Overlap Syndrome

- syndrome with sufficient diagnostic features of 2+ different connective tissue diseases

Vasculitides

- inflammation and subsequent necrosis of blood vessels leading to tissue ischemia or infarction of any organ system
- diagnosis
  - clinical suspicion: suspect in cases of unexplained multiple organ ischemia or systemic illness with no evidence of malignancy or infection; constitutional symptoms such as fever, weight loss, anorexia, fatigue
  - labs non-specific: anemia, increased WBC and ESR, abnormal U/A
  - investigations: biopsy if tissue accessible; angiography if tissue inaccessible
- treatment generally involves corticosteroids and/or immunosuppressive agents

Table 21. Classification of Vasculitis and Characteristic Features

Classification	Characteristic Features
SMALL VESSEL	
Non-ANCA-associated	Immune complex-mediated (most common mechanism)
Predominantly cutaneous vasculitis	Also known as hypersensitivity/leukocytoclastic vasculitis
IgA vasculitis (formely Henoch-Schönlein purpura [HSP]) (see Pediatrics, P86)	Vascular deposition of IgA causing systemic vasculitis (skin, GI, renal), usually self-limiting; most common in childhood
Cryoglobulinemic vasculitis (CV)	Systemic vasculitis caused by circulating cryoproteins forming immune complexes; 60-80% of cases are due to Hepatitis C, 5-10% are due to a CTD (SLE, RA, SS), 5-10% are due to a lymphoproliferative disorder and the remaining 5-10% are idiopathic or "essential". CV may be associated with underlying infection (e.g. hepatitis C) or connective tissue disease
ANCA-associated (i.e. PR3-ANCA) Granulomatosis with polyangiitis (GPA, formerly Wegener's) pR3 (c-ANCA) > MPO (p-ANCA)	Granulomatous inflammation of vessels of respiratory tract and kidneys; initially have URTI symptoms; most common in middle age
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) (50% ANCA positive)	Granulomatous inflammation of vessels with hypereosinophilia and eosinophilic tissue infiltration, frequent lung involvement (asthma, allergic rhinitis), associated with MPO-ANCA in 40-50% of cases. Other manifestations include peripheral neuropathy (70%), GI involvement, myocarditis and rarely coronary arteritis; average age 40s
Microangiopathic polyangiitis (70% ANCA positive, usually MPO)	Pauci-immune necrotizing vasculitis, affecting kidneys (necrotizing glomerulonephritis), lungs (capillaritis and alveolar hemorrhage), skin,; most common in middle age
MEDIUM VESSEL	
Polyarteritis nodosa	Segmental, non-granulomatous necrotizing inflammation Unknown etiology in most cases, any age (average 40-50s), M>F
Kawasaki disease (see Pediatrics, P87)	Arteritis and mucocutaneous lymph node syndrome
LARGE VESSEL	
GCA/Temporal arteritis	Inflammation predominantly of the aorta and its branches >50 yr of age, F>M
Takayasu's arteritis	"Pulseless disease", unequal peripheral pulses, chronic inflammation, most often the aorta and its branches Usually young adults of Asian descent, F>M, risk of aortic aneurysm
OTHER VASCULITIDES	
Buerger's disease ("Thromboangiits Obliterans")	Inflammation and clotting of small and medium-sized arteries and veins of distal extremities, may lead to distal claudication and gangrene, most important etiologic factor is cigarette smoking. Most common in young Asian males
Behçet's disease	Multi-system disorder presenting with ocular involvement (uveitis), recurrent oral and genital ulceration, venous thrombosis, skin and joint involvement; more common in Mediterranean and Asian, average age 30 yr old, M>F
Vasculitis mimicry (i.e. pseudovasculitis)	Cholesterol emboli, atrial myxoma, bacterial endocarditis (SBE), APLS

Features of Small Vessel Vasculitis
- Palpable purpura
- Vesicles
- Chronic urticaria
- Superficial ulcers (erosions)

c-ANCA (i.e. pR3-ANCA): cytoplasmic anti-neutrophil cytoplasmic Ab associated with anti-pR3
p-ANCA (i.e. MPO-ANCA): perinuclear anti-neutrophil cytoplasmic Ab associated with multiple antigens, e.g. myeloperoxidase, lactoferrin (IBD), cathepsin, elastase etc. Of these only antibodies to myeloperoxidase have been associated with the development of vasculitis

Features of Medium Vessel Vasculitis
- Livedo reticularis
- Erythema nodosum
- Raynaud's phenomenon
- Nodules
- Digital infarcts
- Ulcers

Churg-Strauss Triad
- Allergic rhinitis and asthma (often quiescent at time of vasculitis)
- Eosinophilic infiltrative disease resembling pneumonia
- Systemic vasculitis often mononeuritis multiplex/peripheral neuropathy and peripheral eosinophilia

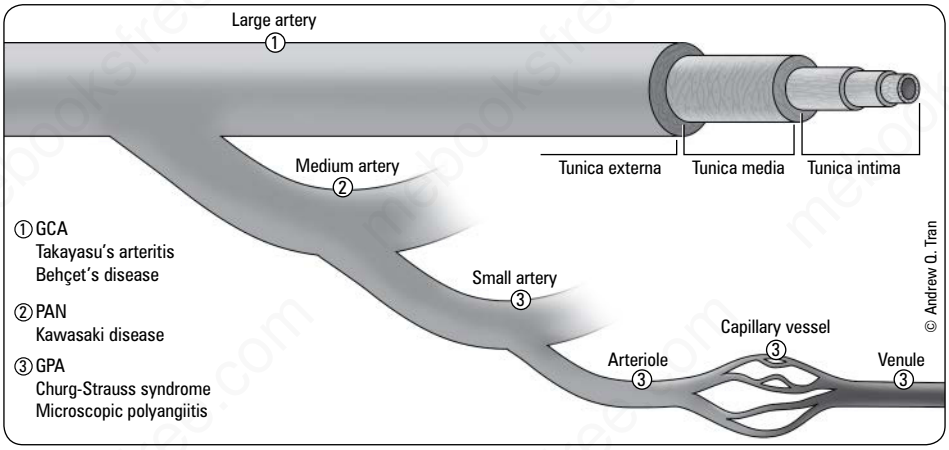

Figure 9. Classification of vasculitides by vessel size

Small Vessel Non-ANCA Associated Vasculitis

CUTANEOUS VASCULITIS

- subdivided into
  - drug-induced vasculitis
  - serum sickness reaction
  - vasculitis associated with other underlying primary diseases (CTD, infections, malignancies – hematologic > solid tumours)

Etiology and Pathophysiology

- cutaneous vasculitis following:
  - drug exposure (allopurinol, gold, sulfonamides, penicillin, phenytoin)
  - viral or bacterial infection
  - idiopathic causes
- small vessels involved (post-capillary venules most frequently)
- usually causes a leukocytoclastic vasculitis: debris from neutrophils around vessels
- sometimes due to cryoglobulins which precipitate in cold temperatures

Signs and Symptoms

- palpable purpura ± vesicles and ulceration, urticaria, macules, papules, bullae, subcutaneous nodules
  - renal or joint involvement may occur, especially in children

Investigations

- vascular involvement (both arteriole and venule) established by skin biopsy

Treatment

- stop possible offending drug
- NSAID, low dose corticosteroids
  - immunosuppressive agents in resistant cases
- usually self-limiting

Small Vessel ANCA-Associated Vasculitis

GRANULOMATOSIS WITH POLYANGIITIS (GPA, formerly known as Wegener's Granulomatosis)

Definition

- granulomatous inflammation of vessels that may affect the upper airways (rhinitis, sinusitis), lungs (pulmonary nodules, infiltrates), and kidneys (glomerulonephritis, renal failure)
- highly associated with c-ANCA by indirect immunofluorescence (IIF) and pR3-ANCA by ELISA; however, changes in ANCA levels do not predict remission or relapse
- incidence 2-3 per 100,000; more common in Northern latitudes

Table 22. Classification Criteria for GPA*

Criteria	Description
1. Nasal or oral involvement	Inflammation, ulcers, epistaxis
2. Abnormal findings on CXR	Nodules, cavitations, etc.
3. Urinary sediment	Microscopic hematuria ± RBC casts
4. Biopsy of involved tissue	Lungs show granulomas, kidneys show necrotizing segmental glomerulonephritis

*Diagnosed if 2 or more of the above 4 criteria present *American College of Rheumatology*, 1990

Classic Features of GPA
- Necrotizing granulomatous vasculitis of lower and upper respiratory tract
- Focal segmental glomerulonephritis

Etiology
- pathogenesis depends on genetic susceptibility and environmental triggers (e.g. infection)
  - dysregulated immune response due to loss of B and T-cell tolerance
  - acute vascular injury mediated by neutrophils and monocytes

Signs and Symptoms
- systemic
  - malaise, fever, weakness, weight loss
- HEENT
  - sinusitis or rhinitis, nasal crusting and bloody nasal discharge, nasoseptal perforation, saddle nose deformity
  - proptosis due to: inflammation/vasculitis involving extra-ocular muscles, granulomatous retrobulbar space occupying lesions or direct extension of masses from the upper respiratory tract
  - hearing loss due to involvement of CN VIII
- pulmonary
  - cough, hemoptysis, granulomatous upper respiratory tract masses
- renal
  - hematuria, proteinuria, elevated creatinine
- other
  - joint, skin, eye complaints, vasculitic neuropathy

Investigations
- blood work: anemia (normal MCV), increased WBC, increased Cr, increased ESR, elevated platelet count, ANCA (PR3 > MPO)
- urinalysis: proteinuria, hematuria, RBC casts
- CXR: pneumonitis, lung nodules, infiltrations, cavitary lesions
- biopsy: renal (segmental necrotizing glomerulonephritis), lung (granulomas, tracheobronchial erosion)
- c-ANCA and ESR often correlate with disease activity and used to monitor response to treatment in some patients

Treatment
- for severe, life or organ threatening disease
  - pulse methylprednisolone x 3 days followed by prednisone 1 mg/kg/d PO + cyclophosphamide 2 mg/kg/d PO for 36 mo OR rituximab 375 mg/m^2 followed by high dose MTX (20-25 mg PO/SC weekly) or azathioprine (2 mg/kg/d PO OD)
- consider plasmapheresis in patients with rapidly deteriorating renal failure or pulmonary hemorrhage

Efficacy of Remission Induction Regimens for ANCA-Associated Vasculitides (RAVE) Trial
NEJM 2013; 369:417-427
Study: Multicentre, randomized, double-blind, double-dummy, non-inferiority trial.
Intervention: Rituximab
Outcome: Complete remission of disease by 6 months, with remission maintained through 18 months.
Results: 64% of the patients in the rituximab group, as compared with 53% of the patients in the cyclophosphamide–azathioprine group, had a complete remission by 6 months. At 12 and 18 months, 48% and 39%, respectively, of the patients in the rituximab group had maintained the complete remissions, as compared with 39% and 33%, respectively, in the comparison group. Rituximab met the prespecified criteria for noninferiority. There was no significant difference between the groups in any efficacy measure, including the duration of complete remission and the frequency or severity of relapses. Among the 101 patients who had relapsing disease at baseline, rituximab was superior to conventional immunosuppression at 6 months (P=0.01) and at 12 months (P=0.009) but not at 18 months.
Conclusion: In patients with severe ANCA-associated vasculitis, a single course of rituximab was as effective as continuous conventional immunosuppressive therapy for the induction and maintenance of remission over the course of 18 months.

Medium Vessel Vasculitis

POLYARTERITIS NODOSA

Definition
- systemic, necrotizing vasculitis of medium sized vessels
- ANCA negative
- 5-10% associated with hepatitis B positivity
- incidence 0.7 per 100,000; affects individuals between 40-60 yr; M:F = 2:1

Table 23. Classification Criteria for PAN*

Criteria	Description
1. Weight loss	>4 kg, not due to dieting or other factors
2. Myalgias, weakness, or leg tenderness	Diffuse myalgias or weakness
3. Livedo reticularis	Mottled, reticular pattern over skin
4. Neuropathy	Mononeuropathy, mononeuropathy multiplex, or polyneuropathy
5. Testicular pain or tenderness	Not due to infection, trauma, or other causes
6. dBP >90 mmHg	Development of HTN with dBP >90 mmHg
7. Elevated Cr or BUN	Cr >130 μmol/L (1.5 mg/dL), BUN >14.3 mmol/L (40 mg/dL)
8. Hepatitis B positive	Presence of hepatitis B surface antigen or Ab
9. Arteriographic abnormality	Commonly aneurysms
10. Biopsy of artery	Presence of granulocytes and/or mononuclear leukocytes in the artery wall

*Diagnosed if 3 or more of the above 10 criteria present — *American College of Rheumatology*, 1990

Etiology and Pathophysiology
- focal panmural necrotizing inflammatory lesions in small and medium-sized arteries
- thrombosis, aneurysm, or dilatation at lesion site may occur
- healed lesions show proliferation of fibrous tissue and endothelial cells that may lead to luminal occlusion

Investigations
- blood work: CBC, ESR, Cr, BUN, p-ANCA, hepatitis B serology
- imaging: angiography
- arterial biopsy

Treatment
- prednisone 1 mg/kg/d PO and cyclophosphamide 2 mg/kg/d PO
- ± anti-viral therapy to enhance clearance of hepatitis B virus

Large Vessel Vasculitis

GCA/TEMPORAL ARTERITIS

Table 24. Classification Criteria for GCA*

Criteria	Description
1. Age at onset ≥50	
2. New H/A	Often temporal
3. Temporal artery abnormality	Temporal artery tenderness or decreased pulsations, not due to arteriosclerosis
4. Elevated ESR	ESR ≥50 mm/h
5. Abnormal artery biopsy	Mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells

*Diagnosed if 3 or more of the above 5 criteria present *American College of Rheumatology*, 1990

GCA Criteria
Presence of 3 or more criteria yields sensitivity of 94%, specificity of 91%

Epidemiology
- most frequent vasculitis in North America
- patients >50 yr
- F:M = 2:1
- North-South gradient (predominance in Northern Europe/US)
- affects extracranial arteries

Signs and Symptoms
- new onset temporal H/A ± scalp tenderness due to inflammation of involved portion of the temporal or occipital arteries
- sudden, painless loss of vision and/or diplopia due to narrowing of the ophthalmic or posterior ciliary arteries (PCA more common); can affect both eyes
- tongue and jaw claudication (pain in muscles of mastication on prolonged chewing)
- PMR (proximal myalgia, constitutional symptoms, elevated ESR) occurs in 30% of patients
- aortic arch syndrome (involvement of subclavian and brachial branches of aorta resulting in pulseless disease), aortic aneurysm ± rupture are late complications
- constitutional symptoms and shoulder/pelvic girdle pain and stiffness

Medical Emergency
If untreated, GCA can lead to permanent blindness in 20-25% of patients
Treat on clinical suspicion

Investigations
- diagnosis made by clinical suspicion, increased ESR, increased CRP, temporal artery biopsy, and possibly U/S or MRI

Treatment
- if suspect GCA, immediately start high dose prednisone 1 mg/kg in divided doses for approximately 4 wk, and then tapering prednisone as symptoms resolve; highly effective in treatment and in prevention of blindness and other vascular complications
- consider low dose ASA to help decrease visual loss

Prognosis
- increased risk of thoracic aortic aneurysm and aortic dissection
- yearly CXR ± abdominal U/S as screening