Antiphospholipid Antibody Syndrome

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Objectives…

- APLS overview
- Revised classification criteria for APLS
- Presentation/clinical manifestations of APLS
- Other specific subtypes of APLS-CAPS/SNAP
- Management guidelines for APLS
- Summary
- References

APS is more common in women (5:1).

Females -more frequently -arthritis, livedo reticularis, and migraine

Males -myocardial infarction, epilepsy and lower extremity arterial thrombosis .

Mean age of onset -31 years

AcA-associated thrombosis- more common than LA-associated thrombosis, with a ratio of 5:1

Primary APLS -aPL in patients with idiopathic thrombosis.

Secondary APS -autoimmune disorders (SLE and RA) and thrombosis is found to have aPL.

Common autoimmune rheumatic diseases with aPL antibodies:

- SLE - 25-50%
- Sjogren's syndrome – 42%
- Rheumatoid arthritis – 33%
- Autoimmune thrombocytopenic purpura - 30%
- Autoimmune hemolytic anemia - Unknown
- Psoriatic arthritis – 28%
- Systemic sclerosis – 25%
- Mixed connective-tissue disease - 22%
- Polymyalgia rheumatica or Giant cell arteritis - 20%
- Behcet syndrome - 20%

Revised classification criteria for APLS

one clinical criteria and one laboratory test=

clinical criteria:

1. Vascular thrombosis

One or more clinical episode of arterial, venous or

small-vessel thrombosis.

2. Pregnancy morbidity=

(a) One or more unexplained deaths of morphologically normal fetuses >/= 10th week, or

(b) One or more premature births of morphologically normal neonates <34th week because of (i) eclampsia or severe preeclampsia or (ii)features of placental insufficiency; or

(c) 3/> unexplained consecutive spontaneous abortions before 10th week, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

Laboratory criteria :

1. Lupus anticoagulant present in plasma

2. acL of IgG and/or Igm isotype -medium or high titer

3. Anti–b-2-GP I IgG and/or Igm isotype

2/> occasions at least **12 weeks** apart.

- **“Definite” APLS** -persistent high-titer aPL with one clinical criteria.

- Laboratory criteria- acL IgG or Igm or lupus anticoagulant in high titers (>40 IgG or Igm or >99th percentile), confirmed on repeat testing 12 weeks later

- Classification like Iry or 2ry APLS is **not** useful at all.
- Instead it is with or without the risk factors for thrombosis.
- Clinical manifestations- No symptoms to imminently life-threatening, catastrophic APS (CAPS).

Additional risk factors for thrombosis

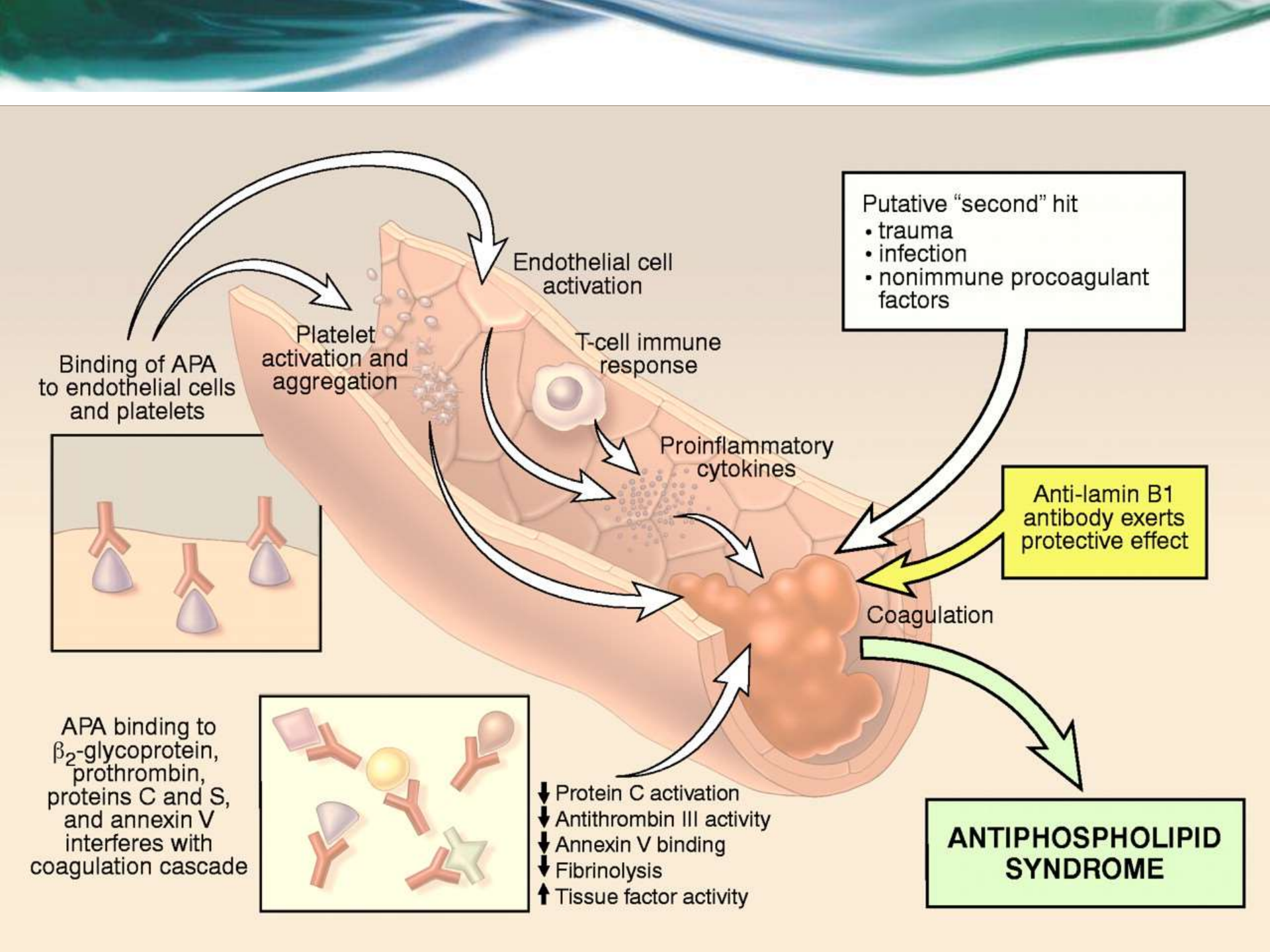
- Age (M-> 55 , F-> 65)
- Risk factor for CVD- HT, DM, elevated LDL or low HDL, smoking, F/H premature CAD, BMI ≥ 30, microalbuminuria, eGFR < 60 ml/min.
- Inherited thrombophilias
- OCP
- Nephrotic syndrome
- Malignancy
- Immobilization
- Surgery

Venous Thrombosis

- Typically DVT in L/L.
- Unusual sites – U/L, intracranial veins, IVC, SVC,hepatic veins (Budd-Chiari syndrome), portal vein, renal vein & retinal vein. Rarely superior sagital sinus.
- Thrombosis of the cerebral veins -acute cerebral infarction.

Arterial Thrombosis

- **Less** common than venous thromboses.
- Most commonly –TIA or stroke (50%) or MI (23%).
- aCL - risk factor for 1st stroke.
- May involve large and small vessels(unusual in thrombophilic disorders or ATH disease).
- Sites- brachial and subclavian, axillary artery (**aortic arch syndrome**), aorta, iliac, femoral, renal, mesenteric, retinal, and other peripheral arteries.


Putative "second" hit
• trauma
• infection
• nonimmune procoagulant factors
Endothelial cell activation
Platelet activation and aggregation
T-cell immune response
Binding of APA to endothelial cells and platelets
Proinflammatory cytokines
Anti-lamin B1 antibody exerts protective effect
Coagulation
APA binding to β_2-glycoprotein, prothrombin, proteins C and S, and annexin V interferes with coagulation cascade
↓ Protein C activation
↓ Antithrombin III activity
↓ Annexin V binding
↓ Fibrinolysis
↑ Tissue factor activity
ANTIPHOSPHOLIPID SYNDROME

Cardiac Disorders

- CAD- thrombotic or embolic.
- Premature ATH accelerated by aPL.
- Routine aPL tests in CAD not recommended unless young age and lack of identifiable risk factors suggest a rare etiology.
- Valvular thickening, vegetations, regurgitation, premature CAD,MI, DCM, CCF, PE, and pul.HT.

Neurologic Disorders

- Ischemic stroke.
- Recurrent small strokes -multiple-infarct dementia.
- Typical APLS with stroke- young and lack other classical risk factors of stroke!
- Chorea, migraine headache, Sneddon's syndrome, seizures, transverse myelitis, GBS, IIH, cognitive dysfunction, psychosis, and optic neuritis are other effects.

- Multiple sclerosis-like presentation -cognitive dysfunction and abnormal MRI.
- Chorea, migraine, seizure, and dysarthria -APLS
- Optic neuritis, bowel and bladder abnormalities, and gait disturbances -multiple sclerosis.
- In APLS -abnormalities are nonenhancing with gadolinium & high titer anti-body.

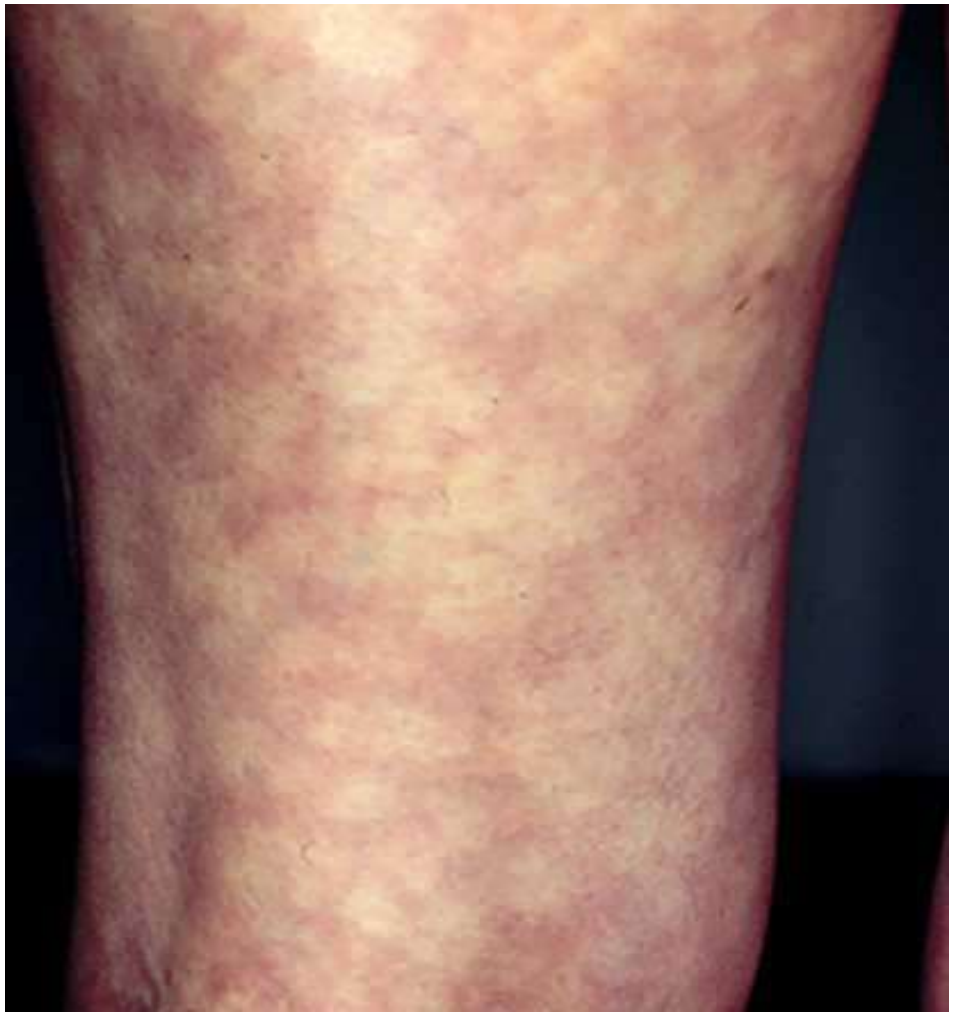
Obstetrical Disorders

- Miscarriages and early fetal loss.
- Eclampsia, IUGR, oligohydramninos, HELLP syndrome, and premature birth, systemic and pulmonary hypertension.
- Of all hereditary and acquired thrombophilias, **APLS is the most common thrombotic defect leading to fetal wastage!**

Dermatologic Disorders

- May be the first sign of APLS.
- Histopathologically -noninflammatory vascular thrombosis.
- Livedo reticularis, necrotizing vasculitis, livedoid vasculitis, cutaneous ulcerations and necrosis, erythematous macules, purpura, ecchymoses, painful skin nodules, and subungual splinter hemorrhages.
- Anetoderma, DLE, cutaneous T-cell lymphoma, and disorders similar to Degos and Sneddon's syndrome
- Livedo reticularis and APLS frequently -cardiac and cerebral thrombotic events, epilepsy, and migraine adaches.

Levido reticularis.



Pulmonary

- Antiphospholipid lung syndrome- thromboembolism, pulmonary HT, ARDS, postpartum syndrome, and others.
- Diffuse alveolar haemorrhages.

Abdominal Manifestations

Box 3 : Summary of the abdominal manifestations associated with the antiphospholipid syndrome	
Abdominal Organ	Manifestations
Liver	Budd-Chiari Syndrome: Hepatic-veno-occlusive disease and occlusion of small hepatic veins Nodular regenerative hyperplasia Hepatic infarction Cirrhosis Portal hypertension Autoimmune hepatitis Biliary cirrhosis Liver transplantation
Intestine	Acute intestinal infarction Intestinal angina Intestinal bleeding High prevalence of aPL but no increased vascular thromboses in inflammatory bowel disease
Spleen	Splenic infarction Autosplenectomy or functional asplenia.
Pancreas	Acute pancreatitis

Renal manifestations

- aPLassociated nephropathy (APLN)
- Thrombosis – RAS and/or malignant hypertension, renal infarction, renal vein thrombosis, thrombotic microangiopathy, increased allograft vascular thrombosis, and reduced survival of renal allografts.
- Non-thrombotic conditions- glomerulonephritis.

Endocrine manifestations

- **Adrenal insufficiency** - most common.
- Circulating aPL- autoimmune thyroid disease, hypopituitarism (including a case of Sheehan's syndrome), DM and rarely ovarian and testicular disease.

Retinal Disorders

- Venous and arterial thrombosis of the retinal vasculature.
- Presentation strongly suggestive - diffuse occlusion of retinal arteries, veins, or both, and neovascularization at the time of presentation.
- optic neuropathy and cilioretinal artery occlusion.

Hematological Disorders

- Thrombocytopenia (<100,000) -20% to 40%.(usually mild)
- Severe thrombocytopenia -CAPS and DIC or TTP.
- aPL-associated thrombocytopenia –aPL with thrombocytopenia (<100,000) confirmed 12 weeks apart and exclusion of TTP, DIC, pseudothrombocytopenia, or HITT.

Catastrophic Antiphospholipid Antibody Syndrome (CAPS)

- A syndrome of multisystem involvement as a manifestation of APLS **(Asherson's syndrome).**
- Less than 1% of APLS patients.
- Multiple small-vessel occlusions leading to MOF and substantial morbidity and mortality.
- Generally of acute onset and defined by involvement of at least three different organ systems over a period of days or weeks.

- Histopathologically- small- and large-vessel occlusions.
- The striking feature of the syndrome- presence of an acute microangiopathy, rather than large-vessel occlusions.

CAPS-presentation..

- Clinical features- **organ and tissue ischemia**
  - Renal failure -renal thrombotic microangiopathy,
  - Acute respiratory failure -ARDS
  - Cerebral injury -microthrombi and microinfarctions
  - myocardial failure -microthrombi
- It develops rapidly following an identifiable triggering factor.
- Trigger factors -Infection, trauma, neoplasia, anticoagulation withdrawal, during pregnancy or peurperium, surgery, and lupus flares.

Preliminary criteria for the classification of CAPS

1. **Evidence of involvement of 3 organ systems, and/or tissues.**
   - **Usually clinical evidence of vessel occlusions, confirmed by imaging.**
   - **Renal involvement -50% rise in S.creatinine, severe HT (>180/100), and/or proteinuria (>500 mg/24h).**
2. **Development of manifestations simultaneously or in <1 week.**
3. **Confirmation by histopathology of small-vessel occlusion in at least one organ/tissue.-significant evidence of thrombosis, although vasculitis may coexist.**
4. **Laboratory confirmation of the presence of aPL (lupus anticoagulant and/or aCL and/or anti b2 GP I)**

- **Definite CAPS**

All four criteria

.Probable CAPS

Criteria 2, 3 & 4, plus 2 organs involved.

- All four criteria, except for the absence of laboratory confirmation of the presence of aPL at least 6 weeks after a first positive result
- Criteria 1,2 & 4
- Criteria 1,3 & 4, plus the development of a third event in >1 week but <1 month, despite anticoagulation treatment.

- Cerebral involvement, mainly stroke, followed by cardiac involvement and infections -**main causes of death.**
- The presence of SLE - related with higher mortality!

Asymptomatic Antiphospholipid Antibodies

- Line between asymptomatic aPL and APLS- development of large or small-vessel thrombosis or pregnancy loss.
- Risk factors for transition to APLS –P/H thrombosis, lupus anticoagulant & elevated aCL IgG.
- Each risk factors increase the risk of thrombosis by fivefold.
- Persistence aPL over time progressively increases thrombosis risk.
- keep the asymptomatic under clinical surveillance for thrombosis.

Probable APLS/pre APLS

- Positive aPL with clinical features suggesting APLS but lack the clinical criteria.
- C.F: livedo reticularis, chorea, thrombocytopenia, fetal loss, and cardiac valvular lesions.
- Livedo reticularis -1st manifestation of APLS (41% of patients).

Seronegative APLS (SNAP)

- Clinical manifestations of APLS, without any recognized aPL.
- Idiopathic arterial or venous thrombosis and initial testing for aPL is negative. Repeat testing months later may be positive

Microangiopathic APLS

- APLS may present with characteristic of microvascular occlusive disease. Eg: TTP, HELLP,Thrombotic MAHA & CAPS.

Drug-Induced APLS

- Eg: chlorpromazine, phenytoin, hydralazine, procainamide, fansidar, quinidine, interferon, and cocaine.
- A common misconception -often immunoglobulin (Ig) M, do not suffer thrombosis.

Infection-Associated APLS

- Autoantibodies are more often IgM than IgG.
- The C.F of typical of APS are less commonly observed.
- Infections associated with aPL and β-2-GP I – associated with thrombosis (leprosy, parvovirus B19, HIV, HCV, CMV)
- Infection -triggering factor in 40% of cases of CAPS.

Malignancy-Associated APLS

- A variety of solid and hematologic malignancies associated with the presence of aPL.

Antiphospholipid Syndrome Antibodies

- Target PL directly- cardiolipin, phosphatidylserine, phosphatidylinositol,phosphatidylethanolamine, phosphatidylglycerol, and phosphatidylcholine.

  APAs -IgG, IgA, and IgM.
- APS antibodies against protein antigens –anionic PL, forming a protein-phospholipid complex. Eg- beta-2-glycoprotein I(β2-GPI) and prothrombin.
- antibodies against annexin V and protein C associated with APLS &SLE.

Lupus anti coagulant(LA)

- Misnomer, associated with thrombosis and not bleeding
- LA inhibits formation of prothrombinase complex.
- It blocks binding of prothrombin and factor Xa to phospholipids, (conversion of prothrombin to thrombin).
- LA can be- IgG, IgA, or IgM.
- LA is found in 10% of SLE.
- LA commonly ass. with venous thrombosis & occasionally arterial disease

- When clinical APLS & assays for ACAs or LACs are **negative**- anti-β2-GpI and antibodies to phosphatidylserine phosphatidylethanolamine, phosphatidylglycerol, phosphatidylinositol, annexin-V, and phosphatidylcholine need to be arranged.

Management of APLS

Box 5 : Currently recommended treatments for antiphospholipid syndrome

Clinical Manifestations	Treatment for thrombosis prevention
Vascular Events	
Asymptomatic[a] aPL- positive patients	No treatment[b]
Venous thrombosis	Warfarin (INR: 2.0–3.0)
Arterial thrombosis	Warfarin (INR: 3.0)[c]
Recurrent thrombosis	Warfarin (INR: 3.0–4.0) + low-dose aspirin (LDA)
Catastrophic APS	Anticoagulation + corticosteroids + IVIG or plasmapheresis

Pregnancy morbidity	
Asymptomatic[a] aPL-positive patients	No treatment[d]
Single pregnancy loss <10 wk	No treatment[d]
Recurrent (pre-) embryonic losses[e] or fetal loss > 10 wk and no history of vascular thrombosis	LDA + prophylactic[f] dose heparin during the pregnancy, heparin for postpartum 6–12 w, and LDA thereafter
Recurrent (pre-)embryonic losses or fetal loss >10 w and history of vascular thrombosis	LDA + therapeutic[f] dose heparin during the pregnancy, warfarin postpartum
History of vascular thrombosis	LDA + therapeutic[f] dose heparin during the pregnancy, warfarin postpartum

- **Prophylactic dose-** Enoxaparin 30–40 mg subcutaneously daily.
- **Therapeutic dose-** Enoxaparin 1mg/kg S/C bd or 1.5 mg/kg/d.
- APLS with cerebral ischaemia -target INR of 3.0 to prevent recurrences. (Low-dose aspirin alone does **not** seem helpful here)
- Once proven thrombosis -long-term (**possibly life-long**) warfarin therapy is advisable.
- Reduce the modifiable vascular risk factors.

- No data indicate the efficacy of warfarin microangiopathic nephropathy, valvular heart disease, livedo reticularis, or leg ulcers.
- No data support its use in asymptomatic bearers of aPL.

- Ximelagatran is the first oral thrombin inhibitor. The active metabolite- melagatran -wider therapeutic window, rapid onset of action, and shorter half-life than warfarin.
- Ximelagatran – no drug interaction
- Ximelagatran is superior to warfarin -prevention of venous thromboembolism after total KJ replacement.
- Good results have been reported with autologous hematopoietic stem cell transplantation (HSCT) in APLS

Box 6: Alternatives to Warfarin

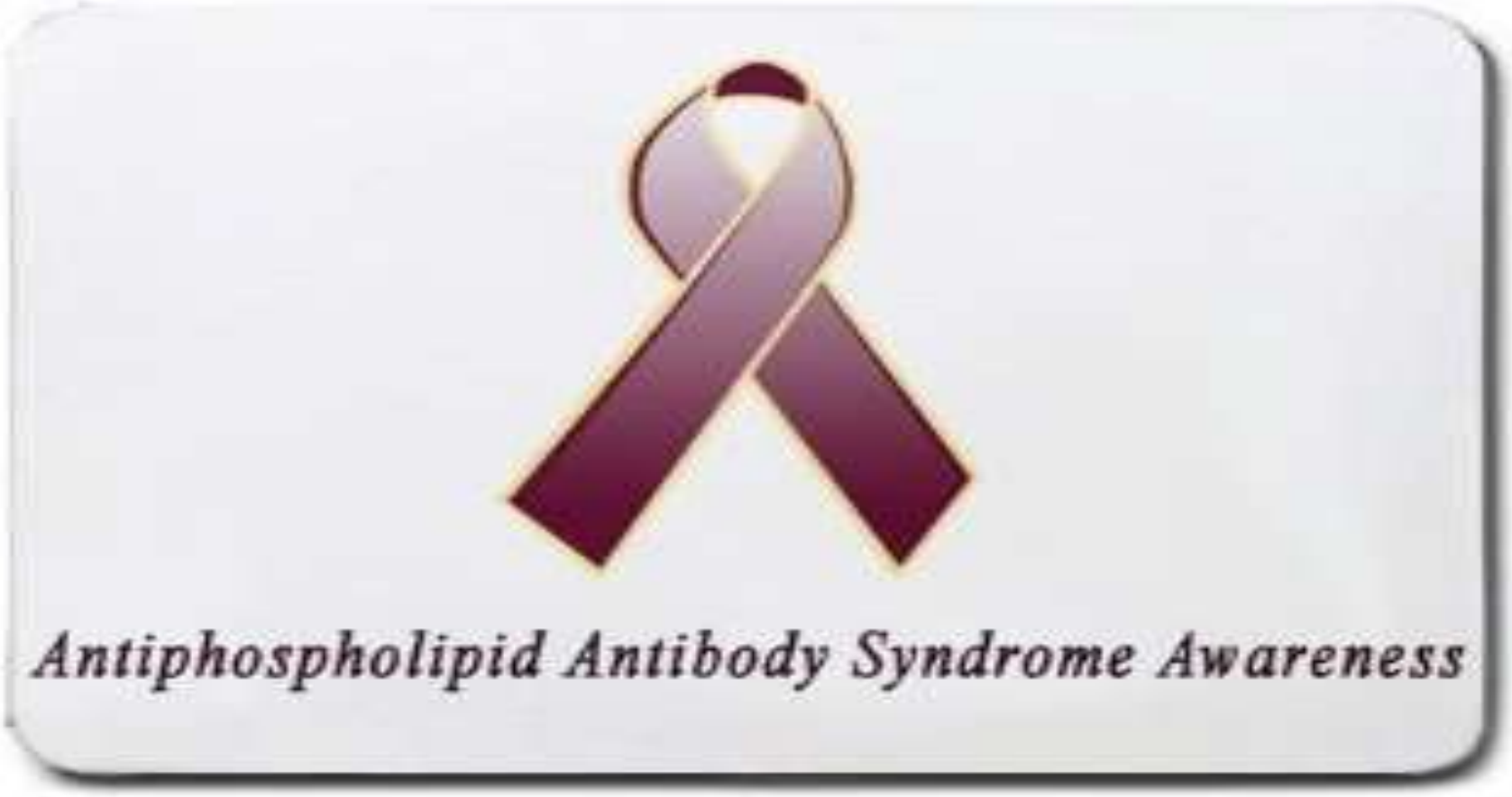
Current	Future
Nonaspirin antiplatelet agents	GPIIb/IIIa-specific antagonists
Indirect and direct thrombin inhibitors	p38MAPK inhibitors
Hydroxychloroquine	Thromboxane A2 inhibitors
Statins	Tissue factor expression inhibition
Rituximab	Complement inhibition
Recombinant human activated protein C	Synthetic peptides
Prostacyclin and prostaglandin	bGPI toleragen
Anticytokine treatment	New anticoagulants in development

Summary….

- Main 3antibodies in APLS- LA,ACL, Anti-b2GPI.
- If all negative with clinical suspician of APLS need further antibody testing.
- Risk factor assessment for thrombosis is important than Iry or IIry.
- Lab criteria -extension of the interval between first and second positive test from 6 to 12 weeks.
- Recognition of other features that serve as diagnostic clues.
- Seronegative APLS (SNAP).
- CAPS is rare but lethal.

References

- Update article in Antiphospholipid antibody syndrome; Renu saigal.Amit Kansal,Manoop Mittal,Yadvinder Singh,Hari Ram;JAPI.MARCH 2010.VOL 58



Thank you!