# Pathogenesis and prognosis of ANCA associated vasculitis

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# Disclosures

Consultant to ChemoCentryx

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# Outline

- Pathogenesis of ANCA vasculitis (experimental and clinical data)
  - ANCA
  - Neutrophils
  - Complement pathway
  - Cellular immunity
- Prognosis of ANCA vasculitis

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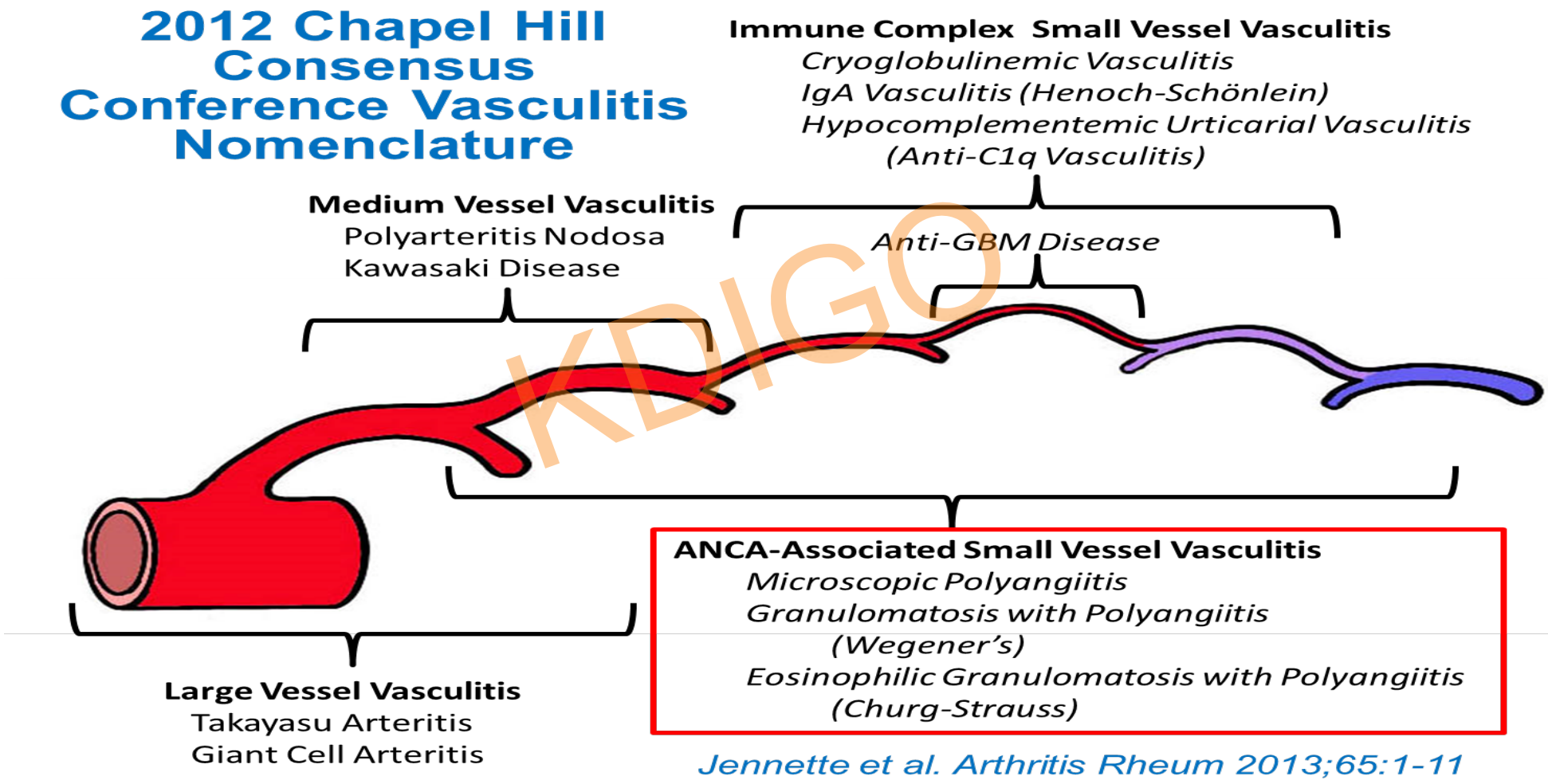
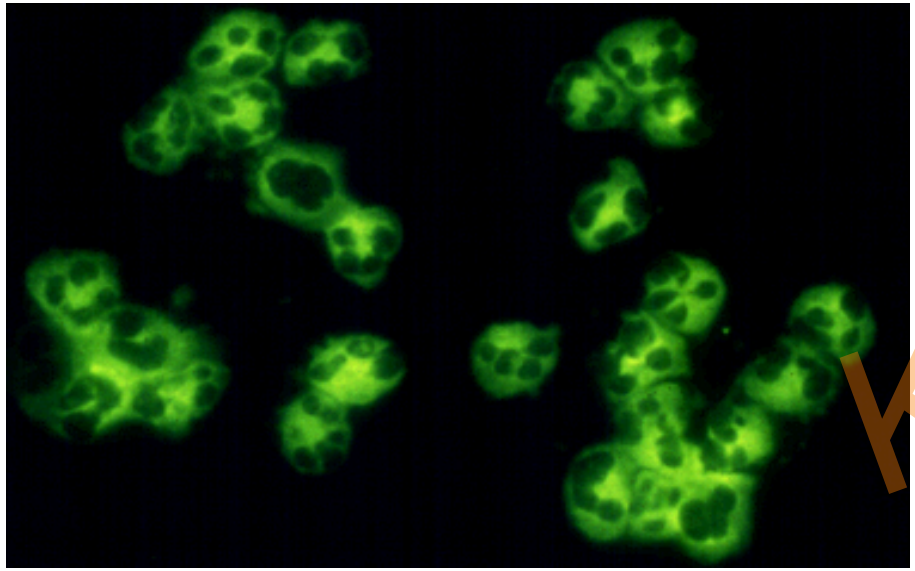
# Vasculitis Nomenclature

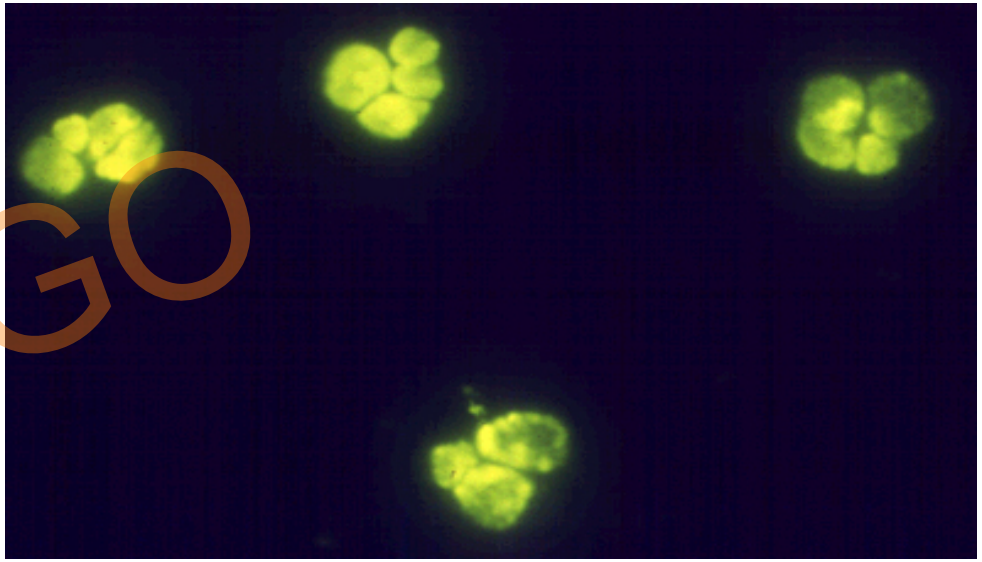



Jennette et al. Arthritis Rheum 2013;65:1-11

# ANCA types



c-ANCA (PR 3)



p-ANCA (MPO and others)

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# ANCA disease associations

| | PR3-ANCA (mostly cANCA) | MPO-ANCA (mostly pANCA) | Other |
|---|---|---|---|
| **ANCA-Associated Vasculitis** | | | |
| GPA | 75% | 20% | 5% ANCA negative |
| MPA | 30% | 60% | 10% ANCA negative |
| EGPA | 5% | 45% | 50% ANCA negative |

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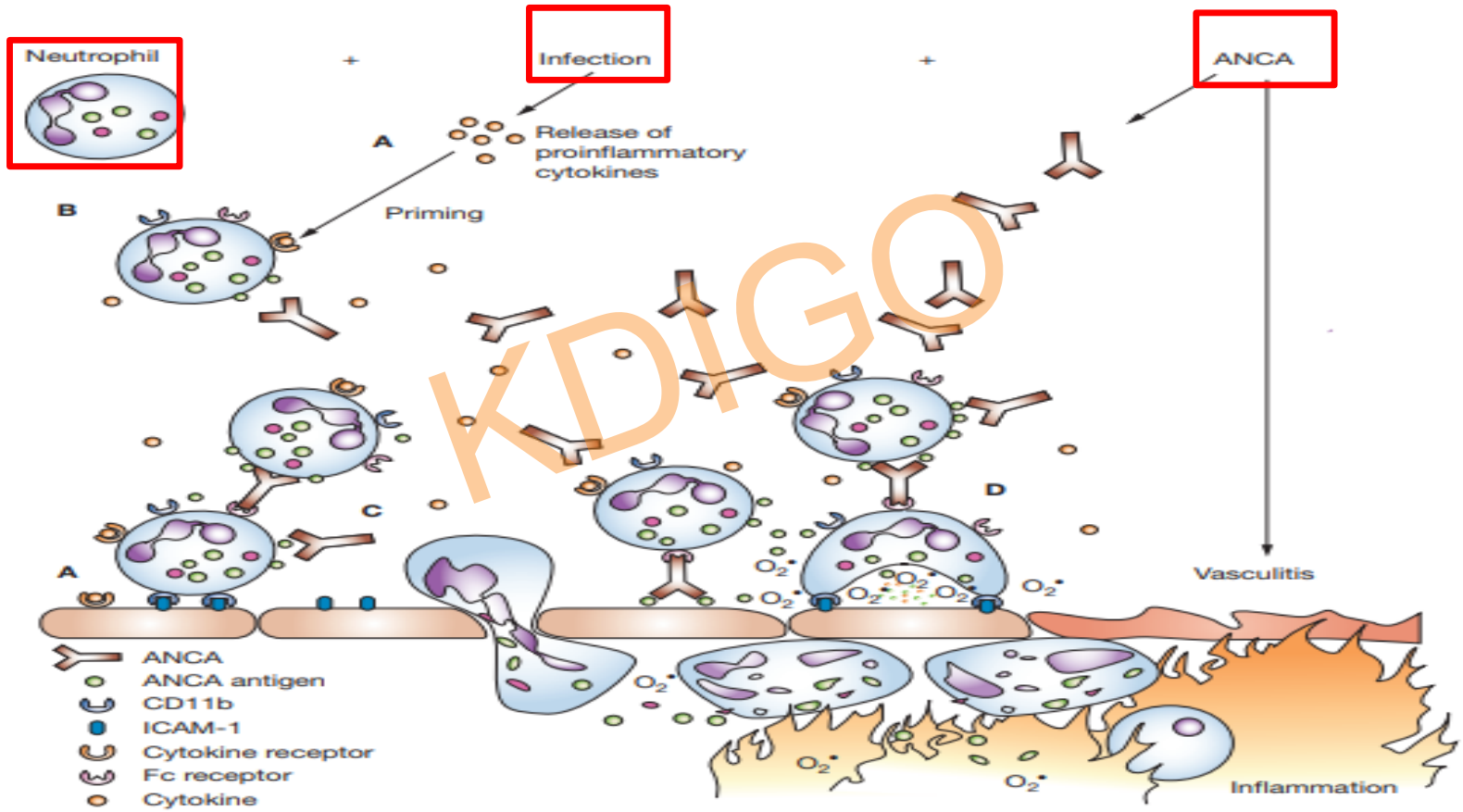
Kallenberg CG et al. Kidney Int 1994

# Pathogenesis of ANCA associated vasculitis

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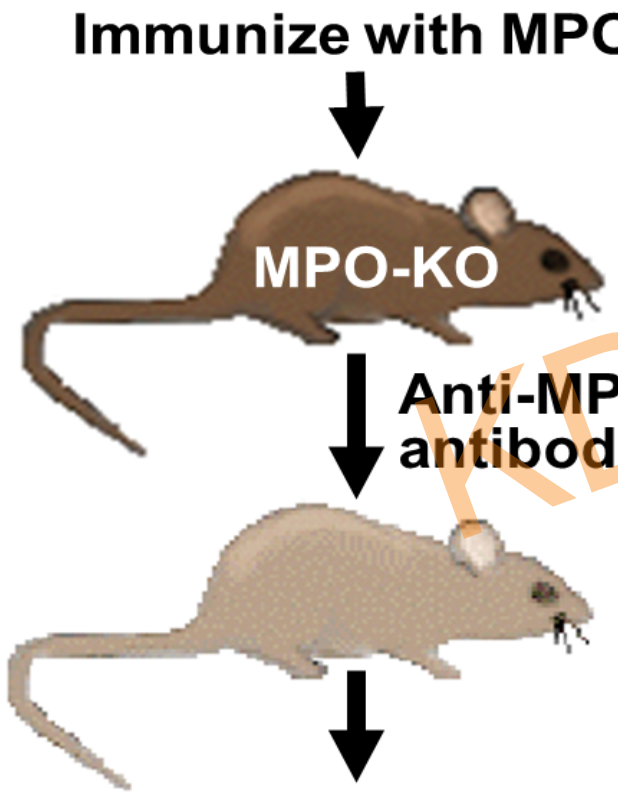
Kellenberg Nature Rev Nephrol 2006

# MPO ANCA mouse model




1) Immunize MPO-knockout mice with murine MPO

2) Transfer anti-MPO IgG into Rag2-/- or B6 mice

3) Cause MPO-ANCA-induced necrotizing and crescentic glomerulonephritis and small vessel vasculitis

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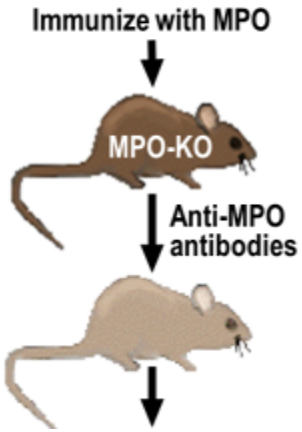
Xiao H et al. *J Clin Invest* 2002

# Animal model: lessons learned from MPO mouse model




- Anti-MPO IgG alone can cause disease
- Neutrophils are required &neutrophil priming exacerbates disease
- Genetic factors modulate disease activity
- Alternative complement pathway is involved
- C5a receptor blockade abrogates disease

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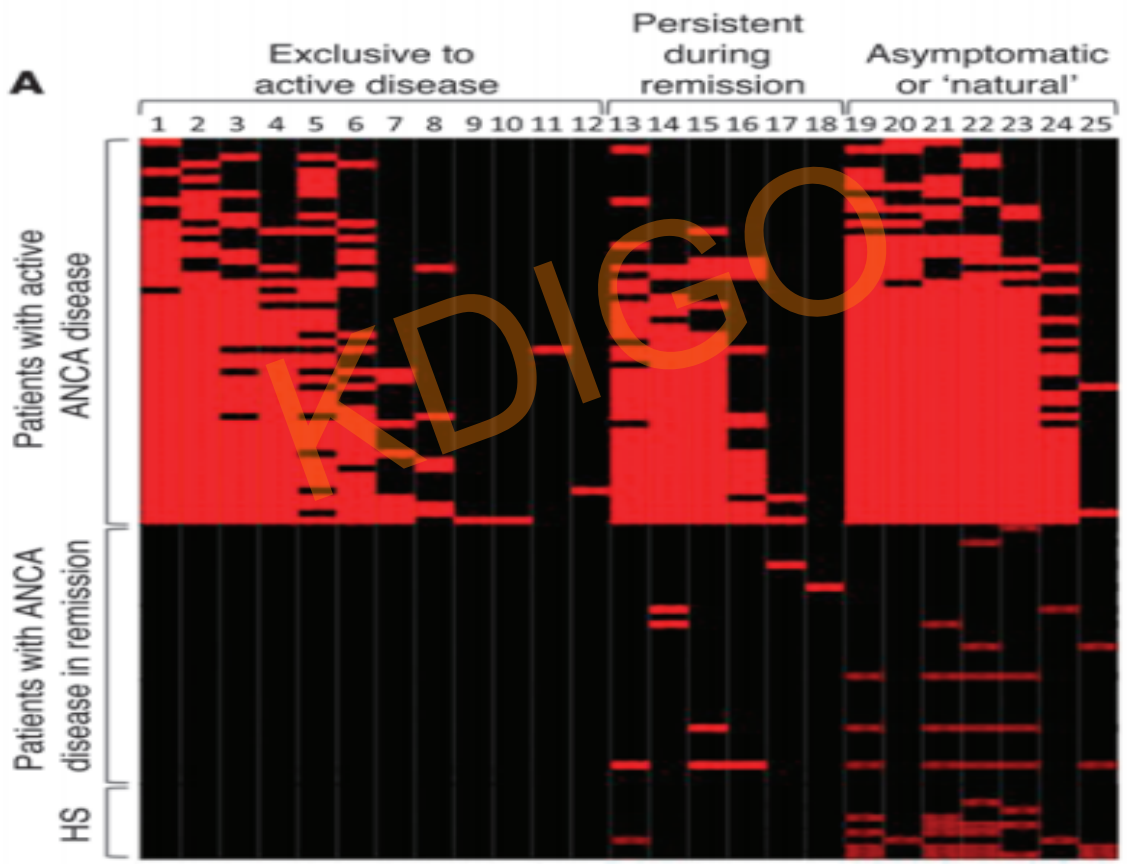
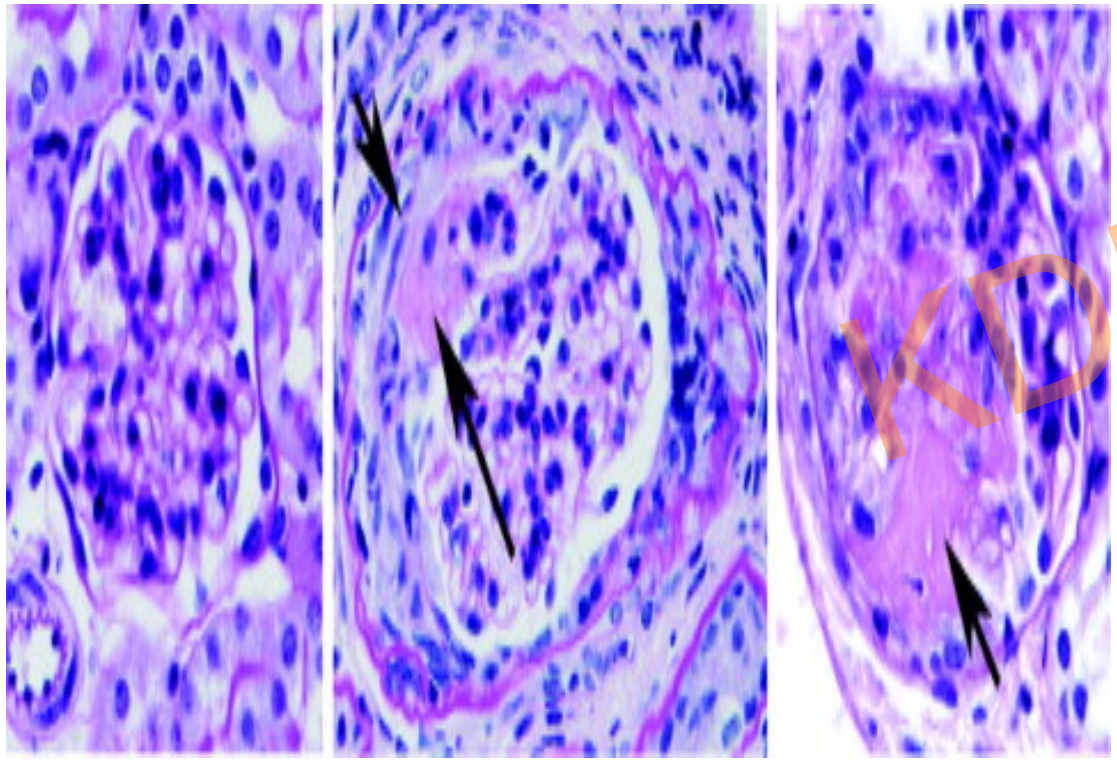
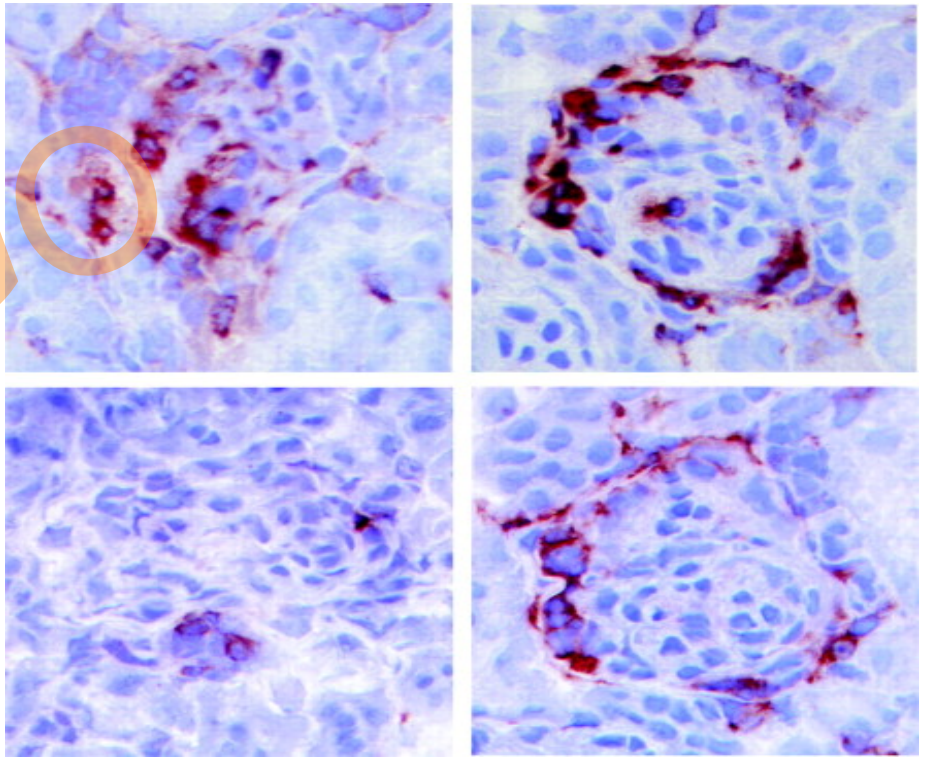
# Not all MPO ANCA are pathogenic




Roth AJ et al. *J Clin Invest* 2013

# Neutrophils are required





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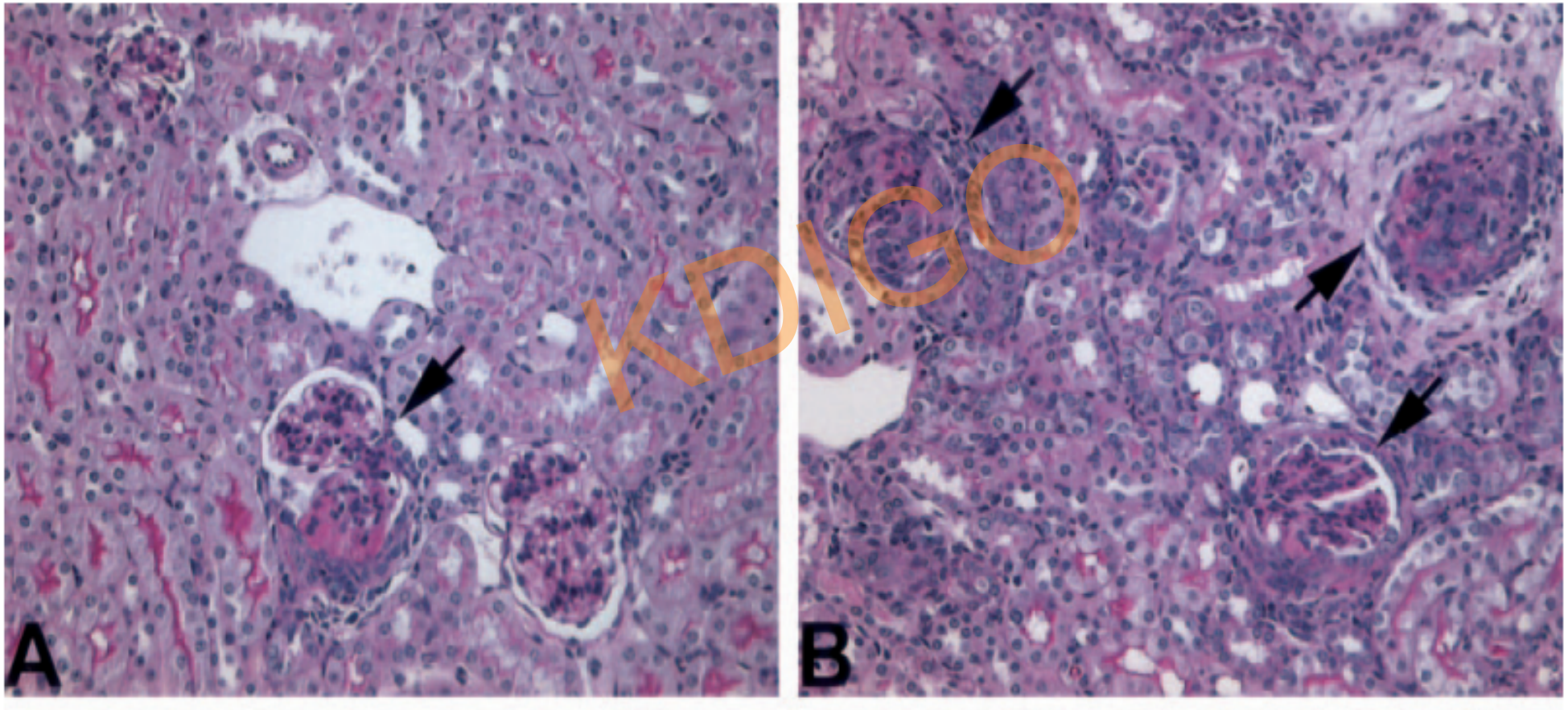
Xiao H et al. *Am J Pathol* 2005

# ANCA and pro-inflammatory cytokines react synergistically

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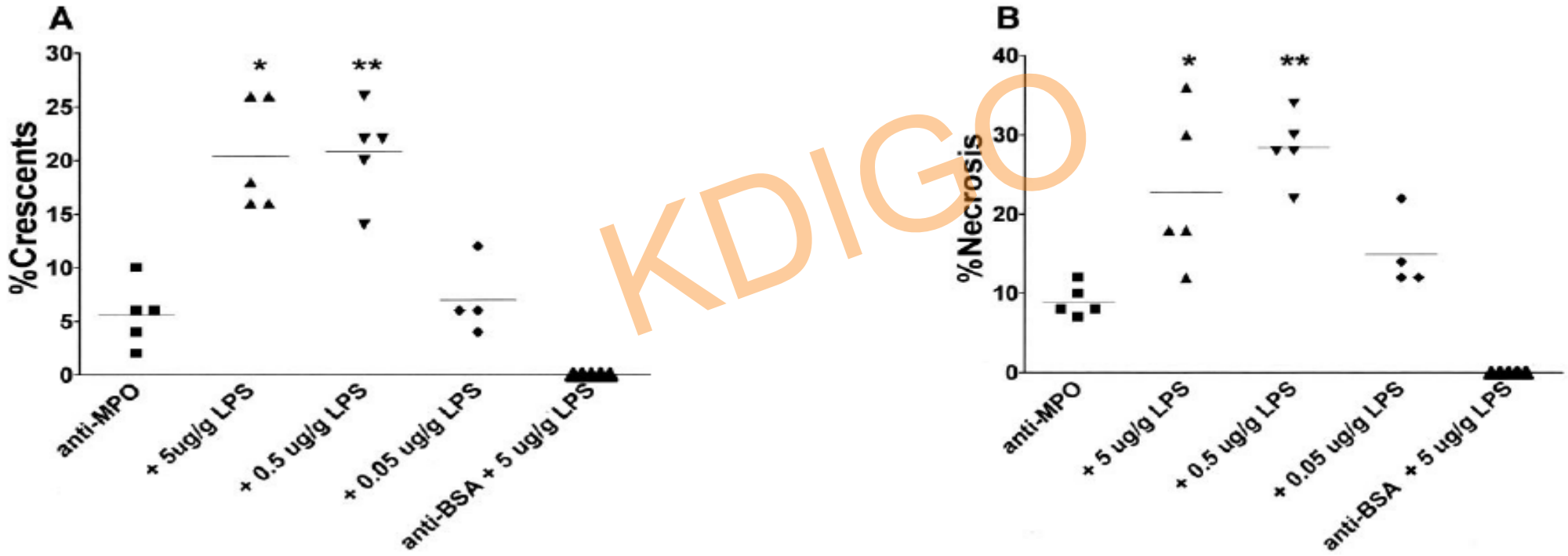
Huugen D et al. *Am J Pathol* 2005

# LPS causes dose dependent increase in renal injury

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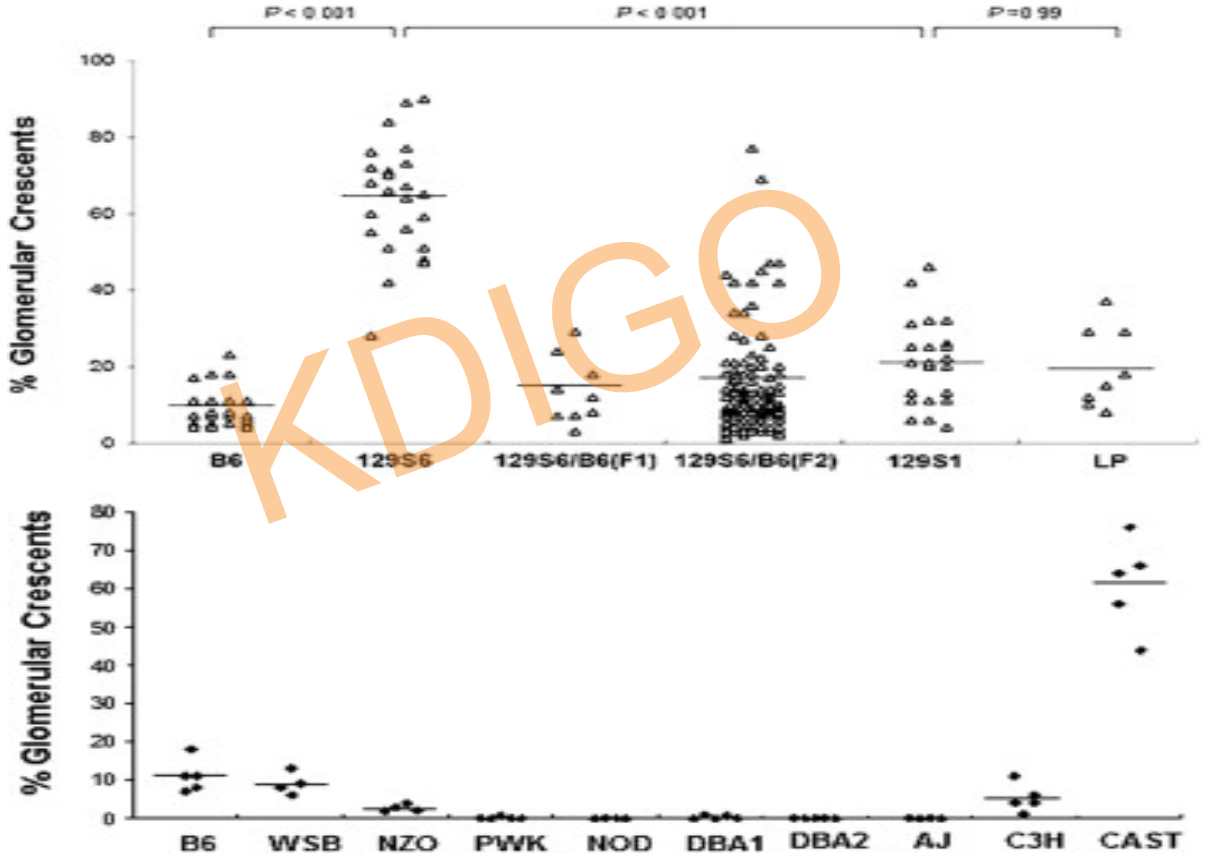
Huugen D et al. *Am J Pathol* 2005

# Disease severity is modulated by genetic factors

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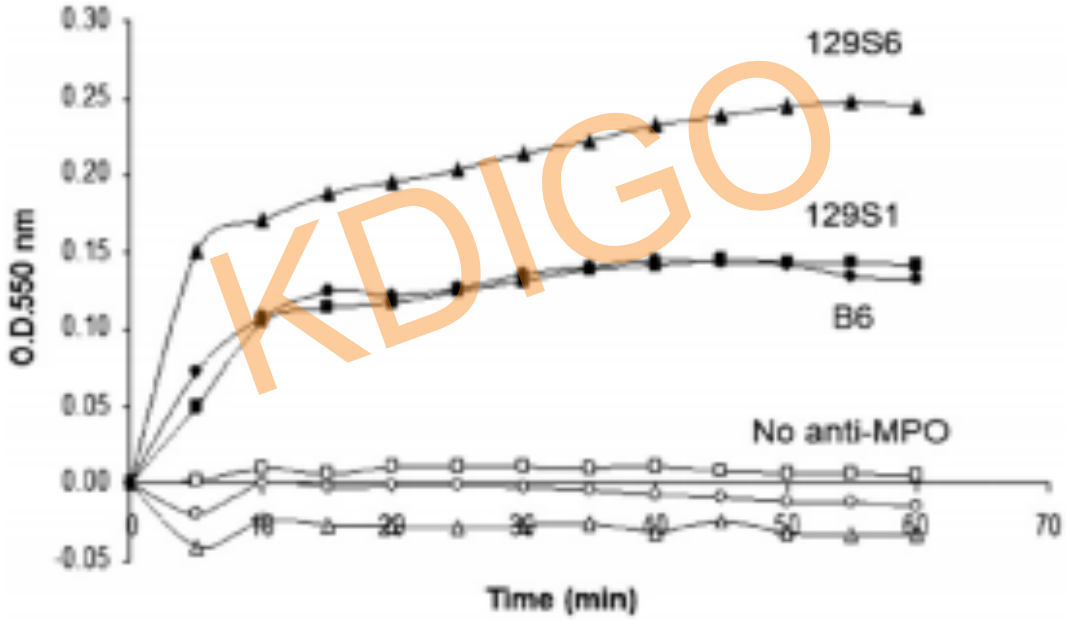
Xiao H et al. *Am J Pathol* 2013

# Genetic differences influence neutrophil activation by anti MPO IgG

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Xiao H et al. *Am J Pathol* 2013

# How about PR3 ANCA?

- Immunized PR 3 deficient mice with recombinant murine PR3
- Mouse developed PR3 antibodies that recognized mouse PR3 on surface of neutrophils
- Passive transfer of mouse PR3 antibodies to naive mice
- No signs of vasculitis seen in kidneys or lungs

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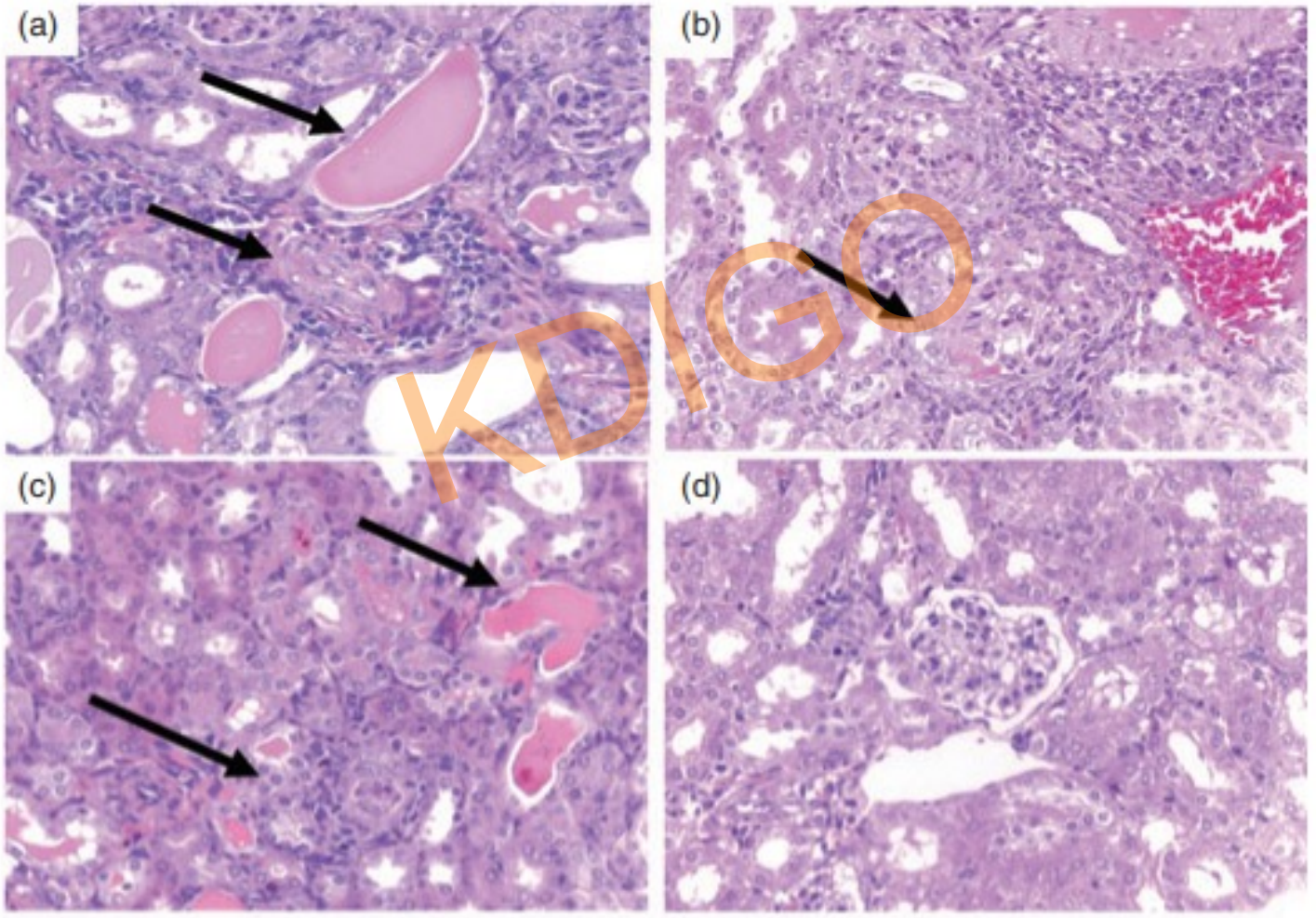
Pfister H et al. *Blood* 2004

# PR3 ANCA causes vasculitis but no granulomas

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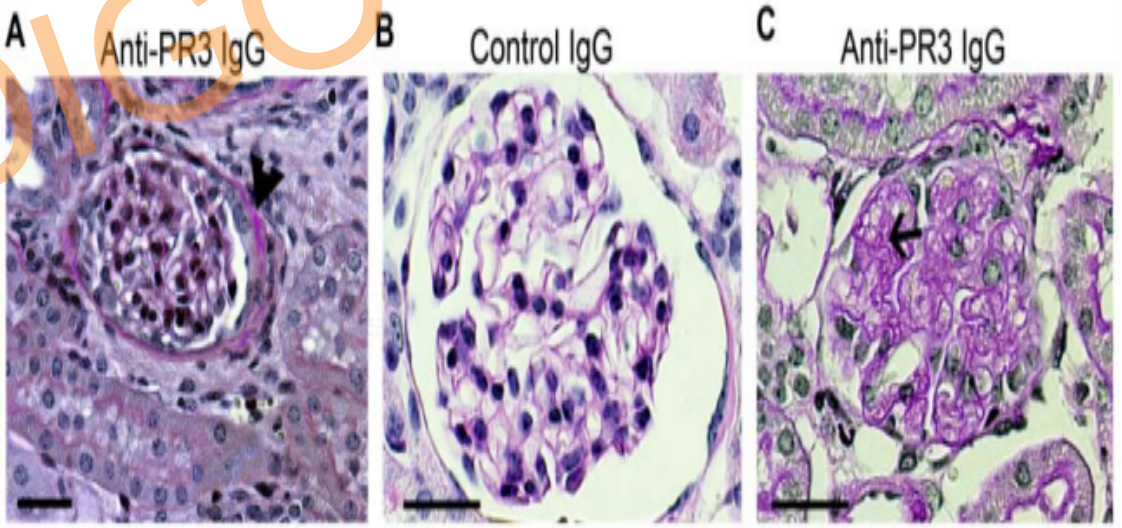
Primo VC et al. *Clin Exp Imm* 2010

# PR3 ANCA in mice with humanized immune system

- Chimeric mice were generated
- Matched chimera mice were treated with human IgG from patients:
  - anti-PR3 positive renal and lung vasculitis
  - patients with non-vasculitic renal disease
  - healthy controls.

**Only anti-PR3 treated mice had pauci-immune proliferative glomerulonephritis and pulmonary vasculitis**

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Little MA et al. *Plos one* 2012

# In vitro studies: ANCA induced neutrophil activation

- Priming of neutrophils is necessary for ANCA induced activation
- Surface expression of MPO and PR3
- Fc¥RIIa and Fc¥RIIIb interaction is involved
- Release of ROS and lytic enzymes
- Conversion of rolling of neutrophils to firm integrin mediated adhesion
- Induction of neutrophil cytotoxicity to endothelial cells

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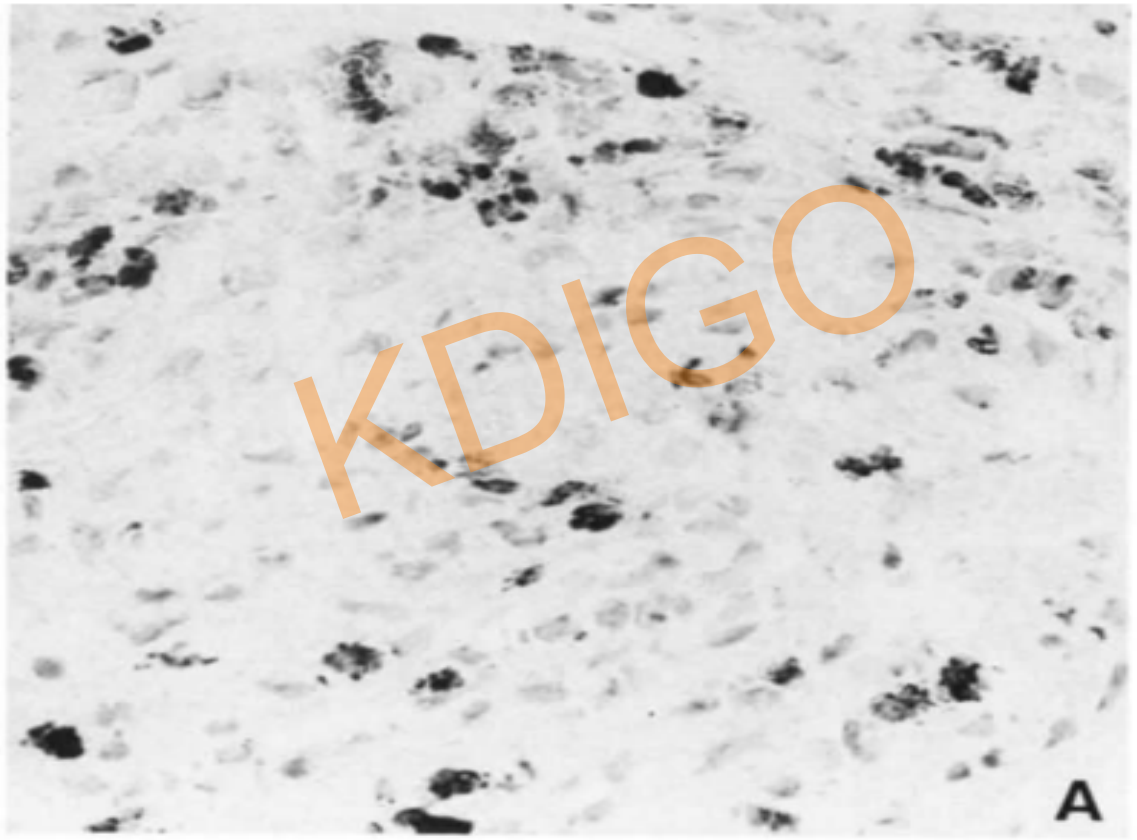
# ANCA induced activation of neutrophils

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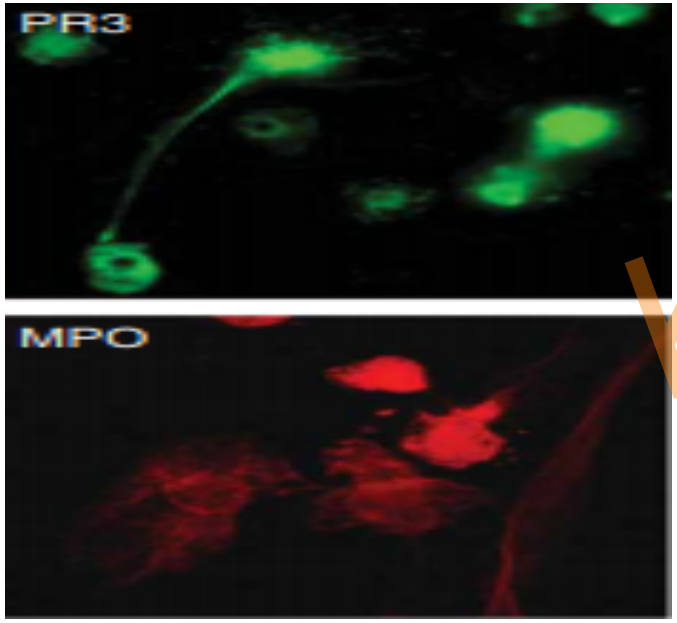
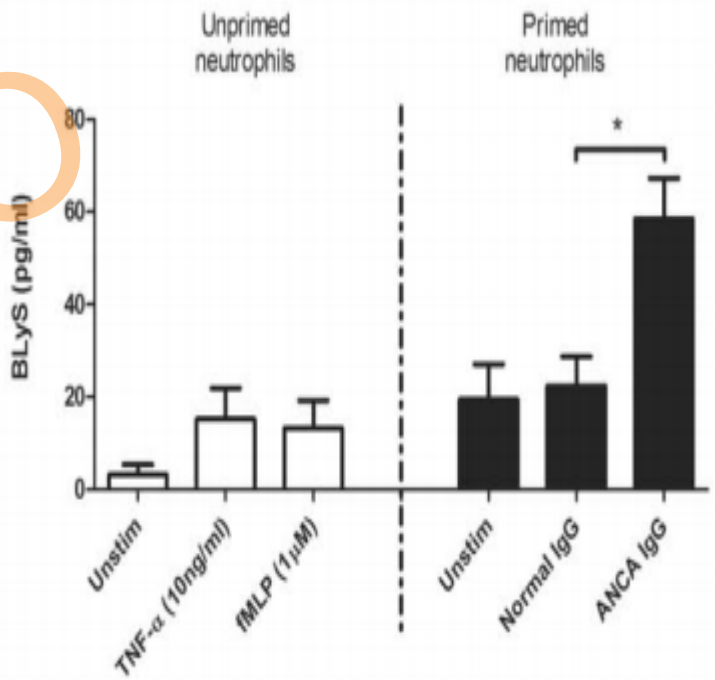
Brouwer et al. KI 1994

# Stimulation of adaptive immune response by activated neutrophils

NETs




B cell activating factors

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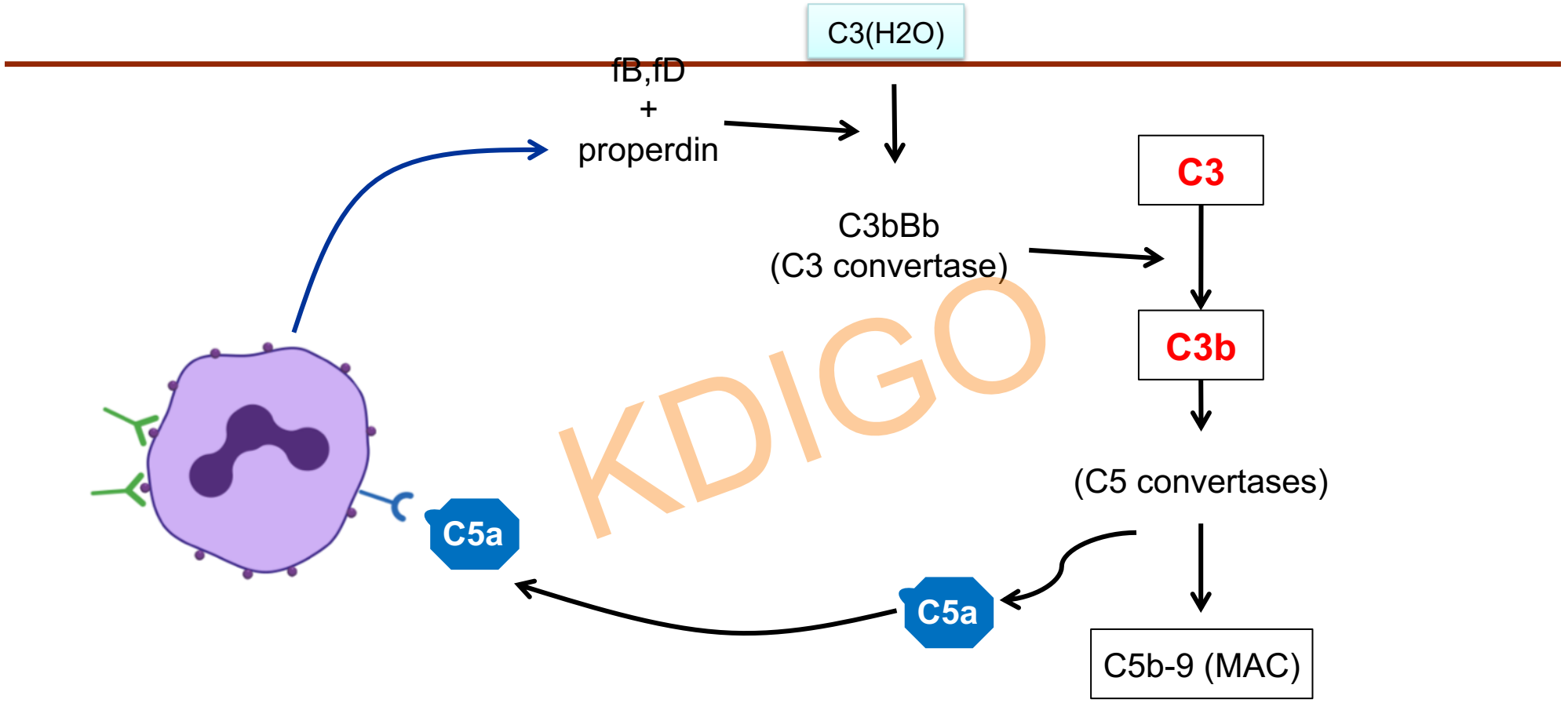
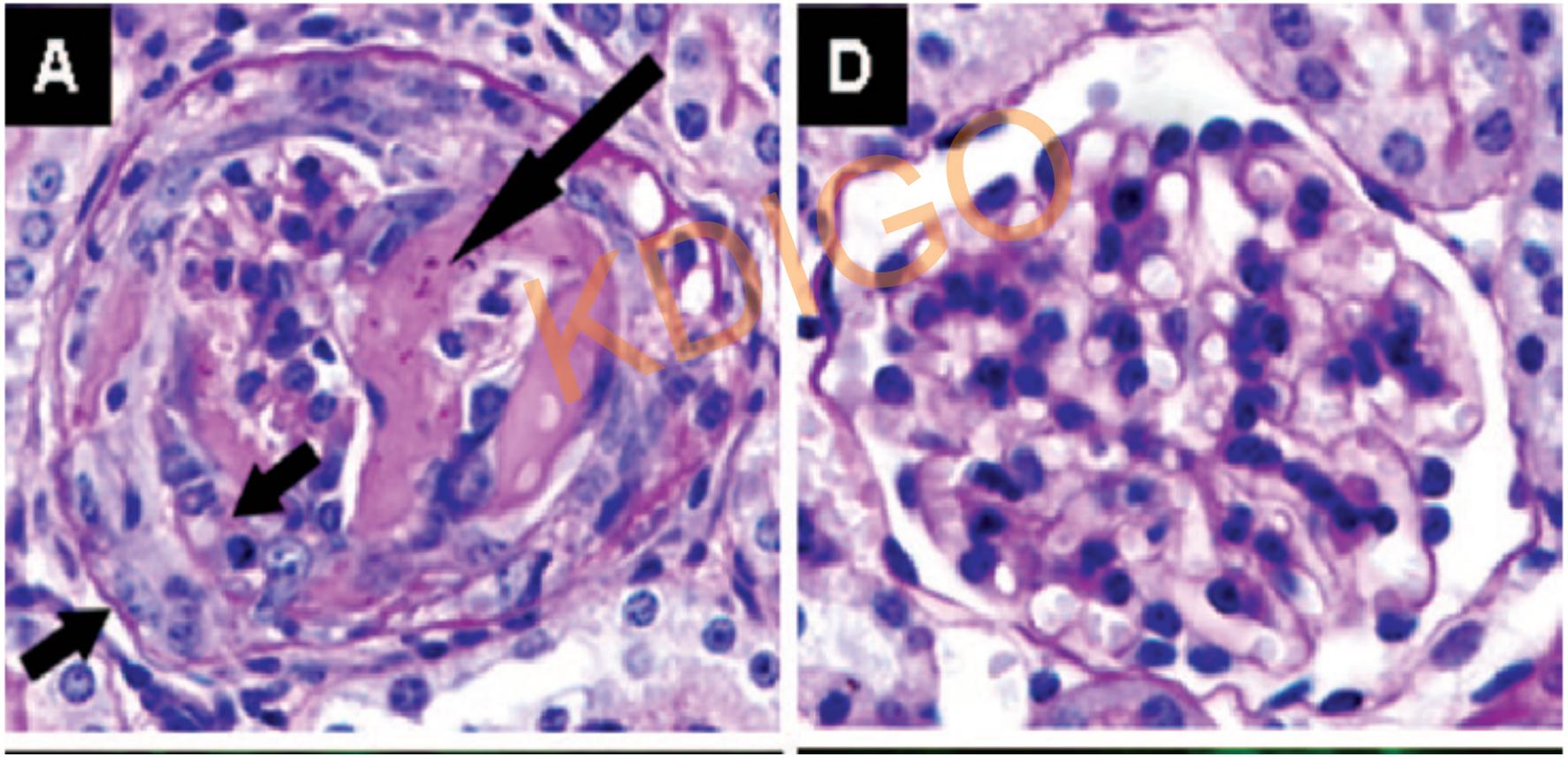
Kessenbrock et al., Nature Med 2009
Holden et al. Ann Rheum Dis 2011

# Complement in ANCA vasculitis



# Complement pathway is involved

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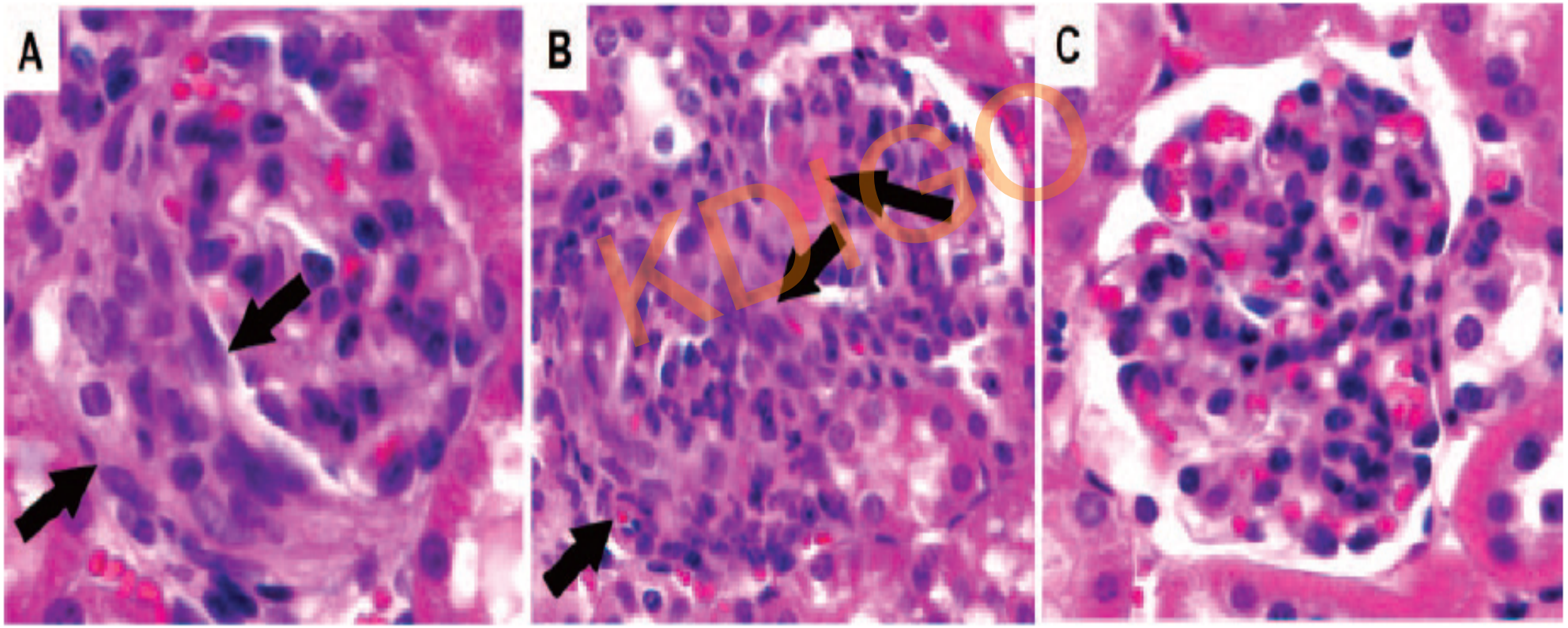
Xiao H et al. *Am J Pathol* 2007

# Alternative complement pathway is involved

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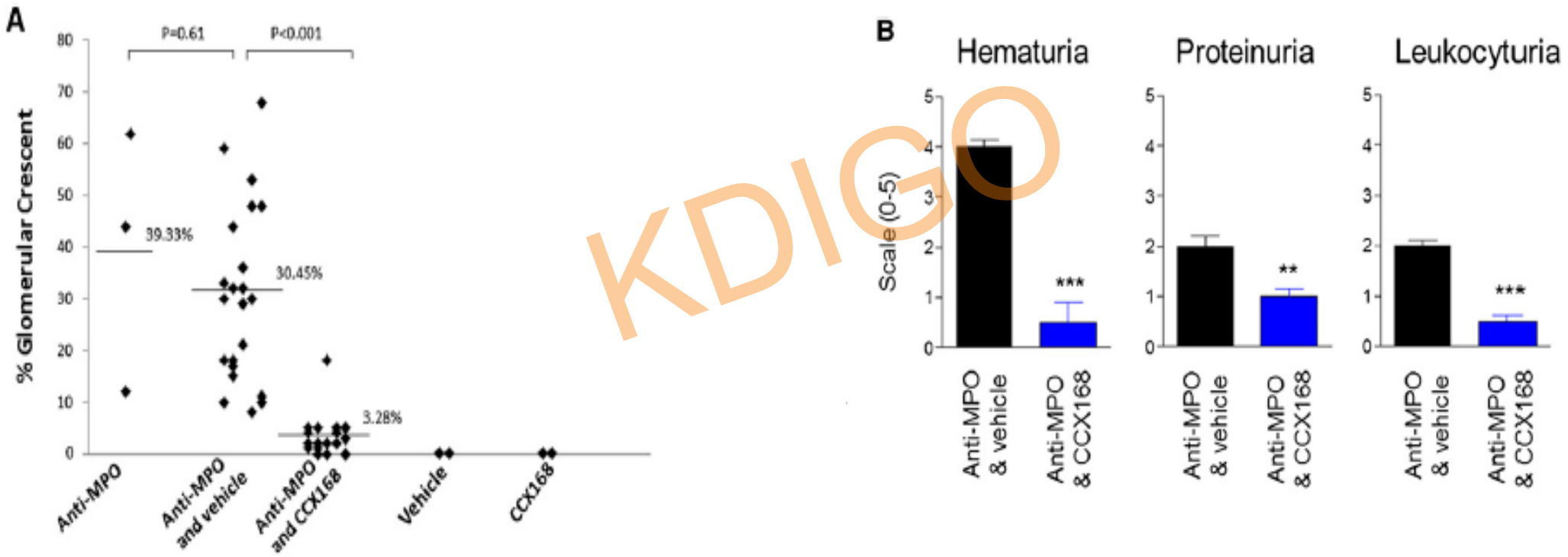
Xiao H et al. *Am J Pathol* 2007

# C5a receptor blockade abrogates disease

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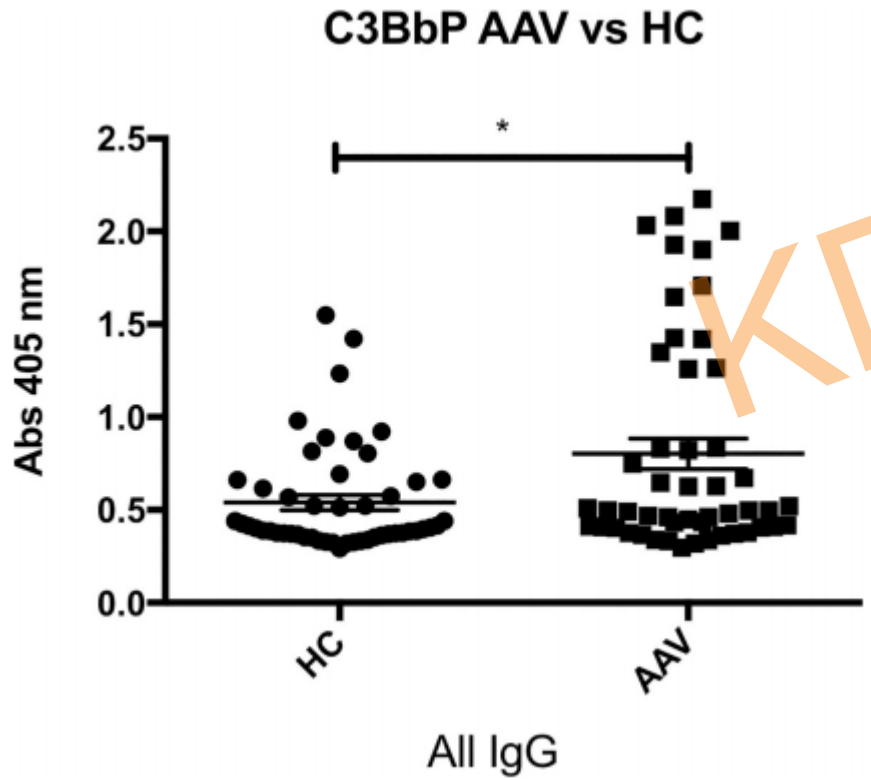
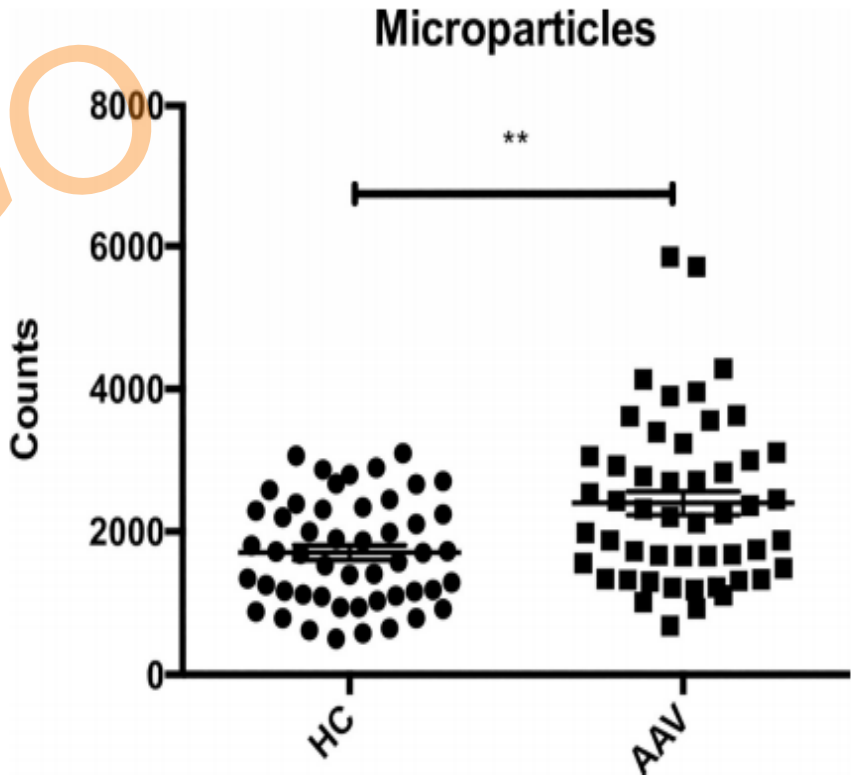
Xiao H et al. *Am J Pathol* 2007

# ANCA stimulated neutrophils have increased capacity to activate alternative complement pathway

**Increased C3Bbp levels in supernatants from AAV neutrophils**




**Increased microparticle release from AAV neutrophils**

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Ohisson S et al., Plos One 2019

# Clinical evidence for ANCA pathogenicity

- AAV caused by transplacental passage of MPO ANCA from mother with MPA
- ANCA titers correlate with disease activity and recurrences in subsets of patients
- Efficacy of rituximab and plasma exchange

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# Clinical evidence for alternative complement pathway activation

- Hypocomplementemia in a subset of patients with severe disease
- Elevated plasma levels of Bb, C3a, C5a, and sC5b–9 and decreased properdin in active disease
- Elevated urinary  levels of Bb, C3a, C5a, and C5b–9 in active disease

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# Complement activation products in MPO and PR3 AAV

**Table 2.** Complement activation with Futhan in the healthy controls and AAV patients*

| | | MPO-positive AAV | | PR3-positive AAV | |
|---|---|---|---|---|---|
| | Healthy controls | Active disease | Disease in remission | Active disease | Disease in remission |
| Bb, μg/ml | 0.62 (0.49–0.65) (26) | 0.66 (0.48–0.79) (14) | 0.74 (0.64–0.90) (21)† | 0.58 (0.50–0.79) (19) | 0.65 (0.58–0.85) (25) |
| Properdin, μg/ml | 14.62 (13.16–17.30) (22) | 15.83 (13.37–21.89) (14) | 17.40 (13.75–20.59) (21) | 15.71 (14.26–19.60) (19) | 14.89 (13.00–18.16) (25) |
| C3a, ng/ml | 29.54 (23.81–38.22) (26) | 67.77 (42.60–93.49) (14)† | 71.58 (45.84–107.60) (21)† | 75.56 (50.84–126.20) (19)† | 52.80 (44.47–67.83) (25)† |
| C5a, ng/ml | 5.50 (4.05–7.53) (26) | 9.47 (8.41–12.95) (13)† | 8.07 (5.67–9.42) (21) | 9.74 (6.42–15.52) (18)† | 7.14 (5.29–8.50) (25) |
| sC5b–9, ng/ml | 114.90 (101.50–135.30) (25) | 166.99 (131.44–217.96) (14)† | 149.94 (128.62–181.51) (21)† | 152.59 (137.52–266.42) (19)† | 143.06 (119.13–173.58) (25) |
| C4d, μg/ml | 0.94 (0.49–1.55) (19) | 2.06 (1.40–3.24) (14) | 1.56 (0.68–2.66) (18) | 1.87 (1.41–3.77) (18)† | 2.02 (1.17–2.91) (18)† |

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Wu EY et al., Arthritis & Rheumatol 2019

# Clinical evidence for alternative complement pathway activation

- Demonstration of complement pathway products in renal biopsies
  - C3 can be demonstrated in ANCA GN and correlates with poor renal prognosis
  - C5b−9, C3d, and factor B, but not C4d, could be detected in active glomerular lesions
  - C3d and properdin staining was associated with the proportion of cellular crescents

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- CLEAR trial: successful use of C5a receptor blocker for remission induction

# T cell involvement in AAV

- Activated T cells can be seen in inflammatory lesions in affected organs, particularly in granulomatous lesions
- Alterations in circulating T cell subsets
- Increased levels of soluble factors indicative of T cell activation detected in plasma of GPA patients
- Numerical and functional alterations in Tregs

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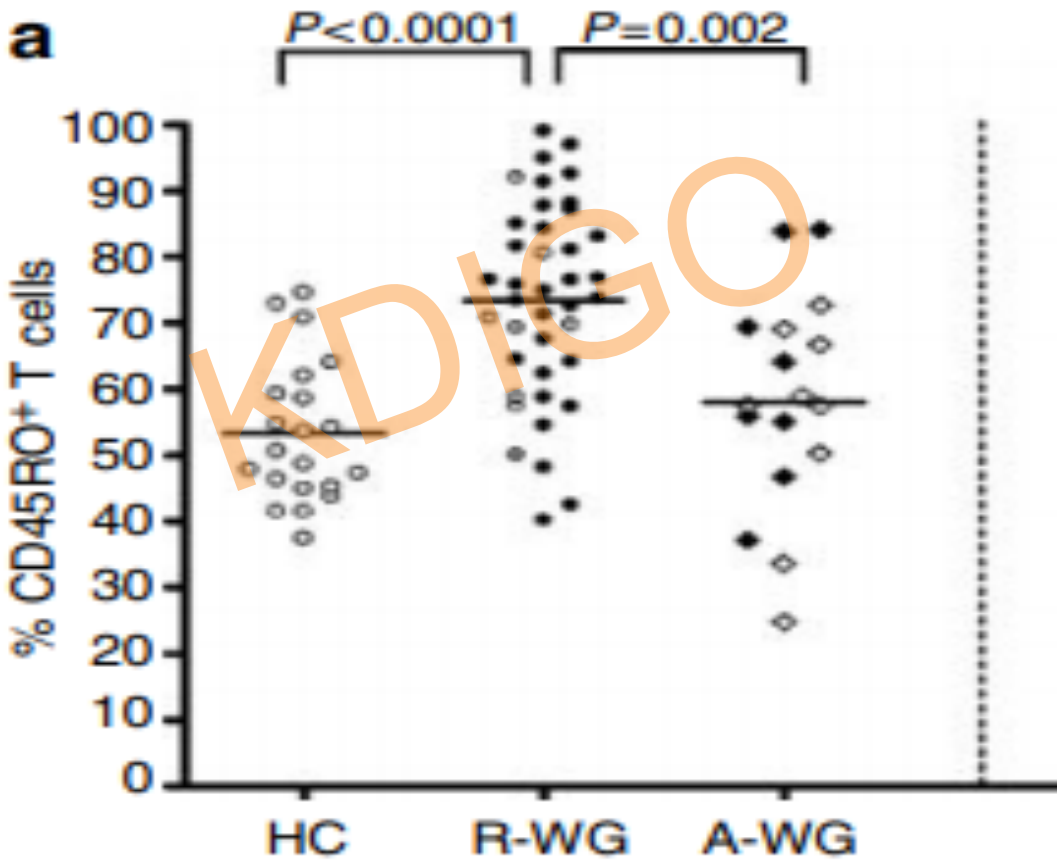
# Memory T cells in AAV

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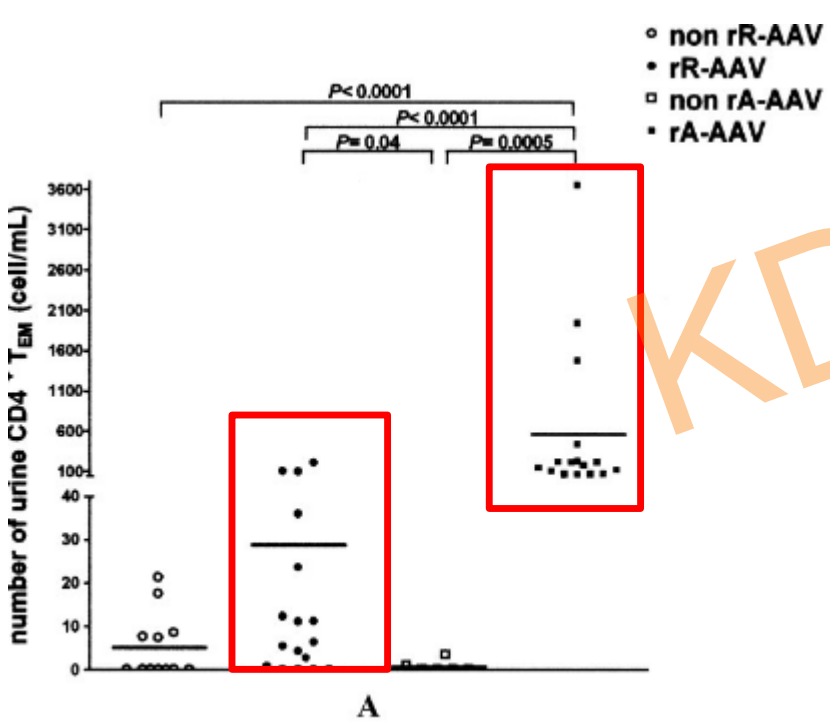
Abdulahad WH et al., Kidney Int 2006

# Memory T cells and renal AAV

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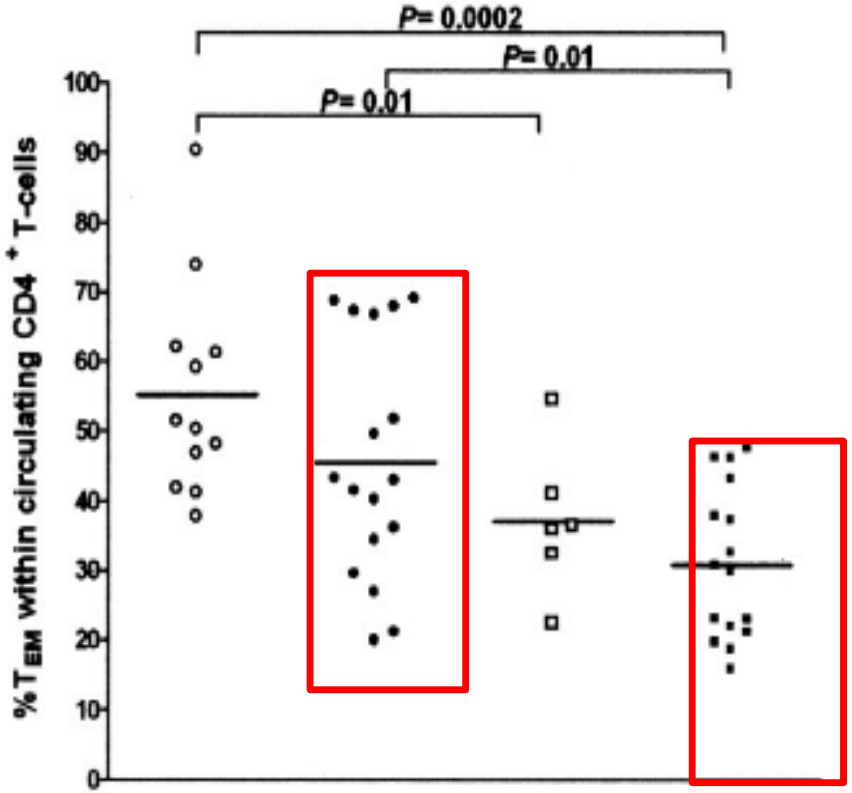
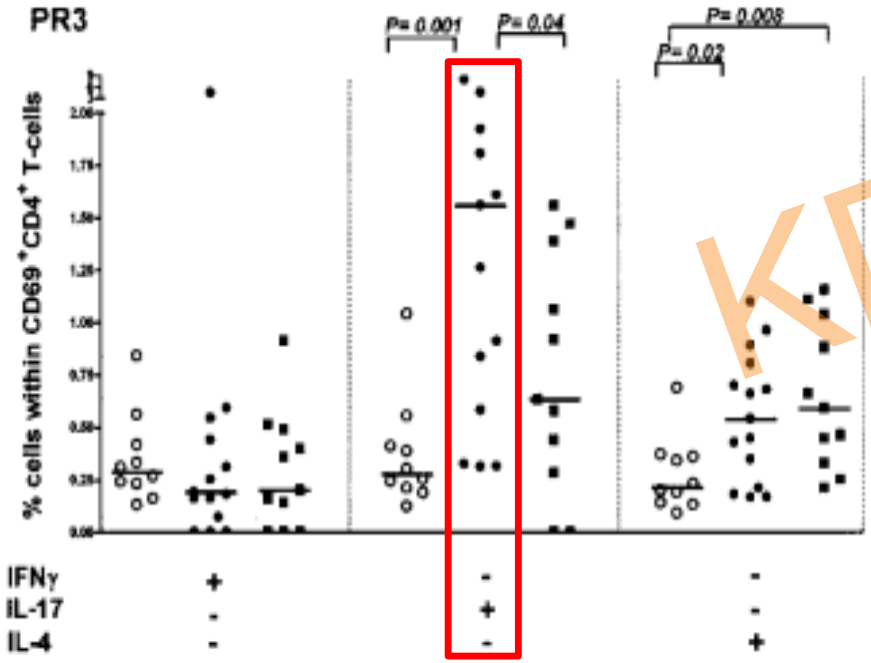
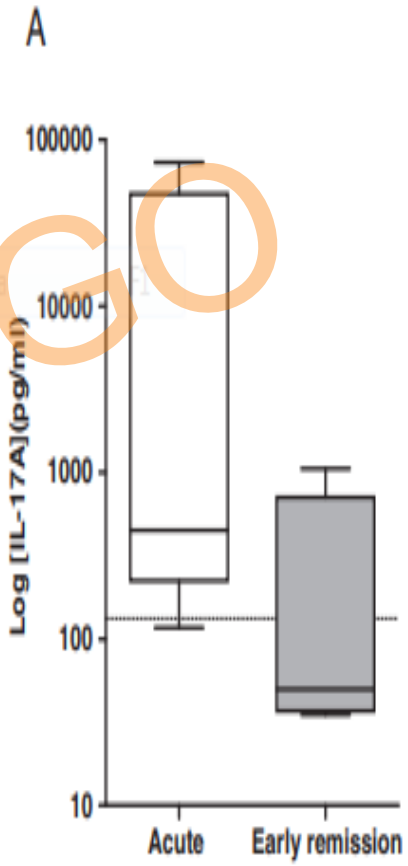
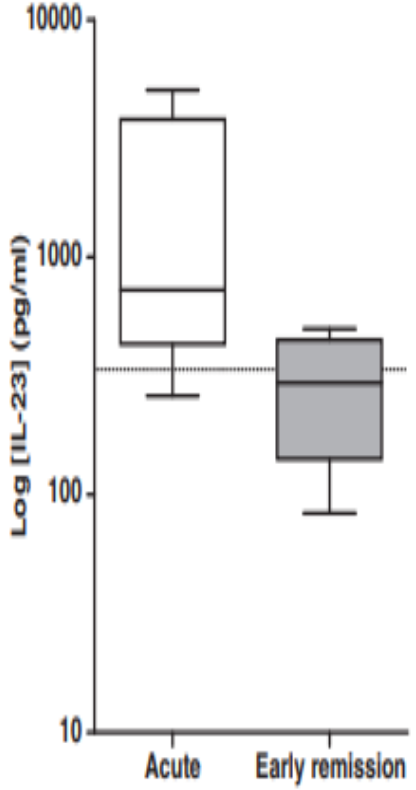



Abdulahad WH et al., Arthritis & Rheum 2009

# What is the phenotype of these T cells?

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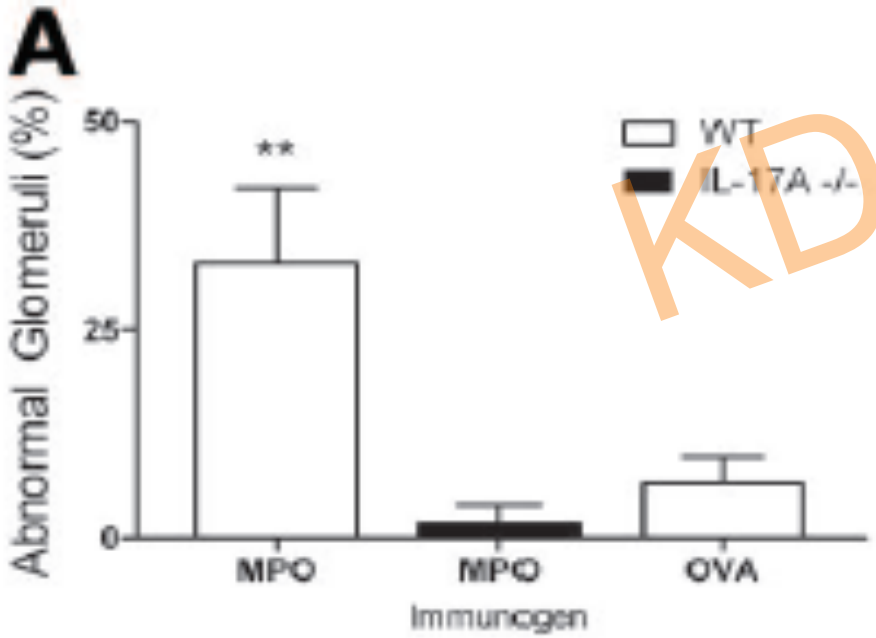
Abdulahad WH et al., Arthritis & Rheum 2008
Nogueira E at al., NDT 2010

# IL17 promotes ANCA GN

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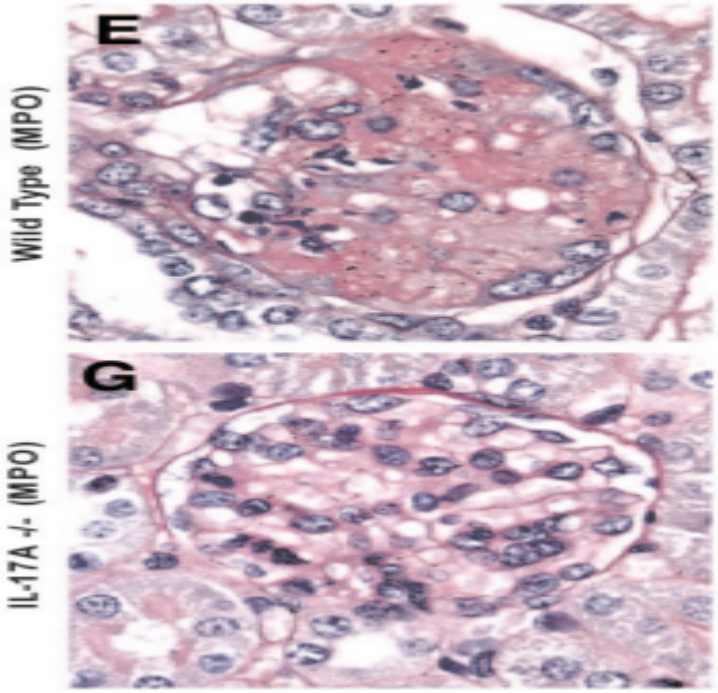
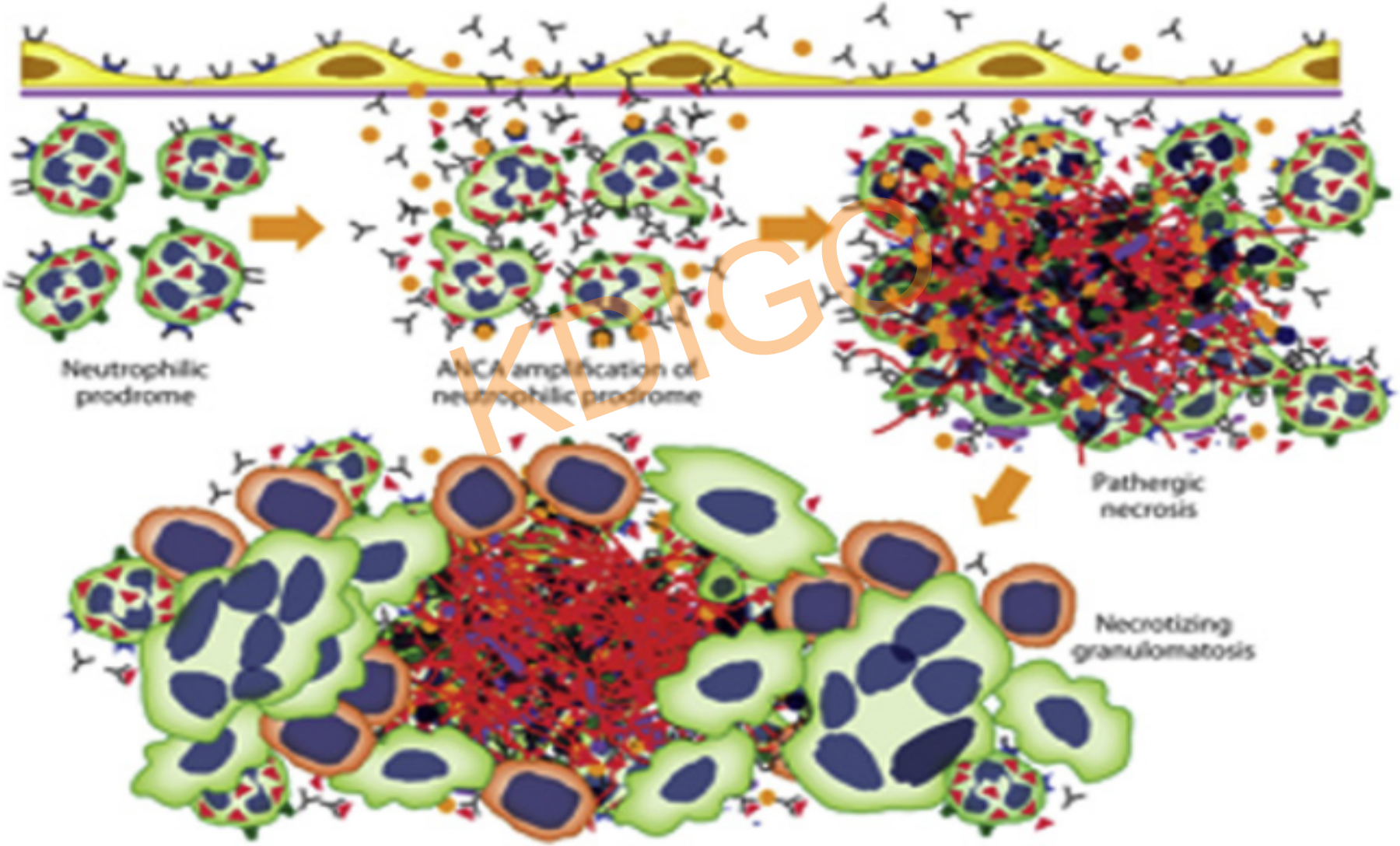



Gan PY et al. *JASN* 2010

# Mediation of extra-vascular inflammation

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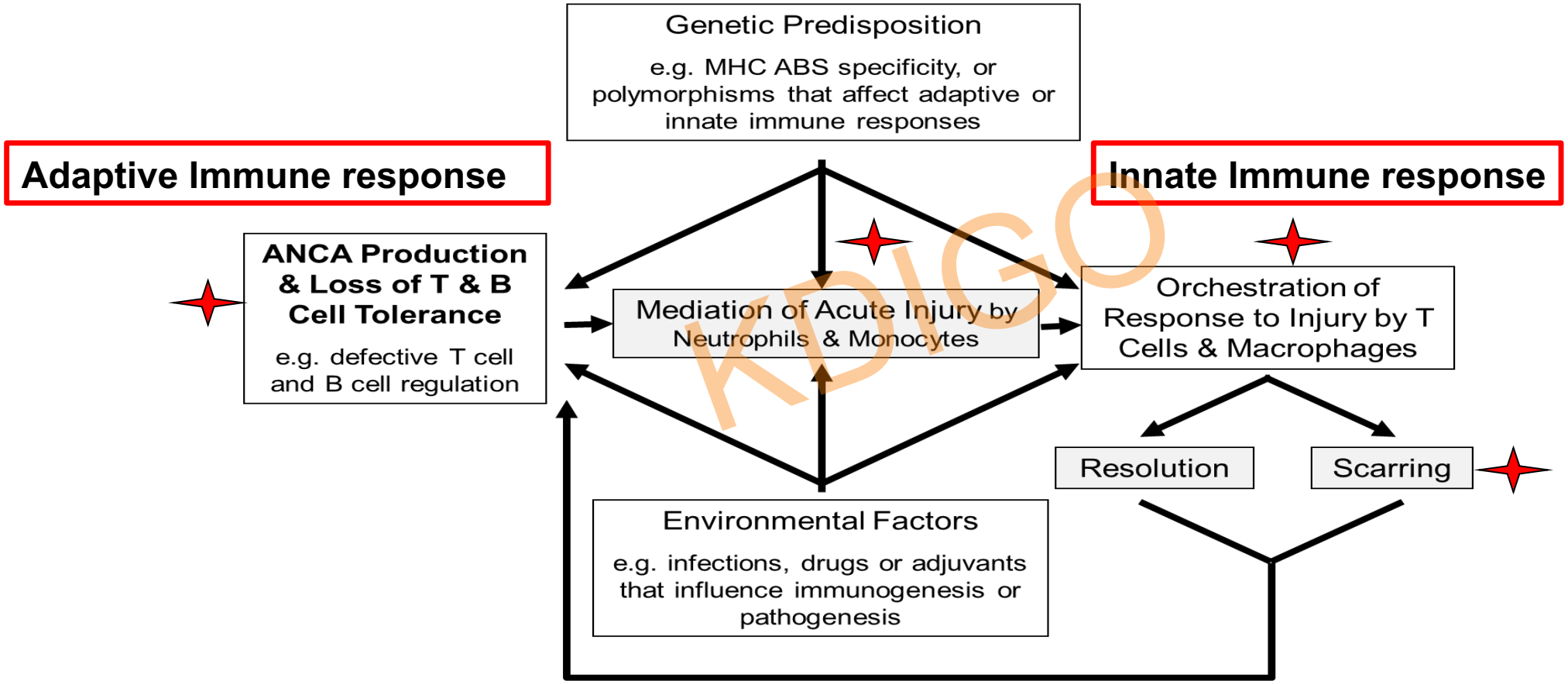
Jennette JC, Falk RJ. Quart J Med, Presse Med 2013, 42:493-8.

# ANCA vasculitis: Pathogenesis and treatment targets

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Jennette JC, Falk RJ. Quart J Med, Presse Med 2013, 42:493-8.

# Prognosis of ANCA associated vasculitis

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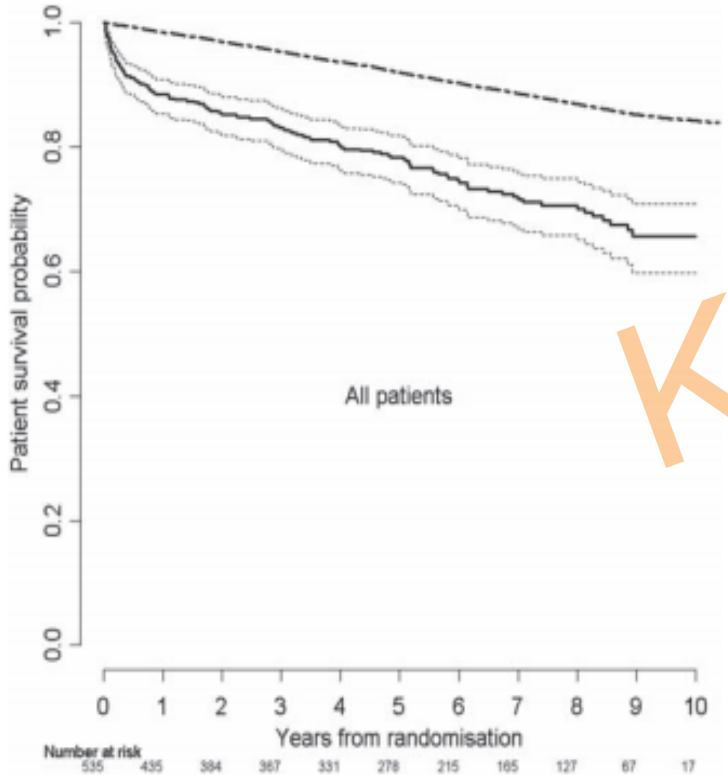
# Immunosuppression has improved patient survival rate

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- 535 AAV patients: 1995 to 2002
- Median FU:5.2 years
- Overall mortality ratio among AAV patients compared to controls was 2.6 (95% CI 2.2-3.1, p< 0.0001)
- Predictors of death: older age, higher BVAS and worse renal function

**Flossmann Oet al, *Ann Rheum Dis* 2011**

# Mortality in AAV: Meta-analysis

- 3338 patients and 1091 deaths (1966-2009)
- 2.7 fold increased risk of death in AAV patients compared to general population

**Table 2** Overall mortality and sensitivity analyses for the 10 studies (14 unique cohorts) in patients with AAV

| Study subset | No. cohorts | No. patients | No. death events | Random-effects meta-SMR (95% CI) | p |
|---|---|---|---|---|---|
| All studies | 14 | 3338 | 1091 | 2.71 (2.26 to 3.24) | |
| Disease definition | | | | | NS |
| GPA only (homogeneous) | 7 | 1987 | 804 | 2.63 (2.02 to 3.43) | |
| AAV mixed (heterogeneous) | 6 | 1125 | 257 | 2.59 (1.99 to 3.37) | |
| Sex | | | | | NS |
| Female | 5 | 611 | 147 | 3.36 (2.10 to 5.38) | |
| Male | 5 | 636 | 172 | 3.11 (2.21 to 4.36) | |
| Study population | | | | | NS |
| Population-based | 4 | 1691 | 763 | 3.37 (2.73 to 4.17) | |
| Hospital/clinic-based | 10 | 1647 | 328 | 2.39 (1.86 to 3.09) | |
| Cohort type | | | | | NS |
| Inception | 9 | 1286 | 270 | 2.30 (1.69 to 3.13) | |
| Non-inception | 5 | 2052 | 821 | 3.22 (2.57 to 4.05) | |
| Midpoint of enrolment period | | | | | NS |
| 1980–1993 | 5 | 1821 | 784 | 3.43 (2.79 to 4.21) | |
| 1994–1999 | 4 | 1003 | 236 | 2.82 (2.14 to 3.72) | |
| 2000–2005 | 5 | 514 | 71 | 1.92 (1.12 to 3.29) | |
| Centre | | | | | 0.05 |
| Multicentre | 7 | 2549 | 983 | 3.27 (2.73 to 3.91) | |
| Single-centre | 7 | 789 | 108 | 1.89 (1.17 to 3.07) | |

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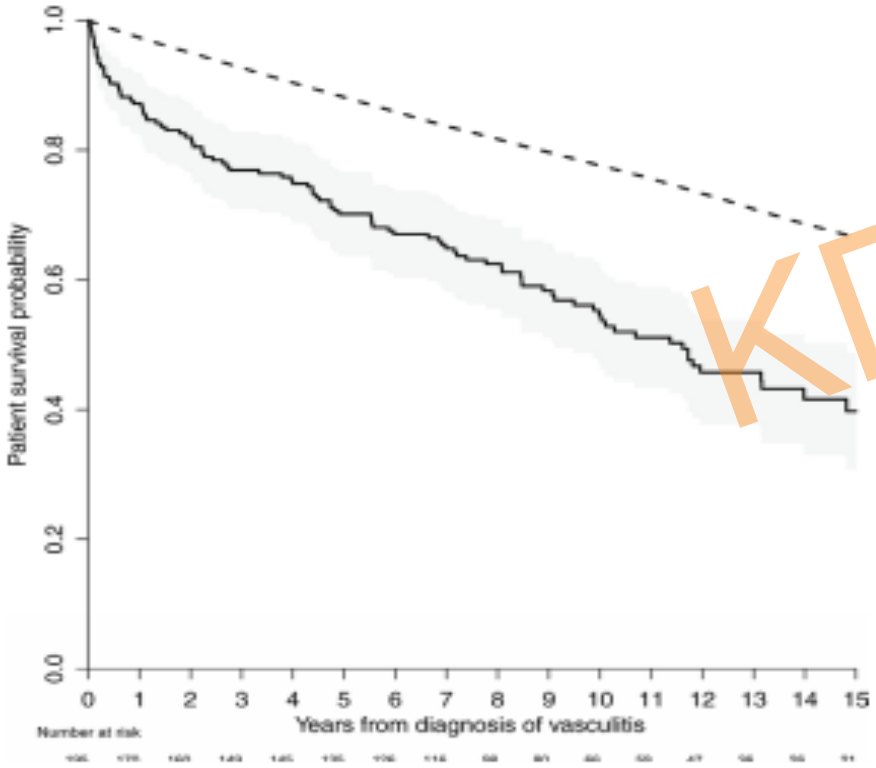
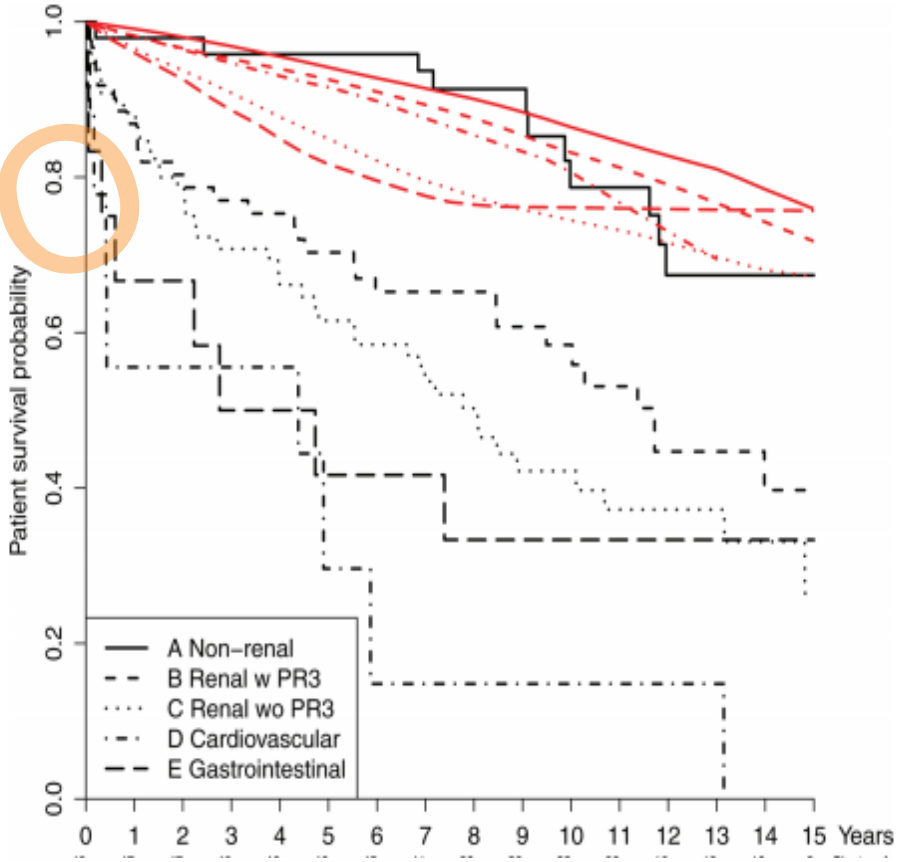
Tan JA, et al. Ann Rheum Dis 2017

# Mortality and disease phenotype

**Significantly increased mortality in AAV, p<0.001**

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Heijl C, et al. RMDOpen 2017

# Improved patient survival over time: US data

*Table.* Average Annual Age-Adjusted AAV-Related Mortality and Average Annual Percent Change in Mortality Rates, by Demographic Characteristic in the United States, 1999 to 2017*

| Variable | Overall Mortality† | | Annual Percent Change (95% CI) | | Average Annual Percent Change in Age-Adjusted Mortality‡, (95% CI), % |
|---|---|---|---|---|---|
| | Deaths, *n* (%) | Age-Adjusted Rate per 1 000 000 Persons (95% CI) | Trend 1 | Trend 2 | |
| **Overall** | 11 316 (100) | 1.86 (1.83 to 1.90) | 1999–2012: −0.6 (−1.4 to 0.2) | 2012–2017: −4.4 (−7.4 to −1.3) | −1.6 (−2.6 to −0.7) |
| **Sex** | | | | | |
| Male | 5688 (50.3) | 2.13 (2.07 to 2.19) | 1999–2011: −0.4 (−1.4 to 0.5) | 2011–2017: −4.3 (−6.8 to −1.7) | −1.7 (−2.7 to −0.8) |
| Female | 5628 (49.7) | 1.65 (1.60 to 1.69) | – | – | −1.4 (−2.1 to −0.7) |
| **Race** | | | | | |
| White, non-Hispanic | 9748 (86.1) | 2.03 (1.99 to 2.07) | – | – | −1.1 (−1.7 to −0.5) |
| Black, non-Hispanic | 479 (4.2) | 0.77 (0.70 to 0.84) | – | – | −0.5 (−2.3 to 1.3) |
| Hispanic | 781 (6.9) | 1.57 (1.45 to 1.68) | – | – | −2.4 (−3.9 to −0.9) |
| **Region** | | | | | |
| Northeast | 1966 (17.4) | 1.66 (1.59 to 1.73) | – | – | −1.2 (−2.1 to −0.3) |
| Midwest | 2939 (25.9) | 2.15 (2.07 to 2.23) | – | – | −1.4 (−2.3 to −0.5) |
| South | 3786 (33.5) | 1.70 (1.64 to 1.75) | 1999–2002: 4.7 (−5.7 to 16.1) | 2002–2017: −1.6 (−2.4 to −0.8) | −0.6 (−2.3 to 1.1) |
| West | 2625 (23.2) | 2.01 (1.93 to 2.09) | – | – | −1.5 (−2.5 to −0.5) |
| **Age§** | | | | | |
| ≤64 y | 3159 (27.9) | 0.63 (0.61 to 0.65) | 1999–2010: 1.3 (−0.3 to 3.0) | 2010–2017: −4.6 (−7.5 to −1.6) | −1.0 (−2.4 to 0.4) |
| 65–74 y | 3000 (26.5) | 7.21 (6.95 to 7.47) | – | – | −2.5 (−3.0 to −1.9) |
| 75–84 y | 3819 (33.7) | 15.23 (14.75 to 15.72) | – | – | −0.7 (−1.5 to 0.1) |
| ≥85 y | 1338 (11.8) | 13.42 (12.70 to 14.14) | – | – | −1.6 (−2.6 to −0.7) |

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Steinberg AW et al., Ann of Int Med 2019

# Causes of early and late mortality in AAV

**Table 3** Causes of death within and after the first year of follow-up, respectively

| Cause of death | <1 Year | | >1 Year | |
|---|---|---|---|---|
| | Primary cause | Contributing factor | Primary cause | Contributing factor |
| Active vasculitis | 11 (18.6) | 17 (28.8) | 6 (8.1) | 7 (9.5) |
| Pulmonary haemorrhage | 6 | | 2 | |
| Infection | 28 (47.5) | 31 (52.5) | 15 (20.3) | 23 (31.1) |
| Pneumonia | 15 | | 8 | |
| Sepsis | 8 | | 7 | |
| CMV | 2 | | | |
| PCP | 3 | | | |
| Cardiovascular | 9 (15.3) | 11 (18.6) | 19 (25.7) | 21 (28.4) |
| Myocardial infarction | 2 | | 4 | |
| Cerebrovascular accident | 2 | | 2 | |
| Pulmonary embolus | 2 | | | |
| Sudden death | 1 | | 3 | |
| Malignancy | 0 (0) | | 16 (21.6) | 18 (24.3) |
| Solid organ | | | 12 | |
| Haematological | | | 4 | |
| Miscellaneous | 6 (10.2) | | 9 (12.2) | |
| Pulmonary fibrosis | 3 | | 3 | |
| Unknown | 5 (8.5) | | 9 (12.2) | |
| Total | 59 | | 74 | |

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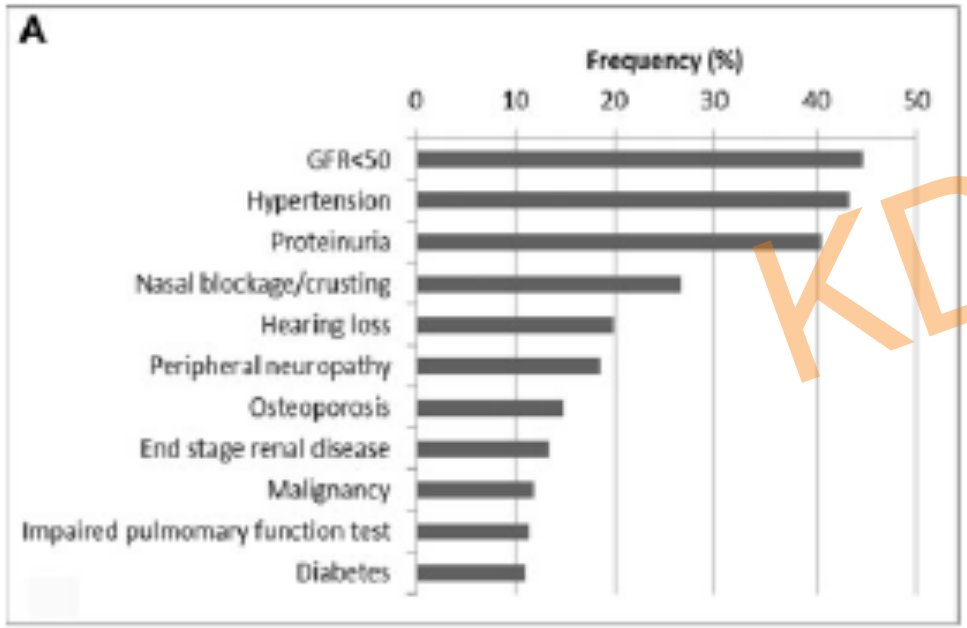
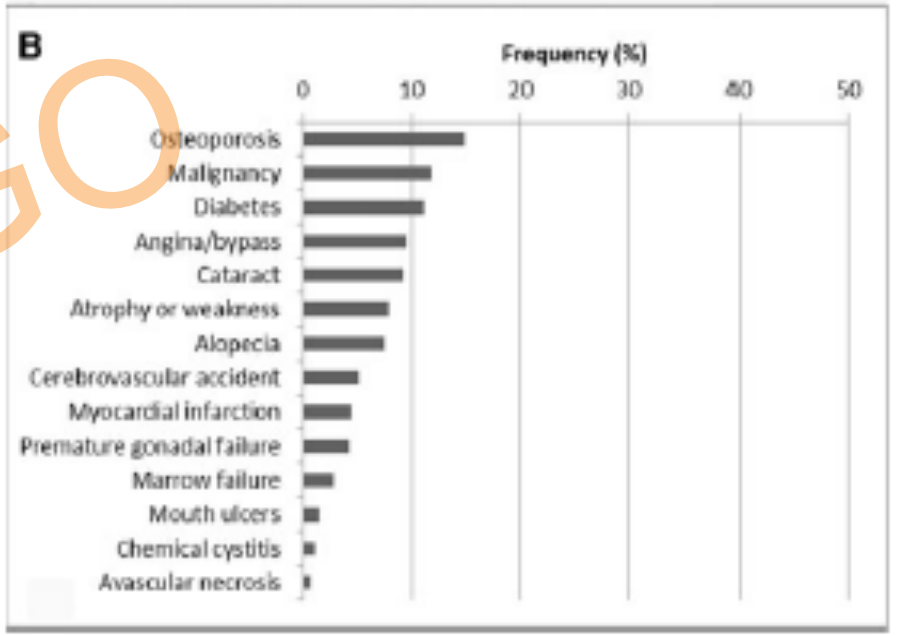
Flossmann O, et al. Ann Rheum Dis 2011

# AAV patients face high morbidity

Most common VDI items




Treatment related VDI items

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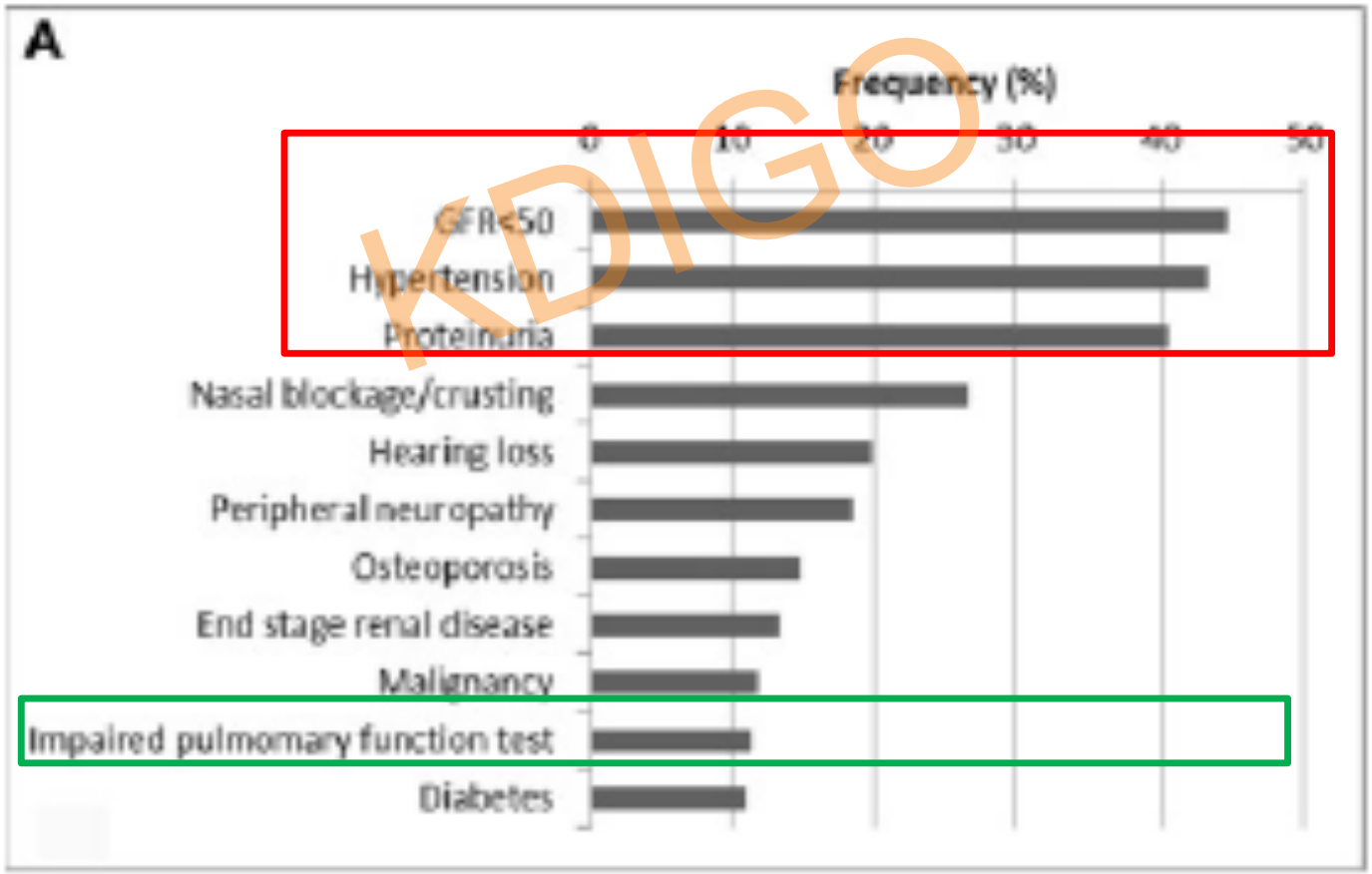
Robson J et al, *Rheumatology* 2015

# Current treatment prevents lung damage more effectively than renal damage

Most common VDI items




KDIGO

Robson J et al, *Rheumatology* 2015

# Clinical predictors of ESRD in AAV patients

TABLE 4 Independent baseline predictors for ESRF with renal relapse as time-varying covariate

| Competing risk | sHR | 95% CI | | *P*-value |
|---|---|---|---|---|
| Age, year | 0.99 | 0.97 | 1.01 | 0.38 |
| Female | 0.84 | 0.43 | 1.64 | 0.61 |
| Anti-PR3+ | 0.94 | 0.32 | 2.79 | 0.92 |
| Anti-MPO+ | 1.40 | 0.47 | 4.15 | 0.54 |
| Serum creatinine, μmol/l | | | | |
| 100–150 | Referent | NA | NA | NA |
| 151–275 | 2.03 | 0.40 | 10.34 | 0.40 |
| 276–500 | 6.63 | 1.63 | 27.00 | 0.01 |
| >500 | 13.82 | 3.12 | 61.18 | <0.001 |
| BVAS | | | | |
| Cutaneous | 0.50 | 0.20 | 1.25 | 0.14 |
| Mucous membranes | 1.59 | 0.77 | 3.29 | 0.21 |
| ENT | 0.54 | 0.27 | 1.09 | 0.09 |
| Chest | 1.70 | 0.85 | 3.40 | 0.13 |
| Cardiovascular | 1.36 | 0.45 | 4.05 | 0.59 |
| Abdominal | 2.35 | 0.90 | 6.16 | 0.08 |
| Nervous | 0.57 | 0.20 | 1.61 | 0.29 |
| Induction therapy | | | | |
| Oral CYC | Referent | NA | NA | NA |
| i.v. CYC | 1.97 | 0.18 | 21.20 | 0.58 |
| MTX | 1.52 | 0.66 | 3.50 | 0.33 |
| Adjunctive therapy | | | | |
| PLEX | 0.37 | 0.15 | 0.88 | 0.03 |
| Renal relapse | 8.86 | 4.19 | 18.72 | <0.001 |

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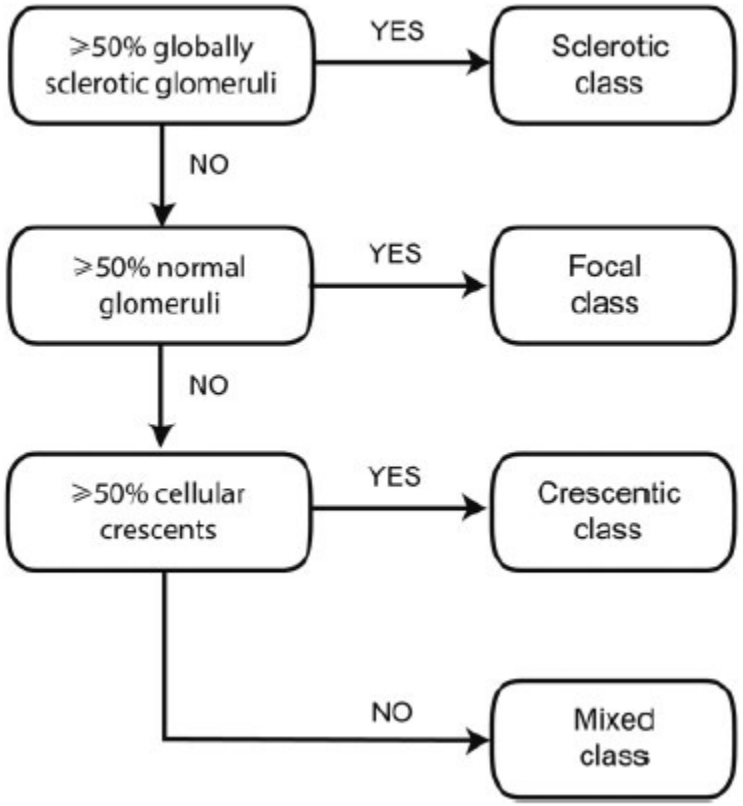
Wester Trejo MAC et al., Rheumatology 2019

# Histologic predictors for ESRD in AAV

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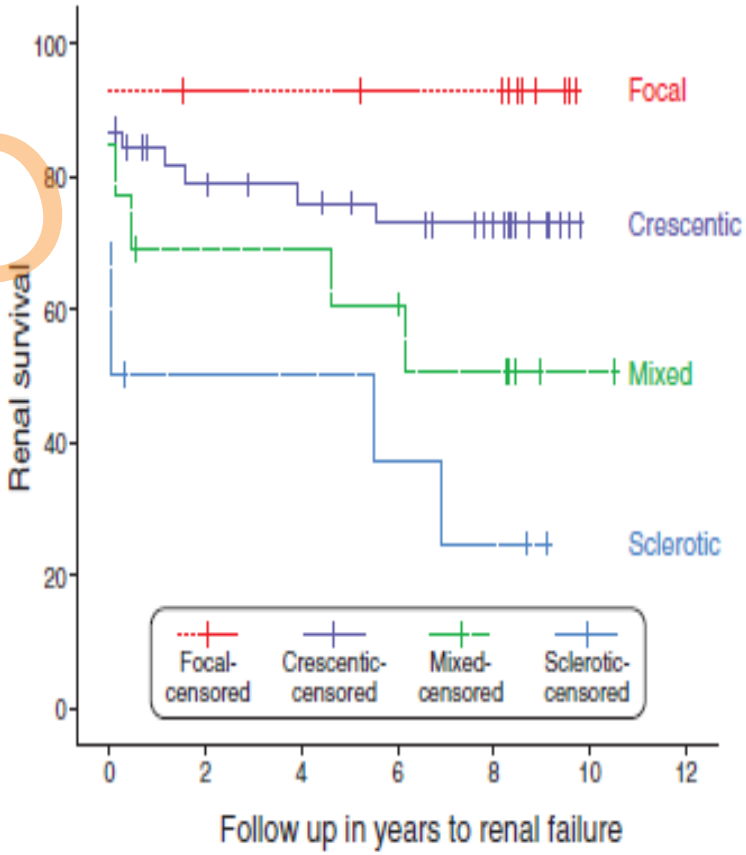
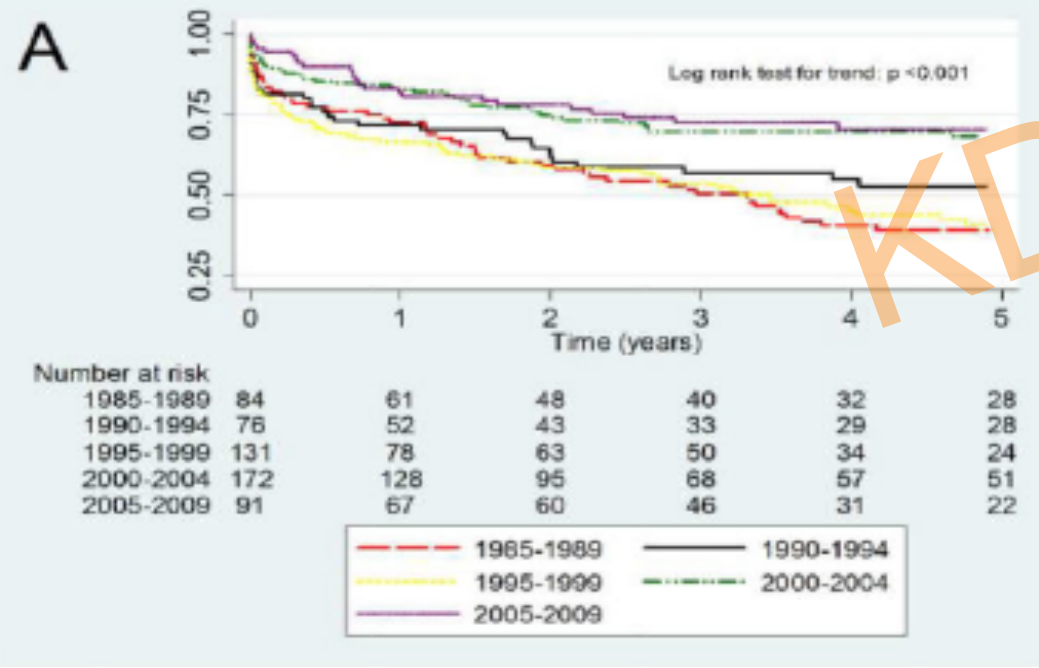


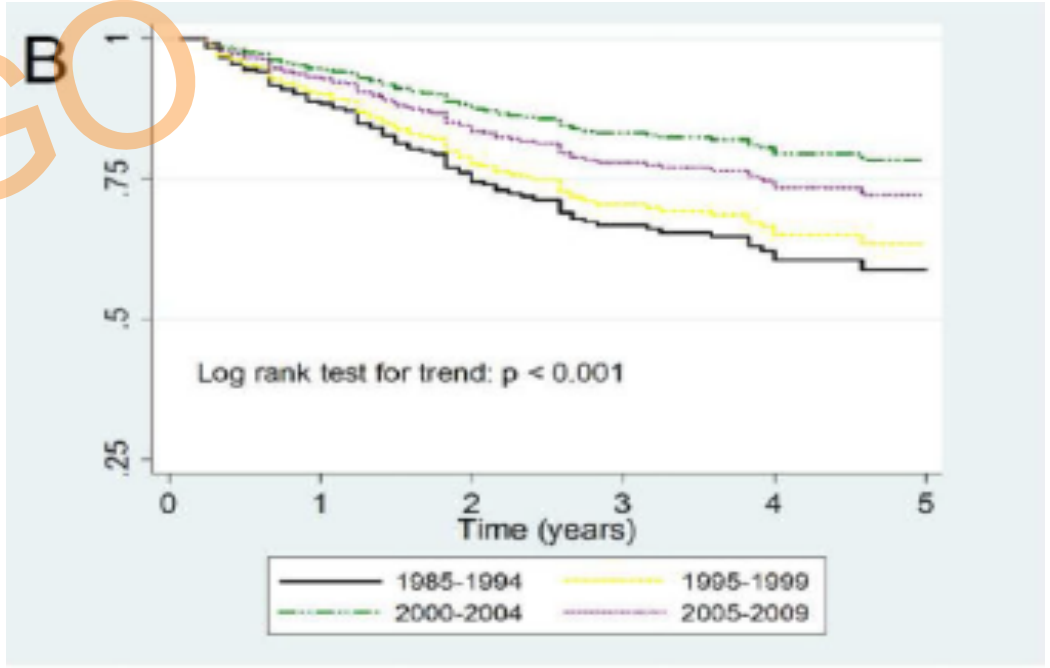

Berden AE et al., J Am Soc Nephrol 2010

# Improvement in trends in ESRD over time

**Kaplan-Meier curve**




**Adjusted curve**

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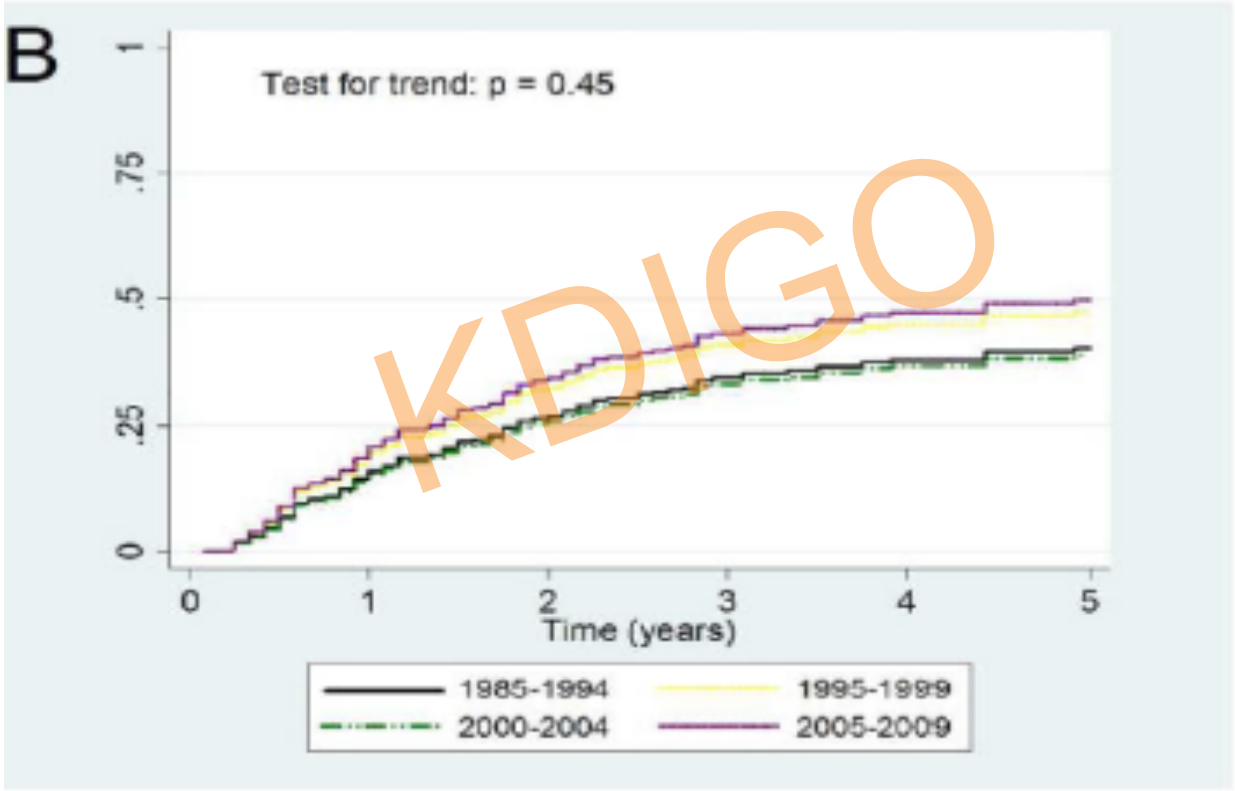
Rhee RL et al, *Arthritis &Rheum* 2016

# No change in trends in risk of relapse over time

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Rhee RL et al, *Arthritis &Rheum* 2016

# Causes of early and late mortality in AAV

**Table 3** Causes of death within and after the first year of follow-up, respectively

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| Pulmonary embolus | 2 | | | |
| Sudden death | 1 | | 3 | |
| Malignancy | 0 (0) | | 16 (21.6) | 18 (24.3) |
| Solid organ | | | 12 | |
| Haematological | | | 4 | |
| Miscellaneous | 6 (10.2) | | 9 (12.2) | |
| Pulmonary fibrosis | 3 | | 3 | |
| Unknown | 5 (8.5) | | 9 (12.2) | |
| Total | 59 | | 74 | |

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Flossmann O, et al. Ann Rheum Dis 2011

# Infections in AAV

**No difference in infection rates In early vs recent cohort**

*Table 2.* Rates of first severe infection among 186 patients with ANCA-associated vasculitis and reference population of 744 persons.

| Infections | AAV, n | AAV, Person-yrs | Rate | Ref., n | Ref., Person-yrs | Rate | Rate Ratio | 95% CI | p |
|---|---|---|---|---|---|---|---|---|---|
| All severe infections | 86 | 740 | 116.2 | 118 | 4602 | 25.6 | 4.53 | 3.39-6.00 | <0.001 |
| All septicemias | 19 | 1039 | 18.2 | 29 | 4906 | 5.91 | 3.09 | 1.64-5.66 | 0.004 |
| Nonspecific septicemia | 9 | 1088 | 8.27 | 9 | 4953 | 1.82 | 4.55 | 1.60-13.8 | 0.02 |
| Gram-negative septicemia | 9 | 1064 | 8.46 | 12 | 4958 | 2.42 | 3.49 | 1.30-9.29 | 0.03 |
| *Staphylococcus aureus* septicemia | 3 | 1095 | 2.74 | 4 | 4959 | 0.81 | 3.40 | 0.50-51.2 | 0.2 |
| Acute URTI | 15 | 1043 | 14.3 | 8 | 4942 | 1.62 | 8.88 | 3.54-25.9 | 0.001 |
| Influenza and pneumonia | 46 | 918 | 50.1 | 73 | 4763 | 15.3 | 3.27 | 2.21-4.76 | <0.001 |
| *Clostridium difficile* | 7 | 1080 | 6.48 | 6 | 4957 | 1.21 | 5.35 | 1.54-23.8 | 0.03 |
| Nonspecific infection | 12 | 1031 | 11.6 | 22 | 4880 | 4.51 | 2.58 | 1.16-5.43 | 0.04 |
| Skin infections | 8 | 1060 | 7.55 | 7 | 4961 | 1.41 | 5.35 | 1.69-19.8 | 0.02 |

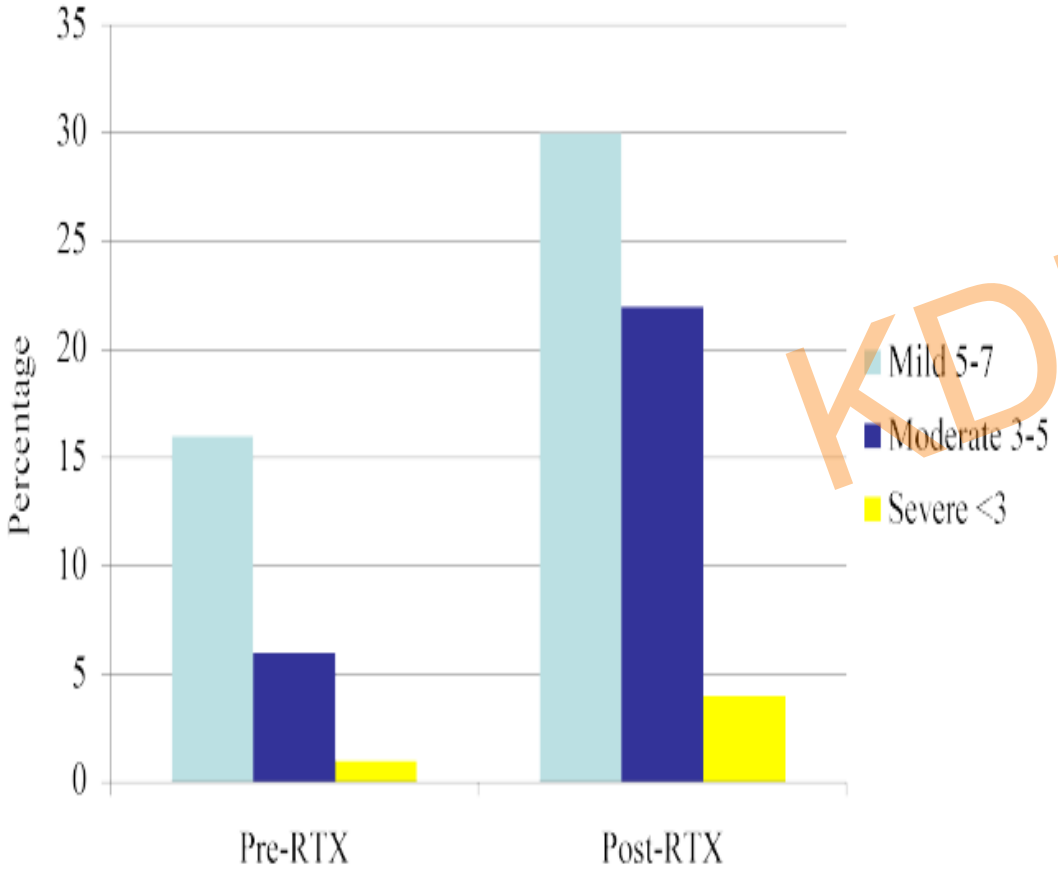
*Table 3.* Rate and rate ratios of severe infections and septicemia in 186 patients with ANCA-associated vasculitis during 2 time periods: the early cohort (1998–2003) versus the recent cohort (2004–2009).

| Infections | AAV, n | AAV, Person-yrs | Rate | Ref., n | Ref., Person-yrs | Rate | Rate Ratio | 95% CI | p |
|---|---|---|---|---|---|---|---|---|---|
| Early cohort | | | | | | | | | |
| All infections | 23 | 175 | 131 | 26 | 974 | 26.7 | 4.91 | 2.68-8.86 | <0.001 |
| All septicemias | 6 | 230 | 26.1 | 3 | 1018 | 2.95 | 8.86 | 1.89-553 | 0.03 |
| Recent cohort | | | | | | | | | |
| All infections | 29 | 168 | 172 | 28 | 918 | 31 | 5.65 | 3.24-9.74 | <0.001 |
| All septicemias | 5 | 218 | 22.9 | 4 | 953 | 4.2 | 5.46 | 1.18-61.1 | 0.7 |

KDIGO

Mohammad AJ et al., J Rheum 2017

# Rituximab and hypogammaglobulinemia

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**Mean percent decline in Ig**

| Antibody | Induction therapy N=52 | Maintenance therapy N=237 |
|---|---|---|
| IgG | 6 (4,8) | 0.6 (-0.2,1.4) |
| IgA | 5 (2,9) | 5 (3,6) |
| IgM | 16 (13,19) | 9 (8,11) |

**Roberts DM et al., J Autoimmunity 2015**
**Cortazar B et al., Arthritis & Rheum 2017**

# Infection type in AAV and recommendations for prevention

- Respiratory infections, esp. Staph aureus
- C. Difficile
- Opportunistic infections: PJP, HZ, CMV
- Hepatitis B reactivation
- PML

- Decrease/withdraw immunosuppression in those at risk for infection and low relapse risk
- Vaccination for Influenza and Pneumococcus
- Prophylaxis with trimethoprim-sulfamethoxazole
- Surveillance with CBC, renal function and immunoglobulins

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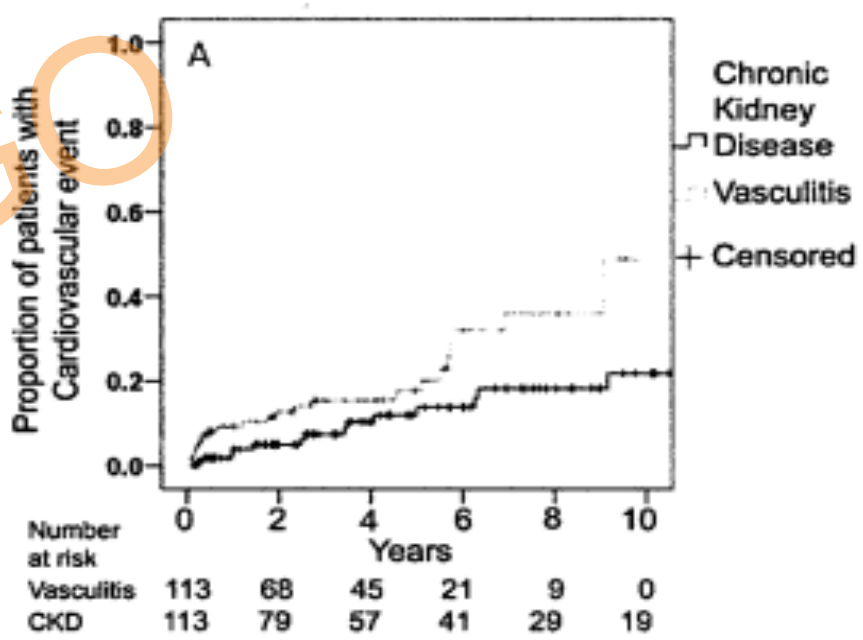
# Risk of cardiovascular disease is increased in AAV

**AAV patients have higher risk of cardiovascular events than those with matched CKD**

- EUVAS data: 14% of 535 patients had at least one CV events over a 5 year follow up

- Age, diastolic hypertension and ANCA type are predictive of CV risk

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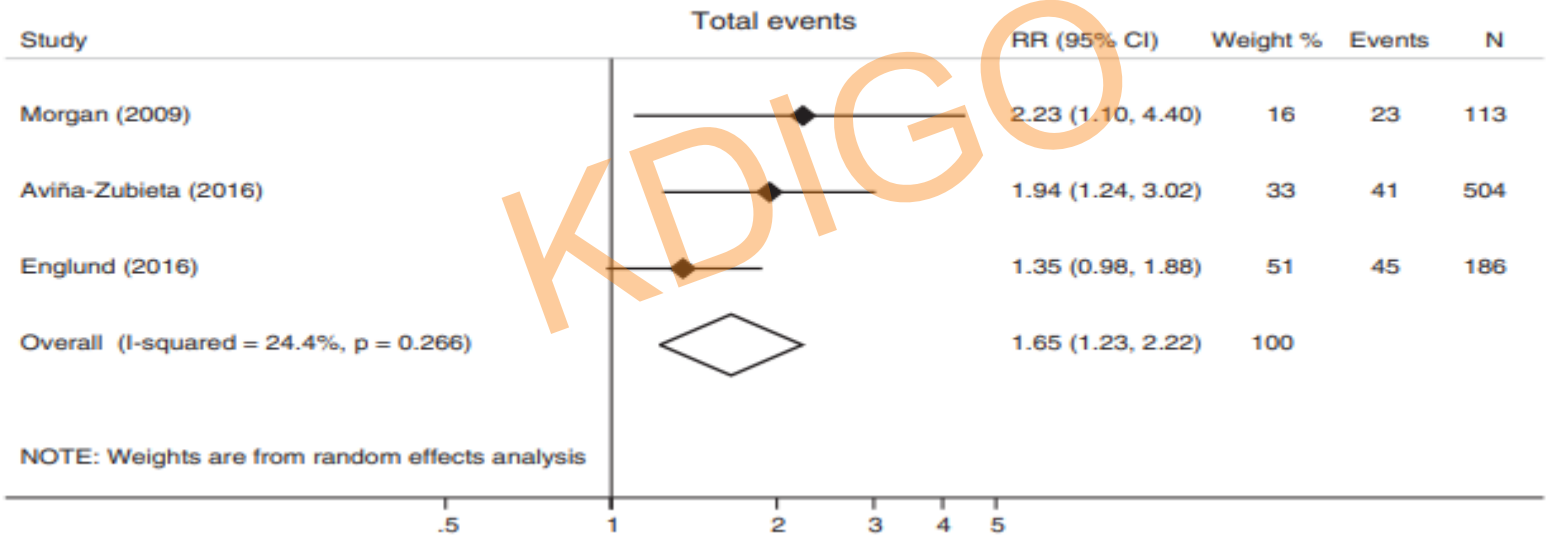
Suppiah R et al., Arthritis Care Res 2011
Morgan MD et al.Arthritis & Rheum 2009

# Risk of cardiovascular disease is increased in AAV

**Patients with AAV have an increase in cardiovascular risk of 65%**

FIG. 2 Meta-analysis on the relative risk for cardiovascular events in ANCA-associated vasculitis




KDIGO

Houben EE et al,
*Rheumatology* 2018

# Risk of malignancy increased in AAV

**Table 2** Calculated age, sex and area SIR for observed cancers at all sites, at all sites excluding NMSC and by site ordered by decreasing numbers of observed cancer cases

| Cancer site | PY | No. of cancers | | SIR (95% CI) | p Value |
|---|---|---|---|---|---|
| | | Observed | Expected | | |
| All sites | 2553 | 50 | 31.71 | 1.58 (1.17 to 2.08) | 0.003 |
| All non-NMSC sites | 2580 | 35 | 27.00 | 1.30 (0.90 to 1.80) | 0.16 |
| By cancer site | | | | | |
| NMSC | 2618 | 15 | 5.39 | 2.78 (1.56 to 4.59) | 0.001 |
| Prostate | 2623 | 8 | 4.40 | 1.82 (0.78 to 3.58) | 0.16 |
| Lung | 2648 | 5 | 3.89 | 1.29 (0.42 to 3.00) | 0.70 |
| Bladder | 2645 | 4 | 1.66 | 2.41 (0.66 to 6.17) | 0.17 |
| Breast | 2645 | 3 | 3.06 | 0.98 (0.20 to 2.87) | 1.0 |
| Colorectal | 2640 | 3 | 3.96 | 0.76 (0.16 to 2.21) | 0.88 |
| Larynx | 2647 | 2 | 0.30 | 6.67 (0.81 to 24.08) | 0.07 |
| Endometrium | 2643 | 2 | 0.61 | 3.26 (0.40 to 11.84) | 0.25 |
| Leukaemia | 2649 | 2 | 0.62 | 3.25 (0.39 to 11.65) | 0.26 |
| Thyroid | 2645 | 1 | 0.18 | 5.56 (0.14 to 30.95) | 0.33 |
| Myeloma | 2649 | 1 | 0.41 | 2.44 (0.06 to 13.59) | 0.67 |
| Liver | 2650 | 1 | 0.56 | 1.79 (0.05 to 9.95) | 0.86 |
| Pancreas | 2650 | 1 | 0.75 | 1.33 (0.03 to 7.43) | 1.0 |
| Non-Hodgkin's lymphoma | 2646 | 1 | 0.90 | 1.11 (0.03 to 6.19) | 1.0 |
| Stomach | 2643 | 1 | 1.11 | 0.90 (0.02 to 5.02) | 1.0 |

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Heijl C et al, *Ann Rheum Dis* 2011

# AAV and malignancy risk

- 138 patients with mean FU of 9.7 years
- 36 developed 85 malignancies, 61 of which were NMSC cancers

**Malignancy risk increased compared to general population**

**Table 2.** SIRs calculated for malignancies overall and per observed malignancy*

| Malignancy type | No. of malignancies observed | SIR (95 CI) |
|---|---|---|
| All malignancies | 85 | 2.21 (1.64–2.92)† |
| NMSC | 61 | 4.23 (2.76–6.19)† |
| Non-NMSC‡ | | |
| Total | 24 | 1.46 (0.93–2.17) |
| By malignancy | | |
| Breast carcinoma | 3 | 2.04 (0.42–5.96) |
| Colon carcinoma | 3 | 1.85 (0.38–5.41) |
| Prostate carcinoma | 3 | 0.99 (0.20–2.89) |
| Lung carcinoma | 2 | 0.75 (0.23–3.30) |
| Soft tissue sarcomas | 2 | 7.69 (0.93–27.79) |
| Unknown primary malignancy | 2 | 3.92 (0.47–14.17) |
| Brain carcinoma | 1 | 5.56 (0.14–30.95) |
| Parotid carcinoma | 1 | 33.33 (0.84–185.72) |
| Bladder carcinoma | 1 | 1.43 (0.04–7.96) |
| Uterus carcinomas | 1 | 4.00 (0.10–22.29) |
| Non-Hodgkin's lymphoma | 1 | 1.37 (0.03–7.63) |
| Renal cell carcinoma | 1 | 2.44 (0.06–13.59) |
| Chondrosarcoma | 1 | 28.57 (0.72–159.19) |
| Esophageal carcinoma | 1 | 2.70 (0.07–15.06) |
| Melanoma | 1 | 1.92 (0.05–10.71) |

KDIGO

Rahmattulla C et al.Arthritis & Rheum 2015

# AAV and malignancy risk decreases with less use of cyclophosphamide

Risk decreased over time

No increase in risk when CYC use was less than one year

**Table 3.** SIRs for malignancy in the AAV patients stratified into various subgroups*

| | n | No. of malignancies observed | SIR (95% CI) | *P* | RR (95% CI) |
|---|---|---|---|---|---|
| Sex | | | | | |
| Male | 87 | 61 | 2.33 (1.64–3.21) | <0.001 | Referent |
| Female | 51 | 24 | 1.93 (1.03–3.31) | 0.041 | 0.83 (0.40–1.60) |
| Age | | | | | |
| ≥61 years | 68 | 44 | 2.20 (1.47–3.18) | 0.001 | Referent |
| <61 years | 70 | 41 | 2.22 (1.39–3.36) | <0.001 | 0.99 (0.55–1.82) |
| Clinical diagnosis | | | | | |
| MPA | 38 | 23 | 1.89 (0.98–3.30) | 0.058 | Referent |
| GPA | 79 | 54 | 2.53 (1.76–3.52) | <0.001 | 1.34 (0.68–2.83) |
| ANCA serotype | | | | | |
| MPO-ANCA | 47 | 16 | 1.87 (0.93–3.34) | 0.076 | Referent |
| PR3-ANCA | 55 | 53 | 2.72 (1.80–3.93) | <0.001 | 1.46 (0.70–3.24) |
| Renal transplantation | | | | | |
| No | 128 | 78 | 2.17 (1.59–2.91) | <0.001 | Referent |
| Yes | 10 | 7 | 3.33 (1.08–7.78) | 0.037 | 1.53 (0.48–3.85) |
| Followup | | | | | |
| 0–5 years | 55 | 6 | 1.60 (0.52–3.73) | 0.414 | Referent |
| >5–10 years | 29 | 19 | 2.91 (1.45–5.21) | 0.004 | 1.82 (0.58–6.67) |
| >10 years | 54 | 60 | 2.17 (1.50–3.03) | <0.001 | 1.36 (0.53–4.44) |
| Year of diagnosis | | | | | |
| Before 2003 | 83 | 73 | 2.43 (1.76–3.26) | <0.001 | Referent |
| In or after 2003 | 55 | 12 | 1.34 (0.49–2.92) | 0.586 | 1.81 (0.77–5.20) |
| Previous malignancy | | | | | |
| No | 124 | 80 | 2.24 (1.64–2.98) | <0.001 | Referent |
| Yes | 14 | 5 | 1.97 (0.54–5.05) | 0.297 | 1.13 (0.41–4.34) |

**Table 5.** SIRs calculated according to duration of cyclophosphamide therapy*

| Cyclophosphamide therapy duration | n | No. of malignancies observed | SIR (95% CI) | *P* | RR (95% CI) | *P* |
|---|---|---|---|---|---|---|
| 0–6 months | 65 | 15 | 1.52 (0.78–2.64) | 0.212 | Referent | – |
| >6–12 months | 21 | 14 | 1.82 (0.79–3.59) | 0.156 | 1.20 (0.43–3.19) | 0.847 |
| >12–24 months | 16 | 30 | 3.83 (1.98–6.70) | <0.001 | 2.53 (1.04–6.17) | 0.040 |
| >24 months | 15 | 18 | 4.67 (2.55–7.83) | <0.001 | 3.08 (1.31–7.32) | 0.008 |

KDIGO

Rahmattulla C et al.Arthritis & Rheum 2015

# Does rituximab decrease the risk of malignancy

**Table 2** SIR for malignancies overall and per observed malignancy site*

| Malignancy or malignancy site | Observed malignancies (n) | Expected malignancies (n) | SIR (95% CI)† | p Value† |
|---|---|---|---|---|
| All sites | 45 | 23.80 | 1.89 (1.38 to 2.53) | <0.001 |
| Non-melanoma skin cancer | 25 | 5.46 | 4.58 (2.96 to 6.76) | <0.001 |
| All malignancies excluding non-melanoma skin cancer | 20 | 18.33 | 1.09 (0.67 to 1.69) | 0.76 |
| Lung | 4 | 2.61 | 1.53 (0.42 to 3.92) | 0.53 |
| Breast | 3 | 2.82 | 1.06 (0.22 to 3.11) | 1.00 |
| Colon or rectum | 3 | 1.98 | 1.52 (0.31 to 4.44) | 0.63 |
| Prostate | 2 | 2.74 | 0.73 (0.09 to 2.64) | 0.97 |
| Bladder | 1 | 0.65 | 1.53 (0.04 to 8.57) | 0.96 |
| Pancreas | 1 | 0.52 | 1.94 (0.05 to 10.81) | 0.81 |
| Testis | 1 | 0.04 | 24.66 (0.62 to 137.41) | 0.08 |
| Ovary | 1 | 0.39 | 2.54 (0.06 to 14.14) | 0.65 |
| Melanoma | 1 | 0.66 | 1.52 (0.04 to 8.49) | 0.96 |
| Tongue | 1 | 0.07 | 13.70 (0.35 to 76.34) | 0.14 |
| Central nervous system | 1 | 0.25 | 3.94 (0.10 to 21.95) | 0.45 |
| Kidney | 1 | 0.49 | 2.03 (0.05 to 11.32) | 0.78 |

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# Patients treated with only rituximab had no increased malignancy risk compared to general population

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**Table 3** SIR stratified according to treatment category*

| Treatment† | Patients (n) | SIR (95% CI)‡ | SIR p Value‡ |
|---|---|---|---|
| Only cyclophosphamide | 119 | 3.10 (2.06 to 4.48) | <0.001 |
| Only rituximab | 41 | 0.67 (0.08 to 2.43) | 0.86 |
| Both | 114 | 1.01 (0.46 to 1.93) | 1.00 |
| None | 48 | 2.10 (0.77 to 4.56) | 0.14 |

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# Relative risk of malignancy and treatment category

Malignancy risk in CYC treated patients was 4.61 fold higher than in RTX treated patients

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**Table 4** Relative risks (RR) according to treatment category

| Treatment* | RR (95% CI)† | p Value† |
|---|---|---|
| Only cyclophosphamide vs only rituximab | 4.61 (1.16 to 39.98) | 0.03 |
| Only cyclophosphamide vs both | 3.05 (1.40 to 7.35) | 0.003 |
| Only cyclophosphamide vs none | 1.48 (0.60 to 4.36) | 0.52 |

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# Malignancy risk and cumulative dose of CYC and RTX

**Table 5** SIR stratified according to cumulative cyclophosphamide and rituximab doses*

| Cumulative dose (g) | Patients (n) | N observed malignancies | SIR (95% CI)† |
|---|---|---|---|
| Cyclophosphamide | | | |
| 0 | 89 | 8 | 1.37 (0.59 to 2.70) |
| 0.1–20 | 207 | 31 | 1.91 (1.30 to 2.71) |
| 20–108 | 16 | 5 | 5.06 (1.64 to 11.82) |
| Rituximab | | | |
| 0 | 167 | 34 | 2.86 (1.98 to 3.99) |
| 0.1–6 | 70 | 7 | 1.41 (0.57 to 2.90) |
| 6–18 | 83 | 3 | 0.45 (0.09 to 1.32) |

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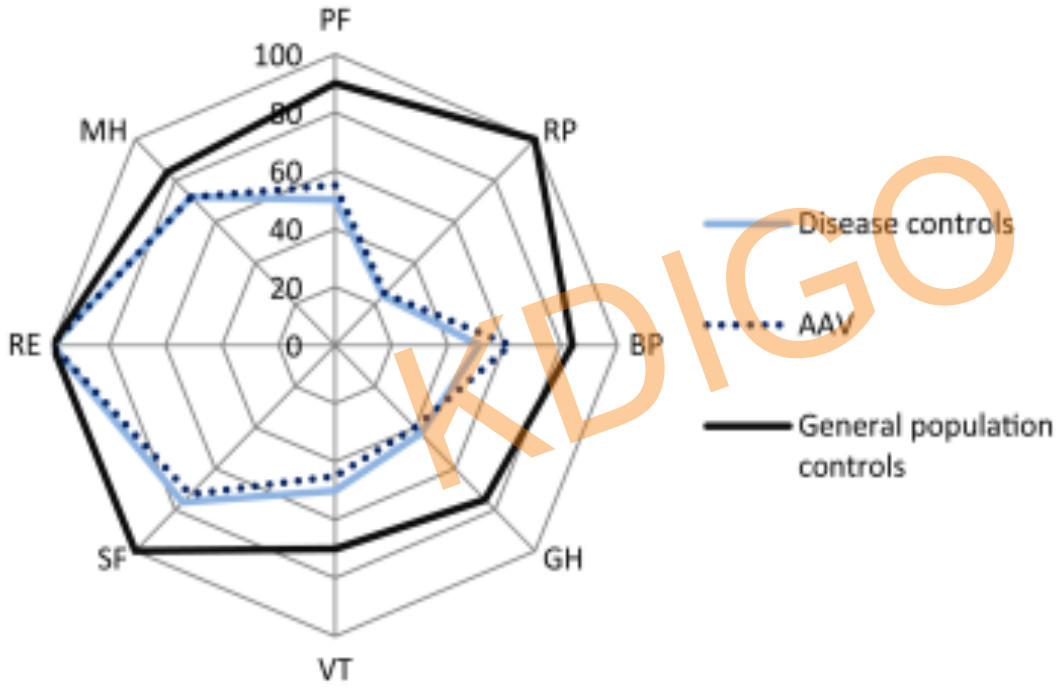
# Quality of life and ANCA vasculitis




410 ANCA patients
318 chronic disease controls
470 healthy controls

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Basu Net al, *Ann Rheum Dis* 2014

# Closing remarks

- MPO ANCA is pathogenic in in vivo and in vitro studies
- PR3 ANCA associated disease is more complex with effector T cells and infectious triggers
- We have become good at controlling active disease at expense of increasing co-morbidities
- Future challenges:
  - Refinement of induction therapy
  - Targeted therapies
  - Relapse prevention
  - Management of disease and treatment associated co-morbidities
  - Addressing patient priorities

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