Recent advances in the classification and management of pulmonary small vessel vasculitides

Dr. Aditya Jindal
5/8/11
• The vasculitides are a set of related disorders characterized by blood vessel inflammation leading to tissue or end-organ injury

• Differentiated from other vascular disorders by the presence of inflammation of the vessel wall as compared to bland vasculopathy
## The Vasculitides

### Primary Vasculitis

- Small-vessel vasculitis
  - Wegener granulomatosis
  - Microscopic polyangiitis
  - Churg-Strauss vasculitis
- Medium-vessel vasculitis
  - Polyarteritis nodosa
  - Kawasaki disease
- Larger-vessel vasculitis
  - Takayasu arteritis
  - Giant cell arteritis

### Immune Complex-Mediated Vasculitis

- Goodpasture syndrome
- Henoch-Schönlein purpura

### Secondary Vasculitis

- Infection
- Malignancy (paraneoplastic)
- Drug-induced vasculitis
- Connective tissue diseases
- Antiphospholipid antibody syndrome
- Inflammatory bowel disease
- Essential cryoglobulinemia

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Classification
To understand a name you must be acquainted with the particular of which it is a name

- Bertrand Russel
Explanation of terminology used for naming, defining classifying, and diagnosing diseases

<table>
<thead>
<tr>
<th>Term</th>
<th>Explanation</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic term</td>
<td>The name of a disease</td>
<td>Wegener's granulomatosis</td>
</tr>
<tr>
<td>Definition of disease</td>
<td>Abnormalities in a patient that warrant assignment of the diagnostic term</td>
<td>Granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium-sized vessels (e.g., capillaries, venules, arterioles, and arteries)</td>
</tr>
<tr>
<td>Classification criteria</td>
<td>Observations that classify a patient into a standardized category for study</td>
<td>Two or more of the following criteria: 1) nasal or oral inflammation, 2) chest radiograph showing nodules, fixed infiltrates, or cavities, 3) hematuria or red cell casts in urine sediment, 4) granulomatous inflammation on biopsy (ACR Committee criteria [9])</td>
</tr>
<tr>
<td>Diagnostic criteria</td>
<td>Observations that demonstrate or confidently predict the presence of the defining features of the disease in a patient</td>
<td>Not yet documented. This would need to be determined by analysis of larger numbers of patients in whom the defining features are unequivocally present</td>
</tr>
</tbody>
</table>

## ACR classification criteria

<table>
<thead>
<tr>
<th>Condition</th>
<th>Criteria</th>
</tr>
</thead>
</table>
| **WG** | Nasal or oral inflammation  
Abnormal chest radiograph  
Active urinary sediment  
Granulomatous inflammation on biopsy  
≥2 of 4 criteria to meet classification as WG |
| **CSV** | Asthma  
Eosinophilia  
Mono- or polyneuropathy  
Pulmonary infiltrates  
Paranasal sinus abnormality  
Extravascular eosinophils  
≥4 criteria to meet classification as CSV |
| **MPA** | No separate classification from classic polyarteritis nodosa |

Sensitivity ➔ 71.0% - 95.3%  
Specificity ➔ 78.7% - 99.7%

Limitations

1. ANCA → developed afterwards

2. No distinction made between poly arteritis nodosa and MPA

3. Evolving diagnostic techniques and pathophysiology has made distinction easier

4. Not intended to be used as diagnostic but as classification criteria
Chapel Hill Consensus Conference (CHCC)

• Held at Chapel Hill, North Carolina

• Goals
  – To reach consensus on the names for some of the most common forms of noninfectious systemic vasculitis
  – To construct root *definitions* for the vasculitides so named

<table>
<thead>
<tr>
<th>Large vessel vasculitis</th>
<th>Medium-sized vessel vasculitis</th>
<th>Small vessel vasculitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giant cell (temporal) arteritis</td>
<td>Polyarteritis nodosa† (classic polyarteritis nodosa)</td>
<td>Wegener’s granulomatosis‡</td>
</tr>
<tr>
<td>Takayasu arteritis</td>
<td>Kawasaki disease</td>
<td>Churg-Strauss syndrome‡</td>
</tr>
<tr>
<td><strong>Medium-sized vessel vasculitis</strong></td>
<td><strong>Small vessel vasculitis</strong></td>
<td><strong>Microscopic polyangiitis† (microscopic polyarteritis)‡</strong></td>
</tr>
<tr>
<td>Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules.</td>
<td>Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels (e.g., capillaries, venules, arterioles, and arteries). Necrotizing glomerulonephritis is common.</td>
<td>Necrotizing vasculitis, with few or no immune deposits, affecting small vessels (i.e., capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs.</td>
</tr>
<tr>
<td>Arteritis involving large, medium-sized, and small arteries, and associated with mucocutaneous lymph node syndrome. Coronary arteries are often involved. Aorta and veins may be involved. Usually occurs in children.</td>
<td>Henoch-Schönlein purpura</td>
<td>Vasculitis, with IgA-dominant immune deposits, affecting small vessels (i.e., capillaries, venules, or arterioles). Typically involves skin, gut, and glomeruli, and is associated with arthropathies or arthritides.</td>
</tr>
<tr>
<td>Essential cryoglobulinemic vasculitis</td>
<td>Essential cryoglobulinemic vasculitis</td>
<td>Vasculitis, with cryoglobulin immune deposits, affecting small vessels (i.e., capillaries, venules, or arterioles), and associated with cryoglobulins in serum. Skin and glomeruli are often involved.</td>
</tr>
<tr>
<td>Cutaneous leukocytoclastic angiitis</td>
<td>Cutaneous leukocytoclastic angiitis</td>
<td>Isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis.</td>
</tr>
</tbody>
</table>

• **Wegener’s granulomatosis**
  – Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels (e.g., capillaries, venules, arterioles, and arteries)

  – *Necrotizing glomerulonephritis is common*

• **Churg-Strauss syndrome**
  – Eosinophil-rich and granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels, and associated with asthma and eosinophilia.
• Microscopic polyangiitis

  – Necrotizing vasculitis, with few or no immune deposits, affecting small vessels (i.e., capillaries, venules, or arterioles)

  – Necrotizing arteritis involving small and medium sized arteries may be present

  – Necrotizing glomerulonephritis is very common

  – Pulmonary capillaritis often occurs
• Recognised that histological samples would not be always available

• Introduced concept of surrogate markers and ANCA

**Limitations**

• Neither diagnostic nor classification criteria
• **Sorensen et al** tested the CHCC for diagnosis and found that only 8 of 27 patients were diagnosed with Wegener’s granulomatosis, and 3 of 12 cases with microscopic polyangiitis.

Surrogate parameters for vasculitis
• New diagnostic criteria:

  – Wegener’s granulomatosis
    1. Biopsy or surrogate parameter for granulomatous inflammation in the respiratory system
    2. Biopsy verified necrotising vasculitis in small to medium sized vessels or biopsy/surrogate parameter for glomerulonephritis or positive PR3-ANCA test
    3. Lack of eosinophilia in blood and biopsy samples
– Microscopic polyangiitis

1. Biopsy verified necrotising vasculitis in small vessels and/or glomerulonephritis with few or no immune deposits

2. Involvement of more than one organ system as indicated by biopsy verified vasculitis in small to medium sized vessels or surrogate parameter for glomerulonephritis

3. Lack of biopsy and surrogate parameter for granulomatous inflammation in the respiratory system

• Lane et al evaluated the Sorensen criteria and found that

  – They were not useful for MPA

  – The exclusion of eosinophilia limited the usefulness of the criteria for WG

• An algorithm to classify ANCA associated vasculitis for epidemiological studies was developed that included MPA and incorporated ANCA

• Known as the **EMEA (European Medicine Agency)** algorithm

• However, this was too cumbersome to use in individual patients
  
Recent revision of the classification scheme based on

1. The traditional approach of classifying vasculitis by size of predominant vessel involved

2. Diagnostic auto-antibodies (ANCA)

3. Current understanding of pathogenesis

Diagnostic and Classification criteria in Vasculitis (DCVAS)

• A major international effort to use data-driven methods to develop
  – A revised single classification system for the vasculitides
  – A validated set of diagnostic criteria for the vasculitides in accordance with standards established by the ACR and the European League Against Rheumatism (EULAR)

• NCT01066208

• Started in February 2010 and expected to be complete by July 2012
Granulomatosis with polyangiitis (Wegener’s)

- The term *Wegener’s granulomatosis* was introduced into the English-language literature by Drs Godman and Churg in 1954

- The name change was triggered by evidence that Dr Friedrich Wegener was a member of the Nazi party before and during World War II

- The parenthetical reference to Wegener’s will be phased out after several years as the new usage becomes more widely known
Management
• Treatment protocols have changed in the last two decades after the first wave of the EUVAS (European vasculitis study group) trials

• EUVAS criteria are objective disease classification instruments that have been developed to assist the clinician in categorizing disease severity so that therapies may be appropriately titrated to disease activity and the associated risk of end-organ injury and/or mortality.
<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localised</td>
<td>Upper and/or lower respiratory tract disease without any other systemic</td>
</tr>
<tr>
<td></td>
<td>involvement or constitutional symptoms</td>
</tr>
<tr>
<td>Early</td>
<td>Any, without organ-threatening or life-threatening disease</td>
</tr>
<tr>
<td>systemic</td>
<td></td>
</tr>
<tr>
<td>Generalised</td>
<td>Renal or other organ threatening disease, serum creatinine &lt; 500 µmol/litre</td>
</tr>
<tr>
<td></td>
<td>(5.6 mg/dl)</td>
</tr>
<tr>
<td>Severe</td>
<td>Renal or other vital organ failure, serum creatinine &gt; 500 µmol/litre</td>
</tr>
<tr>
<td></td>
<td>(5.6 mg/dl)</td>
</tr>
<tr>
<td>Refractory</td>
<td>Progressive disease unresponsive to glucocorticoids and cyclophosphamide</td>
</tr>
</tbody>
</table>

A. Localised disease

- Refers to isolated upper or lower airway disease and a complete absence of other end organ involvement or constitutional symptoms

- Managed with topical therapy, corticosteroids, and/or a single moderate potency cytotoxic agent such as methotrexate or azathioprine
B. Early generalised disease

- Presence of constitutional symptoms and active vasculitis but without any specific threat to organ function
- Standard therapy → Cylophosphamide + steroids

- NORAM (Non-Renal Alternative with Methotrexate) trial
  - Compared methotrexate with cyclophosphamide for the induction of remission in early disease
  - Time to remission (5 m vs 3 m)
  - Relapse rate (74% vs 42%) favored cyclophosphamide
– Methotrexate was better tolerated and had less side affects
  • de Groot K, Rasmussen N, Bacon PA, et al. Randomized trial of
cyclophosphamide versus methotrexate for induction of remission
in early systemic antineutrophil cytoplasmic antibody-associated

• **MYCYC (Mycophenolate Mofetil Versus**
  **Cyclophosphamide for Remission Induction ANCA**
  **Associated Vasculitis) trial**

  – EUVAS sponsored randomised controlled trial
  – Compares mycophenolate mofetil with cyclophosphamide for
    the induction of remission
  – Currently underway
C. Generalised active disease

• Presence of constitutional symptoms and threatened organ function caused by vasculitic activity
• Oral cyclophosphamide plus steroids → standard therapy since the 1970s

• CYCLOPS (Daily Oral Versus Pulse Cyclophosphamide for Renal Vasculitis) trial
  – 149 patients with newly diagnosed generalized active AAV were randomized to pulse intravenous cyclophosphamide (15 mg/kg every 2–3 weeks) or daily oral cyclophosphamide (2 mg/kg/d) plus prednisolone
– No difference in time to remission or proportion of patients who achieved remission (88.1% vs 87.7% at 9 months)

– Pulse group had a lower rate of leukopenia and received a lower total cumulative dose of cyclophosphamide

D. Severe disease

• Presence or threat of immediate organ failure and/or death
  – Rapidly progressive glomerulonephritis and renal failure (creatinine >5.7 mg/dL)
  – Alveolar hemorrhage associated with respiratory failure
  – Cardiomyopathy with heart failure
  – Life-threatening arrhythmias
  – Central nervous system disease
  – Gastrointestinal disease with bowel ischemia or life-threatening hemorrhage

• Standard treatment → Plasma exchange + i/v cyclophosphamide + steroids
• MEPEX (Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis)

– EUVAS sponsored randomised controlled trial
– 137 patients with a new diagnosis of AAV and a serum creatinine level greater than 500 mmol/L (5.8 mg/dL) were included
– All patients received standard therapy with oral cyclophosphamide and oral prednisolone and were then randomized to either 7 plasma exchanges or 3000 mg of intravenous methylprednisolone
– At 3m → 69% of patients treated with plasma exchange were alive and independent of dialysis compared with only 49% in the methylprednisolone group

• A 20 patient case series showed the efficacy of this treatment strategy in alveolar hemorrhage also
• PEXIVAS (Plasma exchange and glucocorticoid dosing in the treatment of ANCA-associated vasculitis)
  
  – EUVAS sponsored
  – Largest international multicenter trial in vasculitis to date
  – Will include 500 patients with ANCA-associated vasculitis with glomerular filtration rate of less than 50ml/min or lung hemorrhage
  – Started in June 2010
    • www.pexivas.bham.ac.uk,
      http://clinicaltrials.gov/ct2/show/NCT00987389
E. Refractory disease

• Disease that does not respond to conventional accepted therapy
• Investigational or unproven therapies are used

1. Rituximab
   – Targets the CD20 antigen on the surface of B cells and clears circulating B cells from the circulation
   – Evaluated in two recent trials

   – RAVE (Rituximab in ANCA-Associated Vasculitis) trial
     • Multicenter, randomized, double-blind, double-dummy, noninferiority trial
     • Compared rituximab with standard cytotoxic therapy for the induction of complete remission by 6 months in patients with severe ANCA-associated vasculitis
• 64% of the patients achieved complete remission compared to 53% in the cyclophosphamide control arm

• More efficacious than the cyclophosphamide-based regimen for inducing remission of relapsing disease; 34 of 51 patients in the rituximab group (67%) as compared with 21 of 50 patients in the control group (42%) (P = 0.01)

• As effective as cyclophosphamide in the treatment of patients with major renal disease or alveolar hemorrhage

• No significant differences between the treatment groups with respect to rates of adverse events
– RITUXVAS (rituximab versus cyclophosphamide in ANCA associated vasculitis) trial

- 44 patients with newly diagnosed ANCA-associated vasculitis and renal involvement were randomly assigned, in a 3:1 ratio, to a standard glucocorticoid regimen plus
  - either rituximab at a dose of 375 mg per square meter of body-surface area per week for 4 weeks, with two intravenous cyclophosphamide pulses (33 patients, the rituximab group)
  - or intravenous cyclophosphamide for 3 to 6 months followed by azathioprine (11 patients, the control group)

- 76% patients in the rituximab group and 82% patients in the control group had a sustained remission (P = 0.68)

- Severe adverse events occurred in 14 patients in the rituximab group (42%) and 4 patients in the control group (36%) (P = 0.77)
• Rituximab-based regimen was not superior to standard intravenous cyclophosphamide for severe ANCA-associated vasculitis
• Sustained-remission rates were high in both groups
• Rituximab-based regimen was not associated with reductions in early severe adverse events

  – Further work is still needed before rituximab is integrated into the standardised management of vasculitis

2. Other agents
   a. Infliximab - chimeric IgGk monoclonal antibody against soluble and membrane-bound TNF
• Has given positive benefit in small trials

b. Anti thymocyte globulin

• Studied in the EUVAS sponsored SOLUTION trial
• 15 patients received ATG for refractory vasculitis
• Partial disease remission was induced in 9/15 and complete disease remission in 4/15
• 2 patients died after drug administration
• 1 of pulmonary hemorrhage
• 1 of infection
• Serum sickness and nonfatal infections were among the notable complications
c. Intravenous immunoglobulin (IVIg)
   • Studied in small clinical trials
   • Effect is generally short-lived
   • Most appropriate in acute situations where conventional therapy is contraindicated especially if severe infection is present

d. WEGENT (Wegener’s Granulomatosis-Entretien) trial
   • 32 induction-refractory (24 WG and 8 MPA) patients were treated with oral CYC in 20 patients, combined with infliximab in 1
   • 15 (75%) achieved remission or low disease activity state, 3 subsequently died of uncontrolled disease and 2 entered remission using several other agents including biological agents

e. Alemtuzumab

f. Deoxyspergualin
F. Remission maintenance

- Less aggressive regimens are used for maintenance of disease remission

- CYCAZAREM (Cyclophosphamide versus Azathioprine for Remission in Generalized Vasculitis) trial
  - EUVAS sponsored randomised controlled trial
  - Patients were initially treated with oral cyclophosphamide and oral prednisolone for induction
  - They were then randomised to
    - Either oral cyclophosphamide for 12 m followed by azathioprine
    - Or directly to azathioprine
No difference in relapse rates (15.5% in the AZA group and 13.7% in the CYC group) [P 0.65; 95% confidence interval (CI) -9.9 to +13.0%] up to the end of the study at 18 months after treatment outset


- IMPROVE (International Mycophenolate Mofetil to Reduce Outbreaks of Vasculitides trial
  - EUVAS sponsored Open-label randomized controlled trial
  - Directly compared mycophenolate mofetil with azathioprine for the maintenance of remission in renal vasculitis
– 156 patients were assigned to azathioprine (n=80) or mycophenolate mofetil (n=76) and followed up for a median of 39 months

– Relapses were more common in the mycophenolate mofetil group (42/76 patients) compared with the azathioprine group (30/80 patients), with an unadjusted hazard ratio (HR) for mycophenolate mofetil of 1.69 (95% confidence interval [CI], 1.06-2.70; P=.03)

– Severe adverse events did not differ significantly between groups

• WGET (Wegener Granulomatosis Etanercept Trial)
  – Concluded that Etanercept has no role

• REMAIN (Randomized Trial of Prolonged Remission Maintenance Therapy in Systemic Vasculitis)
  – Ongoing EUVAS trial
  – Will compare 24 months of therapy with 48 months of therapy
• Leflunomide
  – A small trial compared leflunomide with methotrexate
  – Showed superiority in the leflunomide arm
<table>
<thead>
<tr>
<th>Disease Severity</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 +/- topical therapies</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 (mycophenolate + corticosteroids is currently under investigation)</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 (eg, rituximab)</td>
</tr>
<tr>
<td>Remission</td>
<td>No</td>
<td>Serum creatinine $&lt;120$ μmol/L (1.4 mg/dL)</td>
<td>No</td>
<td>Azathioprine +/- low-dose corticosteroids Mycophenolate +/- low-dose corticosteroids Leflunomide +/- low-dose corticosteroids</td>
</tr>
</tbody>
</table>

EULAR recommendations for the management of primary small and medium vessel vasculitis

1. Patients with primary small and medium vessel vasculitis should be managed in collaboration with, or at centres of expertise

2. ANCA testing (including indirect immunofluorescence and ELISA) should be performed in the appropriate clinical context

3. A positive biopsy is strongly supportive of vasculitis and the procedure is recommended to assist diagnosis and further evaluate patients suspected of having vasculitis

4. A structured clinical assessment, urine analysis and other basic laboratory tests at each clinical visit for patients with vasculitis should be done
5. Patients with ANCA-associated vasculitis should be categorised according to different levels of severity to assist treatment decisions.

6. A combination of cyclophosphamide (intravenous or oral) and glucocorticoids is recommended for remission induction of generalised primary small and medium vessel vasculitis.

7. A combination of methotrexate (oral or parenteral) and glucocorticoid as a less toxic alternative to cyclophosphamide for the induction of remission in non-organ threatening or non-life threatening ANCA-associated vasculitis is recommended.

8. The use of high-dose glucocorticoids as an important part of remission induction therapy is recommended.
9. Plasma exchange for selected patients with rapidly progressive severe renal disease in order to improve renal survival is recommended

10. Remission-maintenance therapy with a combination of low-dose glucocorticoid therapy and, either azathioprine, leflunomide or methotrexate is recommended

11. Alternative immunomodulatory therapy choices should be considered for patients who do not achieve remission or relapse on maximal doses of standard therapy: these patients should be referred to an expert centre for further management and enrolment in clinical trials

Additional points

• Dosage and schedule of cyclophosphamide
  – 15 mg/kg (maximum 1.2 g) iv infusion every 2 weeks for first three doses f/b every 3 weeks for next 3 – 6 doses
  – Dose adjustment can be made based on creatinine levels

• Oral prednisolone or prednisone at 1 mg/kg/day is started alongside and maintained for 1 month, and should not be reduced to less than 15 mg/day for the first 3 months → then tapered to a maintenance dose of 10 mg/day or less during remission

• When a rapid effect is needed, intravenous pulsed methylprednisolone may be used in addition to the oral prednisolone as part of remission induction therapy
• Remission maintenance therapy should be continued for at least 18 months

• The addition of trimethoprim/sulphamethoxazole (800/160 mg twice daily) to standard remission maintenance can reduce the risk of relapse in WG

• Prophylaxis against Pneumocystis jiroveci in all patients being treated with cyclophosphamamide; with trimethoprim/sulphamethoxazole (800/160 mg on alternate days or 400/80 mg daily) is recommended
• Thromboembolic disease in the setting of AAV

  – The Wegener’s Clinical Occurrence of Thrombosis (WeCLOT) study identified that the incidence of thromboembolic disease in patients with WG was 7.0 per 100 person-years, which is the same rate of venous thromboembolic (VTE) disease as for patients with a known prior history of VTE

  – Clinicians should consider patients with AAV to be at higher risk for VTE

Alveolar hemorrhage (AH)

- Defined as bilateral alveolar infiltrates on radiological imaging without an alternative explanation plus at least one of the following
  - Hemoptysis
  - Increased carbon monoxide diffusing capacity
  - Bronchoscopic evidence of hemorrhage
  - Unexplained drop in hemoglobin

- Vasculitis was the third most common cause of AH requiring intensive care support (19% of patients), after thrombocytopenia (27%) and sepsis (22%)

• The majority (80%) of these vasculitis cases with AH are due to ANCA associated vasculitis (AAV)

• AH is the most common respiratory manifestation of AAV, occurring in 24%
• 95% of AH due to pauci immune vasculitis are ANCA +

• AH appears similar in the PR3-ANCA and MPO ANCA groups with regard to clinical features and severity of respiratory failure

• Mild AH is more common (in 24 to 28% of AAV)

• 28% of patients may retrospectively report previous symptoms suggestive of AH for >12 months before diagnosis
Treatment

• Treatment decisions are made based on the EUVAS disease severity grading

• AH may fit into almost any of the categories depending on the disease severity
  – Mild AH without impairment of pulmonary function
  – Moderate AH resulting in impaired pulmonary function but not requiring mechanical ventilation
  – Severe AH requiring respiratory support
  – Refractory AH
• Mild – moderate AH
  – Treated in the same way as mentioned earlier
  – Rituximab has been used in this setting

• Severe AH
  – Cyclophosphamide + glucocorticoids + /- Plasma exchange
  – Recombinant, activated factor VII → useful in case reports in life threatening, uncontrollable AH
  – Extracorporeal membrane oxygenation (ECMO)
At the end

• The prognosis of the pulmonary small vessel vasculitides has improved markedly in the last few years provided timely diagnosis is made and adequate treatment instituted.

• The results of the various trials going on would probably lead to major changes in the nomenclature, classification and management of these disorders.