WEGENER ‘S GRANULOMATOSIS

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WEGENER’S GRANULOMATOSIS

- A rare primary systemic vasculitis (PSV) of childhood.
- Necrotizing granulomatous inflammation of small to medium vessels.
- Typically affecting the upper and lower respiratory tract and the kidneys.
- Incidence 0.03-3.2 per 100,000 children per year.

Arthritis & Rheumatism 2009; 60(11): 3413-24
**Definition and classification criteria of WG**

<table>
<thead>
<tr>
<th>ACR 1990 criteria (2/4)</th>
<th>EULAR/PRESS criteria (3/6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Nasal or oral inflammation</td>
<td>- Nasal or sinus inflammation</td>
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<tr>
<td>- Abnormal chest radiograph (nodules, fixed infiltrates or cavities)</td>
<td>- Abnormal chest radiograph or chest CT scan</td>
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<tr>
<td>- Abnormal urinary sediment (microhematuria or red cell cast)</td>
<td>- Abnormal urinalysis (hematuria and/or significant proteinuria)</td>
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<tr>
<td>- Granulomatous inflammation on biopsy</td>
<td>- Granulomatous inflammation on biopsy/necrotizing pauci-immune GN</td>
</tr>
<tr>
<td></td>
<td>- Subglottic, tracheal, or endobronchial stenosis</td>
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<td></td>
<td>- Anti-PR3 ANCA or c-ANCA staining</td>
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*Source: Arthritis & Rheumatism, Vol. 6, No.11, Nov 2009, p 3413-3424 (American College of Rheumatology 2009)*
Clinical subgroup of WG according to the definitions of the EUVAS

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Organ involvement</th>
<th>Constitutional Symptoms</th>
<th>Presence of ANCA</th>
</tr>
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<tbody>
<tr>
<td>Localized</td>
<td>Upper and/or lower respiratory tract</td>
<td>No</td>
<td>+/-</td>
</tr>
<tr>
<td>Early systemic</td>
<td>Any except renal or imminent organ failure</td>
<td>Yes</td>
<td>Usually +</td>
</tr>
<tr>
<td>Generalized</td>
<td>Renal with serum creatinine ( \leq 500 \mu\text{mol/l} ) and/or other imminent organ failure</td>
<td>Yes</td>
<td>+</td>
</tr>
<tr>
<td>Severe renal</td>
<td>Renal with serum creatinine ( &gt; 500 \mu\text{mol/l} )</td>
<td>Yes</td>
<td>+</td>
</tr>
<tr>
<td>Refactory</td>
<td>Progressive disease despite therapy with corticosteroids and cyclophosphamide</td>
<td>Yes</td>
<td>+/-</td>
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</table>

EUVAS = The European Vasculitis Study Group
Pathophysiology: granulomatous lesion
- WG starts as granulomatous disease in the respiratory tract and systemic vasculitis develops subsequently.
  - early foci of fibrinoid necrosis could be a consequence of PR3-ANCA-induced necrotizing capillaritis.
  - the granulomatous lesion are built up by CD4⁺ T-cells, CD8⁺ T-cells, histiocytes, CD20⁺ B-lymphocytes, neutrophil granulocytes, CD68⁺ macrophages and CD68⁺ multinucreated giant cells surrounding a central necrosis
Pathophysiology: granulomatous lesion
- the central necrosis show an irregular serpiginous pattern coined “geographic necrosis”
- a palisade of epitheloid histiocytes may arrange around the necrotic foci
- the center of the necrosis is acellular or contains PMN leukocytes.
Pathophysiology: **vasculitis**
- the necrotizing vasculitis predominantly affects small vessels and medium-sized vessels
- endothelial cells are the target of the initial injury (swelling, necrosis and deadherence)

In the lung:
- capillaries, venules and arterioles are infiltrated by PMN
- pulmonary microvascular necrotizing capillaritis is the cause of pulmonary hemorrhage
WEGENER’S GRANULOMATOSIS

- Pathophysiology: **vasculitis**
  - **In the kidney**: rupture of the basement membrane subsequent to neutrophil degranulation rise to glomerular capillary thrombosis followed by a cascade of focal segmental crescentic glomerulonephritis
    - the vasculitis is call “pauci-immune” because of few or no immunoglobulin and/or complement deposits are detected.
  - **The skin**: cutaneous vascular immune complex deposits
Pathophysiology: **PR3-ANCA**
- PR3 is the principal target antigen of ANCA
- the detection of PR3-ANCA is highly specific for WG
- interaction of PR3-ANCA with PR3 released from azurophilic granula results in premature degranulation of neutrophil granulocytes, subsequent endothelial cell damage and leukocyte recruitment
**Clinical features**

The most common signs and symptoms at diagnosis
- sinusitis 61%
- lung disease 22-45%
- arthritis/arthalgias 30%
- fever 22 %
- eye disease 13%
- rash 9%
- glomerulonephritis 6%

heterogeneity of organ involvement, mainly affecting the upper airways, lungs and kidneys
Clinical features: upper respiratory tract
- nasal obstruction
- bloody nasal discharge or frank epistaxis
- crusting or mucosal ulcerations
- hoarseness
- chronic sinusitis
- otitis media and mastoiditis
- hearing loss
- saddle nose deformity, septum perforation and inspiratory stridor due to subglottic stenosis are symptoms during later disease stages
WEGENER’S GRANULOMATOSIS

- Clinical features: **lower respiratory tract**
  - ulcerating tracheobronchitis
  - bronchus stenoses subsequent to granulomatous inflammation
  - cavitation of lung nodules
  - asymptomatic, persistent cough, dyspnea, hemoptysis, respiratory failure

- **Common CXR findings**
  - fleeting or persistent densities (67%)
  - nodules (58%)
  - focal atelectasis, pleural effusion, pulmonary hemorrhage, mediastinal or hilar node enlargement are less frequent
- a : nasal deformity (saddle nose)

- b : x-ray film of the neck showing subglottic stenosis

- c : MRI of the neck showing subglottic stenosis

- d : pulmonary involvement
WEGENER’S GRANULOMATOSIS

- Clinical features: **renal involvement**
  - necrotizing glomerulonephritis
  - asymptomatic microhematuria
  - RPGN
  - renal failure with oliguria
  - renal hypertension
- histopathology
  - diffuse extracapillary necrotizing (pauci-immune) glomerulonephritis with necrotizing arteriolitis
Clinical features: **ocular manifestations**
- scleritis
- conjunctivitis
- uveitis
- optic neuritis
- retro-orbital pseudotumor
Clinical features: skin involvement
- skin rash
- erythematous or pruritic macules
- massive nodules
- necrotizing vasculitic ulcerations and gangrene
Clinical features: other manifestations
- joint involvement: arthralgia of the knees, hips, wrists or ankles
- constitutional symptoms: malaise, fever, night sweat and weight loss
- full-blown generalized WG is the pulmonary-renal syndrome
Based on the typical organ involvement confirmed by the histopathological demonstration of vasculitis, granulomatous inflammation and necrosis.

- The vasculitis usually involves small arteries and veins.
- The granulomas may be discrete or confluent with irregular patterns.
ANCA

- a cytoplasmic pattern of ANCA (c-ANCA) was detected in 70-90% of patients with active WG.
- its target antigen was to be PR3
- c-Antineutrophilic cytoplasmic antibodies (c-ANCA) or antibodies to proteinase-3 are highly specific for WG (90-97%).
Diagnosis

- **Biopsy**
  - should be taken to confirm the diagnosis of vasculitis.
    - cutaneous, nasal, transbronchial and renal biopsy
    - **lung biopsy**: the combination of granulomas and vasculitis as well as vasculitis, necrosis and granulomatous inflammation.
    - **renal biopsy**: segmental necrotizing glomerulonephritis, usual focal.
DIAGNOSIS

- **Serologic parameters**
  - elevated ESR, CRP
  - CBC : mild leukocytosis, thrombocytosis, normochromic anemia
    - normo or hypercomplementemtic
    - the soluble IL-2 receptor (sIL-2R) which is shed from lymphocytes activation, use for monitoring disease activity and indicate relapse.
    - UA : a nephritic sediment with dysmorphic erythrocyturia and protienuria indicates renal involvement.
Technical procedures
- CXR: assessment of lung infiltrate and pleural effusion.
  - HRCT: assess pulmonary involvement.
  - BAL: suggestive of alveolitis or pulmonary hemorrhage, helpful in excluding opportunistic infections.
- Abdominal U/S: assess kidney size and renal parenchyma.
- MRI: assessment sinusitis, mastoiditis, orbital granuloma, cerebral vasculitis.
- Echocardiography: assess cardiac involvement.
1. Remission induction therapy

“Standard of care”
- cyclophosphamide 2 mg/kg/day for 1 year post-remission then reduced by 25 mg every 2-3 months.
+ prednisolone 1 mg/kg/day for 1 month, reducing to 10-20 mg/day by 12 weeks.
- to reduce long-term risk of cyclophosphamide, intravenous pulse protocol should be used.
- more relapse in the pulse cyclophosphamide group.
“alternative care, the EUVAS study”
- methotrexate and prednisolone for induction of remission in non-life-threatening, non-renal “early systemic WG”
TREATMENT

- **2. Remission maintenance therapy**
  - continuing oral cyclophosphamide.
  - substitute methotrexate or azathiopine after 3-6 months of cyclophosphamide.
  - persistent ANCA positivity after induction therapy is associated with almost 80% relapse rate at 4 years.
Therapy and selected clinical parameters of patients followed for > 6 months (pediatric WG at SickKids 1984-2005, n = 20)

<table>
<thead>
<tr>
<th>Therapeutic Regimen</th>
<th>No.</th>
<th>Median F/U (mo.)</th>
<th>Median no. flares (range)</th>
<th>Median time to first flare (mo.)</th>
<th>Median time to first additional agent (mo.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid only</td>
<td>3</td>
<td>32.7</td>
<td>3.0(0-4)</td>
<td>6.6</td>
<td>25.6</td>
</tr>
<tr>
<td>Steroid + poCYC</td>
<td>4</td>
<td>44.3</td>
<td>2.0(0-10)</td>
<td>10.1</td>
<td>18.1</td>
</tr>
<tr>
<td>Steroid + ivCYC</td>
<td>2</td>
<td>29.1</td>
<td>2.5(2-3)</td>
<td>18.6</td>
<td>19.5</td>
</tr>
<tr>
<td>Steroid + ivCYC switched to AZA (n=3) or MTX (n=4)</td>
<td>7</td>
<td>28.8</td>
<td>1.0(0-3)</td>
<td>7.9</td>
<td>12.6</td>
</tr>
<tr>
<td>Steroid + MTX (n=2) / AZA (n=2)</td>
<td>4</td>
<td>48.6</td>
<td>2.5(2-4)</td>
<td>17.7</td>
<td>25.5</td>
</tr>
</tbody>
</table>
**RCT for ANCA-associated vasculitis (AAV)**

<table>
<thead>
<tr>
<th>RCT</th>
<th>CYCAZAREM</th>
<th>WGET</th>
<th>NORAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Aims</td>
<td>Maintenance of remission CYC vs AZA</td>
<td>Maintenance of remission Etanercept vs placebo</td>
<td>Induction of remission CYC vs MTX</td>
</tr>
<tr>
<td>- Patients</td>
<td>Generalized AAV (n=155) WG=95, MPA=60</td>
<td>WG=180 (generalized:128, localized:52)</td>
<td>Early non-renal mild AAV WG=89, MPA=6</td>
</tr>
<tr>
<td>- Results</td>
<td>93%</td>
<td>Eta 91%, pla 92% (NS)</td>
<td>NS</td>
</tr>
<tr>
<td><em>rates of induction of remission</em></td>
<td>AZA 16%, CYC 14% (NS) WG 18%, MPA 8% (p=0.03)</td>
<td>NS</td>
<td>MTX 90%, CYC 94% (NS)</td>
</tr>
<tr>
<td><em>rates of relapse</em></td>
<td>NS</td>
<td>Malignancy Eta:6, pla:0</td>
<td>MTX 70%, CYC 47% (p=0.02)</td>
</tr>
<tr>
<td><em>severe adverse effect</em></td>
<td>8</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td><em>death</em></td>
<td>4</td>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>
3. prophylactic treatment
- trimethoprim-sulfamethoxazole reduces respiratory and non-respiratory tract infection.
- nasal mucipirocin ointment may be helpful to eliminate nasal carriage of *Staphylococcus aureus*. 
4. Treatment of refractory disease
- TNF-α blocking agents
  : monoclonal anti- TNF-α antibody (infliximab )
  : human soluble p75 TNF-α receptor fusion protein (etanercept ) .
- anti-B-cell therapy with anti-CD20 antibody ( rituximab )
- IVIG ( total dose 2g/kg )
- T-cell depletion with anti-thymocyte globulin ( ATG )
4. Treatment of refractory disease
- plasmapheresis and immunoabsorption have been applied as adjunctive therapy in severe cases with kidney involvement
- currently recommended indications are concurrent anti-GBM, pulmonary hemorrhage and requiring dialysis during the acute phase.

Allergology International.2007;56:87-96
The Birmingham Vasculitis Activity Score (BVAS/WG)

**PR3-ANCA**
- PR3 is the principal target antigen of ANCA
- the detection of PR3-ANCA is highly specific for WG
- positive c-ANCA and PR3-ANCA titres during follow up identify patients at increased risk of relapse.

Antimyeloperoxidase antibodies (Anti-MPO)
- useful marker of disease activity and a good predictor of relapse in anti-MPO-associated vasculitides (MPA, WG, CSS)

Inflammatory biological variables
- CRP
- ESR

Ann Rheum Dis 2009;68;p 1564-1571
Disease remission and relapse

- more than 80% of patient with WG now survive for longer than 5 years.
- relapse was associated with less intensive initial treatment, lower cyclophosphamide doses and shorter duration of prednisolone with dose > 20 mg/day.
- the clinical individual relevance of rising ANCA titers remain unclear.
Disease-related morbidity and mortality

- permanent morbidity was significantly different from adult: nasal deformity (48% vs 25%)
  subglottic stenosis (35% vs 9%)
- chronic renal failure as a major point of long-term morbidity.
- significant prognostic factors for mortality were age and serum creatinine level at time of referral.