Vasculitis
Workshop

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CANADIAN VASCULITIS NETWORK
CANVASC

VASCULITIS CLINICAL RESEARCH CONSORTIUM

Disclosures (CPx)

- Speaker and consultant fees:
  - Roche (<10,000 CAD)
  - GSK (<10,000 CAD)

- Subventions for CanVasc
  - Roche
  - Euroimmun
  - AARC (grant)

Disclosures (LF)

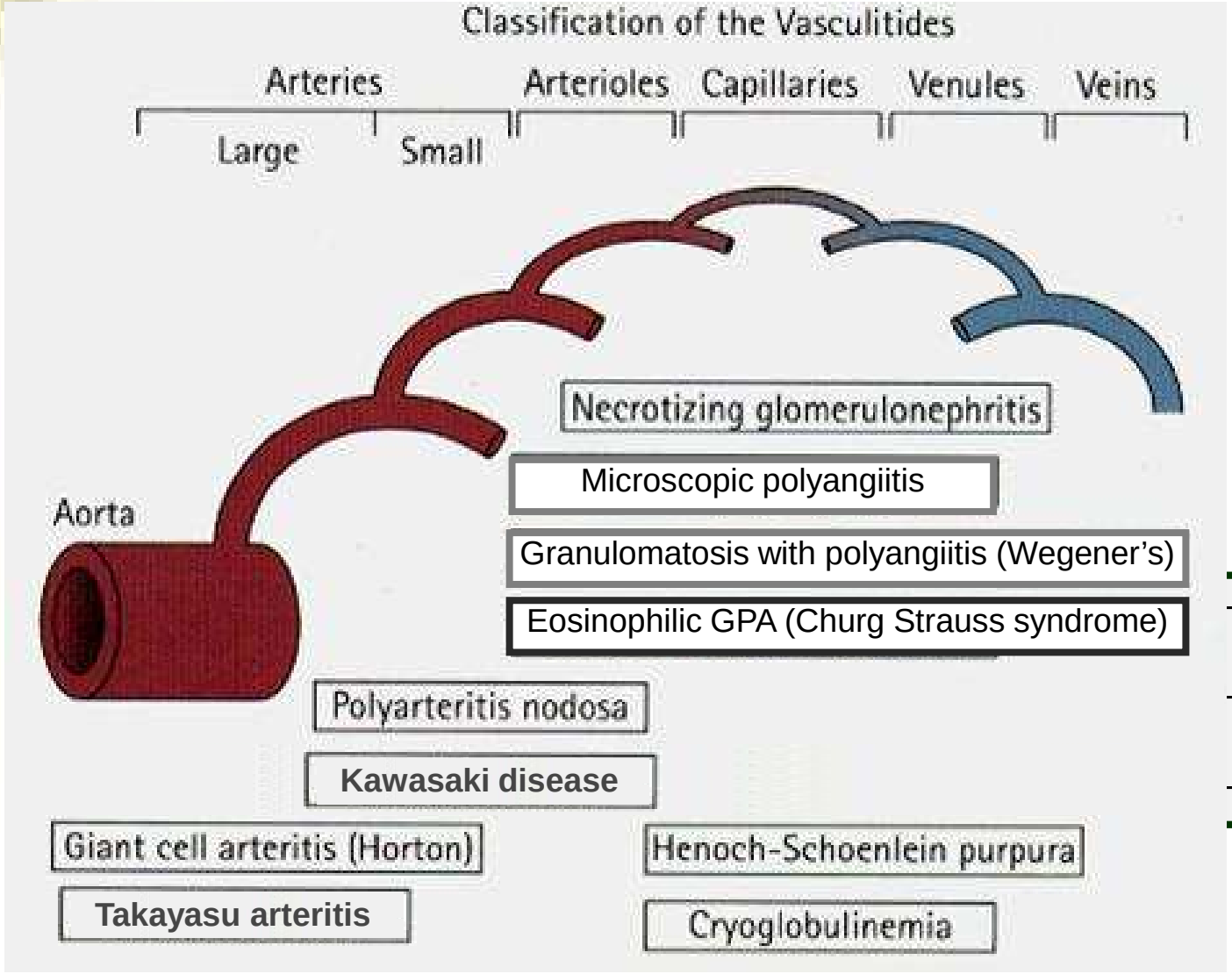
- None

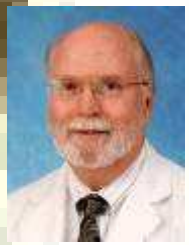
Objectives

- Review
  - some typical vasculitis cases
  - some challenging vasculitis cases

- Review
  - some therapeutic fundamentals in vasculitis
  - some of the unanswered questions…

Chapel Hill Nomenclature





+ antiGBM

+ Behçet

+ CNS-V

Jennette et al. Arthritis Rheum 1994;37:187-92
Falk et al. Arthritis Rheum 2011 Apr;63(4):863-4

Case #1

- 52M with recurrent lesions in both feet

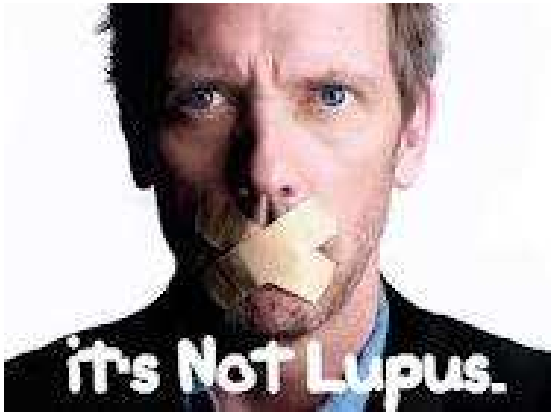
  20 -30 years (2-3X / year)
- 8 months – shins, buttocks, thighs, forearms, and abdomen
- Macular, red, pruritic that develop into purpuric lesions
- Lasts for a week then spontaneously resolves

Case #1

- Swelling in both arms with cold exposure
- Fever and joint pain in both knees
- No other systemic manifestation of a vasculitis

- Family History
  - Father was Hep C (+) / had similar lesions

Differentials ?



A. Cutaneous PAN

B. ANCA associated vasculitis

C. Urticarial vasculitis

D. Cryoglobulinemic vasculitis

E. HCV/non HCV cutaneous porphyria tarda?

F. Other (allergy; T cell lymphoma; mastocytosis…)

Case #1

- Past Medical History /Social History
  - Hypertension and Dyslipidemia
  - Previous smoker, non alcoholic beverage drinker
  - Previous use intranasal cocaine, marijuana no IV drug use, (+) tattoo
  - Hepatitis C diagnosed 10 years ago – routine blood tests / treated with ribavarin and interferon (2002/2004/2010)

Cryoglobulinemic Vasculitis

- Cryoglobulin Syndrome*

- Hepatitis C virus related versus

Non Hepatitis C virus related

(infections, connective tissue diseases, malignancies)

Cryoglobulinemic Vasculitis

- Type I – Isolated monoclonal Ig*
- Type II — mixture of polyclonal Ig in association with a monoclonal Ig, typically IgM or IgA, with rheumatoid factor activity
- Type III — Mixed cryoglobulins consisting of polyclonal immunoglobulins*

Cryoglobulinemic Vasculitis

Preliminary Classification Criteria

>Fever (low grade) , fatigue*

>Articular Involvement*

>Vascular Involvement (purpura,skin ulcers, necrotic skin lesions, Raynaud's, hyperviscocity syndrome)

>Neurological Involvement

(3/4 items sens 70.2% spec 84.5%)

De Vita et al Ann Rheum 2011;70: 1183-90

Cryoglobulinemic Vasculitis

Preliminary Classification Criteria

Laboratory / Investigations

- Reduced C4
- M protein
- (+) RF Plus

With (+) serum cryoglobulins

2/3 (sens 84.2% spec 79.6%)

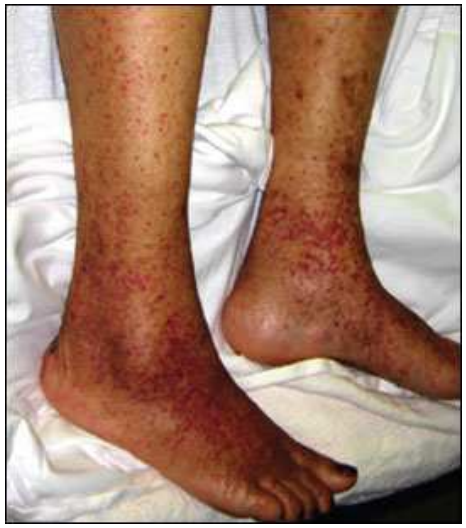
De Vita et al Ann Rheum 2011;70: 1183-90

Cryoglobulinemic Vasculitis

	HCV	Non HCV
Mean age	63.5	58.7
Liver involvement	81% (188/230)	11%(5/42)
Sicca syndrome	24%(56/230)	71%(30/42)
Malignant Lymphoproliferation	18%(42/230)	35% (15/42)

De Vita et al Ann Rheum 2011;70: 1183-90

Case #1



- PE
- Stable vital signs
- No stigmata of liver disease
- Pupuric lesions on the extremities (shins, feet and forearms)
- No synovitis

Case #1

- Labs
- CBC , renal function INR, PTT normal
- ALT 59 , AST 38, ALP 44, GGT 54, Albumin 43
- Cryoglobulin 4 degrees (+) , RF (+) , M protein (+), low C4
- antiCCP negative, ANA and ANCA negative
- CRP 0.6 ESR 24
- Biopsy : leukocytoclastic vasculitis

Therapeutic options?

A. Restart antiviral therapy

B. Corticosteroids

C. Cyclophosphamide

D. Rituximab

E. PLEX

F. IVIG

Cryoglobulinemic Vasculitis
Treatment

Non HCV related

Treatment of underlying disease

(lymphoproliferative disorder or connective tissue disease)

Cryoglobulinemic Vasculitis

Treatment

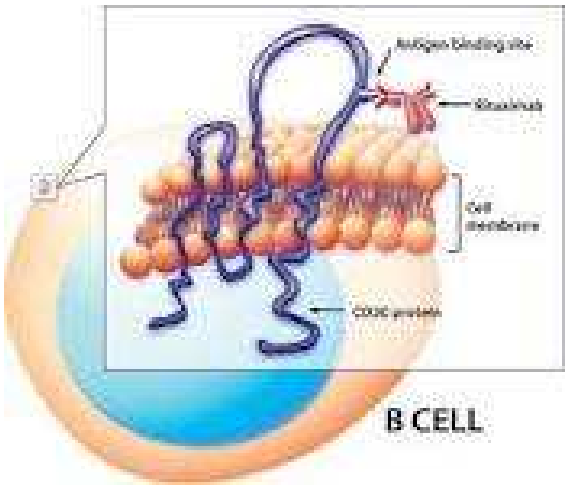
- HCV related
- Interferon alpha - relapses
- Interferon alpha and Ribavarin – more efficacious
- (?) non –responders vs intolerance*

St Clair et al Arthritis & Rheum 64(3)March 2012;604-608

Case #1

- Prednisone – lowest dose 20mg
- Rituximab 375 mg/m2 x 4 weeks

- Remission !



Cryoglobulinemic Vasculitis

Rituximab (RTX)

- Single center open label RCT
- RTX versus best available therapy
- Failed antiviral therapy
- 24 patients enrolled
- Primary endpoint : disease remission in 6 months (BVAS)
- Secondary endpoints: duration of remission & occurrence of severe adverse events *Sneller et al Arthritis and Rheumatism; 64(3) March 2012: 835-842*

Cryoglobulinemic Vasculitis

Rituximab (RTX)

Baseline characteristics – similar

- Remission RTX 83.3% vs 8.3% Control (*p= <0.001*)*
- BVAS – comparable baseline > lower RTX group (*p=0.02*)
- Median duration of remission 7 months
- RTX group : no increase or initiation of immunosuppressive therapy*

- *Sneller et al Arthritis and Rheumatism; 64(3) March 2012: 835-842*

Cryoglobulinemic Vasculitis

Rituximab (RTX)

Labs…

- Peripheral blood B cell depletion* -11/12 RTX
- Cryoglobulins – lower in RTX group

  (*p= less than 0.05*)*

  Complement levels – increased in RTX group *

  HCV replication – not affected by RTX *

Sneller et al Arthritis and Rheumatism; 64(3) March 2012: 835-842

Cryoglobulinemic Vasculitis

Rituximab (RTX)

Adverse events

- Infusion reaction (RTX group)
- No serious infection/ hospitalizations*
- Elevated hepatic transaminase levels : mild and similar in both groups
- No Hypogammaglobulinemia in RTX group
- GFR: Stable RTX group

Sneller et al Arthritis and Rheumatism; 64(3) March 2012: 835-842

Cryoglobulinemic Vasculitis

Rituximab

- RCT Rituximab for the treatment of severe Cryoglobulinemic Vasculitis.

- 59 patients *Randomized 1:1
- Non-Rituximab vs Rituximab
- Endpoints : survival of treatment

De Vita et al, Arthritis and Rheumatism 64(3) ; March 2012 ; 843-853

Cryoglobulinemic Vasculitis

Rituximab

- Superiority of Treatment

  RTX group 63.2% vs Non RTX 4.4%

  (p= <0.0001)

Survival Treatment

  RTX group 64.3% vs Non RTX 3.5%

(p= <0.0001)

De Vita et al, Arthritis and Rheumatism 64(3) ; March 2012 ; 843-853

Cryoglobulinemic Vasculitis

Plasma Exchange

- Case Reports *
- Aim is to clear cryoglobulins and lower viral load
- Severe life threatening renal, neurological, cutaneous manifestations unresponsive to therapy

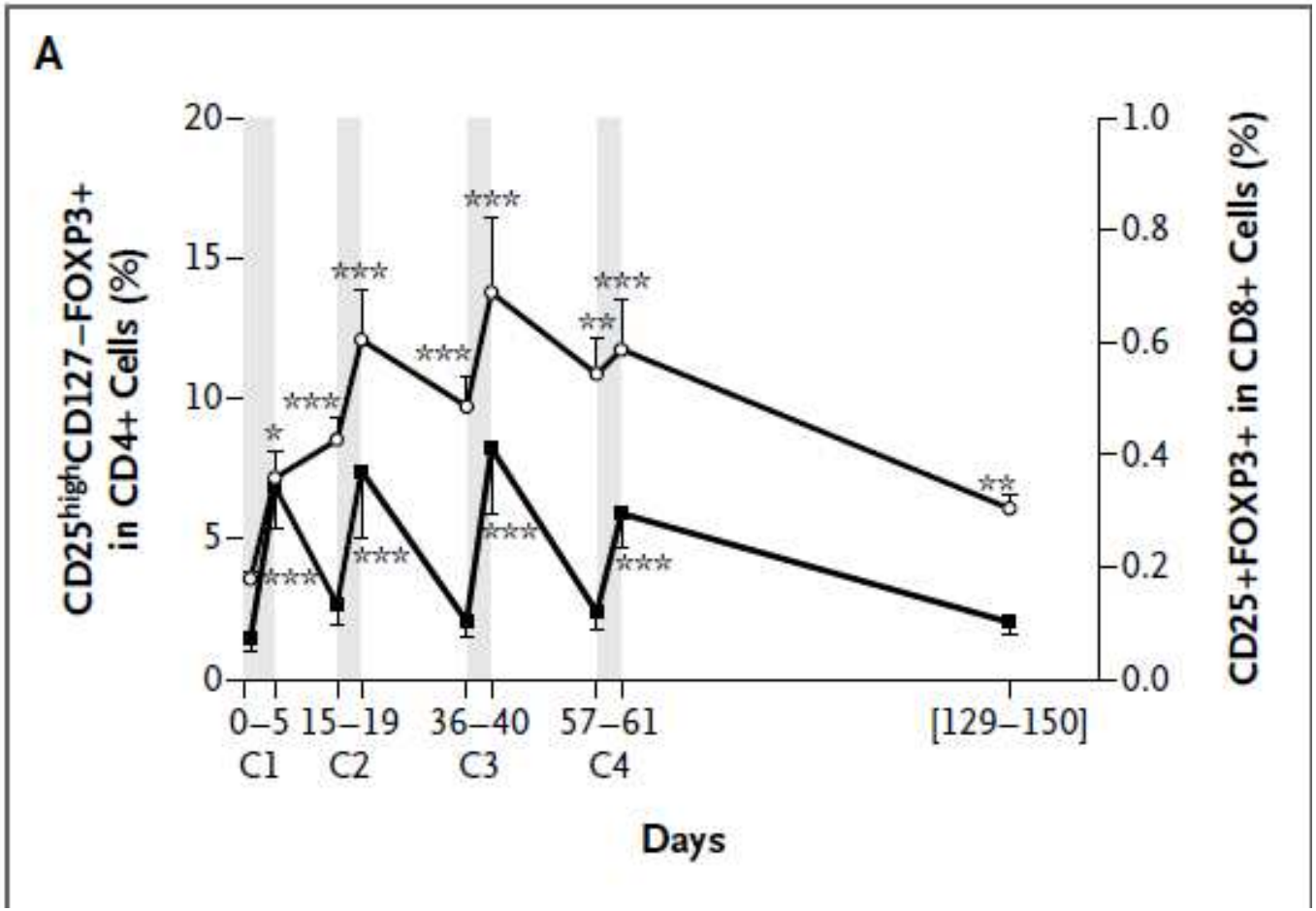
- Mahr et al: Current Opinion 24(3) May 2012 ; 262 - 266

Cryoglobulinemic Vasculitis Interleukin 2

- Single center open label prospective study
- 10 patients with chronic HCV infection with cryoglobulinemic vasculitis
- Resistance or intolerance to antiviral therapy
- Four courses of IL2
- Primary endpoint : increase in, CD25,CD4, FOXP3+

Saadoun et al;NEJM 2011; 365;22 (2067-2077)

Cryoglobulinemic Vasculitis Interleukin 2



- Saadoun et al;NEJM 2011; 365;22 (2067-2077

Case #2

Woman, 70 years-old

Lives alone, 4 healthy daughters & 2 sons

HTN

Otitis in childhood

Non smoker, non drinker

(no recreational drugs)

Case #2

For 1 month: R otitis

→ mastoiditis with R facial palsy

→ mastoidectomy + ceftriax + ciproflox

Creatinine 74 micmol/l, normal CBC

Case #2

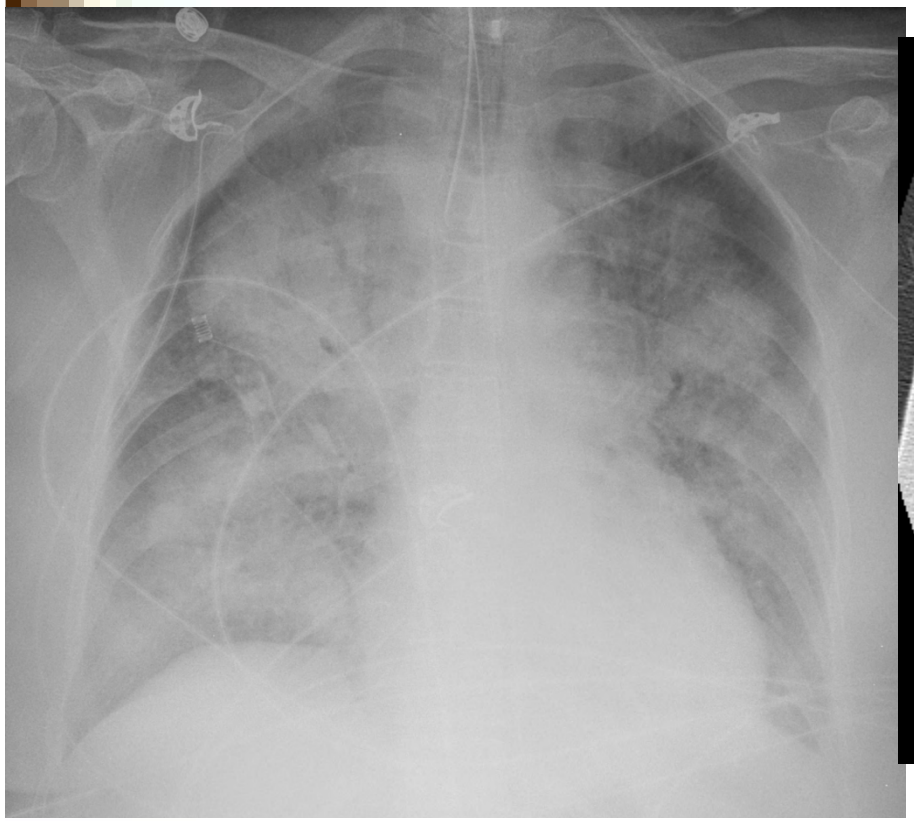
1 week later: fever, SOB, then “septic shock”

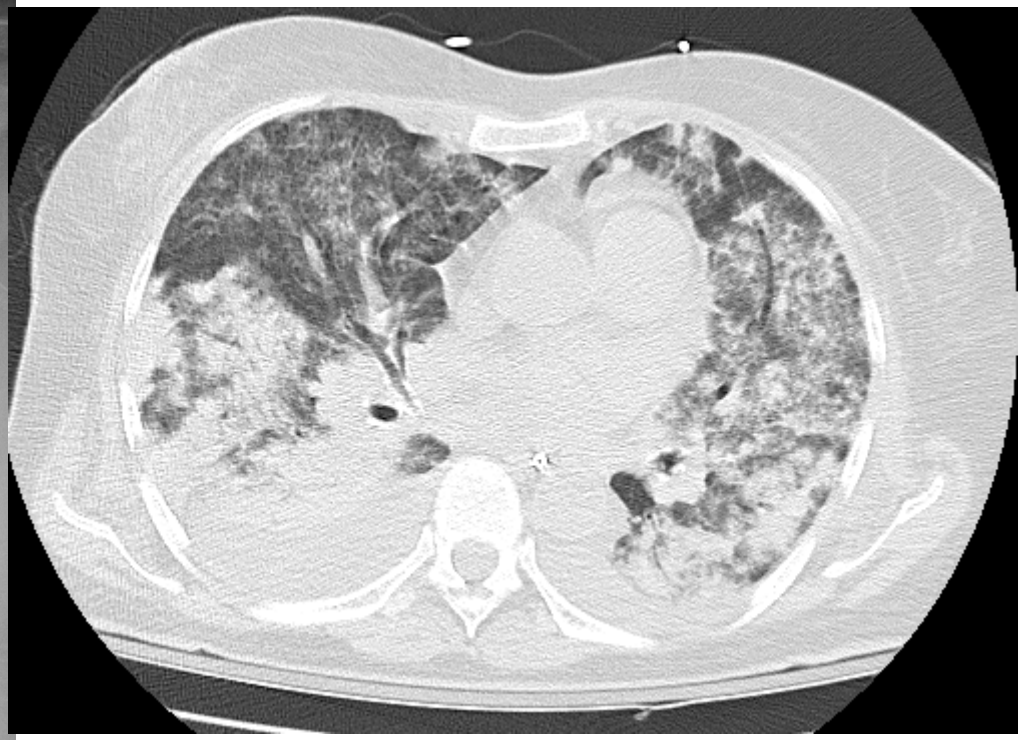
Persistent purulent discharge from R ear

Creatinine 484 micmol/l, Hb 75 g/l
pO2 at 57, SatO2 at 87% under 4 l/min

→ Mechanical ventilation

Case





Case

Bronchoscopy with BALF = alveolar hemorrhage, no germ

Urine = protein 3+, hematuria +

→Tazo + meropenem, dialysis

Case

No skin or neurologic involvement

Normal echocardiography and brain CT scan

ICU? PLEX?

Case

No skin or neurologic involvement

Normal echocardiography and brain CT scan

cANCA antiPR3 > 8 IU

(urine: red blood cell casts)

Biopsy?

Treatment of GPA and MPA

- Non-severe MPA (FFS) = CS alone

Gayraud et al, Arthritis Rheum 2001;44:666-75

- Limited/early systemic GPA = CS + MTX

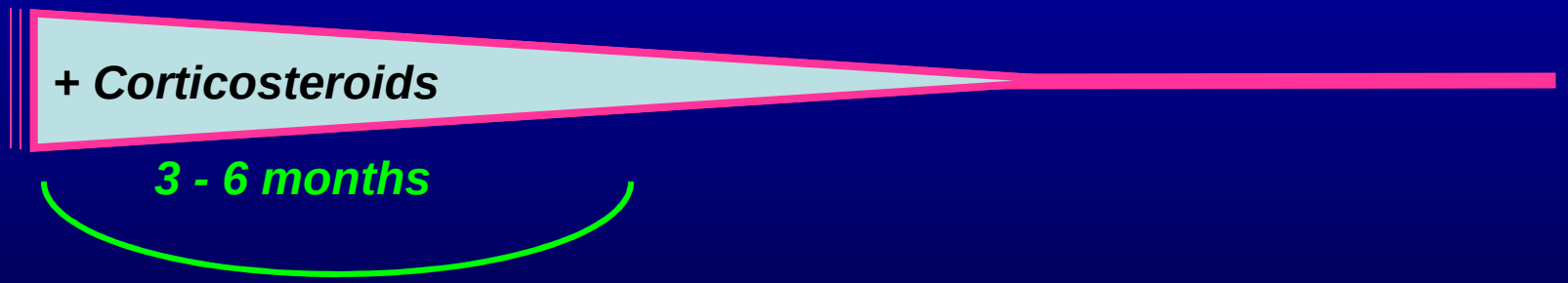
de Groot et al. Arthritis Rheum 2005;52:2461–9

- Severe/systemic GPA and severe MPA = STAGED INDUCTION-MAINTENANCE STRATEGY

Jayne et al, N Engl J Med 2003;349:36-44
Pagnoux et al, N Engl J Med 2008;359:2790-803
Metzler et al. Rheumatology (Oxford). 2007 Jul;46(7):1087-91
Hiemstra et al. 2010 Dec 1;304(21):2381-8.

Treatment of severe GPA/MPA

+ what?



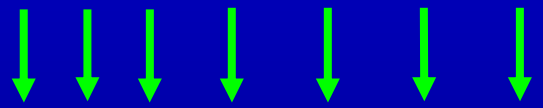
INDUCTION

+ adjuvant/prophylactic measures: cotrimoxazole, osteoporosis treatment, etc

Treatment of severe GPA/MPA

CYCLOPHOSPHAMIDE

15 mg/kg (d1,14,28 then q3wk)



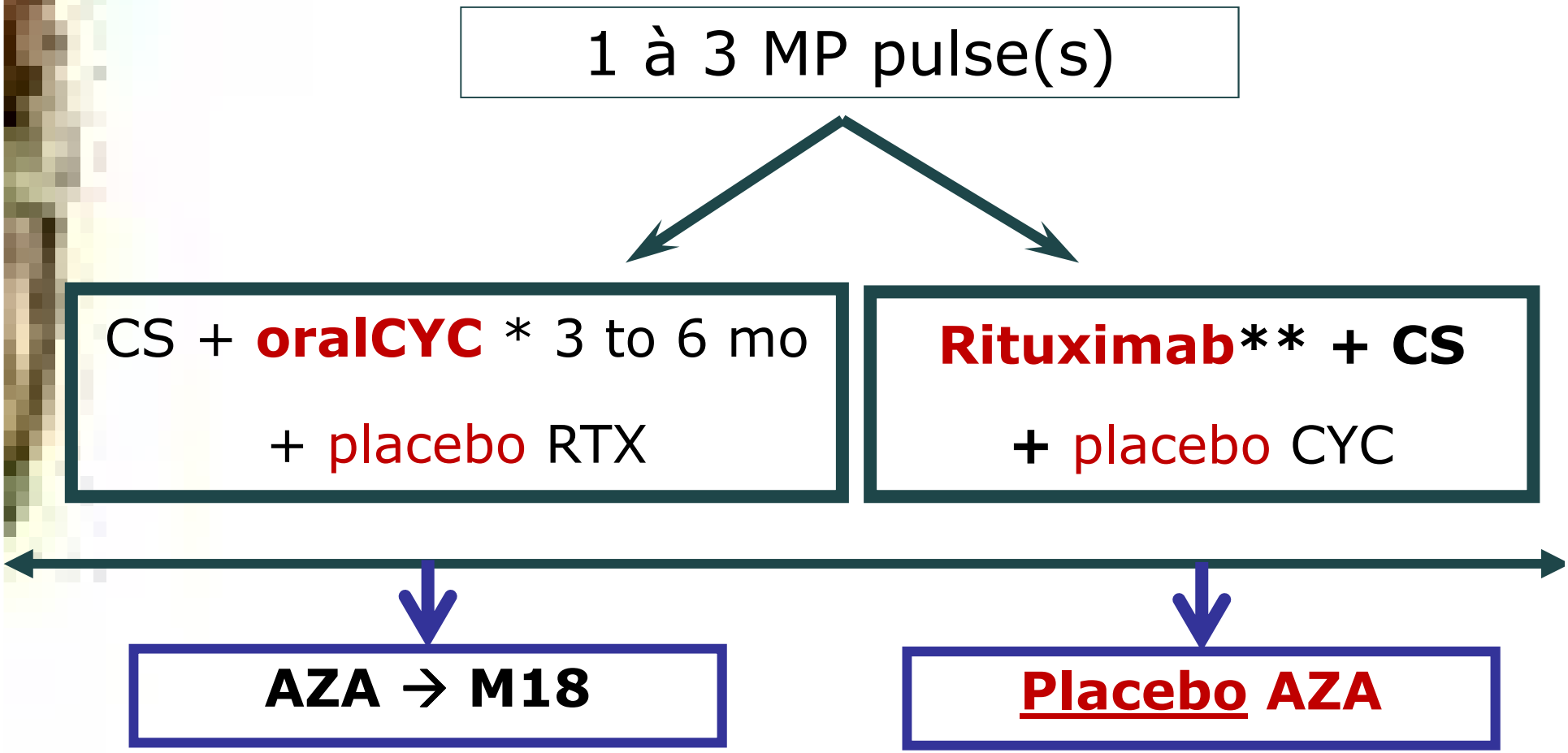
2 mg/kg/d

INDUCTION

+ adjuvant/prophylactic measures: cotrimoxazole, osteoporosis treatment, etc

(<350 µM)

RAVE



* oral CYC 2 mg/kg/d

** RTX 375 mg/m2 x 4

REIMBURSEMENT CRITERIA

For the induction of remission of severely active Granulomatosis with Polyangiitis (GPA) OR microscopic polyangiitis (MPA) as combination treatment with glucocorticoids, in patients who meet all of the following criteria:

1. The patient must have severe active disease that is life- or organ-threatening. At least one supporting laboratory and/or imaging report must be provided. The organ(s) and how the organ(s) is(are) threatened must be specified.
2. There is a positive serum assays for either proteinase 3-ANCA (anti-neutrophil cytoplasmic autoantibodies) or myeloperoxidase-ANCA. A copy of the laboratory report must be provided.
3. Cyclophosphamide cannot be used for the patient for at least ONE of the following reasons:

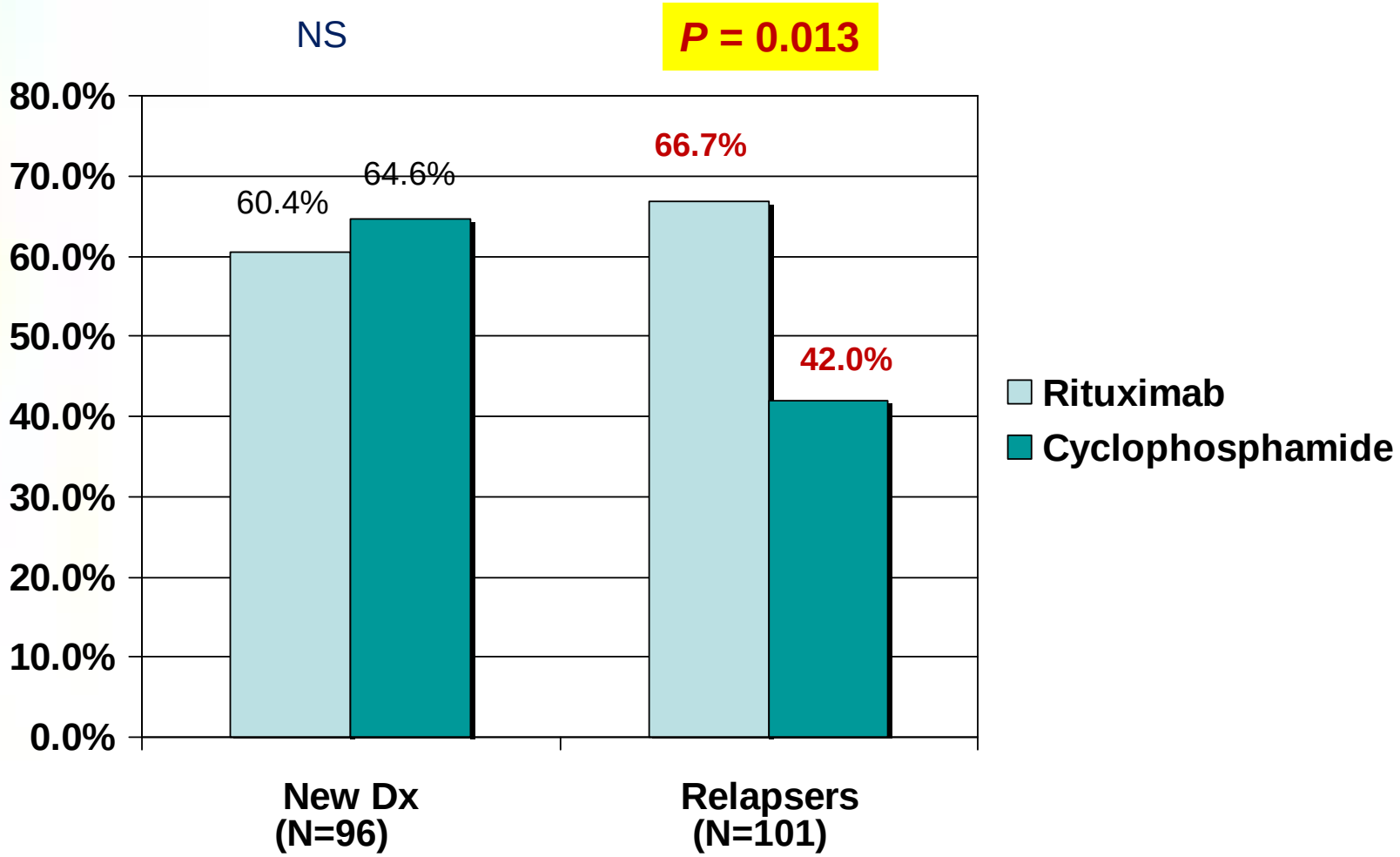
a) The patient has failed a minimum of six IV pulses of cyclophosphamide; OR
b) The patient has failed three months of oral cyclophosphamide therapy; OR
c) The patient has a severe intolerance or an allergy to cyclophosphamide; OR
d) Cyclophosphamide is contraindicated; OR
e) The patient has received a cumulative lifetime dose of at least 25 g of cyclophosphamide; OR
f) The patient wishes to preserve ovarian/testicular function for fertility.

The initial treatment would be a once weekly infusion dosed at 375 mg/m^2 x 4 weeks.

The physician must confirm that the treatment would not be a maintenance infusion as maintenance infusions will not be funded.

Renewals will be considered provided that, the patient meets the same criteria for initial approval and the request for retreatment is made no less than 6 months after the last does of the patient's last treatment cycle with Rituxan.

Better response in relapsers
(vs newly-diagnosed)



Stone JH et al, *N Engl J Med* 2010;363(3):221-32

Message #1

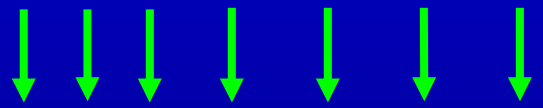
Rituximab is an **alternative** to CYC

YES but still in SPECIFIC PATIENTS/SETTINGS

Treatment of severe GPA/MPA

CYCLOPHOSPHAMIDE

15 mg/kg (d1,14,28 then q3wk)



2 mg/kg/d

INDUCTION

+ adjuvant/prophylactic measures: cotrimoxazole, osteoporosis treatment, etc

CYCLOPS

- Open label RCT
- 149 AASV (40% GPA)
- All with renal disease
- No Iº hypothesis
- Pulse (IV or oral) vs continuous oral CYC
- Remission <u>at 9 mo</u>

Pulse 88.1%

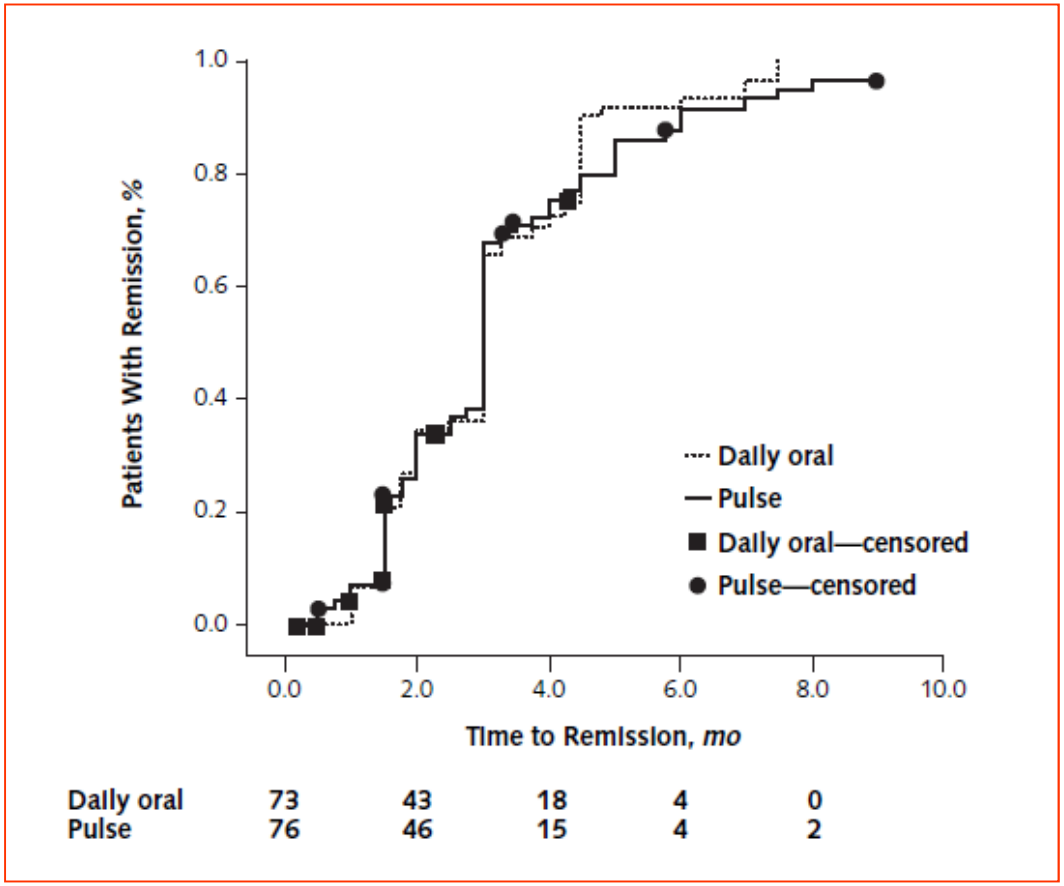
Continuous 87.7%

- DO = higher rate of leukopenia

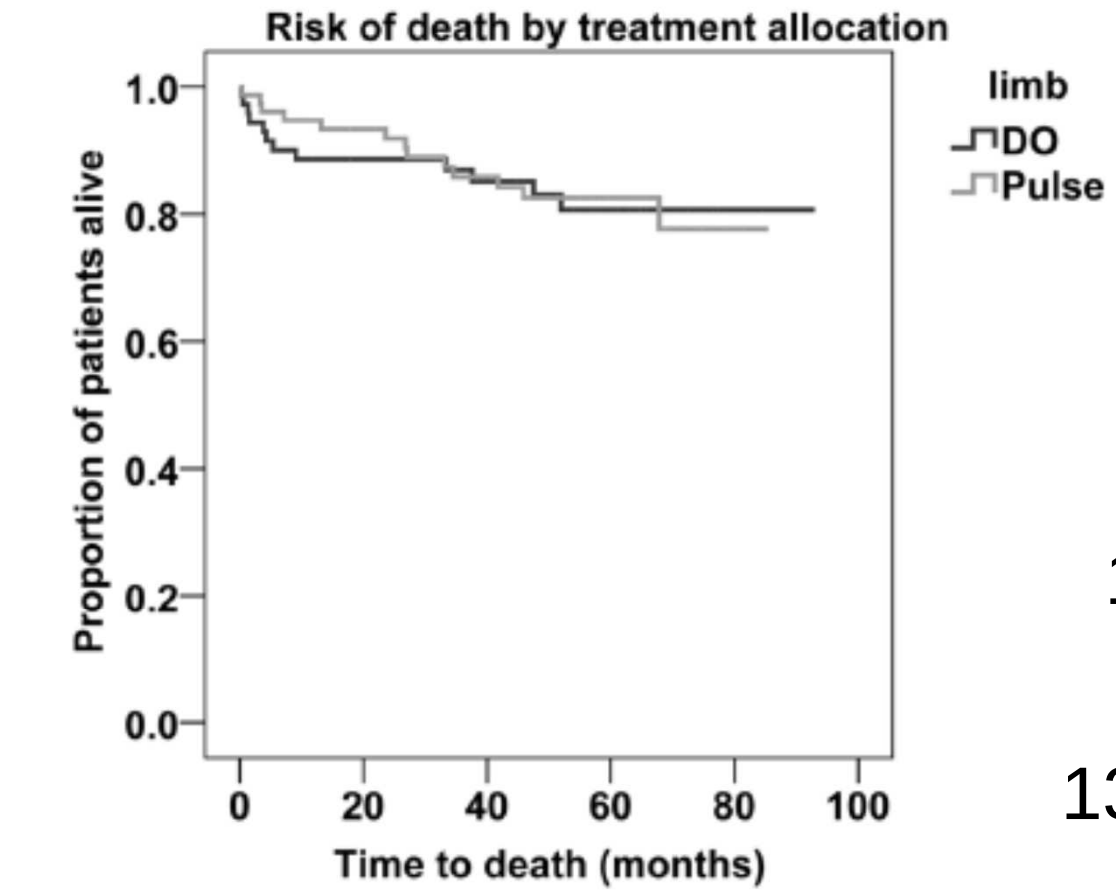
- <u>At 18 mo:</u>

14.5% relapsed

(18.8% IV vs. 9.4% PO)



de Groot et al, Ann Intern Med 2009;150:670-680



Time (months)	0	20	40	60	80
DO (n)	72	55	46	26	2
Pulse (n)	76	64	54	24	3

Figure 1. Patient survival according to treatment allocation. There was no significant difference in mortality risk between patients randomised to pulse cyclophsophamide or daily oral (DO) treatment.

Median duration of follow-up of **4.3 yrs**

DEATHS

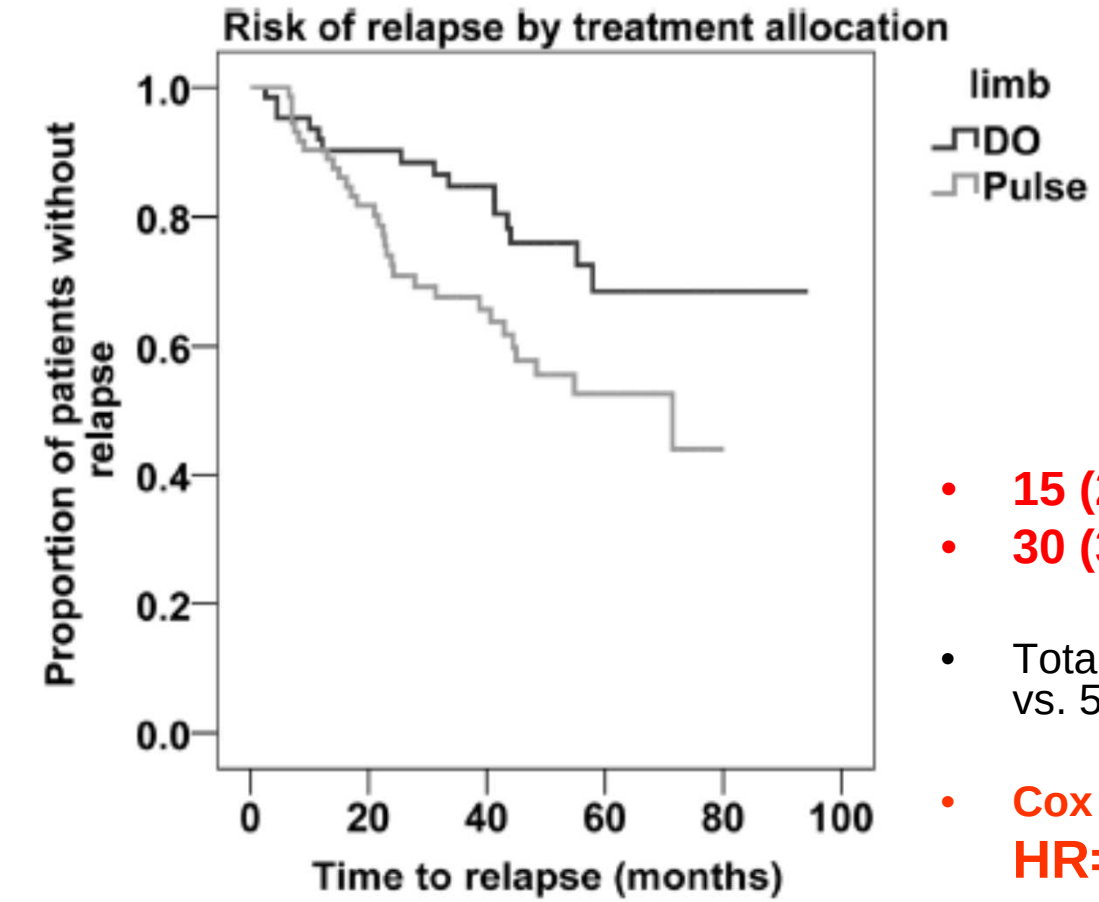
12 patients in DO

vs.

13 in IV pulse group

(NS)

Harper et al. Ann Rheum Dis. 2011 Nov 29. [Epub ahead of print]



Time (months)	0	20	40	60	80
DO (n)	72	55	46	26	2
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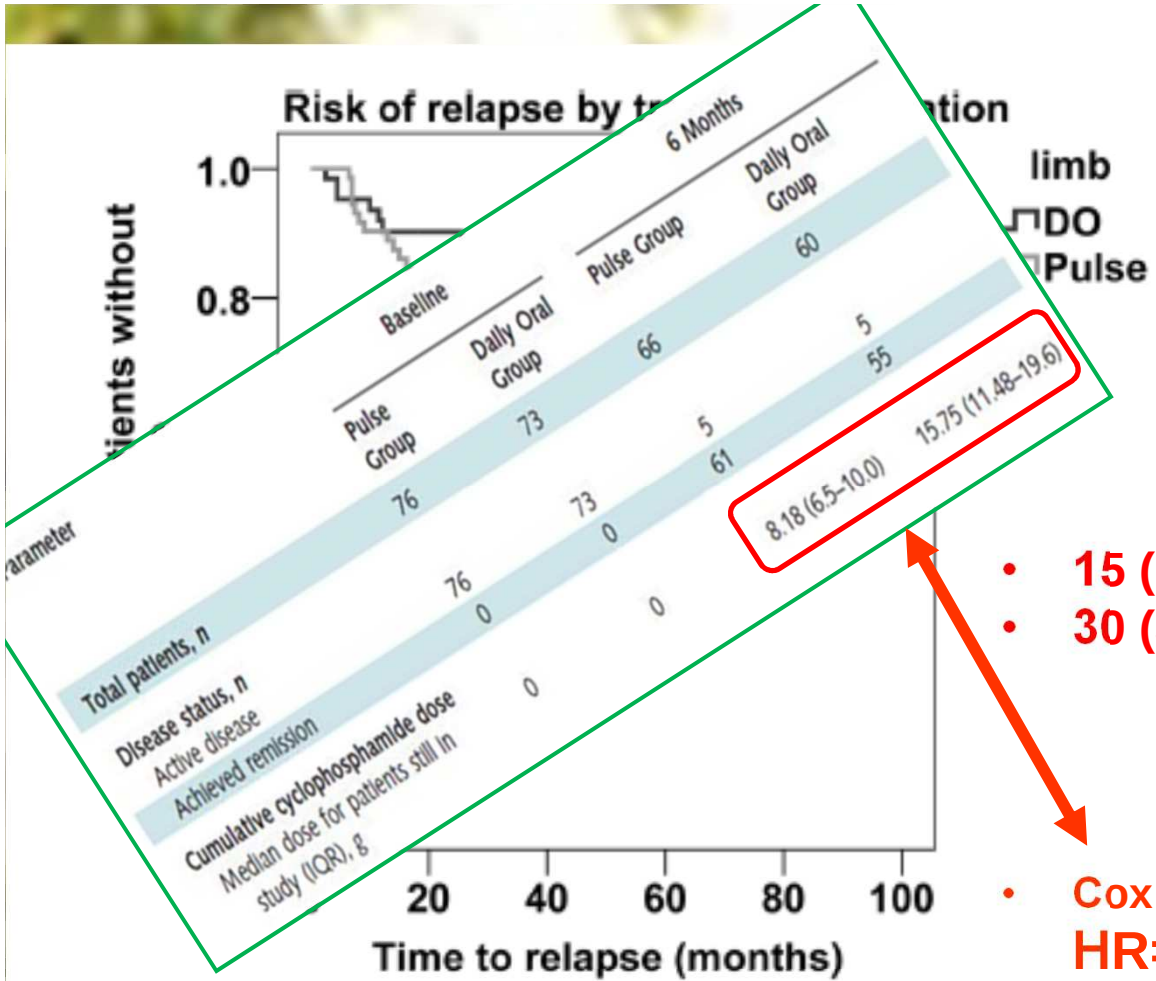
Figure 2. Relapse-free survival in the two treatment arms. Using Kaplan–Meier survival analysis, there was a significantly increased risk of relapse during follow-up in patients randomised to pulse cyclophsophamide rather than daily oral (DO) treatment (p=0.029).

RELAPSES

- **15 (20.8%) DO**
- **30 (39.5%) pulse had ≥1 relapse**

- Total of 21 relapses (10 renal) in the DO vs. 54 (12 renal) in the pulse limb

- **Cox regression analysis**
  HR=0.50, 95% (CI, 0.26-0.93); p=0.029



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- **Cox regression analysis**
  HR=0.50, 95% (CI, 0.26-0.93); p=0.029

Half the relapse rate,
Twice the CYC dose…
Make your choice…

Message #2

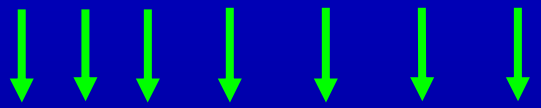
OK… daily oral CYC **MAY** be associated with a lower subsequent rate of relapse

But does it worth giving a double dose of CYC (as compared to IV)?

Treatment of severe GPA/MPA

CYCLOPHOSPHAMIDE

15 mg/kg (d1,14,28 then q3wk)



2 mg/kg/d

+ Corticosteroids

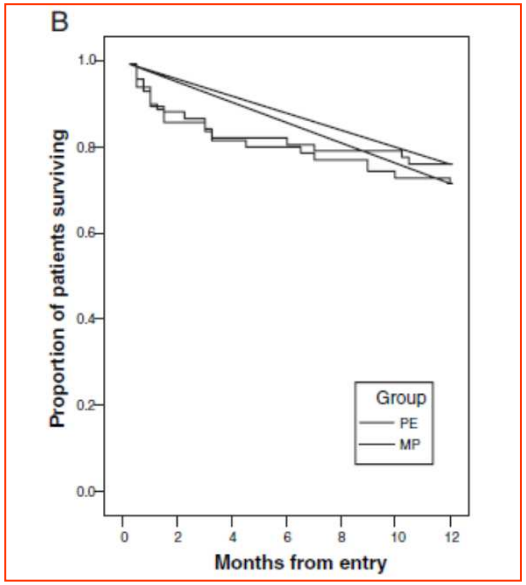
3 - 6 months

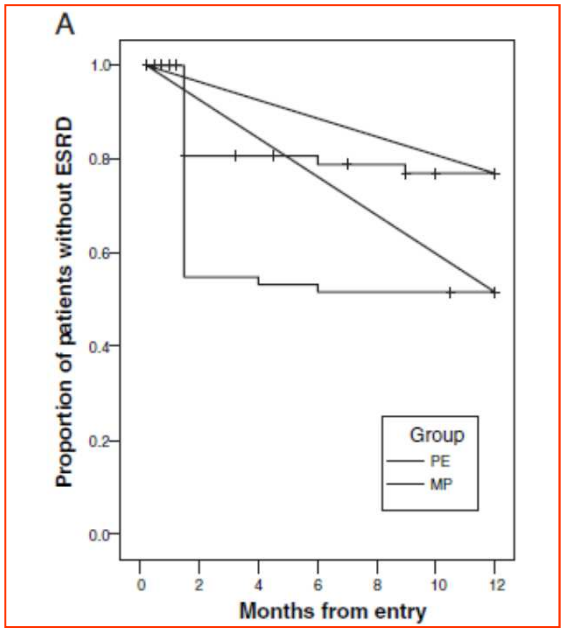
INDUCTION

+ adjuvant/prophylactic measures: cotrimoxazole, osteoporosis treatment, etc

PLASMA EXCHANGE

- **MEPEX**
  - > design for renal recovery rate
  - 137 p. (WG 31%) with Cr ≥ 500 µmol/L (5.8 mg/dl)
  - 7 PE/14 days vs. daily 1g-MP pulses for 3 days

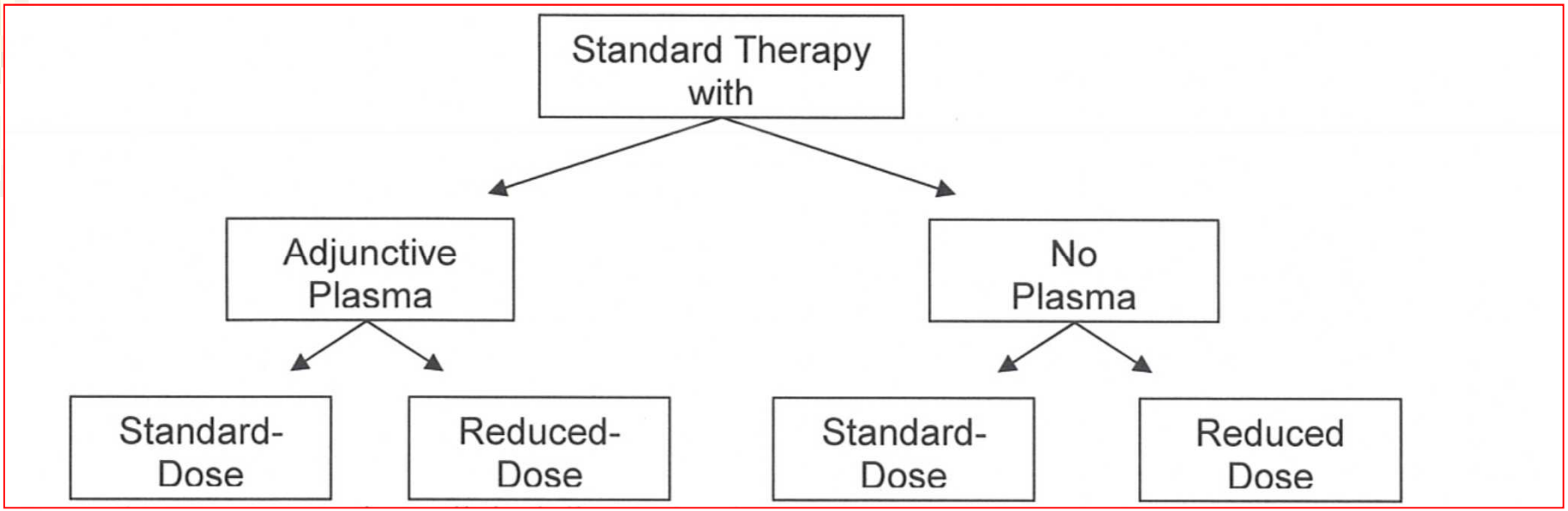




Jayne et al. *J Am Soc Nephrol* 2007;18:2180-8

PEXIVAS

- WORLD WIDE TRIAL, NIH-VCRC sponsored
- 2*2 factorial open-label trial
- Aimed to enrol 500 patients → 150 in 2 years!
- GPA, MPA with AH and/or renal involvement (GFR <50 ml/min)



Message #3

Forget about your prejudices on PLEX in AAV

We DO NOT KNOW the precise place of PLEX and whether it is really beneficial at all!

AASV: INDUCTION-MAINTENANCE STRATEGY

- **CYCAZAREM**
  - Open label randomized trial
  - Superiority design
  - 155 patients (60% WG)
  - 144 Randomized at remission (after oral CYC)
  - **Relapses**

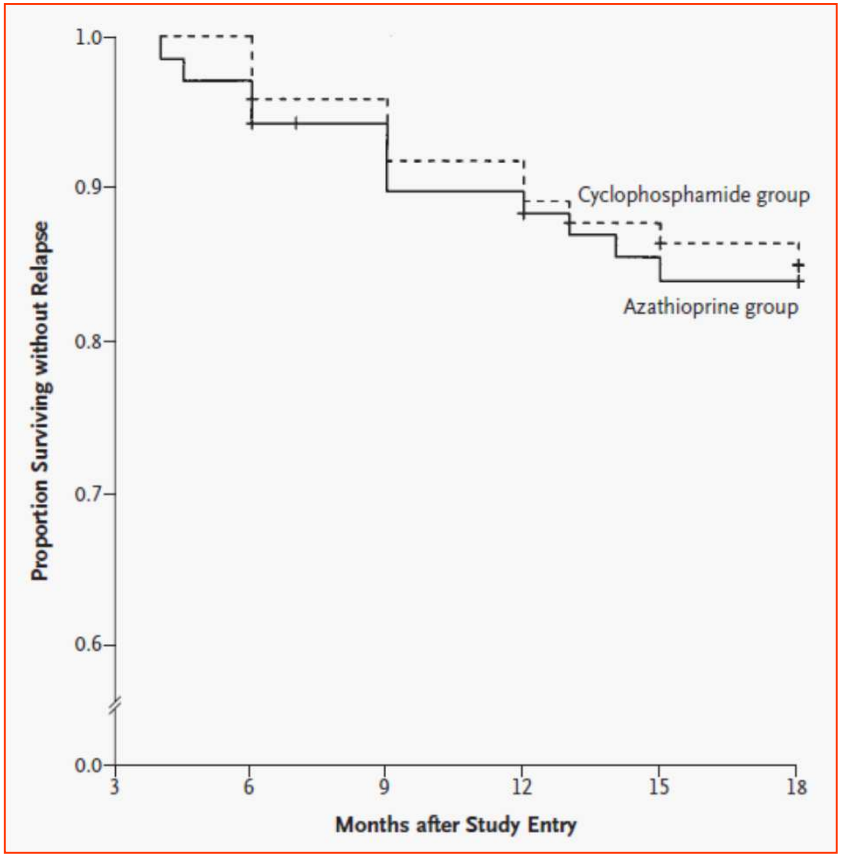
AZA 15.5%

CYC 13.7% (P=0.65)

- Severe AE

AZA 11%

CYC 10% (P=0.94)



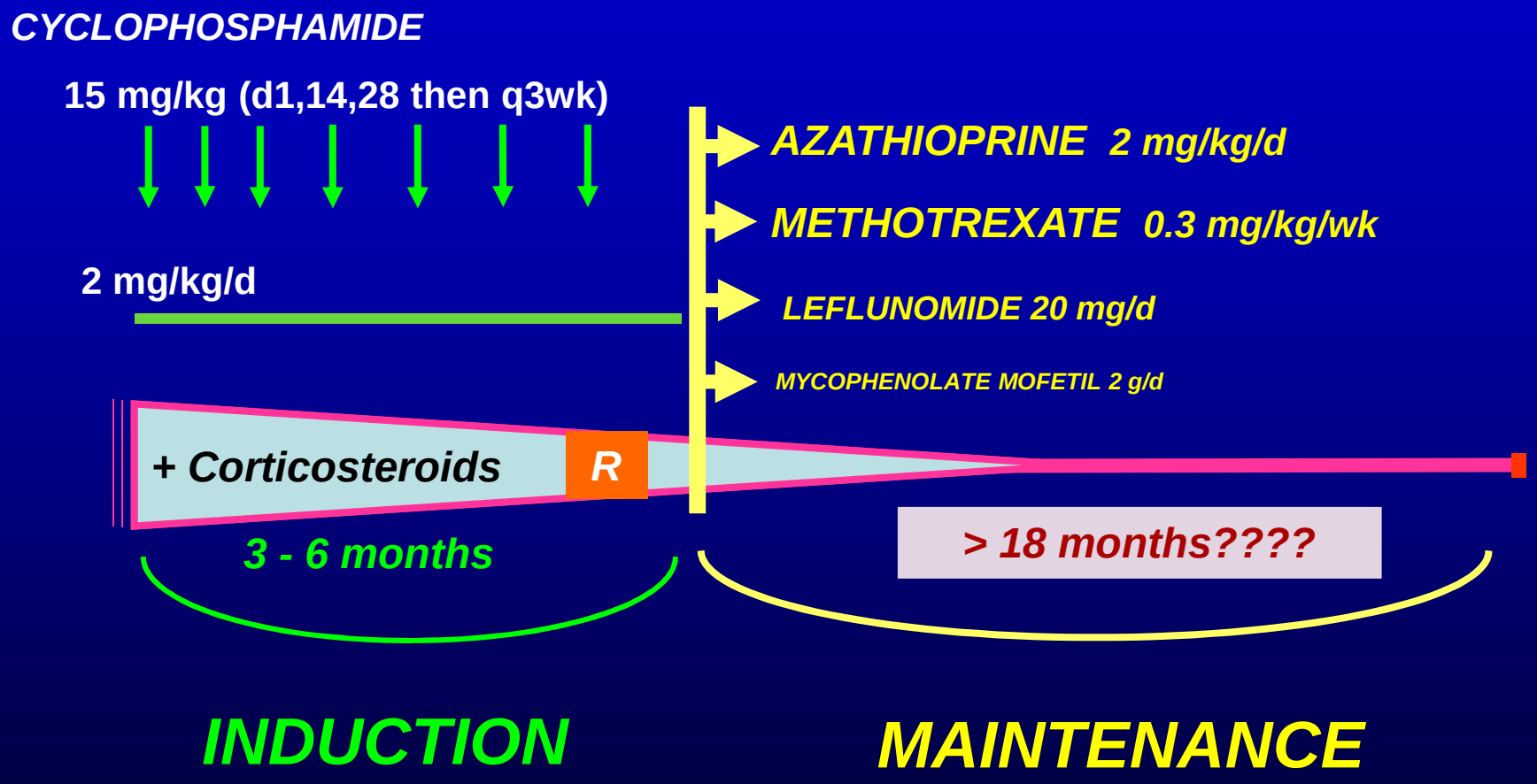
Jayne et al. *N Engl J Med* 2003;349:36-44.

Message #4

REMEMBER

CYC = **NEVER** >6 months!

Treatment of severe GPA/MPA



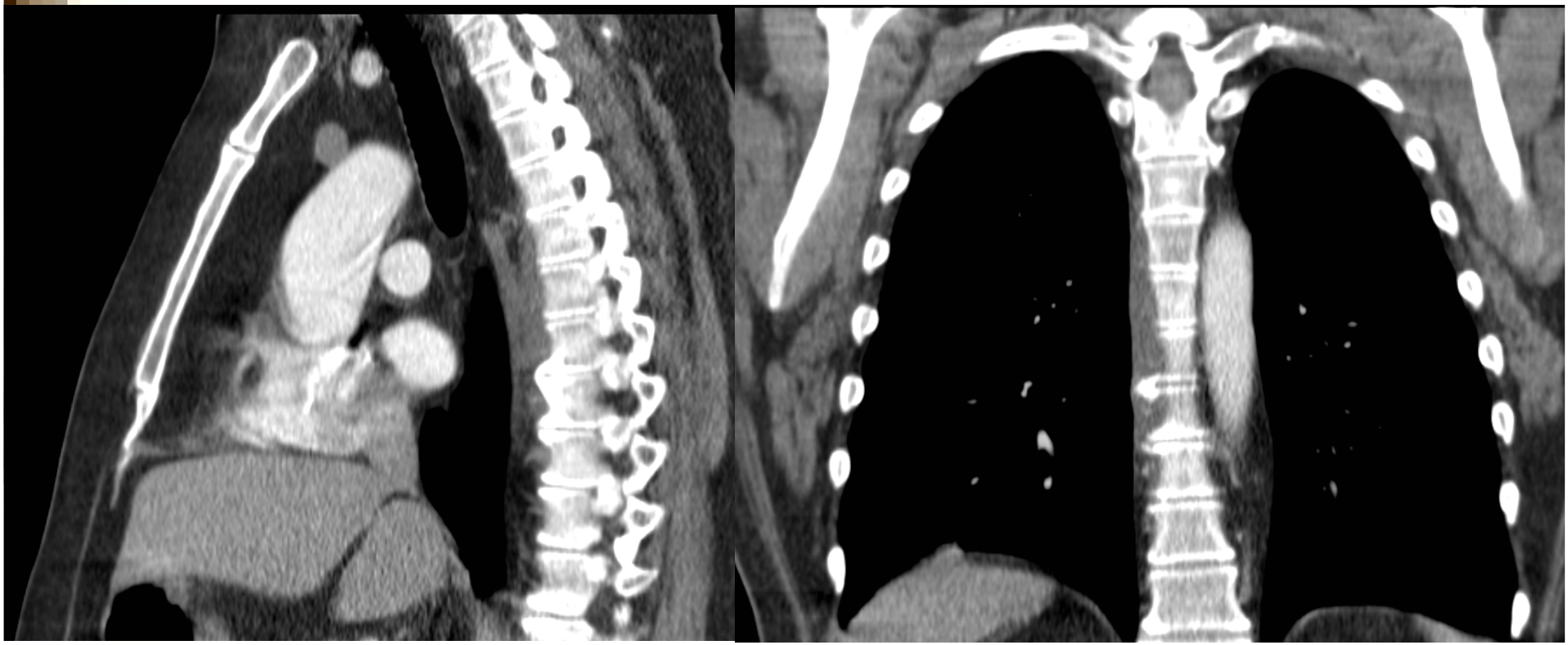
+ adjuvant/prophylactic measures: cotrimoxazole, osteoporosis treatment, etc

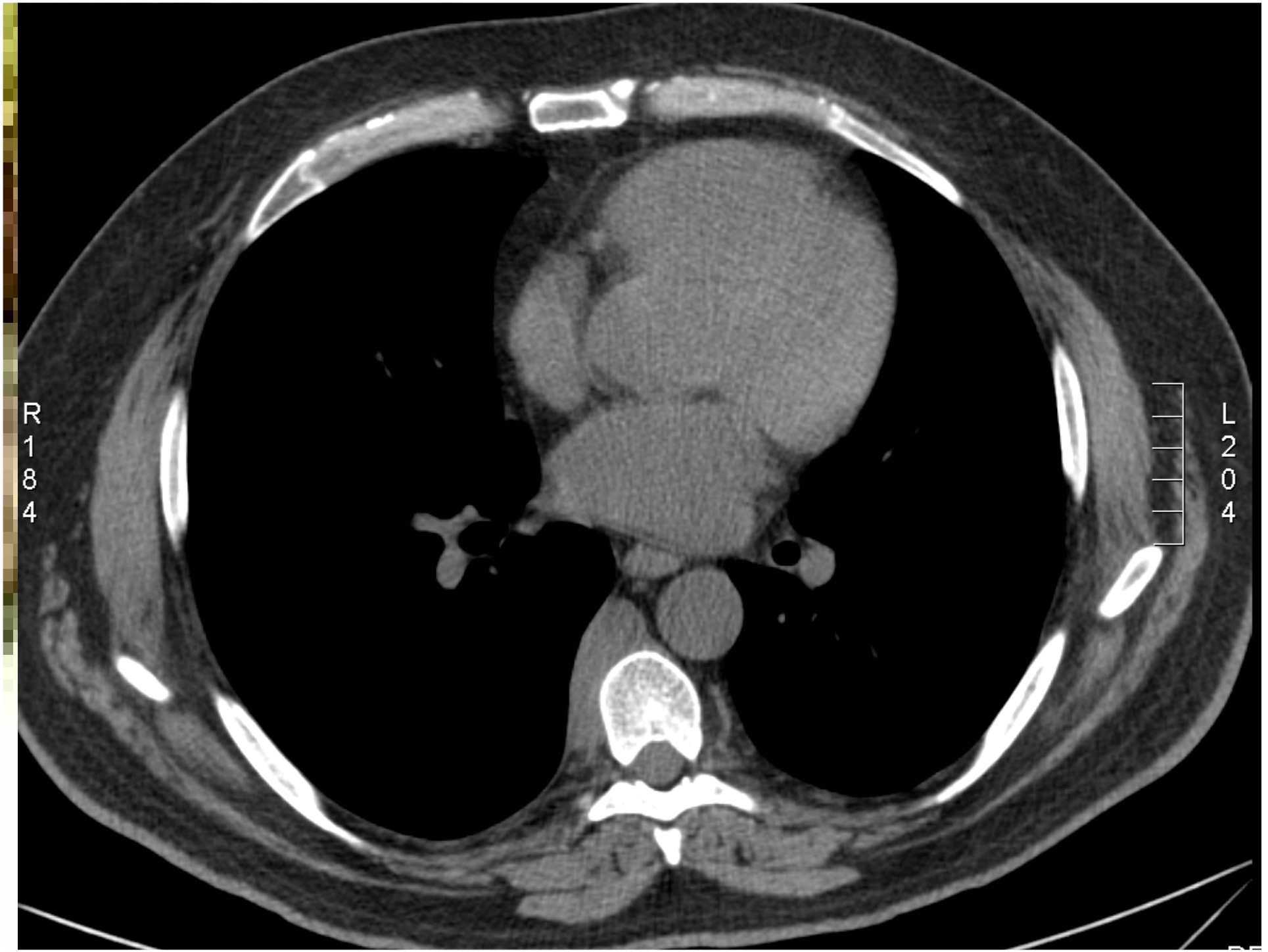
Message #5

We DO NOT KNOW the optimal duration of maintenance therapy

Is 4 better than 2 years? → REMAIN results, mid 2013

Imaging GPA melting pot…

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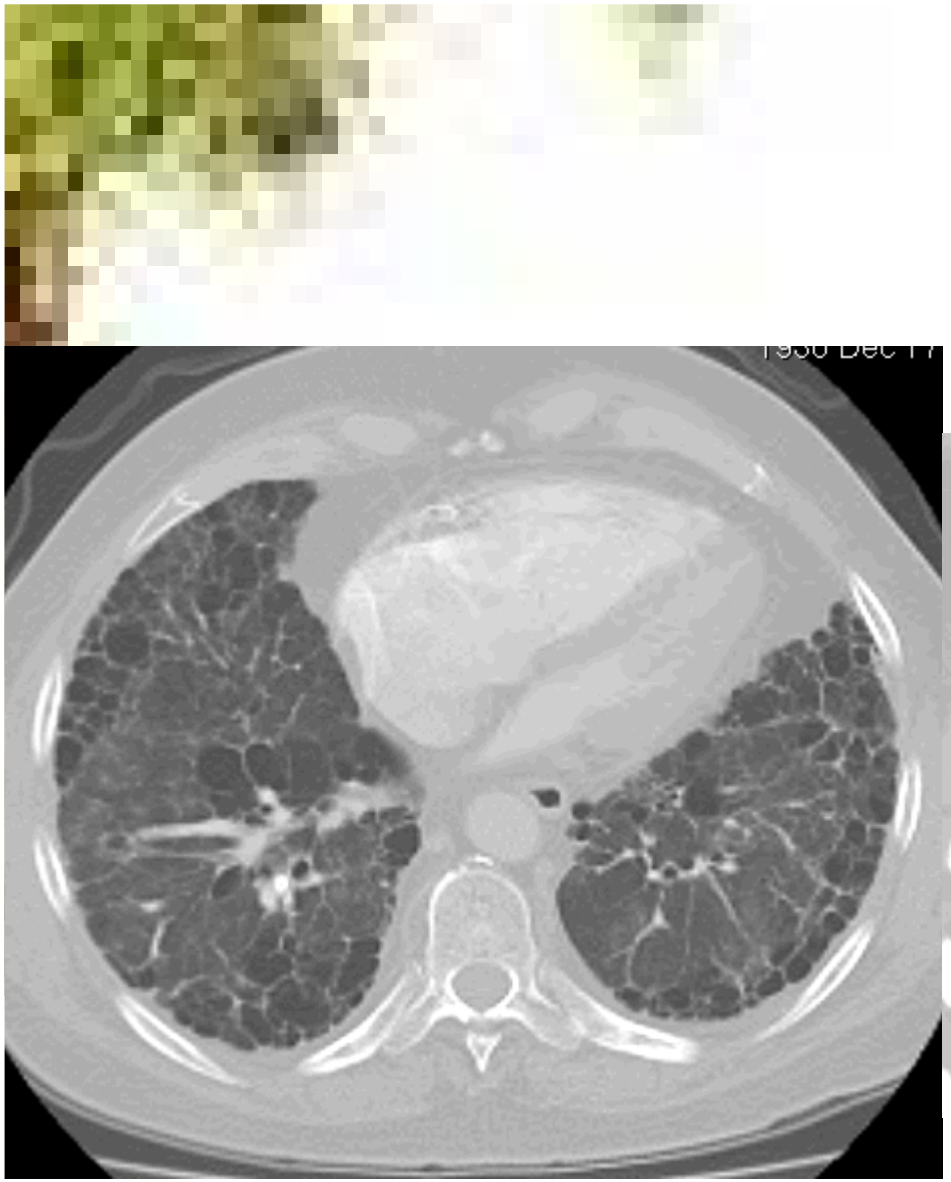
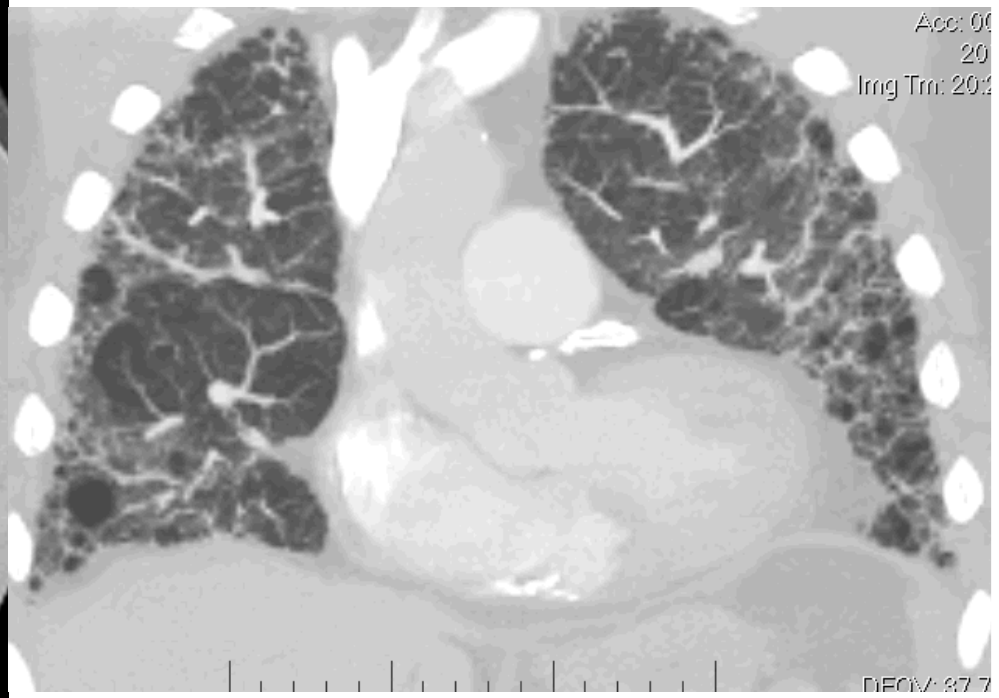
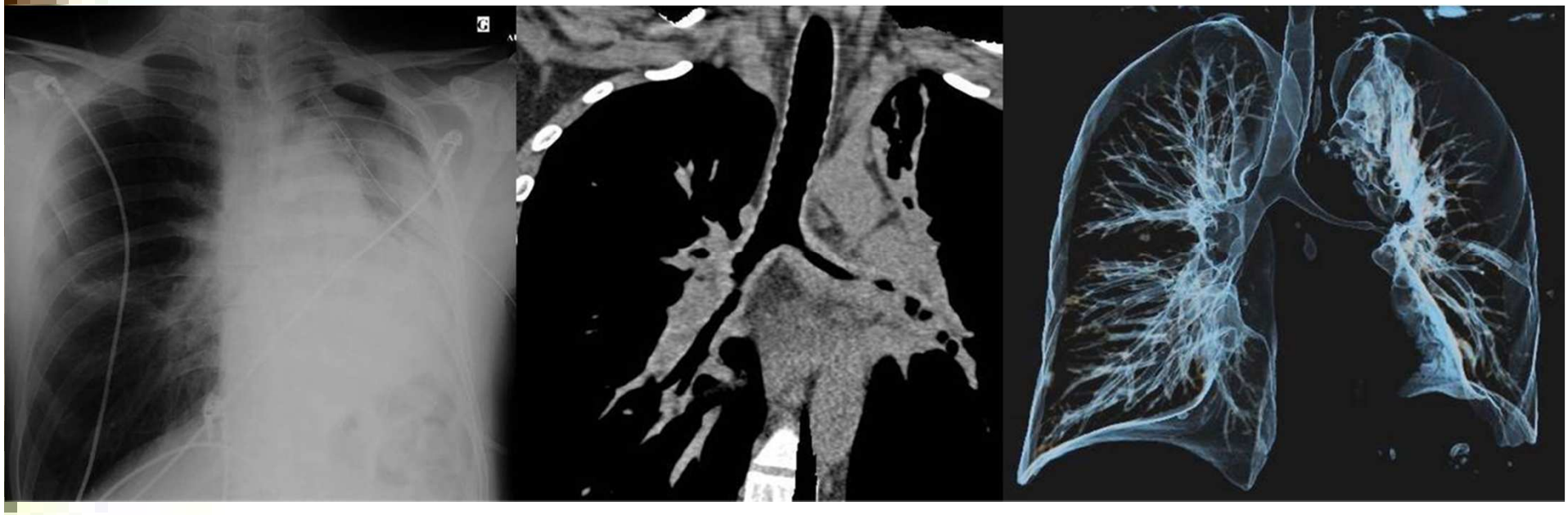
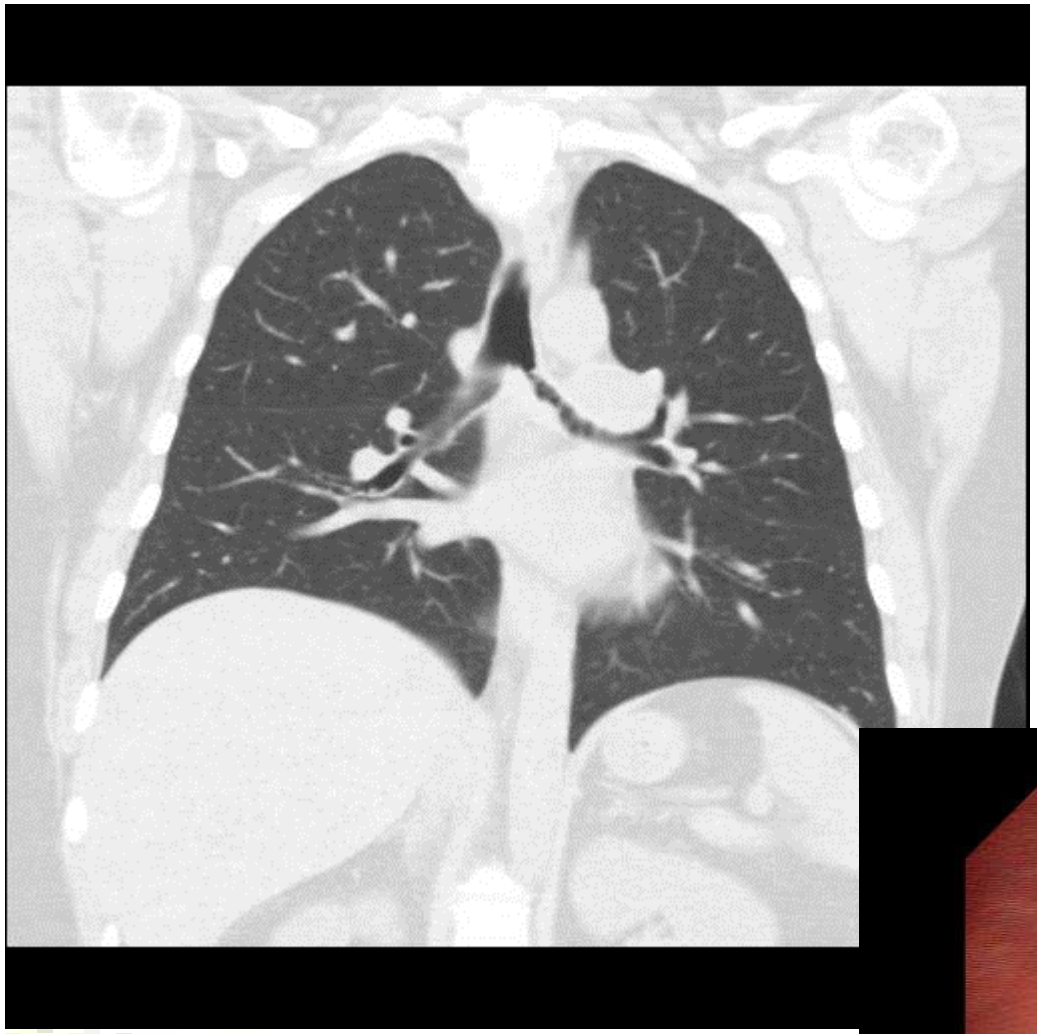
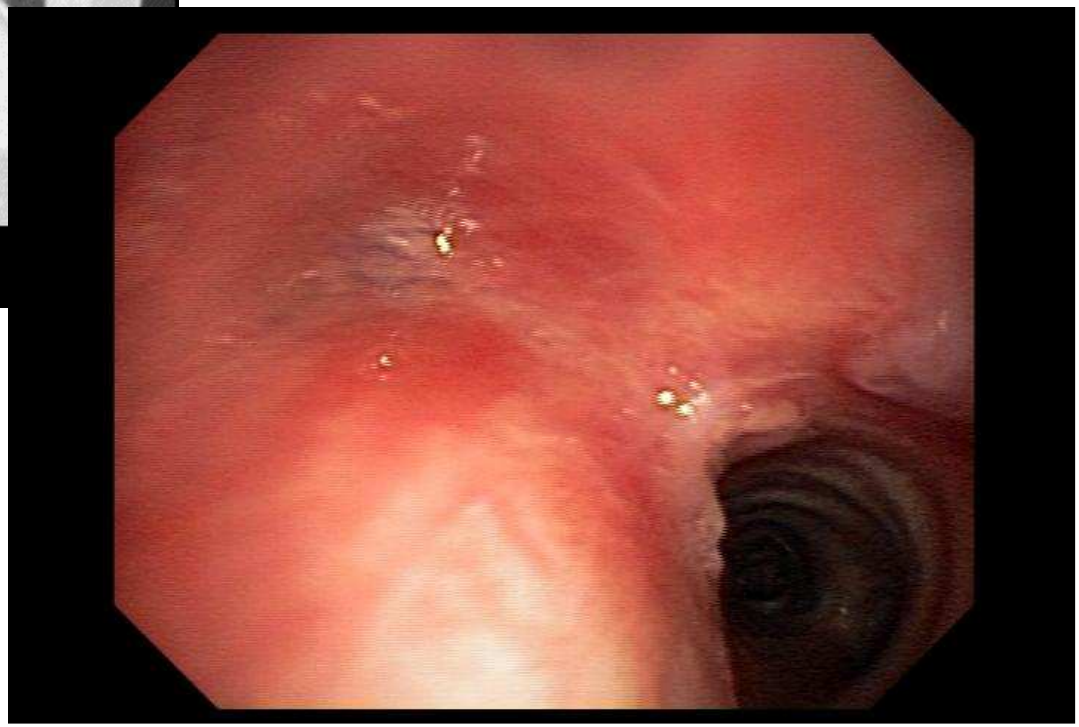
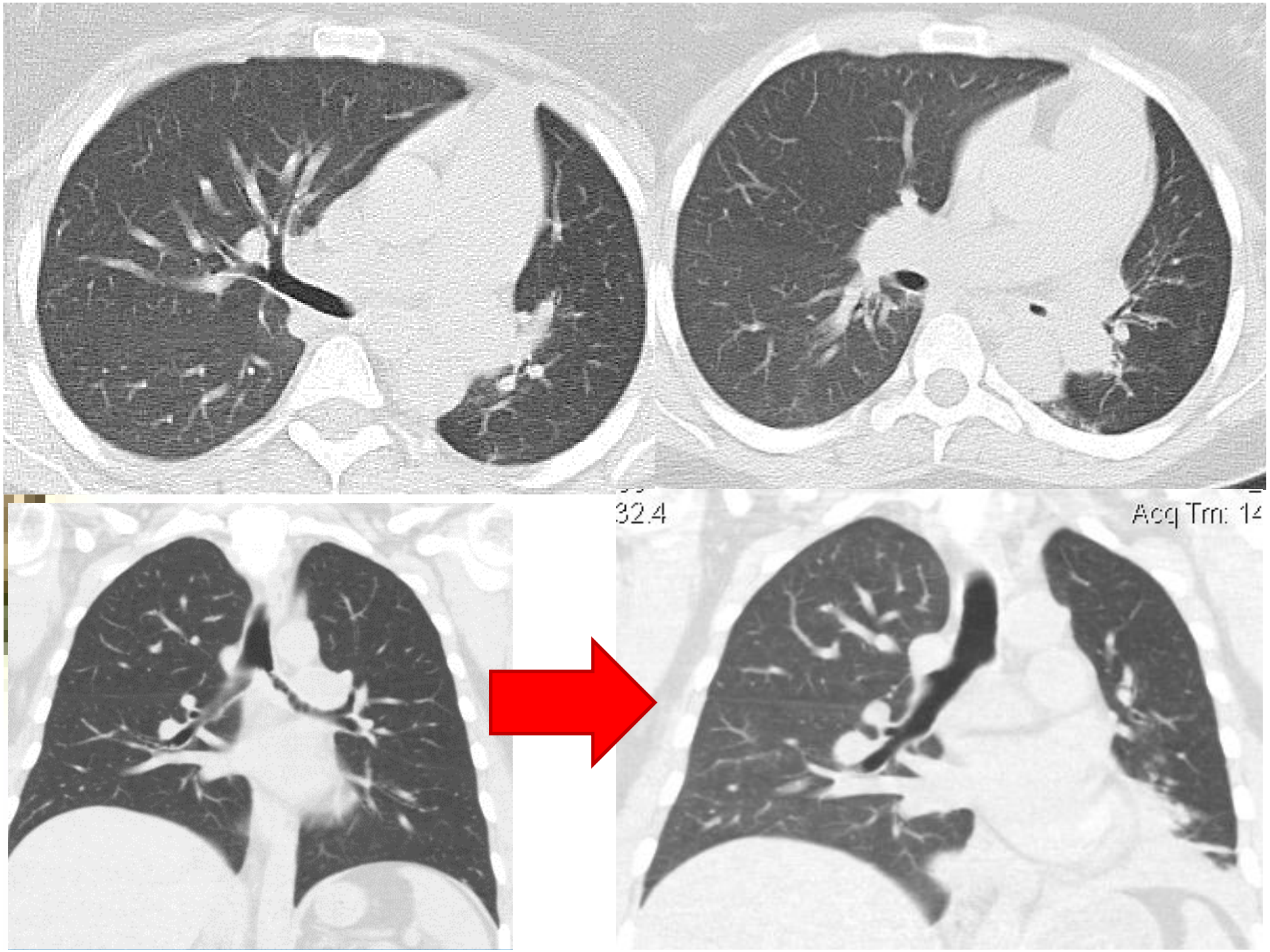


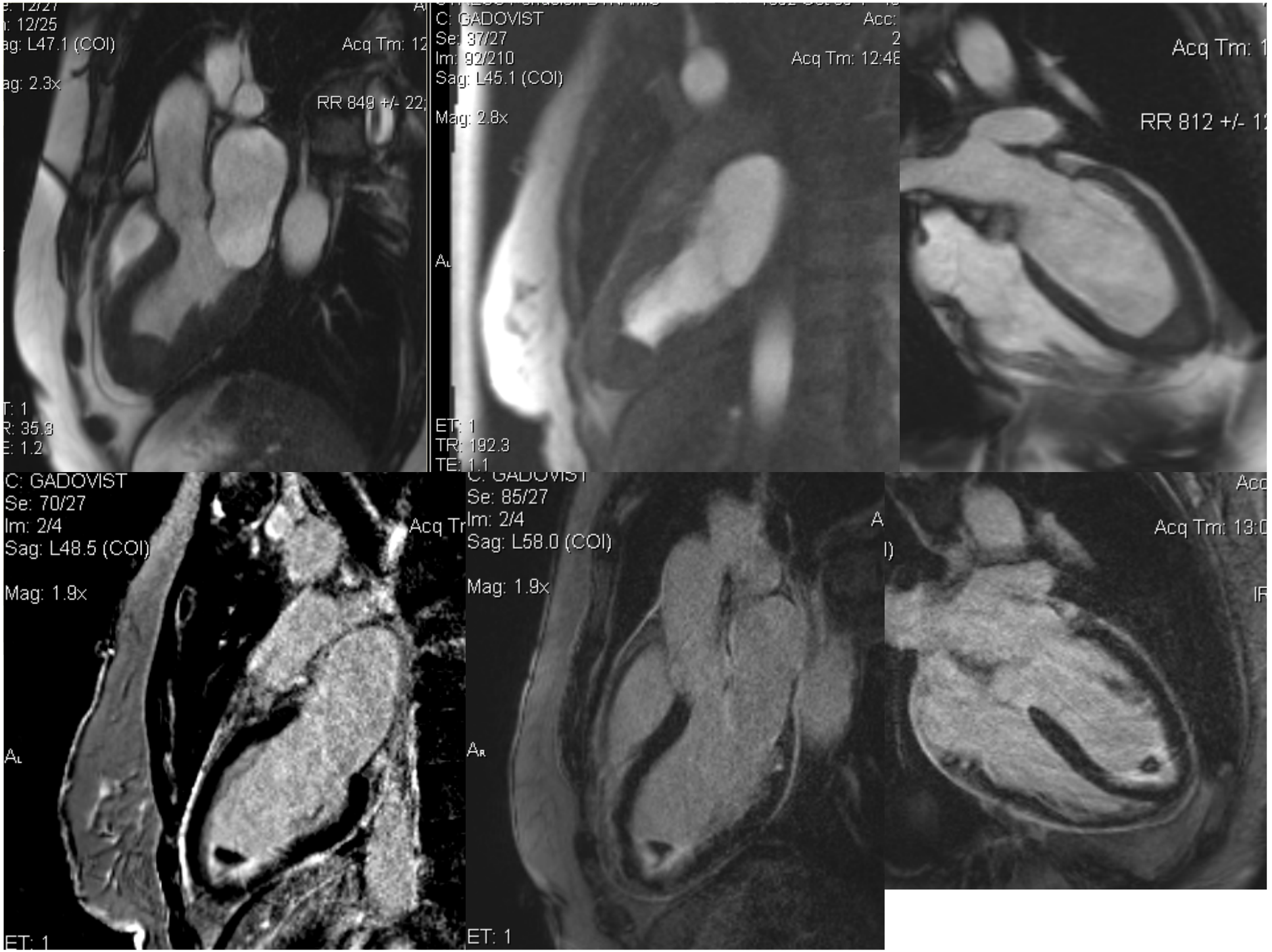








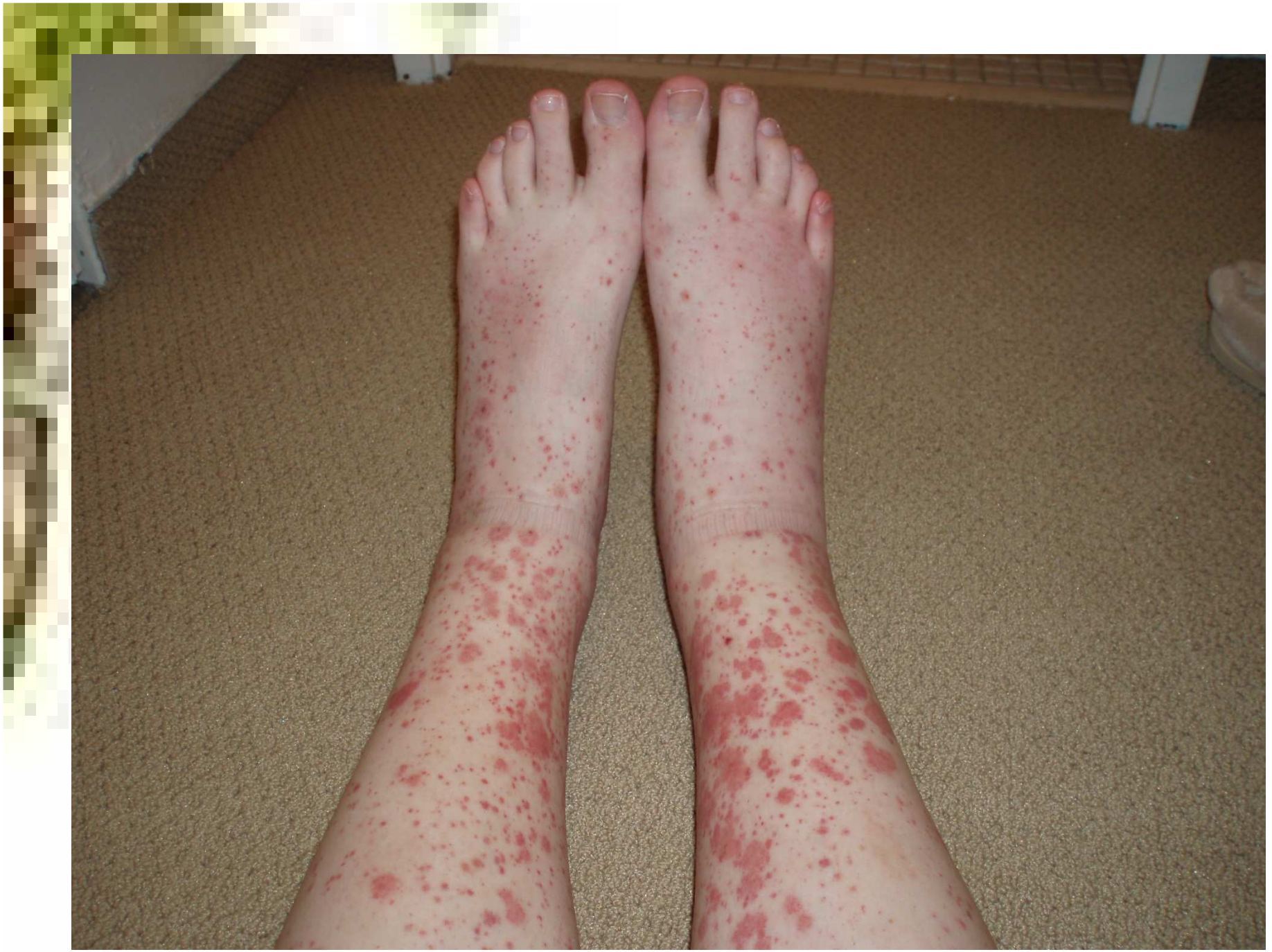

32.4
Acq Tm: 14


: 12/25
ag: L47.1 (COl)
Acq Tm: 12
ag: 2.3x
RR 849 +/- 22;
T: 1
R: 35.8
E: 1.2
C: GADOVIST
Se: 37/27
Im: 92/210
Sag: L45.1 (COl)
Acc:
2
Acq Tm: 12:48
Mag: 2.8x
AL
ET: 1
TR: 192.3
TE: 1.1
Acq Tm: 1
RR 812 +/- 1
C: GADOVIST
Se: 70/27
Im: 2/4
Sag: L48.5 (COl)
Acq Tr
Mag: 1.9x
AL
ET: 1
C: GADOVIST
Se: 85/27
Im: 2/4
Sag: L58.0 (COl)
A
Mag: 1.9x
AR
ET: 1
Acq Tm: 13:0

Case #3

- Woman, 32 years-old
- Married, no children
- No past medical history
- Smoker (5 packs-years), occasional drinks
- No recreational drugs

- For 3 months, heavy legs, and recurrent purpuric and macular skin lesions on lower limbs



Case#3

- CBC, creatinine, LFT, CRP
- ANA, ANCA, cryoglobulin
- Serologies (HBV, HCV, HIV, TPHA-VDRL)
- Urine analysis
- Chest X-ray

- *If nodular:* Ca, CE… PPD, other serologies depending on the context (ricketssioses, yersiniosis…), IBD…

Case #3

- Skin biopsy = LCV

Case #3

- Colchicine 0.6 mg BID
- Dapsone 50 → 100 mg OD *(clofazimine?)*
- (Danazol, 100-300 mg OD, men, menopaused w)
- (Hydroxychloroquine)
- (Sulfasalazine)

- Prednisone
- Azathioprine
- Methotrexate


CANADIAN VASCULITIS NETWORK
CANVASC
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CanVasc
meeting
Montréal, QC
November 22nd, 2012
Registration and information on
http://www.canvasc.ca

April 14 - 17 2013

16th International Vasculitis & ANCA Workshop

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(president)

Organisation :

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