Recent Evidence in VasculitIs SclIence and Treatment



Management of AAV in the clinical setting

LEARNING OBJECTIVES

At the end of this educational program, the participants should be able to:

1. Make a diagnosis of AAV using clinical information, ANCA testing and biopsies, identify and rule out mimickers of vasculitis, and measure disease severity
2. Determine the optimal induction treatment based on risk stratification (phenotype, disease severity, prognostic factors – initial management)
3. Determine the optimal maintenance treatment to prevent relapses (long-term management)
4. Comment on expected treatment outcomes, possible long-term side effects, and how to assess disease-related damage

AAV, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibody

PROGRAM OVERVIEW

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Program Modules	**Lead Authors**
1. Background: ANCA-Associated Vasculitis	All Committee members
2. Patient Case 1 - Making the diagnosis of ANCA-associated vasculitis: Diagnosis, utility of ANCA testing & biopsies	Dr. Simon Carette Dr. Christian Pagnoux
3. Patient Case 2 - Management of definite vasculitis in the clinical setting: Remission and maintenance	Dr. Nader Khalidi Dr. Gerard Cox
4. Patient Case 3 - When is vasculitis not vasculitis? Diagnosis and treatment	Dr. Joanne Bargman Dr. Simon Carette

DISCLOSURE STATEMENT

This program is supported by an educational grant from:

- Hoffman-La Roche

DISCLOSURE OF POTENTIAL FOR CONFLICT OF INTEREST

Facilitator Name

Financial Disclosure

- Pharmaceutical Company Affiliations
- Grants/Research Support
- Speakers Bureau/Advisory Boards
- Consulting Fees

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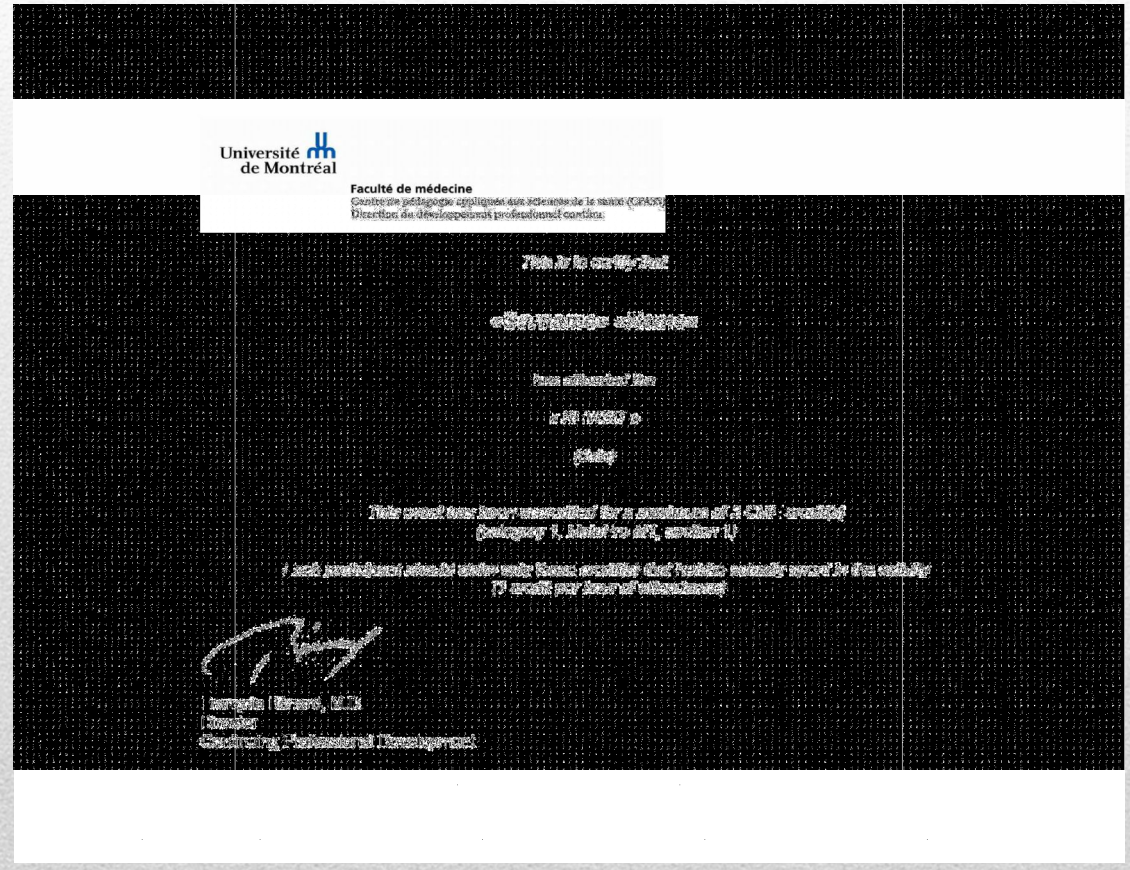
The Division du CPD approves this activity for 3 hours of category 1 (Main Pro-M1)credits for the attending general practitioner (family physician).

For the specialist physician, the Division of CPD approves 1 credit per hour of attendance for a total of 3 credits for the entire activity in accordance with the Maintenance of Certification program of the Royal College of Physicians and Surgeonsof Canada (RCPSC).

For all other participants, this program grants a certificate of attendance of 3 hours.

Participants should claim a number of hours consistent with their attendance.

CERTIFICATE



BACKGROUND: ANCA-ASSOCIATED VASCULITIDES

ANCA-associated vasculitis

Background: ANCA-associated vasculitis (AAV)

- Definitions
- Forms of AAV
- Epidemiology
- Etiology
  - Anti-neutrophil cytoplasmic antibodies
- Diagnosis and subgroups
- Measures of disease activity
- Treatment approaches

AAV, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibody; BVAS, Birmingham Vasculitis Activity Score; DEI, Disease Extent Index; VAI, Vasculitis Activity Index

Vasculitis definition

- Vasculitis: inflammation of blood vessel walls, infiltrated by leukocytes
- Vasculitides have been classified based on the predominant size of affected blood vessels
- Blood vessel damage can lead to vessel occlusion and tissue ischemia, contributing to the clinical manifestations of AAV, which may involve multiple organs of the body
- Vasculitides associated with serum positivity for antineutrophil cytoplasmic antibodies (ANCA) that affect small- (to medium-) sized vessels are commonly known as ANCA-associated vasculitis and include:
  - Granulomatosis with polyangiitis (GPA) (Wegener's)
  - Microscopic polyangiitis (MPA)
  - Churg-Strauss syndrome (CSS/Eosinophilic granulomatous polyangiitis)

Epidemiology of AAV

- Annual incidence of all 3 AAV subtypes (GPA (Wegener's), MPA, and CSS) combined is estimated to be approximately 10 to 20 cases per million[1-3]
- Incidence rates appear to vary in different parts of the world[1-3]
  - The annual incidence of AAV in the United States is approximately 6,000 cases, with an estimated prevalence of 25,000-30,000 cases[4,5]
  - In Canada, the overall annual incidence of AAV, including GPA (Wegener's), CSS, MPA and polyarteritis nodosa (PAN) in patients over 15 years of age is approximately 530 cases, and the estimated prevalence is approximately 4,000 cases[6]
- Incidence peak age is 45 to 65, but AAV can occur at all age[2-3,7]

AAV, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis; CSS, Churg-Strauss syndrome; GPA (Wegener's), granulomatosis with polyangiitis; MPA, microscopic polyangiitis

1. Koldingsnes W, Nossent HC. *Nor Epidemiol*. 2008;18(1):37-48; 2. Ntatsaki et al. *Rheum Dis Clin North Am*. 2010;36(3):447-461; 3. Watts et al. *Nephrol Dial Transplant*. 2008;23(12):3928-3931; 4. Watts RA, Carruthers DM, Scott DG. *Semin Arthritis Rheum.* 1995;25:28-34; 5. Watts RA, Scott DG. *Semin Respir Crit Care Med* 2004;25:455-64; 6. 2010 Canadian Statistics (2008 forecast: MORSE Group); 7.Chen M and Kallenberg CG. *Autoimm Rev*. 2010;9:A293-A298.

Organ involvement of AAV

- AAV: often serious and sometimes fatal
- Symptomatic organ involvement: in isolation or in combination
- Distribution of affected organs may suggest a particular vasculitic disorder

AAV should be suspected in patients presenting with multisystemic symptoms not caused by infections or malignancy such as:[1]

- Renal failure → renal failure glomerulonephritis (renal biopsy)
- Skin rashes
- Pulmonary infiltrates → ranges from fleeting focal infiltrates or interstitial disease to massive pulmonary hemorrhage alveolar capillaritis
- Neurological manifestations

AAV, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis

1.Gómez-Puerta et al. 2009

Diagnosis of AAV

Besides clinical findings

Tests used for diagnosing AAV include:[1-3]

- Blood (or serum) tests
- Urinalysis
- Medical imaging
- Tissue biopsy

AAV, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis; CNS, central nervous system; CSS, Churg-Strauss syndrome; ENT, ear, nose and throat; GPA (Wegener's), granulomatosis with polyangiitis; MPA, microscopic polyangiitis

1. Hunder. 2010; 2. Chung et al. *Radiology*. 2010;255(2):322-341; 3. King and Stone 2010

Characteristics of AAV

	GPA (Wegener's)	MPA	CSS
Granulomatous inflammation	YES (especially respiratory tract)	NO	YES, rich in eosinophils
Pulmonary manifestations	Infiltrates and nodules; alveolar hemorrhage	Alveolar hemorrhage	Asthma, infiltrates (rarely, nodules)
Other frequent manifestations	Perforation of nasal septum; saddle-nose deformity; mononeuritis multiplex; glomerulonephritis+	Mononeuritis multiplex; glomerulonephritis ++	Allergic rhinitis; mononeuritis multiplex

AAV, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis; CCS, Churg-Straus syndrome; GPA (Wegener's), granulomatosis with polyangiitis (Wegener's); MPA, microscopic polyangiitis.

1. Bosch et al. *JAMA*. 2007;298(6):655-669; 2. Langford *J Allergy Clin Immunol*. 2010;125(2 Suppl 2):S216-225; 3. Gómez-Puerta JA, Bosch X. Am J Pathol. 2009;175(5):1790-8.

Antibodies in AAV

The two main ANCA immunofluorescence patterns are:[1]

- Cytoplasmic (cANCA) staining pattern
- Perinuclear (pANCA) staining pattern

ANCAs in AAV are often specific to some neutrophil cytoplasmic proteins in ELISA:[2-4]

- ANCAs directed to proteinase 3 (PR3) are predominantly associated with C-ANCA and GPA (Wegener's)
- ANCAs directed to myeloperoxidase (MPO) are more frequently associated with P-ANCA and MPA or CSS

Not all AAV patients have ANCAs

- Approximately 90% of GPA (Wegener's) patients, 70% of MPA patients, and less than 50% of CSS patients are ANCA +

AAV, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis; CSS, Churg-Strauss syndrome; GPA (Wegener's), granulomatosis with polyangiitis; MPA, microscopic polyangiitis

1. Hagen et al. *Kidney Int*. 1998;53(3):743-753; 2. Kallenberg *Curr Rheumatol Rep*. 2010;12(6):399-405; 3. Langford *J Allergy Clin Immunol*. 2010;125(2 Suppl 2):S216-25; 4. Gómez-Puerta et al. *Am J Pathol*. 2009;175(5):1790-8; 4.

Risk factors for AAV

Infection may be a contributing or triggering factor in GPA[1,2]

- *Staphylococcus aureus* is frequently isolated from upper airways of patients with GPA (Wegener's)
- *S. Aureus* nasal carriage has been linked with higher risk of relapse in GPA (Wegener's)

Environmental factors for GPA (and MPA) include:[1,2]

- Persistent exposure to particulate silica, cattle and/or dust

Genetic factors for AAV may include:[1,3,4]

- A mutation in the *PTPN22* gene (which encodes a protein tyrosine phosphatase) in GPA (as well as a number of other autoimmune disorders)[3]
- Mutations in the alpha-1 antitrypsin gene[3]
- Abnormal expression of several genes, including PR3 and MPO[4]

AAV, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibody; GPA (Wegener's), granulomatosis with polyangiitis

1. Ntatsaki et al. *Rheum Dis Clin North Am*. 2010;36(3):447-61; 2. Watts et al. *Cleve Clin J Med*. 2002;69 Suppl 2:SII84-6; 3. Lionaki S, Jennette JC, Falk RJ. *SeminImmunopathol*. 2007;29(4):459-474; 4. Yang JJ, Pendergraft WF, Alcorta DA, et al. *J Am Soc Nephrol*. 2004;15(8):2103-2114

AAV disease subgroup definition

EUVAS AAV subgroup definitions:[1-3]

- Localized
- Early/systemic
- Generalized
- Severe
- Refractory

There are other definitions that have been used in clinical trials based on:[1-3]

- No constitutional symptoms, ANCA typically negative
- Constitutional symptoms present, ANCA-positive or ANCA-negative
- ANCA-positive
- Refractory to standard therapy
- Severity
- Serum creatinine levels

AAV, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibody; EUVAS, European Vasculitis Study group

1. Hellmich et al. *Ann Rheum Dis* 2007;66;605-17; 2. ECSYSVASTRIAL *Clin Exp Immunol*. 1995;101 Suppl 1:29; 3. Hamour et al. *Ther Clin Risk Manag*. 2010 24;6:253-64

Measurement of disease activity in AAV

AAV disease activity can be measured using:

Birmingham Vasculitis Activity Score (BVAS)[1-2]

- Original 1994 BVAS, BVAS version 3 and/or BVAS/WG for GPA (Wegener's) [3]

AAV, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibody; BVAS, Birmingham Vasculitis Activity Score; EUVAS, European Vasculitis Study group; GPA (Wegener's), granulomatosis with polyangiitis

1. Hellmich et al. *Ann Rheum Dis* 2007;66;605-17; 2. Luqmani et al. *QJM* 1994;87:671–8; 3. Stone et al. *Arthritis Rheum* 2001;44:912–20.

Current treatment approaches for AAV

Treatment for AAV is divided into 2 phases:[1,2]

1. Induction
2. Maintenance

*CSS has not been evaluated in these studies
AAV, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibody; AZA, azathioprine; CSS, Churg-Strauss syndrome;. CYC, cyclophosphamide; EUVAS, European Vasculitis Study group; GPA (Wegener's), granulomatosis with polyangiitis; MTX, methotrexate; MPA, microscopic polyangiitis; TMP-SMX, cotrimoxazole

MAKING THE DIAGNOSIS OF ANCA-ASSOCIATED VASCULITIDES

Diagnosis, utility of ANCA testing and biopsies

Lead Authors: Dr Simon Carette, Dr Christian Pagnoux

CASE REVIEW

BACKGROUND

Mr. JG, 56 years old

- Previously undiagnosed
- Recurrent sinusitis (2 years)
- Rhinitis (+ large crust once)
- Tongue ulcer (2 months)
- Fatigue (2 months)

FAMILY HISTORY

- Divorced, 2 children
- Professional tailor
- Golf Player
  (stopped 1 month ago)
- Past smoker (40 pack-years)
- Brother had laryngeal cancer
  (smoker)



CASE REVIEW

LABORATORY FINDINGS

- Hb 90 g/dL
- ESR 94 mm at first hour
- CRP 180 mg/L
- Serum creatinine 102 µmol/L
- No RBCs, protein 0.28 g/24h

RADIOLOGICAL FINDINGS

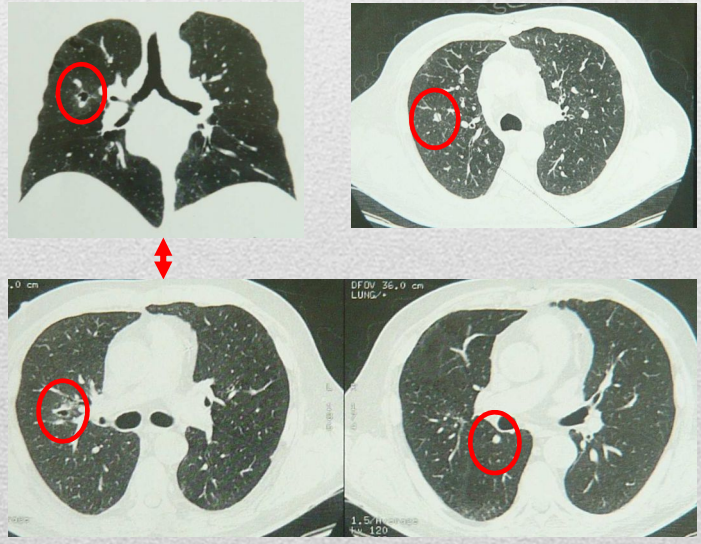
- Chest X-ray: nodules
- CT Scan of sinus
- CT Scan of chest

DIAGNOSIS

- Looks like vasculitis / GPA (Wegener's)



Nasal septum perforation



Nodules (1 with excavation)

ANCA, anti-neutrophil cytoplasmic antibody; CRP, C-reactive protein; CT, computerized tomography; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; GPA (Wegener's), granulomatosis with polyangiitis; RBC, red blood cells

INTERACTION POINT

How can you confirm the diagnosis of vasculitis in this patient?

Would a biopsy help? If so, which tissue would you want to take a biopsy from?

a. Lung
b. Kidney
c. Sinus
d. Oral
e. Other

CONFIRMATION OF GPA (Wegener's)

Histological confirmation of GPA (Wegener's)[1-5]

- Vasculitis
- Necrosis
- Granulomas

GPA (Wegener's), granulomatosis with polyangiitis

1. Devaney et al. Am J Surg Pathol 1990;14:555-64; 2. Travis et al. Am J Surg Pathol 1991;15:315-33; 3. Del Buono et al. Hum Pathol 1991;22:107-10;
4. Hoffman et al. Ann Intern Med 1992;116:488-98; 5. Duna et al. *Rheum Dis Clin North Am.* 1995;949-86

Pathologic yield of head and neck biopsies in GPA (Wegener's)

Pathologic Finding (s)	Frequency (%)
Individual findings	
Vasculitis (V)	26-48
Necrosis (N)	33-53
Granulomatous inflammation (G)	42-53
Combined findings	
V + N	23-30
V + G	17-21
V + N + G	3-16

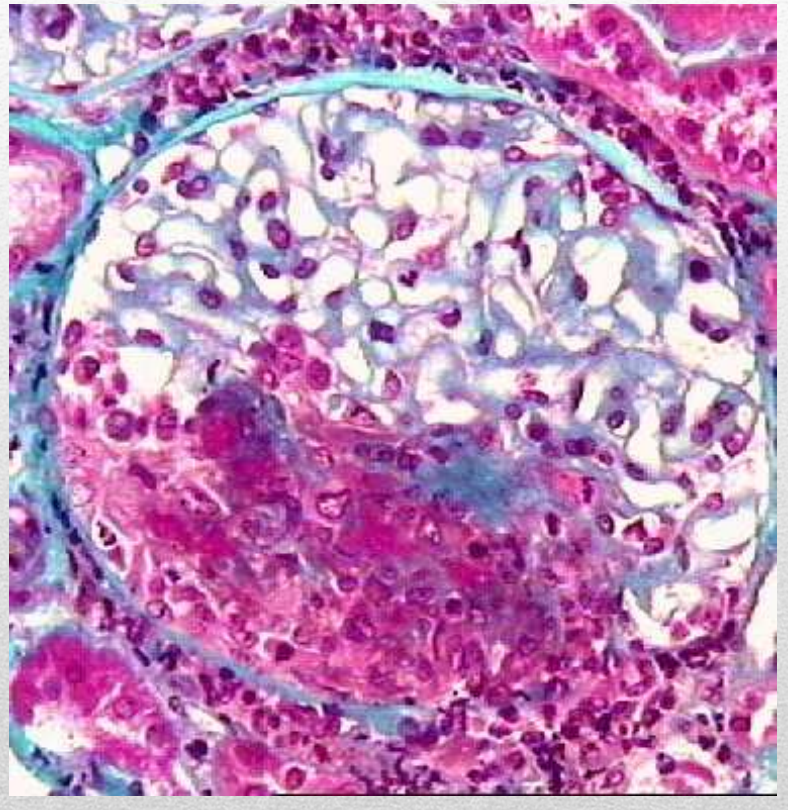
GPA (Wegener's), granulomatosis with polyangiitis
Duna et al. *Rheum Dis Clin North Am* 1995;949-86

Pathologic yield of pulmonary biopsies in GPA (Wegener's)

Pathologic Finding (s)	Frequency (%)
Open lung biopsies (n=82)	
Vasculitis and necrosis	89
Granulomas and necrosis	90
Granulomas + vasculitis + necrosis	91
Transbronchial biopsies (n=59)	
Vasculitis	7
Granulomas and vasculitis	5

GPA (Wegener's), granulomatosis with polyangiitis
Duna et al. *Rheum Dis Clin North Am* 1995;949-86

Renal involvement on renal biopsy



ONLY if renal involvement

- Glomerulonephritis
- Focal, segmental, necrotizing, crescentic
- Pauci-immune
- Vasculitis rarely seen (<15%)
- Granulomas even rarer in GPA (3%)

Duna et al. *Rheum Dis Clin North Am* 1995;949-86

Biopsy of other tissues

Nerve and muscle biopsy

- ONLY if nerve involvement
- Vasculitis in 40 to 60%

Skin biopsy

- ONLY if skin lesion
- >80% but often non specific (“leukocytoclastic vasculitis”)

Biopsy of other lesions

- Orbital tumor, paravertebral tumor… (contributive in >60%)

Duna et al. *Rheum Dis Clin North Am* 1995;949-86

INTERACTION POINT

Could an ANCA test replace biopsy in this patient?

If positive, how confident would you be that this patient has vasculitis?

Sensitivity and Specificity of ANCA

The sensitivity of ANCA depends on:

- The method used to measure ANCA
  - Indirect immunofluorescence (IIF) assay
  - Enzyme-linked immunoabsorbent assay (ELISA)
- The disease itself:
  - GPA (Wegener's), MPA, CSS
- The degree of activity of the disease when the assay is done

The specificity of ANCA depends on:

- The population used as comparators (disease versus healthy controls)

CSS, Churg-Strauss syndrome; GPA (Wegener's), granulomatosis with polyangiitis; MPA microscopic polyangiitis

Hagen et al. *Kidney Int.* 1998;53:743-53; Hagen and van Gurp. *Arthritis Care Res.* 2000;13:341-2

Sensitivity and Specificity of ANCA

Sensitivity

- The IIF assay is more sensitive than the ELISA
- A positive IIF assay should ALWAYS be confirmed by an ELISA
- The sensitivity of ANCA by IIF and/or ELISA is as high as 90% in active generalized GPA (Wegener's) but as low as 60% in limited disease

Specificity

- Compared to disease controls, specificities are:
  - cANCA = 95%
  - pANCA = 81%
  - anti-PR3 = 87%
  - anti-MPO = 91%
- The specificity of the combination of pANCA + anti-PR3 OR pANCA + anti-MPO is as high as 99%

ANCA, anti-neutrophil cytoplasmic antibody; cANCA, cytoplasmic-ANCA; ELISA, Enzyme-linked immunoabsorbent assay; GPA (Wegener's), granulomatosis with polyangiitis; IIF, indirect immunofluorescence; pANCA, perinuclear-ANCA

Hagen et al. *Kidney Int.* 1998;53:743-53; Hagen and van Gurp. *Arthritis Care Res.* 2000;13:341-2

Sensitivity and Specificity of ANCA

ANCA by IIF and/or by ELISA?

	IIF			ELISA		IIF+ELISA		
	C	P	**C/P**	**Anti-PR3**	Anti-MPO	C/PR3	P/MPO	**Global**
Sensitivity for GPA (Wegener's)	64	21	**85 %**	**66%**	24	57	16	**73%**
Specificity for AASV (disease controls)	95	81	**76 %**	**87%**	91	99	99	**98%**

PPV of ELISA for AASV 83% > PPV of IIF 45%

Both positive IIF and ELISA tests: PPV 88% and NPV >97%

Hidden slide for those who prefer this to the 27

AASV, anti-neutrophil cytoplasm antibody; c, cytoplasmic; ELISA, enzyme-linked immunoabsorbent assay; IIF, indirect immunofluorescence assay; MPO, myeloperoxidase; NPV, negative predictive value; p, perinuclear; PPV, positive predictive value; PR3, proteinase-3

Hagen et al. *Kidney Int.* 1998;53:743-53

CASE REVIEW

What is the pre-test probability that he has GPA (Wegener's)?

- Age 56
- Fatigue
- ENT manifestations (septum perforation, rhinitis, sinusitis)
- Tongue ulcer
- Lung nodules
- Normal kidney function (normal urine sediment but mild proteinuria)
- CRP 180 mg/L

ENT, ear, nose and throat; GPA (Wegener's), granulomatosis with polyangiitis

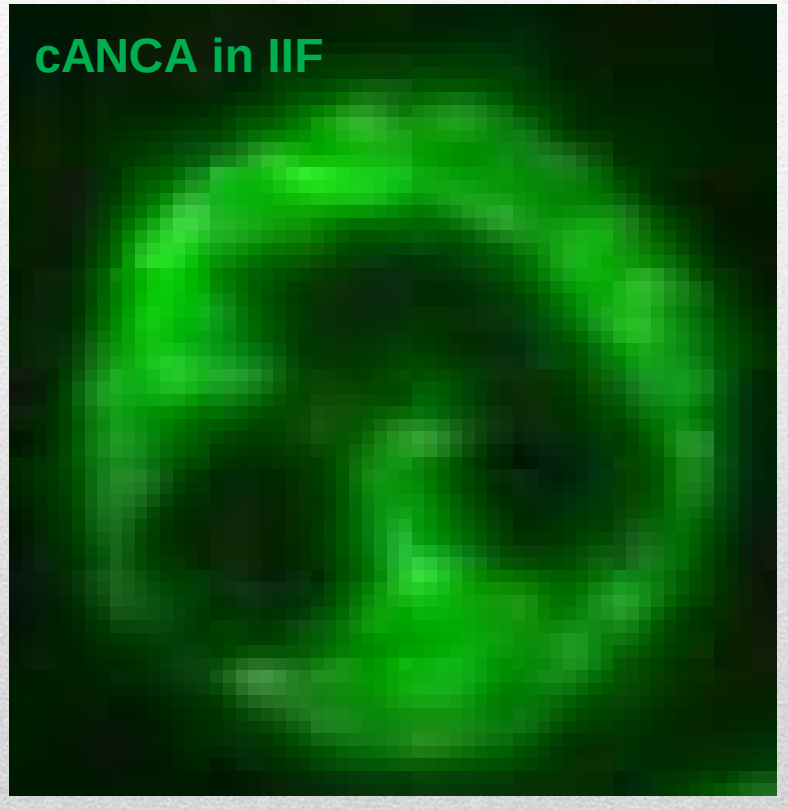
Can ANCA replace histology?

	GPA (Wegener's)	No GPA (Wegener's)	Total
ANCA +	56	1.5	57.5
ANCA -	14	28.5	42.5
	70	30	100

PPV: 56/57.5= 97.3%

ANCA, anti-neutrophil cytoplasmic antibody; GPA (Wegener's), granulomatosis with polyangiitis; PPV, positive predictive value

CASE REVIEW



ANCA test by

IIF

+

ELISA

RESULTS:

➔ Positive cANCA by IIF

➔ Positive anti PR3 by ELISA

= Diagnosis of GPA (Wegener's)

ANCA, anti-neutrophil cytoplasmic antibody; cANCA, ANCA with cytoplasmic fluorescence labelling pattern in IIF; ELISA, enzyme linked immunosorbent assay; IIF, indirect immunofluorescence; PR3, proteinase 3; GPA (Wegener's), granulomatosis with polyangiitis

Hagen and van Gurp. *Arthritis Care Res*. 2000;13:341-2

INTERACTION POINT

What would you have done if ANCA test was positive for pANCA + anti-MPO, rather than cANCA + anti-PR3?

- Or positive for pANCA, but with anti-PR3 or anti-elastase specificity on ELISA?
- Or atypical on IIF, and negative on ELISA?

ANCA, anti-neutrophil cytoplasmic antibody; cANCA/pANCA, ANCA with cytoplasmic/perinuclear fluorescence labelling pattern in IIF; ELISA, enzyme linked immunosorbent assay; IIF, indirect immunofluorescence; MPO, myeloperoxidase; PR3, proteinase 3; GPA (Wegener's), granulomatosis with polyangiitis

Conditions associated with ANCA

IIF	ELISA	Diseases/conditions
cANCA	PR3	GPA (Wegener's), MPA (CSS) Endocarditis, Tuberculosis, amoebiasis
	BPI (bacterial permeability increasing protein)	Cystic fibrosis Infections
pANCA	MPO	MPA, GNRP, CSS (GPA (Wegener's)) Felty's syndrome (RA) Drugs (propylthiouracil +)
pANCA or atypical ANCA	Cathepsine G	Ulcerative colitis Primary sclerosing cholangitis
	Lactoferrin	RA, ulcerative colitis
	Elastase (or PR3)	Cocaine-induced vasculopathy
	Other or unindentified	Infections RA, SLE Ulcerative colitis Drugs

ANCA, anti-neutrophil cytoplasmic antibody; cANCA/pANCA, ANCA with cytoplasmic/perinuclear fluorescence labelling pattern in IIF; CSS, Churg-Strauss syndrome; ELISA, enzyme linked immunosorbent assay; GNRP, rapidly progressive glomerulonephritis; GPA (Wegener's), granulomatosis with polyangiitis; IIF, indirect immunofluorescence; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus

DECISION POINT

GPA (Wegener's) diagnosis

- Highly suggestive clinical and radiological manifestations
- Positive cANCA + anti-PR3
- No evidence of infection (which couldn't anyway explain all the clinical manifestations)

➔ Biopsy not mandatory in this patient (he had none)

➔ However, one may consider:

- ➔ Biopsy of the lingual ulcer (to rule out cancer)
- ➔ Bronchoscopy with lavage (to rule out infection), possibly with transbronchial biopsy

GPA (Wegener's), granulomatosis with polyangiitis; cANCA, ANCA with cytoplasmic fluorescence labelling pattern in indirect immunoflurescence assay; PR3, proteinase 3

INTERACTION POINT

How would you determine disease severity?

Would you consider tailoring treatment of GPA (Wegener's) based on:

- Disease severity?
- Organ involvement?
- Disease activity/extent?

ANCA, anti-neutrophil cytoplasmic antibody; GPA (Wegener's), granulomatosis with polyangiitis

GPA (Wegener's) forms and severity

Definitions for disease stages used for classification of patients with GPA (Wegener's) granulomatosis in clinical trials[1]

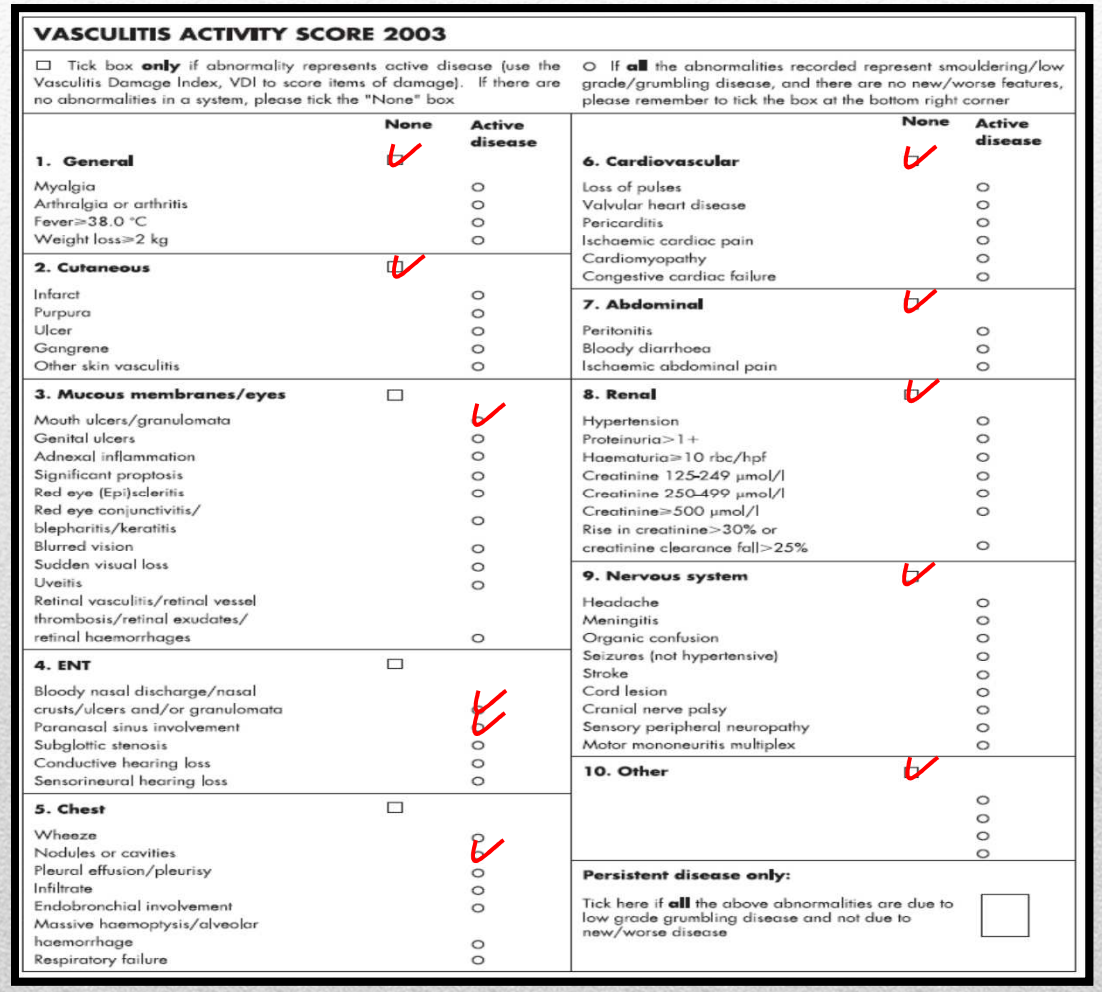
Study group	Clinical subgroup	Systemic vasculitis Outside ENT tract and lungs	Threatened vital organ function	Other definitions	Serum Creatinine (μmol/l)	Reference
EUVAS	Localized	No	No	No constitutional symptoms, ANCA typically negative	<120	
	Early systemic	Yes	No	Constitutional symptoms present, ANCA-positive or -negative	<120	
	Generalized	Yes	Yes	ANCA-positive	<500	Jayne et al[2]
	Severe	Yes	Organ failure	ANCA-positive	>500	Jayne[3]
	Refractory	Yes	Yes	Refractory to standard therapy	Any	Jayne[3]
WGET Research Group/VCRC	Limited	Allowed, but not required	No	Not severe	≤124, if haematuria, but no red blood cell casts present	WGET Research Group[4]
	Severe	Yes	Yes	Organ- or life-threatening disease, implies need for remission induction with CYC	Any	WGET Research Group[4]

Adapted from Hellmich et al.[1]

ANCA, anti-neutrophil cytoplasmic antibody; CYC, cyclophosphamide; ENT, ear, nose and throat; EULAR, European League Against Rheumatism; EUVAS, European Vasculitis Study Group; GPA (Wegener's) granulomatosis with polyangiitis; VCRC, Vasculitis Clinical Research Consortium; WGET, Wegener's Granulomatosis Etanercept Trial

1. Hellmich et al. *Ann Rheum Dis.* 2007;66;605-17; 2. Jayne et al. *N Engl J. Med* 2003;349:36–44; 3. Jayne. *Curr Opin Rheumatol.* 2001;13:48–55; 4. WGET Research Group. *N Engl J Med.* 2005;352:351–61.

Measures of GPA (Wegener's) activity: BVAS



VASCULITIS ACTIVITY SCORE 2003

☐ Tick box **only** if abnormality represents active disease (use the Vasculitis Damage Index, VDI to score items of damage). If there are no abnormalities in a system, please tick the "None" box

○ If **all** the abnormalities recorded represent smouldering/low grade/grumbling disease, and there are no new/worse features, please remember to tick the box at the bottom right corner

	None	Active disease
1. General	☑	
Myalgia		○
Arthralgia or arthritis		○
Fever≥38.0 °C		○
Weight loss≥2 kg		○
2. Cutaneous	☑	
Infarct		○
Purpura		○
Ulcer		○
Gangrene		○
Other skin vasculitis		○
3. Mucous membranes/eyes	☐	
Mouth ulcers/granulomata		☑
Genital ulcers		○
Adnexal inflammation		○
Significant proptosis		○
Red eye (Epi)scleritis		○
Red eye conjunctivitis/ blepharitis/keratitis		○
Blurred vision		○
Sudden visual loss		○
Uveitis		○
Retinal vasculitis/retinal vessel thrombosis/retinal exudates/ retinal haemorrhages		○
4. ENT	☐	
Bloody nasal discharge/nasal crusts/ulcers and/or granulomata		☑
Paranasal sinus involvement		○
Subglottic stenosis		○
Conductive hearing loss		○
Sensorineural hearing loss		○
5. Chest	☐	
Wheeze		○
Nodules or cavities		☑
Pleural effusion/pleurisy		○
Infiltrate		○
Endobronchial involvement		○
Massive haemoptysis/alveolar haemorrhage		○
Respiratory failure		○

	None	Active disease
6. Cardiovascular	☑	
Loss of pulses		○
Valvular heart disease		○
Pericarditis		○
Ischaemic cardiac pain		○
Cardiomyopathy		○
Congestive cardiac failure		○
7. Abdominal	☐	
Peritonitis		○
Bloody diarrhoea		○
Ischaemic abdominal pain		○
8. Renal	☐	
Hypertension		○
Proteinuria>1+		○
Haematuria≥10 rbc/hpf		○
Creatinine 125-249 μmol/l		○
Creatinine 250-499 μmol/l		○
Creatinine≥500 μmol/l		○
Rise in creatinine>30% or creatinine clearance fall>25%		○
9. Nervous system	☐	
Headache		○
Meningitis		○
Organic confusion		○
Seizures (not hypertensive)		○
Stroke		○
Cord lesion		○
Cranial nerve palsy		○
Sensory peripheral neuropathy		○
Motor mononeuritis multiplex		○
10. Other	☐	
		○
		○
		○
		○

Persistent disease only:

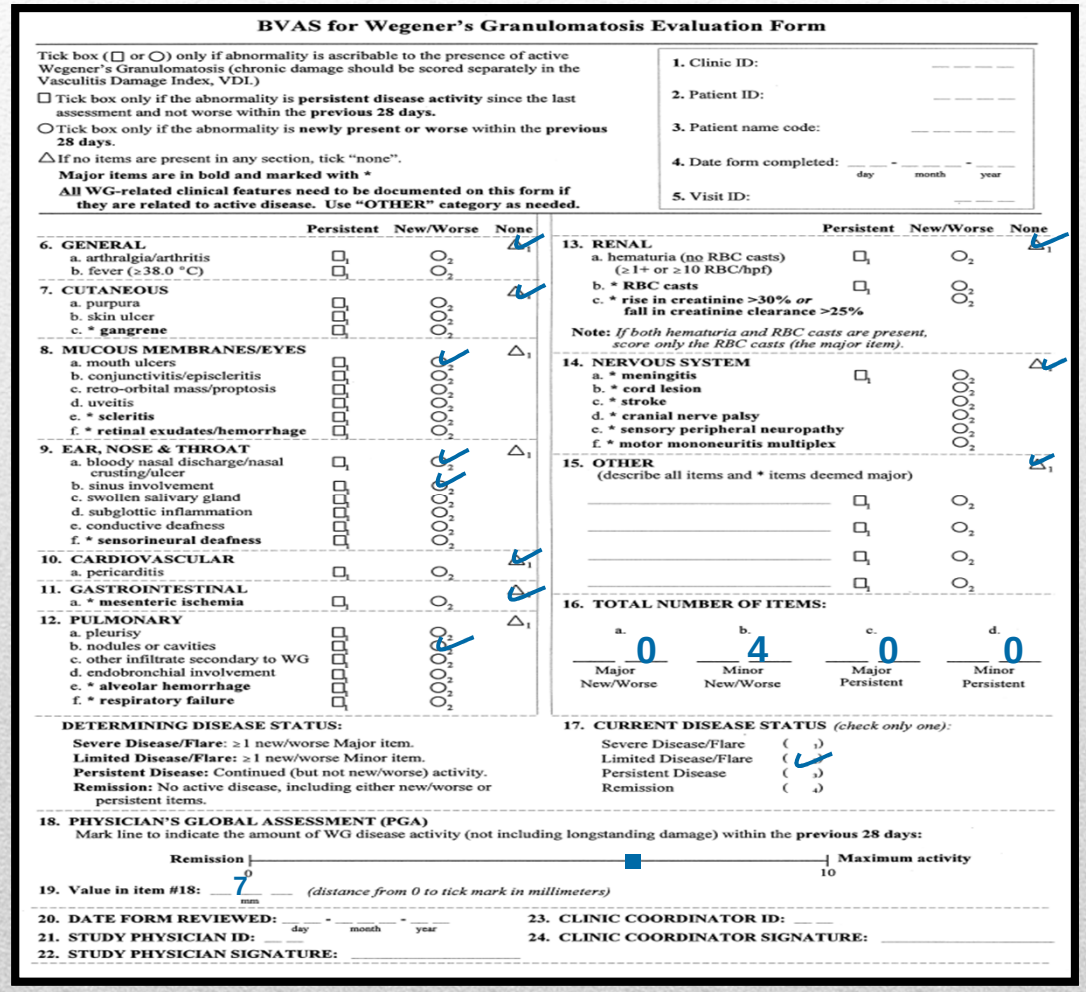
Tick here if **all** the above abnormalities are due to low grade grumbling disease and not due to new/worse disease ☐

Adapted from Mukhtyar et al.[1]

BVAS, Birmingham Vasculitis Activity Score; GPA (Wegener's) granulomatosis with polyangiitis: WG, Wegener's granulomatosis (old nomenclature)

1. Mukhtyar et al. *Ann Rheum Dis*. 2009;68(12):1827-32

Measures of GPA (Wegener's) activity: BVAS/WG



BVAS for Wegener's Granulomatosis Evaluation Form

Tick box (□ or ○) only if abnormality is ascribable to the presence of active Wegener's Granulomatosis (chronic damage should be scored separately in the Vasculitis Damage Index, VDI.)

□ Tick box only if the abnormality is **persistent disease activity** since the last assessment and not worse within the **previous 28 days.**

○ Tick box only if the abnormality is **newly present or worse** within the **previous 28 days.**

△ If no items are present in any section, tick "none".

Major items are in bold and marked with *

All WG-related clinical features need to be documented on this form if they are related to active disease. Use "OTHER" category as needed.

1. Clinic ID: ____
2. Patient ID: ____
3. Patient name code: ____
4. Date form completed: ____ - ____ - ____ (day - month - year)
5. Visit ID: ____

	Persistent	New/Worse	None
6. GENERAL			△1
a. arthralgia/arthritis	□1	○2	
b. fever (≥38.0 °C)	□1	○2	
7. CUTANEOUS			△1 ✓
a. purpura	□1	○2	
b. skin ulcer	□1	○2	
c. * **gangrene**	□1	○2	
8. MUCOUS MEMBRANES/EYES			△1
a. mouth ulcers	□1	○2 ✓	
b. conjunctivitis/episcleritis	□1	○2	
c. retro-orbital mass/proptosis	□1	○2	
d. uveitis	□1	○2	
e. * **scleritis**	□1	○2	
f. * **retinal exudates/hemorrhage**	□1	○2	
9. EAR, NOSE & THROAT			△1
a. bloody nasal discharge/nasal crusting/ulcer	□1	○2 ✓	
b. sinus involvement	□1	○2 ✓	
c. swollen salivary gland	□1	○2	
d. subglottic inflammation	□1	○2	
e. conductive deafness	□1	○2	
f. * **sensorineural deafness**	□1	○2	
10. CARDIOVASCULAR			△1 ✓
a. pericarditis	□1	○2	
11. GASTROINTESTINAL			△1 ✓
a. * **mesenteric ischemia**	□1	○2	
12. PULMONARY			△1
a. pleurisy	□1	○2	
b. nodules or cavities	□1	○2 ✓	
c. other infiltrate secondary to WG	□1	○2	
d. endobronchial involvement	□1	○2	
e. * **alveolar hemorrhage**	□1	○2	
f. * **respiratory failure**	□1	○2	

	Persistent	New/Worse	None
13. RENAL			△1 ✓
a. hematuria (no RBC casts) (≥1+ or ≥10 RBC/hpf)	□1	○2	
b. * **RBC casts**	□1	○2	
c. * **rise in creatinine >30% *or* fall in creatinine clearance >25%**		○2	
Note: *If both hematuria and RBC casts are present, score only the RBC casts (the major item).*			
14. NERVOUS SYSTEM			△1 ✓
a. * **meningitis**	□1	○2	
b. * **cord lesion**		○2	
c. * **stroke**		○2	
d. * **cranial nerve palsy**		○2	
e. * **sensory peripheral neuropathy**		○2	
f. * **motor mononeuritis multiplex**		○2	
15. OTHER (describe all items and * items deemed major)			△1 ✓
_____	□1	○2	
_____	□1	○2	
_____	□1	○2	
_____	□1	○2	

16. TOTAL NUMBER OF ITEMS:

a.	b.	c.	d.
0	4	0	0
Major New/Worse	Minor New/Worse	Major Persistent	Minor Persistent

DETERMINING DISEASE STATUS:

Severe Disease/Flare: ≥1 new/worse Major item.
Limited Disease/Flare: ≥1 new/worse Minor item.
Persistent Disease: Continued (but not new/worse) activity.
Remission: No active disease, including either new/worse or persistent items.

17. CURRENT DISEASE STATUS *(check only one)*:

Severe Disease/Flare ( )
Limited Disease/Flare (✓)
Persistent Disease ( )
Remission ( )

18. PHYSICIAN'S GLOBAL ASSESSMENT (PGA)
Mark line to indicate the amount of WG disease activity (not including longstanding damage) within the **previous 28 days:**

Remission (0) ——■—— (10) Maximum activity

19. Value in item #18: 7 mm *(distance from 0 to tick mark in millimeters)*

20. DATE FORM REVIEWED: ____ - ____ - ____ (day - month - year)
21. STUDY PHYSICIAN ID: ____
22. STUDY PHYSICIAN SIGNATURE: ____
23. CLINIC COORDINATOR ID: ____
24. CLINIC COORDINATOR SIGNATURE: ____

Adapted from Stone et al.[1]

BVAS, Birmingham Vasculitis Activity Score; GPA (Wegener's) granulomatosis with polyangiitis: WG, Wegener's granulomatosis (old nomenclature)

1. Stone et al. *Arthritis Rheum*. 2001;44(4):912-20

DECISION POINT

Early systemic GPA (Wegener's), cANCA and anti-PR3 positive

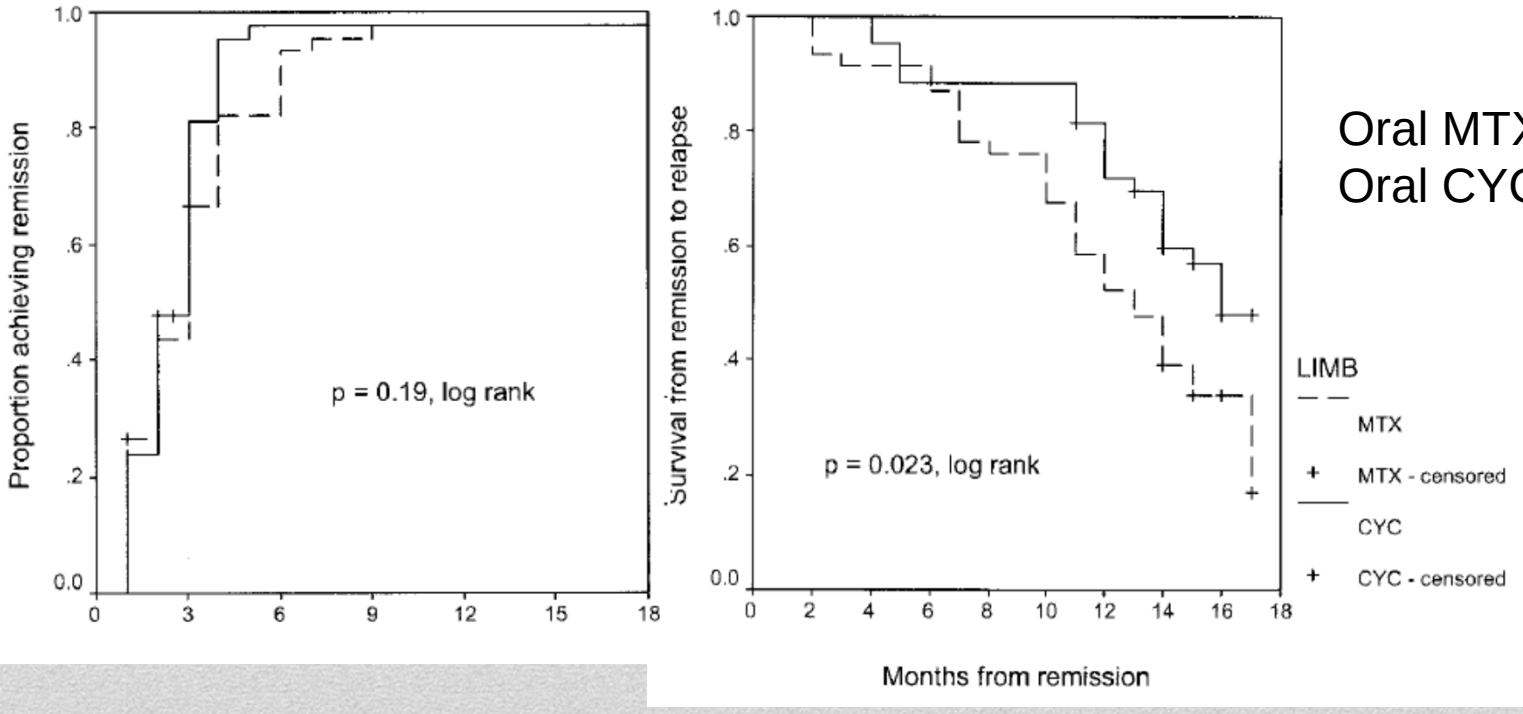
- Age 56 years
- ENT manifestations (septum perforation, rhinitis, sinusitis)
- Tongue ulcer
- Lung nodules (possible past alveolar hemorrhage? low Hb)
- Normal kidney function (normal urine sediment, creatinine 102 µmol/L)
- CRP 180 mg/L
- BVAS=11, BVAS/WG=4

How would you treat this patient?

BVAS, Birmingham Vasculitis Activity Score; BVAS/WG, Birmingham Vasculitis Activity Score/Wegener's granulomatosis;
cANCA, ANCA with cytoplasmic fluorescence labelling pattern in indirect immunoflurescence assay; CRP, C-reactive protein; GPA (Wegener's), granulomatosis with polyangiitis (Wegener's); PR3, proteinase 3; WG, Wegener's granulomatosis (old nomenclature)

Treatment of early systemic GPA (Wegener's) (creatinine <150 µmol/l)

NORAM



Oral MTX n=51
Oral CYC n=49

Remission rate MTX (89.8%) not inferior to CYC (93.5%) (P=0.04)
More delayed with MTX if pulmonary involvement or more extensive disease
Relapse rates at 18 months MTX 69.5% vs. CYC 46.5% (P=0.02)

CYC, cyclophosphamide; GPA (Wegener's), granulomatosis with polyangiitis; MTX, methotrexate
De Groot et al. *Arthritis Rheum.* 2005, 52:2461–9

DECISION POINT

TREATMENT

- Corticosteroids (prednisone) = cornerstone of therapy +++

+

1. For limited/localized/early systemic GPA (Wegener's) = Consider MTX rather then CYC
2. For severe/systemic/generalized GPA (Wegener's) = CYC (or rituximab) ± adjuvant (PLEX…)

Always consider sulfamethoxazole-trimethoprim (prophylaxis against pneumocystosis and/or prevention of relapse), but caution should be exercised when used concomitantly with MTX

CYC, cyclophosphamide; GPA (Wegener's), granulomatosis with polyangiitis; MTX, methotrexate; PLEX, plasma exchange

CONCLUSIONS

GPA (Wegener's) treatment can be tailored based on disease severity

ANCA, anti-neutrophil cytoplasmic antibody; GPA (Wegener's), granulomatosis with polyangiitis

CONCLUSIONS

CONCLUSIONS

- Definition of AAV is histological, but in an important proportion of patients, the combination of ANCA test and clinical findings can be sufficient to support the diagnosis, once the mimickers have been excluded
- Intensity of induction is based on disease severity (localized, early systemic versus generalized, severe or refractory)
- Once induction is achieved, the goal is to maintain remission
- Early cessation of therapy is associated with an increased risk of relapse
- Remission maintenance therapy should be continued for at least 18 months

MANAGEMENT OF DEFINITE VASCULITIS IN THE CLINICAL SETTING

Remission and Maintenance

Lead Authors: Dr Nader Khalidi, Dr Gerard Cox

CASE REVIEW

BACKGROUND

- Ms. SS, 57 year old
- Presented with sinusitis, hemoptysis, fatigue, fevers
- Deteriorating over the last 2 weeks
- Pulmonary nodules



CASE REVIEW

LABORATORY TESTS

- ANCA-positive
- Urinalysis proteinuria, hematuria
- Serum creatinine 115 (baseline Cr 62)
- Hb 102 (baseline 140)
- ESR 100
- Chest X-ray: Bilateral infiltrates

DIAGNOSIS

- AAV: either GPA (Wegener's) or MPA
- Need to quickly rule out other potential causes
- Options: cultures, bronchoscopy, sinus CT, renal and/or open lung biopsy (see case 1)

ANCA, anti-neutrophil cytoplasmic antibody; CT, computerized tomography; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; GPA (Wegener's), granulomatosis with polyangiitis; MPA, Microscopic polyangiitis; RBC, red blood cells

INTERACTION POINT

Which of the following would you consider in acute phase to induce remission, and why?

What is the objective for induction?

1. Corticosteroids
2. Immunomodulating agents (CYC vs. RTX vs. MTX)
3. PLEX
4. IVIG

CYC, cyclophosphamide; IVIG, intravenous immunoglobulin; MTX, methotrexate; PLEX, plasma exchange; RTX, rituximab

DECISION POINT

The objective of induction is to control all aspects of the disease

GPA (Wegener's) has been the most extensively studied

Challenges include:

- Toxicity of induction agent (e.g. CYC)
- Prolonged treatment required
- Relapses are frequent

CYC, cyclophosphamide; GPA (Wegener's), granulomatosis with polyangiitis

GPA (Wegener's) forms and severity

Definitions for disease stages used for classification of patients with GPA (Wegener's) granulomatosis in clinical trials[1]

Study group	Clinical subgroup	Systemic vasculitis Outside ENT tract and lungs	Threatened vital organ function	Other definitions	Serum Creatinine (μmol/l)	Reference
EUVAS	Localized	No	No	No constitutional symptoms, ANCA typically negative	<120	
	Early systemic	Yes	No	Constitutional symptoms present, ANCA-positive or -negative	<120	
	Generalized	Yes	Yes	ANCA-positive	<500	Jayne et al[2]
	Severe	Yes	Organ failure	ANCA-positive	>500	Jayne[3]
	Refractory	Yes	Yes	Refractory to standard therapy	Any	Jayne[3]
WGET Research Group/VCRC	Limited	Allowed, but not required	No	Not severe	≤124, if haematuria, but no red blood cell casts present	WGET Research Group[4]
	Severe	Yes	Yes	Organ- or life-threatening disease, implies need for remission induction with CYC	Any	WGET Research Group[4]

Adapted from Hellmich et al.[1]

ANCA, anti-neutrophil cytoplasmic antibody; CYC, cyclophosphamide; ENT, ear, nose and throat; EULAR, European League Against Rheumatism; EUVAS, European Vasculitis Study Group; GPA (Wegener's) granulomatosis with polyangiitis; VCRC, Vasculitis Clinical Research Consortium; WGET, Wegener's Granulomatosis Etanercept Trial

1. Hellmich et al. *Ann Rheum Dis.* 2007;66;605-17; 2. Jayne et al. *N Engl J. Med* 2003;349:36–44; 3. Jayne. *Curr Opin Rheumatol.* 2001;13:48–55; 4. WGET Research Group. *N Engl J Med.* 2005;352:351–61

Induction treatment and disease severity

Induction treatment intensity should be based on disease severity

- Patients may deteriorate and change their disease severity, and treatment intensity will need to be increased
- Less severe AAV may be treated with MTX 20–25 mg/week (oral or parenteral)
- Use CYC if severe organ dysfunction or life-threatening disease manifestation

AAV, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis; CYC, cyclophosphamide; MTX, methotrexate
Mukhtyar Cet al. *Ann Rheum Dis* 2009;68:310–317

Induction therapy

Extent and severity of GPA (Wegener's) dictates induction therapy

- In the WGET trial those with severe disease received glucocorticoids and CYC but those with limited disease received glucocorticoids and MTX[1]
- In the NORAM trial MTX (20–25 mg/week, oral or parenteral) was compared to CYC for those with only mild renal impairment with a creatinine <150 μmol/L, and without life-threatening disease manifestations[2]

CYC, cyclophosphamide; GPA (Wegener's), granulomatosis with polyangiitis; MTX, methotrexate

1. Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. *N Engl J Med.* 2005 Jan 27;352(4):351-61; 2. de Groot et al. *Arthritis Rheum* 2005 Aug;52(8):2461-9

Induction therapy: Corticosteroids

Untreated GPA (Wegener's) is fatal

- Natural course of severe disease has mean survival of 5 months
- Corticosteroids alone have been shown to prolong median survival by 7.5 months only
- Treatment with additional immunomodulatory agents is mandatory

GPA (Wegener's), granulomatosis with polyangiitis

1. Walton EW. *Br Med J.* 1958;2(5091):265-70; 2. Hollander D, Manning RT. *Ann Intern Med.* 1967;67(2):393-8

Induction therapy: Corticosteroids in combination

Corticosteroids in combination with other medications remain pivotal in induction

- In severe disease consider the use of IV methylprednisolone 500-1000 mg/day for 3 days
- Followed by prednisone 1 mg/kg/day (max 80 mg/day)

1. Hoffman GS, et al. *Ann Intern Med.* 1992;116(6):488-98; 2. Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. *N Engl J Med*. 2005;352(4):351-6;
3. Stone et al. *N Engl J Med.* 2010;363:221-32; 4. Jones et al. *N Engl J Med.* 2010;363:211-20

Induction therapy: Immunomodulation

For the patient with severe disease, there are now several alternatives for induction including:

1. Oral or IV CYC
2. RTX

CYC, cyclophosphamide; IV, intravenous; RTX, rituximab

Induction therapy: Oral cyclophosphamide

One of the largest initial prospective studies of the clinical features, pathophysiology, treatment and prognosis was performed at the National Institutes of Health[1]

- This study involved 158 patients and showed that GPA (Wegener's) is a treatable disease[1]
- Successful induction therapy with oral CYC (2mg/kg/day) and prednisone[1]
- For fulminant disease, patients were given oral CYC 3-5mg/kg/day for several days[1]

The current induction regimen with oral CYC (2mg/kg/day) is 3-6 months[2]

- However, a small number of patients remain refractory to this regimen or experience severe side effects from oral CYC[2]

CYC, cyclophosphamide; GPA (Wegener's), granulomatosis with polyangiitis

1. Hoffman et al. *Ann Intern Med.* 1992;116(6):488-98; 2. Fauci et al. *Ann Intern Med.* 1983;98(1):76-85

Induction therapy: IV cyclophosphamide

The CYCLOPS trial has shown that IV CYC is effective for induction

- This trial compared pulse CYC with daily oral CYC for induction of remission
- The study involved 42 centers in 12 European countries over 18 months and enrolled 149 patients who had newly diagnosed generalized ANCA-associated vasculitis with renal involvement but not immediately life-threatening disease
- Patients were given pulse CYC, 15 mg/kg every 2 weeks for 3 doses then every 3 weeks (76 patients), or daily oral CYC, 2 mg/kg per day (73 patients), plus prednisolone

ANCA, anti-neutrophil cytoplasmic antibody; CYC, cyclophosphamide; IV, intravenous
de Groot et al. *Ann Intern Med*. 2009;150:670-680

Induction therapy: IV cyclophosphamide

Pulsed CYC dose reductions for renal function and age		
	Creatinine (μmol/L)	
Age (years)	< 300	300-500
< 60	15 mg/kg/pulse	12.5 mg/kg/pulse
60-70	12.5 mg/kg/pulse	10 mg/kg/pulse
> 70	10 mg/kg/pulse	7.5 mg/kg/pulse

- Both groups continued on their regimen until 3 months after remission (after which all patients received azathioprine, 2 mg/kg per day orally, until month 18 for remission maintenance)
- The pulse CYC regimen induced remission of ANCA-associated vasculitis as well as the daily oral regimen at a reduced cumulative CYC dose and caused fewer cases of leukopenia

ANCA, anti-neutrophil cytoplasmic antibody; CYC, cyclophosphamide; IV, intravenous
de Groot et al. *Ann Intern Med*. 2009;150:670-680

Bladder toxicity: Recommendations based on Monach et al 2010 literature review

1. Daily oral CYC is associated with an increased risk of both hemorrhagic cystitis and bladder cancer, in a dose-dependent and/or duration-dependent manner
2. Hemorrhagic cystitis that occurs during CYC treatment is associated with an increased risk of bladder cancer years later
3. IV CYC therapy (as prescribed for rheumatic diseases) - low risk of cystitis and probably also of bladder cancer
4. Effectiveness of mesna in preventing cystitis is based on its use with ifosfamide in patients with cancer, and on data from animal models – both are of uncertain relevance to the use of CYC in patients with rheumatic diseases
5. No direct evidence for the effectiveness of mesna in preventing bladder cancer in humans

CYC, cyclophosphamide; Mesna, 2-mercaptoethanesulfonic acid

Monach et al. *Arthritis Rheum*. 2010;62(1):9-21

Proposed recommendations on the use of mesna with CYC to prevent bladder toxicity

1. Explain to patients that the evidence for the benefit of mesna in rheumatologic diseases is not strong
2. Upon starting a first course of oral or IV CYC, discuss the issues with the patient; if the patient expresses no strong preference, do not use mesna.
3. Additional factors to consider when deciding on the use of mesna:
    a. the expense of mesna, especially oral tablet form
    b. the inconvenience of the relatively complex dosing regimen for mesna, particularly for daily dosing
    c. the ability to tolerate hydration during either daily oral or pulse IV therapy with CYC
    d. the total cumulative dose of CYC for patients requiring a repeat course
4. Upon starting a second course of CYC (i.e. >4–6 months of total treatment), particularly with oral dosing, consider recommending mesna

CYC, cyclophosphamide; Mesna, 2-mercaptoethanesulfonic acid
Monach et al. *Arthritis Rheum*. 2010;62(1):9-21

Conclusions on use of mesna with CYC to prevent bladder toxicity

CYC remains an important treatment for patients with various rheumatic diseases

- Additional study of the usefulness of mesna in patients with rheumatic diseases would be welcomed, but unlikely to occur, due to the trend toward developing non–CYC-based therapies
- Decisions regarding the use of mesna will need to be made on an individual basis, taking into consideration the varying attitudes of both physicians and patients toward risk reduction

CYC, cyclophosphamide; Mesna, 2-mercaptoethanesulfonic acid
Monach et al. *Arthritis Rheum*. 2010;62(1):9-21

TMP/SMX

TMP/SMX as prophylaxis for pneumocystis jiroveci (formerly pneumocystis carinii) in all patients being treated with CYC:

- May use 800/160 mg on alternate days or 400/80 mg daily
- If contraindicated consider dapsone 50-100 mg daily or aerosolized pentamidine 300mg every month

CYC, cyclophosphamide; Septra, trimethoprim/sulphamethoxazole

1. Chung et al. *Arthritis Rheum.* 2000;43:1841–8; 2. Ognibene et al. *Am J Respir Crit Care Med* 1995;151:795–9; 3. Jarrousse et al. *Clin Exp Rheumatol.* 1993;11:615–21.

Induction therapy: Rationale for RTX

The rationale for treatment of AAV using RTX based on the following factors:

- Percentage of activated peripheral B cells correlates with disease activity[1]
- Effects of CYC on B cells are associated with treatment efficacy[2]
- B cells have potential pathogenic roles which include autoantibody synthesis, antigen presentation, and costimulation[3]
- Small uncontrolled studies showed promise[4]

AAV, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibody; CYC, cyclophosphamide; RTX, rituximab

1. Martin and Chan, *Immunity* 2004;20:517–527; 2. Popa et al. *J Allergy Clin Immunol* 1999;103:885–894; 3. Keogh et al. *Arthritis Rheum*. 2005;52(1):262-8; 4. Keogh et al. *Am J Respir Crit Care Med*. 2006;173(2):180-7

Induction therapy: Rituximab

Recent trials have shown that RTX is effective in induction therapy

- RAVE compared RTX with daily oral CYC for induction of remission
- The RITUXVAS trial compared RTX + 2-3 IV CYC vs. IV CYC

CYC, cyclophosphamide; RTX, rituximab

Stone et al. *N Engl J Med.* 2010;363:221-32; Jones et al. *N Engl J Med.* 2010;363:211-20

Induction therapy: Rituximab

The RAVE trial had 9 centers and 197 patients with newly diagnosed patients with GPA (Wegener's) or MPA or with a disease flare characterized by:

a. Active disease with a BVAS/WG for GPA (Wegener's) of 3 or greater that would normally require treatment with CYC

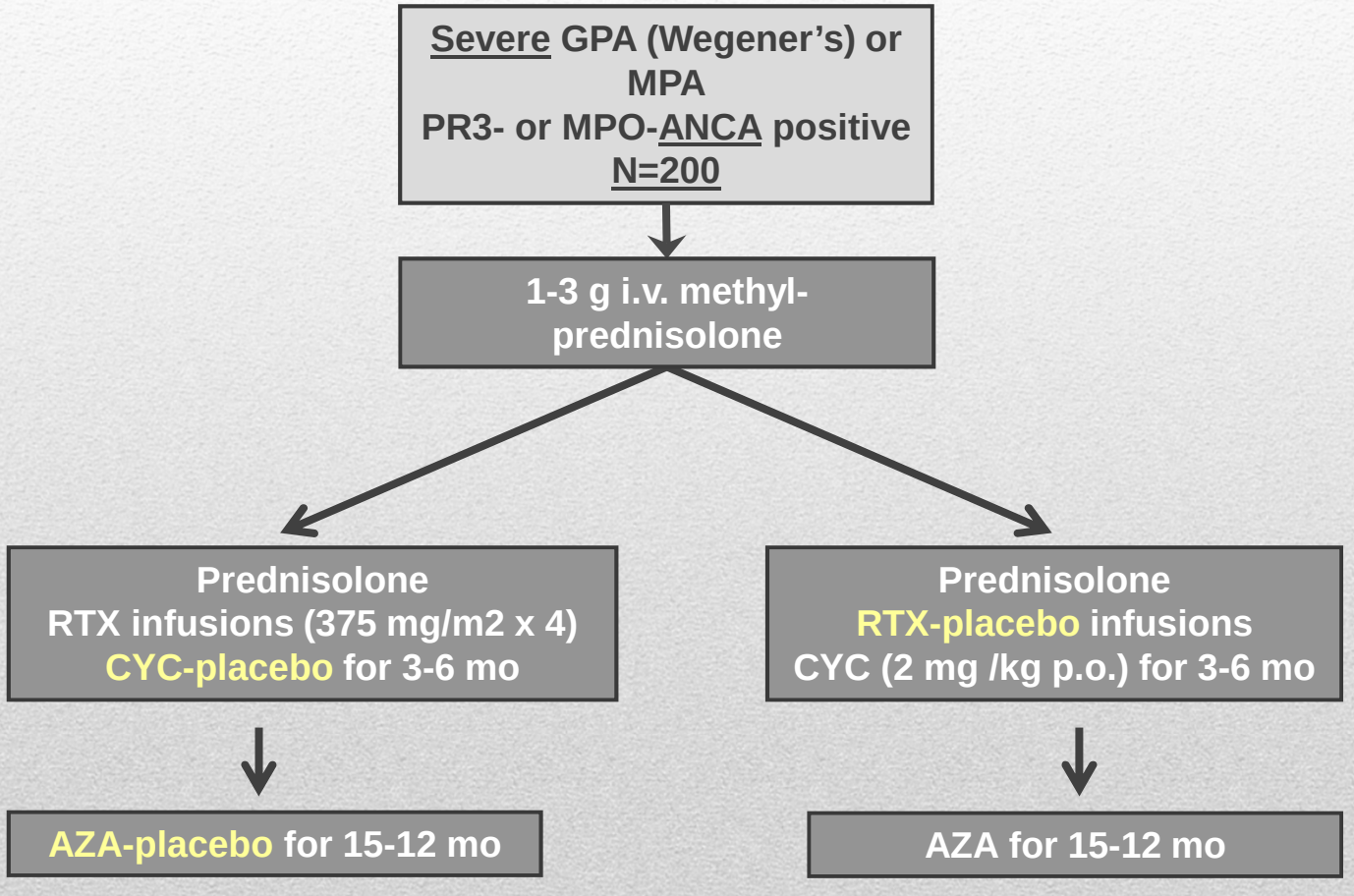
b. MPA disease severe enough to require treatment with CYC

c. Must be positive for either PR3-ANCA or MPO-ANCA at the screening

ANCA, anti-neutrophil cytoplasmic antibody; BVAS/WG, Birmingham Vasculitis Activity Score/Wegener's granulomatosis (old nomenclature); CYC, cyclophosphamide; GPA (Wegener's), granulomatosis with polyangiitis; IV, intravenous; MPA, microscopic polyangiitis

Stone et al. *N Engl J Med.* 2010;363:221-32.

Induction therapy: Rituximab
RAVE trial - study design



AZA, azathioprine; CYC, cyclophosphamide; GPA (Wegener's), granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidse; PR3, proteinase 3; RTX, rituximab

Stone et al. *N Engl J Med.* 2010;363:221-32

Induction therapy: Rituximab RAVE trial - results

RAVE study demonstrated:

- RTX was not inferior to CYC for the induction of remission in severe AAV
- RTX-based regimen was more effective than CYC-based regimen for relapsing disease: 67% RTX vs. 42% (CYC) (p=0.01)

AAV, ANCA-associated vasculitis; AZA, azathioprine; CYC, cyclophosphamide; RTX, rituximab
Stone et al. *N Engl J Med.* 2010;363:221-32

INTERACTION POINT

What is the role of PLEX in induction?

PLEX, plasma exchange

Induction therapy: Plasma Exchange (PLEX)

Early studies of PLEX in idiopathic rapidly progressive glomerulonephritis have yielded mixed results[1]

PLEX is also widely used for patients with lung hemorrhage due to AAV[2]

- This practice comes from cohort data in AAV and experience with anti-glomerular basement membrane disease but has never been rigorously tested[2]
- Contemporary cohort data appears effective only in selected subgroups of patients with lung hemorrhage[2]
- PLEX has the potential to exacerbate hemorrhage through removal of clotting factors; Its use for this indication demands further study[2]

PLEX, plasma exchange

1. Walsh et al. *Am J Kidney Dis*. 2011;57(4):566-74. 988;29(1):1-8; 2. Yamagata et al. *J Clin Apher* 2005;20(4):244-51; 3. ClinicalTrials.gov Identifier: NCT00987389 .

Induction therapy: Plasma Exchange (PLEX)

PEXIVAS trial has been initiated and recruitment has begun (500 patients in 100 centers)[3]

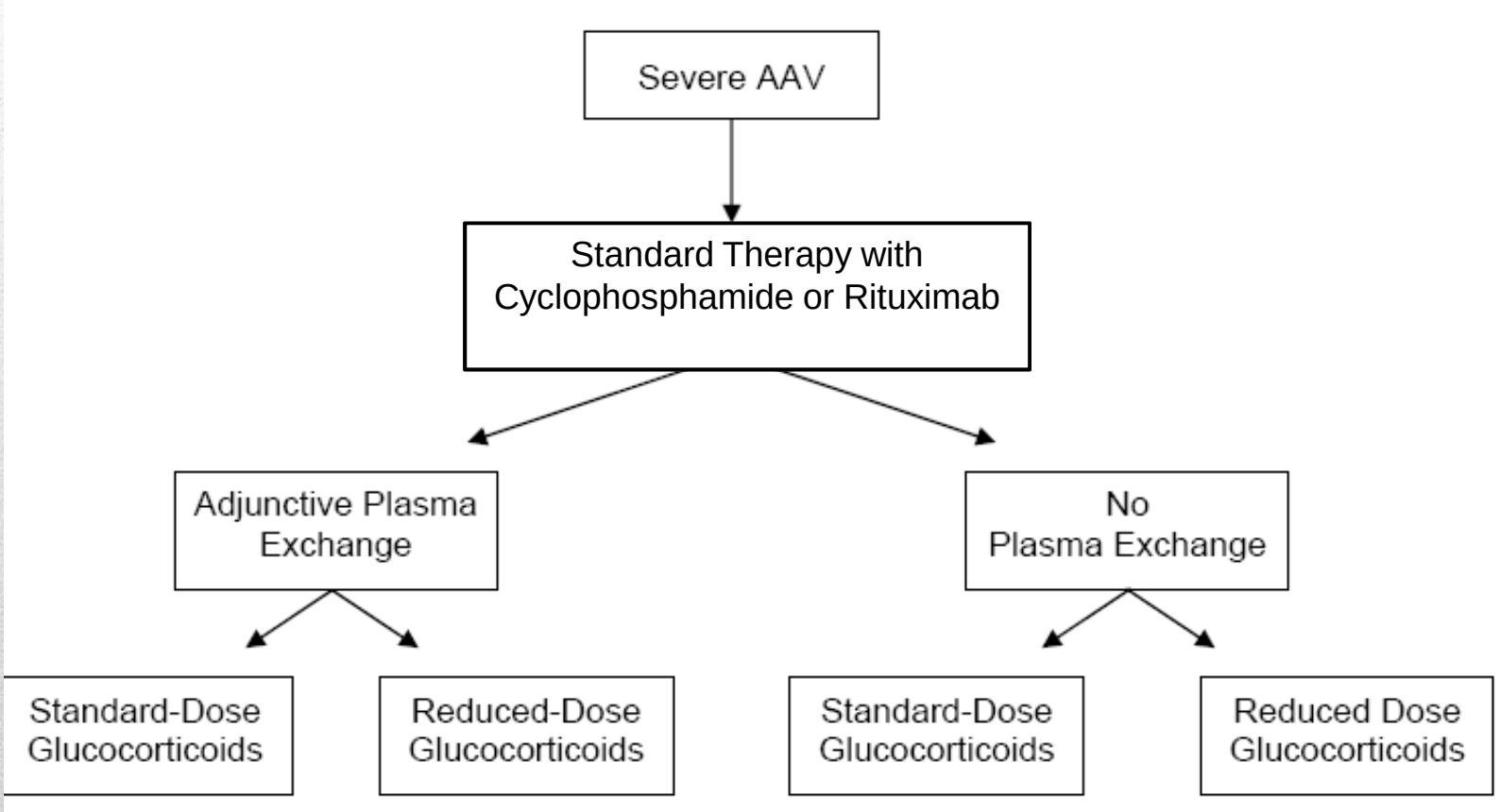
Two goals of PEXIVAS:

1. To assess the role of plasma exchange
2. To compare standard dose steroids with reduced dose steroids

PLEX, plasma exchange

1. Walsh et al. *Am J Kidney Dis*. 2011;57(4):566-74. 988;29(1):1-8; 2. Yamagata et al. *J Clin Apher* 2005;20(4):244-51; 3. ClinicalTrials.gov Identifier: NCT00987389 .

Induction therapy: PEXIVAS study design



AAV, ANCA-associated vasculitis
ClinicalTrials.gov Identifier: NCT00987389.

Osteoporosis prevention

Follow treatment guidelines for the prevention of CS-induced osteoporosis

- AAV is treated with CS in combination with CYC
- One of the major side-effects of this treatment is osteoporosis, which may result in the increased occurrence of fractures
- Osteopenia and osteoporosis are thus frequently observed in patients with AAV
- Cumulative dose of CS therapy is significantly associated with bone loss at the spine and femur

AAV, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis; CS, corticosteroids ; CYC, cyclophosphamide
Boomsma et al. *Osteoporos Int*. 2002;13(1):74-82

INTERACTION POINT

What is the role of IVIG in induction?

IVIG, intravenous immunoglobulin

Induction therapy: IVIG

The role of IVIG in induction:

- For patients who fail to achieve remission and have persistent low activity, intravenous immunoglobulin has been used to achieve remission

IVIG, intravenous immunoglobulin

1. Jayne et al. *QJM* 2000;93:433–9; 2. Martinez V, Cohen P, Pagnoux C, et al. *Arthritis Rheum*. 2008;58(1):308-17.

INTERACTION POINT

If the patient was a 24-year old woman instead of a 57-year old woman, would the treatment approach be different, and why?



FERTILITY CONCERN

Effect of drug therapy on fertility		
Drug	Effect	
	Females	Males
NSAIDs	May inhibit ovulation	No influence on spermatogenesis
Chloroquine, hydroxychloroquine	Does not impair fertility	Does not impair fertility
Sulfasalazine	No influence on fertility	Reversible oligospermia, asthenozoospermia, and teratozoospermia
Cyclophosphamide	Risk of infertility related to cumulative dose and age Consider protecting ovarian function with an GnRH analog	Risk of infertility related to cumulative dose Consider cryopreservation of sperm before treatment

Adapted from Silva et al.

GRH gonadotropin-releasing hormone; NSAIDs nonsteroidal anti-inflammatory drugs; TNF α, tumor necrosis factor .alpha

Silva et al. *Arthritis Care Res*. 2010;62(12):1682-90.

FERTILITY CONCERN

Effect of drug therapy on fertility		
Drug	Effect	
	Females	Males
Methotrexate	No influence on fertility	Reversible impairment of spermatogenesis possible
Leflunomide	No influence on fertility	Few data; no influence on male fertility
Mycophenolate mofetil	Does not impair fertility	Does not impair fertility
Azathioprine	Does not impair fertility	Does not impair fertility
Cyclosporin	Does not impair fertility	Does not impair fertility
TNF α blocker	No influence on fertility	No influence on spermatogenesis or fertility

Adapted from Silva et al.

GRH gonadotropin-releasing hormone; NSAIDs nonsteroidal anti-inflammatory drugs; TNF α, tumor necrosis factor .alpha

Silva et al. *Arthritis Care Res*. 2010;62(12):1682-90.

DECISION POINT

The following options should be considered to be an appropriate treatment choice for a 24-year old woman.

a. IV CYC with birth control
b. MTX with birth control
c. RTX with birth control
d. Oocyte cryopreservation

CYC, cyclophosphamide; MTX, methotrexate; RTX, rituximab

INTERACTION POINT

What is the duration of induction therapy?

- When would you transition to remission maintenance?
- Do you wait for all nodules to disappear before transitioning?
- How and when would you implement tapering of prednisone?
- What do you do about CYC or RTX?

CYC, cyclophosphamide; RTX, rituximab

Maintenance therapy

Once induction is achieved, one should consider an agent to maintain remission.

- The list of these agents include:
  - MTX
  - azathioprine
  - leflunomide
  - mycophenolate mofetil
  - RTX
- Remission maintenance therapy should be continued for at least 18 months (especially in GPA (Wegener's))
- Recently published guidelines by the British Society for Rheumatology recommend therapy for at least 24 months

GPA (Wegener's), granulomatosis with polyangiitis; MTX, methotrexate; RTX, rituximab.
Mukhtyar et al. *Ann Rheum Dis.* 2009;68:310–317; Lapraik et al. *Rheumatology* 2007;46:1615-6.

Maintenance therapy: Azathioprine

In one of the largest prospective trials in AAV, the EUVAS Group treated 155 patients with AZA (2mg/kg) or oral daily CYC

- Upon remission, patients were randomized to continue daily oral CYC at a lower dose (1.5mg/kg) or daily AZA (2mg/kg) along with prednisolone 10mg daily
- At 12 months, patients were then all treated with daily AZA at a lower dose (1.5mg/kg) and prednisolone 7.5mg daily
- Adverse reactions were similar, and relapse rates remained low (AZA 15.5% and CYC 13.7%)

AAV, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis; AZA, azathioprine; EUVAS, European Union Vasculitis Study Group; CYC, cyclophosphamide
Jayne et al. *N Engl J Med.* 2003;349(1):36-44

Maintenance therapy: Methotrexate

MTX can be used to maintain remission 20–25 mg/week, oral or parenteral[1-4]

- The relapse rate:
  - At 18 mo: AZA 17.8% vs. MTX 13.7%[1]
  - At 16 mo: 16%; at 32 mo: 52%[2]
- Toxicity:
  - Grade 3/4: AZA 7.9% vs. MTX 17.4%[1]
  - Requiring withdrawal of maintenance drug: 5%[2]
- Based on these studies, MTX is as good a choice as AZA after induction of remission with CYC and GC

CYC, cyclophosphamide; GC, glucocorticoids; MTX, methotrexate

1. Pagnoux et al. *N Engl J Med.* 2008;359(26):2790-803; 2. Langford et al. *Am J Med.* 2003 15;114(6):463-9; 3. Langford et al. *Arthritis Rheum.* 2000;43(8):1836-40

Maintenance therapy: Leflunomide

LEF (up to 30mg/day) may be more effective than MTX (starting with 7.5 mg/week reaching 20 mg/week after 8 weeks) in remission maintenance, but is associated with more adverse effects

LEF, leflunomide; MTX, methotrexate
Metzler et al. *Rheumatology* (Oxford) 2007;46:1087–91

Maintenance therapy: Mycophenolate

MMF (2000 mg/day) has been used to maintain remission

- The most recent large trial study however compared the use of AZA to MMF and found MMF to be inferior to AZA (IMPROVE trial)

AZA, azathioprine; MMF, mycophenolate mofetil

Langford et al. *Arthritis Rheum.* 2004;51(2):278-83; Hiemstra et al. *JAMA.* 2010; 304 (21): 2381-2388

Maintenance therapy: Rituximab

The potential for RTX is being explored

- The use of maintenance regimens and/or protocolized vs. non-protocolized versions is currently being examined
- Different dosing regimens of RTX maintenance are under investigation with some promising results on efficacy, safety and tolerability, but long-term complications are not fully defined
- Optimal therapeutic regimen remains to be determined

RTX, rituximab

Roubaud-Baudron et al. (ACR/ARHP) Annual Scientific Meeting, November 7–11, 2010; Atlanta, GA: Abstract 2041 (poster); Jones RB, et al. (ACR/ARHP) Annual Scientific Meeting, November 7–11, 2010; Atlanta, GA: Abstract 678 (oral); Cartin-Ceba et al. ACR/ARHP) Annual Scientific Meeting, November 7–11,2010; Atlanta, GA: Abstract 680 (oral)

Maintenance therapy: Corticosteroids

After 2–4 weeks of the full dose, the CS dose should be progressively decreased and, in the absence of relapse, CS can be stopped after 9–24 months

- Wide variety of opinion on how to taper
- Low dose CS (prednisone 10mg/day or less) are used to maintain remission
- The target dose 10mg/day or less should be after remission has been successfully induced (< 6 months)

CS, corticosteroids

Jayne et al. *N Engl J Med*. 2003 Jul 3;349(1):36-44; Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. *N Engl J Med*. 2005 Jan 27;352(4):351-61; Stone et al. *N Engl J Med* 2010;363:221-32; Jones et al. *N Engl J Med*. 2010;363:211-20; Walsh M, Merkel PA, Mahr A, Jayne D. *Arthritis Care Res.* (Hoboken). 2010;62(8):1166-73.

Treatment for refractory disease

A failure of induction therapy is not a relapse

- Approximately 10% are refractory
- Some patients experience significant side effects (hemorrhagic cystitis or cytopenias) to CYC

Treatment of relapse

- Increase steroids
- Prescribe CYC, if not previously given
  - If IV CYC was used, change to oral
- RTX
- Add PLEX
- Add IVIG

CYC, cyclophosphamide; IV, intravenous; PLEX, plasma exchange; RTX, rituximab

CONCLUSIONS

Induction treatment intensity should be based on disease severity (localized, early systemic, generalized, severe or refractory)

- Induction phase – CYC or RTX (for sever), MTX (early systemic or localized)
- Once induction is achieved, the goal is to maintain remission – AZA or MTX
- Rescue treatment for refractory disease – RTX, oral CYC, IVIG
  - PLEX under investigation for severe patients
- Early cessation of therapy is associated with an increased risk of relapse
- Remission maintenance therapy should be continued for at least 18 months

AZA, azathioprine; CYC, cyclophosphamide; IV, intravenous; PLEX, plasma exchange; RTX, rituximab

WHEN IS “VASCULITIS” NOT VASCULITIS?

Diagnosis and Treatment

Lead Authors: Dr. Joanne Bargman, Dr Simon Carette

CASE REVIEW

BACKGROUND

- Mr. JN
- 74-year old lifelong smoker
- Hypertension
- Coronary artery disease
- Chronic obstructive pulmonary disease (COPD)
- Abdominal aortic aneurysm (3 cm diameter, annual ultrasounds)
- Developed fever, cough productive of yellow sputum with streaks of blood
- Family doctor prescribed antibiotics, but patient continued to deteriorate

CASE REVIEW

Patient presented to the ER:

- Temperature 37.8° C
- BP 90/50 (on ACE inhibitors)
- Hypoxic
- Coughing bloody sputum in ER
- Serum creatinine 288 μmol/L (usually 120 μmol/L)
- Urinalysis (via foley): 4+ blood, 1.0 g/L protein
- Microscopy: many RBC, occasional finely granular cast

ACE, angiotensin converting enzyme; BP, blood pressure; RBC, red blood cells

INTERACTION POINT

What do you think is the likeliest cause of this patient's pulmonary symptoms?

a. He has a pulmonary-renal syndrome

b. The presence of microhematuria is strongly suggestive of glomerulonephritis

c. The likeliest cause of hemoptysis is pulmonary vasculitis

d. He should have a kidney biopsy as soon as he is stabilized

e. The low-grade fever essentially rules out the possibility of vasculitis

INTERACTION POINT

What is the differential diagnosis of this patient's "pulmonary-renal syndrome"?

a. Bacterial pneumonia PLUS pre-renal failure

b. Bacterial pneumonia PLUS acute tubular necrosis (ATN)

c. Bacterial pneumonia PLUS systemic vasculitis

d. Systemic vasculitis involving lungs and kidneys

e. Legionnaire's disease (pulmonary disease plus acute interstitial nephritis)

APLS ; antiphospholipid antibody syndrome; SLE, systemic lupus erythematosus

INTERACTION POINT

The patient has been admitted to the ICU.

Of the following treatments, which one is LEAST indicated?

a. Order a STAT ANCA level
b. A trial of normal saline loading
c. Broad spectrum antibiotics
d. Legionella titres
e. Empiric IV pulse with methylprednisolone

APLS ; antiphospholipid antibody syndrome; SLE, systemic lupus erythematosus

DISCUSSION POINT

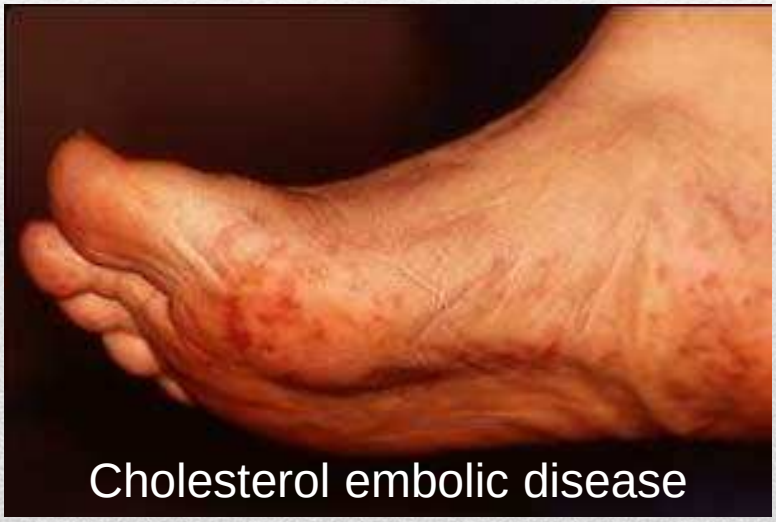
Ensuring that the patient has vasculitis

- In “true” vasculitis, it is important to start treatment quickly
- In setting of a high pre-test probability, many clinicians will empirically start therapy at least with high-dose corticosteroids
- The risk of corticosteroids has to be weighed against the benefit of early therapy

DISCUSSION POINT

Mimickers of vasculitis:
A long list

- Pneumonia + acute tubular necrosis
- Systemic lupus erythematosus
- Anti-glomerular basement membrane (GBM) disease (Goodpasture syndrome)
- Cholesterol embolic disease (shown)
- IV drug use/Infective endocarditis
- Atrial myxoma with emboli
- Calciphylaxis
- Thrombotic microangiopathy
- Fibromuscular dysplasia
- Lymphomatoid granulomatosis
- Type IV Ehlers Danlos syndrome



Cholesterol embolic disease

AAV, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis

Mimicker of Vasculitis: Cholesterol Embolic Disease

Showers of atheromatous emboli released from the aorta

"Downstream" arterial occlusions:

- Digital ischemia: blue toes (shown)
- Bowel ischemia
- Acute kidney injury

What causes the cholesterol emboli to dislodge from the aorta

- Mechanical disruption, most commonly from angiography where catheter advanced through the aorta
- Anticoagulation with defibrination of atheroma hanging on the aortic wall
- Spontaneous



Digital ischemia: blue toes

Mimicker of vasculitis: Cholesterol Embolic Disease

Clinical features depend upon where the emboli go:

- Abdominal ischemia
- Livedo reticularis and blue macules or patches
- Acute kidney injury with microhematuria and proteinuria
- Hypocomplementemia
- Peripheral and urinary eosinophilia



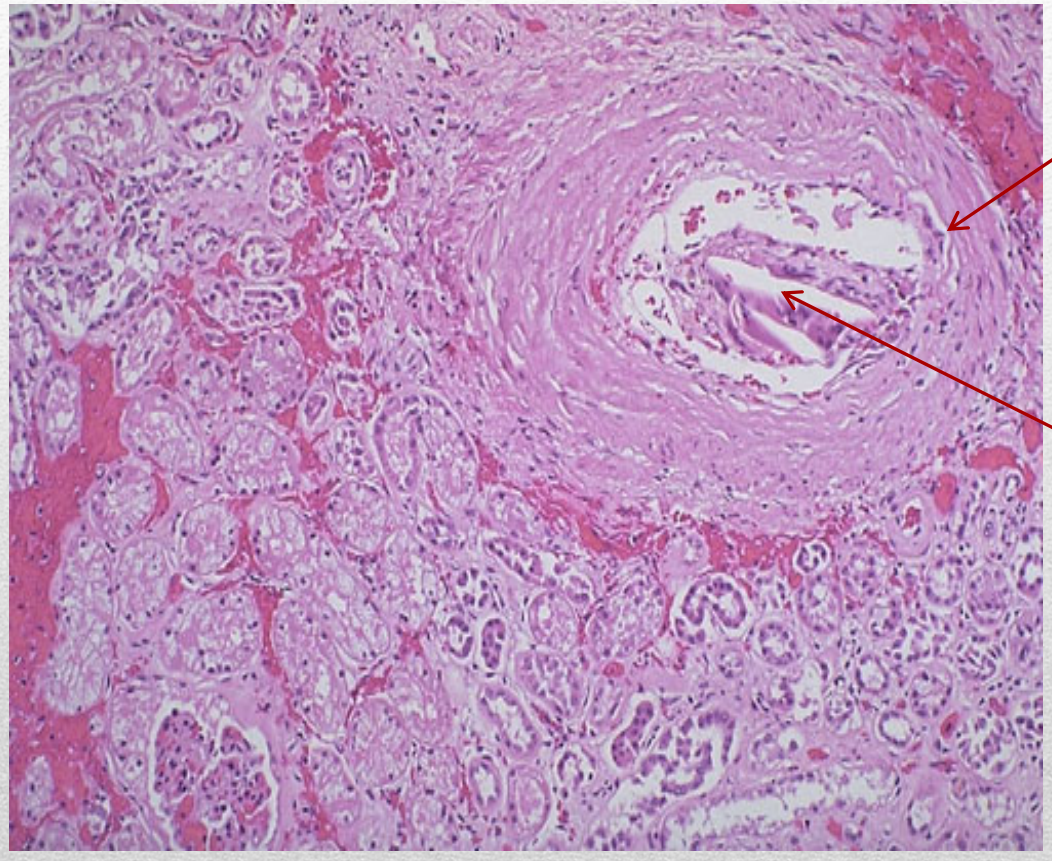
Cholesterol emboli after coronary angioplasty[1]



Livedo reticularis and blue macules or patches

1. Rana O, McCrea W. *N Engl J Med*. 200623;354(12):1294.

Renal biopsy:
Cholesterol Embolic Disease



Interlobular artery

Lumen filled with embolic debris and cholesterol clefts

Cholesterol Embolic Disease: Acute kidney injury

The increase in serum creatinine can be episodic or "stuttering" over several days after the insult

- This pattern is the result of successive showers of cholesterol emboli
- In acute kidney injury after angiography, this pattern can help distinguish it from contrast nephropathy

Cholesterol Embolic Disease: Treatment and outcome

No particular therapy

- Stop anticoagulation if possible
- Many patients succumb to mesenteric ischemia
- Irreversible renal failure necessitating dialysis
  - Reports of slow improvement in renal function and ability to come off dialysis months later

CASE REVIEW

BACKGROUND

- Ms. JM
- 48-year old woman
- Type 2 diabetes
  - Diabetic nephropathy on hemodialysis
- Medications: calcium, antihypertensives, low dose coumadin for clots in her dialysis line
- Developed bilateral leg discomfort
  - On examination: livedo reticularis on both legs observed



CASE REVIEW

Over the next 2 weeks:

- Falling hemoglobin
- Ulcerating skin lesions on lower abdomen and thighs

Skin biopsy:

- Evidence of necrosis
- No evidence of vasculitis
- Extensive vascular and subcutaneous calcification compatible with calciphylaxis

INTERACTION POINT

What is calciphylaxis?

- What leads to its development?
- And what tissues are usually affected?

Calciphylaxis

Described about 50 years ago by Hans Selye

- With the proper "conditioning" environment, a "challenge" with a new agent can lead to sudden development of vascular calcification and consequent necrosis
- Usually in skin and soft tissue, although visceral involvement has been described
- Almost always described in patients with kidney failure, although there are recent reports in HIV
- Typical patient is obese and female
- The classical "conditioning" was hyperparathyroidism and elevated calcium-phosphorus product
- More recently, a major risk factor is therapy with coumadin
  - Impairs vitamin K-dependent regeneration of matrix GLA protein, an important factor that prevents calcification

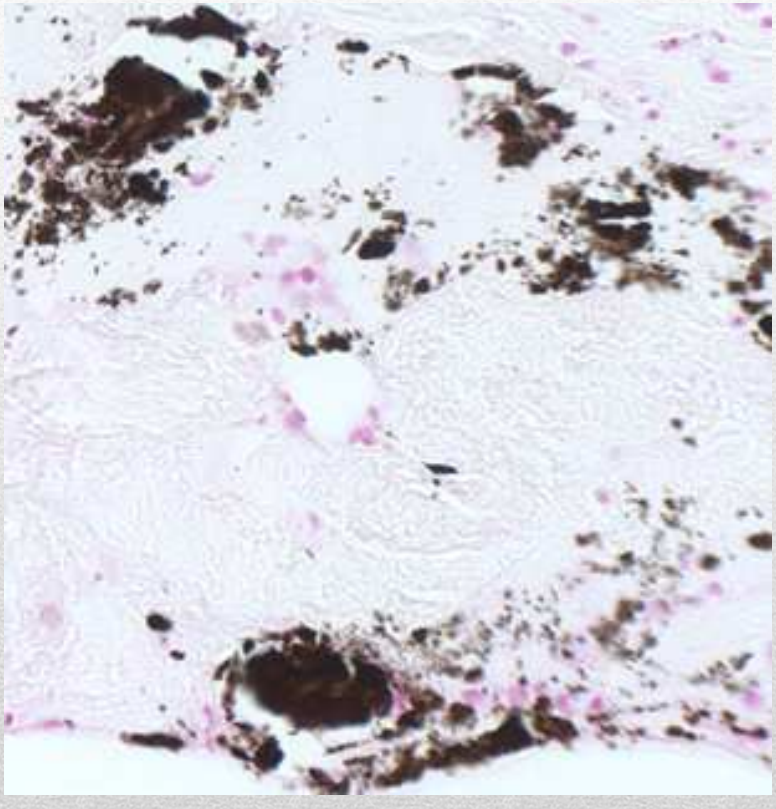
Calciphylaxis lesions on the legs



Pliquett RU, Schwock J, Paschke R, Achenbach H. *BMC Nephrol*. 2003;4:8

Calciphylaxis:
Skin biopsy (calcium stain)

- Extensive deposition of calcium in the epidermis and subcutis
- No evidence of active inflammation or vasculitis



INTERACTION POINT

How is calciphylaxis diagnosed and treated?

Calciphylaxis: Diagnosis and treatment

Diagnosis

Should be made clinically in the susceptible patient

- Livedo reticularis
- Painful subcutaneous nodules
- Progressive and multifocal necrotizing skin lesions, particularly on the calves, thighs, breast and abdomen

Calcification of skin and subcutis necessary but not sufficient for the diagnosis

Treatment

Discontinue coumadin

Optimize PTH/calcium/phosphorus status

Discontinue oral calcium, iron and vitamin D

Hyperbaric oxygen

Intravenous thiosulphate

Intravenous bisphosphonate

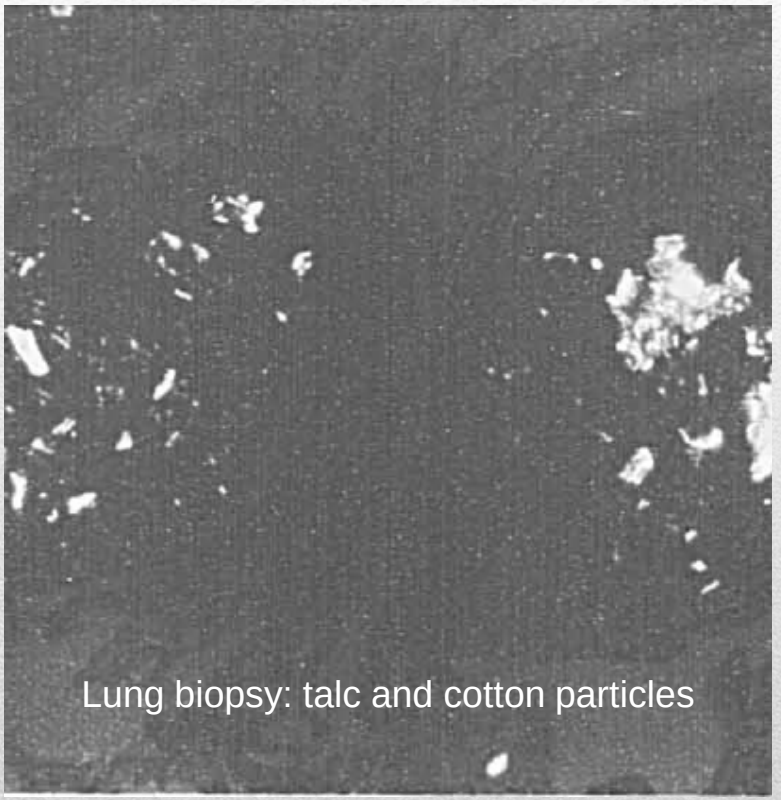
IV vitamin K

Careful wound management

Mimicker of vasculitis: A cautionary tale

Young asthmatic woman with Hickman line

- Presented with new hypoxemia, skin ulcers, fevers, anemia, ESR > 100
- Chest CT shows new central reticulonodular pattern
- Extensive ID workup negative
- ANCA negative but diagnosed as vasculitis
- Underwent open lung biopsy
- Lung biopsy demonstrated talc and cotton particles (shown), suggestive of IV drug use
- Left against medical advice but subsequently died of OD
- Patent foramen ovale



Lung biopsy: talc and cotton particles

Khanna D, Drehmer TJ. *South Med J*. 2001;94(5):505-7.

CASE REVIEW

BACKGROUND

- Mr. PC
- 35-year old, single, referred by ENT to rule out GPA (Wegener's)

PAST HISTORY:

- Smoker 10 pack-year
- Cocaine: daily use x 3 years but NONE for the past 5 years

ALCOHOL:

- 3-5 beers on weekends

GPA (Wegener's), granulomatosis with polyangiitis

CASE REVIEW

HPI:

- One year ago: First episode of sinusitis. Treated with antibiotics
- For the past 6 months: Headaches, nasal congestion, crusting +++, epistaxis 3-4/week

FUNCTIONAL INQUIRY:

- Occasional tinnitus
- Nil else

GENERAL PHYSICAL EXAMINATION:

- Normal

NOSE:

- “like if a bomb has exploded”
- Large nasal septum perforation, crusts, blood

CASE REVIEW

LABORATORY INVESTIGATION:

- CBC: Normal
- Serum creatinine: 62 μmol/L
- Urine: 3-5 RBC hpf
- ESR: 31
- cANCA (IIF): negative
- pANCA (IIF): positive (1:320)
- CT sinuses: polypoid lesion left maxillary sinus + mucosal hypertrophy

cANCA, cytoplasmic-ANCA; IIF, indirect immunofluorescence; pANCA, perinuclear-ANCA
Hagen et al. *Kidney Int.* 1998;53:743-53; Hagen and van Gurp. *Arthritis Care Res.* 2000;13:341-2

INTERACTION POINT

Does he have limited Wegener's? What would you recommend at this stage?

a. ANCA by ELISA
b. Nasal mucosal and septum biopsy
c. Renal biopsy
d. Urine for toxicology
e. Nasal cultures for bacteria and fungus

CASE REVIEW

Urine for toxicology was NOT ordered…

Biopsy (nasal mucosa and septum)

- Acute on chronic inflammation
- Some necrosis
- No vasculitis or granulomas

Cultures:

- *Staph aureus* and *pseudomonas aeruginosa*

ANCA (ELISA)

- PR3-ANCA: 5 (N < 2 IU/ml)
- MPO-ANCA: 1 (N < 6 IU/ml)

ANCA, anti-neutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3

ANCA immunotesting

A positive ANCA IIF must be confirmed by ELISA

- Only ANCA directed against PR3 and/or MPO have been associated with vasculitis
- pANCA can react with other antigens (cathepsin, lactoferrin, elastase etc…) but in general they are not associated with vasculitis

cANCA, cytoplasmic-ANCA; IIF, indirect immunofluorescence; ELISA, enzyme linked immunosorbent assay; MPO, myeloperoxidase; pANCA, perinuclear-ANCA; PR3, proteinase 3

Langford . *J Allergy Clin Immunol*. 2010;125(2 Suppl 2):S216-25; 2. Gómez-Puerta and Bosch. *Am J Pathol*. 2009;175(5):1790-8.

ANCA in patients with CIMDL

25 patients with cocaine-induced midline destructive lesions (CIMDL)

- P-ANCA:17/25 (76%); C-ANCA: 2/25 (8%)
  - PR3-ANCA: 11/19
  - MPO-ANCA: 0/19
  - HNE-ANCA: 18/19
- 3/6 patients with negative ANCA had + HNE- ANCA

The combination of:

- pANCA by IIF and positive PR3-ANCA by ELISA but negative MPO-ANCA is highly suggestive of CIMDL
- Testing for HNE-ANCA may discriminate between the 2 conditions as HNE-ANCA are NOT found in patients with GPA (Wegener's)

cANCA, cytoplasmic-ANCA; IIF, indirect immunofluorescence; ELISA, enzyme linked immunosorbent assay; GPA (Wegener's), granulomatosis with polyangiitis); MPO, myeloperoxidase; pANCA, perinuclear-ANCA; PR3, proteinase 3

Wiesner et al. *Arthritis Rheum*. 2004;50(9):2954-65

CONCLUSIONS

There are many mimickers of vasculitis (e.g. cholesterol embolic disease, acute kidney injury, calciphylaxis, pneumonia and acute tubular necrosis)

- ANCA has been found in patients with cocaine-induced midline destructive lesions (CIMDL)
- It is important to ensure that a patient has “true” vasculitis, and to start treatment quickly
- In setting of a high pre-test probability, many clinicians will empirically start therapy at least with high dose corticosteroids (risk of corticosteroids must be weighed against the benefit of early therapy)

CONCLUSIONS

CONCLUSIONS

- Definition of vasculitis is histological, but in an important proportion of patients, the combination of ANCA test and clinical findings can be sufficient to support the diagnosis
- Intensity of induction is based on disease severity (localized, early systemic, generalized, severe or refractory)
- Once induction is achieved, the goal is to maintain remission
- Early cessation of therapy is associated with an increased risk of relapse
- Remission maintenance therapy should be continued for at least 18 months