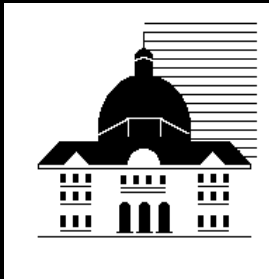


CATASTROPHIC A.P.S.

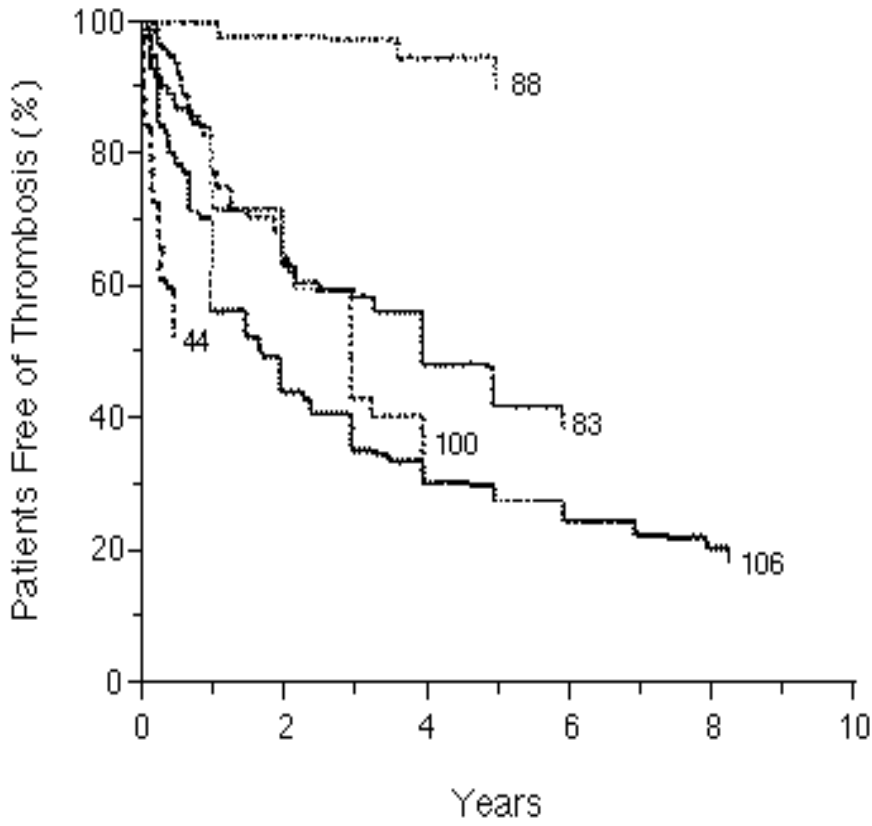
Paris, 2008



Jean-Charles PIETTE
Internal Medicine Department
National Reference Center
Pitié -Salpêtrière Hospital
Paris, France.

**The Management of Thrombosis in the Antiphospholipid-Syndrome.
 Khamashta MA et al
 N Engl J Med 1995, 332:993**

- Warfarin (INR, ≥ 3) with or without aspirin
- Aspirin only
- Warfarin (INR, < 3) with or without aspirin
- No treatment
- During 6 mo after cessation of any warfarin treatment



Kaplan–Meier Analysis of the Interval from Each Episode of Thrombosis or Change in Treatment to the Next Episode of Thrombosis or Censoring Event in the Same Patient, Throughout the Follow-up Period, According to Antithrombotic Treatment.

International consensus statement on preliminary classification criteria for definite APS. Arthritis Rheum 1999, 42: 1309-11

CLINICAL CRITERIA

1. VASCULAR THROMBOSIS (arterial, venous, **or small vessel**)

≥ 1 clinical episodes in any tissue or organ, confirmed by imaging or doppler or histopathology (except for superficial VT) --> no significant vessel wall inflammation.

2. PREGNANCY MORBIDITY

≥ 1 unexplained deaths of a morphologically normal fetus at or **beyond the 10th week of gestation**, with normal fetal morphology (ultrasound or direct examination)

OR

≥ 3 unexplained consecutive abortions **before the 10th week of gestation**, excluding maternal anatomic or hormonal abnormalities and parental chromosomal causes.

OR

≥ 1 premature births of a morphologically normal neonate at or before the 34th week of gestation due to severe (pre)eclampsia or severe placental insufficiency

LABORATORY CRITERIA (2 or more occasions, at least 6 weeks apart)

1. Anticardiolipin antibody IgG and/or M, **MEDIUM** or **HIGH** titer, by a standardized ELISA for β 2-glycoprotein I-dependent anticardiolipin antibodies.

2. Lupus anticoagulant present in plasma according to the guidelines of the ISTH

Definite APS: ≥ 1 of clinical criteria AND ≥ 1 of laboratory criteria

**THE CATASTROPHIC
ANTIPHOSPHOLIPID SYNDROME**

Ronald ASHERSON

J Rheumatol 1992, 19: 508-512

« CATASTROPHIC » APS

SIMULTANEOUS OCCURRENCE

MICRO >> MACROVASCULATURE

MULTIPLE ORGAN FAILURE

kidneys, heart, lung, brain... adrenal

50% DEATH

CATASTROPHIC APS

- **1992** < 10 cases
- **1998** 50
- **2001** 130
- **2008** > 300 cases

**Mortality in the catastrophic antiphospholipid syndrome:
causes of death and prognostic factors in a series of 250 patients.**

Bucciarelli S, et al. Arthritis Rheum 2006 Aug;54:2568-76

Table 1. Demographic, clinical, and laboratory features of 250 patients with CAPS*

Demographics	
Sex, no. female/no. male	177/73
Age at the time of CAPS, mean \pm SD years	37 \pm 14
Diagnosis, no. (%) of patients	
Primary APS	116 (46.4)
SLE	100 (40)
SLE-like	12 (4.8)
Other	22 (8.8)
No. (%) with precipitating factors†	143 (56)
No. (%) with CAPS as the first manifestation of APS	116 (46.4)



Main organ involved, no. (%)†	
Kidney	180 (70.6)
Lung	163 (63.9)
Brain	158 (62)
Heart	131 (51.4)
Skin	128 (50.2)
Liver	85 (33.3)
Intestine	60 (23.5)
Peripheral veins (thrombosis)	59 (23.1)
Spleen	48 (18.8)
Adrenal gland	33 (12.9)
Peripheral arteries (thrombosis)	27 (10.6)
Pancreas	19 (7.5)
Retina	17 (6.7)
Peripheral nerve	12 (4.7)
Bone marrow	10 (3.9)

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APS and the KIDNEY

"APS NEPHROPATHY"

TMA, FIH, organized thrombi,
fibrous arterial occlusion, FCA



HYPERTENSION

Moderate to Malignant

PROTEINURIA

LOSS OF RENAL FUNCTION

RENAL VEIN THROMBOSIS

RENAL INFARCTION

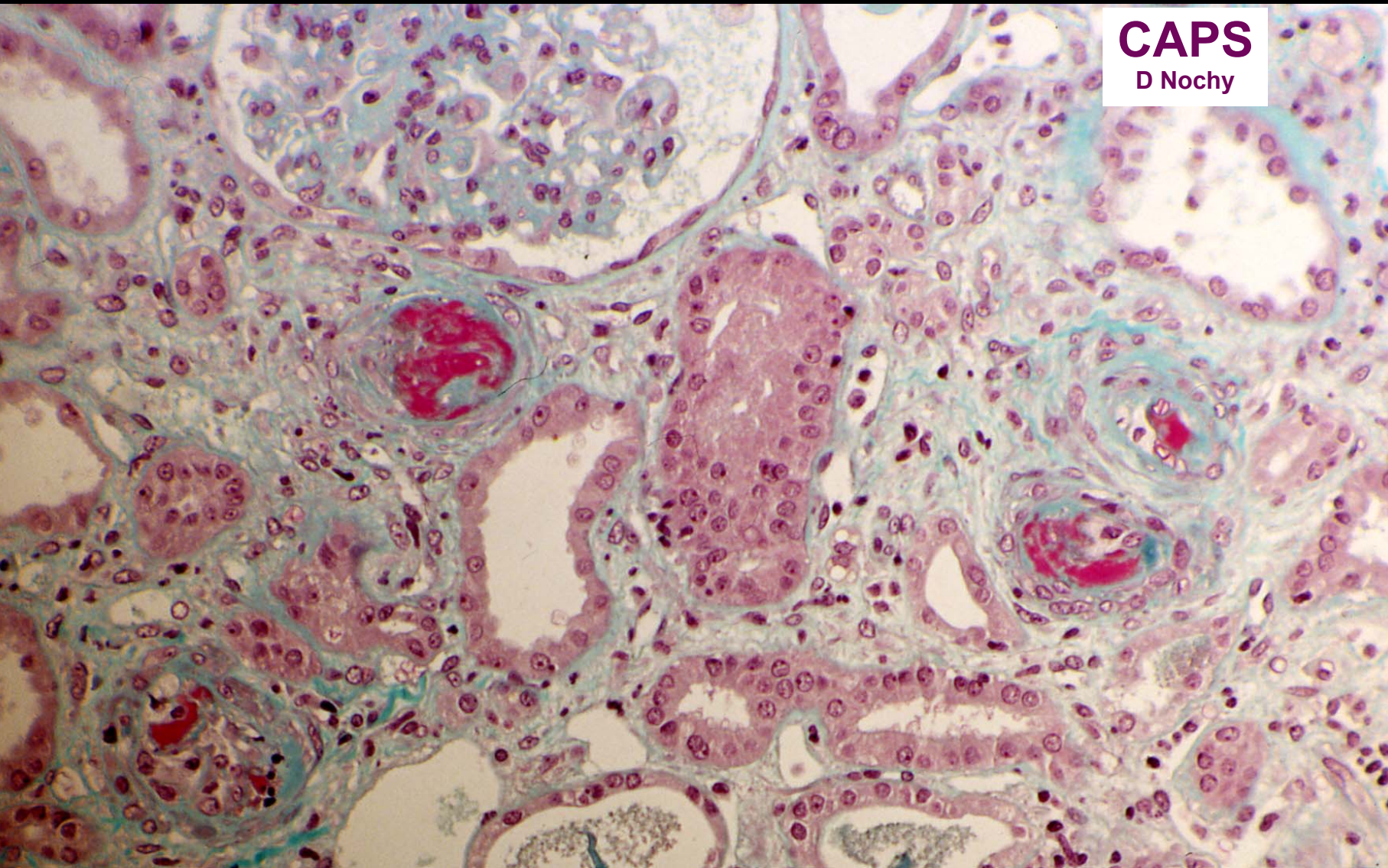
RENAL ARTERY "STENOSIS"

ESRF-APS

AV fistula thrombosis

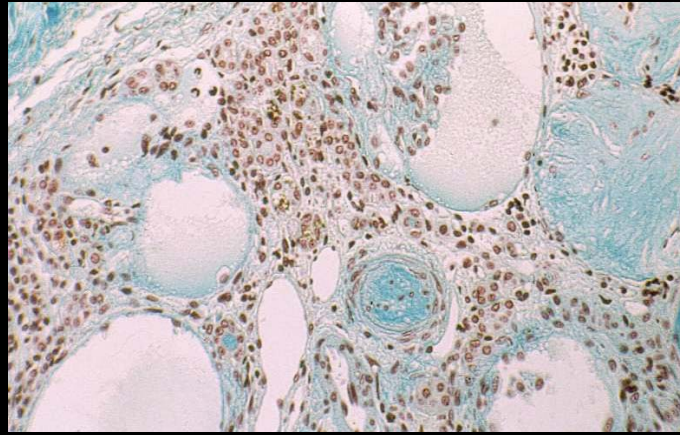
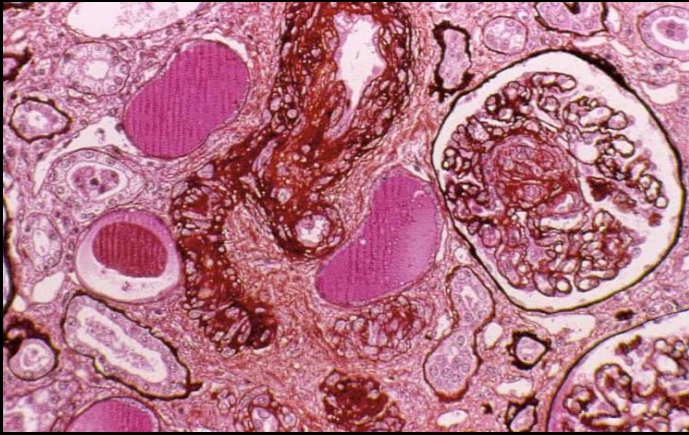
RENAL ALLOGRAFT FAILURE

CAPS
D Nochy



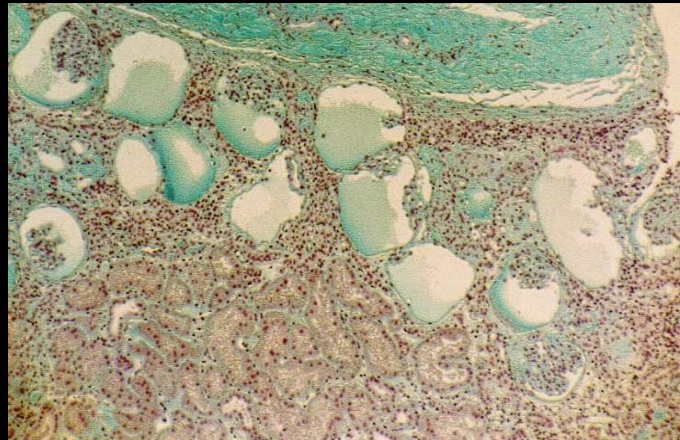
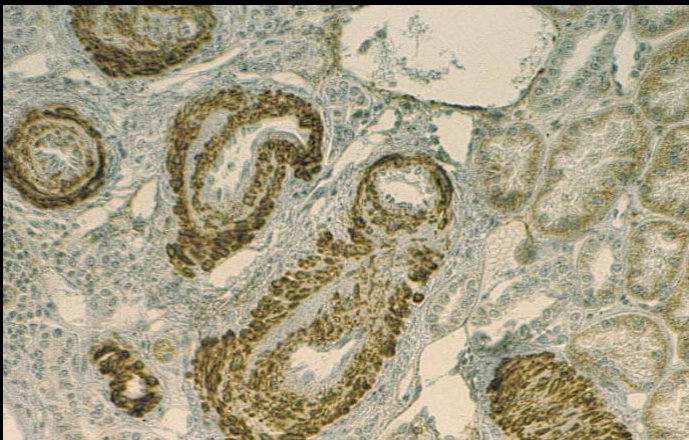
APS nephropathy (APSN)

TMA

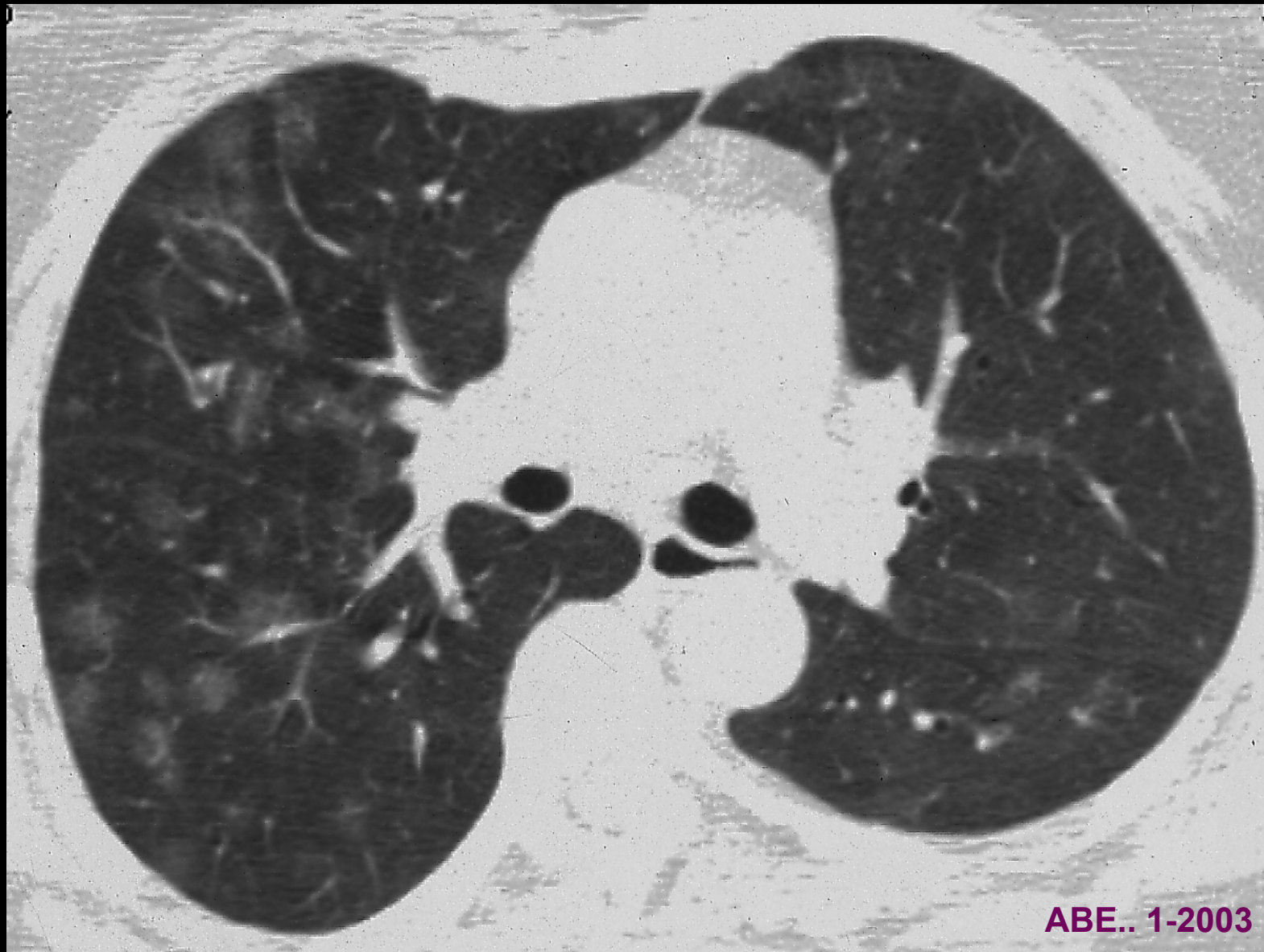


Fibrous
occlusion

FIH



FCA



ABE.. 1-2003

**The acute respiratory distress syndrome in catastrophic antiphospholipid syndrome: analysis of a series of 47 patients.
Bucciarelli S et al. ARD 2006;65:413**

- Pulmonary involvement was reported in 150 of 220 patients with catastrophic APS (68%) and 47 patients **(21%) were diagnosed as having ARDS.**
- Nineteen (40%) of these patients died. Pathological studies were undertaken in 10 patients and thrombotic microangiopathy was present in seven.
- There were no differences in age, sex, precipitating factors, clinical manifestations, or mortality between catastrophic APS patients with and without ARDS.

Main organ involved, no. (%)†	
Kidney	180 (70.6)
Lung	163 (63.9)
Brain	158 (62)
Heart	131 (51.4)
Skin	128 (50.2)
Liver	85 (33.3)
Intestine	60 (23.5)
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Bucciarelli S, et al. Arthritis Rheum 2006 Aug;54:2568-76

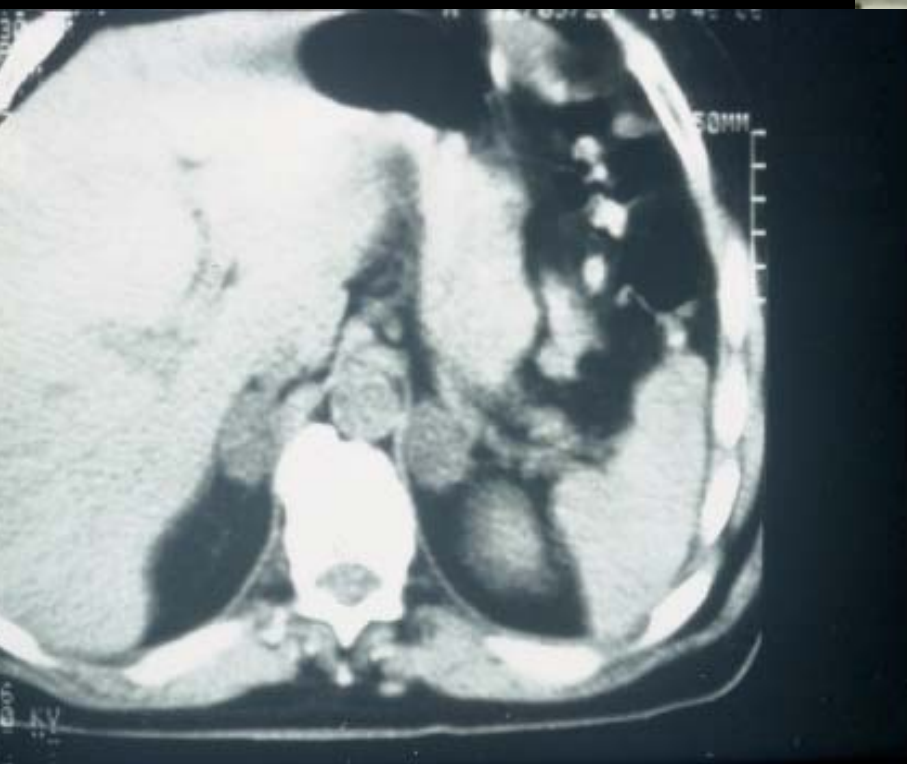




Main organ involved, no. (%)†	
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Lung	163 (63.9)
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Bucciarelli S, et al. Arthritis Rheum 2006 Aug;54:2568-76



**Adrenal involvement in the antiphospholipid syndrome:
clinical and immunologic characteristics of 86 patients.
Espinosa G et al. Medicine (Baltimore) 2003;82:106-18**

Males: 55%

Mean age at presentation : 43 +/- 16 years.

Primary APS: 71%

Within "catastrophic APS " : 33 %

Presenting clinical manifestation of APS: 36%

Symptomatology highly *variable* according to prior steroid treatment

Abdominal pain

Adrenal failure: mainly acute (post-operative) / subacute / rarely chronic

Latency (discovery on CT scan)

Diagnosis

Hormonal status (cortisol, ACTH, stimulation test)

Imaging: CT scan - MRI

LA: 97 % - aCL 93 % (mainly IgG)

Death: 36% of patients with outcome data available

Secondary adrenal atrophy

Main organ involved, no. (%)†	
Kidney	180 (70.6)
Lung	163 (63.9)
Brain	158 (62)
Heart	131 (51.4)
Skin	128 (50.2)
Liver	85 (33.3)
Intestine	60 (23.5)
Peripheral veins (thrombosis)	59 (23.1)
Spleen	48 (18.8)
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**Mortality in the catastrophic antiphospholipid syndrome:
causes of death and prognostic factors in a series of 250 patients.**

Bucciarelli S, et al. Arthritis Rheum 2006 Aug;54:2568-76

and even testes..

**Mortality in the catastrophic antiphospholipid syndrome:
causes of death and prognostic factors in a series of 250 patients.**

Bucciarelli S, et al. Arthritis Rheum 2006 Aug;54:2568-76

Laboratory features, no./no. tested (%)‡	
IgG aCL	197/236 (83.5)
IgM aCL	92/221 (41.6)
IgA aCL	3/71 (4.2)
Lupus anticoagulant	173/223 (77.6)
Disseminated intravascular coagulation	33/221 (14.9)
Thrombotic microangiopathic hemolytic anemia	19/221 (8.6)

* CAPS = catastrophic antiphospholipid syndrome; SLE = systemic lupus erythematosus; aCL = anticardiolipin antibodies.

† In relation to 255 episodes of CAPS.

‡ Lupus anticoagulant (LAC) was present in 173 of 223 patients tested (77.6%). In 63 patients (36.4%), the case records stressed that LAC was detected according to the guidelines of the International Society on Thrombosis and Hemostasis (Scientific Subcommittee on Lupus

THROMBOCYTOPENIA IN *aPS* - II -

PATHOPHYSIOLOGY

Abnormal destruction

Consumptive

DIC, TTP, MΦA

Immune-mediated

ATP

Drug-induced (HIT,..)

Infection

SLE

"P"APS

+++

+++

+

+

++

++

+

+

+

±

rare

Hypoproliferative
 Ineffective thrombopoiesis
 Abnormal distribution
 Dilutional

**CAPS presenting
with
an I.N.R. > 10 ?**

**Mortality in the catastrophic antiphospholipid syndrome:
causes of death and prognostic factors in a series of 250 patients.**

Bucciarelli S, et al. Arthritis Rheum 2006 Aug;54:2568-76

Death:

45 % (pooled data)

33 % (2001-5)

**Mortality in the catastrophic antiphospholipid syndrome:
causes of death and prognostic factors in a series of 250 patients.**

Bucciarelli S, et al. Arthritis Rheum 2006 Aug;54:2568-76

Table 2. Major cause of death and findings of histopathologic studies in patients with CAPS*

	No. (%) of patients with CAPS
Major cause of death (n = 81)	
Cerebral involvement	22 (27.2)
Stroke	15 (18.5)
Cerebral hemorrhage	4 (4.9)
Encephalopathy	3 (3.7)
Cardiac involvement	16 (19.8)
Cardiac failure	14 (17.3)
Arrhythmias	2 (2.5)
Infection	16 (19.8)
Bacterial sepsis	10 (12.3)
Fungal sepsis	3 (3.7)
<i>Pneumocystis carinii</i> pneumonia	2 (2.5)

**Mortality in the catastrophic antiphospholipid syndrome:
causes of death and prognostic factors in a series of 250 patients.**

Bucciarelli S, et al. Arthritis Rheum 2006 Aug;54:2568-76

Autopsy

Histopathologic features (n = 58)	
Microthrombosis	49 (84.5)
Kidney	32 (65.3)
Heart	27 (55.1)
Lung	24 (48.9)
Brain	24 (48.9)
Spleen	12 (24.5)
Skin	11 (22.4)
Gut	10 (20.4)
Liver	10 (20.4)
Adrenal gland	8 (16.3)
Infarction	31 (53.4)
Brain	19 (61.3)
Heart	9 (29)
Spleen	6 (19.4)
Kidney	5 (16.1)
Lung	5 (16.1)
Adrenal gland	3 (9.7)
Thrombosis of large vessels	11 (18.9)
Pulmonary embolism	7 (12.1)
Nonbacterial thrombotic endocarditis	16 (27.6)
Acute respiratory distress syndrome	4 (6.8)
Alveolar hemorrhage	3 (5.2)
Budd-Chilari syndrome	1 (1.7)
Adrenal hemorrhage	1 (1.7)

**Mortality in the catastrophic antiphospholipid syndrome:
causes of death and prognostic factors in a series of 250 patients.**

Bucciarelli S, et al. Arthritis Rheum 2006 Aug;54:2568-76

Prognostic factors

Higher death rate :

- SLE 59 vs 38 % (p = .003)**
- ANA 66 vs 49 % (p = .02)**
- No anticoagulant...
78 vs 37 % (p < .00001)**

Mortality in the catastrophic antiphospholipid syndrome:
causes of death and prognostic factors in a series of 250 patients.

Bucciarelli S, et al. Arthritis Rheum 2006 Aug;54:2568-76

Treatment in 242 episodes

Treatment used

Anticoagulation	85 %
Steroids	78 %
Cyclophosphamide	31 %
Plasmapheresis	30 %
Ig IV	21 %

Recovery according to treatment

anticoagulation 63 % vs 22 % ($p < 0.0001$)

anticoagulation + steroids + PE 78% (NS)

anticoagulation + steroids + PE and/or IViG

ANTI-PHOSPHOLIPID SYNDROME

GOAL: TRY TO

ELIMINATE
CIRCULATING
AP ANTIBODIES

PREVENT THEIR
"DELETERIOUS"
EFFECTS

SHORT TERM

Sometimes

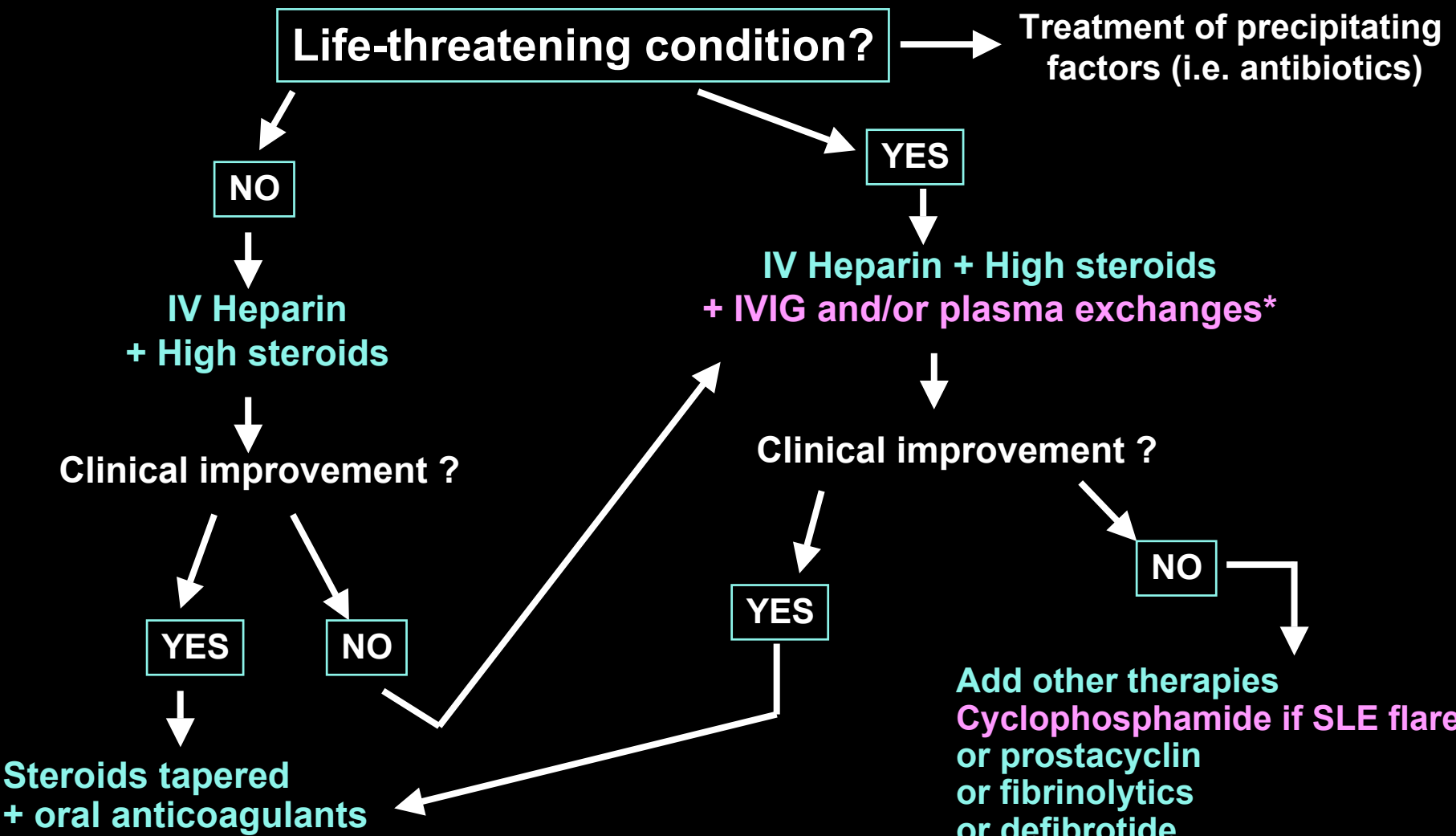
+++

LONG TERM

Utopian and/or
Hazardous *

++

Clinical suspicion of catastrophic APS



Long term outcome of catastrophic antiphospholipid syndrome survivors.
Erkan D, Asherson RA, Espinosa G, Cervera R, Font J, Piette JC, Lockshin MD.
Ann Rheum Dis. 2003;62(6):530-3

63/136 (46%) patients died at the initial event. Of the remaining 73 patients, information was available for 58 (79%).

Thirty eight (66%) patients did not develop further APS related events during an average follow up of 67.2 months.

Eleven (19%) patients developed further APS related events but were still alive.

No patients developed further catastrophic APS.

Nine (16%) patients died: due to multiple organ failure (three patients); myelofibrosis (one); pneumonia (one); and APS related events (four).

+ Residual damage...

CAPS - DIAGNOSIS

Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines.

Asherson RA et al. Lupus 2003;12:530-534

- 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 (lupus anticoagulant and/or anticardiolipin antibodies)*****

* Usually, clinical evidence of vessel occlusions, confirmed by imaging techniques when appropriate. **Renal involvement is defined by a 50 % rise in serum creatinine, severe systemic hypertension (>180/100 mm Hg) and/or proteinuria (>500 mg/24 hours).**

** For histopathological confirmation, significant evidence of thrombosis must be present, although vasculitis may coexist occasionally.

*** If the patient had not been previously diagnosed as having an APS, the laboratory confirmation requires that presence of antiphospholipid antibodies must be detected on

Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines.

Asherson RA et al. Lupus 2003;12:530-534

- 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 (lupus anticoagulant and/or anticardiolipin antibodies)**

- Definite catastrophic APS:**

- All 4 criteria

- Probable catastrophic APS:**

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

Classification algorithm of catastrophic APS

Evidence of involvement of organs, systems, and/or tissues and
Development of manifestations simultaneously or in less than a week* and
Laboratory confirmation of the presence of aPL

**≥3 organs/
systems/tissues**

**2 organs/
systems/tissues**

Confirmation by histopathology of small vessel
occlusion in at least 1 organ or tissue

YES

NO

YES

NO

DEFINITE

PROBABLE

PROBABLE

NO

Validation of the preliminary criteria for the classification of catastrophic APS.

Cervera R, et al

Ann Rheum Dis 2005;64:1205-9

It should be emphasized that these criteria are mostly empirical and have been accepted for classification purposes and *are not intended to be used as strict diagnostic criteria in a given patient.*

Catastrophic APS: Differential diagnosis

T.T.P. and other TMA

Heparin I.T. - including adrenal -

Endocarditis, bacterial

Endocarditis, marantic (cancer)

Myxoma

Cryoglobulinemia

...

Amoura Z, Costedoat-Chalumeau N, Veyradier A, Wolf M, Ghillani-Dalbin P, Cacoub P, Meyer D, Piette JC.

Thrombotic thrombocytopenic purpura with severe ADAMTS-13 deficiency in two patients with primary antiphospholipid syndrome.

Arthritis Rheum 2004;50:3260-3264

Catastrophic APS: Differential diagnosis

T.T.P. and other TMA

Heparin I.T. - including adrenal -

Endocarditis, bacterial

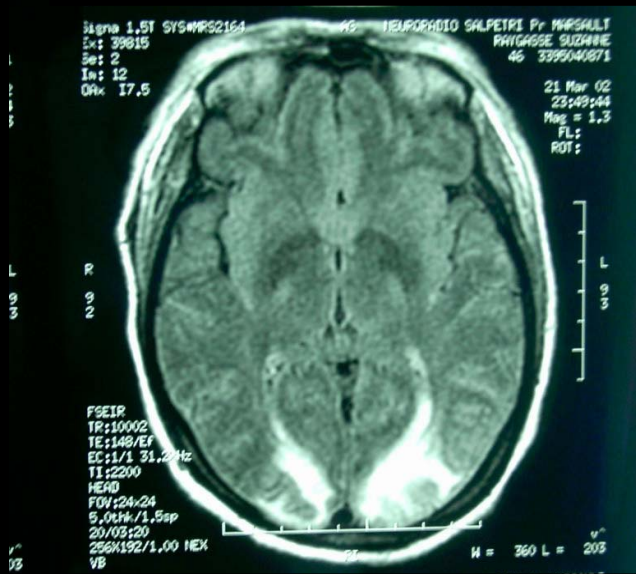
Endocarditis, marantic (cancer)

Myxoma

Cryoglobulinemia

...

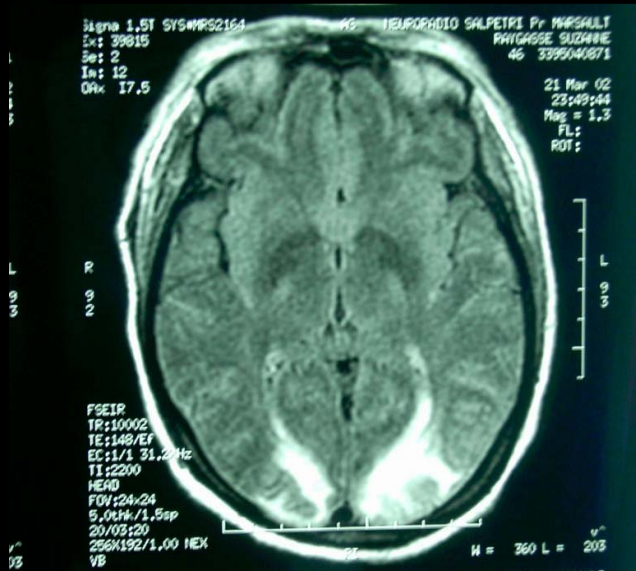
P.R.E.S.



RAYG. S.

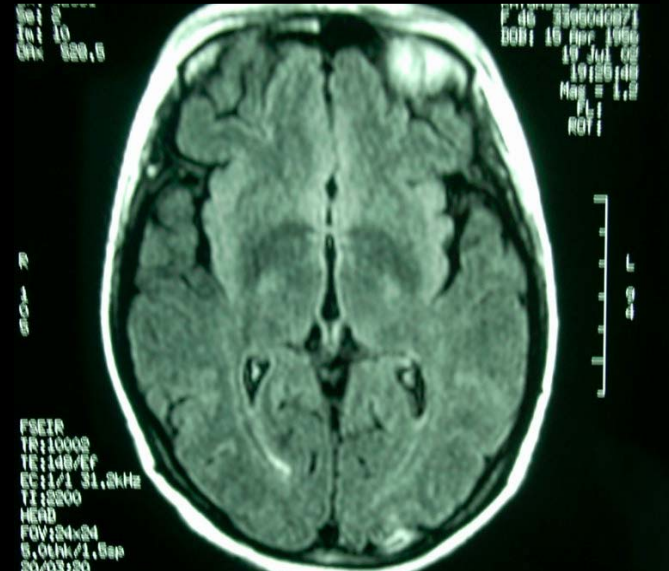
March 2002 Renal failure, Hypertension

Posterior Reversible Encephalopathy Syndrome



March 2002

RAYG. S.



July 2002

CATASTROPHIC APS

« Prevention » ...

Most common precipitating factors in 80 patients with catastrophic APS

Infections		35%
Respiratory tract	15 %	
Cutaneous	8 %	
Urinary tract	6 %	
Surgery, trauma & invasive procedures		13%
Neoplasia		8%
Anticoagulation withdrawal* / low INR		8%
Obstetric complications**		6%
Lupus flares		5%
Oral contraceptives		3%
No factor identified		35%

* 2 days...

** O.I.T.

Not in this series

Perioperative medical management of antiphospholipid syndrome: Hospital for Special Surgery experience, review of the literature and recommendations. From Erkan D, Leibowitz E, Berman J, Lockshin MD. *J Rheumatol* 2002; 29: 843-9.

Preoperative assessment

Surgical and interventional procedures should be the last option in the management of APS patients

Platelet >100,000/ μ l due to APS requires no specific therapy; thrombocytopenia does not protect against thrombosis

Perioperative considerations

Minimize intravascular manipulation for access and monitoring

Prevent infective endocarditis

Set pneumatic blood pressure cuffs to inflate infrequently to minimize stasis in the distal vascular bed

Avoid tourniquets

Maintain high suspicion that any deviation from a normal course may reflect arterial or venous thrombosis

Collapse may result from adrenal involvement

Perioperative anticoagulation

Keep periods without anticoagulation to an absolute minimum

Employ pharmacologic and physical antithrombosis interventions vigorously and start immediately before the operation, continuing until the patient is fully ambulating

Be aware that APS patients can develop recurrent thrombosis despite appropriate prophylaxis

Be aware that current conventional doses of antithrombotic agents can result in underanticoagulation ;

APS patients may benefit from an aggressive approach with higher-than-standard doses

Thanks