Core Curriculum Course Nephrology 2017

Vascular and glomerular diseases

Part I: vasculitis and systemic diseases: pathophysiology, diagnosis and treatment

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Nomenclature of vasculitides

• **Definition**: Vasculitis is an inflammation of blood vessel walls which must be present at least at some time during the course of the disease. Some vasculitides have characteristic tissue injury unrelated to vasculitis.

• **Vasculitis categorization according to**:
  • Type of vessel affected
  • Etiology
  • Pathogenesis
  • Type of inflammation
  • Organ distribution
  • Clinical manifestations
  • Genetic predisposition
  • Demography

*Jennette et al. Arthritis and Rheum. 2013*
First: type (size) of vessels

**Large vessels** → aorta and his branches

**Medium vessels** → visceral arteries and veins

**Small vessels** → intraparenchymal vessels

**LVV (large vessel vasculitis):** affects large arteries more often than other categories of vasculitis.

**MVV** → predominantly medium arteries or veins

**SVV** → predominantly small arteries or other small vessels
Large vessel vasculitis

- Large vessels may not be the predominant type of vessels affected and large artery injury may not be the cause of the most significant morbidity
- Aspecific clinical signs: fever, arthragia, weight loss + ischemia ↔ narrowing of vessels

**Renovascular hypertension** TAK >> GCA

<table>
<thead>
<tr>
<th>TAK</th>
<th>GCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Often granulomatosis</td>
<td></td>
</tr>
<tr>
<td>Arteries supplying extremities</td>
<td>Carotid and vertebral arteries</td>
</tr>
<tr>
<td>Giant cells</td>
<td></td>
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<tr>
<td>&lt; 50 years</td>
<td>&gt; 50 years</td>
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<tr>
<td>Often named temporal arteritis</td>
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</table>

**Treatment:**
- CS 0.5 - 1 mg/kg 1-2 month and tapper – CYC when refractory
- ACEi if HTN or indication of bypass surgery
Medium vessel vasculitis (Polyarteritis nodosa: PAN)

• (Kawasaki disease: infants and young children with mucocutaneous lymph node syndrome and coronary artery lesions)

• **PAN**: 40-60 years, more acute and necrotizing than LVV

• Aspecific symptoms: fever, arthralgias, myalgias, weight loss

• + peripheral neuropathy (mononeuritis)

• GI involvement 50% (pain, blood in the stool) 
  → rare bowel infarction or perforation

• **Renal involvement**  → infarction and hemorrhage
  + HTN

• Red inflammatory nodules on the skin
Polyarteritis nodosa

• **Pathology:**
  - Necrotizing arteritis
  - Segmental transmural fibrinoid necrosis with infiltrating leukocytes (neutrophiles or later mononuclear cells)
  - Presence of pseudoaneurysms

• **Diagnosis:**
  - **No** GN, No lesion in small vessel and NO ANCA
  - Angiography show pseudoaneurysm

• **Treatment:**
  CS + CYC
  CS alone if < 50 y, NO cardiac, gut and renal involvement
  Association with Hep B → CS 1mg/kg 1 wk + antiviral
  + PEX *(Guillevin et al. J Rheumatol 1993)*
  Case reports with Rituximab
# Small vessel vasculitides

<table>
<thead>
<tr>
<th>ANCA-associated vasculitis (AAV)</th>
<th>Immune complex SVV</th>
</tr>
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<tbody>
<tr>
<td>Microscopic polyangeitis (<strong>MPA</strong>)</td>
<td>Anti-GBM disease (<strong>anti-GBM</strong>)</td>
</tr>
<tr>
<td>Granulomatosis with polyangeitis (<strong>GPA</strong>)</td>
<td>Cryoglobulinemic vasculitis (<strong>CV</strong>)</td>
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<tr>
<td>Eosinophilic granulomatosis with polyangeitis (<strong>EGPA</strong>)</td>
<td>IgA vasculitis (<strong>IgAV or HS</strong>)</td>
</tr>
<tr>
<td><strong>Single organ AAV</strong></td>
<td>Hypocomplementememic urticarial vasculitis (<strong>HUV or anti-C1q vasculitis</strong>)</td>
</tr>
<tr>
<td>Intraparenchymal artery vasculitis</td>
<td></td>
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<tr>
<td>Necrotizing vasculitis</td>
<td></td>
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<tr>
<td><strong>ANCA⊕ MPO or PR3</strong></td>
<td><strong>Anti-GBM</strong></td>
</tr>
<tr>
<td><strong>ANCA⊖ = seronegative AAV</strong></td>
<td><strong>Cryoglobulins</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Low complement</strong></td>
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</table>
ANCA-associated SVV (AAV)
## ANCA-associated vasculitis

<table>
<thead>
<tr>
<th></th>
<th>MPA</th>
<th>GPA</th>
<th>EGPA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Necrotizing arteritis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No granulomatosis</td>
<td>90</td>
<td>80</td>
<td>45</td>
</tr>
<tr>
<td>Skin</td>
<td>40</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>Lungs</td>
<td>50</td>
<td>90</td>
<td>70</td>
</tr>
<tr>
<td>Ear, nose, throat</td>
<td>35</td>
<td>90</td>
<td>50</td>
</tr>
<tr>
<td>Musculo-skeletal</td>
<td>60</td>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td>Neurologic</td>
<td>30</td>
<td>50</td>
<td>70</td>
</tr>
<tr>
<td>GI system</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

Jennette et al Arthritis Rheum 2013
Jennette et al AJKD 1994
Pathophysiology of AAV

• ANCA are pathogenic: clinical evidence

  • Correlation between ANCA titer and
    • Response to treatment
    • Recurrence of the disease

  Boomsma Arthritis Rheum 2000

• Efficacy of anti B cells and PEX
  Stone NEJM 2010
  Falk NEJM 2010
  Szpirt NDT 2011

• Transplacental passage of MPO-ANCA induced
  pneumo-renal syndrome in neonate
  Schlieben AJKD 2005
Pathophysiology of AAV

• **ANCA are pathogenic: In vitro evidence**

  • **ANCA IgG activate neutrophils**
    • Oxygen radical $P^\circ$ and degranulation
    • Sensitization of neutrophils by low dose TNF$\alpha$ increase the reaction

  *McGrath CJASN 2011*  *Falk Proc Natl Acad Sci 1990*  *Charles J Leukoc Biol 1991*

  • **ANCA bind Fc receptors + cross-linking with Fab’2**
    • Same neutrophil, adjacent neutrophil and floating Ag-ANCA complex

  *Williams JASN 2003*  *Savage Adv Exp Med Biol 1993*

    • MPO and PR3 released at the site of inflammation $\rightarrow$ bind endothelial cells $\rightarrow$ ANCA binding and complement activation

  *Yang Am J Pathol 2001*

  • **Endothelial injury by ANCA activated neutrophils**

  *Kessenbrock Nat Med 2009*  *Ewert KI 1992*  *Mulder Clin Exp Immunol 1995*
Pathophysiology of AAV

• **ANCA are pathogenic: Animal models**

  • **MPO-ANCA IgG → NCGN in mice**
    - MPO KO mice → immunization → Ab transfer to WT mice
      The severity of the disease depends on the mouse strain
      - *Xiao J Clin Invest 2002*  
      - *Xiao Lab Investig 2010*
    - Depletion of neutrophils by NIMP-R14 → no disease
      - *Xiao Am J Pathol 2005*
    - BMTx from MPO KO to WT mice → NCGN
      - *Schreiber JASN 2006*

  • **Alternative complement pathway activation**
    - Complement depletion (cobra venom factor), C5 KO mice, Factor B KO Mice → No NCGN
      - *Xiao Am J Pathol 2007*
    - **ANCA activated neutrophils → C3a and C5a**
    - **C5 inhibiting monoclonal Ab (BB5.1) → No NCGN**
      - *Huugen KI 2007*
Pathophysiology of AAV

• Immunogenesis of the ANCA autoimmune response: Role of neutrophils

  • Neutrophils do not normally express ANCA Ag unless they are stimulated (TNFα)

    McGrath CJASN 2011
    Falk Proc Natl Acad Sci 19900
    Charles CJASN 1991
    Mulder Clin Exp Immunol 1995

• In case of degranulation → NETs
  • Neutrophil Extracellular Traps – Chromatine strands decorated with cytoplasmic proteins (including MPO and PR3)
  • NETs are particularly effective at dysplaying Ag to dendritic cells → internalization and presentation of the Ag on HLA molecules

    Sangaletti Blood 2012
Pathophysiology of AAV

• Immunogenesis of the ANCA autoimmune response: Role of T cells

  • Tregs are abnormal in number and function
    Jennette KI 2010
    Morgan Immunology 2010

  • Increased IFNg- producing T cells
    Chavele Arthritis Rheum 2010

  • IL-23 induces differentiation of CD4+ T cells $\rightarrow$ Th cells $\rightarrow$ production of IL-17, IL-6 and TNFα
    • IL-23 levels correlated with disease activity
    Nogueira NDT 2010
Pathophysiology of AAV

• Immunogenesis of the ANCA autoimmune response: Dysregulation of B cells

• B cells are responsible for the production of antibodies → ANCA

• Bregs CD5+ are in reduced number in AAV patients
  
  Bunch CJASN 2013

• Increased production
  • BAFF (B cell activating factor)
  • BLyS (B lymphocyte Stimulator)
  • Both produced by neutrophils

Krumbholtz J Autoimmun 2005
Sanders Ann Rheum Dis 2006
Nagai Nephron Clin Pract 2011
Genetic predisposition Initiating Ag

FcR

Alternative pathway activation
Pathology of AAV

• Glomeruli
  • Focal fibrinoid necrosis with GBM disruption
  • Crescents
  • No mesangial or endocapillary proliferation
  • Pauci-immunity

• TI
  • Interstitial inflammation
  • Necrotizing medullary capillaritis

• Vessels
  • Fibrinoid necrotizing arteritis with neutrophils
  • Rarely transmural lymphocytic arteritis
Pathology of AAV

- **Glomeruli**
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Extravascular granulomatosis

GPA

EGPA
Treatment of AVV

• No treatment, poor prognosis

• **Treatment for all** except dialysis-dependant patients with severe tubular atrophy and sclerotic injury of nearly all glomeruli

  *de Lind van Wijngaarden JASN 2007*

• **Remission** of 57% of patients with GFR < 10 ml/min

  *Hogan Ann Intern Med 2005*

• 44% of the 69 patient became **RRT free** (MEPEX)

  *Jane JASN 2007*
Treatment of AVV

• Cyclophosphamide (CYC)

  • Addition of CYC to CS improved remission rate from 55 to 85%
    
    *Hogan* Ann Intern Med 2005
    *Nachman* JASN 1996

  • Daily oral or IV pulses
    
    • IV pulses associated with:
      • Half the cumulative dose
      • Less leukopenia
      • Fewer infections
      • Increased number of patients requiring RRT
    
    *Walter* BMC Nephrol 2010

  • Daily oral duration 3 to 6 months (77% + 16% remissions)
    
    *Hogan* Ann Intern Med 2005

  • IV pulse duration max 6 months
    Stop after 3 months if RRT-dependant and no extrarenal active lesions
    
    *de Lind van Wijngaarden* JASN 2007
    *Nachman* JASN 1996
Treatment of AVV

• **Plasmapheresis (PEX)**
  - Indicated in **advanced kidney disease**
    - SCr > 5.66 mg/dl
    - RRT

  *Jane JASN 2007*

• Indicated in **alveolar hemorrhage**
  *Nachman JASN 1996*
  *Holguin Am J Med Sci 2008*

• **MEPEX**
  - 137 p: randomization PEX vs oral CYC
    - 69% vs 39% kidney recovery (3 months)

  *Jane JASN 2007*
Treatment of AVV

• Rituximab (RTX)

  • RITUXVAS trial (n= 44)
    • RTX 375 mg/m$^2$ weekly (x4) + CYC 15 mg/kg IV QOW (2x)
      vs CYC 15 mg/kg IV QOW (3x) + every 3 weeks (total 10 pulses)
    • + CS pulses and oral
    • Similar response rate: 76% vs 82%
      
      *Jones NEJM 2010*

  • RAVE (n = 197)
    • RTX 375 mg/m$^2$ weekly (x4) vs oral CYC 2 mg/kg + CS (5-6 months)
    • Switch to AZA or placebo AZA after remission 3-6 months
    • RTX non-inferior: 64% vs 53% primary end-points (difference not significant)
    • In relapsing disease RTX
      RTX 34/51 (67%) remission vs CYC 21/50 (42%) remission; *p = 0.01*
      
      *Stone NEJM 2010*

• RAVE long term
  Non inferiority maintained until 18 months
  In relapsing disease RTX superior until 12 months (18m, *p = 0.06*)

  *Specks NEJM 2013*
Treatment of AVV

- **Rituximab (RTX):** Belgium 010514
- Reimbursement for GPA and MPA severe and active

1. **Induction of remission**
   a) **Relapse** after remission induced by CYC
   b) **Refractory** to CYC
   c) **CI** to CYC administration
      - Hypersensitivity to CYC
      - Severe medullary depression
      - Severe impairment of liver or kidney function
      - Urinary infection or hemorrhagic cystitis
      - Urinary obstruction
      - Active infection
      - Pregnancy or breast feeding
      - Woman with child desire

2. **BVAS/WG ≥ 3**
## Treatment of AVV

1. **BVAS/WG ≥ 3**

### 1. GENERAL
- a. Arthralgia/Arthritis
- b. Fever (> 38 degrees OC)

### 2. CUTANEOUS
- a. Purpura
- b. Skin Ulcer
- c. *Gangrene

### 3. MUCOUS MEMBRANES/EYES
- a. Mouth ulcers
- b. Conjunctivitis/Episcleritis
- c. Retro-orbital mass/Proptosis
- d. Uveitis
- e. *Scleritis
- f. *Retinal exudates/Hemorrhage

### 4. EAR, NOSE & THROAT
- a. Bloody nasal discharge/Nasal crusting/Ulcer
- b. Sinus involvement
- c. Swollen salivary gland
- d. Subglottic inflammation
- e. Conductive deafness
- f. *Sensorineural deafness

### 5. CARDIOVASCULAR
- a. Pericarditis

### 6. GASTROINTESTINAL
- a. *Mesenteric ischemia

### 7. PULMONARY
- a. Pleurisy
- b. Nodules or Cavities
- c. Other infiltrate secondary to WG
- d. Endobronchial involvement
- e. *Alveolar hemorrhage
- f. *Respiratory failure

* X3
Treatment of AVV

1. BVAS/WG ≥ 3

| 8. RENAL |
|------------------|------------------|
| a. Hematuria (no RBC casts) (> 1 or > 10 RBC/hpf) * | □ | ○ |
| b. *RBC casts and/or Glomerulonephritis on biops |
| Note: If both hematuria and RBC casts are present, score only the RBC casts (the major item) | □ | ○ |
| c. *Rise in Creatinine > 30% or fall in Creatinine clearance > 26% | □ | ○ |

| 9. NERVOUS SYSTEM |
|------------------|------------------|
| a. *Meningitis | □ | ○ |
| b. *Cord lesion | □ | ○ |
| c. *Stroke | □ | ○ |
| d. *Cranial nerve palsy | □ | ○ |
| e. *Sensory peripheral neuropathy | □ | ○ |
| f. *Motor mononeuritis multiplex | □ | ○ |

| 10. OTHER (Describe all items and * items deemed major) |
|------------------|------------------|
| a. | □ | ○ |
| b. | □ | ○ |
| c. | □ | ○ |
| d. | □ | ○ |

* For the Belgian reimbursement, hematuria can be considered as a major item like the RBC casts - cf. publication in the Official Gazette on 18 April 2014.

| 11. TOTAL NUMBER OF ITEMS: |
|------------------|------------------|
| Major New/Worse | □ | □ |
| Minor New/Worse | □ | ○ |
| Major Persistent | □ | □ |
| Minor Persistent | □ | □ |

X3
Treatment of AVV

• **Rituximab (RTX):** Belgium 010514

• **Mode of administration**
  - **Methylprednisolone** 1000 mg/1-3 days before 1st RTX administration
  - **Oral prednisone** 1 mg/kg (methylprednisolone 0.8 mg/kg)
  - **375 mg/m²** at D1, D8, D15 and D22
  - From 50 mg/h to 100 mg/h after 30 min → increase by 50 mg/h every 30 min with a maximum of 400 mg/h
  - **Antibioprophylaxis (Pneumocystis)** → **Trimethoprim** 400 mg/d
# Treatment of AVV

<table>
<thead>
<tr>
<th>Agent</th>
<th>Route</th>
<th>Initial dose</th>
</tr>
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<tbody>
<tr>
<td>Cyclophosphamide(^a)</td>
<td>i.v.</td>
<td>0.75 g/m(^2) (\times) 3-4 weeks. Decrease initial dose to 0.5 g/m(^2) if age &gt; 60 years or GFR &lt; 20 ml/min per 1.73 m(^2). Adjust subsequent doses to achieve a 2-week nadir leukocyte count &gt; 3000/mm(^3).</td>
</tr>
<tr>
<td>Cyclophosphamide(^b)</td>
<td>p.o.</td>
<td>1.5-2 mg/kg/d, reduce if age &gt; 60 years or GFR &lt; 20 ml/min per 1.73 m(^2). Adjust the daily dose to keep leucocyte count &gt; 3000/mm(^3).</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>i.v.</td>
<td>Pulse methylprednisolone: 500 mg i.v. daily (\times) 3 days.</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>p.o.</td>
<td>Prednisone 1 mg/kg/d for 4 weeks, not exceeding 60 mg daily. Taper down over 3-4 months.</td>
</tr>
<tr>
<td>Rituximab(^c)</td>
<td>i.v.</td>
<td>375 mg/m(^2) weekly (\times) 4.</td>
</tr>
<tr>
<td>Plasmapheresis(^d)</td>
<td></td>
<td>60 ml/kg volume replacement. <em>Vasculitis:</em> Seven treatments over 14 days if diffuse pulmonary hemorrhage, daily until the bleeding stops, then every other day, total 7-10 treatments. <em>Vasculitis in association with anti-GBM antibodies:</em> Daily for 14 days or until anti-GBM antibodies are undetectable.</td>
</tr>
</tbody>
</table>
Treatment of AVV

• Mycophenolic acid (MMF): insufficient data

• **Stassen Ann Rheum Dis 2007**
  • 32 patients who could not be treated with CYC
  • *CR in 78% ➔ relapse 52 %*
  • *PR 19% ➔ relapse 100 %*

• **Hu NDT 2008**
  • 35 patients ➔ 18 MMF, 17 CYC
  • Remission 14/18 (77.8 %) MMF vs 8/17 (47.1 %) CYC
  • BVAS more decreased in MMF group

• **Silva CJASN 2010**
  • 13/17 patients MMF + CS ➔ remission
  • 1 relapse after 18 months
Treatment of AVV

- **Maintenance therapy**

- **At least 18 months** (except dialysis-dpt patients with no extrarenal manifestation)
  
  
- **AZA 1-2 mg/kg**  
  *Jane NEJM 2003*

- **MMF 2 x1 g if intolerant to AZA**  
  *Hiemstra JAMA 2010*

- **Trimethoprim-sulfamethoxazole in patients with respiratory tract disease**  
  *Stegeman NEJM 1996*

- **Methotrexate (0.3 mg/kg/wk) if intolerance to AZA and MMF**  
  *Pagnoux NEJM 2008*
Immune complex small vessel vasculitis
Anti-GBM diseases
Anti-GBM disease

• Description of 9 cases in 1958 by Ernest Goodpasture

• Acute renal failure and alveolar hemorrhage

• Another pneumo-renal syndrome

• Between 0.5 to 0.9 cases/million/year (5 to 9 new cases in Belgium/year)

• 2 peaks of occurrence: 20-40 (male) and 60-80 (female)

« The lungs gave the impression of having been injected with blood through the bronchi so that all the air spaces were filled »
Anti-GBM disease: clinical manifestations

• **Kidney**
  - Hematuria with dysmorphic erythrocytes (acantocytes)
  - Proteinuria (rarely nephrotic range)
  - Acute renal failure
  - Bad prognosis: anuria and ESRD

• **Pulmonary hemorrhage**
  - Hemoptysis
  - Dyspnea → respiratory distress
  - Pulmonary fibrosis
  - Pulmonary/subarachnoid hemosiderosis

• **Possible convulsion in case of choroid plexus lesions**
Anti-GBM disease: pathophysiology

- Auto-immunity against $\alpha_3(IV)NC1$: carboxy-terminal part, non-collagenic of type IV collagen

- $\alpha_1$ and $\alpha_2$: ubiquitous.

- $\alpha_3$ to $\alpha_6$: specific.

- $\alpha_3$: GBM, pulmonary alveoles + (cochlea, cornea, Bruch membrane, choroid plexus and some endocrine glands)

- Association with HLA Ag class II:
  - DR15
  - DR4
Anti-GBM disease: precipitating factors

For the disease

• Kidney inflammation

• Kidney trauma

Exposition to $\alpha_3$ chain of type IV collagen?

For alveolar hemorrhage

Hydrocarbon could play a role in conformational change and exposition of neoepitopes of $\alpha_3$-COLIV-NCI
Anti-GBM disease: pathophysiology

- GBM disruption
- Fibrin and fibronectin deposition
- Inflammatory cell chemo-attraction
- Epithelial proliferation
Antibody mediated disease: pathology

**RPGN**

**Crescentic GN**

« One hit disease »

Variable tubular atrophy

Correlation between atrophy and renal prognosis
Anti-GBM disease: pathology

**Immunofluorescence**

- Linear deposition of IgG and C3 (sometimes + IgA)

**Pathognomonic**
Anti-GBM disease: pathophysiology of alveolar lesions

- Alveolar basement membranes normally protected by epithelial cells

- Exposition of the alveolar basement membrane associated to:
  - Toxic substances
  - Tobacco
  - Infections

- Exceptionnal: lesions of the choroid plexus or eye
Anti-GBM disease: pulmonary hemorrhage
Treatment of anti-GBM disease

• No treatment, poor prognosis

• **Treatment for all** except dialysis-dependant patients with 100% crescentic GN and no pulmonary involvement
  
  *Levey Ann Intern Med 2001*

• **Good prognosis when treated**
  
  • Patient survival 67-94% (12 months)
  • Kidney survival 15-58% (12 months)

• **Prognostic factors** for bad kidney survival
  
  • SCr > 5.7 mg/dl
  • Dialysis at presentation
  • 100% crescents

  *Levey Ann Intern Med 2001*
  *Johnson Medicine 1985*
  *Cui Nephron Clin Pract 2005*
Treatment of anti-GBM disease

• **Corticosteroid**
  • IV pulses 3 x 1000 mg
  • 0.6 mg/kg/d and taper over 16 weeks

• **CYC**
  • 2 mg/kg/d orally for 3 months

• **Plasmapheresis**
  • 4-liters exchange daily for 14 days or until anti-GBM undetectable

*Levey Ann Intern Med 2001
Johnson Medicine 1985
Jindal Kidney Int Suppl 1999*
Cryoglobulinemic vasculitides
Cryoglobulinemic vasculitis

- **Cryoglobulins**
  - Immunoglobulins or mixture of immunoglobulins and complement components that precipitate at temperature below 37°
  - Detectable levels of CG w/o clinical expression
    - 15-20% HIV
    - 15-25% connective tissue diseases
    - 40-65% HCV (especially genotype I)
    - 64% HIV + HCV

  
  

- **Cryoglobulinemia**
  - Systemic inflammatory syndrome that involves small-to-medium vessel with vasculitis
  - Prevalence 1/100,000
Cryoglobulinemic vasculitis: Brouet classification

• **Type I (5-25%)**
  • Isolated **monoclonal Ig** (IgG or IgM, rarely IgA or free light chains)
  • Secondary to Waldenström’s macroglobulinemia or multiple myeloma

• **Type II (40-60%)**
  • Mixture of **polyclonal Ig with a monoclonal Ig** (IgM or IgA) with rheumatoid factor activity
  • Often due to persistent viral infections (HCV, HIV)

• **Type III (40-50%)**
  • Polyclonal Ig
  • Often secondary to connective tissue diseases

*Brouet Am J Med 1974*
Cryoglobulinemic vasculitis: Type I

• **Pathogenesis**
  - Lymphoproliferative disorder $\rightarrow$ high levels of monoclonal cryoglobulin $\rightarrow$ hyperviscosity
  $\rightarrow$ Vessel obstruction or inflammatory vasculitis (immune complex deposition)

• **Clinical presentation**
  - Many patients are asymptomatic
  - Signs due to hyperviscosity and thrombosis:
    - Raynaud
    - Digital ischemia
    - **Livedo reticularis**
    - purpura
  - Variable neurologic symptoms due to hyperviscosity
  - Arthralgia or arthritis
  - Renal involvement (30%) $\rightarrow$ thrombotic and hypocellular lesions (not inflammatory GN)
Cryoglobulinemic vasculitis: Type I
Cryoglobulinemic vasculitis: Type I

• Treatment

  • Treatment of the underlying disease

  • Treatment of hyperviscosity syndrome → plasmapheresis
Cryoglobulinemic vasculitis: Type II and III

• **Pathogenesis**
  
  • Chronic inflammatory state (connective tissue diseases or infections)
  • Hyperactivation and/or proliferation of B cells with selective expansion of CG-producing B clone
    
    *Ramos-Casals J Rheumatol 2009*
    *Ferraccioli Clin Exp Rheumatol 1996*
    *De Re Rheumatology 2006*

• **In HCV infections**
  
  • HCV may directly infect B cell (CD81)  *Pileri Science 1998*

  • Ag-specific or non-specific immune complex containing HCV particules may activate B cells
    *Agnello NEJM 1992*
    *Agnello Semin Immunopathol 1997*
    *Charles Blood 2008*

  • Lower number of circulating suppressor T cells in patients with symptomatic CG
    *Boyer Blood 2004*
Cryoglobulinemic vasculitis: Type II and III

• Clinical presentation

• Non-specific symptoms: fatigue
• Skin: purpura, infarction, hemorrhagic crusts, ulcers
• Musculoskeletal: arthralgia or myalgia, arthritis
• Neuropathy: rarely clinically significant
  • EMG abnormalities in 70 to 80 % of the patients
• Pulmonary: mainly subclinical presentation
  • Dyspnea, cough, pleurisy

• Renal: < immune complex disease → MPGN or mesangial proliferation
  → Proteinuria – hematuria; rarely nephrotic or nephritic syndrome
Cryoglobulinemic vasculitis: Type II and III
Cryoglobulinemic vasculitis: Type II and III

• Treatment: Immunosuppressive therapy if rapidly progressive, organ-threatening or life-threatening course of the disease:

  • **GN** associated with rapidly progressive course or nephrotic range proteinuria
  • Severe threatening **digital ischemia** threatening amputation
  • **GI vasculitis** associated with pain or bleeding
  • Rapidly progressive **neuropathy**
  • **CNS vasculitis** → stroke or acute cognitive impairment
  • **Pulmonary vasculitis** associated with pulmonary hemorrhage or respiratory failure
  • **Heart failure**
Cryoglobulinemic vasculitis: Type II and III

**Treatment: 1. Rituximab**

- 64 vs 4 % at 12 months and 61 vs 4 % at 4 months had treatment success (when compared to « conventional » therapy) in 59 patients.
  
  *De Vita Arthritis Rheum 2012*

- 10/12 vs 1/12 remission (6 months) when RTX is compared to current therapy (?)
  
  *Sneller Arthritis Rheum 2012*

- 93 HCV-associated mixed cryoglobulinemia: PegIFN + ribavirin vs RTX followed after 1 month by PegIFN and ribavirin
  
  Same response rate (74 vs 73%) but earlier response with RTX (5.4 vs 8.4 months)
  
  *Saadoun Blood 2010*

- Retrospective study, 87 patients
  
  → complete remission in 44% of neuropathy, 87% of cutaneous ulcers and 95 % of GN
  
  *Ferri Autoimmun Rev 2011*
Cryoglobulinemic vasculitis: Type II and III

- Treatment 1: Rituximab
  - RTX regimen
  - 375 mg/m² at weekly intervals
  - 1000 mg separated by a 2-week interval (day 0 and day 14)
  - 375 mg/m² at weekly intervals followed by additional doses at day 49 and 77
  - Antimicrobial prophylaxis with bactrim

Not available in Belgium in this indication
Cryoglobulinemic vasculitis: Type II and III

• **Treatment:** 2. Cyclophosphamide

  • If RTX unavailable
    • If RTX fails to produce a clinical response
    • If RTX is not tolerated

  • Combined with plasma exchange

  • 2 mg/kg/day orally for 2-4 months

  
  *Dammacco NEJM 2013*
  *Pietrogrande Autoimmun Rev 2011*
  *Sandri Nephron Clin Pract 2011*
  *Frankel Q J Med 1992*
  *Mazzi Int J Artif Organs 1999*
Cryoglobulinemic vasculitis: Type II and III

• **Treatment:** 3. Corticosteroids

  • **Rapid taper** because infections are a common serious complication of immunosuppression in cryoglobulinemia and the risk of viral infection reactivation is high.

  *Landau J Rheumatol 2010*

  • IV methylprednisolone 7.5 to 15 mg/kg 1-3 days
  
  • Followed by 1 mg/kg orally equivalent prednisone 2-4 weeks
  
  • Followed by 40 mg for 2 weeks
  
  • Followed by 20 mg for 2 weeks
  
  • Taper 5 mg/wk
Cryoglobulinemic vasculitis: Type II and III

- **Treatment:** 4. Plasmapheresis
  - **Indicated if:**
    - Hyperviscosity syndrome
    - Life-threatening cryoglobulinemia
    - Rapidly progressive GN (crescentic) who require dialysis
    - **CYC** rather than RTX!
      - D’Amico KI 1989
      - Frankel Q J Med 1992
      - Madore JASN 1996
      - Campise NDT 1999
      - Guillevin Ther Apher Dial 2003
      - Cavallo J Neurol 2009
      - Rockx Transfus Apher Sci 2010
      - Szczepiorkowski J Clin Apher 2010

- **10-14 daily sessions** or **3 sessions/week during 2-3 weeks**

- **3 liters albumin** *(must be warmed !)*
IgA vasculitis (Henoch-Schönlein)
# IgA vasculitis (Henoch-Schonlein): diagnostic criteria

## Table 1

Summary of classification criteria for Henoch-Schonlein purpura (HSP) diagnosis.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR 1990 [9]</td>
<td>≥2 of the following:</td>
</tr>
<tr>
<td></td>
<td>1. Palpable purpura, not thrombocytopenic</td>
</tr>
<tr>
<td></td>
<td>2. Bowel angina</td>
</tr>
<tr>
<td></td>
<td>3. Wall granulocytes on biopsy</td>
</tr>
<tr>
<td></td>
<td>4. Age ≤20 years at disease onset</td>
</tr>
<tr>
<td>Michel et al. 1992 [12]</td>
<td>≥3 of the following: HSP; ≤2 of the following: HV</td>
</tr>
<tr>
<td></td>
<td>1. Palpable purpura, not thrombocytopenic</td>
</tr>
<tr>
<td></td>
<td>2. Bowel angina</td>
</tr>
<tr>
<td></td>
<td>3. Gastrointestinal bleeding</td>
</tr>
<tr>
<td></td>
<td>4. Hematuria</td>
</tr>
<tr>
<td></td>
<td>5. Age ≤20 years at disease onset</td>
</tr>
<tr>
<td></td>
<td>6. No history of medication intake at disease onset</td>
</tr>
<tr>
<td>CHCC 1994 [13]</td>
<td>Vasculitis, with IgA-dominant immune deposits, affecting small vessels (ie, capillaries, venules, or arterioles); typically involves skin, gut, and glomeruli and is associated with arthralgias or arthritis</td>
</tr>
<tr>
<td>Helander et al. 1995 [17]</td>
<td>Palpable purpura, not thrombocytopenic with LCV + ≥3 of the following:</td>
</tr>
<tr>
<td></td>
<td>1. Vascular IgA deposition</td>
</tr>
<tr>
<td></td>
<td>2. Age ≤20 years at disease onset</td>
</tr>
<tr>
<td></td>
<td>3. Gastrointestinal involvement</td>
</tr>
<tr>
<td></td>
<td>4. Upper respiratory tract infection prodrome</td>
</tr>
<tr>
<td></td>
<td>5. Mesangiproliferative glomerulonephritis with or without IgA deposition</td>
</tr>
<tr>
<td>EULAR/PRINTO/PRES 2010 [20]</td>
<td>Palpable purpura, not thrombocytopenic/petechiae (mandatory) + ≥1 of the following</td>
</tr>
<tr>
<td></td>
<td>1. Diffuse abdominal pain</td>
</tr>
<tr>
<td></td>
<td>2. Histopathology: typical LCV with predominant IgA deposits or proliferative glomerulonephritis with predominant IgA deposits</td>
</tr>
<tr>
<td></td>
<td>3. Arthritis or arthralgias</td>
</tr>
<tr>
<td></td>
<td>4. Renal involvement (proteinuria: &gt;0.3 g/24 h or &gt;30 mmol/mg of urine albumin to creatinine ratio on a spot morning sample; and/or hematuria, red blood cell casts: &gt;5 red cells per high power field or ≥2 + on dipstick or red blood cell casts in the urinary sediment)</td>
</tr>
</tbody>
</table>

ACR. The American College of Rheumatology; HV, hypersensitivity vasculitis; CHCC, Chapel Hill Consensus Criteria; LCV, leukocytoclastic vasculitis; EULAR/PRINTO/PRES, European League Against Rheumatism/Paediaetic Rheumatology International Trials Organization/Paediaetic Rheumatology European Society.

Yao-Hsu Autoimmun Rev 2014
IgA vasculitis (Henoch-Schonlein): clinical manifestations

- 70-90% of cases occur < 20 year old (17)
- Rare during summer months
- 50% preceded by an upper respiratory infection (streptococcus)
- Other infectious agents, vaccinations or insect bites have been implicated

Levy Adv Nephrol Necker Hosp 1976
Saulsbury Cleve Clin J Med 2002

- Tetrad:
  - Palpable purpura without thrombocytopenia
  - Arthritis/arthralgia
  - Abdominal pain
  - Renal disease
IgA vasculitis (Henoch-Schonlein): clinical manifestations

• **Skin**
  - Erythematous, macular or urticarial wheals → coalescence → ecchymoses, petechiae and palpable purpura
  - Symetrically distributed

• **Arthritis/arthralgia**
  - Transcient and migratory, oligoarticular
  - No sign of inflammation

• **GI symptoms**
  - Mild: nausea, vomiting, colicky pain, transient ileus
  - Severe: hemorrhage, bowel ischemia and necrosis, perforation, intussusception

• **Renal disease**
  - Hematuria +/- red cell casts +/- proteinuria
  - Rare nephrotic range proteinuria, elevated creatinine levels and HTA
IgA vasculitis (Henoch-Schonlein): pathogenesis

- Deposits are principally composed of IgA 1
- Abnormal glycosylation (deficiency of galactose and/or sialic acid) \( \rightarrow \) decreased hepatic clearance
  
  - Yang Autoimmun Rev 2008
  - Kiryluk KI 2011

- Binding to mesangial cells \( \rightarrow \) proliferation

- IgA autoantibodies
  - IgA rheumatoid factor
  - IgA anticardiolipin
  - IgA antiendothelial cell

  - Saulsbury Zarthritis Rheum 1992
  - Kawakami Br J Dermatol 2006
  - Fujieda Arch Dis Child 1998

- IgA1 of HSP patients bind \( \beta 2 \) glycoprotein 1 (\( \beta 2 \)GP1)

- Crossreaction with endothelial cells \( \rightarrow \) complement-dependent cell lysis

  - Yang Br J Dermatol 2012
IgA vasculitis (Henoch-Schonlein): renal pathology

- Variable mesangial cellularity and expansion (IgA deposition)
- Dominant IgA deposition (+ C3 and IgG) → mesangial and along GBM
- Cellular crescent formation
- EM: amorphous deposits in the mesangium + subendothelial deposits
- Rare necrotizing vasculitis
- Interstitial inflammation
- Acute tubular injury
IgA vasculitis (Henoch-Schonlein): renal pathology
IgA vasculitis (Henoch-Schonlein): Treatment

• Supportive therapy

• **ACEi or ARB** if persistent proteinuria > 0.5 g/d

• **6-months course of CS** if PU > 1 g/d and GFR > 50 ml/min after ACEi or ARB

• **Crescentic HSP** ➔ see AAV
<table>
<thead>
<tr>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated microhaematuria + proteinuria &lt;0.5 g per day, GFR normal, no hypertension</td>
<td>Proteinuria &gt;0.5-1 g per day + reduced GFR + hypertension</td>
<td>Acute or rapid loss of GFR</td>
</tr>
</tbody>
</table>

**Annual or bi-annual monitoring**
- For at least 10 years

**Optimize supportive therapy**
- For 3-6 months

<table>
<thead>
<tr>
<th>GFR &gt;50 ml/min/1.73 m²</th>
<th>GFR 30-50 ml/min/1.73 m²</th>
<th>GFR ≤30 ml/min/1.73 m²</th>
</tr>
</thead>
</table>

**Proteinuria**
- <1 g per day and GFR stable: Continue supportive therapy
- ≥1 g per day and/or GFR decline*: Continue supportive therapy

**Nephrotic syndrome or crescentic GN with RPGN course**
- Continue supportive therapy
- + immunosuppression†

**AKI due to macrohaematuria or other common causes**
- Supportive therapy

---

*Value of immunosuppression unknown. Critically weigh pros and cons.
†No immunosuppression (except if RPGN).
‡6-month course of corticosteroids.

*Floge Nat Review Nephrol 2013*
Systemic lupus erythematosus (SLE)
SLE: clinical manifestations

• Constitutional symptoms
  • Fatigue (80-100%) associated with decreased exercise tolerance
  • Myalgia (no CK)
  • Weight loss (decreased appetite, side effects, gastrointestinal disease)
  • Fever (50%)

• Arthritis (90%)
  • Arthritis with inflammation, migratory and symmetrical, rarely deforming (65-70%)

• Mucocutaneous
  • Butterfly rash
  • Discoid lesions
  • Alopecia
  • Painless oral and/or nasal ulcers (30%)

• Raynaud phenomenon (16-40%)
SLE: clinical manifestations

• **Gastro-intestinal tract**
  • Pancreatitis
  • Colitis
  • Peritonitis
  • Side effects

• **Pulmonary**
  • Pleural effusion → pleurisy
  • Pneumonitis, interstitial lung disease
  • Pulmonary hypertension
  • Alveolar hemorrhage

• **Cardiovascular**
  • Pericarditis
  • Libman-Sachs verrucus endocarditis
SLE: clinical manifestations

- **Neurologic**
  - Cognitive defects
  - Delirium
  - Psychosis
  - Peripheral neuropathies

- **Ophtalmologic**
  - Keratoconjunctivitis sicca (Sjögren)
  - Scleritis or uveitis

- **Hematologic**
  - **Cytopenia**
    - Leukopenia (50%)
    - Mild anemia or hemolytic anemia
    - Thrombocytopenia (acute <-> active disease)
  - **Lymphadenopathy and splenomegaly**
  - **Thrombophilia**
    - Antiphospholipid syndrom
    - Nephrotic syndrom
SLE: Precipitating factors

• UVB exposure

• Infections

• Stress

• Surgery

• Pregnancy
  • Risk of relapse in the immediate post-partum period
  • Hormonal adjuvant for ovulation induction
  • Therapeutic abortions
### SLE: Diagnosis: ACR criteria 1997

- **4/11 criteria**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malar rash</td>
<td>Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds</td>
</tr>
<tr>
<td>Discoid rash</td>
<td>Erythematous raised patches with adherent keratotic scaling and follicular plugging</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>Skin rash as a result of unusual reaction to sunlight</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>Oral or nasopharyngeal ulceration, usually painless</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Nonerosive arthritis involving 2 or more peripheral joints → tenderness, swelling or effusion</td>
</tr>
<tr>
<td>Serositis</td>
<td>Pleurits OR</td>
</tr>
<tr>
<td></td>
<td>Pericarditis</td>
</tr>
<tr>
<td>Renal disorders</td>
<td>Persistent proteinuria &gt; 0.5 g/d OR</td>
</tr>
<tr>
<td></td>
<td>Cellular casts</td>
</tr>
<tr>
<td>Neurologic disorders</td>
<td>Seizures or psychosis</td>
</tr>
<tr>
<td>Hematologic disorders</td>
<td>Hemolytic anemia OR</td>
</tr>
<tr>
<td></td>
<td>Leukopenia (&lt;4000) OR</td>
</tr>
<tr>
<td></td>
<td>Lymphopenia (&lt;1500) OR</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia (&lt; 100.000)</td>
</tr>
<tr>
<td>Immunologic disorders</td>
<td>Anti-DNA OR</td>
</tr>
<tr>
<td></td>
<td>Anti-SM OR</td>
</tr>
<tr>
<td></td>
<td>Positive antiphospholipid antibody (anticardiolipin or lupus anticoagulant)</td>
</tr>
<tr>
<td>Antinuclear antibody</td>
<td>/immunofluorescence</td>
</tr>
</tbody>
</table>
SLE: Diagnosis: SLICC 2012

• 4/17 criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute cutaneous lupus</td>
<td>Malar rash, photosensitive rash</td>
</tr>
<tr>
<td>Chronic cutaneous lupus</td>
<td>Discoid lesions</td>
</tr>
<tr>
<td>Nonscarring alopecia</td>
<td></td>
</tr>
<tr>
<td>Oral or nasal ulcers</td>
<td></td>
</tr>
<tr>
<td>Joint disease</td>
<td>Sinovitis or tenderness</td>
</tr>
<tr>
<td>Serositis</td>
<td>Pleurits or pericarditis</td>
</tr>
<tr>
<td>Renal disorder</td>
<td>Persistent proteinuria &gt; 0.5 g/d or cellular casts</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Seizures or psychosis or mononeuritis multiplex,...</td>
</tr>
<tr>
<td>Hemolytic anemia</td>
<td></td>
</tr>
<tr>
<td>Leukopenia or lymphopenia</td>
<td>&lt; 4000 or &lt; 1000</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>&lt; 100,000</td>
</tr>
<tr>
<td>ANA</td>
<td></td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td></td>
</tr>
<tr>
<td>Anti-Sm</td>
<td></td>
</tr>
<tr>
<td>Antiphospholipid</td>
<td></td>
</tr>
<tr>
<td>Low complement</td>
<td>Low C3 and C4 or low CH50</td>
</tr>
<tr>
<td>Direct Coombs’ test</td>
<td></td>
</tr>
</tbody>
</table>
SLE: Differential diagnosis

- **Rheumatoid arthritis**
  - ANA + in 50% of RA and RF + in 30% of SLE
  - **Anti-cyclic citrullinated peptides (CCP)** more specific of RA

- **Rhupus**
  - Overlapping features of SLE and RA

- **Mixed connective tissue disease**
  - Overlapping features of SLE, scleroderma and polymyositis
  - **Antibodies against U1 ribonucleoprotein (RNP)**

- **Systemic sclerosis (scleroderma)**
  - Raynaud, GO reflux, sclerodactyly, telangiectasias, HTA, ARF
  - **Anti-Scl-70**

- **Sjögren’s syndrome**

- **Behçet’s disease**

- **Dermatomyositis and polymyositis**
  - **Anti-JO-1**
SLE: Clinical renal manifestations

• Renal involvement should be investigated in all patients at repeated interval

• **Proteinuria** > 0.5 g/d

• → nephrotic syndrome

• **Active sediment** with cellular casts and/or leucocyturia

• Variable degree of **renal failure**.

• **No kidney biopsy** if proteinuria < 0.5 g/d, bland urinary sediment and stable renal function
SLE: Pathologic classification: ISN/RPS 2004

• **Class I:** isolated mesangial immune deposits, normal light microscopy

• **Class II:** Mesangial proliferative GN: mesangial hypercellularity and matrix expansion
  Mesangial immune deposit (+ subendothelial ?)

• **Class III:** Focal proliferative GN: < 50% of the glomeruli are affected → active or inactive endo- or extracapillary proliferation
  Subendothelial and mesangial immune deposits
  A, A/C or C

• **Class IV:** diffuse proliferative GN: > 50% of the glomeruli are affected
  Segmental or global (S or G)
  A, A/C or C

• **Class V:** Membranous GN: subepithelial deposits « full house »

• **Class VI:** advanced sclerosing lesions
SLE: Pathologic classification: ISN/RPS 2004
SLE: Treatment: Induction phase

• Class II: mesangial proliferation

  • Proteinuria < 1g/d $\rightarrow$ treat lupus as dictated by the extrarenal manifestations

  • Proteinuria > 3 g/d $\rightarrow$ CS or CNI as for MCNS

  • ACEi.
SLE: Treatment: Induction phase

- **Class III and IV: segmental or diffuse proliferative lupus**
  - **CS:** 1 mg/kg prednison tapering over 6-12 months according to clinical response.
  - **IV CYC:** 1 g/m2 monthly for 6 months
    - **OR** • **IV CYC:** 500mg every two weeks for 3 months (Eurolupus) for caucasians (except maybe rapidly progressive renal disease?)
      - **OR** • **Oral CYC:** \(\rightarrow\) equivalent efficacy, more side effects
      - **OR** • **MMF:** equivalent to oral CYC and IV CYC
      - **OR** • **Enteric-coated MMF:** equivalent

References:
- Austin NEJM 1986
- Boumpas Lancet 1992
- Donadio NEJM 1978
- Gourlet Ann Intern Med 1996
- Houssiau Ann Rheum Dis 2010
- Houssiau Arthritis Rheum 2002
- Chan JASN 2005
- Appel JASN 2009
- Traitanon Lupus 2008
**SLE: Treatment: Induction phase**

- **Class III and IV: segmental or diffuse proliferative lupus**

- **Azathioprine**: same efficacy to induce remission but higher relapse rate and higher risk of doubling SCr  
  *Grootscholten KI 2006*  
  *Grootscholten Arthritis Rheum 2007*

- **Cyclosporine (4-5 mg/kg)**: vs CYC (various regimen) ⇒ no difference in response or remission. No difference in adverse events.  
  *Zavada Lupus 2010*

- **Multitarget therapy**: Tacrolimus (4mg/d) + MMF (1g/d) + Oral CS: vs IV CYC ⇒ 90% vs 45% achieved complete or partial remission (p= 0.002)  
  *Bao JASN 2008*
SLE: Treatment: Class V

• Normal renal function and non-nephrotic proteinuria
  • Antiproteinuric and antihypertensive drugs
    
    Jafar Ann Intern Med 2001
    Wilmer JASN 2003
    Giatras Ann Intern Med 1997

• CS and immunosuppression as dictated by the extrarenal manifestations of Lupus

• Nephrotic proteinuria: Treat
  
  • CS
  • CYC
  • CNI: more relapse after stopping
  • (MMF)
  • (Azathioprine)

  Donadio Adv Nephrol Necker Hosp 1977
  Gonzalez-Dettoni Adv Nephrol Necker Hosp 1985
  Austin JASN 2009
  Austin JASN 2009
SLE: Treatment: Other considerations

- **Hydroxychloroquine (Plaquenyl)** 6-6.5 mg/kg in all patients with LN
  - \( \nabla \) *ESRD, CV events, thrombotic events*

- **Class VI**
  - Treat as dictated by extrarenal manifestations of lupus

- **Relapse**
  - Resume initial effective therapy
  - MMF if risk for excessive CYC exposure

- **Resistant disease**
  - Repeat biopsy
  - Alternative therapy
  - **Rituximab** *Ginzler NEJM 2005, Garcia-Carrasco Lupus 2010*
  - IV Ig *Rauova Lupus 2001*
  - CNI *Ogawa Lupus 2010, Ogawa Mod Rheumatol 2007, Miyasaka Mod Rheumatol 2009*
Pathogenesis of SLE and LN at the basis of new treatment approaches (I)

- **Pathogenesis of autoimmunity outside the kidney**
  - Genetic factors
  - Environmental triggers
  - Impaired silent cell death and dead cell removal
  - Antiviral immunity
  - Aberrant lymphocytes proliferation
  - Flares triggered by transient auto-antigen loads or unspecific immune activation

Lech et al. JASN 2013
Pathogenesis of SLE and LN at the basis of new treatment approaches (II)

• **Pathogenesis of autoimmunity inside the kidney**
  • Accumulation of immune complexes
  • Intra-renal induction of cytokines, chemokines, and adhesion molecules
    • IL-6, IFN-α, TNF-α, ...
    • Activation of complement
  • Insufficient regeneration and tissue scarring

Multiple therapeutic targets

Chan et al. Nat. Rev. Nephrol. 2015
Anti B-cell therapies (I)

- Surface molecules
  - Rituximab, Ocrelizumab, Ofatumumab
  - Epratuzumab
  - Anti-CD19
  - CD40

- Growth/survival factors
  - Belimumab
  - Atacicept
  - Blisibimod
  - Tabalumab

- Immunoglobulin receptors
  - Abetimus sodium

- Proteasomes
  - Bortezomib, Carfilzomib and Delanzomib
Anti B-cell therapies (II)

- **Rituximab (Chimeric anti-CD20 anti-body)**
  - RCT study on add-on therapy (LUNAR)\(^1\)
    - LN patients (III, IV +/- V) (n = 169)
    - Induction by MMF (> 2g/day), CS and Rituximab (1g J1, 15, 168, and 182)
    - **No difference between groups** at 52 weeks for CR
      - No statistical difference on PR (31% in RTX vs 15% in placebo group)
    - Reasons for this failure
      - Follow-up of only 52 weeks
      - High dose of CS for induction
      - Retreated with rituximab half way
      - MMF does not combine well with rituximab\(^2\)
      - Underpowered
    - Analysis of the subgroup of AA, trend towards improved response rates (p = 0.2)
    - Significant serological improvement in the treated group

Anti B-cell therapies (III)

- **Rituximab**
  - Induction therapy (RITUXILUP)\(^1\)
    - Prospective observational study (n = 50)
    - LN (III, IV +/- V)
    - J0 - J14 1g Rituximab (+ 500 mg MP) + MMF (2-3 g per day)
    - 86% (n = 45) at 37 weeks, achieved complete biochemical remission or PR
    - By 1 year, **CR was achieved in 50% (n = 26) and PR in 34% (n = 17)**
    - 12 relapses occurred in 11 patients at a median time of 65 weeks

Anti B-cell therapies (IV)

• **Ocrelizumab (humanized anti-CD20 anti-body)**

  • BELONG study\(^1\)
    - RCT, LN stage III, IV
    - Add-on therapy with CS and MMF or CYC (n = 381)
    - **Terminated early due to increased risk of infections**
      - Principally in MMF group (≥ 1 g IV MP)
    - Renal response rates with Ocrelizumab were numerically but not statistically significant compared to placebo
      - More effective with the Euro-Lupus regimen

Anti BAFF (BLyS) therapies (I)

Anti BAFF (BLyS) therapies (II)

- **Belimumab** (anti-BAFF anti-body)
  - BLISS 52\(^1\) and BLISS 76\(^2\)
  - Phase III, RCT, 52 weeks
  - **Active LN or CNS lupus were excluded**
  - Associated with SOC (no induction treatment)
  - **Higher response rates** with Belimumab than with placebo (p < 0.05)
    - A dose-response pattern
    - Reduced CS used
  - Reducing the risk of severe flare compared to placebo (p = 0.023) and reduced serological activity (p < 0.05)
  - Rates of AEs were not significantly different

Anti BAFF (BLyS) therapies (III)

- Numerical improvement in patients with ≥ 1 g/24h proteinuria
  - Renal Remission rates (A)
  - Time to first renal remission (A)

- Renal flare rate (pooled population) (B)

- Renal SELENA - SLEDAI improvement in patients with baseline renal involvement receiving MMF ($p = 0.03$)

BLISS trials (Dooley et al. Lupus. 2013)
Anti BAFF (BLyS) therapies (V)

- **Atacicept**
  - Recombinant fusion protein
    - Binds BlyS and APRIL
    - Higher immunosuppressive effects
  - **Study from Ginzler et al.**¹
    - Phase II/III RCT, Class III and IV LN
    - Atacicept 150mg + CS and MMF as induction
    - **Stop for high rate of hypogammaglobulinemia and infection**
  - **Study from Isenberg et al.**²
    - Phase I-II RCT, 52-weeks, LN and CNS lupus were excluded
    - Atacicept 150 mg arm
      - **Discontinued prematurely due to two deaths**
      - Suggested **beneficial** effect versus placebo in **flare rates** and time to first flare
    - In the ITT population, no difference in flare rates with Atacicept 75 mg

B-cell therapies in the pipeline

**Blisibimod**
- Fusion protein that binds soluble BAFF
- Study from Furie et al.\(^1\)
  - Primary end point not met (SRI-5)
  - Significantly greater reductions in proteinuria (p=0.045)

**Tabalumab**
- Anti-body that binds both soluble and membrane forms of BLYS
- ILLUMINATE\(^2\) trials
  - ILLUMINATE-2, improvement in SRI-5 (p=0.002)

**Epratuzumab**
- Anti-CD22 anti-body
- Study from Wallace et al.\(^2\)
  - Phase IIb, double-blind RCT
  - Higher response with BILAG endpoint

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Novel B-cell therapies studies

• **Rituximab**
  - In active class III and IV LN, Comparison of the Efficacy of Two Rituximab Treatment Regimens in Patients With LN Resistant to Conventional Treatments (NCT01765842)

• **Rituximab and Belimumab**
  - Treatment of LN with a combination of rituximab and CYC, or a combination of rituximab and CYC followed by treatment with Belimumab. Efficacy and safety of this drug combination (NCT02260934)

• **Ocrelizumab**
  - Parallel-group study designed to evaluate the efficacy and safety of Ocrelizumab added to SOC (CS plus one of two immunosuppressant regimens) compared with placebo added to SOC in patients with Class III or IV LN (NCT00626197)

• **Belimumab**
  - Evaluate the Efficacy and Safety of Belimumab plus SOC vs Placebo Plus SOC in Adult Subjects With Active LN (NCT01639339)

• **Blisibimod**
  - Evaluate the Efficacy and Safety of Blisibimod Administration in Subjects With SLE (NCT01395745)
T-cell co-stimulation modulators (I)

Yujuan et al. NCP.2014
T-cell co-stimulation modulators (II)

**Abatacept**
- Fusion protein that suppresses T cell activation
- **Study from Furie et al.**¹
  - RCT, add-on therapy with CS and MMF for LN III and IV (n = 298)
  - **No statistical difference in CRR**
    - Post hoc analysis (CR criteria from LUNAR trial)
      - CRR over 20% compared with 6% (p < 0.05)
- **Study from Forgosó-Loyo et al.**²
  - ACCESS trial (n = 134)
    - RCT, LN III/V (+/- V)
    - Add-on therapy CYC induction (ELNT) and AZA
  - **Primary end point not met** (CRR)
  - No higher rate of flare in the second part of the study

**Anti-CD40L mAb**
- **Study from Boumpas et al.**³
  - Open label pilot study, LN III/IV (+/- V)
  - **Thrombotic event (MI): stopped the study prematurely**

Novel T-cell co-stimulation modulators studies

• **Abatacept**
  • Phase 3 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Abatacept or Placebo on a Background of MMF and CS in the Treatment of Subjects With Active Class III or IV Lupus Nephritis recruiting now (NCT01714817)

• **Milatuzumab**
  • Anti-CD74 ab, SC at different dose levels for 4 weeks to determine if Milatuzumab helps to control lupus (SLE) (NCT01845740)
Anti-cytokine and anti-inflammatory therapies

Chan et al. Nat. Rev. Nephrol. 2015
Anti-cytokine therapies (I)

• **Sirukumab**
  - Monoclonal antibody specific to IL-6
  - Study from Van Vollenhoven et al.¹
    - RCT, LN III/IV (persistent proteinuria (≥ 0.5 g/d) despite MMF or AZA ± CS, and stable AREB/ACE)
    - **Study was stopped prematurely**
    - Did not achieve a median improvement in proteinuria

• **Tocilizumab**
  - Chimeric IL-6 receptor inhibitor
  - Study from Illei et al.²
    - Open label trial
    - Improvement of SELENA-SLEDAI score and biological parameters
      - Lost after 20 weeks of follow-up
    - **Increased risk of neutropenia**

Anti-cytokine therapies (II)

• **Bindarit**
  - Inhibitor of MCP-1 synthesis
    - Up regulated in patients with acute LN
    - Selectively inhibits mRNA synthesis of MCP-1
  - **Study from Ble et al.**<sup>1</sup>
    - Double-blind, 24 weeks (n=22)
    - Proliferative LN (III/IV)
    - MP 1 g/2days 1 week and tapering down afterwards
    - At week 2 introduction of Bindarit 1200 mg a day
  - **Anti-albuminuric effect**
    - Inhibition of CCL2 production by podocytes
    - No SE and no impact on other urine or blood biomarkers
    - No CYC at induction

Anti-inflammatory therapies

• **Laquinimod**
  - Anti-inflammatory agent (quinolone-3-carboxamide)
    • Reducing pro-inflammatory cytokine and transcription factor
    • Polarizing T cells toward Tregs and away from TH1 and TH17
  - **Study from Jayne et al.**¹
    • Phase IIa, RCT, Placebo-Controlled (24 weeks) (n = 46)
    • Active LN (III/IV), in combination with SOC (MMF and CS)
      • **Greater improvement in kidney function and proteinuria**

• **Anti-TWEAK (BIIB023)**
  - Tumor necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK) and its receptor fibroblast growth factor inducible 14 (FN14)
  - Activates NF-kB in renal tubular cells and promotes renal tubular epithelial cell proliferation, inflammation, and apoptosis
  - Phase 3 LN trial (anti-TWEAK)
    • **Did not demonstrate sufficient efficacy to warrant continuation of the study**

Anti-cytokine therapies in the pipeline (I)

- IFN signature
  - IFN-induced genes correlate with the activity of lupus, LN and damage index

- **Sifalimumab**
  - IFN-\(\alpha\) mAb, blocks most of IFN-\(\alpha\) subtypes
  - Study from Petri et al.\(^1\)
    - Dose dependent reversal of IFN signature in SLE patients
    - **No statistically significant differences in clinical activity**

- **Rontalizumab**
  - Humanised IgG1 antibody against all IFN-\(\alpha\) isoforms
  - ROSE study\(^2\)
    - Moderate to severe **extra-renal** SLE
    - Response rates in BILAG and SRI were identical

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Anti-cytokine therapies in the pipeline (II)

• **Human IFN-α kinoid**
  - **Study from Lauwerys et al.**
    - **IFN-K**, induces polyclonal antibodies that neutralize all 13 subtypes of IFN-α
    - Dose-escalation study vs placebo in 28 women with mild to moderate SLE
    - IFN-K induced anti-IFNα antibodies in all immunized patients
    - Serum complement C3 levels were significantly increased in patients with high anti-IFNα antibody titers

• **Anakinra**
  - **IL-1** antagonist, effective in RA patients
  - Uncontrolled trials have demonstrated beneficial effects

• **Eculizumab**
  - Monoclonal antibody directed at complement component **C5**
  - **Study from Furie et al.**
    - No impact on SLEDAI or laboratory values

Anti-inflammatory or anti-fibrotic therapies in the pipeline

• **Tamibarotene**
  - Synthetic retinoids that are ligands only for a/b retinoic acid receptors
    - Increased gene expression of an NF-kB factor
    - Increased Tregs and decreased TH17 cells
    - Downregulation of the anti-inflammatory cytokine IL-10
  - Trial on tamibarotene in SLE is planned

• **Fresolimumab**
  - Humanized monoclonal antibody that neutralizes all 3 isoforms of TGFβ
  - Preservation of kidney function in patients who have had progressive scarring
  - No study ongoing on LN
Novel anti-cytokine therapies studies

**Medi-546**
- Anti–IFN-a receptor monoclonal antibody, to block all the subtypes of IFN directly by the receptor interaction
- Evaluate the long-term safety of MEDI-546 in adults with moderate to severe active SLE. Currently enrolling participants (NCT01753193)

**Anifrolumab**
- Antagonist human monoclonal antibody that targets INF-α receptor 1
- Placebo-controlled, Study Evaluating the Efficacy and Safety of Anifrolumab in Adult Subjects With Active Proliferative Lupus Nephritis (NCT02547922)
New approach and management of LN

1. Autoimmunity Develops
   - Genetic Predisposition + Environmental Trigger
   - Accumulation of apoptotic debris
   - Autoantigens are presented by dendritic cells
   - T cell-B cell interactions are facilitated
   - Dendritic cells produce interferon-α
   - Autoreactive B cells proliferate
   - Plasma cells produce autoantibodies

2. Acute Kidney Injury
   - Immune complexes accumulate in kidneys
   - Complement Activated
   - Leukocytes recruited to kidneys
   - Leukocytes activated by complement and through their Fc receptors
   - Intrarenal cytokines/chemokines are expressed by leukocytes and renal parenchymal cells
   - Inflammatory response amplified
   - Intra-renal dendritic cells produce interferon-α
   - Intra-renal B-T cell interactions; autoantibody production
   - Kidney specific autoimmunity initiated

3. Chronic Kidney Injury
   - Fibrosis

Novel Biomarkers
- Peripheral B Cells
- BAFF Level
- Anti-chromatin antibodies

Therapies
- Anti-B cell Therapy
- Anti-T cell Therapy
- Anti-IFNγ Therapy

Cytokines
- IFN-α, IFN-γ, TNF-α, TWEAK-Fn14, IL-6, IL-1β, IL-18, IL-10, IL-17

Chemokines
- IL-8, MCP-1, RANTES, IP-10, MIP-1

Growth factors
- TGFβ, BAFF

Anti-inflammatory Therapy
- Anti-complement Therapy
- Anti-cytokine Therapy

Anti-Fibrosis Therapy
SLE: drug-induced Lupus

- Most often the drug **induce autoantibodies** but most of the patients **do not develop the disease**
- 15000 – 30000 cases/year in the US
- **Pathogenesis?**
- Can **induce lupus** in a predisposed patient
  - Can **exacerbate underlying lupus**
  - Can **cause separate syndromes** of drug-induced lupus
- **Genetic factors**
  - Association with HLA Ag
  - Acetylator status (¶ synthesis of N-acetyltransferase) → procainamide and hydralazine
- **Anti-histone Ab**
  - Alone in drug-induced lupus (80% + in SLE)
  - Not the same complex (H2A-H2B or H1-H3-4 vs H1-H2B)
SLE: drug-induced Lupus

• **Definite causing drugs**
  - **Minocycline** (Klinotab, Minocin, Mino50), **Diltiazem** (Progor, Tildiem), **Isoniazide** (Nicotibine), **Anti-TNFα** (Remicade, Enbrel, Humira, Simponi, Cimzia), **Interferon α** (Intro A, Pegasys, Pegintron, Roferon)
  - + procainamide, Hydralazine, penicillamine, Quinidine, Chlorpromazine, Practolol

• **Probable causing drugs**
  - **Anticonvulsants:** **Phenytoine** (Diphantoine, Epanutin), **Ethosuximide** (Zarontin), **Carbamaezpine** (Tegretol)
  - **PTU**
  - **Antimicrobial:** **Sulfonamides**, **Rifampicine** (Rifadine), **Nitrofurantoine** (Furadantine)
  - + **βBlockers**, **Lithium** (Camcolit, Maniprex), **Captopril** (Capoten), **IFNγ**, **HCT**, **Sulfalazine** (Salazopyrine), **Terbinafine** (Lamisil), **Amiodarone** (cordarone), **Ticloidine** (Ticlid), **Docetaxel** (Taxotere)

• **Possible causing drugs**
  - **Penicilline**, **Tetracycline**, **Valproate** (Depakine), **Statins**, **Lamotrigine** (Lamictal), **Timolol** (Cosopt, Xalacom, Timabak)
SLE: drug-induced Lupus: Treatment

• STOP the offending medication

• Do not rechallenge

• Symptomatic therapy

• Hydroxychloroquine if symptoms do not clear within 4-8 weeks

• Rarely systemic glucocorticoids if severe pleurisy or pericarditis