Organization

- Case presentation
- History
- Definition
- Focus on small, medium, and large size vasculitis (specifically ANCA associated vasculitis): WG, CSS MPA and Takayasu.
- Pathogenesis
- Update in treatment modalities.
Brief history

• Kussmaul and Maier published the first definite report of a patient with necrotizing arteritis in 1886.
  - They described a patient with fever, anorexia, muscle weakness, paresthesia, myalgia, and oliguria
  - Found to have nodular inflammatory lesion in medium sized and small arteries throughout the body.
Brief history

• They called this condition Periarteritis Nodosa. The modern name is more pathologically accurate: Polyarteritis Nodosa.

- By the 1950s many investigators had realized that there were a number of clinically and pathologically distinct forms of vasculitis (e.g., dermal venules, glomerular capillaritis and pulmonary capillaritis). These were described as the microscopic form of periarterities by Goodman and Churg.
• By 1950, two variants of vasculitis with associated necrotizing granulomatous inflammation had been recognized:
  – Wegener’s granulomatosis and
  – Churg-Strauss syndrome.
• In 1994 the term microscopic polyangiitis was advocated by an international consensus conference on vasculitis nomenclature.
History

• In 1931 Klinger initially reported a vasculitis which was later described in more detail by Wegener.
• In 1951 Churg and Strauss described 13 patients who had asthma, eosinophilia, granulomatous inflammation, necrotizing systemic vasculitis and necrotizing glomerulonephritis.
• Now called Churg-Strauss syndrome.
WHAT IS VASCULITIS?

- Inflammation of vascular structures
  - Artery
  - Veins
  - Capillaries
  - Caused by immune and other mechanisms and manifested by features of systemic or localized organ dysfunction
Vasculitis in North America

- Multicenter study of 1020 patents in 1990 by the ACR: 807 of 807 of patients met diagnostic criteria

<table>
<thead>
<tr>
<th>Disease</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giant cell (temporal) arteritis</td>
<td>27%</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>15%</td>
</tr>
<tr>
<td>Wegener granulomatosis</td>
<td>11%</td>
</tr>
<tr>
<td>Henoch –Schonlein purpura</td>
<td>10.5%</td>
</tr>
<tr>
<td>Takayasu arteritis</td>
<td>8%</td>
</tr>
<tr>
<td>Churg- Strauss syndrome</td>
<td>2.5%</td>
</tr>
</tbody>
</table>
Organ Involvement.

The lung is frequently involved in primary vasculitides especially Wegener's Granulomatosis.

- eyes
- ears
- nose
- sinuses
- oral cavity and salivary glands.
- trachea and bronchi.
Pathogenesis

- Inflammation of large arteries such as the aorta and its major branches occurs in a number of disorders such as:
  - Kawasaki's syndrome
  - Behcets
  - RA
  - Syphillis
  - TB.
Aortitis and large-vessel arteritis are characteristics of two entities:
  – Giant-cell arteritis
  – Takayasu arteritis

These arteritides involve similar histologic abnormalities but differ in age of onset and vascular structures that are targeted

They share a pathogenesis that separates them from other vasculitides.
Pathogenesis

- Cellular immune responses involving
  - T cells
  - Antigen presenting cells
  - Macrophages
  - These cells are fundamental elements in
    - Giant-cell arterities
    - Takayasu
Pathogenesis

Key observation:
• T-cell dependent disease
• T-cell activation requires specialized antigen presenting cells: dendritic cells
• Activation of monocytes and microphages is responsible for systemic inflammatory syndrome.
• End result is an occlusive vasculopathy caused by rapid proliferation of intima or formation of an aneurysm.
Pathogenesis

• Activated dendritic cells produce a variety of adhesion molecules that regulate leukocyte transport
• They produce the chemokines CCL19 and CCL2, which play a role in attracting T-cells and microphages.
Pathogenesis

• In healthy arteries, immature dendritic cells, have a role in maintaining T-cell unresponsiveness: **Immunoprivilege**

• In vasculitis patients the dendritic cells are matured and activated
  – produce cytokines interleukins 6 and 18
  – express CD86, a co-receptor required for T-cell and dendritic cell activation.
Pathogenesis

• Adaptive Immune response, resulting in arterial wall injury
• Activation and trapping of dendritic cells in arterial adventitia
• CD4 T cell enters the microenvironment of the arterial wall, interacting with dendritic cells and secreting cytokines
Pathogenesis

- Interferon $\gamma$ is a critical cytokine that regulates the differentiation and function of macrophages.
- Macrophages in the adventitial layer supply inflammatory cytokines IL-1 and IL-6.
- Macrophages in the media secrete metalloproteinases that play a critical role in oxidative injury through production of reactive oxygen intermediates.
Pathogenesis

- Protein nitration occurs in endothelial cells lining neo-capillaries.
- Toxic aldehydes are formed in the process of lipid peroxidation.
- Smooth muscle cell undergo apoptosis.
- The response to arterial injury is shown in panels c and d.
Pathogenesis

• In patients with ample production of platelet-derived growth factor and vascular endothelial growth factor, rapid and exuberant intimal hyperplasia ensues, causing luminal occlusion.
Takayasu’s Arteritis

• First case was described in 1908 by Dr Mikito Takayasu at the annual meeting of Japan Ophthalmology Society.

• He described a peculiar “wreathlike” appearance of blood vessels in the back of retina.

• It is now known that the blood vessel malformation is due to arterial narrowing in the neck, and that absence of pulse in some patients, occurs because of narrow blood vessels to the arm.
Takayasu Arteritis

- Uncommon, yet reported worldwide
- Predilection for Asians
- Female:male ratio is 8:1
- Age of onset is typically 15-30
- Inflammation narrows blood vessels, leading to thrombosis
- Late stage may give rise to aneurysm
- Occasionally involves the pulmonary and coronary arteries, as well as the aorta and its branches.
Takayasu arteritis

• Signs and symptoms:
  – About ½ of the patients initially develop malaise, fever, night sweats, weight loss, althralgia and fatigue
  – This phase gradually subsides and is followed by a more chronic stage characterized by focal symptoms, e.g.:
    • syncope
    • transient visual disturbances caused by ischemia in the carotid and vertebrobasilar arteries
Takayasu Arteritis

- Symptoms and signs:
- Muscles atrophy may affect the face and arms.
- Obstruction in the descending thoracic aorta sometimes produces signs of aortic coarctation
- If the abdominal aorta affected, particularly renal artery, renovascular htn may result.
Takayasu arteritis

- Can also cause coronary artery inflammation producing angina or MI
- Signs of arterial obstruction may be absent until blockage becomes severe, resulting in:
  - Diminished or absent pulse and low BP.
Takayasu arteritis

• **Diagnosis**
  – May be suspected in patients who develop symptoms that suggest ischemia of organs supplied by the aorta or its branches, or who develop decreased or absent peripheral pulses
  – Arterial bruits and right–left or upper extremity-lower extremity discrepancies in pulses or BP are also suggestive.
Takayasu’ arteritis

• **Diagnosis:**
  – Confirmation requires aortic arteriography, or MRI to evaluate all vessel branches
  – Characteristic radiographic findings include:
    • stenosis, obstruction, and irregularities in vessel lumens
    • collateral pathways around obstructed vessels
    • aneurysms
  – Laboratory Tests: nonspecific
    • if there is an intitial systemic illness, anemia or a marked elevation in ESR are common.
Takayasu’s arteritis

• Prognosis and treatment:
  – May rarely spontaneously remit or stabilize.
  – Major complications like MI, severe HTN, heart failure, and aneurysm occurs in 50%
  – Accelerated artherosclerosis may be a late complication
  – With treatment, 95% of patients without complications survive > 5yrs.
Takayasu arteritis

• **Treatment**
  – Corticosteroids may dramatically relieve symptoms and lessen long term vascular complications
  – Prednisone 60mg po once/day is continued until symptoms subside and is tapered 5mg/day q2 wks until dose is 10mg/day
Takayasu's arteritis

- Corticosteroid Rx may be necessary for months or years
- Duration is guided by symptoms, signs, vascular images and ESR.
- Methotrexates or other cytotoxic drugs can be added in corticosteroid-resistant cases
- A platelet inhibitor, e.g. aspirin 325mg/day, may be helpful
- Ace inhibitors may be effective in treating HTN, especially if renovascular.

ANCA-Associated Vasculitides

• ANCA = Anti-neutrophil cytoplasmic antibodies
• In 1982 Davies and associates detected antibodies that reacted with neutrophil cytoplasm in 8 patients with pauci-immune necrotizing GN and small vessel vasculitis.
• In 1985 Van der Woude and his collaborators generated substantial interest by suggesting that detection of ANCA was a useful diagnostic and prognostic marker for diagnosis of WG.
ANCA Associated Vasculitis

• ANCA are specific for antigen in neutrophil granules and monocytes lysosomes
• Can be detected with indirect immunofluorescence microscopy by using alcohol–fixed neutrophil as substrate
• Two major antigens in patients with vasculitis:
  – Antimyeloperoxidase (MPO-ANCA)
  – Antiproteinase 3 (PR3-ANCA)
ANCA Associated vasculitis

- Approximately 90% of cytoplasmic ANCA are PR3-ANCA and approximately 90% of peri-nuclear ANCA are MPO-ANCA.
- Either ANCA specificity may occur in a patient with any type of ANCA-Associated vasculitis.
  - PR3-ANCA: most patients have Wegner’s Granulomatosis
  - MPO-ANCA: most patients have Micropolypolyangitis or Churg Strauss syndrome.

ANCA-Associated Vasculitis

- Several mechanisms have been put forward to explain how ANCA-target antigen interactions could result in necrotizing vasculitis.
- One theory suggests that neutrophils may be primed by pro-inflammatory cytokines such as IL-1, TGF-B, TNF or microbial products, resulting in translocation of small quantities of ANCA antigen to the surface of neutrophil, which then become accessible to ANCA.

Thorax 1998 53:220-227
Wegener’s Granulomatosis

• Necrotizing granulomatous disorder
• Triad:
  – necrotizing granulomas of lungs and kidneys
  – generalized focal necrotizing vasculitis of arteries and veins
  – focal necrotizing glomerulonephritis
• Capillaritis: seen in 40%
• Limited WG: respiratory disease without renal involvement.

Wegener’s Granulomatosis

ACR criteria for WG:
1) Nasal or oral inflammation
2) Abnormal chest roentgenograph
3) Abnormal urine segment
4) Granulomatous inflammation on biopsy
   (or hemoptysis if no biopsy is available)

This definition has a diagnostic sensitivity of 88% and specificity of 92%.
Wegner’s Granulomatosis

- Demographics:
  - Average age: 45
  - male:female 2:1
  - >90% are Caucasian
- Rhinorrhea, purulent or bloody nasal discharge, mucosal drying, crusting
- Epistaxis in 85%
- Ulcerating lesions of larynx and trachea in 30%, hemoptysis, cough, wheeze.
- Superinfection, particularly from S. aureus

Thorax 1998;53;220-227
Wegener’s Granulomatosis

- **Pulmonary involvement**
  - Lower respiratory tract > 90%
  - Cough, hemoptysis > 95%
  - Dyspnea, chest pain > 5-55%

- Clinical presentation varies from subacute nonspecific respiratory illness to rapid progressive ARDS

Source: Thorax 1998;53;220-227
Wegener’s Granulomatosis

- Airway involvement:
  - Overall involvement 15%
  - Subglottis stenosis 5-23%
  - Mild stenosis in chronic cases and in patients with stable disease.
  - Symptoms of airway involvement are insidious

- PFTS and inspiratory and expiratory FV loops may aid in follow-up
Wegener’s Granulomatosis

CXR

- Unilateral 15%
- Bilateral 45%
- Infiltrates 63%
- Nodules 31%
- Infiltrates with cavitation 8%
- Nodules are more common in lower lungs: 50% cavitation
- Ct: perivascular distribution of nodules
Wegener’s Granulomatosis: C-ANCA

- Positive C-ANCA without clinical disease is not diagnostic of WG
- Negative ANCA does not exclude vasculitis
- Clinically important target specific antibodies: pr3ANCA and anti-MPO-pANCA
- Renal WG with c-ANCA is aggressive
WEGENER’S GRANULOMATOSIS

- Rx: corticosteroid + cyclophosphamide complete remission in >90%
- Median time to remission: 12 months
- Milder cases: corticosteroids alone
- Rx of airway stenosis: dilation, laser, stent insertion
- Relapses occur in up to 50% of patients
- Methotrexate has been used to maintain remission (AJM 2003:114:463-69)
WEGENER GRANULOMATOSIS

- Relapse is associated with viral or bacterial infection (S. aureus)
- Nasal carriage rate for S. aureus is higher in patients with WG
- Trimethoprim 160mg + sulfamethoxazole 800mg/day is effective
- Remission rate sulfa = 82%, no sulfa, 60%.
- Sulfa had to be stopped in 20% (side effects)

NEJM 1996;335;16-20
WEGENER GRANULOMATOSIS

- Prospective, observational cohort analysis of multicenter, randomized, double-blind, placebo-controlled treatment trial
- 180 pts. assessed for occurrence of DVT/PE
- 13 pts had DVT/PE before enrollment
- 16 DVT/PE occurred in 167 pts during 27 months (7 per 100 VS 1 per 100 in SLE)
- Suggest possible increased incidence of venous thrombosis with ANCA associated vasculitis

Chest 2006;129;452-465
MICROSCOPIC POLYANGITIS

- Pauci–immune systemic vasculitis
- Small vessels vasculitis
- Focal and segmental necrotizing glomerulonephritis (main clinical features)
- No histological evidence of granulomatosi
- Pulmonary capillaritis is the most common lesion

Chest 2006;129;452-465
Microscopic Polyangitis

- Mean age 50 yrs; male>>female
- Renal impairment is common.
- P-ANCA in 75% of pts
- Pulmonary hemorrhage in up to 30%
- Lung involvement is an important contributory factor in morbidity and mortality
- Some will progress to typical WG.

Chest 2006:129;452-465
Churg-Strauss syndrome

- Also known as allergic granulomatosi and angiitis.
- CSS make up only 2.5% of all vasculitis in North America
- Two diagnosis lesions:
  - Granulomatous or nongranulomatosi
  - Extravascular necrotizing granulomas
- Renal involvement is rare
Churg-Strauss syndrome

ACR criteria (>4 of the following):

- Asthma
- Peripheral blood eosinophilia >10%
- Mononeuritis or polyneuritis
- Non–fixed pulmonary infiltrates
- Paranasal sinus abnormality
- Patient with > 4 criteria: 85% sensitivity and 100% specificity
Churg-Strauss syndrome

- Hypereosinophilia in blood
- High serum IGE
- PANCA-mpo + in 75%
- C-ANCA + in 25%
- Common: allergic rhinitis, nasal polyps, nasal crusting and septal perforation
Churg-Strauss Syndrome

ACR study:

– Asthma is present in all patients
– Age at onset:
  • rhinitis 28yrs,
  • asthma 35yr;
  • CCS 38yrs
– Male:female 1:1
– Anemia 80%
– Granulomas 40%
– Tissue eosiphilia 50%
– Transient lung infiltrates 70%
Churg-Strauss Syndrome: CXR

- Patchy and occasionally diffuse avelar – interstitial infiltrates
- Perihilar in distribution
- Upper two thirds of the fields
- Pleural effusion
- CT – SCAN: Ground glass attenuation

CHEST 2006;129;452-465
General principles:

• Therapy for the vasculitides relies on aggressive immunosuppression
• Complications of therapy are common and may be severe
• Accurate and frequent assessment of disease severity is needed—grading scheme proposed by the European vasculitis study group (EUVAS)
TREATMENTS

• Treatment is divided into two part model
• An initial remission- induction phase that requires more intensive immunosuppression therapy used to control active disease
• Maintenance phase in which less intensive therapy is used, minimizing the adverse side effects while still maintaining disease remission
## Treatment (EUVAS)

<table>
<thead>
<tr>
<th>Disease Classification</th>
<th>Constitutional Symptoms</th>
<th>Renal Function</th>
<th>Threatened Organ Function</th>
<th>Treatment Options for Induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited</td>
<td>No</td>
<td>Serum creatinine $&lt; 120 , \mu\text{mol/L}$ (1.4 mg/dL)</td>
<td>No</td>
<td>Corticosteroids OR methotrexate OR azathioprine</td>
</tr>
<tr>
<td>Early, generalized</td>
<td>Yes</td>
<td>Serum creatinine $&lt; 120 , \mu\text{mol/L}$ (1.4 mg/dL)</td>
<td>No</td>
<td>Cyclophosphamide + corticosteroids or methotrexate + corticosteroids</td>
</tr>
<tr>
<td>Active, generalized</td>
<td>Yes</td>
<td>Serum creatinine $&lt; 500 , \mu\text{mol/L}$ (5.7 mg/dL)</td>
<td>Yes</td>
<td>Cyclophosphamide + corticosteroids</td>
</tr>
<tr>
<td>Severe</td>
<td>Yes</td>
<td>Serum creatinine $&gt; 500 , \mu\text{mol/L}$ (5.7 mg/dL)</td>
<td>Yes</td>
<td>Cyclophosphamide + corticosteroids + plasma exchange</td>
</tr>
<tr>
<td>Refractory</td>
<td>Yes</td>
<td>Any</td>
<td>Yes</td>
<td>Consider investigational or compassionate use agents (see text)</td>
</tr>
</tbody>
</table>

*Data are from references 67, 83, 86, 97, 116, and 121–127.*
TREATMENT

• The timing of the transition from the induction to maintenance
• The result of the Cyclophosphamide vs Azathioprine for remission in generalized vasculitis trial demonstrated that patients with active generalized disease may be transitioned from oral cyclophosphamide to Azathioprine once a clinical remission has occur within (3-6 months)
Treatment

• Novel agents / biological agents:
• TNF-a has been implicated in the pathogenesis of vasculitis
• TNF-a inhibitors represent a major advance in the treatment of RA and it has been hypothesized that these agents may be helpful in treating vasculitides
Treatment

• Rituximab:
  – monoclonal anti-CD 20 antibody that target a subset of B lymphocytes,
  – effective treatment for B cell lymphoma and now vasculitis

• The result of a series of 11 pts with active ANCA Associated vasculitis
  – The authors find that they were able to induce remission in all 11 pts and that ANCA titers become undetectable in 8 of the 11 pts.

• Case series in literature suggest that rituximab may be useful in treating refractory vasculitis

Chest 2006;129;452-465
Summary

• Considerable advances have been made in the management of and therapy for vasculitis.
• The introduction of novel agents combined with increased clinical awareness of the complex and competing considerations in the management of these patients, allows us to anticipate further improvement in the outcomes of patients with this severe disease.
Reference

• Stephen K. Frankel, Gregory : Update in the diagnosis and management of pulmonary vasculitis: Chest 2006;129;452-465.
• M Griffith and Brett: Thorax 2003 ;58;543-546.
THANK YOU

• ANY ?
Pathogenesis

• Progress in understanding giant – cell arteritis has derived from three key observations.
• First, it is now clear that giant – cell arteritis is T cell - dependent disease.
• Second, T cell activation in nonlymphoid environment of the arterial wall requires specialized antigen presenting cells.
• Third the blood determines the site specificity of giant – cell arteritis
• End result is an occlusive vasculopathy caused by rapid proliferation of the intima or formation of aortic aneurysm caused by destruction of the arterial wall.
In a healthy arteries, dedritics cells have gene –expression profile characteristics of that of an immature cells rolls includes:

- Maintenance of T-cell unresponsiveness
- Do not express the costimulatory CD 80 and CD 86.
- The inhibition of T-cell by immature dendritic cell is called immunoprivillege
• The dendritic cells are matured and activated.
• They produce inflammatory cytokines interleukin6, 18, and express CD86.
• These matured dendritic cells have acquired ability to maintain the activation of T cells.
• N ENGL J MED 349;2
Pathogenesis

- Activation and trapped of dendritic cell in arterial adventitia generates the condition for recruitment and stimulation antigen specific T cells.
- CD4 cell enter the microcirculation and interact with dendritic cell and begin to secret cytokines.
- Interferon-gamma is critical cytokines that regulates the differentiation and function of macrophages. (functional commitment is closely linked to there location in arterial wall.)
Pathogenesis 3B

- Protein nitration occurs in endothelial cell lining.
- Toxic aldehydes are formed in the process of lipid peroxidation and smooth muscle apoptosis.
- Reactive oxygen intermediate also trigger cellular activation.
- By induction of aldose reduction.
Pathogenesis 3 C AND D.

- The response of artery to injury is shown here.
- In panel c, arteritis does not necessarily result in luminal stenosis.
- In patients with ample of platelet-derived growth factor, rapid and exuberant intimal occlusion and hyperplasia occurs, causing vascular occlusion. (Panel d)
Pathogenisis

- Antineutrophil cytoplasmic antibodies
  Are circulating autoantibodies which identify a specific subpopulation of patients with systemic vasculitis.
  Were originally detected by immunofluorescence and two distinct patterns were describe (C-ANCA) which is directed against protien-3 (p-ANCA) which is directed against myloperoxidase
Pathogenesis

• Proteinase-3 and myeloperoxidase usually reside within azurophilic granules in neutrophil and are normally involved in host defence against invading organism.

• Several mechanisms have been put forward to explain how ANCA interacting with target antigen could result in necrotizing vasculitis.
Pathogenesis

• One theory suggest that neutrophils may be primed by pro-inflammatory stimuli such cytokines
  - IL-1
  - TGF-B
  - TNF or microbial products which result in translocation of small quantities of ANCA antigen to the surface of neutrophil which then become accessible to ANCA
• ANCA has been shown to enticed primed neutrophils to release reactive oxygen species and lysosomes enzymes.
• Also ANCA facilitates neutrophil adherence to vascular endothelial cells and indirectly mediates endothelial cell injury.

Thorax 1998;53;220-227
Evaluation

• Begins with a detail history and Physical examination
• Close attention must be paid to some conditions mimicking vasculitis (connective tissue dx, malignancy, drug toxicity, sarciodosis, and interstitial lung disease)
• Labs testing is critical

Cbc, liver function test, urinalysis with microscopic examination to help identify renal, hepatic and metabolic abnormalities.

- Cryoglobulemia and hepatitis B and C should be ruled out.

Anti SS-A/Ro and anti-ssB/La for SLE and Sjogren syndrome, anti-Scl-70 and anticentimere antibodies for systemic sclerosis.
Diagnosis

- Must be based on accumulated data not on ANCA/PR3/MPO testing alone.
- Images studies can be very helpful
  - CXR, CT scan of chest, sinusitis and abdomen.
  - angiogram, echo and MRI.
- The utility of bronchoscopy is limited to the evaluation of alveolar hemorrhage, infection and endobronchial lesions as seen in WG.
- Transbronchial biopsy specimen are by and large insufficient to make diagnosis.
diagnosis

• Surgical lung biopsy gives a definitive diagnosis in clear majority of cases.
• Use of VATS has significantly reduced morbidity and mortality
• Renal biopsy is commonly done in the setting of acute GN
• The finding of a segmental necrotizing GN without immune deposite reflects systemic vasculitis in most cases.
WEGENER GRANULOMATOSIS

- The C-ANCA is positive in more than 90% of patients with active "classical" WG.
- In limited WG i.e. (without active GN) the sensitivity may be as low as 43%.
- About 5% of patients with classical WG are found to have p-ANCA, which also associated with other vasculitis such as
  - CCS, Microscopic polyangities, crescentric GN and other inflammatory disorders.

Pulmonary clinical presentation

- WG: The lung is the most frequently involved organ.
- Necrotizing granulomatosis disorder.
- Triad: Necrotizing granulomas of the lungs and kidneys, generalized focal necrotizing vasculitis of arteries and veins, and focal necrotizing granulomatosis.
- Capillaritis: Seen in 40%
Wegener granulomatosis.

- ACR criteria for WG.
  - Nasal or oral inflammation
  - Abnormal chest roentogengraph
  - Abnormal urinary sediment
  - Granulomatous inflammation on biopsy (if biopsy is not available, hemoptysis can be substituted as fourth criteria)
  - This definition has a diagnostic sensitivity of 88% and specificity of 92%.
Wegener's granulomatosis

- Age 45yrs M:F 2:1 >90% are Caucasians.
- Rhinorrhea, purulent or bloody nasal discharge, mucosal drying, crusting
- Epistasis in 85%
- Ulceration lesions of larynx and trachea in 30% hemoptysis, cough, wheeze
- Superinfection, particularly from S. aureus is common.
Wegener's granulomatosi.

- Pulmonary involvement:
- Lower respiratory tract >90%
- Cough, hemoptysis >95%
- Dyspnea, chest pain 5-55%
- Clinical presentation varies from subacute nonspecific respiratory illness to rapidly progressive ARDS.
WEGENER'S GRULOMATOSIS

- Airway involvement
- Overall involvement 15%
- Subglottics stenosis 5-23%
- Mild stenosis
- Symptoms of airway involvement are insidious
- PFTs and inspiratory and expiratory FV loops may aid in f/u.
WEGENER GRANULOMATOSIS
WEGENER GRALOMATOSIS
Histopathology of WG. Geographic vasculitis and granulomatous infla
WEGENER GRANULOMATOSIS

- **CXR:**
  - Unilateral 55%
  - Bilateral 45%
  - Infiltrates 63%
  - Nodules 31%
  - Infiltrates with cavit 8%
  - Nodules are more common in lower lobes
  - CT: Perivascular distribution of nodules.
Wegener granulomatosis

- Prognostically: Poor outcomes correlates with advance age
- More severe renal impairment
- Alveolar hemorrhage
- Protinase (PR)-3 positivity.
- Diagnosis of WG as opposed to CSS or MPA.

Chest 2006;129.2.452.
Microscopic polyangiitis

- Pauci –immune systemic vasculitis
- Small vessels vasculitis
- Focal and segmental necrotizing GN (main feature)
- No histologic evidence of granulomatosis
- Pulmonary capilaritis is most common lesion in MP.
MICROSCOPIC POLYANGITIS

- Age 50yrs :M>F
- Renal impairment is common
- p- ANCA-mpo present in 75%
- Pulmonary hemorrhage in up to 30%
- Lung involvement is an important contributory factor in mortality and morbidity
- Some progress to typical WG.
Microscopic polyangitis  Cxr and histology
Churg –strauss syndrome

- Also known as allergic granulomatosis and angitis.
- CSS makes up only 2.5% of all vasculitides in North America
- Two diagnostic lesion:
  - Granomatous or nongranulomatous angitis
  - Angiitis is disseminated; affects arteries and veins in lungs and systemic circ.
- Renal involvement is rare.
Churg-strauss syndrome

- ACR criteria (>4 of the following)
- Asthma
- Peripheral blood eosinophilia >10%
- Mononeuritis or polyneuritis
- Non-fixed pulmonary infiltrates.
- Paranasal sinus abnormality
- Patient with >4 criteria: 85% sensitivity and 100% specificity.
- America Coll Rheumathol 1990.
Churg–strauss syndrome

- Hypereosinophilia in blood
- High serum IgE
- P-ANCA-mpo + in 75%
- C-ANCA+ in 25%
- Common: allergic rhinitis, nasal crusting and nasal septal perforation
- Eosinophilic lung infiltrates.
- America college of rheumat 1990
Churg-strauss syndrome

- Asthma is present in all patients
- Age at onset: rhinitis 28yrs, asthma 35yrs, CSS 38yrs
- Male:female 1:1
- Anamia 80%
- Granuloma 40%
- Tissue eosinophilia 50%
- Transient lung infiltrates 70%
- Amer college of rheumatol 1990.
Churg-strauss syndrome

- CXR
- Patchy and occasionally diffused or patchy alveolar – interstitial infiltrates
- Perihilar in distribution
- Upper two third of the fields
- Pleural effusion in 30%
- CT SCAN
- Ground –glass attenuation
Histology of churg-strauss syndrome.
Takayasu vasculitis

- The first case of takayasus arteritis was described in 1908 by Dr Mikito Takayasu
- Described a peculiar ‘wreathlike’ appearance blood vessels in the retina.
- It is now known that the blood vessels malformation that occurs in the retina are due to arterial narrowing in the neck
- The absence of pulses noted in some patients occur because of narrowing of blood vessels to the arms.
Takayasu arteritis

• Who gets it:
• A woman under the age of 40.
• Male : female 9:1
• More common in Asian women.
• In North America the annual incidence estimated to be 2.6 per million people.

Takayasu's arteritis

- Two phases:
- Systemic phase patients have signs of an active inflammatory illness
- Constitutional symptoms
  - fever
  - Fatigue
  - Weight loss
  - Arthritis
  - Aches and pains.
Takayasu's arteritis

- Occlusive phase:
  - Patients begin to develop symptoms caused by the narrowing of affected arteries.
  - Pain that occurs with repetitive activities (claudication)
  - Dizziness upon standing, HA, and visual problems.
  - Some of the vessels may be so narrowed that arterial pulses cannot be felt. (pulseless dx)
Takayasus arteritis

• Diagnosis: can be very difficult
• Unfortunately, it is very common for the disease to smoulder in the walls of large blood vessels for years, causing non-specific symptoms.
• Until major complications such as stretching of the aortic valve, stroke, etc.
• Once the diagnosis is suspected, it is confirmed with angiogram and MRI.
Takayasu's arteritis angiographic picture
Takayasu's arteritis CT findings

• CT typically shows thickening high attenuation of the involved vessels wall usually the thoracic aorta or brachiocephaic artery and frequent mural calcification.
Treatments

- Therapy relies on aggressive immunosuppression and such, complications of therapy are common and may be severed.
- The degree of immunosuppression is titrated to reflect the severity of the disease so that disease control is achieved while minimizing the potential side effects.
Treatment

• To this end the European Vasculitis Study Group (EUVAS) is recommended based on disease classifications
  - Limited
  - Early, generalized
  - Active, generalized
  - Severe
  - Refractory
• Limited: localized disease of upper airways
• These patients have no systemic symptoms, end organ function not threatening and no renal involvement
• As such therapy can often be limited to a single agent such as corticosteroids, azathioprine or methotrexate
• Early, Generalized: Is distinguished from active, generalized disease by whether or not organ function is threatened
• For the two classes of the disease the first line of therapy has remain cyclophosphamide plus corticosteriod
• Acceptable regimen finding increasing favor is methotrexate plus corticosteriods has more (favorable side-effect)

• Supported by mtx vs cyclophosphomide studies for early and active generalized disease.
Treatment

• Active, generalized disease:
• Use of oral cyclophosphamide plus oral corticostriod remain the first-line of therapy.
• There is now evidence that therapy with pulse IV cyclophosphamide may be as effective as oral with few side effects.
• However, the dialy Oral Vs Pulse cycophosphamide for renal vasculitis by EUVAS comparing the efficacy of both therapy has not been published.
Treatment

• Severe disease: defined by the presence of severe renal involvement (creatinine con > 5.7)
• DAH or other life-threatening disease
• Such patient should receive a combination therapy consist of cylophosphamide, corticosteroids, and plasma exchange
• Based on several case reports and case series of 20 pts published by Klemmer et al, this strategy also appear to be effective for treatment of DAH
### Table 2—EUVAS Grading of Disease Severity and First-Line Treatment Options for Induction Therapy*

<table>
<thead>
<tr>
<th>Disease Classification</th>
<th>Constitutional Symptoms</th>
<th>Renal Function</th>
<th>Threatened Organ Function</th>
<th>Treatment Options for Induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited</td>
<td>No</td>
<td>Serum creatinine &lt; 120 μmol/L (1.4 mg/dL)</td>
<td>No</td>
<td>Corticosteroids OR methotrexate OR azathioprine</td>
</tr>
<tr>
<td>Early, generalized</td>
<td>Yes</td>
<td>Serum creatinine &lt; 120 μmol/L (1.4 mg/dL)</td>
<td>No</td>
<td>Cyclophosphamide + corticosteroids or methotrexate + corticosteroids</td>
</tr>
<tr>
<td>Active, generalized</td>
<td>Yes</td>
<td>Serum creatinine &lt; 500 μmol/L (5.7 mg/dL)</td>
<td>Yes</td>
<td>Cyclophosphamide + corticosteroids</td>
</tr>
<tr>
<td>Severe</td>
<td>Yes</td>
<td>Serum creatinine &gt; 500 μmol/L (5.7 mg/dL)</td>
<td>Yes</td>
<td>Cyclophosphamide + corticosteroids + plasma exchange</td>
</tr>
<tr>
<td>Refractory</td>
<td>Yes</td>
<td>Any</td>
<td>Yes</td>
<td>Consider investigational or compassionate use agents (see text)</td>
</tr>
</tbody>
</table>

*Data are from references 67, 83, 86, 97, 116, and 121–127.*
TREATMENT

- Refractory Disease: patient who have not responded to cytotoxic agents, high dose corticosteroids or plasma exchange
- Therapies with agents such as (novel agents/ biological agents)
  - Infliximab
  - Rituximab
  - Antithymocytes globulin have been suggested.
Treatment

- Maintenance: therapy is less aggressive than induction therapy
- Associated with less adverse effects
- Following the induction of remission with agent such as cyclophosphamide, pts are converted to azathioprine or methotrexate with low dose corticosteroid
- If pts unable to tolerate azathioprine or mtx, second line agent include mycophenolate mofetil or cyclosporine.
- The timing of the transition from induction to maintenance, has been subject of debate some suggest 12 month cause of induction tx, other support clinical criteria.
- Chest 2006;129;452-465.
Treatments

• Interesting studies by WGET trial
• Prospective, observational cohort analysis of multicenter, randomized, double blind, placebo-controlled treatment trial
• 180 patients assessed for occurrence of DVT and PE.
• 13 patients had DVT/PE before enrollment
• 16 DVT/PE occurred in 167 pts during 228 person-year of prospective follow-up
• 7 per 100 vs 1 per 100 in SLE.
• Ann Intern Med 2005;142:620-6
Treatment

- Relapse is associated with viral or bacteria infection (S.aureus)
- Nasal carriage rate for S.aureus is higher in WG pts.
- Trimethoprim 160mg + sulmethoxazole 800mg/d is effective
- Remission rate 82% sulfur Vs 60% no sulfur
- 20% had side effect due to sulfur
Treatment

• Novel/ biological agents:
  • Rituximab is a monoclonal anti-CD 20 antibody that targets a subset of B lymphocytes
  • The result of a series of 11 patients with active ANCA-associated vasculitis, who had either received maximal doses of cyclophosphamide or contraindications were treated with rituximab.
  • The authors found they were able to induce remission in all 11 pts and ANCA titer become undetectable in 8 of 11 pts.
  • Rituximab may be useful in treatment of refractory vasculitis.
Treatment

- Anti-T-cell (antithymocyte globulin)
- A (EUVAS –sponsored ) open –lable study of 15 pts with refractory WG.
- Were treated with ATG found 13 of 15 achieved either a partial (9 out of 15) or complete. 4 out 15 achieved complete disease remission. 2 pts died of DAH and infection
- Given the poor prognosis of severe, refractory ANCA-associated vasculitis, ATG should be considered for these type of patients.
Treatment

- For takayasu: may rarely spontaneously remit or stabilized
- Corticosteroid, required for all patients
- Often dramatically relieve symptoms and lessen vascular complications
- Prednisone 60mg po once/day until symptoms subsides, tapered 5mg/day q2wk until the dose is 10mg/day.
Treatment

• Treatment may be necessary for many months or years
• Duration is guided by symptoms, signs, vascular images and ESR, active disease can be present despite normal ESR.
• Methotrexate and other cytotoxic agents can be added in corticosteroid resistant cases.
• Asprin may be helpful
• Hypertension should be treated aggressively with ACE Inhibitors (renovascular)