Help het kreat stijgt! Lab, graag met spoed een ANCA en een anti-GBM

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Afdeling Nefrologie

Spoed ANCA en anti-GBM?

- wanneer is er een indicatie voor deze bepalingen met spoed?
- wat kan / moet er bepaald worden
- wat wordt er gedaan met de uitslag

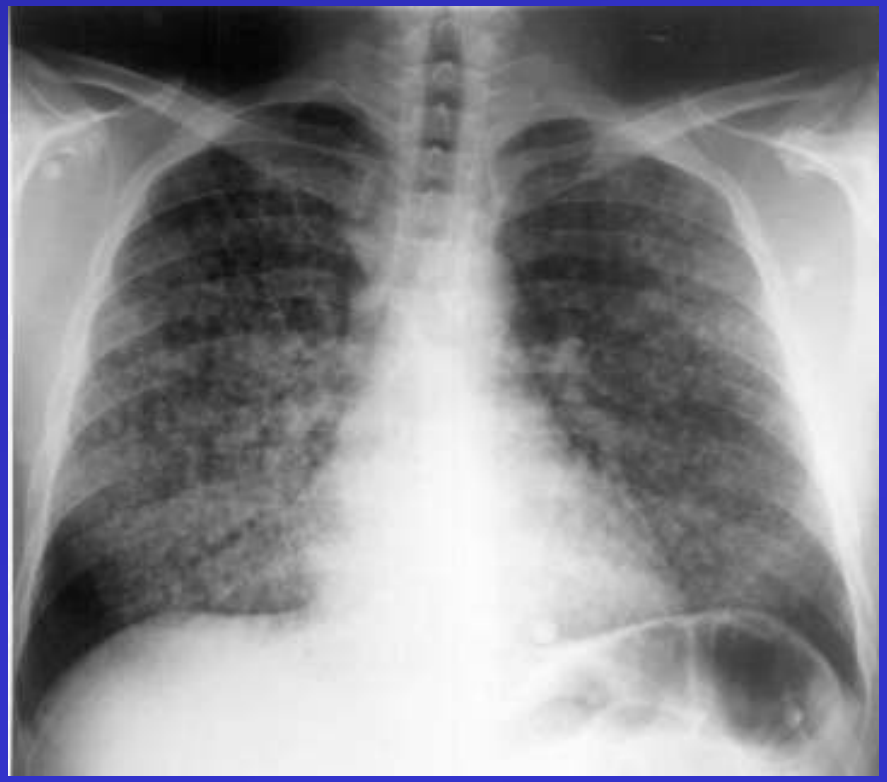
Wanneer zijn ANCA en anti-GBM van belang?

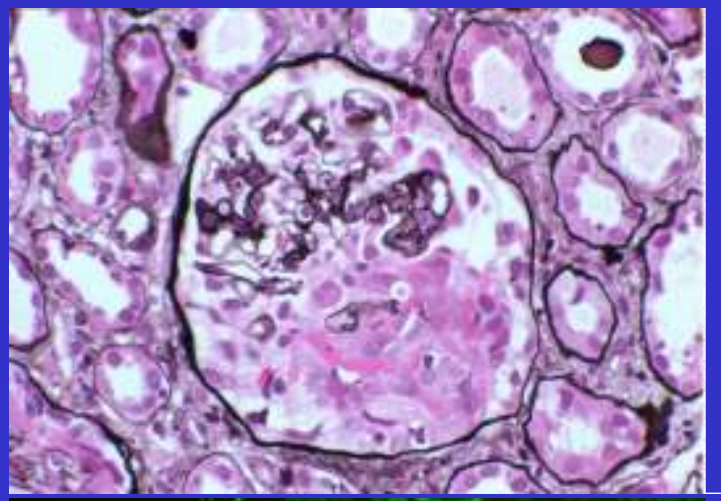
- ANCA: PR3-ANCA en MPO-ANCA
  - kleine vaten vasculitis: veel orgaansystemen aangedaan
  - geïsoleerde glomerulonefritis
- anti-GBM
  - ziekte van Goodpasture
  - RPGN
  - alveolaire bloedingen (diffuus, respiratoir falen)

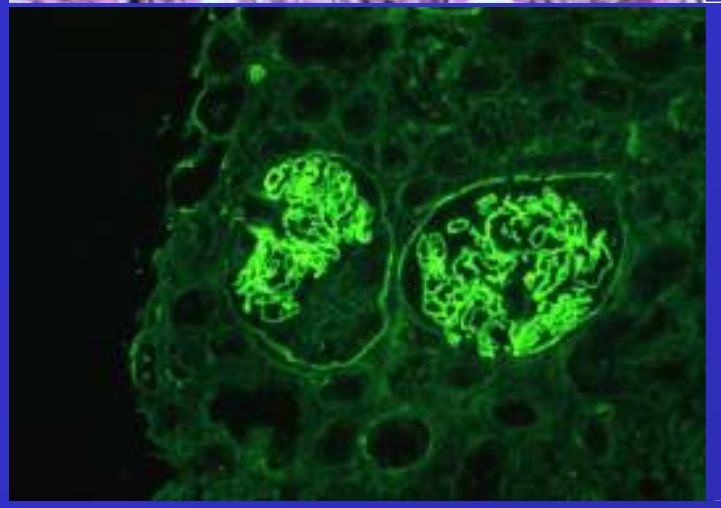
Ernest Goodpasture
1886-1960

The significance of certain pulmonary lesions in relation to the etiology of influenza
American Journal of the Medical Sciences, Thorofare, N.J., 1919; 158: 863-870.

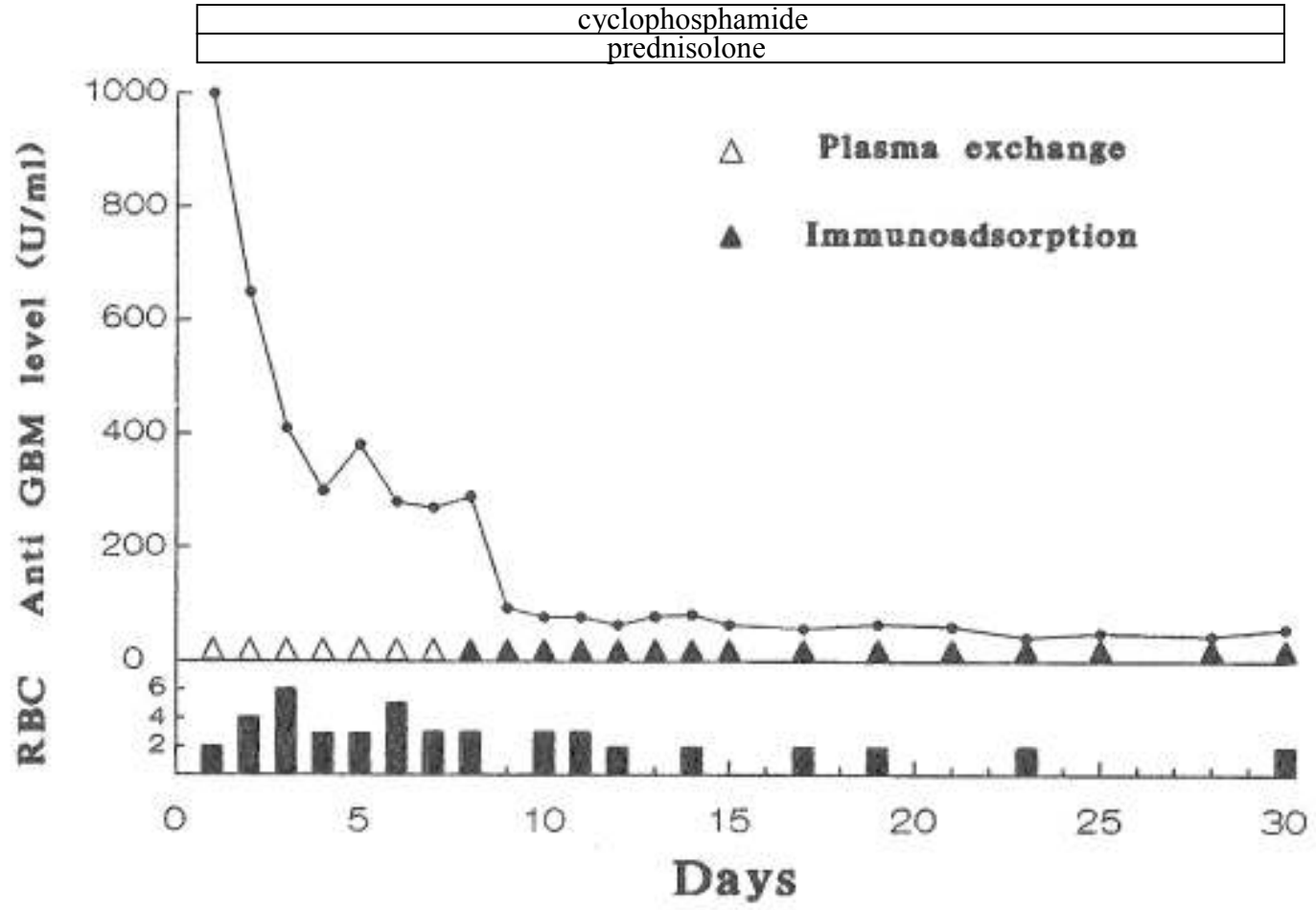
Goodpasture's disease (anti-GBM disease)







Anti-GBM titer and disease



ANCA-geassocieerde vasculitis

- vaak een multi-orgaan aandoening
  - multiple orgaan dysfuncties
  - breed palet aan presentaties
  - verschillende vormen
    - * ziekte van Wegener
    - * microscopische polyangiitis
    - * Churg-Strauss syndroom
    - * renal limited vasculitis / NCGN

ANCA-geassocieerde glomerulonefritis

- acute glomerulonefritis / RPGN (>25% ↓ GFR < 3 maanden)
  - pauci-immuun (~negatieve IF op biopt)
  - *immuuncomplex glomerulonefritis*
  - *lineaire fluorescentie (anti-GBM)*
- kenmerken glomerulonefritis moeten aanwezig zijn
- zeer frequent meest opvallende uiting / meest bedreigend

normale glomerulus

zieke glomerulus

filtratie oppervlak ↓↓

filtratie selectiviteit ↓↓

ANCA-specificity and classification/sensitivity

539 patients with primary vasculitis/necrotizing glomerulonephritis 1980-2008 in Groningen

Diagnosis	PR3	MPO	none	positive (%)
WG (n=364)	324	25	16*,**	96%
CSS (n=36)	-	23	13	64%
MPA (n=85)	16	67	2*	98%
NCGN (n=54)	4	47	3*	94%

* 4 of 16, 1 of 2, and 1 of 3 showed anti-elastase antibodies
** 11 of 16 ENT limited WG

Casus A: man, geboren 1974 (1)

VG: blanco
beroepsmilitair

A: sedert 3 weken progressief kortademig zonder koorts
laatste week toenemend hoesten met enige hemoptoë
laatste maand ca. 2-3 kg afgevallen, slechte eetlust
wisselend wat hoofdpijn
geen andere klachten/bijzonderheden

Med: paracetamol, verder geen

Intox: rookt niet, geregeld alcohol (<10^{E}/week), geen drugs

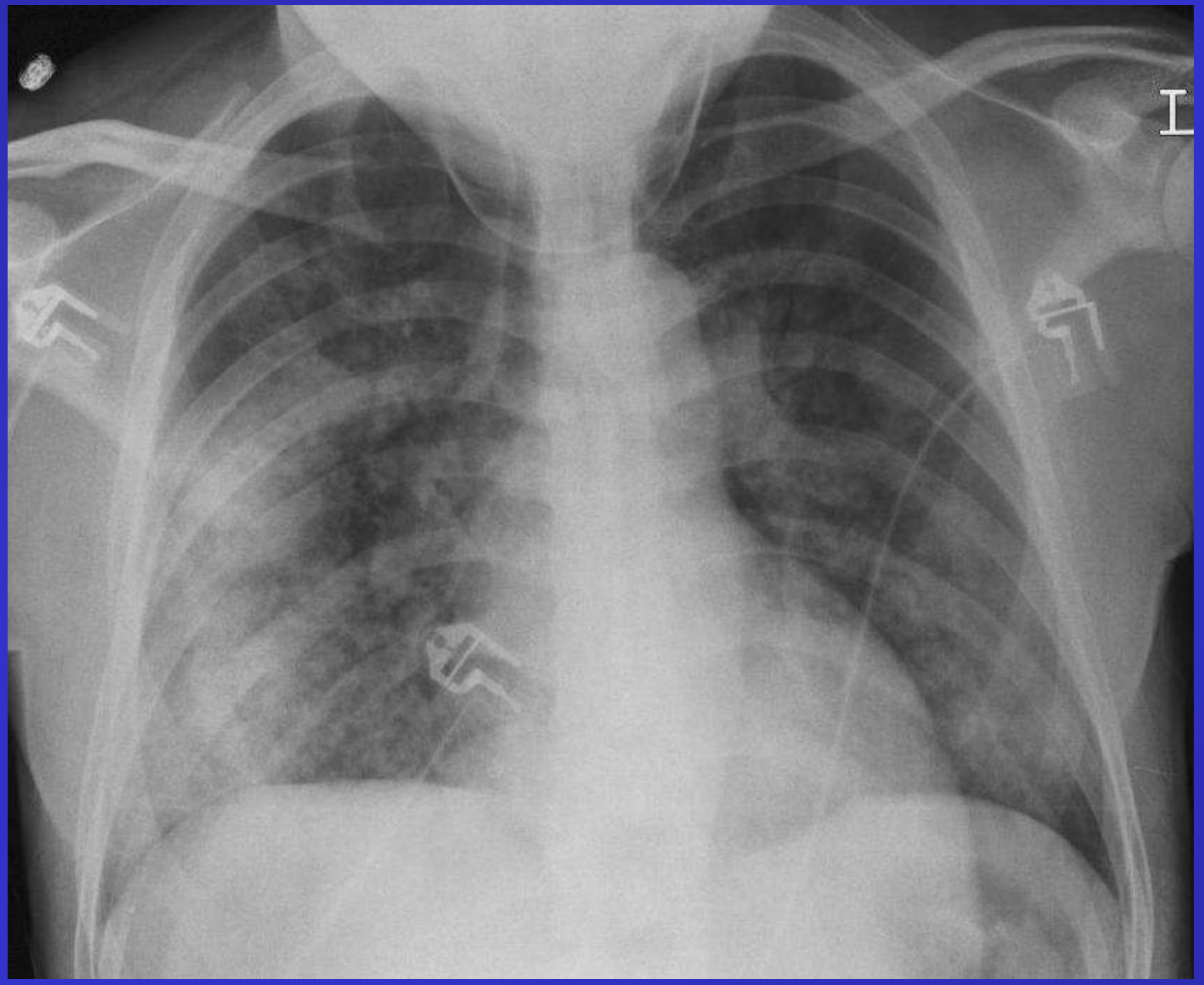
LO: tachypnoisch (26/min), RR 170/105, pols 100 RA
lijkt anemisch
crepitaties over beide longen

Casus A: man, geboren 1974 (2)

Lab: Hb 4.8 mmol/l, leuko's 12.7 x 10^9/l, trombo's 201 x 10^9/l
BSE > 100 mm, CRP 95 mg/l
Na 133 mmol/l, K 4.1 mmol/l, kreatinine 1178 µmol/l
ureum 41.8 mmol/l, LDH 375 U/l, albumin 28 g/l
calcium 2.07 mmol/l, fosfaat 2.60 mmol/l

ABGA: pH 7.44, pCO_2 3.9 kPa, pO_2 6.9 kPa,
bicarbonaat 20 mmol/l, SO_2 0.86

urine: ± 50 ery's pgz, ± 40% dysmorf (acanthocyten);
geen celcilinders
eiwit 3+



Werkdiagnose en differentiaal diagnose?

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Definitie pulmonaal-renaal syndroom

Strict:
Klinisch beeld ten gevolge van snel progressieve glomerulonefritis en capillaritis van de alveolaire vaten (Goodpasture syndrome)

Clinical:
Pesentatie met (vermoed) acuut nierfalen in combinatie
Met infiltratieve longafwijkingen verdacht voor alveolaire bloeding

Medical emergency (renal and respiratory failure)

Differentiaal diagnose bij pulmonaal-renaal syndrom

- Kleine vaten vasculitis
    * PR3- en MPO-ANCA geassocieerd
    * anti-GBM
    * andere vormen van SVV (HSP, SLE, cryo, drug induced)
- Nierfalen met volume overload / hartfalen
    * chronic/acute glomerulonephritis, diabetes
    * atherosclerose / hypertensieve nefrosclerose
    * microangiopathie (MAHA) / HUS / TTP
    * endocarditis
- Nierfalen ten tijde / van ten gevolge van pulmonale infectie
    * legionella, mycoplasma, streptococcus
    * hemorrhagic fever with renal syndrome (Hanta virus)
- Cardiovasculair (nierarterie stenose)

Reported diagnosis in pulmonary-renal syndrome[1-3]

number of patients	142
age	60 (19-84)
male / female	60% / 40%
dialysis dependent	40% - 86%
ventilatory support	27% - 57%
diagnosis	
MPA/WG	87
anti-GBM	22
other	33
serological findings	
PR3-/MPO-ANCA	94
anti-GBM	22

[1]Saxena R, etal. J Intern Med 1995;238:143-52 / [2]Niles JL, et al. Arch Int Med 1996;156:440-5
[3]Gallagher H, et al. Am J Kidney Dis 2002;39:42-7

Mogelijke diagnostiek pulmonaal-renaal syndroom (1)

- Anamnese en lichamelijke onderzoek
  * kenmerken van specifieke ziekten
  * gids voor verdere (invasieve) diagnostische stappen
- Serologie
  * ANCA
  * anti-GBM
  * ANA
  * complement
- Andere laboratorium parameters
  * thrombocyten, LDH, diff
- Radiologie
  * echo nieren/urinewegen
  * CT-scan

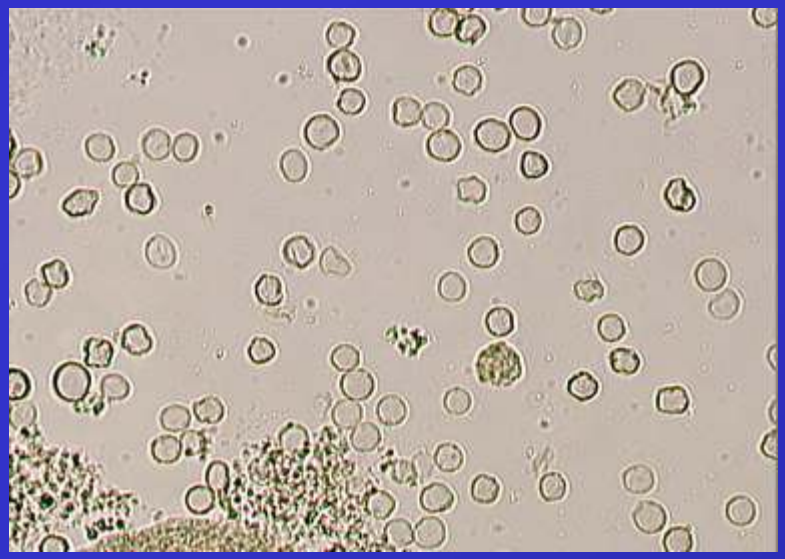
Mogelijke diagnostiek pulmonaal-renaal syndroom (2)

- Bronchoscopie / broncho-alveolaire lavage
  * kan alveolaire bloeding bevestigen
  * kweken / cytologie
  * histologie?
- Nierbiopsie
  * type glomerulonefritis
  * immunofluorescentie
- Open long biopsie / VATS
  * histologie

“Vrijdagmiddagpakket” pulmonaal-renaal syndroom

- urinare sediment
  * glomerulaire haematurie
- X-thorax
  * vaak niet conclusief
- Echo nieren/urinewegen
  * urologische problemen
  * niergrootte
  * tumor / cystes etc. (biopsie)
- SSS: speedy specific serology
  * ANCA
  * anti-GBM
- Nierbiopsie

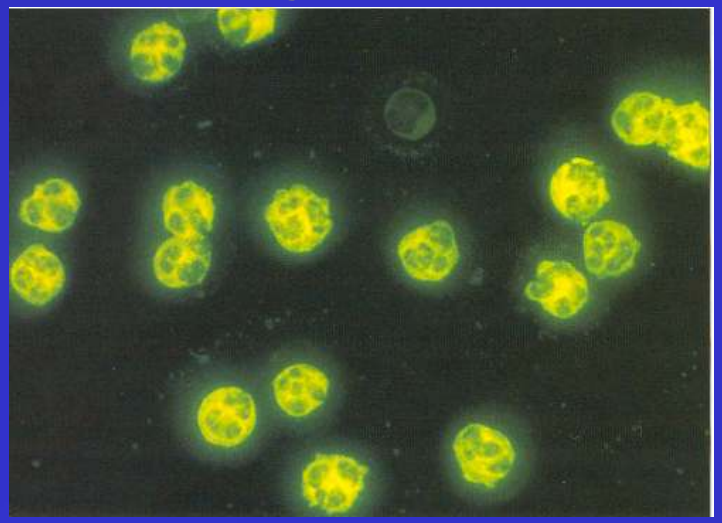
Diagnostic policy: urinary sediment



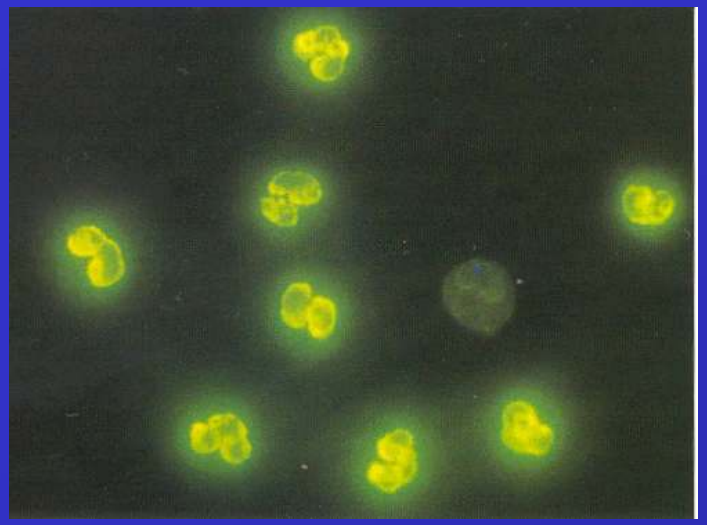
ANCA

Indirecte immuunfluorescentie op ethanol gefixeerde garnulocyten

* duurt ca. 4 uur (arbeidsintensief)
* resultaat
  - C-ANCA/P-ANCA/A-ANCA/neg
  - vals negatieven zeer zeldzaam



C-ANCA



P-ANCA

ANCA-determination

- indirect immunofluorescense on ethanol fixed neutrophils
- antigen specific ELISA (capture ELISA)
- results ANCA screening Jan 2001 - Sept 2002 (n=2813)
- IIF positive in 427 (15.2%)
- ELISA positive in 79 (2,7%)

fluorescence	PR3	MPO	negative
C-ANCA (n=29)	29	-	-
P-ANCA (n=232)	5	38	189
atypical ANCA (n=109)	1	6	102

ANCA: a plethora of antigenic specificities (mostly lacking clinical relevance)

Table 3. Disease associations of ANCA defined by immunofluorescence patterns and antigen specificities

IIF pattern	Antigens	Disease associations
C-ANCA	PR3 alone	Wegener's granulomatosis (80–90%) Microscopic polyangiitis (20–40%) Primary pauciimmune crescentic glomerulonephritis (20–40%) Churg–Strauss syndrome (35%)
C-ANCA (atypical)	BPI alone BPI, MPO, CG, etc., often multiple	Cystic fibrosis (80%) Inflammatory bowel disease Primary sclerosing cholangitis Rheumatoid arthritis
P-ANCA	MPO alone	Microscopic polyangiitis (50%) Primary pauciimmune crescentic glomerulonephritis (50%) Churg–Strauss syndrome (35%)
	Multiple specificities including: • HMG1/2 • catalase • αenolase • actin	Inflammatory bowel disease Rheumatoid arthritis Drug-induced vasculitis Autoimmune liver disease
	also, • lactoferrin • lysozyme • elastase • cathepsin G	Drug-induced syndromes
	• defensin	Some parasitic infestations
Atypical ANCA	Multiple specificities see above	Drug-induced systemic vasculitis Inflammatory bowel disease Rheumatoid arthritis

Granulocyte-specific ANA is a form of P-ANCA; many laboratories do not distinguish between P-ANCA and atypical ANCA, and for this reason the frequencies of atypical ANCA are not given. Data are from references given in the text.

Savige et al. *Kidney Int* 2000;57:846-62

Cohort PR3- en MPO-ANCA-positieven 2001-2002

PR3-ANCA: n=35

- actieve vasculitis: 34 (28 WG, 5 MPA)
- vals positief: 1 Non-Hodgkin lymfoom KNO gebied

⟶ PPV: 97% (95% CI 85 - 100%)

MPO-ANCA: n=44

- actieve vasculitis: 31 (4 WG, 23 MPA)
- vals positief: 13 (RA 4, SLE 3, CAH 2, colitis 2)

⟶ PPV: 70% (95% CI 55 - 83%)

Diagnostic performance of PR3-ANCA detection: commercial direct ELISA

Table 2 Diagnostic performance of commercially available enzyme linked immunosorbent assay kits for detection of PR3-ANCA compared with direct immunofluorescence using cut off levels provided by the manufacturer

Test	Provided cut off	Sensitivity	Specificity
IFT (CA)	1:16	73.3	98
IHELI	<2.5 neg, >5 pos	66.7	100
A	>2.0	60.0	100
B	<10 neg, >15 pos	13.3	100
E	<7 neg, >10 pos	46.7	100
F	>15	26.7	98
G	>3.5	60.0	100
H	<0.9 neg, >1.1 pos	60.0	98
I	>20	60.0	100
J	>2	60.0	100
K	<20 neg, <30 pos	60.0	100
L	<10 neg, >20 pos	40.0	100
M	>15	26.7	96

CA, C-ANCA; IFT, indirect immunofluorescence technique; IHELI, in-house enzyme linked immunosorbent assay; neg, negative; pos, positive; PR3-ANCA, antineutrophil cytoplasmic antibodies to proteinase 3.

Holle JU, et al. Ann Rheum Dis 2005;64:1773-9.

Diagnostic performance of MPO-ANCA detection: commercial direct ELISA

Table 3 Diagnostic performance of commercially available enzyme linked immunosorbent assay kits for detection of MPO-ANCA compared with direct immunofluorescence using cut off levels provided by the manufacturer

Test	Provided cut off	Sensitivity	Specificity
IFT (PA)	1:16	86.7	98
IHELI	>20	60.0	100
A	>6	26.7	100
B	<10 neg, >15 pos	66.7	98
E	<7 neg, >10 pos	60.0	100
F	>15	53.3	100
G	>9	46.7	100
H	<0.9 neg, >1.1 pos	66.7	100
I	>20	46.7	100
J	>6	53.3	100
K	<20 neg, >30 pos	46.7	100
L	<20 neg, >25 pos	60.0	100
M	>15	53.3	100

IFT, indirect immunofluorescence technique; IHELI, in-house enzyme linked immunosorbent assay; MPO-ANCA, antineutrophil cytoplasmic antibodies to myeloperoxidase; neg, negative; PA, P-ANCA; pos, positive.

Holle JU, et al. Ann Rheum Dis 2005;64:1773-9.