Anti-Neutrophil Cytoplasm Antibody associated vasculitis

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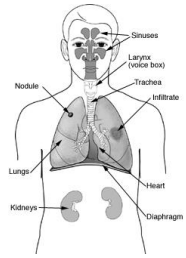
Anti-Neutrophil Cytoplasm Antibody (ANCA) associated vasculitis

Rare Diseases (10-20 pmp/year in UK)

Cause severe inflammation
- Kidneys
- Lungs
- Ear/nose/sinuses
- Eyes
- Everything else

Age commonest 65-75 but any age possible

Male :Female = 1:1



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Three diseases

- Granulomatosis with polyangiitis (GPA) = Wegener's Granulomatosis
- Microscopic polyangiitis (MPA) = historically part of polyarteritis nodosa
- Eosinophilic granulomatosis with polyangiitis (MPA) = Churg-Strauss Syndrome

- No diagnostic criteria

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What is ANCA?

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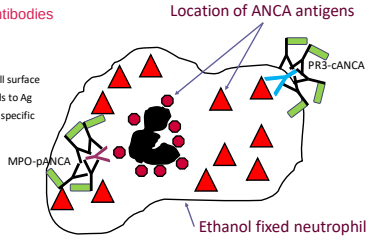
Anti-neutrophil cytoplasm antibodies

Detected by IIF

- Ethanol fixed neutrophils
- Express several intracellular Ag on cell surface
- Patients serum containing ANCA binds to Ag
- Pattern of fluorescence seen reflects specific antigen that ANCA bind to



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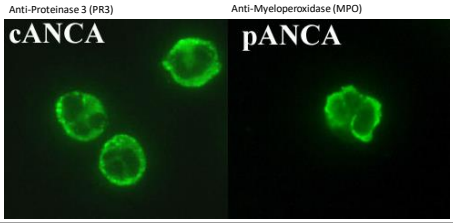
Anti-neutrophil cytoplasm antibodies



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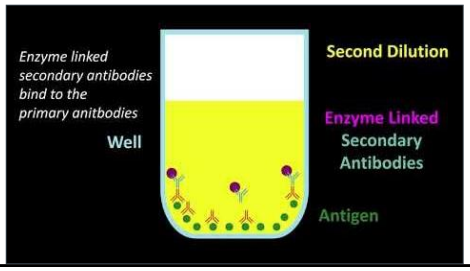
ELISA for antigen specificity



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Clinical Features

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Granulomatosis with polyangiitis

- Commonest systems
  - Upper airway
  - Lower airway
  - Kidneys
  - Eyes
  - Skin
- Usually prodrome for months/years
- Commonly relapsing
- Associated with
  - Cytoplasmic ANCA
  - Anti-Proteinase 3 antibodies
- Granulomatous inflammation
  - Airways
  - Eyes

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Microscopic polyangiitis

- Commonest systems
  - Kidneys
  - Lower airway
  - Eyes
  - Skin
  - PNS
- Usually shorter onset
- Less likely to relapse
- Associated with
  - Perinuclear ANCA
  - Anti-Myeloperoxidase antibodies
- No granulomatous inflammation

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Eosinophilic granulomatosis with polyangiitis

- Late onset progressive asthma
- Peripheral neuropathy
- Nasal polyps
- Myocarditis
- CNS vasculitis
- Pulmonary infiltrates
- Peripheral eosinophilia
- 70% ANCA negative

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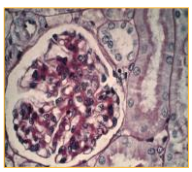
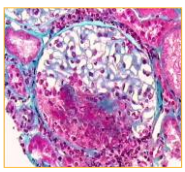
Renal Involvement


Normal Glomerulus


Renal Vasculitis

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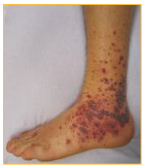
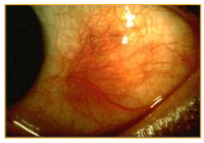
Skin and eye disease



Vasculitis rash



Scleritis

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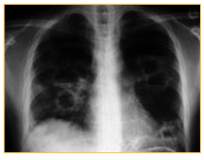
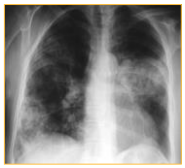
Lung disease



Granulomas



Pulmonary haemorrhage

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Making a diagnosis

- No diagnostic criteria
- Any or all of
  - Clinical history
  - Examination
  - Immunology
  - Radiology
  - Tissue
- The more evidence the better

- These do not exclude a diagnosis
  - ANCA negative
  - No inflammatory response
  - Only systemic symptoms
  - Very localised disease
  - Atypical presentation

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Role of ANCA in diagnosis

NB – only true if clinical picture consistent with diagnosis

	GPA		MPA		EGPA	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
c-ANCA	81.3	99.5	2.5	92.8	6.5	92.8
c-ANCA plus PR3-ANCA	69.0	99.8	0		6.5	94.2
p-ANCA	3.6	94	65.0	94.2	6.5	92.8
p-ANCA plus MPO-ANCA	1.8	99.3	47.5	99.5	4.3	99.2
ANCA positive by IIFT	84.9	93.0	67.5	87.0	13.0	86.5
ANCA by IIFT + PR3/MPO-ANCA	70.3	99.1	47.5	93.7	10.9	93.4

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Differential diagnoses

Chronic infection	Systemic diseases	Drug induced vasculitis	Artefactual
• TB • SBE associated with ANCA • HIV • HBV • Syphilis • Bartonella (and more)	• IBD • SLE • Sarcoidosis • Cancer • Lymphoma	• Cocaine • Hydralazine • Propylthiouracil • Anti-TNF	

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Neutrophil activation by ANCA

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In Vitro Flow Model

Normal IgG ANCA IgG

Courtesy of Dr Judith Calderwood, University of Birmingham

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Intra vital ANCA induced neutrophil endothelial adhesion

Rat mesentery

Courtesy of Prof Mark Little, Trinity College Dublin

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Treating Vasculitis

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Treatment goals

Patient centred approach to therapy

- Keep people alive
- Minimise disease related organ damage
- Use the minimum necessary immunosuppression to control the disease
- Minimise drug related adverse effects
  - Acute and chronic
- Reduce dose/drugs where possible

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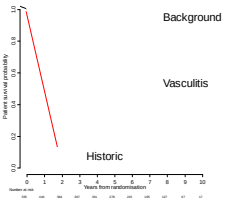
Immunosuppression saves lives

- **535 patients with ANCA-associated vasculitis recruited 1995-2002**
- **Median follow up 5.2 years**



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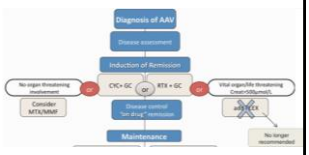
Remission induction

- Corticosteroids
  - More rapid tapering that previously
- Cyclophosphamide (pulsed) and Rituximab are equivalent
- Methotrexate or Mycophenolate only for non-organ threatening disease
- Prophylaxis
  - Bones
  - PJP
  - Gastro
  - Not nystatin



Adapted from: BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis Rheumatology (Oxford). 2014;53(12):2306-2309. doi:10.1093/rheumatology/keu445 Rheumatology (Oxford) | © The Author 2014. Published by Oxford University Press on behalf of the British Society for Rheumatology. All rights reserved. For Permissions, please email: journals.permissions@oup.com

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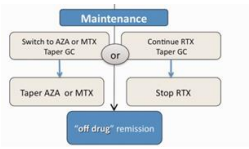
Remission maintenance

- Low dose prednisolone (12-18 months – low evidence)
- Cyclophosphamide or rituximab initial therapy
  - Azathioprine or methotrexate first line maintenance
  - Mycophenolate 2nd line (double relapse risk)
- Rituximab for induction at relapse
  - Rituximab maintenance 6 monthly for 2 years



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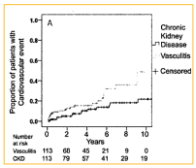
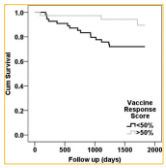
Cardiovascular disease and infection are biggest causes of death

Cardiovascular events



Vaccine response predicts death from infection



Morgan et al. Association of Low B Cell Count and IgG Levels With Infection, and Poor Vaccine Response With All-Cause Mortality in an Immunosuppressed Vasculitis Population Arthritis Care Res (Hoboken). 2016 Jun;68(6):854-60. doi: 10.1002/acr.22757.

Morgan et al. Increased incidence of cardiovascular events in patients with antineutrophil cytoplasmic antibody-associated vasculitides: a matched-pair cohort study Arthritis Rheum 2009 Nov;60(11):3492-500. doi:10.1002/art.24957.

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Relapsing and refractory disease

- Minor relapse
  - Increase steroids and steroid sparing agent (eg azathioprine)
- Major relapse
  - As for initial induction – rituximab 1st line if previously received cyclophosphamide
- Refractory disease
  - Switch cyclophosphamide/rituximab
  - Consider intravenous immunoglobulin, anti-T cell, anti-TNF

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Summary

- High index of suspicion for people with unexplained multisystem inflammation
  - No diagnostic criteria
  - Negative ANCA does not exclude diagnosis
  - Beware infection and cancer as differential diagnoses
- Treat promptly to minimise damage and increase survival
  - Tailored to disease severity and co-morbidity
  - Minimise immunosuppression where possible
  - Follow treatment protocols
- Prophylaxis
  - Side effects of treatment
  - Cardiovascular risk
  - Infection risk
  - Skin cancer risk

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Cases

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Case A

- 85 year old man
- Dialysis dependent AKI, pulmonary infiltrates, rash and arthralgia
- Pre-exising CKD3, hypertension, type II DM
- Urinalysis blood+++, protein++
- cANCA+ IIF, anti-MPO 85, CRP 156
- What is the appropriate management?

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Case B

- 28 year old woman
- Admitted with bilateral pneumonia + UTI
- Requiring support for poor cardiac function
- CRP 154, creatinine 128µmol/L
- Urine smokey – blood+++, protein+++
- Likely diagnosis?

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Case C

55 year old woman born in India Moved to UK in 20's	Chronic hearing loss, rhino-sinusitis, previous scleritis/keratitis, small lung nodules, peripheral neuropathy	Normal kidney function & urinalysis	Nasal biopsy: non-specific nasal mucosal inflammation	CRP=40 ANCA +ve IIF -ve ELISA
Treated with steroids and cyclophosphamide	6 weeks later T2-T5 spinal cord compression with granulomatous inflammation of dura	Surgical decompression	What diagnosis?	What management?

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Case D

87 year old woman ANCA vasculitis 2009 MS 2012	Taking azathioprine 50mg daily and prednisolone 5 mg alt days	Persistent unexplained CRP =300 (self-limiting hip pain and swelling 3 months ago)	Awoke profoundly deaf in both ears, some tinnitus, occasional vertigo
TM look normal	No other symptoms	Diagnosis?	Management?

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Case E

- 52 year old man with LV assist device
- Multiple medications: carvedilol, digoxin, doxazosin, fluconazole, furosemide, hydralazine, lansoprazole, perindopril,
- Unwell for 4 months since staph aureus infection of drive line
- Anaemia, drenching sweats, fatigue, myalgia, arthralgia, ENT symptoms
- Normal renal function
- Acute phase response
- Nil else localising

- Diagnosis?
- Treatment?

Immunology

pANCA +IIF,
MPO+ve ELISA,
ANA+ve,
dsDNA+ve,
ENA-ve,
IgG>20,
TTG+ve,
cardiolipin IgM+ve,
RF-ve,

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Any questions?

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