Vasculitides

- **Large Vessel Disease (large arteries)**
  - **Giant Cell Arteritis (GCA) / Temporal Arteritis** (most common vasculitis)
    - **Epidemiology**
      - elderly white female
    - **Etiology**
      - unknown
    - **S/S**
      - Constitutional Symptoms
        - 40% of GCA presents atypically with just fever (big cause of FUO) or weight loss!!!
        - 45% have PolyMyalgia Rheumatica (PMR) whereas only 15% of PMR have GCA
      - Vasculitis
        - 1° Extracranial Branches of the Carotid Artery
          - Headache (typically unilateral and temporal but any type of headache can occur)
          - Jaw or Tongue Claudication
          - Scalp Tenderness
          - Optic Nerve Ischemia resulting in Diplopia, Ptosis, Transient/Permanent Blindness ("Amaurosis Fugax")
          - Temporal Artery Nodulation, Enlargement, TTP, Absent Pulsations
          - CVA
        - 2° Branches of the Aorta
          - 17x Increased r/o Thoracic Aortic Aneurysm (late uncommon complication but it is the most common cause of mortality)
          - Limb Ischemia
  - **Diagnosis**
    - ACR 1990 Diagnostic Criteria (>3/5 Sensitivity 93% Specificity 92%)
      - >50yo
      - New Headache
      - Temporal Artery PEx Findings
      - ESR >50 mm/hr
      - + Bx
    - Labs: Elevated APRs
      - Some pts have normal APRs
    - Bx: Panmural Mononuclear Cell (Lymphocytes/Macrophages) Infiltration w/ or w/o Granulomas with Multinucleated Giant Cells
      - Typically you miss 3% of cases if you do unilateral biopsies but no one really does bilateral biopsies
      - Biopsy can be positive for up to 2wks following steroid therapy
      - Sensitivity of biopsy is dependent upon length of biopsy taken (must be >2cm) and how carefully it was examined (examine multiple portions b/c skip lesions occur often)
      - Therefore negative biopsies should always be questioned if strong clinical suspicion (9-44% of pts with clinical diagnosis had negative biopsy)
      - Problems: expensive, discomfort, facial nerve damage, infection, skin necrosis, stroke due to interruption of collateral circulation
      - NB other types of vasculitis affect the temporal artery (this can be differentiated by biopsy – there should not be fibrinoid necrosis)
  - **Doppler Ultrasound**
    - Acute: hypoechoic "halo sign" 2/2 vessel wall edema (69% sensitive and 82% specific)
    - Chronic: hyperechoic 2/2 vessel wall fibrosis
    - NB can also be used to direct biopsy by surgeon
  - **Treatment**
    - If you suspect based on clinical symptoms (remember atypical presentation sometimes) then start prednisone (1mg/kg/d, most doctors give 60mg STAT) IMMEDIATELY to protect vision, DO NOT WAIT UNTIL YOU GET BIOPSY RESULTS BACK, untreated GCA likely leads to blindness in 25% of pts
      - NB if eye is symptomatic then give solumedrol 1g IV QD x3d
    - If symptoms do not resolve than increase dose and reconsider diagnosis, continue steroids until symptoms are brought under control (do not treat ESR), typically 4-6wks, then taper gradually (decreasing by 20mg each month with a goal of 10mg/d then decrease 2mg each month with a goal of 5mg/d) continue this dosage for up to 2yrs!!! b/c if steroids are stopped prematurely then relapse usually occur (despite this very long taper there is still a 63% relapse rate)
      - Modifications leading to lower doses and faster tapers are being investigated b/c of the high SE rate using the current traditional approach
• Following APRs and symptoms are poor markers for disease remission b/c even if APRs are normal and pt is asymptomatic some pts have been found to have aortic aneurysms years later!!! (hence very long taper)
• Studies are underway to assess the use of methotrexate and anti-TNFs in decreasing steroid use and relapse rate
• In a study it was found that platelet count had the highest correlation with blindness therefore some recommend that a baby aspirin be given may also be helpful if S/S of CVA are present

- Takayasu’s Arteritis
  - Epidemiology
    - Adult females from 1° South/East Asians 2° Hispanics
  - Pathology
    - Vasculitis of Aorta and its major contributories esp subclavian/innominate arteries but also including carotid, coronary, pulmonary, renal, and temporal arteries
    - Acute then Chronic Focal Pan Granulomatous Inflammation with T-cell infiltration (NB very hard to get tissue samples) followed by degeneration of internal elastic lamina, adventitial fibrosis, and neovascularization (different from GCA)
      - DDx
        - Infection: Syphilis (diffuse not focal inflammation and localized to thoracic aorta), TB, Mycoses
        - Collagen Disease {aneurysms not stenoses are more common}: Ehlers-Danlos, Marfan’s
        - FibroMuscular Dysplasia (FMD) (primary site are renal arteries but other sites can be affected including carotid, mesenteric, iliac, usually no constitutional symptoms, Bx would show just bland proliferative changes no true inflammation)
        - Sarcoidosis
  - S/S
    - Triphasic Pattern (taking years to even decades)
      - Early: Constitutional Sx
      - Mid: Inflammatory “Active” Phase w/ Sx
        - Pain/TTP over involved vessels if superficial
      - Late: Fibrotic “Burn-Out” Phase
        - Asymmetric and Decreased BP/pulses b/t R & L and upper vs lower
        - Aortic Regurgitation
        - Bruits
        - Ischemia: Limb claudication, Renovascular HTN, TIA/CVA
  - Diagnosis
    - Angiography
    - Bx is not part of diagnosis b/c so hard to get
  - APRs
    - Clinical Criteria (>3/6)
      - >40yo
      - Ext claudication
      - Decreased brachial artery pulse
      - SBP difference >10mmHg b/t arms
      - Bruits over subclavian or aorta
      - Arteriogram
  - Prognosis
    - 20% have a monophasic self-limited course
    - 60% have a chronic course but it responds well to therapy
    - 20% have chronic course despite therapy
  - Tx
    - Steroids
    - Antiplatelets
    - Methotrexate if refractory
    - Variable/unpredictable treatment
    - Angioplasty
    - Bypass grafting

- Medium Vessel Disease (arteries/veins)
  - PolyArteritis Nodosa (PAN)
    - Epidemiology
      - Adult
    - Mechanism
- Focal necrotizing medium arteritis with microaneurysms and beading stenosis
- A small subset of PAN pts have viral infections 1°, HBV, 2°, HCV, HIV

**S/S**

- **General Principles**
  - many different presentations from local (one organ) to diffuse (many organs) from chronic/mild to acute/fulminant
  - polyarteritis = any organ can be affected, but usually the lungs and glomerular kidneys are spared (unlike other vasculitides)
  - should always be considered in the diagnosis of unexplained organ dysfunction

**Constitutional Symptoms (90%)**

- MS (65%): myalgia/myositis and arthralgia/arthritis
- P/CNS (50%): peripheral neuropathy esp mononeuritis multiplex
- GI (40%): ischemia heart disease from coronary arteritis

**Diagnosis**

- Labs
  - Elevated APRs
  - Leukocytosis and Anemia
  - Seronegative
  - Test for HBV, HCV, HIV

- NB: typically if you have a good site to biopsy then biopsy (eg. sural nerve, skin, muscle etc), if not proceed to angiography of viscera

**Treatment**

- Steroids
- Poor Prognostic Indicators: azotemia/proteinuria, cardiomyopathy, GI involvement, CNS involvement
- Overall 5-year survival is 80% with a <10% relapse rate
- Treat underlying cause (virus)

- ANCA Small Vessel Disease (arterioles, capillaries, venules), causes pulmonary-renal syndrome, small vessel necrotizing granulomatous vasculitis with frequent IC (aka "pauci immune GN") but the presence of circulating Antibodies to Neutrophil Cytoplasmic Antigens (ANCA), Cytoplasmic ANCA (cANCA) target proteinase 3 (PR3) which causes a cytoplasmic IF staining pattern on ethanol fixed neutrophils vs Perinuclear ANCA (pANCA) target myeloperoxidase (MPO) which causes a perinuclear IF staining pattern on ethanol fixed neutrophils. ANCA can be directed at other antigens in other disease like IBD, RA, etc or even w/ drugs. Therefore if you are concerned about vasculitis then you must corroborate ANCA IF positivity hence which is specific for vasculitis... order: "p/cANCA IF and MPO and Proteinase-3 Ag ELISA", the role of ANCA in vasculitis is uncertain, in general ANCA titers do not correlate with activity of disease
  - Wegener's Disease (80% renal 90% pulm)
    - Epidemiology (none)
    - S/S (mild/indolent in up to years or rapidly progressive in up to days)
      - Pulmonary
        - Upper respiratory tract (chronic sinusitis/rhinitis/otitis leads to cartilage destruction w/ nasal septum perforation, saddle nose deformity w/ bloody discharge, etc)
        - Lower respiratory tract (laryngotracheal dz w/ classically subglottic stenosis, cough, hemoptysis, dyspnea, pleuritis NB always rule out infection b/c these pts are immunocompromised)
    - Renal (indolent GN leading to glomerulosclerosis in years to RPGN)
    - Other: Eye (conjunctivitis, scleritis), Skin (purpura, ulcers, etc), MS (arthralgia, myalgias), Neuro (peripheral neuropathies esp mononeuritis multiplex and central neuropathy)
  - Dx
  - Serum: 90-40% +cANCA
  - Biopsy
  - CXR/CT of sinuses/ chest: single/multiple nodules, cavities, and infiltrates
  - Tx
  - Initial Therapy
    - Mild: Bactrim DS PO Qd NB there is some evidence that Staph infection is the underlying cause for many vasculitides hence the use of Bactrim in treatment
    - Mod: Prednisone (1mg/kg/d, can give methylprednisolone x3d if very ill)
    - Severe: Cyclophosphamide (2mg/kg/d, can go up to 5mg/kg/d x3d if very ill)
    - Monitor: UA Qmo forever b/c these pts are immunocompromised
  - Microscopic PolyAngiitis (MPA) (90% renal 50% pulm)
    - S/S (same but minimal upper respiratory tract dz)
Dx (Serum: 70% +pANCA and 10% +cANCA)
Tx (same)
Prognosis (same except 35% achieve remission and disease mortality is 25%)

Churg-Strauss Syndrome (CSS) (45% renal 70% pulm)
Pt: ~50yo pt but often pt has had subtle symptoms for decades
Stages
- Prodromal Phase (~20yo) Atopic Disease w/ severe refractory asthma (highly variable CXR) and allergic rhinoconjunctivitis (but no eczema)
- Eosinophilic Phase (~30yo) Eosinophilia and Eosinophil Organ Infiltration but no significant organ dysfunction
- Vasculitic Phase (~40yo) Systemic Vasculitis w/ Multiorgan Dysfunction w/ Constitutional
Symptoms
  - 1° Skin: subcutaneous nodules on extensor surfaces, palpable purpura or petechia/echymoses, erythematous maculopapular rash, tender subcutaneous nodules (highly variable)
  - 2° CNS: mononeuritis multiplex that progresses to polyneuropathy
  - 3° Renal: focal segmental glomerulonephritis
  - CV: CHF, pericarditis, ischemia (less common but most common cause of death)
  - GI: eosinophilic gastroenteritis
  - MS: myalgias/arthritis

Dx
- Bx: small vessel necrotizing granulomatous vasculitis w/ eosinophils and elevated IgE
- Blood: eosinophilia, IgE, +RFs, hypergammaglobulinemia, elevated APRs, anemia, leukocytosis

Tx (like Wegener’s)
Prognosis
- Prior to steroid treatment 50% died w/in 3mo of onset of vasculitis BUT now with steroids 5yr survival is 70% with relapse of 25% after treatment
- NB there was the belief that the use of leukotriene inhibitors in asthma “developed” CSS but now the thinking is that when added for steroid sparing effect the decrease dose of steroid simply unmasked the underlying vasculitis which can only be treated with steroids
- NB an unusual association between cocaine and CSS has been reported

IC/Hypersensitivity Small Vessel Disease (NB major sign is leukocytoclastic vasculitis aka neutrophils have infiltrated the perivascular space)
- Henöch-Schönlein Purpura
  - Pt: young children ~4yo during winter/spring time
  - Pt had prior strep/viral URT infection (other RFs: vaccination, insect bite, meds, etc), the IgA/C3 that is formed and deposits results in
    - Skin (hemorrhagic urticaria (palpable purpura) on extremities and buttocks)
    - MS (polyarthralgia/arthritis esp hips/knees/ankles)
    - GI (ab pain and bowel ischemia)
    - Renal (Gs seen in 35% of pts with <5% progressing to FSRD higher if adult pt)
- Tx: self-limited and thus Tx is not indicated but some use NSAIADs/prednisone for acute symptomatic treatment esp for MS/GI dz but they have no proven benefit in Renal/skin dz
- Prognosis: last 6wks, recurs in 40% of pts frequently w/in the first 3mo, only 1% disease mortality but variable course

Cutaneous Leukocytoclastic Vasculitis (most common type of vasculitis)
- S/S: Usually only skin (palpable purpura, necrotic papules, ulcers, urticaria) therefore must exhaustively exclude systemic involvement especially occult GN, usually multiple recurrences
- Etiology: Primary 30% vs Secondary 70% to drugs (penicillin, aspirin, amphetamines, thiazides, chemicals, immunizations), infection (strept throat, SBE, TB, hepatitis, staph), tumor, foreign particles aka serum sickness
- Dx: Bx of small vessel vasculitis + leukocytoclastic
- Tx: treat underlying cause if secondary or if primary then NSAIADs, antihistamines, dapsone, colchicines, low dose prednisone, rarely cytotoxic agents as only limited to skin and thus not deadly

Serum Sickness (refer)
Cryoglobulinemia Vasculitis (refer)
Connective Tissue Disease Vasculitis (refer)

Other
Kawasaki Disease aka Mucocutaneous LN Syndrome
- Vasculitis of unknown etiology but believed to be infectious
- Asian Male Children (80% <4yo, 20% 4-8yo, rare >8yo)
- Winter/Spring following exposure carpet cleaners and large bodies of water
- Most common cause of acquired heart disease in children!!
- Criteria
- Fever (>104 x>5d) + >4/5
  - Unilateral Cervical LAD
  - Bilateral Conjuctival Infections w/o Exudates
  - Mucocutaneous Lesions (red cracked lips, erythematous oropharynx, strawberry tongue)
  - Trunical Lesions (polymorphous exanthema)
  - Extremity Lesions (induration of hands/feet w/ erythematous palms/soles and desquamation of fingers/toes)
- Other Sx: sterile pyuria, thrombocytosis, aseptic meningitis, elevated APRs
- Complications: Coronary Artery Aneurysm with Thrombosis that can lead to MI and Hydrops of Gallbladder
- Treatment
  - Acute: High Dose ASA and IVIG
  - Chronic: Low Dose ASA
- Chilbain’s
  - Looks like Raynaud’s but not
- Buerger’s Disease aka Thromboangitis obliterans
  - young men who smoke cigarettes
  - acute inflammation of small/medium sized vessels of extremities
  - presents with ischemic claudication
  - Tx: stop smoking
- Behçets Disease (Pronounced “Beshets”)
  - Epidemiology
    - Young (30yo) Eastern Mediterranean / Middle Eastern Men (esp Turkey) and Asian Women (esp Chinese)
  - Pathogenesis
    - Chronic Relapsing Multisystem Autoimmune Vasculitis
      - NB affects all sizes (small to large) and all types (arteries and veins, though venous vessels are more common) of vessels
      - Arterial involvement leads to stenosis or aneurismal dilation
      - Venous involvement leads to thrombosis
  - S/S
    - International Study Group Diagnostic Criteria: Oral Ulcers + >2 of the following
      - Recurrent (>3x/yr) Aphthous Oral Ulcers
        - Usually the first symptom to come and the last to leave
        - Usually more extensive (multiple) and severe (larger) than common oral ulcers
        - Most last a few weeks but some pts have ulcers continuously
        - Less common in smokers!!!
      - Genital Ulcers
        - seen in 75% of pts
        - similar in appearance to but less recurrent than aphthous oral ulcers
        - most commonly found on scrotum (men) and vulva (women)
        - often set when they heal
        - often there is also epididymitis (men) and salpingitis (women)
      - Cutaneous Lesions: 1º Erythema Nodosum, Pseudofolliculitis, Acneiform Nodules 2º Papules/Nodules, Palpable Purpura, Superficial Thrombophlebitis, Pyoderma Gangrenosum, Naillfold Capillary Abnormalities, Dermatographism (skin changes in response to light scratching)
        - Seen in 75% of pts
      - Ocular Disease: 1º Anterior Uveitis (that may progress to Hypopyon), Posterior Uveitis, Retinal Vasculitis 2º Vascular Occlusion, Optic Neuritis, Neovascularization, Cataracts, Glaucoma
        - Seen in 50% of pts
        - most common cause of morbidity b/c can progress to blindness
      - Positive Pathergy Test
        - Seen in 50% of pts
        - >5mm erythematous papule/pustule that develops 1-2d after a skin prick by a needle
        - reflects neutrophil hyperactivity
  - Other Affected Systems (usually a later finding)
    - Joint: nonerosive/asymmetric arthritis
      - Seen in 50% of pts
      - Usually involves medium joints (knee, ankle, elbow, wrist)
    - CNS: focal parenchymal lesions, vascular thrombosis, cerebral vasculitis, aseptic meningitis/encephalitis
      - Seen in 20% of pts
• common to have personality changes, psychiatric disorders, dementia
• peripheral neuropathy is very uncommon
• one of the most common causes of morbidity and mortality
  o Large Vessel: Aorta, Pulmonary, S/IVC, Coronary, Cerebral
    • Seen in 20% of pts
    • Can result in hemorrhage, stenosis, aneurysm formation, thrombus formation, et al
    • one of the most common causes of morbidity and mortality
  o GI: cecal ulcers with perforation, portal vein thrombosis
    • Seen in 20% of pts
    • one of the most common causes of morbidity and mortality
  o Renal: GN, vessel thrombosis/stenosis/dilation
  o Cardiac, Pulm, et al

• Diagnosis
  • Clinical Diagnosis based on above criteria
  • No Pathognomonic Lab Test but usually APRs are elevated and some very non-specific auto-antibodies are present
    o ANCA
    o Anti-Endothelial Cell Ab
    o Anti-Cardiolipin Ab
    o Anti-Saccharomyces cerevisiae Ab
    o Anti-alpha-tropomyosin Ab
  • DDx: Reiter’s Syndrome, IBD, HSV

• Treatment
  • Mild Disease (eg. Mucocutaenous Dz, et al)
    o Skin: Topical/Intralesional Steroid and
    o Anterior Eye: Topical Mydriatics and Topical Steroids or Systemic Steroids
    o Systemic: PO Colchicine
  • Severe Disease (Posterior Eye and CNS Dz)
    o Systemic: Steroids ± Immunosuppressants (Methotrexate, Thalidomide, Azathioprine, anti-TNF-alpha, Cyclosporine, IFN-alpha)
  • NB the literature on the treatment consist primarily of case reports and small case series with few follow-up studies to confirm findings of preliminary reports and few randomized clinical trials
  • NB anticoagulate