usually suspected. The activated partial thromboplastin time (aPTT) is often used to test for LA. If this test is normal, more sensitive coagulation tests are performed, including the modified Russell viper venom time (RVVT), platelet neutralization procedure (PNP), and kaolin clotting time (KCT). Normally, two of these tests (the aPTT and the RVVT) are performed to detect whether lupus anticoagulant is present.⁽⁴⁶⁾

e) Antiphosphatidic Acid and antiphosphatidylinositol

Phosphatidic Acid and phosphatidylinositol are negatively charged phospholipid. In mice infusion of antibodies against phosphatidic acid and antiphosphatidylinositol produced thrombotic effects.⁽⁶⁹⁾

f) Antiphosphatidylcholine

Phosphatidylethanolamine is a class of neutral phospholipids that incorporates choline as a head group. It is a major component of biological membranes, which is more common on the exoplasmic or outer leaflet of a cell membrane.⁽⁷¹⁾

g) Antiphosphatidylethanolamine

phosphatidylethanolamine is a class of neutral phospholipids. Phosphatidylethanolamine present normally in both layers of cell membranes. Its prevalence in antiphospholipid syndrome is about 95%. It is associated with thrombosis by blocking of the protein C pathway. It may bind to coagulation factor XI. Binding of these antibodies require that the phospholipid bind some plasma proteins like kininogens.⁽⁷²⁾

h) Anti beta₂ glycoprotein I (β₂GPI)

β₂GPI is a normal phospholipid-binding plasma glycoprotein, a single-chain 50 kD polypeptide. Its function is unclear, although it may function as a natural anticoagulant. It is the main antigen to which aPLs bind. It is normally present in serum at a concentration of 200 mg/mL, is a member of the complement control protein family, and has five repeating domains and several alleles. An octapeptide in the fifth domain and critical bonds are necessary for both phospholipid binding and antigenicity; a first domain site activates platelets. In vivo, β₂GPI binds to phosphatidylserine on activated or apoptotic cell membranes, including those of trophoblasts, platelets, and endothelial cells. Under physiologic conditions, β₂GPI may function in the elimination of apoptotic cells and as a natural anticoagulant.

Other, less relevant antigens targeted by aPLs are prothrombin, annexin V, protein C, protein S, high and low molecular weight kininogens, tissue plasminogen activator, factor VII, factor XI, factor XII, complement component C4, and complement factor H.

In experimental animal models, passive or active immunization with viral peptides, bacterial peptides, and heterologous β₂GPI induces polyclonal aPLs and clinical events associate with APS. These data suggest that pathologic autoimmune aPL is induced in susceptible humans by infection via molecular mimicry.

However, infection induced aPLs (syphilitic and non-syphilitic treponema, *Borrelia burgdorferi*, human immunodeficiency virus, *Leptospira*, or parasites) are usually β₂GPI independent and bind phospholipids directly. Drugs (chlorpromazine, procainamide, quinidine, and phenytoin) and malignancies (lymphoproliferative disorders) can also induce β₂GPI independent aPLs. Conversely, autoimmune aPLs bind β₂GPI or other phospholipid binding plasma proteins, which in turn bind to negatively charged phospholipids such as cardiolipin as identified by three independent groups in 1990, (β₂GPI dependent aPLs).

Low levels of aPLs may be present normally; one of the functions of normal aPLs may be to participate in the physiologic removal of oxidized lipids.

β_2 GPI antibodies are more specific than aCL in predicting thrombosis, differentiating pathogenic (autoimmune) from nonpathogenic (infection or drug- induced) antibodies. Since β_2 GPI is an absolute requirement for binding of autoimmune aCL to cardiolipin in ELISA. ^(46,73)

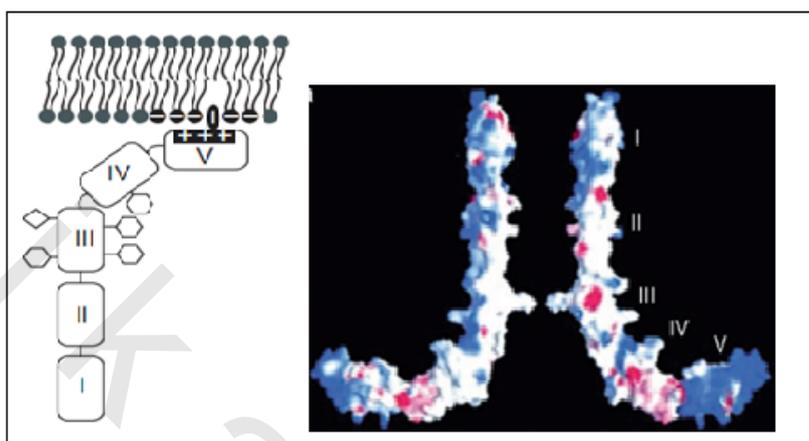


Figure (7): Two views, related by 180° rotation of the electrostatic potential surface of β_2 -GPI. The molecule has five distinct domains. ^(46,73)

Its prevalence in antiphospholipid syndrome is about 60-90%. IgG titers has been shown to correlate with brain thrombosis. In patients with APS, where the presence of anti- β_2 -glycoprotein I was predictive of a recurrent thromboembolic event, IgG and IgM are related to thrombosis, while IgA is related to recurrent abortion and skin ulcers, livedo reticularis, heart valve disease and pulmonary hypertension. ⁽⁶⁹⁾

i) Antiprothrombin

Its prevalence in APS is about 50-90%. Antiprothrombin antibodies may inhibit the activation of prothrombin into thrombin. They are therefore expected to be anticoagulant. However antiprothrombin IgG inhibits activated protein C thus increasing the risk of thrombosis. ⁽⁶⁹⁾

j) Anti-protein C, protein S

These proteins are components of the anticoagulant pathway. Anti-protein C, S are associated with increased risk of thrombosis. ⁽⁶⁹⁾

k) Anti-annexin V

Annexin is a calcium dependent anionic PL-binding protein (preferably binds to PS on platelet surfaces), expressed by placental and vascular endothelium. It plays a thromboregulatory role at the vascular-blood interface by shielding anionic PL from forming a complex with coagulation proteins in the circulation produces its anticoagulant effect. Annexin V could play an important role in the clinical manifestations of APS,

particularly in obstetrical complications. Anti-annexin V antibodies have a role in (PS) exposure on the cell surfaces, which produce proinflammatory and procoagulant activities.⁽⁷⁴⁾

I) Antikininogen

Kininogen is found in low and high molecular weights and is one of the early participants of the intrinsic pathway of coagulation, together with Factor XII (Hageman factor) and prekallikrein. Disruption of kallikrein-kinin system may be a risk factor for early gestational losses.⁽⁷⁵⁾

Table (4): Opposing effects of antiphospholipid antibodies on coagulation.^(76,77)

Procoagulant Effect	Anticoagulant Effect
<ul style="list-style-type: none"> • Inhibition of the activated protein C pathway. • Up-regulation of tissue factor pathway. • Inhibition of antithrombin III (IgG aPLs that react with heparin sulfate have been shown to inhibit the formation of antithrombin III complexes) . • Inhibition of annexin V. • Inhibition of anticoagulant activity of β_2 glycoprotein I. • Inhibition of fibrinolysis. • Activation of endothelial cells. • Enhanced expression of adhesion molecules by endothelial cells and adherence of neutrophils and leukocytes to endothelial cells. • Activation and degranulation of neutrophils. • Potentiation of platelets activation. • Enhanced binding of β_2glycoprotein I to membranes. • Enhanced binding of prothrombin to membranes. 	<ul style="list-style-type: none"> • Inhibition of activation of factor IX. • Inhibition of activation of factor X. • Inhibition of activation of prothrombin to thrombin.

Genetic predisposition

- Familial association: Relatives of persons with known APS are more likely to have aPL antibodies. One study showed a 33% frequency.⁽⁷⁸⁾
- HLA associations: Studies have revealed an association between aCL antibody and groups of individuals who carry certain HLA genes, including DRw53, DR7 (mostly people of Hispanic origin), and DR4 (mostly whites).⁽⁷⁸⁾
- A cluster of 50 upregulated genes may have an effect on the occurrence of thrombosis in aPL-positive individuals.⁽⁷⁸⁾

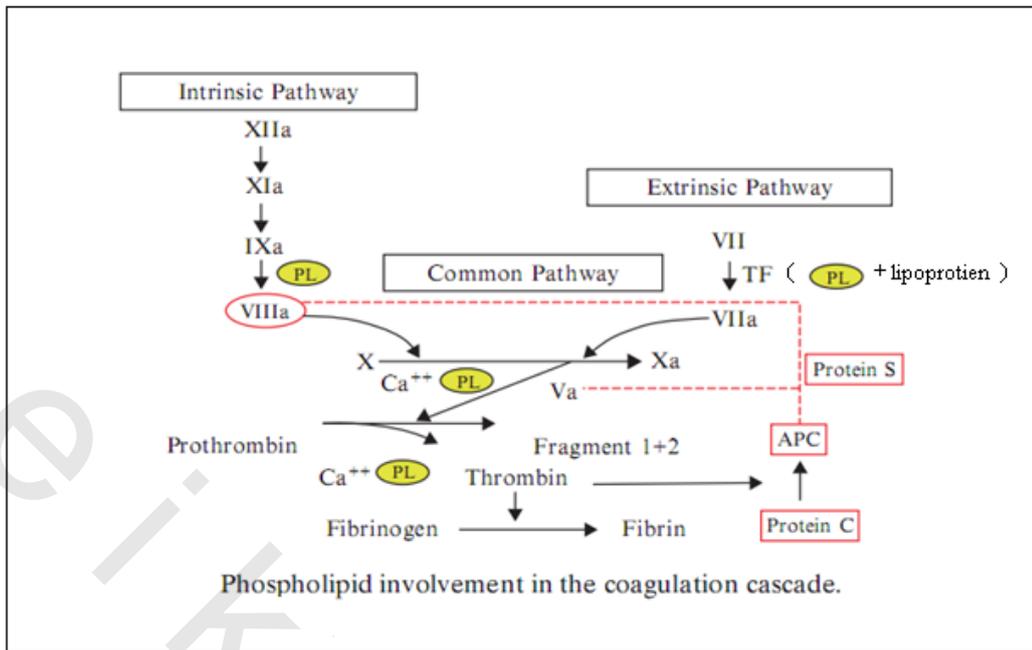
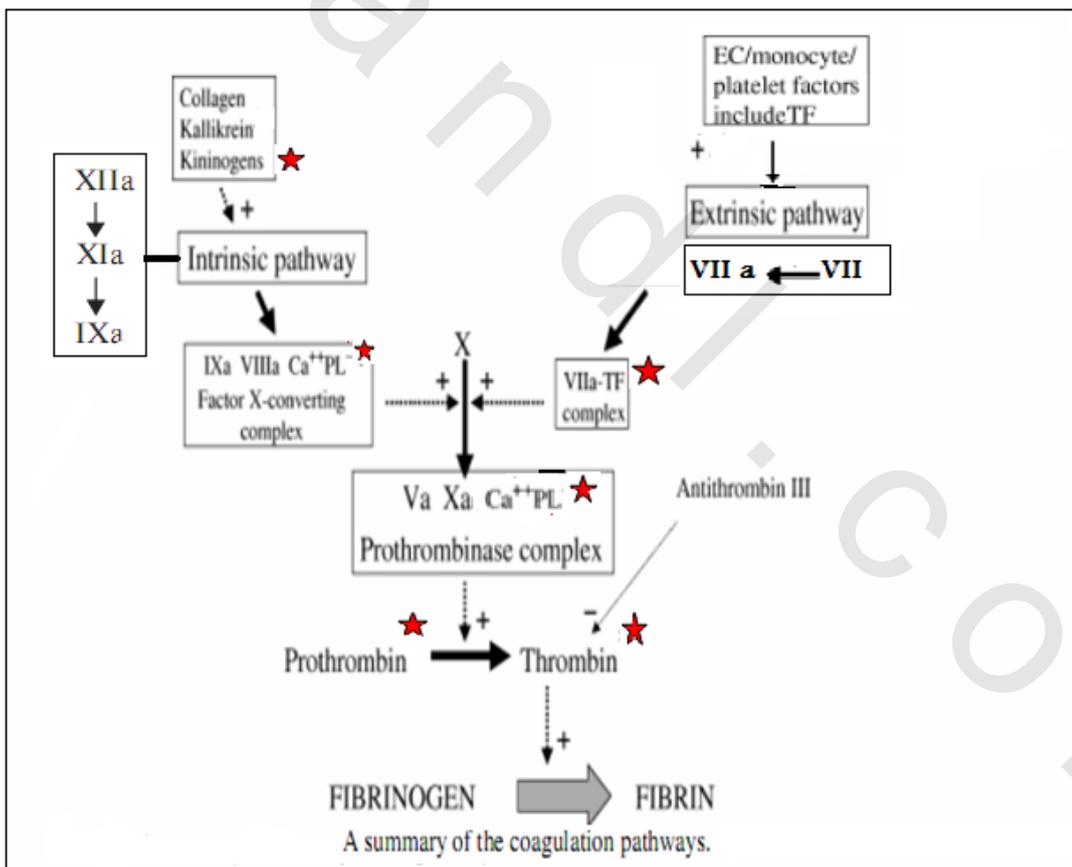


Figure (8): Phospholipid involvement in the coagulation pathway.⁽⁶⁹⁾



★ Asterisks indicate potential sites of action of antibodies in APS

Figure (9): Potential sites of action of antibodies in APS.⁽⁷⁶⁾

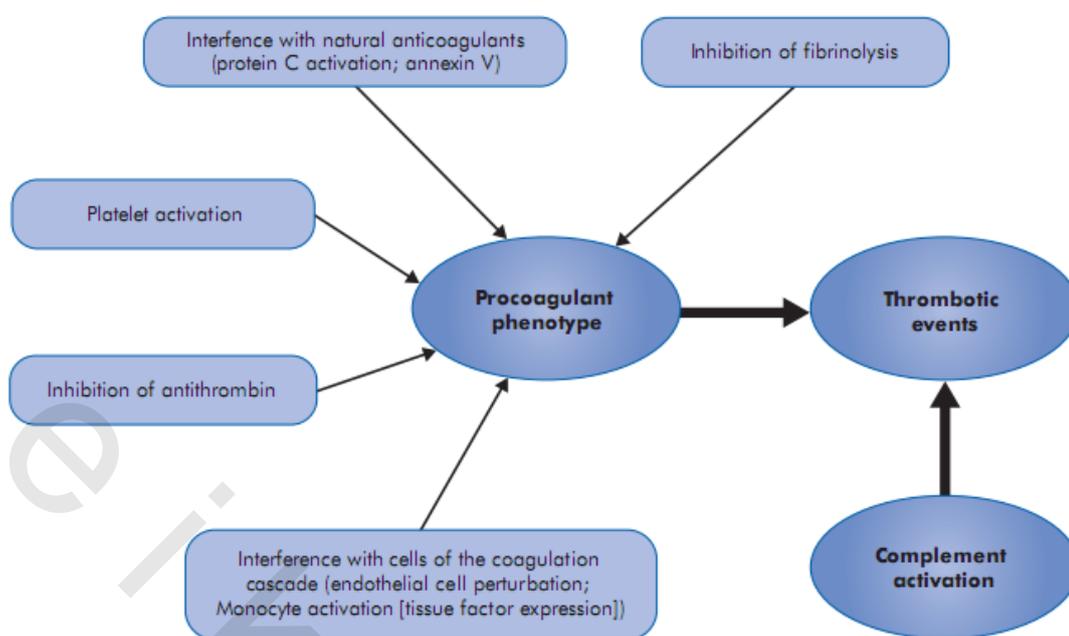


Figure (10): Antiphospholipid antibodies pathogenic mechanisms mediating thrombosis⁽⁷⁷⁾

Types of Antiphospholipid Syndrome:

- **Primary antiphospholipid syndrome:** Patients have no evidence of any definable associated disease.⁽⁷⁹⁾
- **Secondary antiphospholipid syndrome:** It is often associated with (SLE) and less frequently with infections, drugs and other diseases.⁽⁸⁰⁾ Examples of associating conditions:

Common autoimmune or rheumatic diseases^(80,81)

SLE (25-50%), Sjögren syndrome (42%), Rheumatoid arthritis (33%),
 Autoimmune thrombocytopenic purpura (30%),
 Autoimmune hemolytic anemia,
 Psoriatic arthritis (28%), Systemic sclerosis (25%),
 Mixed connective-tissue disease (22%),
 Polymyalgia rheumatica (20%),
 Giant cell arteritis (20%), Behçet syndrome (20%).

Infections^(80,82)

Syphilis, Hepatitis C infection, HIV infection,
 Human T-cell lymphotropic virus type 1 infection,
 Malaria, Bacterial septicemia.

Drugs⁽⁸⁰⁾

Procainamide, quinidine, propranolol, hydralazine,
Phenytoin, chlorpromazine, Interferon alfa, quinine,
amoxicillin, Oral contraceptives.

Malignancy⁽⁸¹⁾

Lymphomas and leukemias,
Solid tumors e.g. renal-cell carcinoma,
Lung carcinoma and ovarian cancer.

Table (5): 2006 preliminary criteria for the classification of definite antiphospholipid syndrome.^(46,83)

Clinical Criteria
<p>1- Vascular thrombosis: ≥ one arterial, venous, or small vessel thrombosis in any tissue or organ, confirmed by imaging or histopathology in the absence of significant evidence of inflammation in the vessel wall</p> <p>2- Pregnancy morbidity: ≥ One unexplained death of a morphologically normal foetus at or beyond the tenth week of gestation, OR ≥ One premature birth of a morphologically normal neonate at or beyond the 34th week of gestation, due to severe preeclampsia, eclampsia, or placental insufficiency, OR ≥ Three unexplained consecutive spontaneous abortions before the tenth week of gestation (maternal anatomic or hormonal abnormalities and chromosomal causes excluded)</p>
Laboratory criteria
<p>1- Medium or high titers of IgG and/or IgM aCL measured by a standardized ELISA for β2-glycoprotein I-dependent aCL</p> <p>2- A positive lupus anticoagulant test, detected according to the guidelines of the ISTH.*</p> <p>3- Anti-β2GPI of IgG and/or IgM isotype in serum or plasma (in titre > 99th percentile)</p>

A Definite APS is considered to be present if at least one clinical and one laboratory criteria are met.

B Positivity should be present on two or more occasions at least 12 weeks apart for any of the tests.

★ ISTH: International society of thrombosis & hemostasis

Seronegative antiphospholipid syndrome

The patient (with migraine, stroke, several previous miscarriages, thrombocytopenia, and livedo reticularis, whose aPL tests are negative) is considered to have this syndrome.⁽⁸⁴⁾ Three possibilities of “seronegative APS:

May be:

The diagnosis may be wrong; the patient has a different coagulopathy such as protein C, protein S or antithrombin III deficiency, malignancy, polycythemia, thrombocytosis, dysfibrinogenemia, paroxysmal nocturnal hemoglobinuria, homocystinuria should be in mind and excluded.^(84,85)

Or:

It may be due to a ‘laboratory’ problem. The conventional testing failing to pick up cases with antibodies directed against different phospholipids or protein co factors. Routine screening tests (anticardiolipin and lupus anticoagulant) may miss some cases. Antibodies may be directed for example against other phospholipids such as phosphatidyl ethanolamine, or against components of the protein C pathway or annexin V. The discovery of β_2 -glycoprotein I raised hopes that screening would become more comprehensive and that anti- β_2 GPI testing might pick up number of cases of APS negative by older tests.^(83,86)

Or:

It is conceivable that previously positive aPL tests have now reverted to negative, either acutely by “consumption” during an acute thrombotic episode, or slowly over time.⁽⁸³⁾

* **N.B.:** Persons with aPL antibodies are at risk of developing APS, although the presence of these antibodies might be transient, without any clinical significance.⁽⁵⁰⁾

* **N.B.:** People with past or current syphilis may have false positive results without being at risk for thrombosis, as is the case with other infection-, medication-, or neoplasm-induced transient antibodies.⁽⁶⁾

* **N.B.:** presence of IgA anticardiolipin and IgA anti- β_2 -glycoprotein antibodies suggest the presence of antiphospholipid syndrome.⁽⁸⁷⁾

Clinical manifestations of antiphospholipid syndrome

APS patients can have disorders in various body systems including every organ in the human body.⁽⁸⁸⁾

Organ system primary pathogenic process: Many of the clinical manifestations of the antiphospholipid syndrome listed in this table can occur as a result of thromboembolism of large vessels, thrombotic microangiopathy, or both. Manifestations of the antiphospholipid syndrome whose pathogenic origin is uncertain (e.g., thrombocytopenia) are also listed as manifestations of thromboembolism of large vessels.⁽⁸⁹⁾

Table (6): Clinical manifestations of antiphospholipid syndrome⁽⁸⁹⁾

Organ/ system	Large vessel thromboembolism	Thrombotic microangiopathy
Arterial	Thrombosis of the aorta, axillary, carotid, hepatic, ileofemoral, mesenteric, pancreatic, popliteal, splenic, or subclavian artery	
Cardiac	Angina, myocardial infarction, cardiac valvular vegetations, valvular abnormalities, intracardiac thrombi, nonbacterial thrombotic (Libman–Sacks) endocarditis, peripheral embolization, or atherosclerosis	Myocardial infarction, myocardial micro-thrombi, myocarditis, or valvular abnormalities
Cutaneous	Superficial thrombophlebitis, splinter hemorrhages, leg ulcers, distal cutaneous ischemia, infarcts of the skin, blue toe syndrome, or acrocyanosis	Livedo reticularis, superficial gangrene, purpura, ecchymoses, or subcutaneous nodules
Endocrine and reproductive	Adrenal infarction, adrenal failure, testicular infarction, prostate infarction, necrosis of the pituitary gland, or pituitary failure	
Gastrointestinal	Budd–Chiari syndrome, hepatic infarction, intestinal infarction, splenic infarction, esophageal perforation, ischemic colitis, infarction of the gall bladder not attributable to gallstones, pancreatitis, or ascites.	Intestinal, hepatic, pancreatic, and splenic infarctions or gangrene
Hematologic	Thrombocytopenia, hemolytic anemia, or hemolytic–uremic syndrome and thrombotic thrombocytopenic purpura	Disseminated intravascular coagulation (catastrophic APS syndrome only)
Neurologic	Transient ischemic attack, cerebrovascular accident (thrombotic or embolic), chorea, seizures, multi-infarct dementia, transverse myelitis, encephalopathy, migraines, pseudotumor cerebri, cerebral venous thrombosis, mononeuritis multiplex, or amaurosis fugax	Microthrombi or microinfarctions.
Obstetric	Pregnancy loss, intrauterine growth retardation, HELLP syndrome (hemolysis, elevated liver enzymes, and a low platelet count in association with preeclampsia), oligo-hydramnios, uteroplacental insufficiency, or preeclampsia	
Ophthalmological	Thrombosis of the retinal artery, thrombosis of the retinal vein, or amaurosis fugax.	Retinitis
Pulmonary	Pulmonary emboli, pulmonary hypertension, pulmonary arterial thrombosis, or alveolar hemorrhage	Acute respiratory distress syndrome or alveolar hemorrhage
Renal	Thrombosis of the renal vein, thrombosis of the renal artery, renal infarction, hypertension, acute renal failure, chronic renal failure, proteinuria, hematuria, or the nephrotic syndrome	Acute renal failure (often requiring dialysis), thrombotic microangiopathy, or hypertension
Venous	Deep venous thrombosis of the legs or thrombosis of the adrenal, hepatic, mesenteric, portal, or splenic vein or of the inferior vena cava	
Miscellaneous	Perforation of the nasal septum or avascular necrosis of bone	

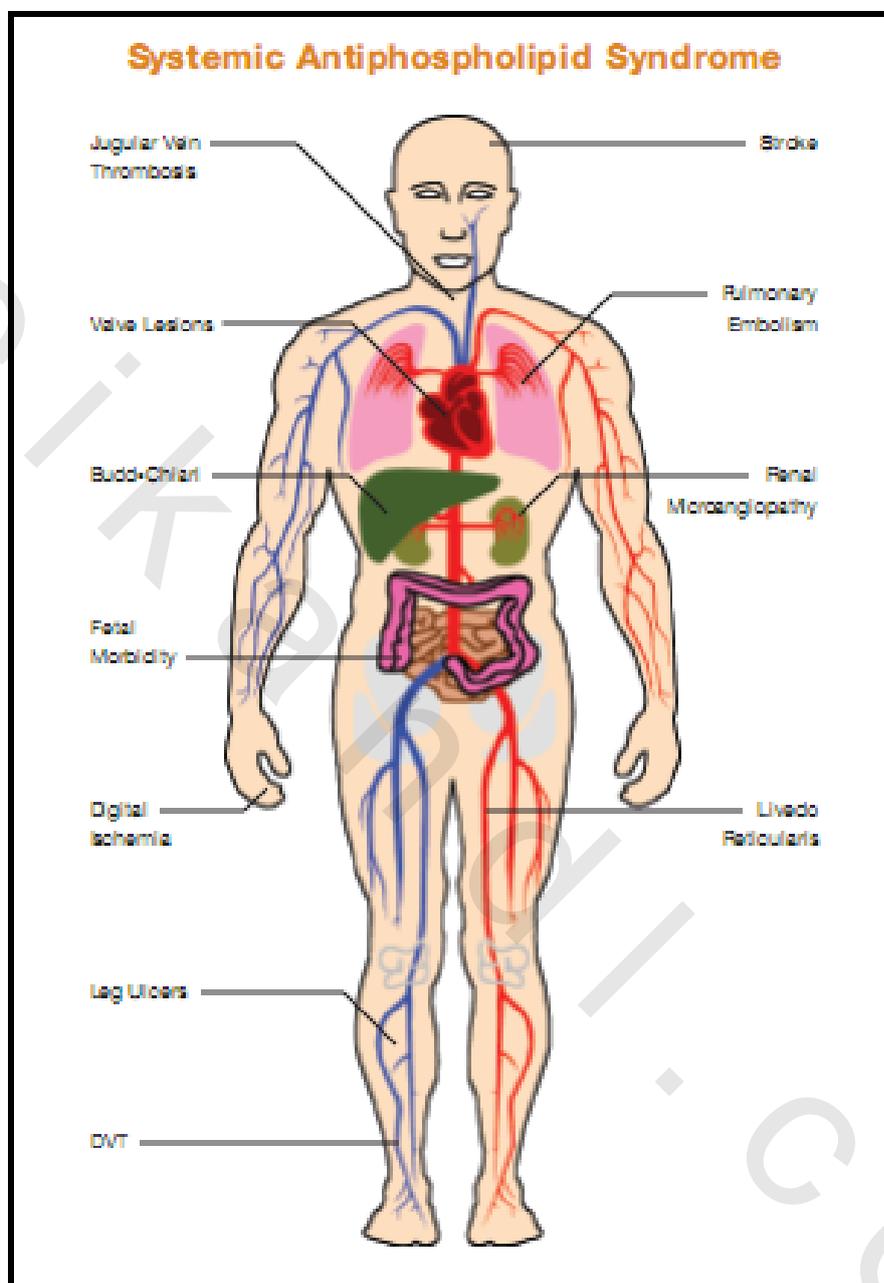


Figure (11): Major characteristics of APS include: deep vein thrombosis, pulmonary emboli, myocardial infarction, stroke, livedo reticularis, heart valve disease, recurrent abortions, skin ulcers, impaired blood supply to the fingers, budd-chiari syndrome, and small vessel disease of the kidneys.⁽⁸⁸⁾

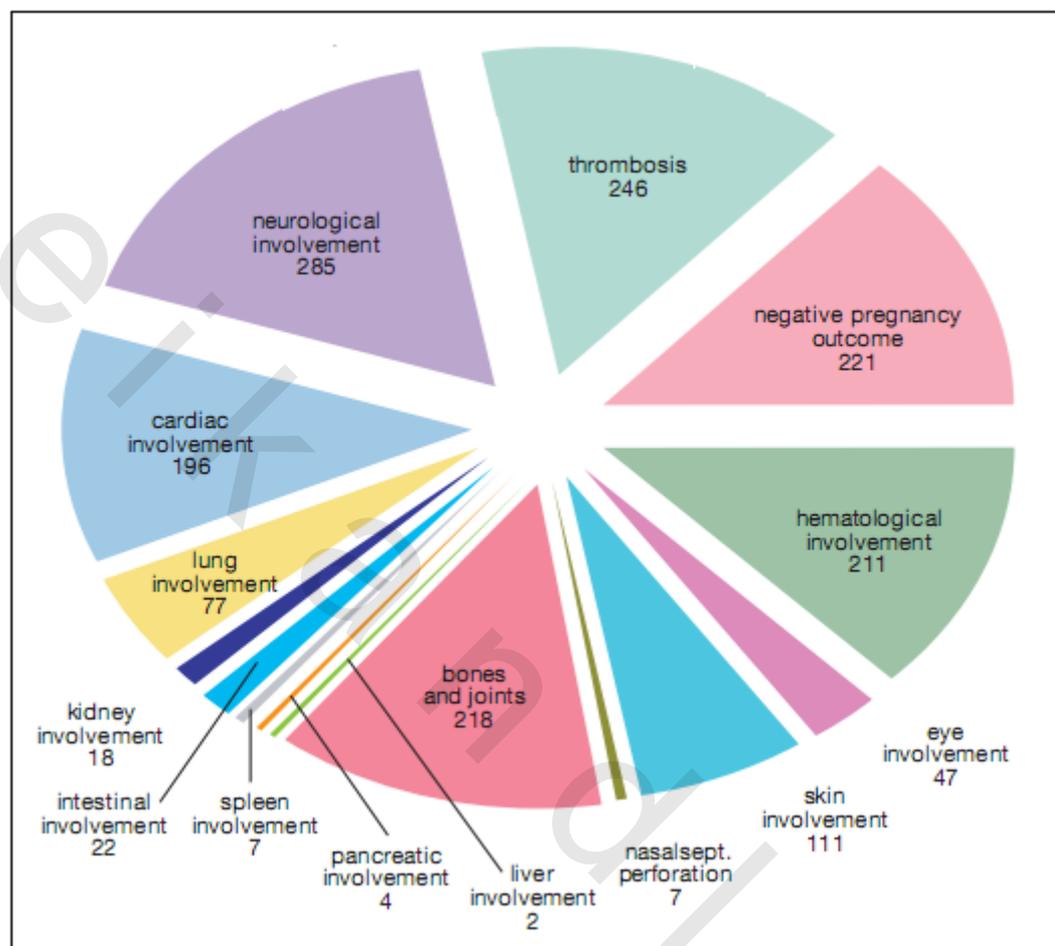


Figure (12): A diagram representing the clinical manifestations in 1000 patients having APS. The common clinical manifestations are thrombosis, strokes, pregnancy failure, involvement of blood system, heart injury, and in addition damage to the lungs, eyes, kidneys, skin, joints, bones and abdominal viscera.⁽⁸⁸⁾

Catastrophic antiphospholipid (Asherson syndrome)

The catastrophic variant of APS (CAPS) is an accelerated form of this syndrome, resulting in multiorgan failure due to multiple small vessel occlusions.

Preliminary criteria for the classification of catastrophic APS:⁽⁹⁰⁾

- 1- Evidence of involvement of three or more organs, systems and/or tissues.
- 2- Development of manifestations simultaneously or in less than a week.
- 3- Confirmation by histopathology of small vessel occlusion in at least one organ or tissue
- 4- Laboratory confirmation of the presence of antiphospholipid antibodies (LA and/or aCL)

Definite catastrophic APS:

All the four criteria are fulfilled.

Probable catastrophic APS:

- All the 4 criteria, except for involvement of only 2 organs systems and/or tissues.
- All the 4 criteria, except for the absence of laboratory confirmation at least 6 weeks apart due to the early death of a patient never previously tested for aPL prior to the catastrophic APS event.
- Criteria of 1,2 &4 are fulfilled.
- 1, 3 &4 and the development of a third event in more than a week but less than a month.

Patients may develop catastrophic APS de novo without previous history of thrombosis, either associated with a primary APS or SLE.⁽⁹⁰⁾

Global antiphospholipid syndrome score (GAPSS)

The recent clinical development is that of global scores to assess the risk of development of thrombosis and pregnancy morbidity in SLE patients with aPL. In 2012 Otomo et al. developed the aPL Score (aPL-S). By testing multiple aPL patients they successfully evaluated its efficacy for the diagnosis of APS and predictive value for thrombosis. Later, Sciascia et al. performed a validation study of this score and found that although the aPL-S was a useful quantitative index for diagnosing APS, it did not take into account associated conventional risk for thrombosis (i.e. hypertension, hyperlipidaemia, diabetes or smoking) in addition to the aPL profile.

Furthermore, it did not evaluate the risk of loss of pregnancy, the other prominent complication associated with the presence of aPL. In this issue of Rheumatology, Sciascia et al. present the development and validation of a new risk score: the Global APS Score (GAPSS) is derived from the combination of independent risk for both thrombosis and loss of pregnancy, taking into account not only the aPL profile, but also

- The conventional cardiovascular risk factors,
- The autoimmune antibody profile (i.e. antinuclear, anti-dsDNA or anti-ENA antibodies) and
- The use of thromboprophylactic drugs (i.e. low-dose aspirin, oral anticoagulants and hydroxychloroquine).

The GAPSS includes IgG/IgM aCL (5 points), IgG/IgM anti-b2GPI antibodies (4 points), LA (4 points), IgG/IgM anti-phosphatidylserineprothrombin complex antibodies (3 points), hyperlipidaemia (3 points) and arterial hypertension (1 point). A GAPSS cut-off value of 510 points appears to have the best diagnostic accuracy (sensitivity, specificity and positive and negative predictive values). Therefore this new score seems to provide a substantial improvement in risk prediction of thrombosis or pregnancy loss in SLE.

Future prospective studies are needed to confirm these promising expectations and overcome some limitations of this study. For instance, the prognostic value of the aPL level or the persistence of aPL positivity as well as the concomitant presence of genetic thrombophilic factors (i.e. factor V Leiden mutation) should be assessed in the development of a risk prediction score. Additionally this score should also be validated in patients without SLE (i.e. asymptomatic aPL carriers and primary APS patients) as well as in patients from different ethnic and national groups.⁽⁹¹⁾