Tell me more about vasculitis…

Lisa Willcocks

Consultant in Nephrology and Vasculitis, Addenbrooke's Hospital

Talk overview

- **Case study**

- **ANCA-associated vasculitis**
  - **What is ANCA vasculitis?**
  - **What causes ANCA vasculitis?**

Case history

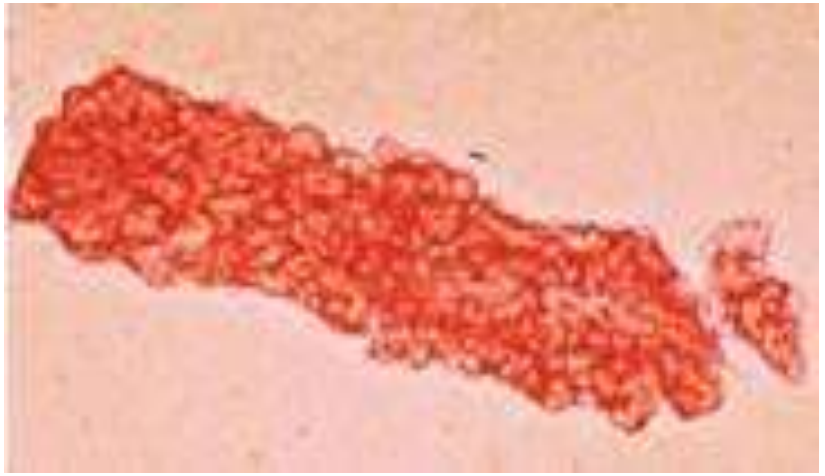
- 45 yr old man, architect
- Myalgia, weight loss, rash, fevers, blue fingers and toes
- PMH: none
- DH: recent antibiotics for “cellulitis”
- SH: non-smoker

Investigations – blood tests

- **Hb 9.1g/dl WBC 11.2×10^9 Plats 567×10^9**
  - **Anaemic**
- **Na 145mmol/l K 5.4mmol/l Creat 146μmol/l**
  - **Reduced kidney function**
- **ESR 98mm/hour CRP 146mg/l**
  - **High levels of inflammation**

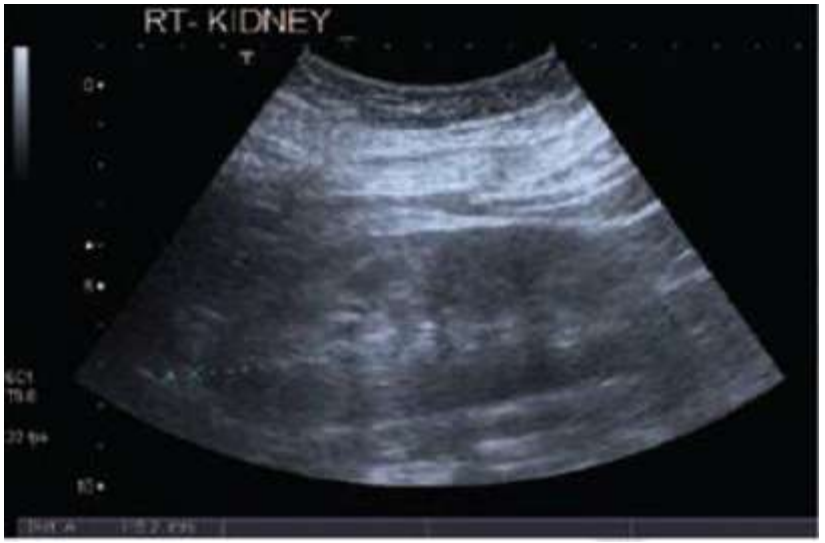
Investigations

- **Urine dipstick : Blood ++ protein +++ leucocytes+**



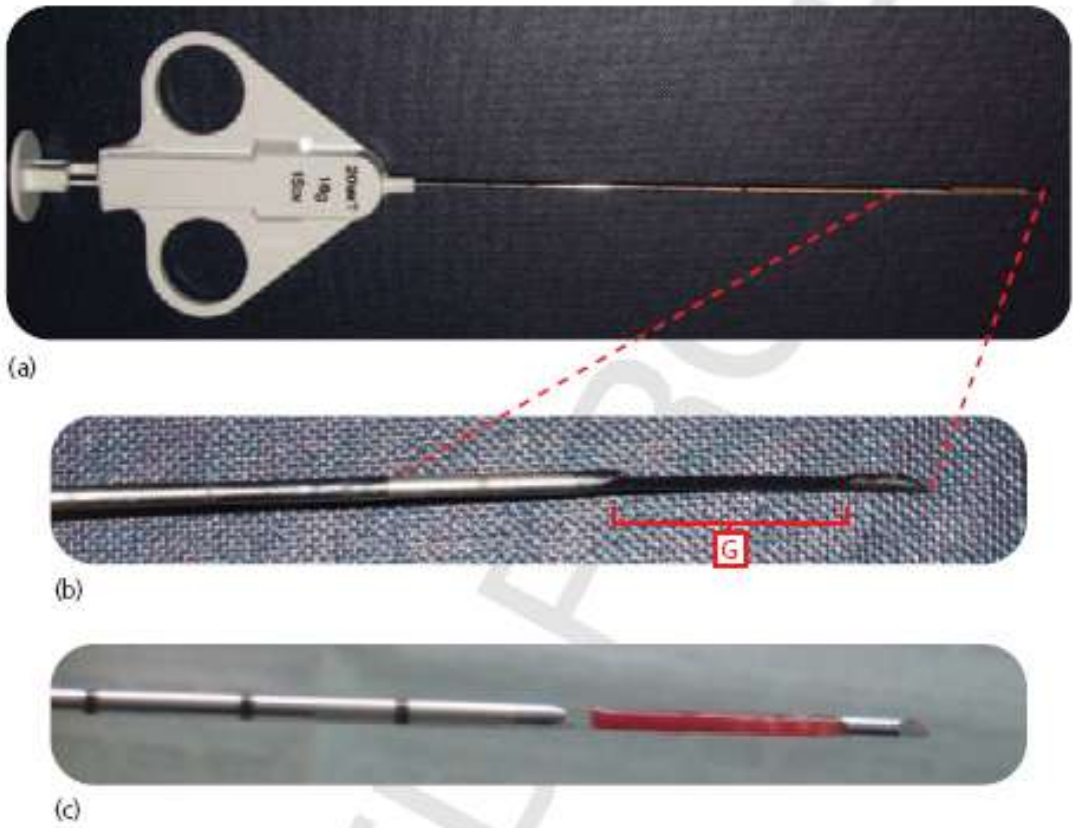
- **Albumin:creatinine ratio 106 μg/mg = protein in the urine**

- **Ultrasound renal tract : Normal kidneys**



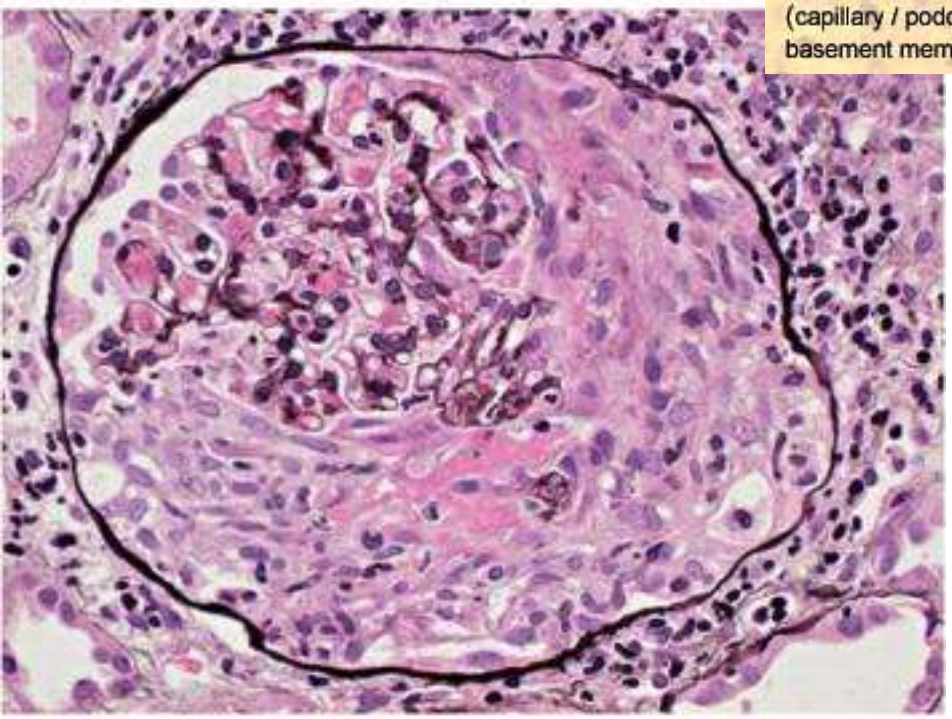
Investigations

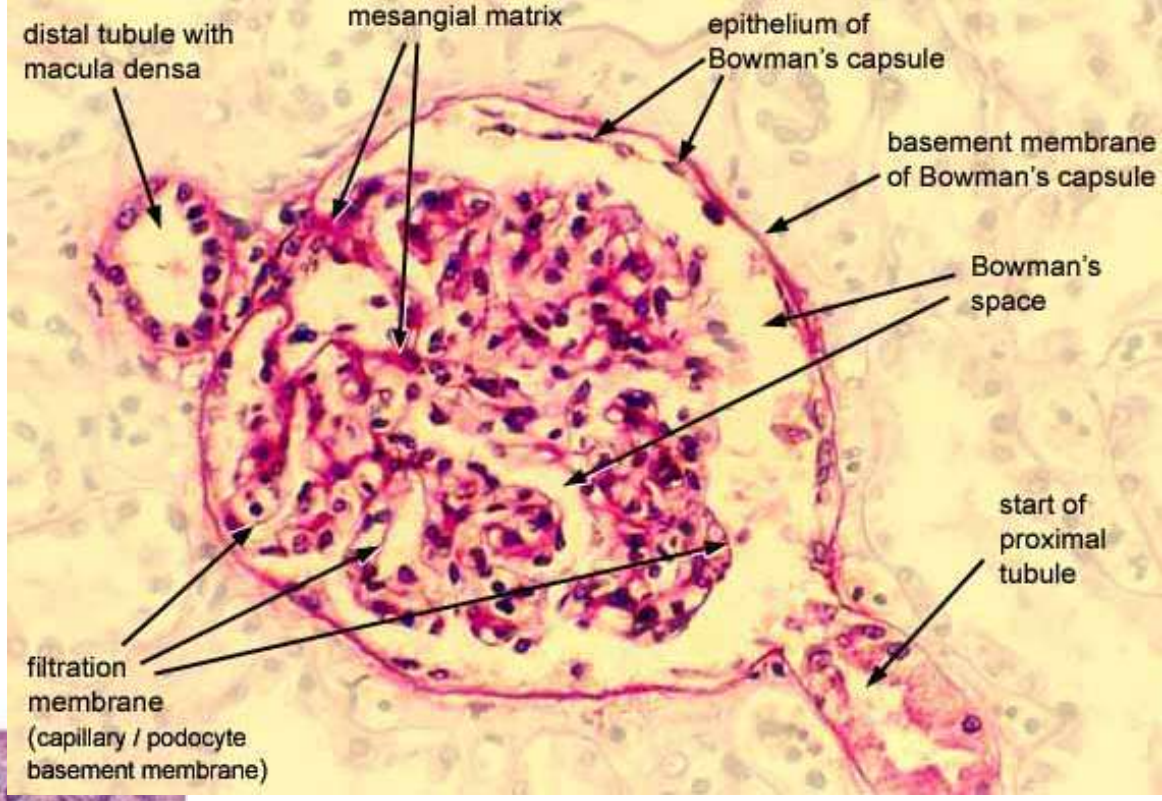
- **RENAL BIOPSY**



Menna Clatworthy 2009

Renal Biopsy





- **Inflammation within the glomeruli (the filters) of the kidney**

Diagnosis

- Renal biopsy – "Crescentic glomerulonephritis"

- **p Anti-Neutrophil Cytoplasmic Antibody** positive (Anti-MPO titre 504)

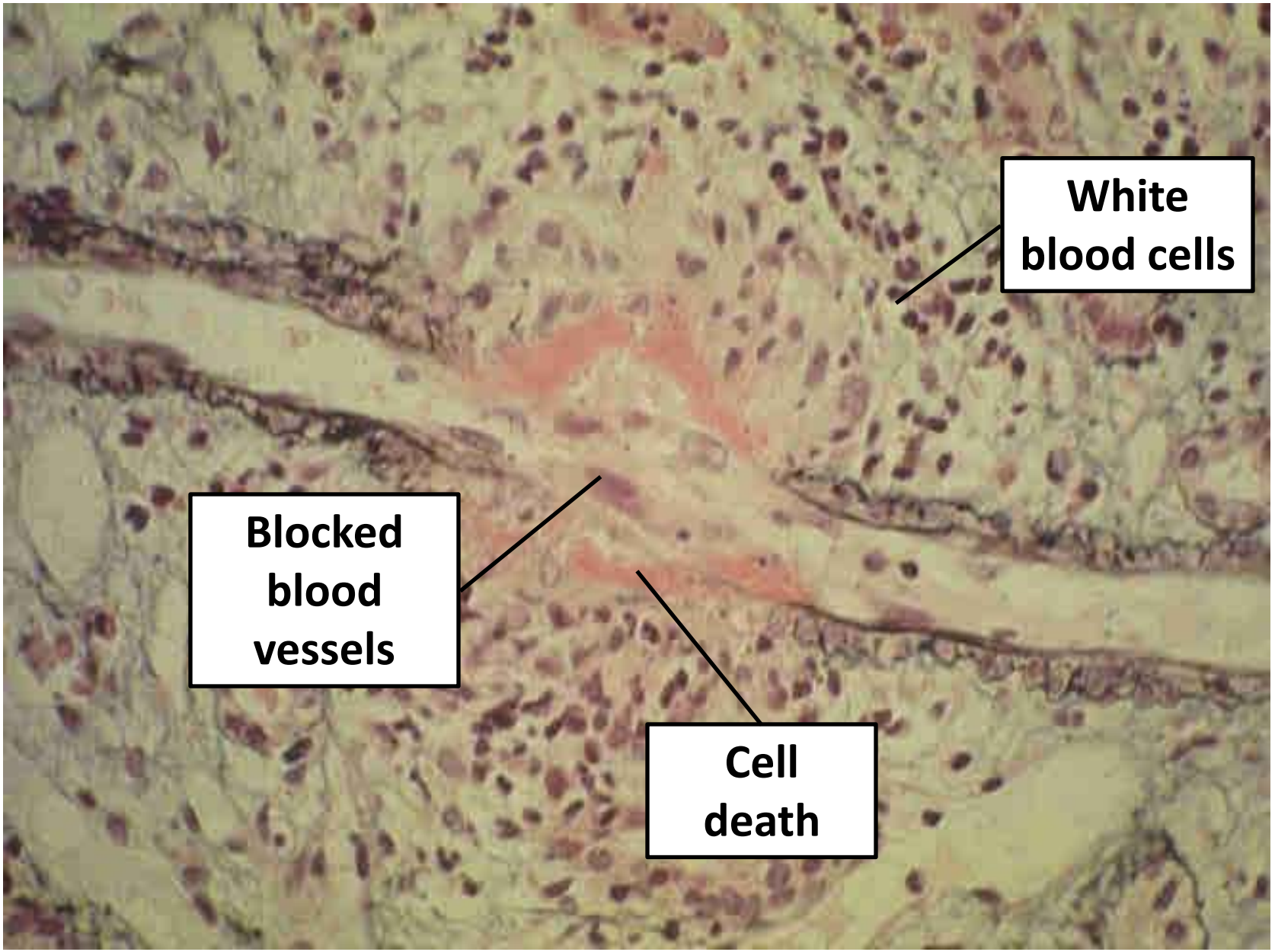
ANCA associated vasculitis – microscopic polyangiitis (MPA)

WHAT IS ANCA VASCULITIS?

What is Vasculitis?

- **Group of autoimmune diseases**
- **Inflammation of blood vessels**
  - **Blood vessels in different organs may be affected**
  - **Typically skin, joints, kidneys and lungs**
  - **Prognosis varies depending on pattern of organ involvement**
  - **Treatment also depends on organs involved**

Vasculitis – under the microscope

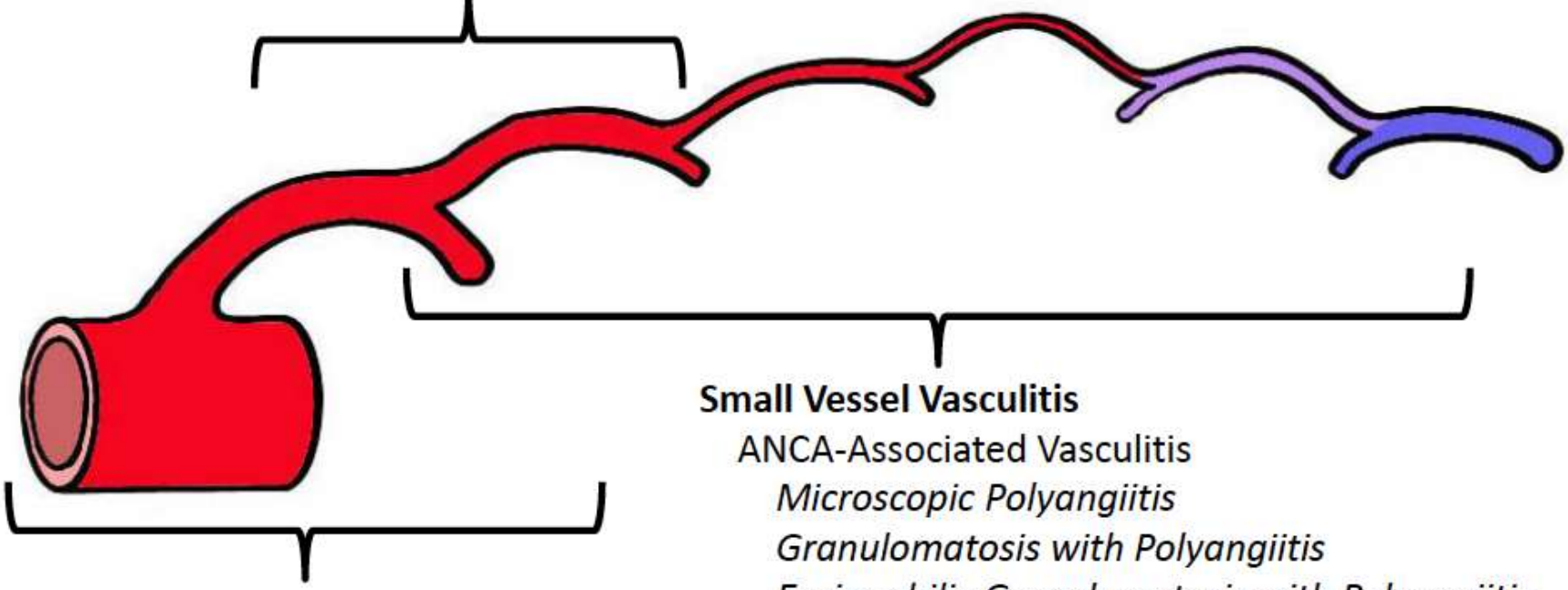


WHAT ARE THE DIFFERENT TYPES OF VASCULITIS?

Vasculitis meeting on classification Chapel Hill 1992, 2012

2nd International Consensus Conference on the Nomenclature of Systemic Vasculitidies 2012

Medium Vessel Vasculitis
Polyarteritis Nodosa
Kawasaki Disease



Small Vessel Vasculitis
ANCA-Associated Vasculitis
Microscopic Polyangiitis
Granulomatosis with Polyangiitis
Eosinophilic Granulomatosis with Polyangiitis
Immune Complex SVV
Anti-GBM Disease
Cryoglobulinemic Vasculitis
IgA Vasculitis (Henoch-Schönlein)
Hypocomplementemic Urticarial Vasculitis (Anti-C1q Vasculitis)

Large Vessel Vasculitis
Takayasu Arteritis
Giant Cell Arteritis

Jennette et al, *Arthritis Rheum* 2012

Medium Vessel Vasculitis
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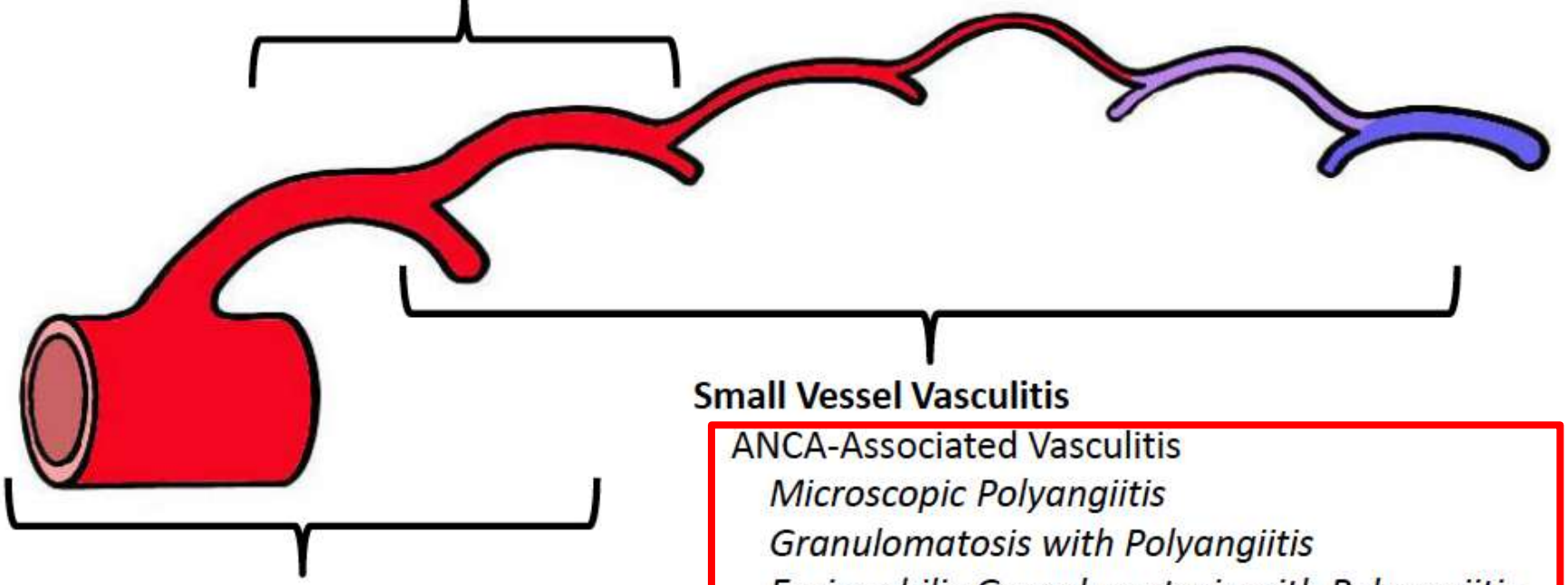
Kawasaki Disease



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Large Vessel Vasculitis
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Jennette et al, *Arthritis Rheum* 2012

EDITORIALS www.jasn.org

Granulomatosis with Polyangiitis (Wegener's): An Alternative Name for Wegener's Granulomatosis

ARD

Granulomatosis with polyangiitis (Wegener's): An alternative name for Wegener's granulomatosis

Ronald J Falk, Wolfgang L Gross, Loïc Guillevin, et al.

Ann Rheum Dis 2011 70: 704

AAV = GPA + MPA

Eosinophilic granulomatosis with polyangiitis (eGPA)

ALLERGIC GRANULOMATOSIS, ALLERGIC ANGIITIS, AND PERIARTERITIS NODOSA *

JACOB CHURG, M.D., and LOTTE STRAUSS, M.D.

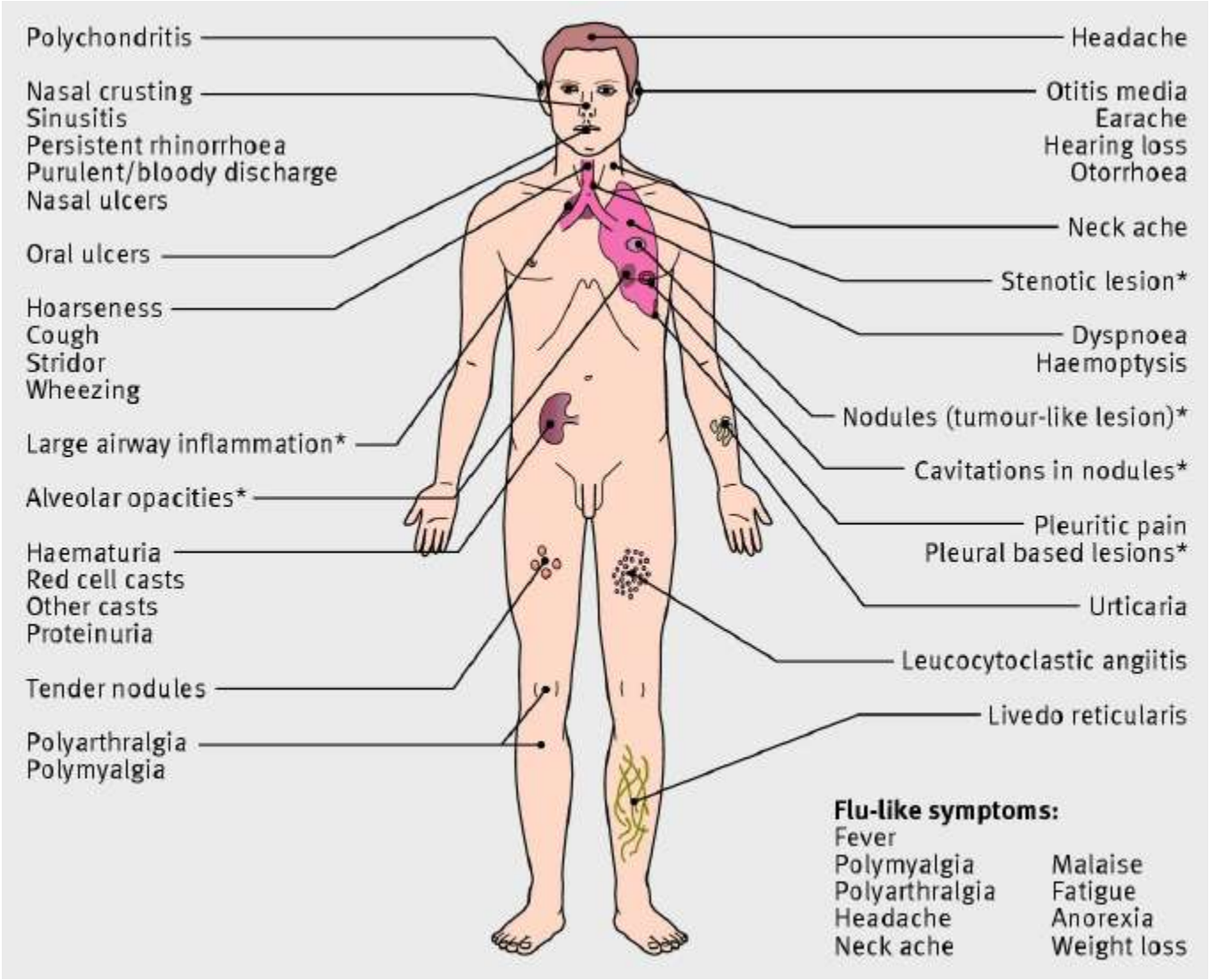
(From the Laboratories, Division of Pathology, the Mount Sinai Hospital, New York 29, N.Y.)

* Read by title at the Forty-sixth Annual Meeting of The American Association of Pathologists and Bacteriologists, Boston, April 15 and 16, 1949.
Received for publication, June 16, 1950.

AAV = GPA + MPA + eGPA

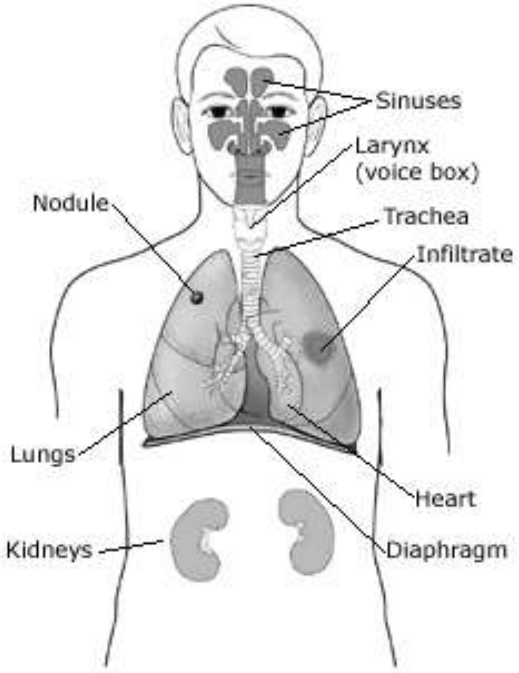
WHAT ARE THE SYMPTOMS OF ANCA VASCULITIS?

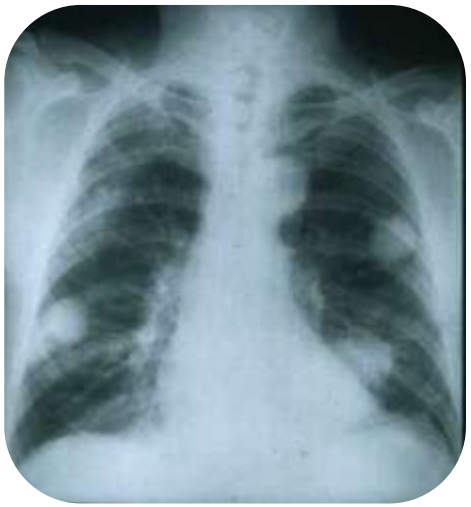
Clinical features



Berden et al BMJ 2012

Clinical features

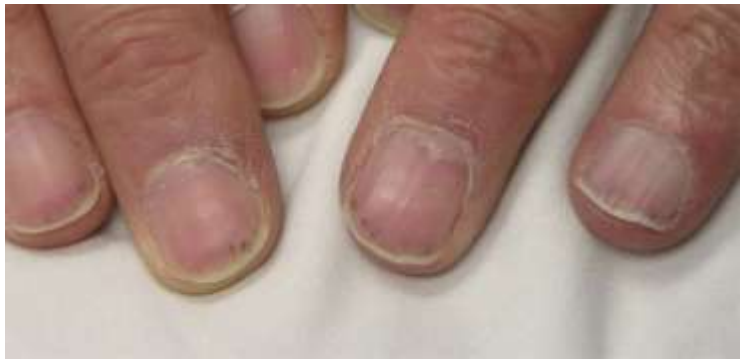




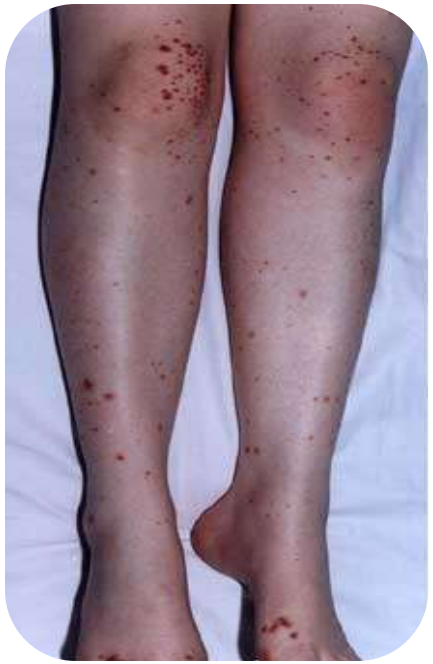
Small vessel vasculitis

Granulomatosis with polyangiitis (Wegeners)

- **May involve URT, lungs, kidneys, skin, joints, nerves, eyes, meninges**
- **Granuloma**
- **Blood tests: cANCA/PR3**



Clinical features

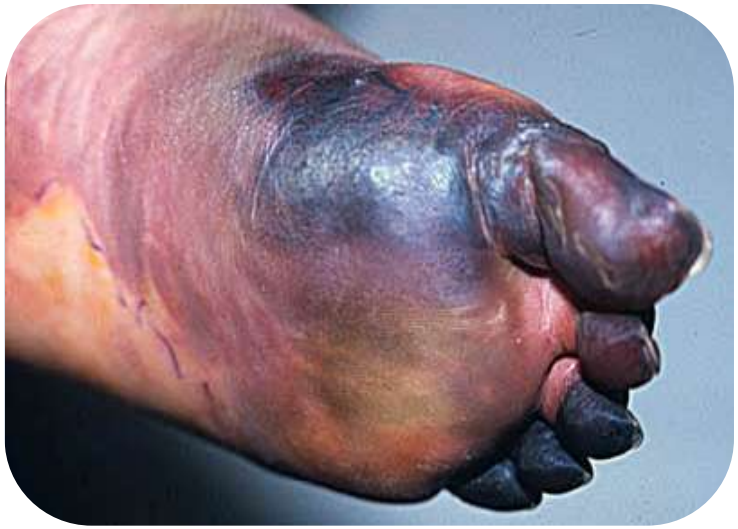


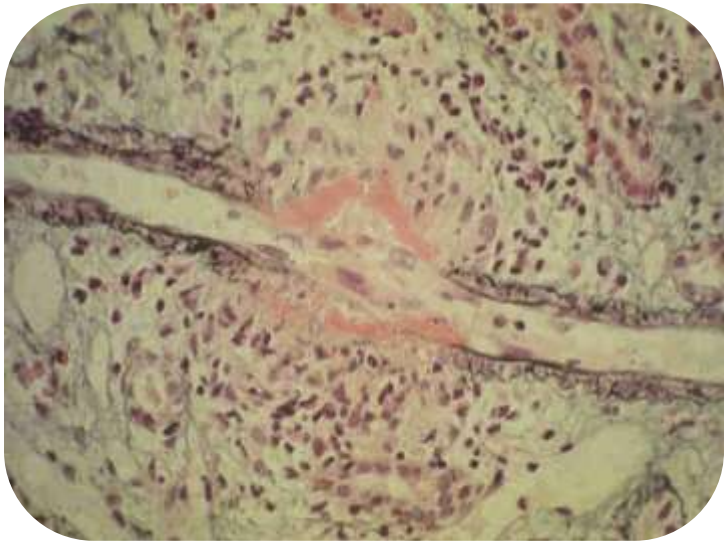
Small vessel vasculitis

- Microscopic polyangiitis

- **Skin, joints, kidneys, lungs, nerves, eyes.**

- **Blood tests: pANCA/anti-MPO**

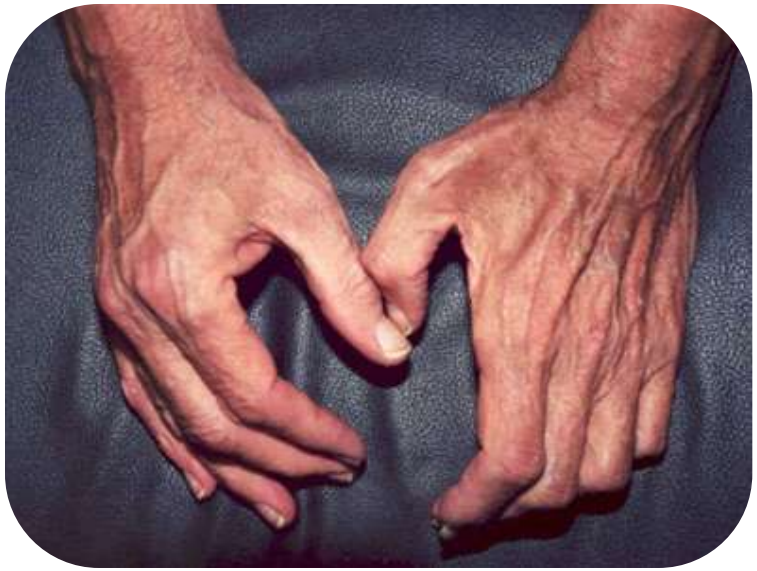




Clinical features

Small vessel vasculitis

-Churg-Strauss syndrome



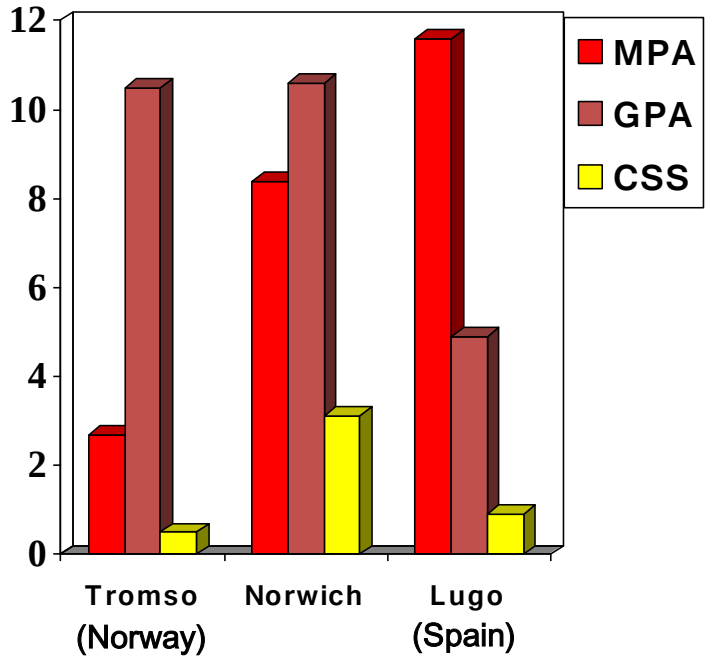
- Asthma, URT, nerves, gut, heart
- Histology: Eosinophilic vasculitis
- Blood tests: High eosinophils, ANCA+ve in < 50%

WHO GETS ANCA VASCULITIS?

Vasculitis : Epidemiology

How common is AAV?

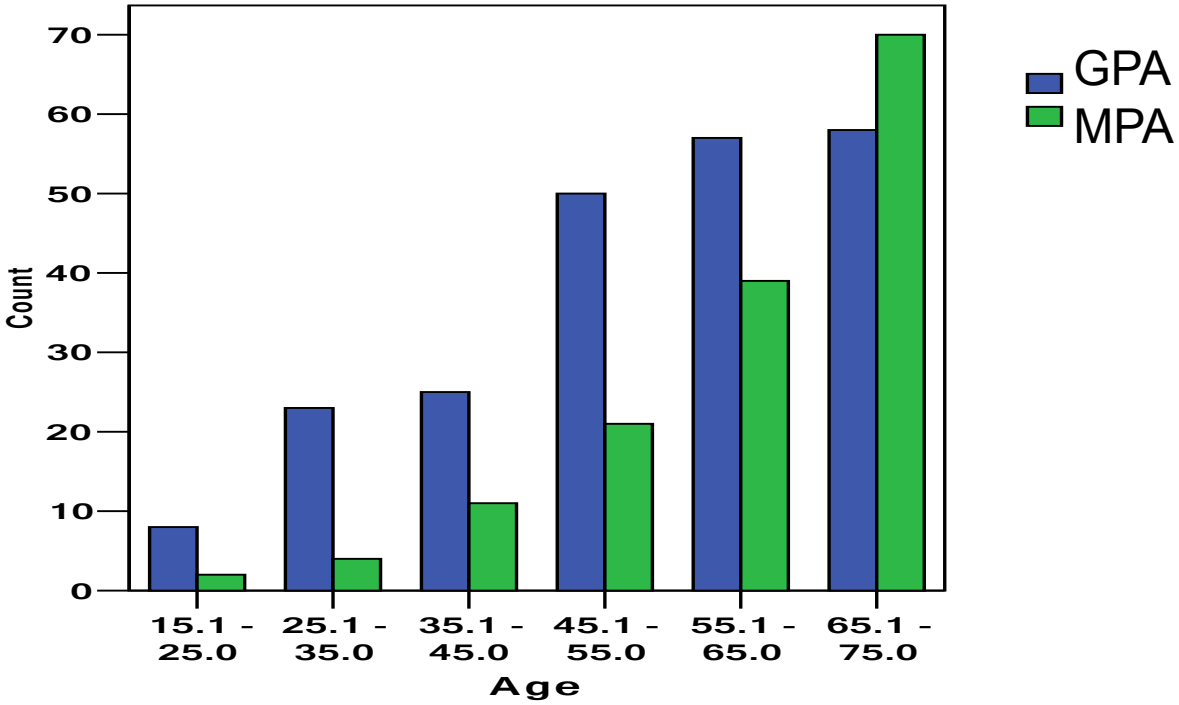
- In UK : Incidence of AAV = 20/pmp
- Geographical variation



Vasculitis : Epidemiology

Who is affected by AAV?

- Older age



Vasculitis : Epidemiology

Who is affected by AAV?

- Occupation

Risk	
	OR
Farming	2.3
Livestock	2.9
Silica	3.0

Vasculitis : Epidemiology

Who is affected by AAV?

- Flares associated with infection

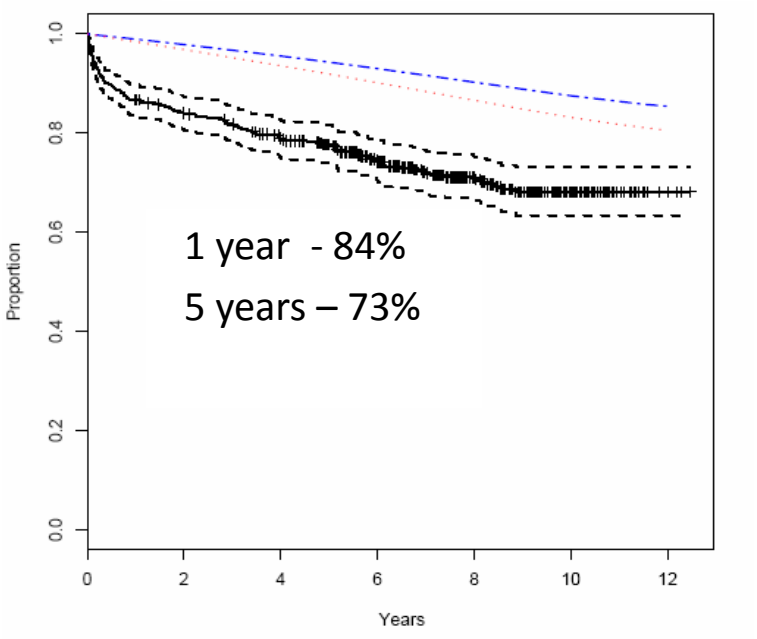
• Nasal carriage of *Staph aureus* present in 65% of patients with GPA versus 20% of controls

• Nasal carriage of SA strongly associated with relapse in GPA

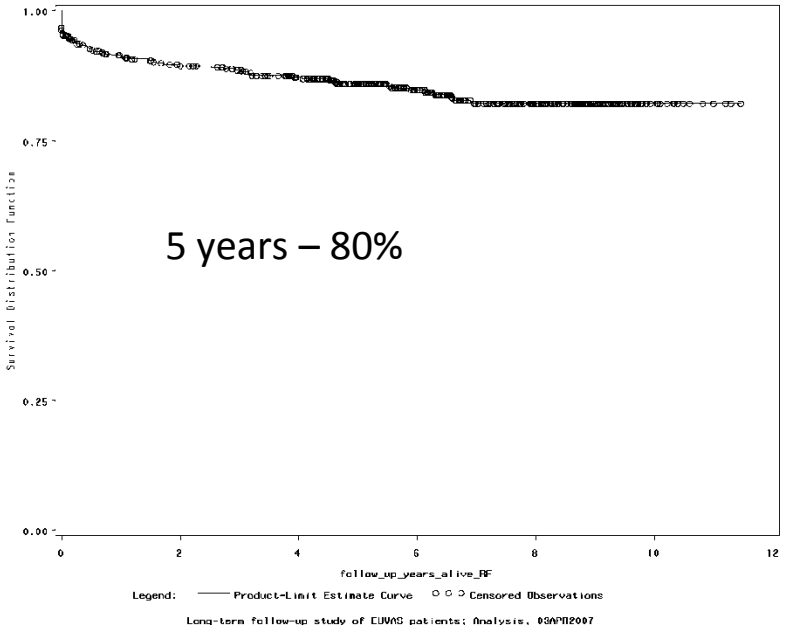
DOES ANCA VASCULITIS AFFECT LIFE EXPECTANCY?

Survival and End Stage Renal Disease in AAV

Patient survival



Renal survival



Flossmann et al, *Ann Rheum Dis* 2010

Survival in AAV

- Before treatment (1960s) average survival was 5 months, with 82% patients dead after one year
- With treatment, increased risk of death = 2.6x that of age-matched controls
- Death within the first year is usually from infection or active vasculitis
- After 1 year, increased risk of death = 1.3x age-matched controls, from infection, CVD or cancer

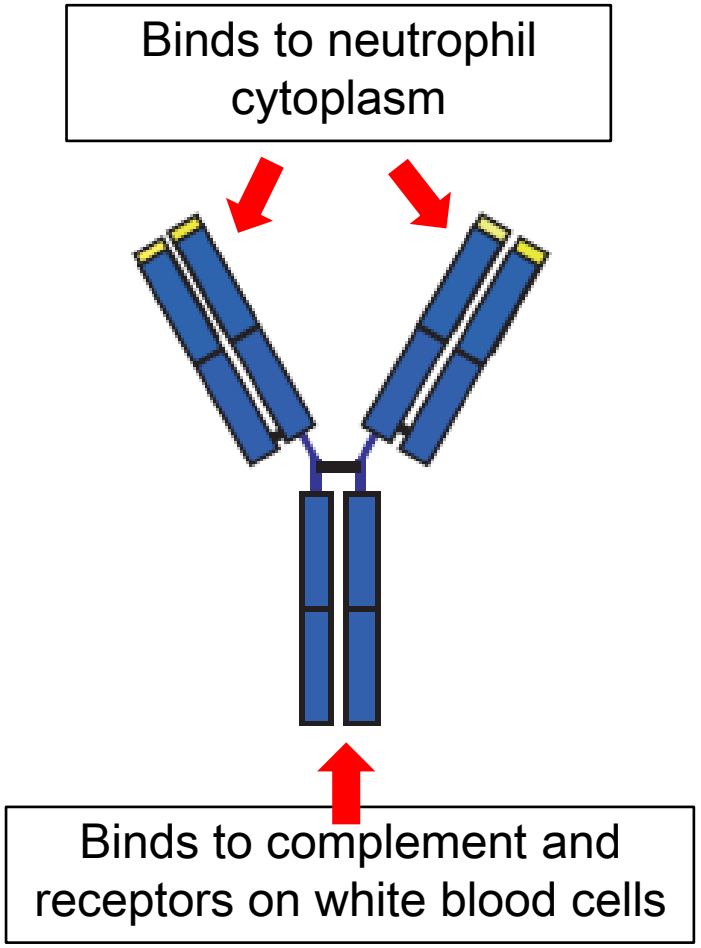
Flossman et al, Ann Rheum Dis 2011

WHAT CAUSES ANCA VASCULITIS?

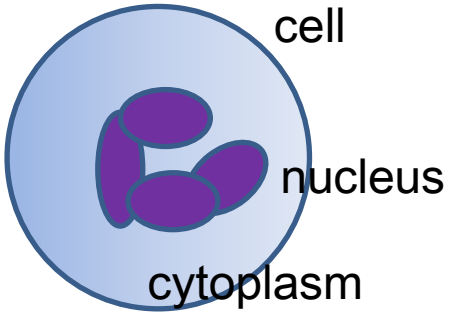
What are ANCA?

Anti Neutrophil Cytoplasmic Antibody

- **Antibodies are a key part of the immune system**
- **Should be directed against viruses and bacteria**
- **In autoimmune disease, target self, "loss of tolerance"**
- **In ANCA vasculitis, antibodies target neutrophils, white blood cell**

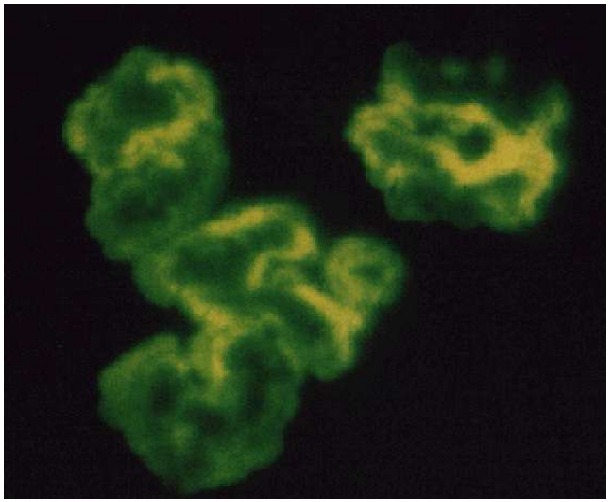


ANCA-associated vasculitis



Anti Neutrophil Cytoplasmic Antibody

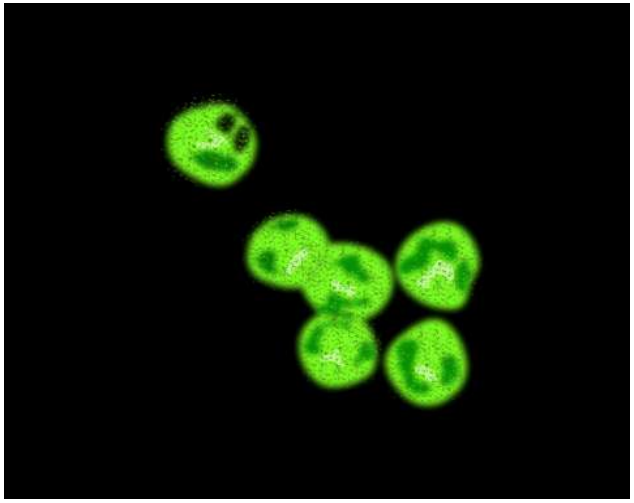
pANCA



Perinuclear

Myeloperoxidase

cANCA



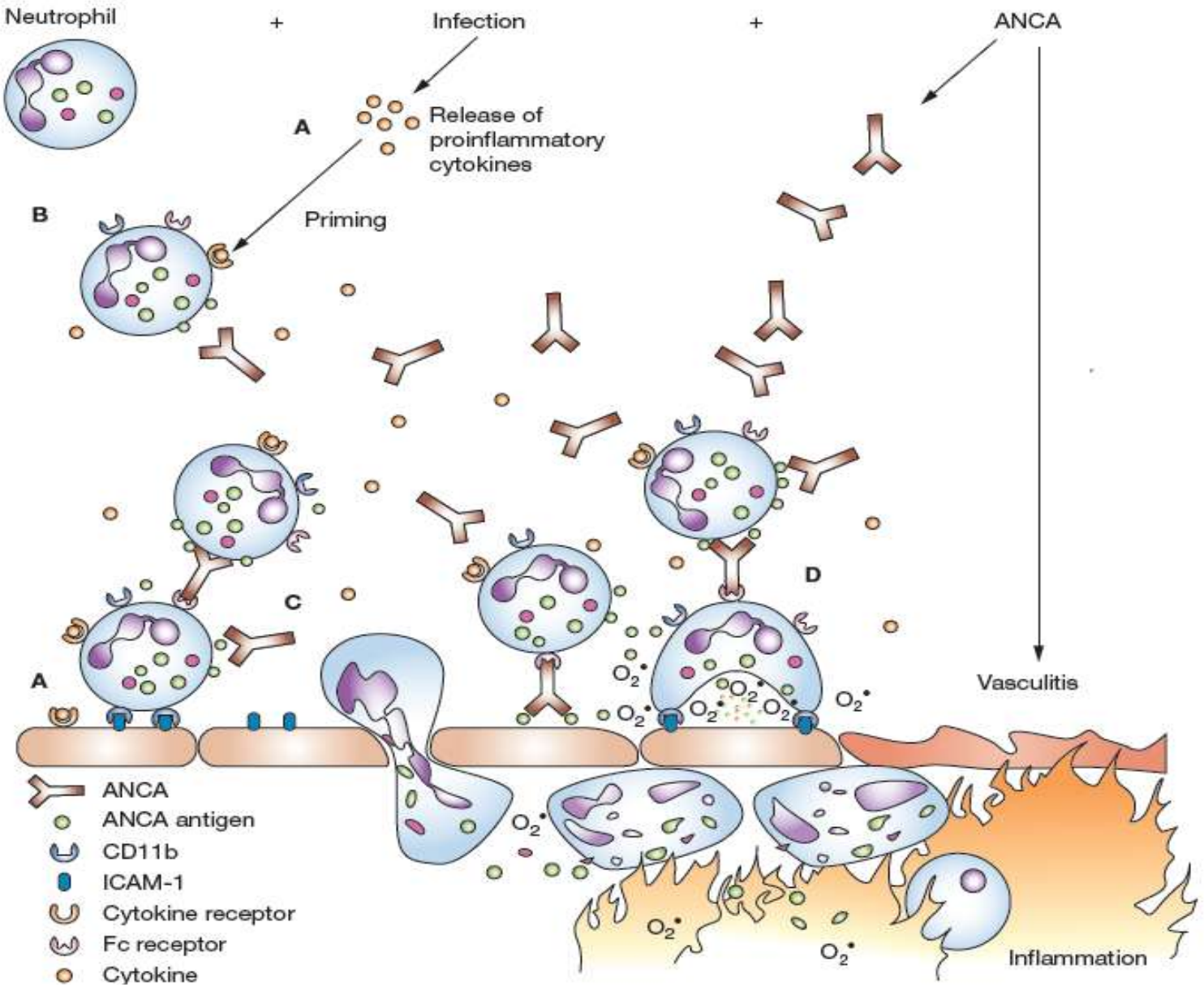
Cytoplasmic

Proteinase-3

Disease associations of ANCA

	PR3-ANCA(%)	MPO-ANCA (%)
Granulomatosis with polyangiitis	70-80	10
Microscopic Polyangiitis	30	60
Churg Strauss Syndrome	<5	40

Does ANCA cause vasculitis?

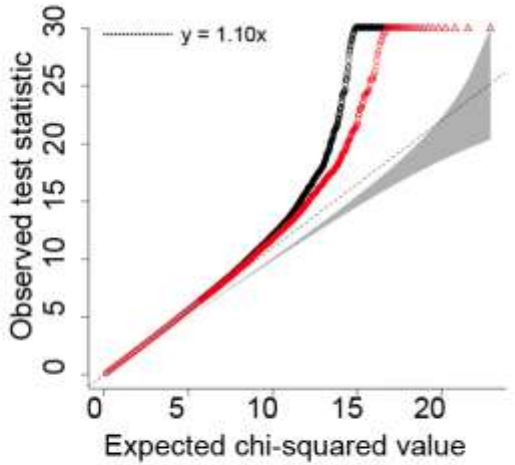


GENETICS AND ANCA VASCULITIS

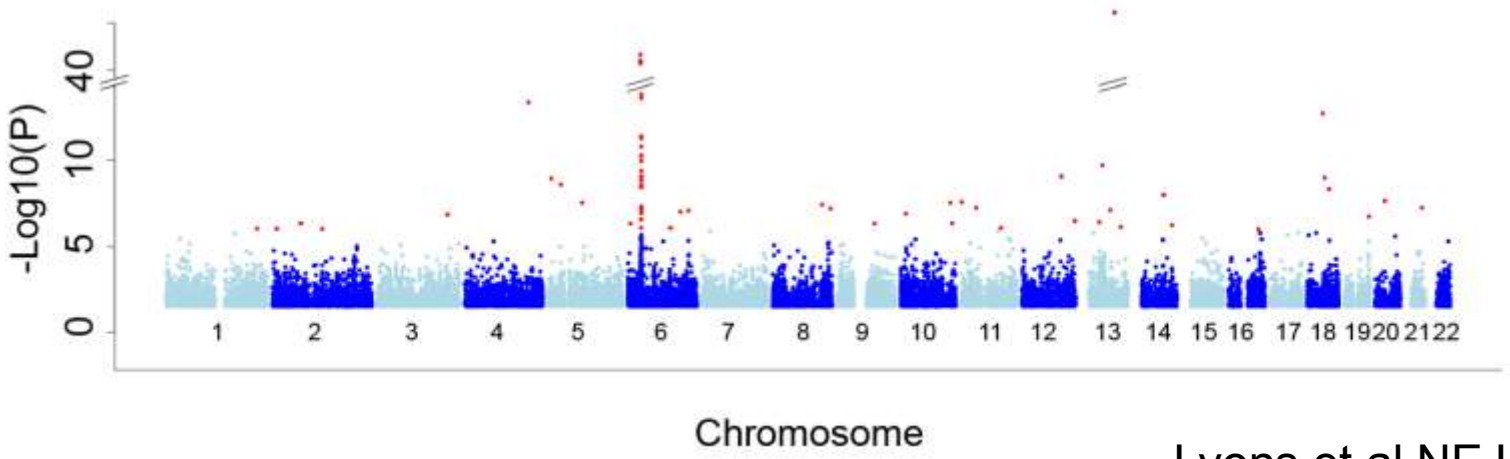
ORIGINAL ARTICLE

Genetically Distinct Subsets within ANCA-Associated Vasculitis

Genotyped 612,676 SNPs across 914 UK cases and 5,259 UK controls



AAV has a genetic component



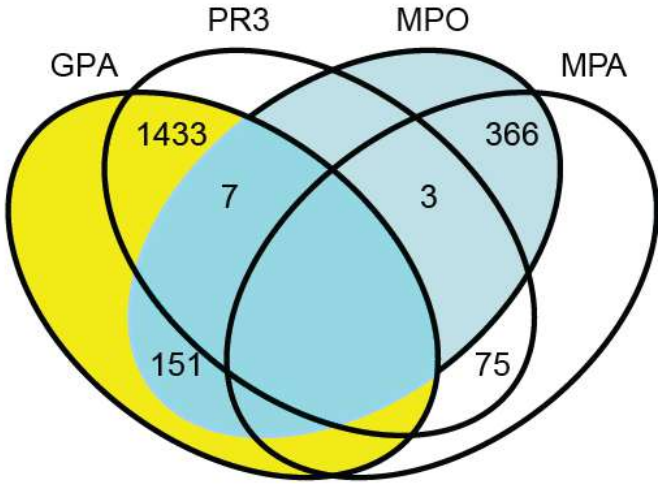
Lyons et al NEJM 2012

GPA and MPA are distinct genetic entities

Locus	Overall analysis 2267 v 6858		Clinical syndrome					
			GPA v MPA 1683 v 489		GPA v Control		MPA v Control	
	OR	P	OR	P	OR	P	OR	P
HLA-DP	3.67	1.5×10^{-71}	3.49	1.9×10^{-27}	5.39	3.1×10^{-85}	1.60	1.3×10^{-03}
SERPINA1	0.59	2.4×10^{-09}	0.74	1.7×10^{-01}	0.54	4.4×10^{-10}	0.76	1.7×10^{-01}
PRTN3	0.83	6.6×10^{-04}	0.81	3.9×10^{-02}	0.78	2.6×10^{-05}	0.99	9.3×10^{-01}

Lyons et al NEJM 2012

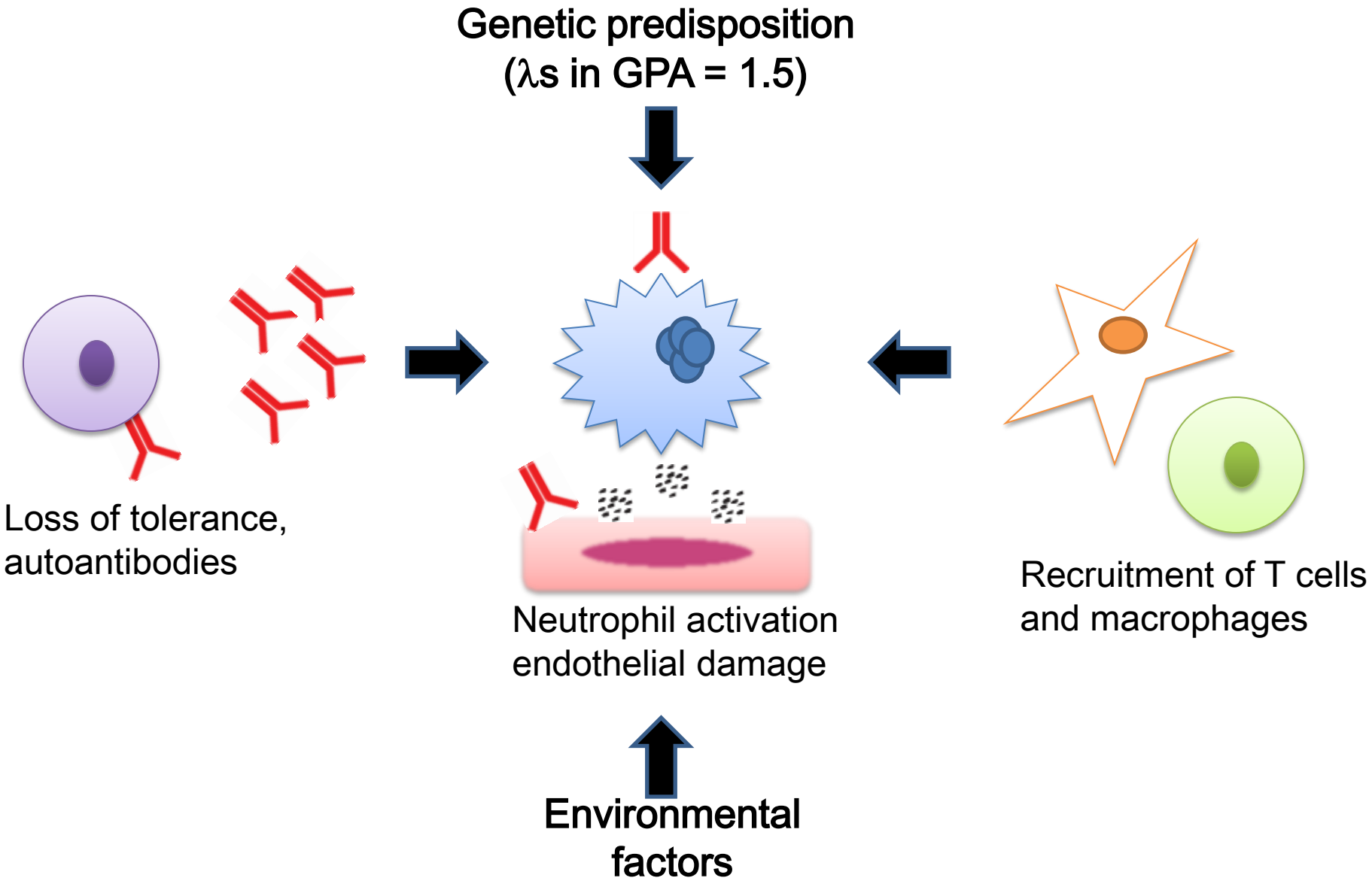
ANCA status not clinical syndrome best defines the observed genetic associations



	GPA						MPA					
Locus	PR3 v MPO		PR3 v Control		MPO v Control		PR3 v MPO		PR3 v Control		MPO v Control	
	1433 v 151						75 v 366					
	OR	P	OR	P	OR	P	OR	P	OR	P	OR	P
HLA-DP	5.24	4.9×10^{-24}	7.51	3.7×10^{-86}	1.60	9.2×10^{-02}	2.76	6.9×10^{-04}	2.49	9.8×10^{-05}	1.50	1.4×10^{-01}
HLA-DQ	1.46	3.1×10^{-02}	0.86	7.8×10^{-05}	0.62	2.1×10^{-05}	1.34	6.9×10^{-01}	0.79	4.7×10^{-01}	0.68	1.4×10^{-05}
SERPINA1	0.63	1.9×10^{-01}	0.52	1.2×10^{-10}	0.72	4.3×10^{-01}	0.37	2.8×10^{-03}	0.31	1.5×10^{-05}	0.78	9.8×10^{-01}
PRTN3	0.61	2.3×10^{-03}	0.73	3.9×10^{-07}	1.22	2.2×10^{-01}	0.60	1.1×10^{-01}	0.65	1.3×10^{-01}	1.03	7.7×10^{-01}

Lyons et al NEJM 2012

Summary


Genetic predisposition
(λs in GPA = 1.5)
Loss of tolerance,
autoantibodies
Neutrophil activation
endothelial damage
Recruitment of T cells
and macrophages
Environmental
factors

Acknowledgements

Vasculitis and Lupus Service
Addenbrooke's Hospital, Cambridge

- David Jayne
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- Afzal Chaudhry
- Menna Clatworthy
- Rachel Jones
- Rona Smith
- Alina Casian
- Liz Wallin
- Stella Burns
- Jane Hollis
- Karen Dahlsveen

ANY QUESTIONS?

Treatment - Immunosuppressants

- **Prednisolone** (reduces production of inflammatory mediators)
- **Methotrexate** (inhibits folate synthesis)
- **Cyclophosphamide** (inhibits DNA synthesis)
- **Azathioprine** (inhibits purine synthesis)
- **Mycophenolate mofetil (MMF)** (inhibits purine synthesis)
- **"Biologics"**
  - Rituximab – depletes B cells
  - Alemtuzumab - depletes lymphocytes

Treatment

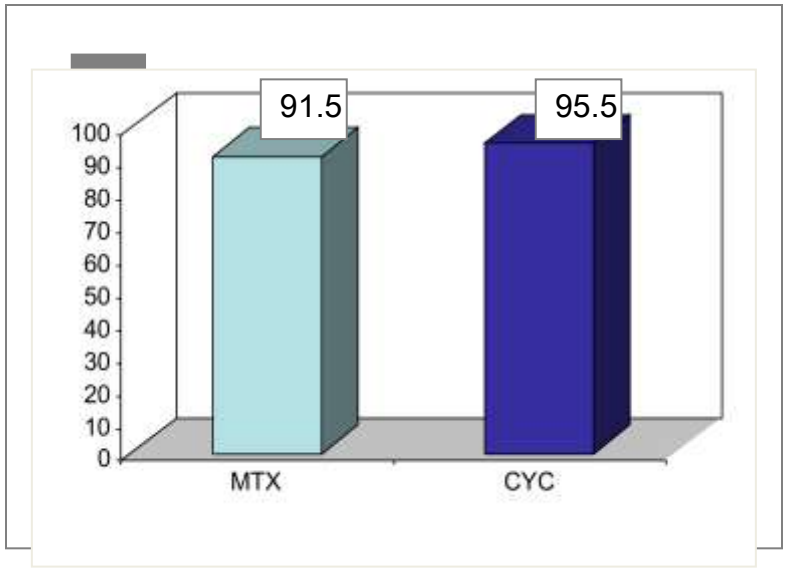
Disease classification	Definition	Treatment
Early systemic vasculitis	Constitutional symptoms, Cr<120, no vital organ threatened	Methotrexate or cyclophosphamide and steroids

Treatment

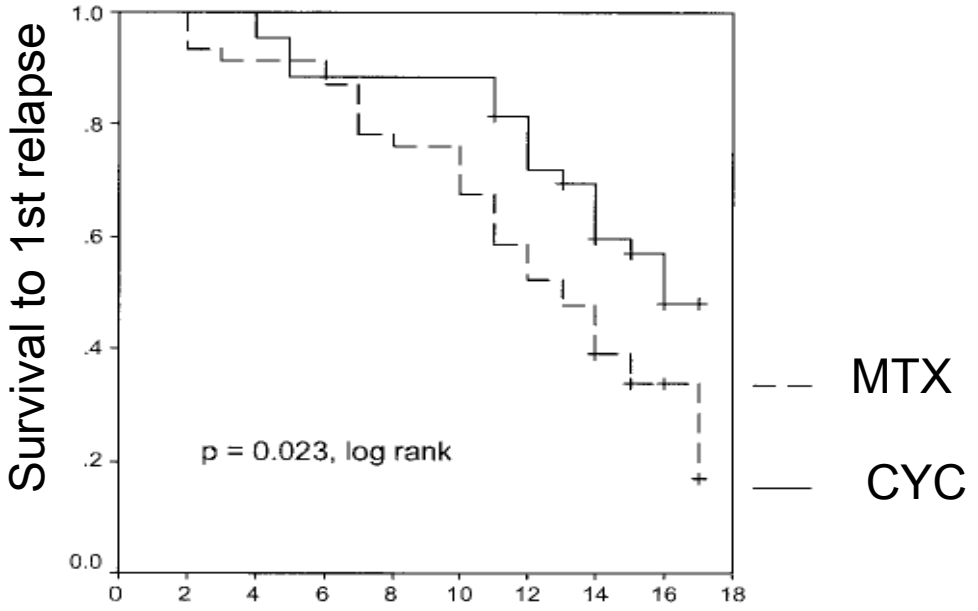
NORAM

- Methotrexate equivalent at 18 months to cyclophosphamide for non-severe disease

Remission



Relapse



p = 0.02

N=100

de Groot et al, *Arthritis Rheum* 2005

Treatment

NORAM – Long term follow up

- The median duration of follow up was 6 years

- No difference in survival, serious infection, malignancy, or severe organ failure

- Patients in the MTX received corticosteroids, CYC, and other immunosuppressive agents (azathioprine, MTX, and/or mycophenolate mofetil) for longer periods than the CYC group

- The cumulative relapse-free survival tended to be lower in the MTX group ($P = 0.056$).

Faurschou et al, *Arthritis Rheum* 2012

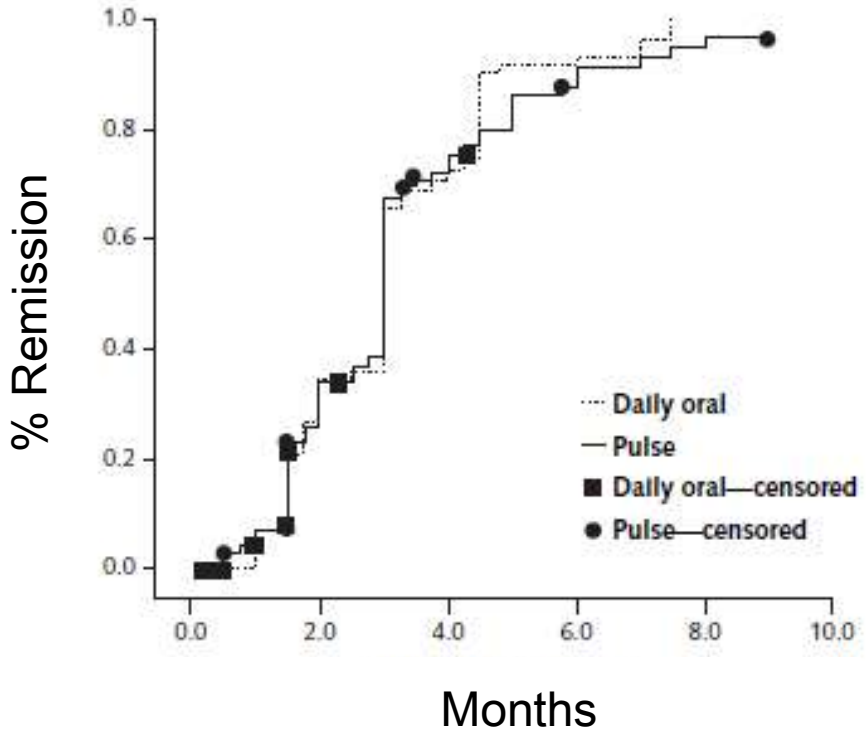
Treatment

Disease classification	Definition	Treatment
Early systemic vasculitis	Constitutional symptoms, Cr<120, no vital organ threatened	Methotrexate or cyclophosphamide and steroids
Generalised vasculitis	Cr<500, dysfunction of a vital organ	Steroids + cyclophosphamide for remission induction then steroids + azathioprine for maintenance

Treatment

CYCLOPS

- IV pulse instead of daily oral cyclophosphamide induction
- n=149

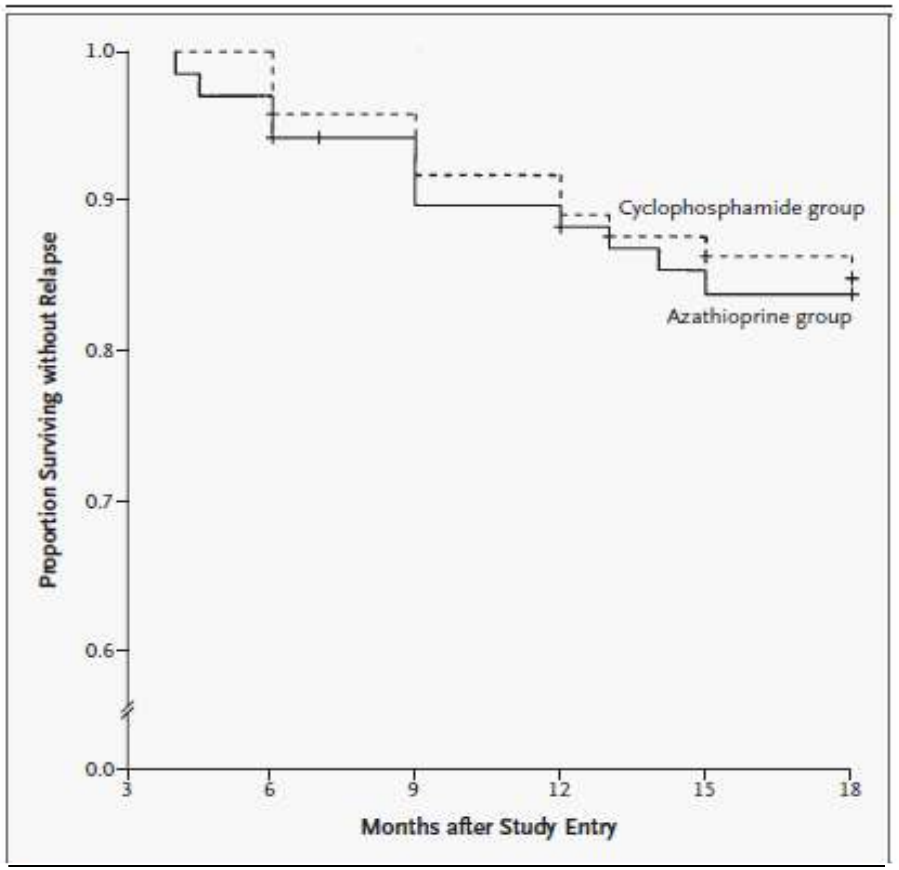


de Groot et al, *Ann Int Med* 2009

Treatment

CYCAZAREM

- Switch to azathioprine on remission from 3-6 months
- n=155

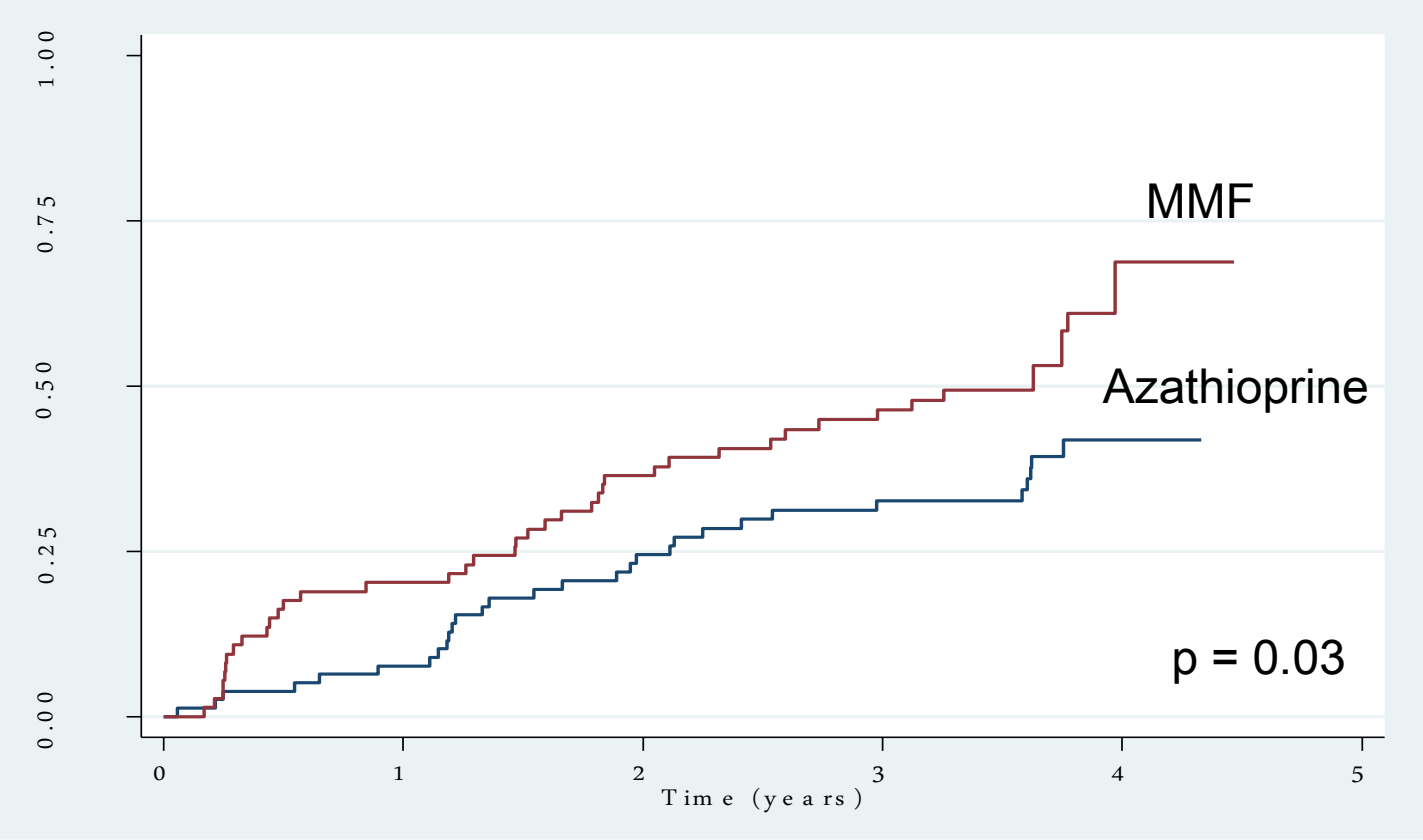


Jayne, *N Engl J Med* 2003

Treatment

IMPROVE

- Azathioprine superior to MMF for remission maintenance
- n=156



Hiemstra, *Ann Int Med* 2010

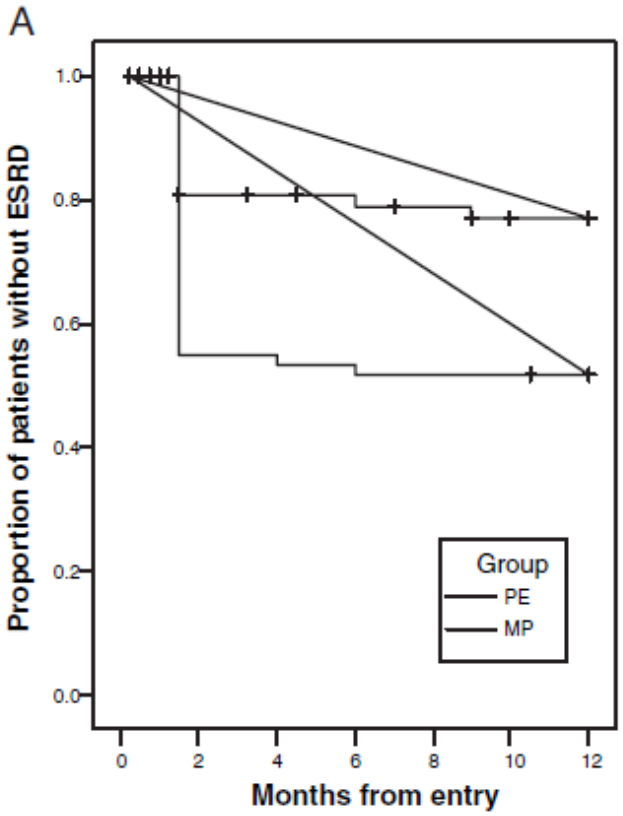
Treatment

Disease classification	Definition	Treatment
Early systemic vasculitis	Constitutional symptoms, Cr<120, no vital organ threatened	Methotrexate and steroids
Generalised vasculitis	Cr<500, dysfunction of a vital organ	Steroids + cyclophosphamide for remission induction then steroids + azathioprine for maintenance
Severe renal or pulmonary vasculitis	Serum Cr>500 or alveolar haemorrhage	Plasma exchange, steroids + cyclophosphamide for remission induction then steroids + azathioprine for maintenance

Treatment

MEPEX

- **Creatinine > 500 μmol/l**
- **Reduced incidence of ESRD after plasma exchange**



MP = 3x1g methylprednisolone

PE = Plasma exchange

N = 137, p = 0.04

Jayne et al, *J Am Soc Nephrol* 2007

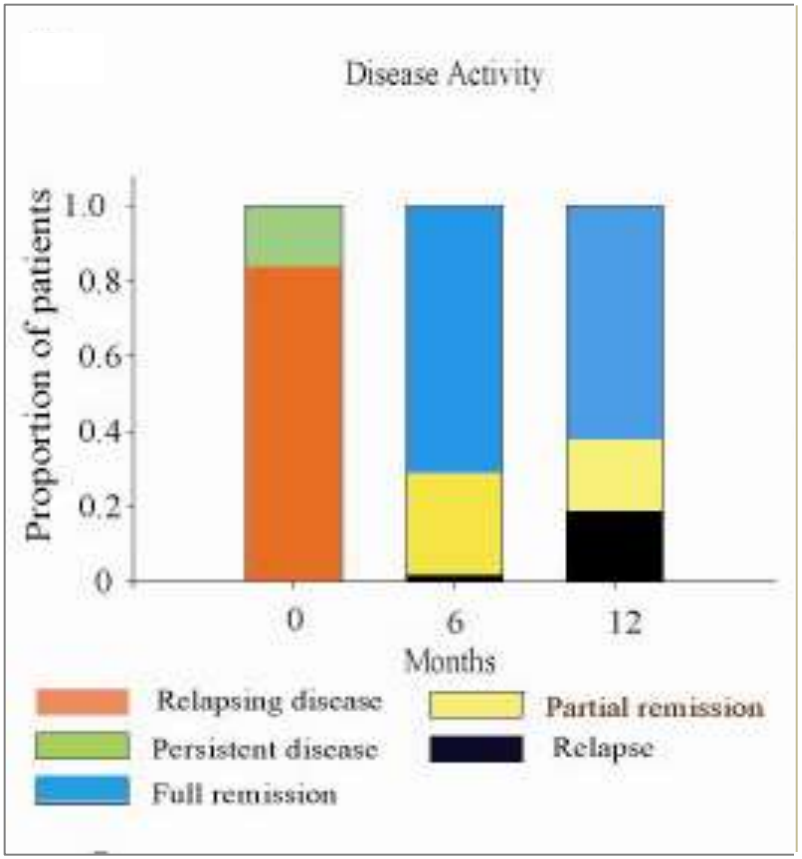
Treatment

Disease classification	Definition	Treatment
Early systemic vasculitis	Constitutional symptoms, Cr<120, no vital organ threatened	Methotrexate and steroids
Generalised vasculitis	Cr<500, dysfunction of a vital organ	Steroids + cyclophosphamide for remission induction then steroids + azathioprine for maintenance
Severe renal or pulmonary vasculitis	Serum Cr>500 or alveolar haemorrhage	Plasma exchange, steroids + cyclophosphamide for remission induction then steroids + azathioprine for maintenance
Refractory vasculitis	Vital organ dysfunction, no response to standard therapy	Rituximab

Treatment

Rituximab to treat AAV

- **Retrospective study of 65 patients**
- **Full remission 75%, immunosuppression withdrawn and steroids tapered**



Jones, *Arthritis Rheum* 2009

Treatment

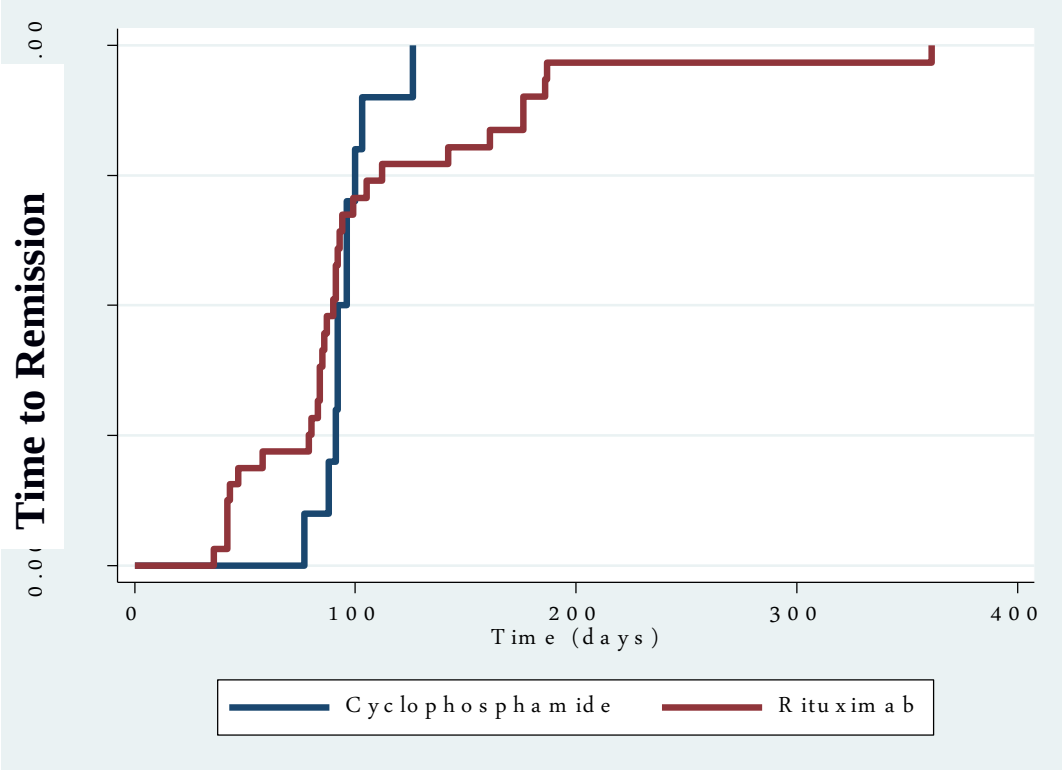
Randomised Trial Results - Rituximab

- 'RITUXVAS' Jones et al, NEJM 2010
  - N=44
  - New renal AAV
  - FU 12 months
- 'RAVE' Stone et al, NEJM 2010
  - N=200
  - New/relapsing AAV
  - Severe renal excluded
  - FU 6 months

RITUXVAS

Sustained remission at 6 months

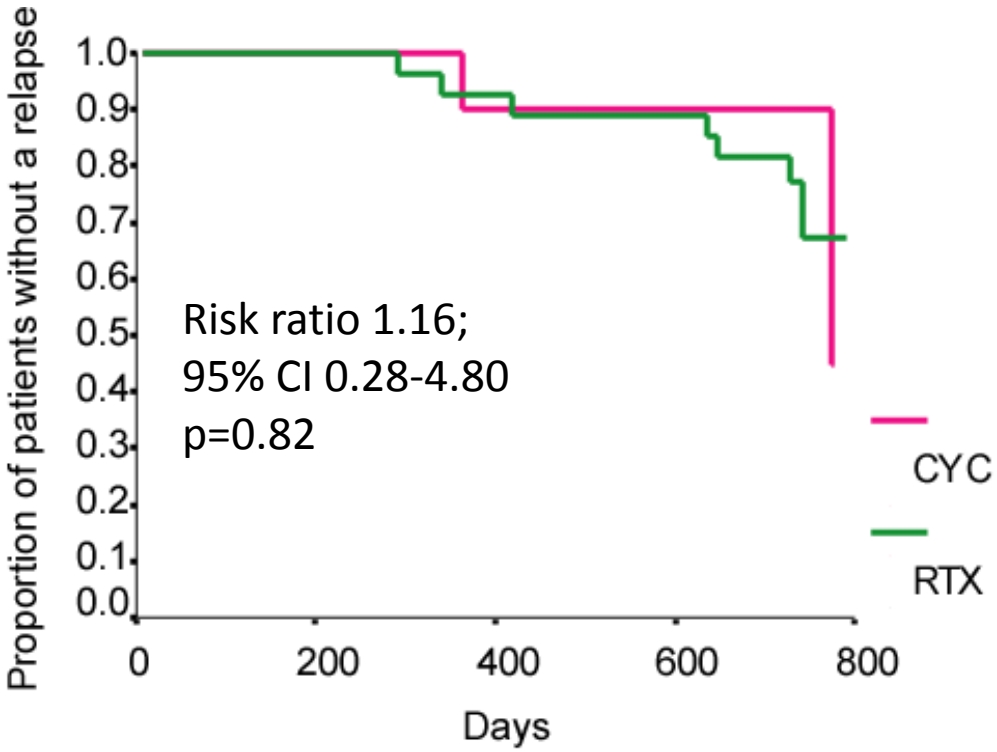
	RTX	CYC
Sustained remission	25/33 (76%)	9/11 (82%)
No sustained remission	2 incomplete response 6 deaths	1 incomplete response 1 death



Jones et al, NEJM 2010

Two year outcome data - RITUXVAS

	RTX N=27	CYC N=10
Relapse	**7 (26%)**	**2 (20%)**
Major	1 (3%)	2 (18%)
Minor	6 (18%)	0 (0%)

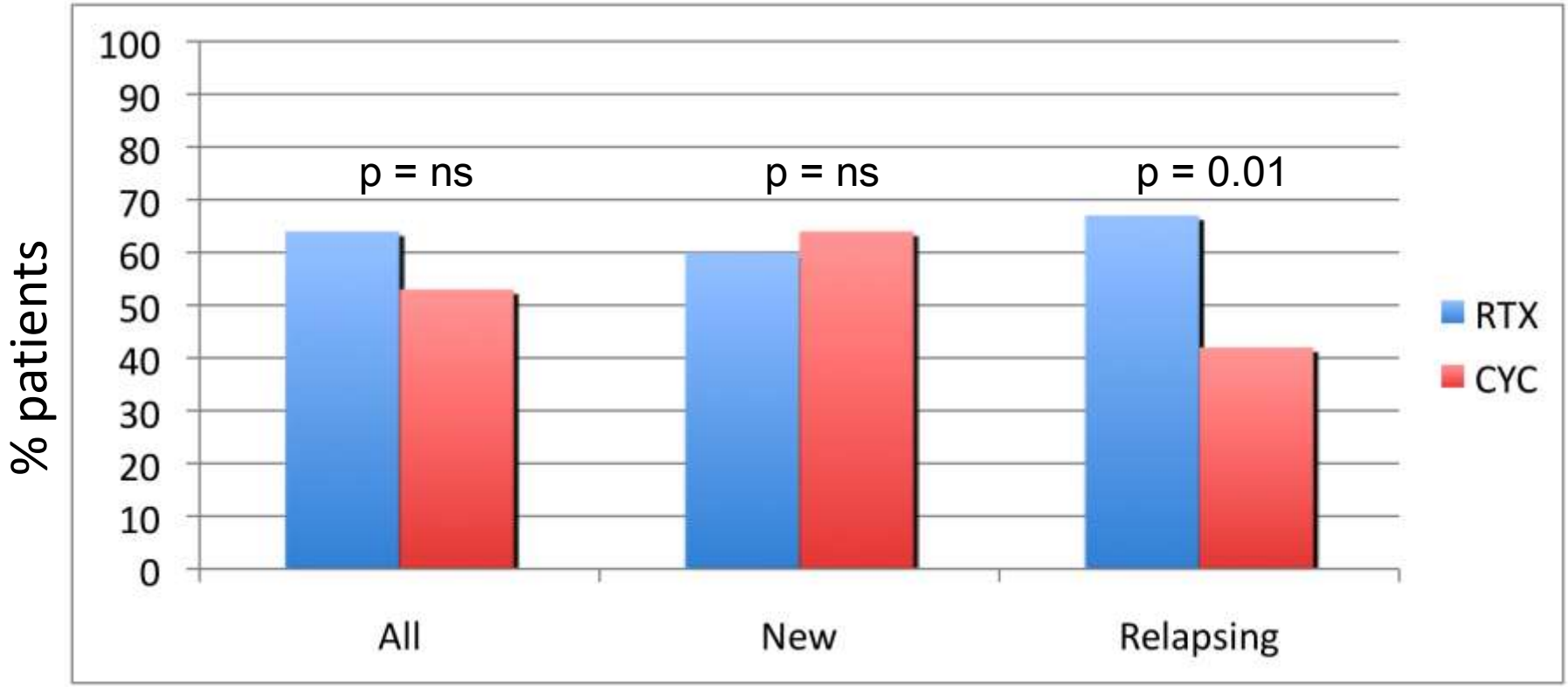


Similar adverse event rates in the two groups

Jones et al, oral presentation ASN/ACR 2010

RAVE

- **Randomised study of 197 new and relapsing AAV**
- **Cyclophosphamide or rituximab**
- **Primary endpoint = steroid-free remission at 6 months**

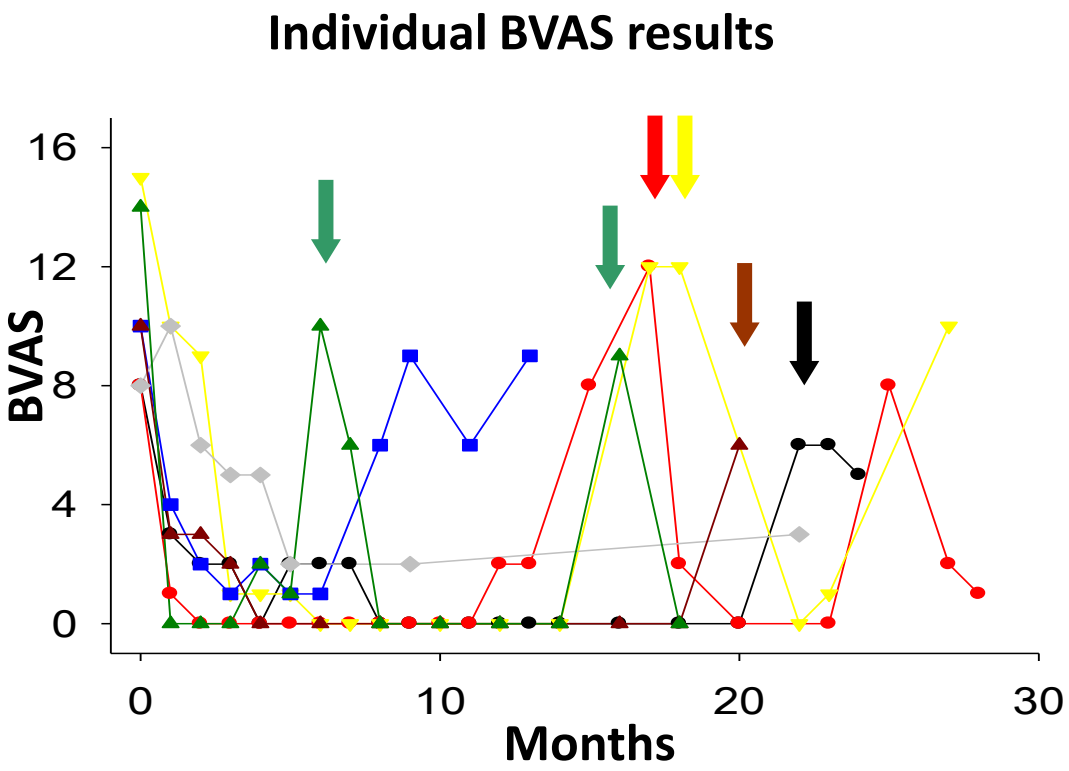


Stone J et al, *N Engl J Med* 2010

Treatment

Rituximab retreatment for relapsing disease

- 11 refractory patients
- 9 achieved complete remission
- 58% relapsed after median 12 months
- Retreatment successful



Smith, Arthritis Rheum 2006

Treatment

Rituximab retreatment for remission maintenance

- Retrospective study of 3 groups of patients, treated with either
  - Group A (n = 28) received rituximab induction and further rituximab at the time of subsequent relapse.
  - Group B (n = 45) received routine rituximab re-treatment for 2 years
  - Group C (n = 19) were patients in group A who subsequently relapsed and began routine re-treatment for 2 years.
- Remission achieved in 93% of group A, 96% of group B, and 95% of group C.
- At 2 years, relapses had occurred in 73% in group A, 12% in group B ($P < 0.001$), and 11% in group C ($P < 0.001$)

Smith, Jones et al, Arthritis Rheum 2012

Treatment

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Refractory vasculitis	Vital organ dysfunction, no response to standard therapy	Rituximab

Treatment – Future directions?

- **Rituximab as induction and maintenance therapy (first line)?**
- **MMF to replace cyclophosphamide as induction therapy?**
- **Plasma exchange as well as methylprednisolone in severe pulmonary and/or renal vasculitis?**
- **Alemtuzumab in refractory disease?**