DM SEMINAR
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The Pulmonary Vasculitides

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Pulmonary vasculitis-an classification perspective:

The vasculitides are a group of clinically diverse conditions charac. by involvement of blood vessels in an inflammatory, occlusive and often destructive process.

The lungs are affected in isolation or with systemic vasculitis often because of:

1. Large vascular bed
2. Proximity to inhaled antigens
3. Presence of vaso-active cells
4. Versatility of the immune system.

Classification of the vasculitis has been notoriously controversial and a surfeit of systems exist.

These are a group of uncommon diseases and only 500 cases of confirmed Wegener's and 80 patients of Churg-strauss over 30 yr period in Mayo Clinic till 1995. There are about 50 histological confirmed cases of Wegener's in India.

Classification Of The Pulmonary Vasculitis:

- A) **lung is the major involved organ:** Includes WG, Churg-Strauss, microscopic polyangiitis, Necrotizing sarcoid granulomatosis
- B) **Lung may be involved**: Takayasu's arteritis, Behcet's syndrome, Classic PAN, cryoglobulinemic Vasculitis, Henoch-schonlein purpura.
- C) **Part of the spectrum**: CT-assoc vasculitis and vasculitis secondary to infection, drugs, or irradiation

Descriptive(Leibow)	Pathological(Saldana)
Classic WG Limited WG	lymphocytes depleted, vasculitis
Necrotizing sarcoid granulomatosis lymphomatoid granulomatosis	benign lymphocytic, vasculitis
bronchocentric granulomatosis	malignant lymphocytic, vasculitis
Churg-strauss	eosinophilic vasculitis.

Clinicopathological Classification Of The Pulmonary Vasculitis:

GROUP 1: Distinct Syndromes. Lung Involvement Invariable

Wegener's granulomatosis
Necrotizing sarcoid granulomatosis
Microscopic polyangitiis
Churg-strauss
lymphomatoid granulomatosis
bronchocentric granulomatosis
Takayasu's
Goodpasture's syndrome

GROUP 2: Distinct Syndromes. Nonspecific pathology. Lung Involvement variable

Henoch-schonlein Purpura
SLE
Sjogren's
Hypersenstivity Angitis
R.A
PSS
Polymyositis/dermatomyositis
Cryoglobulinemia
Behcet's

GROUP 3: Vasculitis due to infection.

A.. Specific: bacterial/fungal/ parasitic
B. non-specific: IE/ Sepsis

GROUP 4: Physical agent induced vasculitis: radiation/ cold

GROUP 5: Overlap syndromes.

Pathogenic Categories of Vasculitis

- **DIRECT INFECTION OF VESSELS**
  - Bacterial vasculitis (e.g., neisserial)/ Spirochetal vasculitis (e.g., syphilitic)/Mycobacterial vasculitis (e.g., tuberculous)/ Rickettsial vasculitis (e.g., Rocky Mountain spotted fever)/ Fungal vasculitis (e.g., aspergillosis)/Viral vasculitis (e.g., herpes zoster)

- **NONINFECTIOUS IMMUNOLOGIC INJURY**

  Immune complex-mediated vasculitis
  - Cryoglobulinemic vasculitis
  - Henoch-Schonlein purpura
  - Serum sickness vasculitis
  - Lupus vasculitis
  - Rheumatoid vasculitis
  - Infection-induced immune complex vasculitis (e.g. by hepatitis virus)
  - Some drug-induced vasculitis (e.g., sulfonamide-induced vasculitis)
  - Some paraneoplastic vasculitis
  - Goodpasture's syndrome (mediated by anti-GBM antibodies)

  Anti neutrophil cytoplasmic autoantibody (ANCA)-mediated)
  - Wegener's granulomatosis
  - Microscopic polyangiitis
  - Churg-Strauss syndrome
  - Some drug-induced vasculitis (e.g., thiouracil-induced vasculitis)

- **Cell-mediated vasculitis**
  - Giant cell arteritis
  - Takayasu's arteritis
  - Kawasaki disease

The anti-neutrophil cytoplasmic antibody: 1.role in diagnosis

- Seminal work done by Davies and Van der Woude.
- Artifact of ethanol fixation due to re-distribution of MPO.
- Patterns on IIF are referred to as C-ANCA & P-ANCA. Corresponding antigens are varied.

Wegener's granulomatosis	C-ANCA (75%-80%)	PR3
	P-ANCA (10%-15%)	MPO
	Negative (5%-10%)	
Microscopic polyangiitis	C-ANCA (25%-35%)	PR3
	P-ANCA (50%-60%)	MPO
	Negative (5%-10%)	
Churg-Strauss syndrome	C-ANCA (25%-30%)	PR3
	P-ANCA (25%-30%)	MPO
	Negative (40%-50%)	

Other ANCA assoc diseases:

IF Pattern	Antigen	Vasculitides	Other diseases
C-ANCA	**PR3**	Wegener's Microscopic PAN Pauci-immune GN Churg-Strauss	Subacute bacterial endocarditis* Type I autoimmune hepatitis* Leprosy* Type I diabetes* Amebiases Chromo mycosis*
C-ANCA	**(atypical) BPI alone** **BPI, MPO, cathepsin G**		Cystic fibrosis Inflammatory bowel disease
P-ANCA	**MPO alone**	Microscopic polyangiitis Pauci-immune GN Churg-Strauss syndrome	
	Multiple specificities: **actin, HMG1/2**, **catalase, a-enolase**, **azurocidin, lactoferrin**, **lysozyme, elastase**, **cathepsin G, defensin**		Type I autoimmune hepatitis Inflammatory bowel disease Primary sclerosing cholangitis Systemic lupus erythematosus Rheumatoid arthritis Drug induced vasculitis Infections (HIV, fungal, parasites)
Atypical ANCA	**Multiple specificities** (as above)		Drug induced vasculitis Inflammatory bowel disease Rheumatoid arthritis Malaria/HIV.

BIOLOGICAL ACTIVITIES OF PR3

Regulation of differentiation

- Truncation of NF-kB
- Hydroxylation of Hsp 28
- Truncation of Sp126
- Component of leukemia-associated inhibitor

Impact on cytokine network

- Conversion of IL-8 to active form
- Conversion of TNF-a to active form
- Conversion of IL-1b to active form
- Activator of latent TGF b
- Enhances IL-8 production by endothelial cells

Other substrates and physiological functions

- Cleavage of C1 inhibitor
- Cleavage and inactivation of the thrombin receptor
- Cleavage of matrix macromolecules (elastin, fibronectin, laminin, vitronectin, type IV collagen)
- Activator of MMP-235

Effect on endothelial cells

- Internalization into cells
- Induction of apoptosis
- Activates signaling molecules
- Stimulates tissue factor production

BIOLOGICAL ACTIVITIES OF MPO

- Bactericidal through enzymatic production of hypochlorous acid
- Functions as a peroxidase to produce free radicals causing lipid peroxidation of low-density lipoproteins
- Produces oxidants that activate cell-signaling pathways
- Produces hypochlorous acid activates NF-kB transcription factor
- Produces advanced glycation end products at sites of inflammation
- Internalized by endothelial cells causing increased free radical production
- Tyrosine nitration of vascular ECM proteins

Problems in ANCA interpretation:

IIF

- Only typical patterns have diagnostic value.
- Poor inter-observer reliability.
- Confusion between ANA and p-ANCA interpretation.

ELISA:

As sensitive as IIF testing

De-naturing of target antigen causes false-

Commercial kits fare poorly in sensitivity.

Assuming a prevalence of 20%, the PPV of C-ANCA is 66% and p-ANCA is 30%

1.Wegener's granulomatosis

- Estimated prevalence of WG is13-30 cases per million /5-year
- From 1979-88, WG listed as the cause of death in 1784 death certificates.
- Peak incidence in the 4.th- 6.th decades of life
- No gender predominance.

Godman and Churg criteria for Wegener's- the Wegener's triad (1954)

1. necrotizing granulomatous inflammation of the upper and lower airways.
2. generalized focal necrotizing vasculitis involving both arteries and veins.
3. focal necrotizing glomerulonephritis.

American College Of Rheumatology classification for Wegener's:

≥2 of the following criteria

- Urinary sediment with RBC casts or >5 RBC'S/ hpf.
- Abnormal findings on the chest radiography (nodules, cavities and fixed infiltrates)
- Oral ulcers or nasal discharge
- Granulomatous lesion on biopsy**$**

1.Granulomatous phase without vasculitis will be missed!!
2.Classification criteria only-not a diagnostic formulation.

Upper airways involved in 90% of WG.

Nasopharynx :60-80%

- epistaxis
- septal perforation
- nasal congestion/ pain
- mucosal ulcers
- strawberry gingival hyperplasia
- saddle nose 10-25%; reconstruction 92% success

Sinus involvement:

Chr. Sinusitis

CT useful> 85%

- thickening/clouding sinuses 75%
- erosion/ destruction of bones 25-50%

MRI: thickening ↑ granulomas ↓ } T2 intensity

Ear: 30-50%

- Chr. Sinusitis
- Chr. Mastoiditis
- Hearing loss

Active disease a. middle ear destr.n

b. vasculitis of cochlea

Infection c. CSOM

d. TM perforation

Sequelae e. granulation in mastoid

Salivary gland:

facial N. palsy rare.

Airway involvement in Wegener's:

- Stenosis in 10 to 30% of patients with WG. Symptoms are nonspecific
- Presentation is with dyspnea, wheezing, stridor, and change in voice.
- Concomitant involvement of the Nasopharynx or sinuses is the rule(97%).
- May develop years after the initial diagnosis of WG with inactive disease.
- The site of tracheal stenosis is usually circumferential and localized, extending 3 to 5 cm below the glottis.
- Extensive endobronchial abnormalities were noted in 11 patients with N CxR
- Flow-volume loops may be insensitive and FOB must in all.
- Circumferential narrowing of the trachea due to a mature scar was observed in 20 (74%) cases; friability or acute inflammation was noted in only seven patients (26%)

The impact of medical therapy in altering the course of endobronchial WG not clear. Aggressive immunosuppressive therapy is warranted when an active inflammatory component demonstrable.

Disease localized to the airways may not respond to medical treatment.

In this circumstance, alternative treatment modalities include

- CO_2 or Nd:YAG laser,
- Dilatation ±intratracheal CS injections,
- placement of Silastic airway stents,
- tracheostomy
- Laryngeal–tracheal reconstruction, and
- partial tracheal resection

Surgical intervention or manipulation of the airways minimized during flares.

Intralesional injection with long-acting CS and intratracheal dilatation is efficacious in treating SGS.

Long-term follow-up by an otolaryngologist is essential to monitor response

Radiology of Wegener's:

- multiple nodules from 0.3 -10 cm in diameter and are usually bilateral. smooth or spiculated
- 50% eventually cavitate esp.> 2 cm in diameter. typically have thick walls and shaggy, irregular inner borders

Lee KS, Kim: Eur Radiol 2003;13:43–51

- 27 (90%) had nodules or masses.
- Cavitation >1nodule was present in 13 (48%) of these 27 patients
- The nodules ranged from 1 to 32 in number (mean 8) mostly sub pleural or per bronchially

- Also common is air space consolidation or GGO.
- These are seen in 50% as diffuse, wedge-shaped pleural based, peri bronchial and patchy. Diffuse consolidation or GGO is seen in 8% & usually DAH.

- Pleural effusions in 12 to 25%.may be unilateral or bilateral, small or large.

- Other Features that can rarely pleural thickening, ptx, hydroptx, or pyoptx.

- Mediastinal lymph node enlargement in 20% of patients.

Lung Biopsy in WG.

SLBx is optimal to establish a firm diagnosis of pulmonary WG.

vasculitis and necrotizing granulomas are found on SLB in >90% of patients.

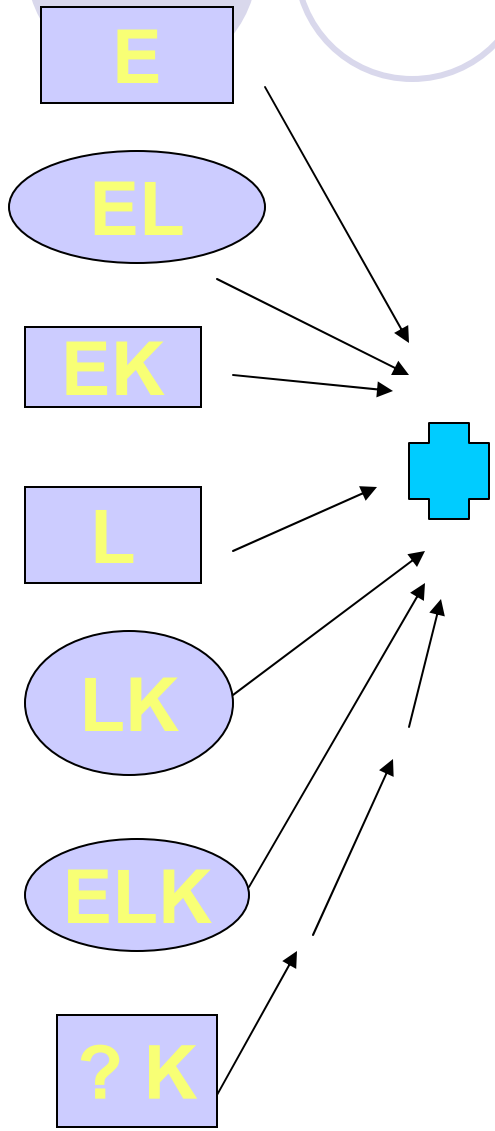
Micronecrosis or containing neutrophils and mononuclear cells appear to be early lesions,

Later findings include geographic necrosis, granulomatous infiltration, vasculitis, and varying degrees of fibrosis.

SLBx in pulmonary WG cited the (n=87) Travis. Am J Surg Pathol 1991;15:315–333

vascular inflammation (acute or chronic)	94%,
parenchymal necrosis	84%,
scattered giant cells	79%
areas of geographic necrosis	69%
granulomatous micro abscesses with giant cells	69%
Neutrophilic micro abscesses	65%
poorly formed granulomata(59%), capillaritis	31%
and fibrinoid necrosis	11%

Organ involvement in Wegener's:



BIOPSY

or(?)

C-ANCA

Others sites:

Eye+ orbit

Skin

CNS

Joints

Wegener's granulomatosis: extent of disease at diagnosis (ELK)

	Mayo series n=323	DeRemee[1] n=50	Gross[2] n=46	Bambery[3] n=15
E alone	12	28	59	0
L alone	11	16	13	0
EL	20	16	13	20
EK	16	8	4	7
LK	17	10	4	20
ELK	24	22	7	53

1. DeRemee: Mayo Clinic Proc 51:777;1976
2. Gross: Sarcoidosis 6:15;1989.
3. Bambery, S.K.Jindal et al Sarcoidosis 6 (suppl) :103;1989

Therapies in Wegener's Granulomatosis:

Goals of treatment for Wegener's granulomatosis

1. Patient survival
2. Induce remission of active disease
3. Reduce disease relapse
4. Minimize therapeutic toxicity
   - Use the least toxic yet effective treatment option
   - Actively pursue strategies to prevent and monitor for toxicity
   - Use treatment regimens at doses and schedules on which there data.

Current therapies though effective in inducing remission are wanting in reducing relapses and high in toxicity.

Challenges in conducting therapeutic trials in Wegener's granulomatosis

1. Rarity of Wegener's granulomatosis
2. Potential for active disease to be life threatening
3. Available treatment of established efficacy
4. Definition of outcome measures
5. Imprecise means of assessing active disease
6. Extended follow-up is necessary to fully assess relapse and to reach study endpoints

Management of Wegener's according to stage and evidence:

TABLE 1
CLINICAL SUBGROUPING ACCORDING TO DISEASE SEVERITY AT PRESENTATION FOR ANCA-ASSOCIATED VASCULITIS[3]

Clinical subgroup	Constitutional symptoms	Typical ANCA status*	Threatened vital organ function	Serum creatinine (μmol/L)
Localized	No	Negative	No	<120
Early systemic	Yes	Positive or negative	No	<120
Generalized	Yes	Positive	Yes	<500
Severe	Yes	Positive	Organ failure	>500 if renal; hypoxia if pulmonary
Refractory†	Yes	Positive or negative	Yes	any

1.Localized disease:

WG affecting the upper or lower respiratory tract alone without constitutional disturbance.

Has been treated with prednisolone alone or with the antibiotic combination, septran.

Role of Septran in Wegener's:

DeRemee reported in 1985 that improvement in 11 of 12 patients with WG occurred with TMP-SMX.

Possible modes of activity:

1. anti-inflammatory & inh. formation of O2 radicals by activated neutrophils.
2. WG are related to antimicrobial effects and inhibition of S. aureus driven proliferation of T lymphocytes and B lymphocytes, immunoglobulin and cytokine production.

T/S has been found in several reports to be beneficial in limited WG.
Interpretation of these results is confounded by
1.their retrospective nature 2.by the use of concurrent immunosuppressive agents 3.by the difficulty in defining active upper airways disease, and 4.by the lack of controlling for infection.

Two prospective studies found no role in limited WG.

1.Hoffman GS:*Sarcoidosis Vasc Diffuse Lung Dis* 1996, **13**:249-252.
2.Reinhold-Keller E, De Groot K**.** *Q J Med* 1996, **89**:15-23

Maintenance regime by Stegman: NEJM 96- only URT flares.

Never to be used alone in systemic vasculitis.

Always in patients on CYS as PCP prophylaxis.

2.Early systemic disease:

- Comprises A. localized WG with constitutional disturbance
  or
  B.WG which is multi-focal but without threatened organ function.

- Cyclophosphamide & steroids has been standard therapy

- Several uncontrolled studies have reported disease remission in 60-70% with Methotrexate and steroids used for induction therapy.

Methotrexate may be used in Wegener's as:

1. induction therapy

2. maintenance therapy.

Remission maintenance in WG:

NIH (n=32) with a F/U of 31 months.

CR 100% with no deaths and relapse rate of 16%

1.INDUCTION.COMPARISON OF THREE STUDIES OFMETHOTREXATE AND PREDNISONE IN WEGENER'S GRANULOMATOSIS

	Sneller et al (1995)	de Groot et al (98)	Stone et al 99
Total number	42	17	19
MTX/PRED as initial regimen (%)	36	65	100
> 3 organs at start of treatment (%)	60	NA *	74
GN at start of treatment (%)	50	12	47
ANCA(%)	83	76	84
Max MTX dose/week	25.0 mg	0.3 mg/kg	22.5 mg
Route of MTX	Oral	Intravenous	Oral Starting
PRED dose	1 mg/kg/d	10 mg/d (median)	40
PRED tapered to QOD	Yes	No	No
Improved (%)	83	59	89
Remission (%)	71	35	74
Developed GN on treatment (%)	2	29	5
Relapse (%)	27	33	50
Deaths (%)	7	0	0
Hepatotoxicity (%)	24	0	32
Opportunistic infections (%)	10	0	0
MTX pneumonitis (%)	7	0	0
Leukopenia (%)	7	0	0

- The control of early renal vasculitis, with normal or modest creatinine elevation with Methotrexate is more controversial
- Two studies have reported stabilization of excretory function;
- Others have found renal vasculitis to predict refractory, progressive disease after Methotrexate
- Inability to reduce the steroid dose and relapsing disease have been predictive of more widespread vasculitis after Methotrexate Therapy.

1.Langford CA. Arthritis Rheum 2000; 43:1836-1840.

2.de Groot K, Reinhold-Keller. Arthritis Rheum 1996; 39:2052-2061

3. Stone JH, Tun W, Hellman DB. J Rheumatol 1999; 26:1134-1139.

In the **NORAM** trial,100 newly diagnosed patients with s. Cr <150mol/l and no life or organ-threatening involvement randomized to Mtx and Cyc.

At the primary endpoint (remission at 6 m), equal remission (MTX 89.8% vs CYC 93.5%).

The relapse rate at 1 yr was unacceptably high (69.5% MTX and 45% CYC).
Mean time to relapse was 13.5months.

3.Generalized/renal disease

1985: Walton 82% mortality at 1 yr.(median 5 mo) BMJ 88;265-70.

1970s: high dose CS improved survival to 12.5 months

NIH cohort 57 patients 70-90's

45 progressive GN on steroids

17% limited WG into remission.

Hence CS never used alone in WG.

A 6-MONTH CORTICOSTEROID TAPER

Initiate treatment with 1 mg/kg/d of prednisone for the first month up to a max of 80 mg/d.

After 1 month, prednisone is tapered by 10 mg/wk. The goal is to achieve a dose of 20 mg/d by the end of 8 to 10 weeks of therapy.

Then, maintain dose of 20 mg/d for 2 weeks.

Then, reduce dose by 2.5 mg/wk until a dose of 10 mg/d is reached.

Then, reduce dose by 1 mg/wk until off.

*Patients with fulminant disease may receive intravenous methyl prednisone (1 g/d for 3 days) at the start of corticosteroid therapy. For patients with limited disease, the initial dose of corticosteroids may be lower (e.g., 0.5-0.8 mg/kg/d).

Cyclophosphamide for Generalized Wegener's:

Data from historic controls show the marked improvement in disease remission induction with CYC.

Current remission rates are 75-90% but relapse rates are still 50%.

This is at expense of marked toxicity.

COMPARISON OF TWO LARGE WEGENER'S GRANULOMATOSIS COHORTS

	Bad Bramstedt (N = 155)	NIH(N = 158)
Median follow-up (years)	7	8
Patients taking CYC/ CS	92%	84%
MESNA use	Yes	No
Alternate-day corticosteroid tapering	No	Yes
Complete remission achieved	54%	75%
Relapses (after complete remission)	60%	50%
Overall mortality	14%	20%
Mortality (2 to WG or treatment)	12%	13%
Serious infections	26%	46%
Deaths as a result of infection	3%	3%
Myelodysplasia	8%	2%
Cyclophosphamide-induced cystitis	12%	43%
Bladder cancer	<1%	3%

Cyc is a powerful agent with good remission rates but has unacceptable toxicity in the long run.

Some of these(gonadal, bladder Ca, MDS/ Leukemia) are dose dependent

USING CYCLOPHOSPHAMIDE SAFELY

Limit duration of CYC use (ideally 3-6 months for remission induction)

Take medication in morning; Drink eight 8-oz glasses of water daily

Adjust dose to maintain white blood cell count greater than 4000 mm3

Check complete blood count every 2 weeks and a urinalysis monthly

Adjust dose for renal dysfunction (see algorithm below)*

Always use *Pneumocystis carinii* prophylaxis

Long-term surveillance for CYC-induced bladder injury (annual urinalyses, with cystoscopy as indicated by hematuria or abnormal cytologic findings)

Creatinine Clearance (mL/min)	**CYC Dose (mg/kg/d)**
>100	2.0
50-99	1.5
25-49	1.2
15-24	1.0
<15 or on dialysis	0.8

This result is multiplied by a factor of 0.8 for women.

Recent studies have aimed to reduce exposure

A. by using pulse rather than continuous administration or

B. by switching to an alternative drug once remission has been obtained

APPROACH A. PULSE Cyclophosphamide

CONS:

•Two open, prospective studies of pulse Cyclophosphamide for superiority to oral administration for induction of sustained remission.

•It did not appear more successful in this setting; those with more extensive organ involvement and high ANCA titers had a poor therapeutic response.

•In contrast, continuing disease activity despite pulsed, intravenous Cyclophosphamide has responded to conversion to a daily oral regime.

PROS:

- 2 non-randomized controlled trials and 3 RCT'S have investigated whether pulsed Cyclophosphamide is safer and as effective as daily oral administration for the induction of remission.

1.Guillevin Arth Rheum 97;2187-98.n=50
2.Adu et al QJM 97;401-9.n=47
3.Haubitz Arth Rheum 98;1835-47.

- None sufficiently powered to make any conclusions about efficacy
- One study clearly showed a higher relapse rate after intravenous pulse use.
- All of the studies concluded that adverse effects were more frequent with daily oral Cyclophosphamide. This was only the primary end-point in the study by Adu. The studies by Guillevin and Haubitz were both stopped early due to more adverse effects in the daily oral arms.
- The high number of adverse events has been associated with
  A. the steroid dose used in these trials and
  B. with the protocols for tapering cyclophosphamide.

- A meta-analysis has summarized results from these trials

CRITICAL ANALYSIS OF TRIALS COMPARING 'PULSE' TO DAILY ORAL CYCLOPHOSPHAMIDE[20]

	Daily oral	Pulse	Comparison
Remission rate	77%	93%	Odds ratio 0.3
Relapse rate	29%	42%	Odds ratio 2.2
Infection	58%	39%	Odds ratio 0.24
Death	22%	20%	No difference
End-stage renal failure	15%	17%	No difference
Cyclophosphamide dose	34 g	17 g	$P < 0.001$

The 11 non-randomized studies comprised 202 patients on pulse CYC. Pulses of CYC were given at doses of 375–1000 mg/m2 per pulse at 1- to 4-week intervals with variable steroid and adjuvant therapy regimens.

Remission was achieved in 112/191 evaluable patients.
Relapse occurred in 68/135 patients.
Leucopenia, infection, hemorrhagic cystitis and death were rare

The CYCLOPS study is currently comparing the efficacy of daily oral to pulsed Cyclophosphamide for renal vasculitis in 160 patients..

Strategy 2: use of Azathioprine as maintenance.

AZA has also been evaluated for remission maintenance.

Initial reports from open-label series suggested that AZA may be able to maintain remission following induction with daily CYC

Fauci A, Haynes. *Ann Intern Med* 83, 98:76-85.

The CYCAZAREM trial compared AZA and CYC for maintenance of remission in patients with moderate renal involvement (cr<500 mol/l).

155 patients with AAV studied.

119(77%) achieved remission by 3 months.
There were seven deaths during the induction phase and one withdrawal.

Randomized to AZA or CYC.
At 12 months both groups received AZA (1.5 mg/kg/day) and prednisolone (7.5 mg/day).

There was no difference in relapse rates (15.5% in the AZA group and 13.7% in the CYC gr. up to the end of the study at 18 months after treatment outset.

This suggests that CYC can be safely withdrawn following induction of remission.

The REMAIN study is evaluating the optimum duration of therapy.

Severe renal disease:

Use of plasma exchange & pulse steroids.

- The delayed diagnosis of renal vasculitis increases the risk of the development of renal failure by the time of presentation.
- Progression to ESRD is not inevitable, and recovery is possible in many.
- The addition of pulsed MP or PE or both to standard Rx has been advocated to increase the chances of renal recovery.
- A pooled analysis of existing data suggests that plasma exchange may be superior in this regard but numbers are small and inclusion criteria and immunosuppressive regimens varied.

RENAL SURVIVAL IN PROSPECTIVE TRIALS INCLUDING PATIENTS PRESENTING WITH RENAL FAILURE DUE TO RENAL VASCULITIS. TREATMENT WITH OR WITHOUT PLASMA EXCHANGE

	No.	Plasma exchange	No plasma exchange
Glockner	12	5/8	3/4
Pusey	19	10/11	3/8
Cole	11	3/4	2/7
Levy	20	9/11	5/9
Guillevin	8	4/6	1/2
Haubitz	22	6/12	2/10
(Jayne)†	26	9/16	4/10
Total		46/68 (67%)*	20/50 (40%)

- **The MEPEX** trial is comparing the rates of renal recovery for those with an initial creatinine over 6 mg/dl between the addition of 3 g of mp and 7 PE, in addition to standard Rx.

- Preliminary data suggest that renal outcome was better in the plasma exchange-treated group in overall rate of dialysis-free survival.
- Death rates were similar in the two groups.
- These results were maintained at the 1-yr follow-up.

- In a RCT of 32 patients with Wegener's granulomatosis of varying severity, PE improved outcome.

Szpirt WM RNaPJ. Plasma exchange and cyclosporine A in Wegener's: Int J Artif Organs 1996; 10:501.

- Plasma exchange aims to
  - deplete circulating pathogenic autoantibodies;
  - other effects, such as the removal of cytokines,
  - complement, and coagulation factors, and less well-defined
  - immunoregulatory phenomena may also contribute

- AASVC is the most frequent cause of DAH & pulmonary renal syndrome, and this presentation carries a high mortality.
- No prospective therapeutic studies are available.

Other newer agents in AASVV:

1.Mycophenolate mofetil

Preliminary data promising.

1.**Nowack et al JASN 99; 1965-71**

open-label, prospective standardized study OF I G MMF twice per day 11 AASV following remission induction with daily CYC. Of the 11 patients, one WG patient (9%) relapsed in the 14th month of maintenance therapy. Well tolerated

2.Nachmann (n=12) JASN 2K(33% relapse)

3. Stegman. Used as a induction.

The IMPROVE trial of the EUVAS is testing MMF as a remission maintenance therapy

2. IVIG

Jayne 93 Lancet 1137.

3 Open label trials and 1 rct

Found no utility of IVIG in WG of varying stages beyond 3 months

3.Leuflonamide:

Interesting new option drawn from R.A therapy.

Metzler Arth Rheum 99: 5315.n=20

1 yr 755 remission.

4. Cyclosporine.

2 trials of 5 & 7 patients available.

1.2/5 relapse on reducing dose

2. Haubitz. NO ROLE.

5. Deoxyspergualin

Synthetic analog of spergualin, a product of *Bacillus laterosporus*
In a prospective open-label study by Birck et al,N=20 patients with AASV who had resistance or contraindications to standard therapy
Leukopenia. Mild to moderate infections were observed, not associated with mortality or sepsis.
Disease improvement was said to occur in 70% of cases, although
outcome measures were not clearly defined.

TNF-α inhibitors:

Anti-TNF- therapy ,has proved extremely successful and is now widely used to treat these patients for R.A and IBD

At present most reports of TNF- blockade in vasculitis relate to case series or small uncontrolled trials.

The WGET placebo-controlled trial of etanercept in Wegener's granulomatosis reported that in 180 patients etanercept was not effective at either induction or maintenance of disease remission when used in addition to conventional therapy

NEJM 352;27, 2005

Rituximab.

Data as case reports or as small series < 10 only.

Promising drug in refractory disease for remission induction.

Karina A. Keogh AJRCC **173. pp 180–187, 2006**

2. Microscopic polyangiitis.

- *Necrotizing vasculitis with few or no immune deposits affecting small vessels (ie, capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs*.
- Key to the Chapel Hill definition is the requirement for few or no immune deposits.
- Current definition of classic PAN allows necrotizing inflammation of small and medium arteries, but not of the smallest vessels.
- Incidence of MP of 3-9 patients per million population/year.
- Slight male preponderance with Peak incidence in the 55- to 74-yr group.
- Associations exist with 1.silica 2.solvent exposure 3.drugs:propylthiouracil, hydralazine and penicillamine.

Majority of patients with MP will have ANCA, they may be either MPO-ANCA or PR3-ANCA.

Hammersmith Hospital (MPO-ANCA and PR3-ANCA 45% each)
CHCC: MP3>PR3

Patients describe a prodromal illness of fever(45%), weight loss (35–60%), myalgia (40%), and arthralgia (30–60%) which precede diagnosis by up to 2 years.

Purpuric rash in 30% at diagnosis(leukocytoclastic vasculitis).

Renal dis. FSGN in >90%, Pauci-immune, varying ages and chronicity.

Pulmonary involvement in MP most often presents as
alveolar hemorrhage,
pleurisy, pleural effusions
and pulmonary fibrosis may be seen.
Alveolar hemorrhage is seen in up to 30% of patients worse prognosis

.

- Pulmonary fibrosis is an increasingly recognized feature of MP, predominantly associated with MPOANCA. Poor prognostic feature. All associated with previous DAH

- GI features more common & CNS/ eye less common than WG.

MP and WG defined as necrotizing vasculitis affecting the small vessels, commonly with glomerulonephritis.

Diagnosis of MP on clinical, histological, and serological evidence of a systemic small vessel vasculitis in the absence of marked upper respiratory tract disease

However, evidence is emerging that ANCA specificity does affect

1. renal biopsy,
2. the course and
3. outcome of the disease

Therapy in Microscopic polyangiitis:

Induction	0–3 months	Cyclophosphamide	2–2.5 mg/kg/day orally
			Dose reduced in elderly or in renal failure
		Prednisolone	1 mg/kg/day
			Tapering to 20 mg/day
Adjunctive	0–2 weeks	Plasma exchange	7–10 exchanges of 60 mL/kg over 2 weeks
		Methylprednisolone	10–15 mg/kg IV × 3 doses over 3 days
Maintenance	From 3 months if in remission	Azathioprine	2 mg/kg/day
			Tapering slowly
		Prednisolone	20 mg/day
			Tapering slowly

1-year survival rate of 84% & 5-year survival rate of 76%.

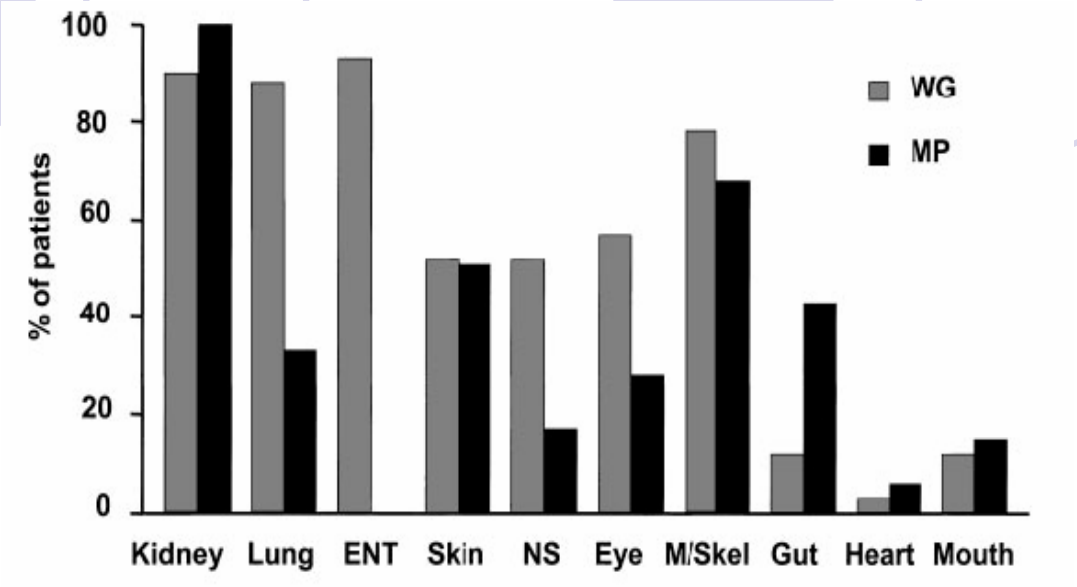
Survival was lower in those patients with ESRD (64% and 53% at 1 and 5 years, respectively).

Of those patients presenting with a creatinine of 5.4 mg/ dl, 45% went on to end-stage renal failure

Booth: Am J Kid Dis 2005

If plasmapheresis is used as a routine, 74% have independent renal f.n at 2 months

Organ specificity of the ANCA –related vasculitis:



Wegener's or MPA?? Why bother..

Splitters.

Renal lesions seem to depend on the disease (and ANCA type)

MPA presents with more indolent lesions
chronicity decreases response/ worsens prognosis.

Prognosis differs

Outcome in tendency to relapse differs

Lumpers.

Therapy is the same

Both WG and MPA can be MPO-ANCA +

Overlap syndromes exist

Churg-Strauss syndrome:

- Eosinophil -rich and granulomatous inflammation involving the respiratory tract, necrotizing vasculitis affecting small to medium-sized vessels, and associated with asthma and eosinophilia.

Criteria for CSS

Lanham's criteria:
Asthma,
peak peripheral blood AEC>1.5 x 106/cc, systemic vasculitis> 2 or more extra-pulmonary organs

ARA criteria (requires 4 of the following six findings):
asthma,
eosinophilia >10%,
neuropathy,
nonfixed pulmonary infiltrates,
PNS abnormality,
extra vascular Eosinophils

Phases

Three distinct phases:

- **Phase 1(prodromal**): Long h/o rhinitis with nasal polyps → late onset asthma
- **Phase 2:** Increasing peripheral blood and tissue eosinophilia - waxing and waning course
- **Phase 3:** Systemic vasculitis

Not all patients express a sequential staging of the illness and may present with only one or two manifestations

Pulmonary manifestations

Respiratory symptoms common presenting symptoms
Thoracic involvement is seen in all patients over course

Vasculitic process with a varying degree of eosinophilic infiltration cause infiltrates.

CxR:

Non-segmental airspace disease: 72%
Transient Löeffler's pneumonia: 40%
Multiple nodular lesions with rare cavitation or diffuse interstitial pattern
Pleural effusion
Pericardial effusion

HRCT findings

- Consolidation or GGO (95%): patchy, peripheral or geographic
- Pulmonary nodules 0.5-3.5cm (12%)
- Cavitation uncommon
- Bronchial wall thickening or bronchial wall dilatation (35%)
- Interlobular septal thickening due to edema (6%)

Am J Roentgenology 1998

4.Behcet's syndrome

Criteria for diagnosis of BD.

In the absence of other clinical explanations patients must have:

(1) Recurrent oral ulceration (aphthous or herpetiform) observed by the physician or patient recurring at least three times in one 12 month period

+ two of the following:

(2) Recurrent genital ulceration

(3) Eye lesions:

- anterior uveitis;
- posterior uveitis (cells in the vitreous observed by slit lamp examination); or
- retinal vasculitis observed by an ophthalmologist.

(4) Skin lesions:

- erythema nodosum;
- pseudofolliculitis;
- papulopustular lesions or acneiform nodules in post-adolescent patients not on corticosteroids

(5) Positive skin pathergy test read by a physician at 48 hours—that is, a 2 mm erythematous papule or pustule at the prick site 48 hours after the application of a sterile hypodermic 20–22 gauge needle which obliquely penetrated avascular antecubital skin to a depth of 5 mm.

Pulmonary features in Behcet's:

- Thoracic involvement occurs in 25% and pulmonary manifestations in 5%(1% to 18%). More than 598 features in 585 cases of Behçet's reported.
- Data from Japanese autopsy registry: involvement in 75%
- These problems can be classified into 3 groups
  - (1) pulmonary artery aneurysm (PAA),
  - (2) pulmonary parenchymal changes, and
  - (3) a miscellany including pulmonary A occlusion, pleural effusion, and pulmonary obstructive airway disease.
- 2.nd most common site of involvement, preceded by the aorta.

PAA

- Mean age 30.1 yrs. Male sex(89%). Hemoptysis is the predominant symptom.
  - Rupture of an aneurysm with erosion into a bronchus and
  - The development of in situ thrombosis
- The mean interval between the diagnosis of BD and the manifestation of PAA was 5.5 years. BD and PAA were co-diagnosed in 25.

- The aneurysms may be single or multiple, unilateral or bilateral, and measure 1 to 7 cm in Diameter.
- Aneurysm formation more on the right (59%) and in the lobar arteries (54%).
- The R LL commonly affected (35%) followed by the LLL & MPA
- Venous thrombosis or subcutaneous thrombophelebitis were common (78%).
- PAA was the only accepted manifestation of BD in two cases.
- Though DVT of lower limb frequently accompanies pulmonary artery aneurysms, PTE is very rare in Behçet's disease.
- Assessment is with CT and MRI. Conventional angiography is not recommended imaging
- 1-year and 5-year survival were 57% and 39% respectively

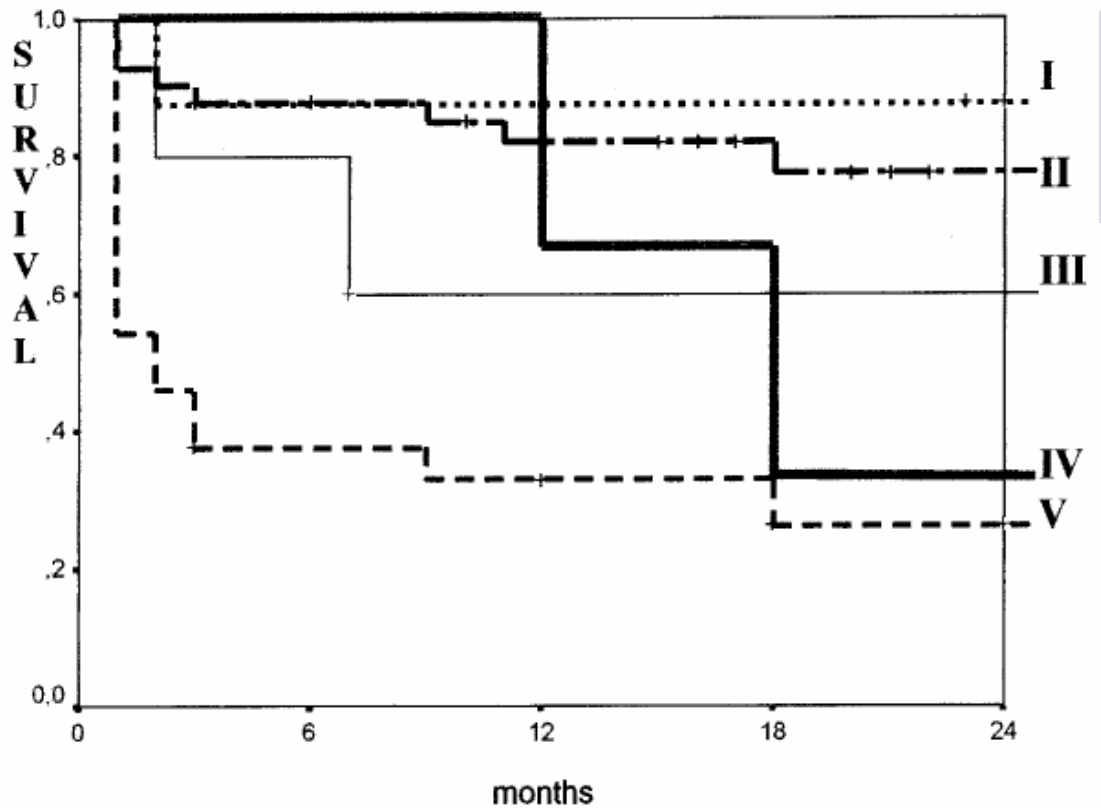
Non-PAA manifestations:

- Pulmonary artery aneurysms have varied course. Hemorrhage can result in focal, multifocal, or diffuse airspace consolidation.

- Atelectasis, volume loss, wedge shaped, or linear shadows, ill defined, nodular or reticular opacities have been described in Behçet's disease.
- Recurrent pneumonia, COP, eosinophilic pneumonia and pleurisy are other features describes with Behcet's.
- Pleural effusion may be due to 1.vasculitis of the pleura or 2.SVC thrombosis

Other thoracic features:

- SVC thrombosis is a more prevalent finding than arteritis.
- Pseudo-aneurysms of the aortic arch as well as the subclavian and coronaries have been described in Behçet's
- Mediastinal mass, mediastinitis & chyloptysis have been seen.
- Cardiac intramural thrombosis has been rare but fatal complication reported (n=25)



1.embolization±immunosuppression (n 8)
II: immunosuppresion (n 36);
III: anticoagulation ±immunosuppresion (5)
IV: embolization+ immunosuppresion anticoagulation (n 3);
V: surgery ±immunosuppresion

Outcomes in Behcet's with PAA

- BD patients have a bad outcome with anticoagulation.
- The patients treated with embolization with or without immunosuppresion have a better prognosis
- Patients who underwent surgery with or without immunosuppressive therapy had the highest mortality rate.
- Aneurysmorrhaphy, lobectomy, bilobectomy, pleurectomy, aneurysmectomy and pneumonectomy are procedures that have been used in BD.

5.Pulmonary manifestations of Takayasu's arteritis:

The diagnosis of Takayasu's is clinical and aided by the presence of features outlined by Ishikawa's criteria (or Sharma & Jain's in Indians).

Disease occurs in two stages: 'pre-pulseless stage' and 'pulseless stage'.

80% of patients are between 11 and 30 years.

Diminished or absent pulses in 84–96% with claudication and BP discrepancies.

Vascular bruits in 80–94% ;the carotids, subclavian & abdominal vessels common.

Hypertension in 33–83% (RAS) ;seen in 28–75% of patients.

Takayasu's retinopathy in up to 37% of patients. A.R occurs in 20–24%

CCF associated with hypertension, A.R, and D.C.M

Sharma S,
Clin Radiol 1990;42:177–82.

Pulmonary artery involvement in 14–100% of patients.
Oligaemic lung fields on plain chest *x* ray correlate a third of cases.
Pulmonary artery disease shows little correlation with systemic disease.

Table 1 Prevalence of Pulmonary Arterial Involvement in Takayasu's Arteritis

Author (ref #)	Cases	Frequency of Involvement (%)	Imaging
Sharma et al[9a]	44	14.3	IV-DSA
Yamada et al[9b]	30	50	MRA
Sheikhzadeh et al[9]	78	16	CDA
Vanoli et al[9c]	15	60	SPET
Ogawa et al[9d]	57	56	SPET

The survival rate at 5 years after diagnosis was 80.3% after which the survival curve flattened.

Current therapy involves steroids for patients in the inflammatory stage and angioplasties in the stenotic phase.

Second line therapies after failure of steroids(50%) include Methotrexate and azathioprine.

6. Diffuse alveolar hemorrhage:

Hemorrhage may occur with or without capillaritis.

Diffuse Alveolar Hemorrhage without Capillaritis

Inhalational toxins
Mitral stenosis
Severe coagulopathy
Iatrogenic anticoagulation
Renal failure
Thrombocytopenia
Other acquired or autoimmune coagulopathies
Infections
Endocarditis
HIV-assoc
Neoplasms
Lymphangioleiomyomatosis
Tuberous sclerosis
Pulmonary veno-occlusive disease
Pulmonary capillary hemangiomatosis
Diffuse alveolar damage or acute lung injury
Anti-glomerular basement membrane disease
Systemic lupus erythematosus
Idiopathic pulmonary hemosiderosis
Drugs

Diffuse Alveolar Hemorrhage with Capillaritis

Primary Vasculitis

ANCA-associated vasculitis
Wegener's granulomatosis
Microscopic polyangiitis
Churg-Strauss syndrome
Behcet's disease
Henoch-Schonlein purpura
Isolated Pauci-immune pulmonary capillaritis

Secondary Vasculitis

Collagen vascular diseases
Systemic lupus erythematosus
Rheumatoid arthritis
Mixed connective tissue disorder
Polymyositis
Primary or secondary APLA
Drug-induced vasculitis

7.Necrotizing sarcoid granulomatosis (NSG).

- Pulmonary vascular involvement is common in necrotizing sarcoid granulomatosis (NSG).
- NSG usually involves small- and medium-sized muscular arteries & veins.
- Though considered a variant of Sarcoidosis, important differences exist.
- Patients with NSG rarely have hilar adenopathy.
- The histopathology of NSG includes
  - granulomatous pneumonitis,
  - ‘‘sarcoidlike’’ granulomas, and vasculitis.
  - Widespread regions of coagulative necrosis are key to the histological differentiation of NSG from sarcoid.
- NSG requires aggressive immunosuppresion. Inadequate treatment is associated with a high mortality rate
- Failure to achieve a rapid response from high-dose corticosteroid therapy mandates the addition of a cytotoxic AGENT.

Fungal pulmonary vasculitis:

Necropsy data on the etiology of the fungal pulmonary vasculitis(23 patients)

Bambery, S.K.Jindal et al Sarcoidosis 6 (suppl) :103;1989

Aspergillosis	19
renal failure(RPRF/ ATN/ Amyloid)	8
hepatic failure(FHF/ Reye's)	3
septicemia	2
colitis(IUC/CDAD/Ischemic)	4
neoplasia	2
immune deficiency	2
normal	2
Mucormycosis	4
renal failure(RPRF/ ATN/ Amyloid)	3
normal	1

Suspect fungal lesion in a febrile patient with nodular lung lesions if:

Prolonged i.v hydration

steroids± BSAB'S

Renal failure

Leukopenia

Diabetes mellitus