

Antiphospholipid Antibody Syndrome

**Brandusa Florica
Rheumatology rounds
April 22, 2008**

Objectives

- To review the etiology and pathogenic mechanisms of APS
- To learn about diagnostic methods
- To underline the clinical presentation
- To understand the treatment principles and be aware of future directions

Case scenario

- 43F, previously healthy
- 1 month hx of episodic discoloration of the distal 3rd and 5th fingers of the left hand +/- pain in the same area
 - onset after 1-2 wks of L arm cellulites due to a spider bite
 - getting worse – severe pain/more frequent
 - triggered by cold
 - well demarcated
 - spontaneously reversible

Case scenario

- PMH - no chronic illnesses, no surgeries, but long-time smoker
- Meds - none
- Working as a financial analyst
- ROS - no rashes, oral ulcers, photosensitivity, alopecia, chest pains, SOB, GERD, dysphagia, joint pains, or stiffness

Case scenario

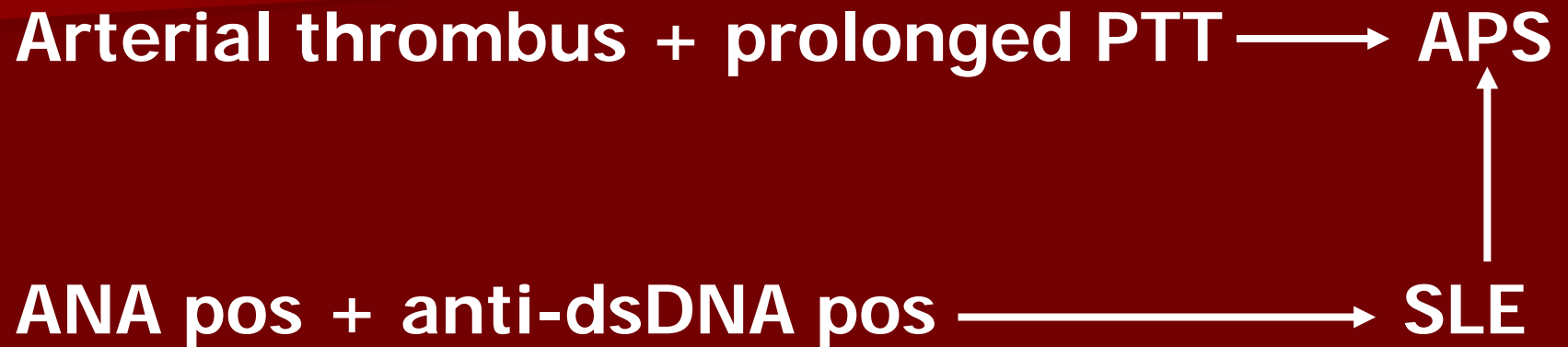
- BP 160/90 HR 101, regular
- Radial & ulnar pulses present
- Neurovascular exam normal
- Purplish discoloration, blanches

Case scenario



Case scenario

- Hb 117, WBC 13.3, Plt 326, Cr 131, BS 4.9
- INR 1.24, PTT 73.0, ESR 127, CRP 22,
- ANA 3.6, anti-dsDNA 132,
- Hepatitis B and C negative, Cryoglobulins negative
- Urinalysis >3g protein
- Arterial doppler U/S of left arm - occlusion of distal left ulnar artery, decreased flow to fingers 2, 3, and 5, with collaterals



Other considerations

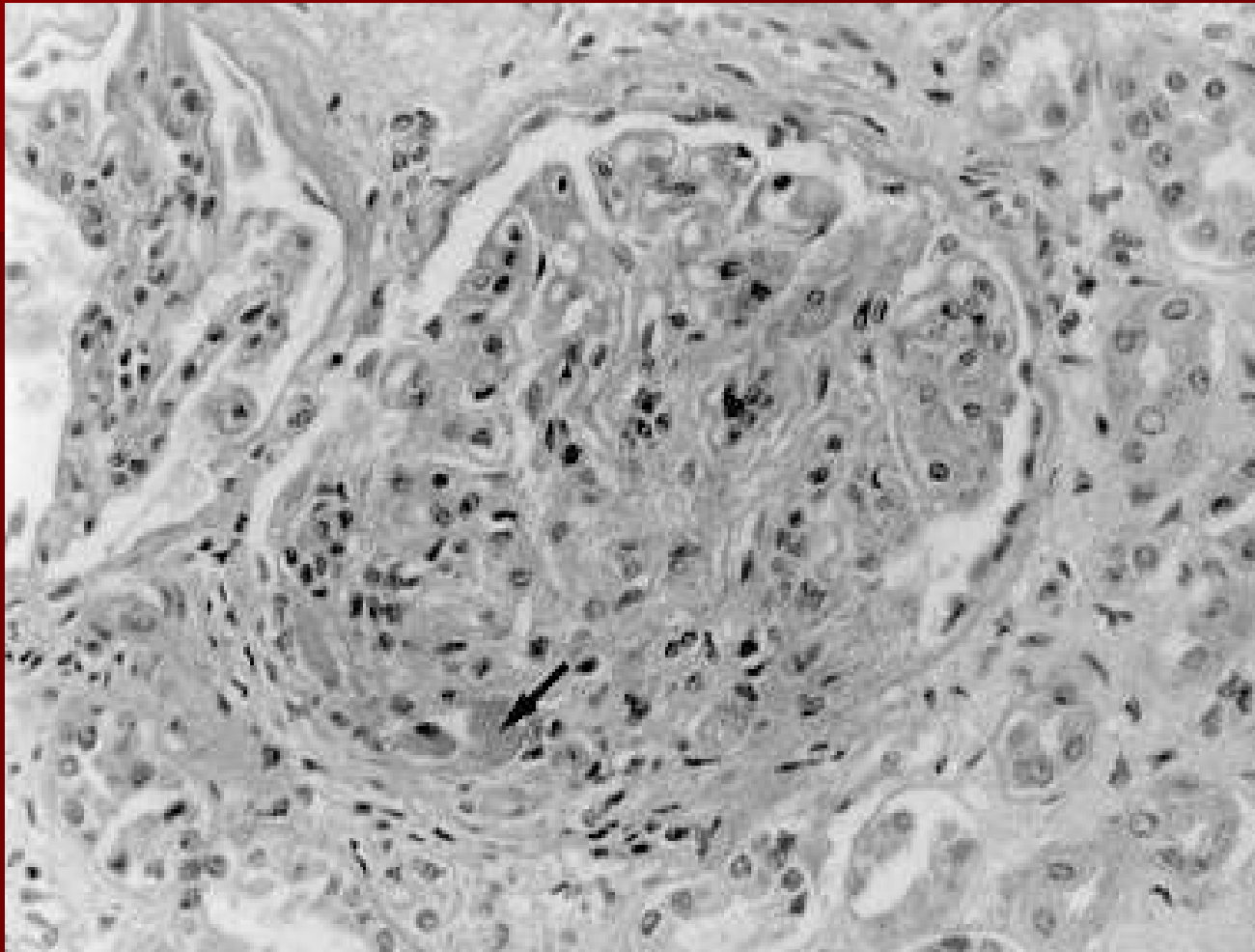
- Endocarditis
- Vasculitis
- Thromboangiitis obliterans

Case scenario

- PTT 73
- 50:50 mix 67
- Russel viper venom - positive
- ACA IgG 54
- ACA IgM 21

Case scenario

- Creatinine 130 - 150
- Proteinuria (0.67 g/day)
- No active sediment
- Kidney biopsy:
 - focal glomerular microthrombosis,
focal glomerulosclerosis,
mild acute and chronic tubular degenerative
changes.



Focal glomerular microthrombosis

Antiphospholipid Syndrome

- Most common acquired thrombophilia
- Described by Hughes (1983)

A syndrome characterized by the association of:

- thrombosis, obstetric complications and/or thrombocytopenia
- antibodies against phospholipids or against proteins bound to phospholipids.

Antiphospholipid Syndrome - Etiology

- Combination of genetic background and environmental factors: infection, trauma, drugs
 - infections – molecular mimicry with B2GPI

Table I. Examples of infectious agents reported to be associated with antiphospholipid antibodies and manifestations attributed to the antiphospholipid syndrome (APS).

Infectious agent	Presence of anticardiolipin antibodies	APS manifestation
Hepatitis C virus	IgG	Thrombosis, brain infarction
Varicella-zoster virus	IgG, IgM	Pulmonary embolism, thrombosis
Parvovirus B19	IgG	Thrombosis
Cytomegalovirus	IgG, IgM	Thrombosis
Human immunodeficiency virus	IgG, IgM, IgA	Leg ulcer necrosis, arterial and venous thrombosis and embolism, vasculitis, livedo reticularis, thrombocytopenia

Antiphospholipid Antibodies

10% of healthy donors, 30-50% of SLE patients

- **LA antibodies** are directed against plasma proteins bound to anionic phospholipids
- **aCL antibodies** are directed against phospholipids bound to proteins
 - Can be IgA, M, or G (subclasses 1-4)
 - IgG (esp G2) associated with a greater risk of APS
- **Anti β_2 GPI antibodies** are directed against a plasma protein that binds phospholipid with high affinity

Antiphospholipid Antibodies

■ **Lupus Anticoagulant (LA) Antibodies**

- Prolonged coagulation in phospholipid-dependent in vitro tests (aPTT, PT, dRVVT)
- Failure to correct with 50:50 mix
- Correction of coagulation time by adding phospholipid

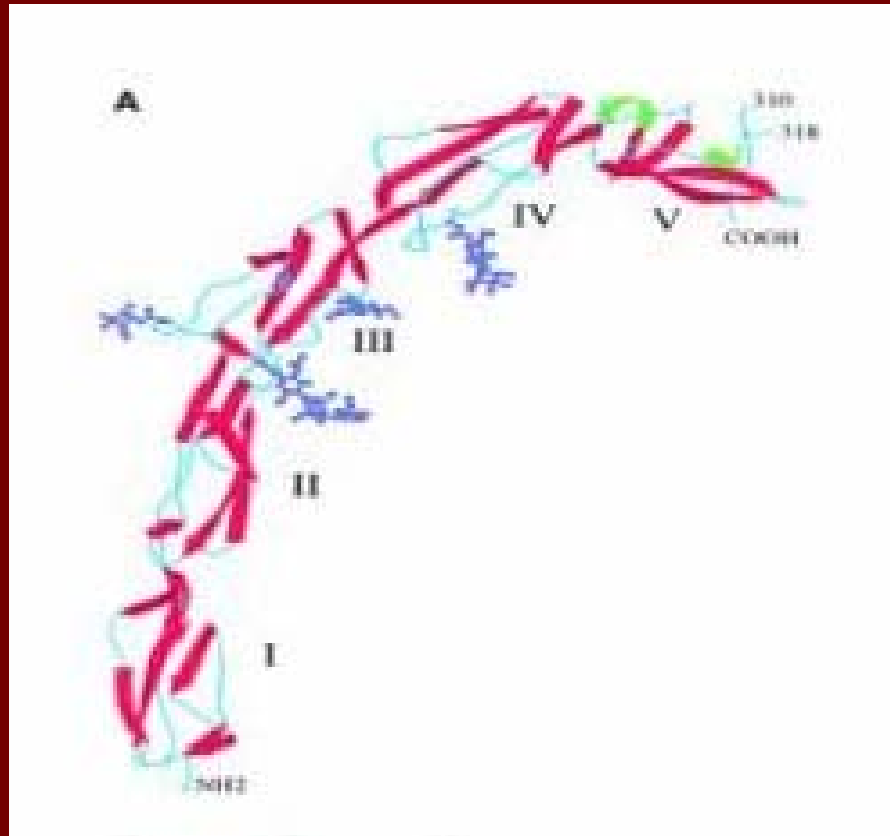
■ **Anticardiolipin (aCL) Antibodies**

- ELISA assay in the presence of bovine B2GPI

■ **Anti-Beta 2 Glycoprotein I Antibodies** **(β_2 GPI)**

- ELISA assay using human B2GPI coated plates
- **most specific**

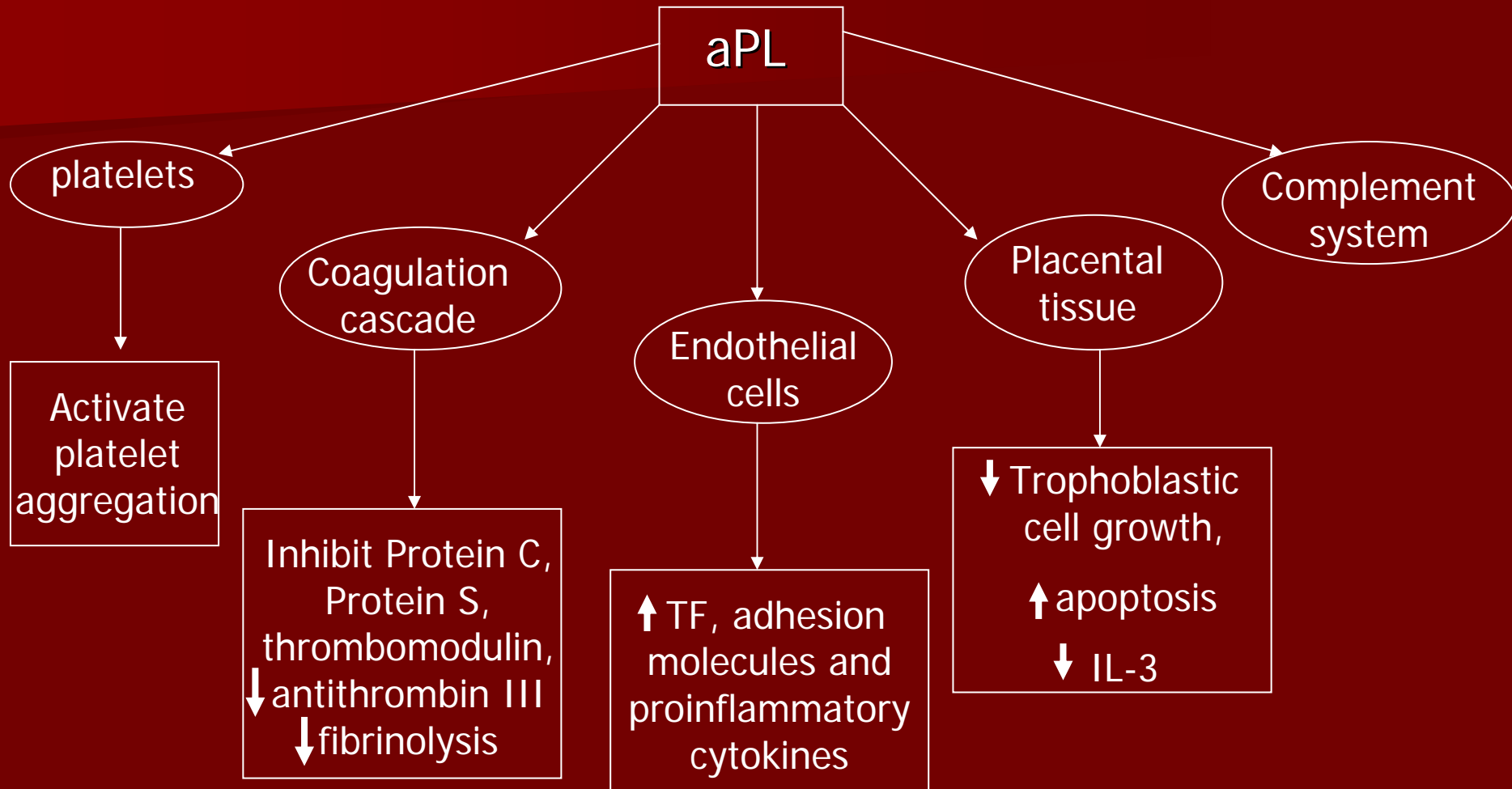
Beta 2 Glycoprotein I



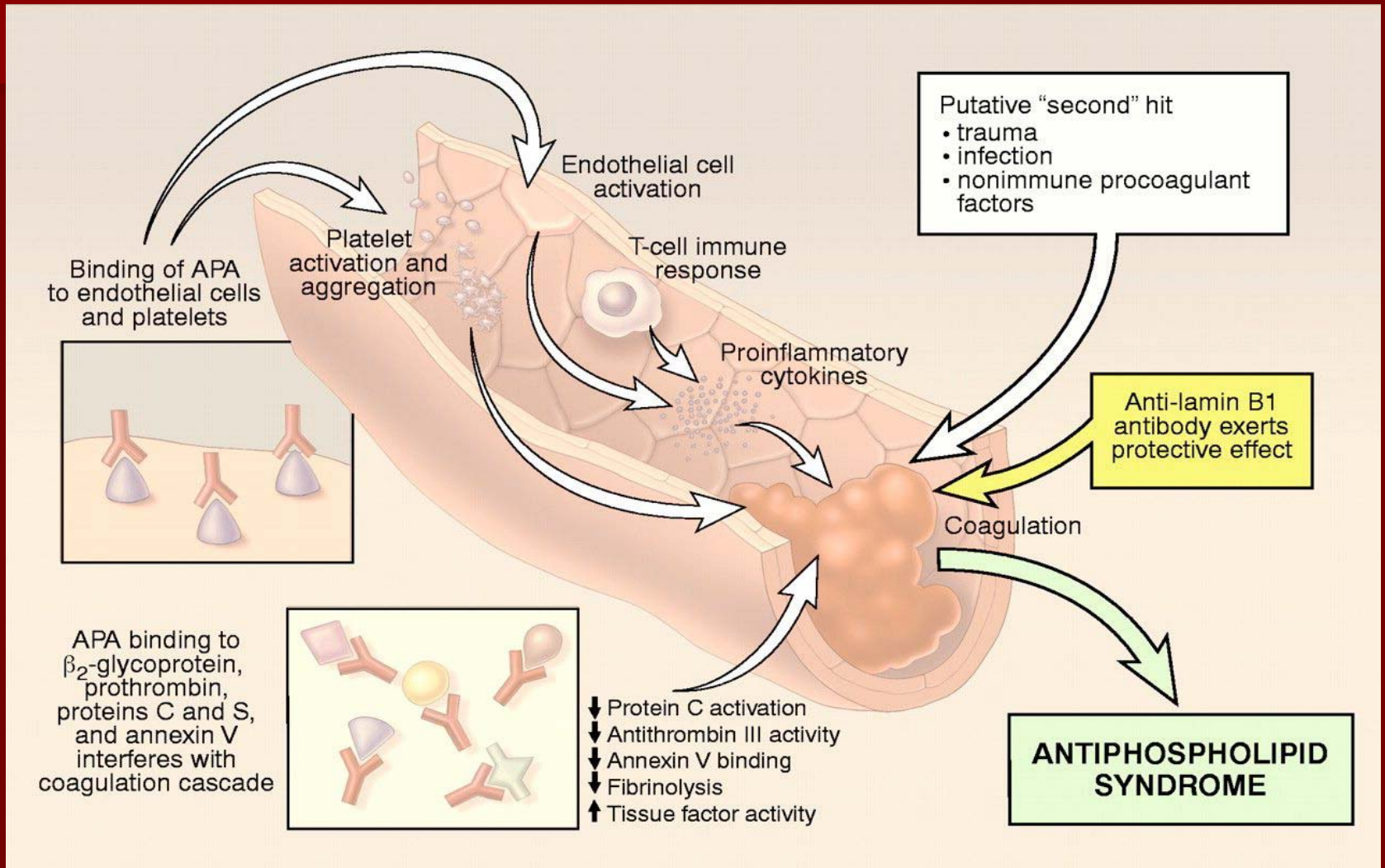
Beta 2 Glycoprotein I

- natural inhibitor of coagulation and platelet aggregation
 - Inhibits contact activation of coagulation cascade
 - Inhibits conversion of prothrombin to thrombin
- most aPL antibodies recognize Domain I of β_2 GPI
- binding of antibody increases binding affinity for phospholipids

APS Pathophysiology



APS Pathophysiology



Diagnosis - Clinical Criteria

- **Vascular thrombosis**: arterial, venous, or small vessel, in any tissue or organ, confirmed by objective validated criteria
- **Pregnancy morbidity**:
 - Unexplained fetal death at or beyond 10 weeks gestation
 - Premature birth before 34 weeks gestation because of eclampsia, severe pre-eclampsia, or placental insufficiency
 - Three or more consecutive spontaneous abortions before 10 weeks gestation

Diagnosis - Laboratory criteria

- **Lupus anticoagulant**, present on at least 2 occasions, at least 12 weeks apart
- **Anticardiolipin antibodies** (ACA), IgG or IgM >30 units for both, present on at least 2 occasions, at least 12 weeks apart
- **Anti-beta-2-glycoprotein I antibodies** (anti-B2GPI), IgG or IgM >20 units for both, present on at least 2 occasions, at least 12 wks apart

A diagnosis of APS should not be made if a period of greater than five years separates the clinical event and positive laboratory test.

Antiphospholipid Syndrome

General features	Both venous and arterial thrombosis Recurrent pregnancy loss Prominent neurological features Occasional thrombocytopenia
Cardiovascular	MI Syndrome X Accelerated atheroma Focal arterial stenotic lesions
CNS	Stroke and TIA Memory loss Movement disorders Seizures Visual disturbance
ENT	Balance problems
Renal	Microvascular thrombosis Renal artery stenosis (and hypertension) Renal vein thrombosis Transplant complications

Gastroenterology	Abdominal angina Bowel infarction Liver function abnormalities Budd–Chiari Syndrome
Skin	Livedo reticularis Skin ulcers
Blood	Thrombocytopenia Marrow ischaemia
Endocrine	Addisons Pituitary infarction
Orthopaedic	Avascular necrosis Ischaemic fractures
Psychiatry	Memory loss
Surgery	Pro-thrombotic risk
Immunology	Related autoimmune diseases

Euro-Phospholipid Study

- 1000 patients with APS: 820 (82%)F, 180 (18%)M, F:M(5:1)
- Mean age at the onset 34 ± 13 years
- 53% primary APS,
36% APS associated to SLE,
5% associated to lupus-like syndrome,
5% associated to other diseases.
- catastrophic APS - 8 (0.8%) patients, in 6 at the onset.

Euro-Phospholipid Study - clinical features in 1000 patients with APS

Manifestations	No.	(%)
<i>Peripheral thrombosis</i>		
Deep vein thrombosis	389	(38.9)
Superficial thrombophlebitis in legs	117	(11.7)
Arterial thrombosis in legs	43	(4.3)
Venous thrombosis in arms	34	(3.4)
Arterial thrombosis in arms	27	(2.7)
<i>Neurologic manifestations</i>		
Migraine	202	(20.2)
Stroke	198	(19.8)
Transient ischemic attack	111	(11.1)
Epilepsy	70	(7)
Multiinfarct dementia	25	(2.5)
Chorea	13	(1.3)
<i>Pulmonary manifestations</i>		
Pulmonary embolism	141	(14.1)
Pulmonary hypertension	22	(2.2)

<i>Cardiac manifestations</i>		
Valve thickening/dysfunction	116	(11.6)
Myocardial infarction	55	(5.5)
Angina	27	(2.7)
Myocardiopathy	29	(2.9)
Vegetations	27	(2.7)
<i>Intraabdominal manifestations</i>		
Renal manifestations	27	(2.7)
Gastrointestinal	15	(1.5)
Splenic infarction	11	(1.1)
Pancreatic infarction	5	(.5)
Addison's syndrome	4	(.4)
Hepatic manifestations	7	(.7)
<i>Cutaneous manifestations</i>		
<i>Livedo reticularis</i>	241	(24.1)
Ulcers	55	(5.5)
Pseudovasculitic lesions	39	(3.9)
Digital gangrene	33	(3.3)

Euro-Phospholipid Study - clinical features in 1000 patients with APS

Ophthalmologic manifestations

Amaurosis fugax	54	(5.4)
Retinal artery thrombosis	15	(1.5)
Retinal vein thrombosis	9	(.9)
Optic neuropathy	10	(1)

Hematological manifestations

Thrombocytopenia (< 100,000/ μ l)	296	(29.6)
Hemolytic anemia	97	(9.7)

Obstetric manifestations (pregnant female = 590)

Pre-eclampsia	56	(9.5)
Eclampsia	26	(4.4)

Fetal manifestations (pregnancies = 1580)

Early fetal losses (< 10 weeks)	560	(35.4)
Late fetal losses (> 10 weeks)	267	(16.9)

Autoimmunity reviews 7,
2008: 174-178.

Catastrophic APS

Preliminary criteria:

1. Involvement of three or more organs or tissues
2. Development of manifestations simultaneously or in < 1 week
3. Histopathologic evidence of small-vessel occlusion in at least one type of tissue
4. Presence of lupus anticoagulant, anticardiolipin antibodies or both

Definite diagnosis:

All four criteria met

Probable diagnosis:

2 organs or tissues involved, and the 2nd, 3rd and 4th criteria met; or

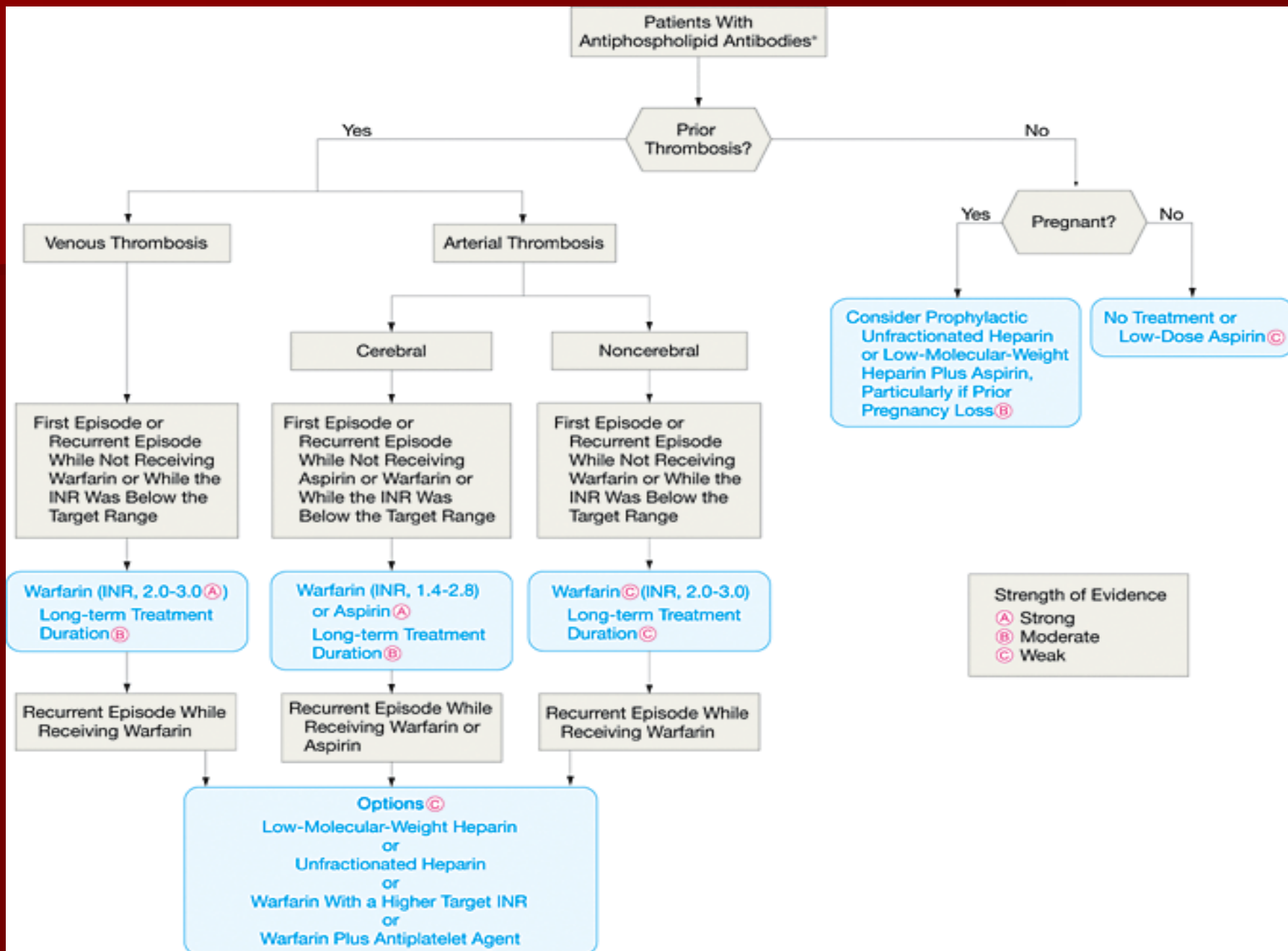
All 4 criteria met and negative test for LA or anticardiolipin antibody > 6 wks after the first positive test or death within that period; or

First, 2nd and 4th criteria met; or

First, 3rd and 4th criteria met and development of a third manifestation in >1 wk but <1 mo despite anticoagulation

APS Treatment

- **Pregnancy loss - 90% benefit with ASA and LMW heparin**
- **In pregnancy, treat with ASA + LMWH even without history of thrombosis**
- **Venous thrombosis - high risk of recurrence**
- **If INR > 3, improved outcome over 2 years**
- **10% risk of recurrence on anticoagulants**
- **Asymptomatic - no treatment (?ASA)**



Future directions of treatment of APS

- Peptide-specific therapy: peptide with B2GPI epitopes recognized by aPL or B2GPI blocking Ab
- Inhibitors of intracellular signaling triggered by aPL
- Complement activation inhibitors
- Anti-TNF α agents
- Anti CD20 agents

Case scenario

- Anticoagulated with LMWH
- Started on coumadin
- Started on high dose prednisone
- ACEi for hypertension and proteinuric renal failure
- CCB, nitro patch, bupropion

Follow-up after 2 months

Presented to ER with:

- 3 wks hx of retrosternal CP, SOB and fatigue, Raynoud's phenomenon of R hand and visual changes

Patient non-adherent with recommended Tx.

- BP 179/100 HR 113
- Dusky R 4th digit, hyperesthesia R 1st digit, necrosis tip of L 3rd digit
- Palpable radial and ulnar pulses, good capillary refill

Trop 0.21, EKG - no ischemia, 2 DEcho - N,

WBC 17.3, Cr 181, INR 1.15, PTT 45.8

Ophthalmology ex - BRVO, macular edema, HTN
retinopathy

Summary

- APS – under-recognized autoimmune disease that accounts for a significant proportion of thromboembolic disease and recurrent pregnancy loss
- The etiology and pathophysiology involves aPL as “first hit” and environmental factors, including infection as “secondary hit”
- APS - complex disorder with evolving diagnostic criteria
- Anticuagulation rather than immunosuppression is the current mainstay of therapy
- Well-designed prospective studies are required to complete the understanding of the optimal treatment.