Updates from the 15th ANCA workshop

Christian Pagnoux, MD, MSc, MPH

Mount Sinai Hospital, Toronto, Canada

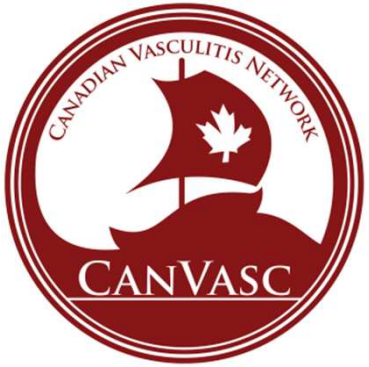
Cochin Hospital, Paris, France

Nataliya Milman, MD

Ottawa, Canada

Simon Carette, MD, MPhil, FRCP

Mount Sinai Hospital and TWH/UHN, Toronto, Canada



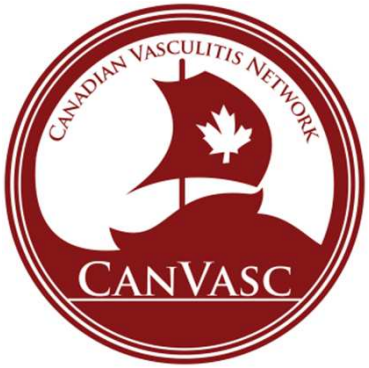
Chapel Hill Old Well

Updates from the 15th ANCA workshop (part 1)

Christian Pagnoux, MD, MSc, MPH

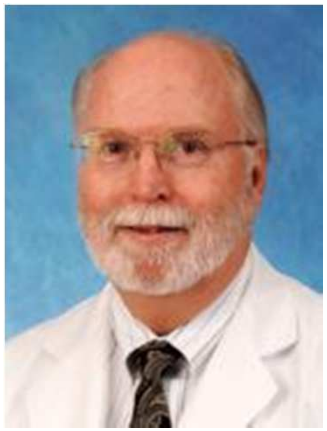
Mount Sinai Hospital, Toronto, Canada

Cochin Hospital, Paris, France



Chapel Hill Nomenclature

- LVV: GCA and TA
- Medium-sized: PAN, KD



Charles Jennette
Jennette et al. *Arthritis Rheum* 1994;37:187-92

Chapel Hill Nomenclature

- LVV
- Medium-sized
- Small-sized vessels:
  - GPA, MPA, EGPA = ANCA-ASV
  - HSP
  - + antiGBM (Goodpasture)

Chapel Hill Nomenclature

- LVV
- Medium-sized
- Small-sized vessels
- CNS vasculitis, Cogan
- Vasculitis with systemic disease
  - Lupus, RA
  - Behçet

Chapel Hill Nomenclature

- LVV
- Medium-sized
- Small-sized vessels
- CNS vasculitis, Cogan
- Vasculitis with systemic disease
- Vasculitis associated with infection (HBV, HCV...)
- Other secondary vasculitis (drugs, toxics/cocaine…)

Classification

- International effort to devise
  - Classification criteria
  - Diagnostic criteria

→ DCVAS study

PR3 versus MPO AASV…

- Distinct clinical differences
- Granulomatous disease

- Animal model

- Different geographical distribution
  - PR3 Northern countries (EU, US)
  - MPO South, East Asia and Japan

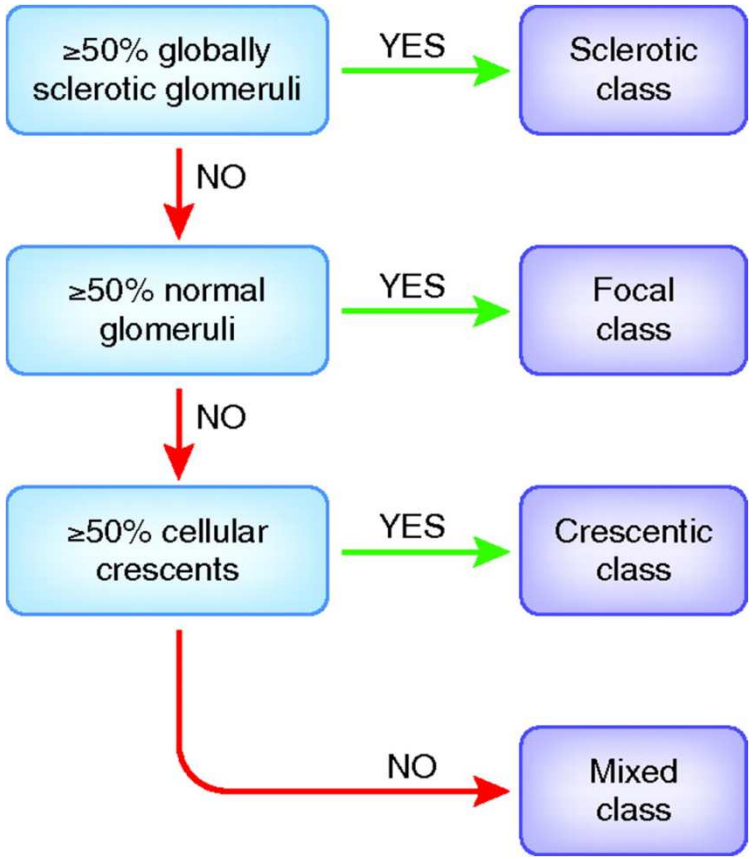
PR3 versus MPO AASV…

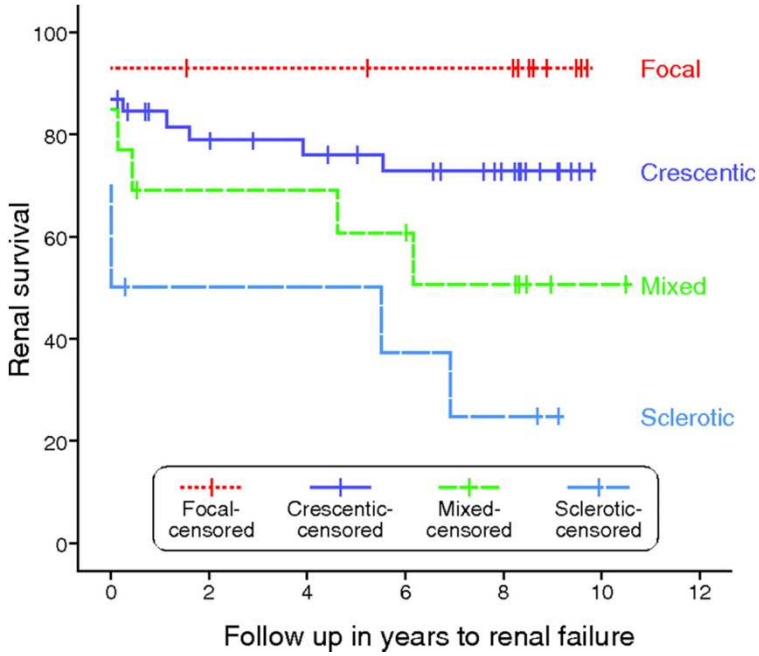
- Different time peak distribution
  - PR3 GPA peaks in 1996-98, 2005-07
    (4.5 → 17.4/million/year)
  - No peak for MPO MPA (5.8/million/year)

Watts et al, Norwich UK

- Relapse and mortality rates
  - PR3 = higher risk of relapse
  - MPO = higher mortality rate,
    higher risk of ESRD

Pathological classification of AASV-glomerulonephritis

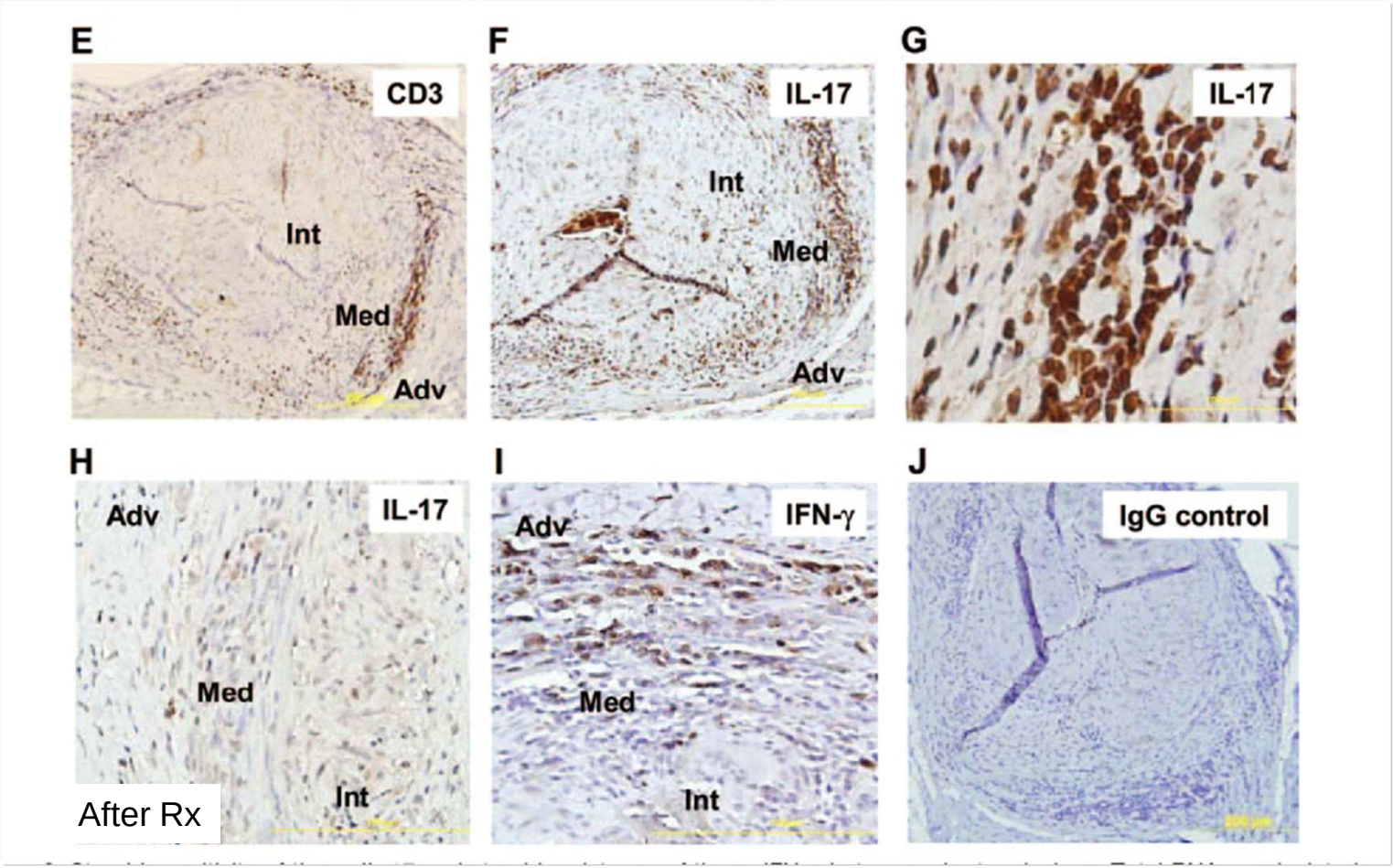




n=100 CYCAZAREM + MEPEX

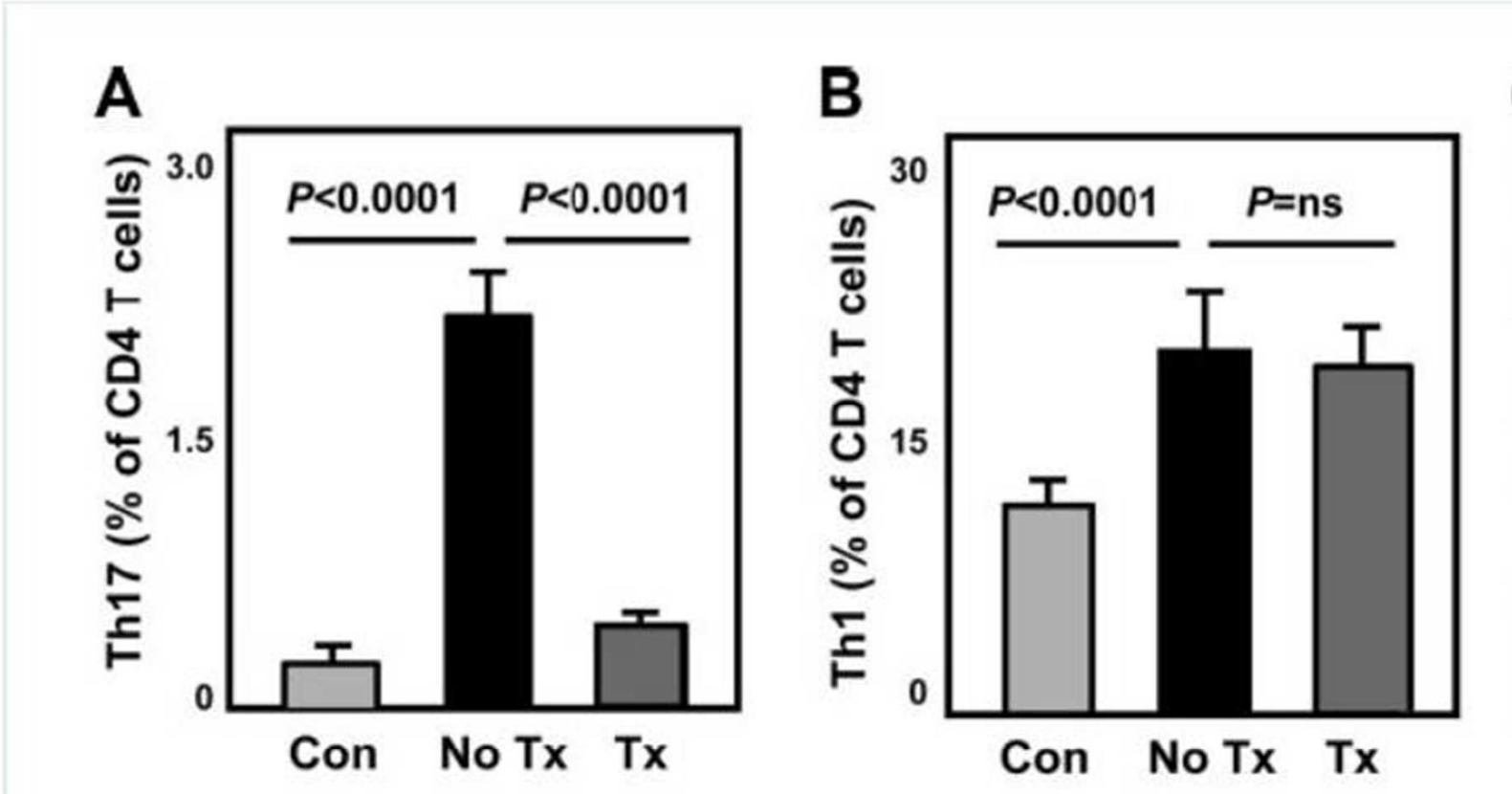
Bajema I, Leiden, NL – Berden et al, J Am Soc Nephrol. 2010 ;21:1628-36

TH17 / IL17 in GCA



Weyand et al, *Circulation* 2010;121:906-915

TH17 vs TH1 in GCA



GCA and LVV

- Physiopathology
  - TH1, TH17

  → Differential TLR distribution and expression in normal human vessels

Cornelia Weyand

CSS / EGPA

- FVSG cohort
- Mepolizumab trial

Julia Holle, Germany

PACNS

- The difficulties to establish a definitive diagnosis remain…
- Biopsy is rarely performed

Leonard Calabrese, Cleveland US

- EPCs and CECs as potential surrogate markers of activity and/or diagnosis?

Deb et al, Hannover, Germany

Eleftheriou et al, London, UK

GPA and MPA

- antiLAMP2 controversy
- ANCA in tuberculosis
- antiPR3 mouse model
- Complement in AASV

Mouse model NOD

- NOD scid mice (lack B, T, NK)
- Irradiated at 8 weeks
- Injected with mobilized human hematopoietic stem cells
- At 6 weeks post-TBI: human $CD45^+$ 18% chimerism

- Pre-treated with LPS IP
- Purified IgG from 3 anti$PR3^+$ patients, healthy donors or subjects with other kidney disease

Little et al., Birmingham, UK

Complement in AASV

- Protection from disease in C5 and factor B K.-O. mice

Xiao et al., Am J Pathol. 2007

- C5a primes neutrophils for ANCA-induced oxydative burst
- C5a-receptor deficient mice are protected for GN

Schreiber et al., J Am Soc Nephrol. 2009

C5aR antagonist CCX168

- Completely blocked anti-MPO induced GN in mice
- Orally administered
- Phase I = well tolerated, with excellent oral bioavailability (40 healthy subjects)
- 94% reduction in C5a-induced CD11b upregulation on neutrophils (*ex vivo)*

Dairaghi et al. Phase 1. [ACR abstract]. *Arthritis Rheum* 2010;62 Suppl 10 :2032

GPA and MPA

- antiLAMP2 controversy
- ANCA in tuberculosis
- antiPR3 mouse model
- Complement in AASV

- Microparticles (endothelial-, platelet-, neutrophil-MPs, MP tissue factor activity, MP-mediated thrombin generation)
- cf-DNA/NETs in active AASV (and DCs maturation)
- Epigenetic (silencing defects)
- Retinoic acid to block transcriptional activator of MPO and PR3

Therapeutic updates

- CYCLOPS
- CYCAZAREM
- MEPEX

} Long term follow-up

- Duration of corticosteroid therapy

- Rituximab (results at 18 months)
  - RAVE
  - RITUXVAS