Wegener’s Granulomatosis
• Definition
• History
• Epidemiology
• Clinical symptoms
• Pathophysiology
• Treatment
Wegener granulomatosis (WG) is a complex, immune-mediated disorder, which along with microscopic polyangiitis and Churg-Strauss syndrome, comprises a category of small vessel vasculitis related to antineutrophil cytoplasmic antibodies (ANCAs), characterized by a paucity of immune deposits.
1931: **Klinger** described a 70-year-old physician with constitutional symptoms, joint symptoms, proptosis, widespread upper respiratory tract inflammation, saddle nose deformity, glomerulonephritis, and pulmonary lesions.

1936: **Wegener** reported three patients with similar clinical features and published his findings on their distinct clinical and histopathologic findings. Postulated ‘septic’ vasculitis.

1954: **Goodman and Churg**: definitive description of WG characterized by triad of pathological features:

1) systemic necrotizing angiitis
2) necrotizing granulomatous inflammation of the respiratory tract
3) necrotizing glomerulonephritis
Epidemiology of WG

- Incidence in US: appx. 10 per million
- Prevalence in US: appx. 3 per 100,000 persons.
- Much higher prevalence as 80% of 5-year survival with treatment.
- Age specific increase: peak age 65-74
- More common in individuals of northern European descent
- Slight male predominance
Clinical Features of Wegener’s Granulomatosis

<table>
<thead>
<tr>
<th>General</th>
<th>Major</th>
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<tbody>
<tr>
<td>Weight loss</td>
<td>Glomerulonephritis progressing to renal failure: 70-80% with WG</td>
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<tr>
<td>Malaise</td>
<td>Lung involvement: pulmonary hemorrhage, granulomas</td>
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<tr>
<td>Fever</td>
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<tr>
<td>Arthralgia</td>
<td></td>
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<tr>
<td>Myalgia</td>
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<tr>
<td>Upper respiratory tract disease</td>
<td></td>
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<td>Mouth ulcers</td>
<td></td>
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<td>CNS manifestation</td>
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Renal Pathology

- Early
  **Fibrinoid necrosis** of capillary loops

- Later
  Diffuse proliferative, pauci-immune
  GN with basement membranes
  ruptures and cells in Bowman’s space
  with **crescent formation**.

- End-Stage
  Sclerosed glomeruli

Main pathologic difference between WG and MPA is the absence of
granulomatous inflammation in MPA
ANCAs are directed against antigens (PR3 (C-ANCA), MPO (P-ANCA)) present within the primary granules of neutrophils and monocytes; these antibodies produce tissue damage via interactions with primed neutrophils and endothelial cells.
Risk Factors / Initiating Events

- Infection (Anti LAMP2 / mimicry)
- Genetic factors (PTPN22)
- Drugs (thiol, hydrazine containing compounds)
- Alpha-1 antitrypsin deficiency (AAT is primary in vivo inhibitor of PR3)
- Environmental Exposure (silica dust, mercury, lead)
ANCA in WG

- Anti-Proteinase 3 (PR3) in 70 to 80% of patients
- Anti-Myeloperoxidase (MPO) in approximately 10%
- New ANCA subtype: auto-antibodies to lysosomal associated membrane protein-2 (LAMP-2) present in almost all individuals with FNGN
Pathogenicity of ANCA

- **Animal Model:**

  MPO knockout mice immunized with mouse MPO $\rightarrow$ formation of anti-MPO splenocytes and anti-MPO antibodies

  RAG-2 deficient mice (lacking T- and B- cells) that received anti-MPO splenocytes developed crescentic GN and systemic necrotizing vasculitis. Immunization with non-MPO antibody producing splenocytes displayed only a mild immune complex GN.

  RAG-2 deficient and wild-type mice were injected with anti-MPO developed a pauci-immune glomerulonephritis.

- **Human Model:**

  Placental transmission of maternal anti-MPO antibodies caused pulmonary-renal syndrome in the newborn. Syndrome resolved after treatment with glucocorticoids and supportive therapy, and with the eventual disappearance of maternal ANCA.

LAMP-2 in WG / Molecular Mimicry

- prevalence twice that of anti-MPO and anti-PR3 in FNGN

- Human LAMP-2 epitope (P41-49) has 100% homology with bacterial adhesion molecule FimH (P72-80) of gram negative bacteria (E. Coli, Klebsiella, Proteus)

- Rats immunized with FimH develop pauci-immune FNGN and also develop antibodies to rat and human LAMP-2

- monoclonal antibody to human LAMP-2 induces apoptosis of human microvascular endothelium in vitro.

- 9 of 13 patients (69 percent) were infected with bacteria expressing FimH (most commonly E. Coli) in the 12 wks before the clinical presentation of ANCA-positive FNGN, suggesting the presence of molecular mimicry

Exposure to FimH during infection induces synthesis of antibodies to an epitope shared by FimH (P72-80) and hLAMP-2 (P41-49)

ANCA production

- Autoantibody response to exposed epitopes of target antigen (PR3, MPO)
- Auto-antigen complementarity
- Role of T Cells (higher CD4+ T cell and monocytic activation, high levels of Th1 cytokines, TNF alpha, IFN-gamma)
- B-Cell activation (target for rituximab)
- Neutrophil activation (Th1 stimulates neutrophils/monocytes)
- Endothelial cell
- Frequent disease flare with infection (“primed neutrophils”)
Model of Pathogenesis of Granulomatous Inflammation in WG
Therapeutic Immune Response Targets

In Wegener granulomatosis, an inciting antigen (perhaps proteinase 3 [PR3]) activates dendritic cells.\(^a\)

Antigen-loaded activated dendritic cells travel from the lungs to peripheral lymph nodes and present antigen to naive CD4+ T cells, which differentiate into activated antigen-specific T cells.

Interleukin 12 (IL-12) produced by activated dendritic cells skew the T cells to a type 1 helper (Th1) phenotype.

Proliferating activated Th1 cells return to the lungs where antigen persists. Interferon γ (IFN-γ) and tumor necrosis factor α (TNF-α) secreted by Th1 cells (predominantly CD4+ CD28−) induce macrophage migration and maturation and eventual granuloma formation and tissue destruction.

Chronic T cell activation may promote affinity maturation of autoreactive B cells that results in secretion of PR3-antineutrophil cytoplasmic antibodies (ANCA) in the granulomas.\(^b\)

Treatment

Consists of two phases:

1. Remission induction

2. Remission maintenance
# EULAR Classification

<table>
<thead>
<tr>
<th><strong>Category</strong></th>
<th><strong>Definition</strong></th>
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<tbody>
<tr>
<td>Localized</td>
<td>Upper and/or lower respiratory tract disease without any other systemic involvement or constitutional symptoms.</td>
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<tr>
<td>Early systemic</td>
<td>Any, without organ-threatening or life-threatening disease</td>
</tr>
<tr>
<td>Generalized</td>
<td>Renal or other organ-threatening disease, serum creatinine $\leq 5.6$ mg/dL (500 micromol/L).</td>
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<tr>
<td>Severe</td>
<td>Renal or other vital organ failure, serum creatinine $\geq 5.7$ mg/dL (500 micromol/L)</td>
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<tr>
<td>Refractory</td>
<td>Progressive disease unresponsive to glucocorticoids and cyclophosphamide.</td>
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Remission Induction

**Cyclophosphamide** is started at 1.5-2mg/kg/d PO or 0.5 to 1g/m2/month IV until stable remission induced. (3-6 months)
- Alkylates guanidine nucleotides
- Blocks cell division
- Lymphopenia, mainly of B cells
- Reduces antibody levels

Daily PO vs. monthly IV show similar rate of remission. Daily PO has lower rate of relapse and higher rate of leukopenia/infection. (CYCLOPS trial)

**Glucocorticoid Pulse** with methylprednisolone 7-15mg/kg to max. 1000mg/day for 3 days, then 1mg/kg/d prednisone po daily for 2-4 weeks then taper, if significant improvement is seen, decreased by 5mg/wk.

Glucocorticoid monotherapy is NOT generally considered, given low remission rate compared to cyclophosphamide (56 versus 85 percent) and higher relapse rate.

Combination Rx induces remission in 85-90% of patients usually in 2-6months, about 75% experiencing complete remission

randomized trial of 149 patients with ANCA-associated vasculitis
- pulse IV cyclophosphamide (15 mg/kg every 2 to 3 weeks) or
- daily oral cyclophosphamide (2 mg/kg per day until remission then
1.5mg/kg for 3 months).

No difference in the time to remission or the percentage of patients who achieved remission by 9 months (88 percent in both groups)

After remission, 19 (14.5 percent) relapsed (10 major and 9 minor). More relapses in the IV pulse cyclophosphamide group (13 versus 6), however not statistically significant and study was not designed or powered to assess an effect on relapse.

Pulse cyclophosphamide was associated with a significantly lower cumulative cyclophosphamide dose (8.2 versus 15.8 g) and a lower rate of leukopenia (26 versus 45 percent).

CYCLOPS

Figure 2. Time to remission (Kaplan-Meier curves) for the pulse and daily oral cyclophosphamide groups.

<table>
<thead>
<tr>
<th>Time to Remission, mo</th>
<th>Daily oral</th>
<th>Pulse</th>
<th>Daily oral—censored</th>
<th>Pulse—censored</th>
</tr>
</thead>
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<tr>
<td>0.0</td>
<td>73</td>
<td>76</td>
<td>43</td>
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<td>2.0</td>
<td>43</td>
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</tr>
<tr>
<td>4.0</td>
<td>18</td>
<td>15</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>6.0</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
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Sample sizes are listed for each group: missing data are from patients who were withdrawn or died.

Figure 4. Measures of disease activity for the pulse and daily oral cyclophosphamide groups.

Rituximab vs. Cyclophosphamide

- Cyclophosphamide a/w severe side effects, incl. leukopenia, infections, bladder injury, cancer, ovarian failure.

- B-cell level correlate with disease activity calling for B-cell targeted therapy

- Treatment with rituximab has led to remission rates of 80 to 90% among patients with refractory ANCA-associated vasculitis.

- Uncontrolled studies suggest that rituximab is effective and may be safer
RITUXIVAS

44 Patients underwent randomization

Both received Glucocorticoid

33 Were assigned to rituximab group

6 Died before 12 mo
1 at 0 mo
3 at 2 mo
1 at 3 mo
1 at 10 mo

27 Remained in trial at 12 mo

33 Were included in analysis at 12 mo

11 Were assigned to control group

1 Died before 12 mo
(at 0 mo)

10 Remained in trial at 12 mo

11 Were included in analysis at 12 mo

Primary endpoint:
sustained remission
BVAS of 0 for 6 mths

Adverse events


Rituximab
375mg/m²/wk  x 4wks
+ 2 IV cytoxan pulses

IV cytoxan monthly for 3-6months then Azathioprin

Both received

Primary endpoint:
sustained remission
BVAS of 0 for 6 mths

Adverse events

RITUXIVAS

- Sustained-remission rates were not superior in rituximab group. In both groups >90% of survivors had sustained remission.

- Rituximab not a/w reductions in early severe adverse events. (42% vs 36%)
Rituximab 375mg/m²/wk x 4wks + daily placebo-cytoxan
Pt w/ remission between 3-6m, switched from placebo-cytoxan to placebo-AZA

Inclusion criteria:
+ ANCA, severe disease, BVAS >3

Primary: BVAS of 0 and successful prednisone taper at 6 months
Secondary: BVAS 0 w/ <10mg prednisone at 6 months, rates of adverse events.

RAVE

• In RAVE trial rate of adverse events was equivalent in the 2 study groups.

• Also showed elevated number of malignant conditions within short period.

• Rituximab was superior to po cytoxan for the induction of remission in relapsing disease.

• Confounding effect of glucocorticoid therapy >> long term data needed to answer question of duration of remission, incidence of remission in rituximab+glucocorticoid group.
Plasmapheresis / MEPEX trial

- 137 patients with new Dx of WG/MPA, Cr > 5.7 mg/dL. 69% required HD

- 3 months survival (69% vs 49%)

- Reduced progression to ESRD at 1 year (19% vs 42%)

- No difference in mortality at one year (27% vs 24%)

Figure 1. Enrollment, patient survival, and renal outcome during the trial.

Plasmapheresis for Pulmonary Hemorrhage

- No randomized trial performed in ANCA vasculitis, only retrospective review of 20 patients with diffuse alveolar hemorrhage (DAH) and ANCA-associated small vessel vasculitis.

- All patients underwent daily full plasma volume plasma exchange until DAH improved, which was then changed to alternative day apheresis therapy until the DAH resolved.

- All received IV methylprednisolone (7 mg/kg per day) for 3 days, and all but 2 received intravenous cyclophosphamide (0.5 g/m2 of body surface area).

- DAH resolved in all 20 patients, with the mean number of apheresis treatments being 6.15 (range of 4 to 9). There were no complications due to apheresis. 1 patient died because of a pulmonary embolism. Among the 7 patients who did not require dialysis, the serum creatinine fell significantly by the time of discharge (4.5 to 2.4 mg/dL (398 to 212 micromol/L)).