Primary glomerulonephritides

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Contents of the lecture

- definition of GN
- classification
- clinical presentation and epidemiology
- proliferative PGN (IgAN)
- non-proliferative PGN
  - MGN
  - MCD
  - PSGS
- podocytopaties and slit diaphragm
- summary
Definition of glomerulonephritis

Glomerulonephritides are supposedly immunologically mediated glomerular diseases, often, but not always, inflammatory in nature.
Classification of GN

- **etiology**
  - primary (idiopathic)
  - secondary (as a part of systemic organ involvement: AAV, LN…)

- **clinical course**
  - acute
  - RPGN
  - chronic (possible acute onset)

- **mechanism of glomerular damage**
  - proliferative
  - non-proliferative

- BUT: combinations and interferences (IgANxHSP; RPGN x WG)
Mechanisms of glomerular damage

1. glomerular inflammation – inflammatory pathways
2. ultrastructural changes – non-inflammatory pathways
Glomerular inflammation

1. Exsudation of neutrophils and/or macrophages

2. Proliferation of mesangial and/or endothelial cells
Ultrastructural changes in non-proliferative vs. proliferative glomerulonephritides
Simplified classification of primary glomerulonephritides

1. Proliferative - mesangiopathies
   - IgA nephropathy
   - membranoproliferative GN
2. Nonproliferative - podocytopathies
   - minimal change disease
   - focal segmental glomerulosclerosis
   - membranous nephropathy
3. Diseases with endothelium as primary target
   - preeclampsia, HUS/TTP
   - type III and IV LN,
   - AAV
Clinical presentation

- very variable
- urinary findings
  - HU:
    - glomerular (phase contrast!)
    - isolated vs. combined with PU;
    - micro vs. macro
  - PU
    - low range vs. nephrotic
    - selective (albiminuria) vs. non-selective
  - combination of HU + PU
  - (normal)
- renal function
  - normal vs. declined (rapid /RPGN/ or slow)
- BP
  - usually hypertension
  - normal
- nephritic vs. nephrotic conditions
I love you, urine
Epidemiology – facts:

- relatively rare disease (~ incidence bioptically proven primary GN 30-40/PMP)
- numerous subtypes
- significant part of GN unrecognised – „clinically silent“ (incidental dg)
- important role of renal biopsy (cave: different local indication policy)
- national (or large population) registries of RB
- variation:
  - geographical (e.g. IgAN: Asia – Europe – North America)
  - ethnicity (e.g. Indians)
  - population group (e.g. elderly vs. children, gender)
Czech Registry of Renal Biopsies

country population 10.3 millions

Male/femal ratio % (n = 7665)
Czech Registry of Renal Biopsies

Presence of erytrocyturia % (n = 7665)
Czech Registry of Renal Biopsies

Presence of proteinuria % (n = 7665)

![Bar chart showing the percentage of proteinuria from 1995 to 2007. The y-axis represents the percentage of proteinuria ranging from 0% to 100%, and the x-axis represents the years 1995 to 2007. The chart shows the distribution of proteinuria into different categories: none, <3g, 4-10g, >10g, and NA.]
Czech Registry of Renal Biopsies

S-creatinine level % (n = 7665)
Czech Registry of Renal Biopsies

Presence of arterial hypertension % (n = 7665)
Czech Registry of Renal Biopsies

Selected primary GN (n = 7665)
Patients with isolated hematuria in %
(n = 643 of 4004 RB)
Czech Registry of Renal Biopsies

Patients with nephrotic proteinuria in % (n = 1557 of 4004 RB)
Primary glomerulonephritides as a cause of nephrotic syndrome
Korbet et al., AJKD, 1996, 27: 647 - 651
## Incidence of GN
(PMP values, different European registries)

<table>
<thead>
<tr>
<th>Country</th>
<th>GN – total</th>
<th>IgAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Czech (Rychlík, 2004)</td>
<td>47</td>
<td>11.2</td>
</tr>
<tr>
<td>Italy (Coppo, 1998)</td>
<td>-</td>
<td>8.4</td>
</tr>
<tr>
<td>Denmark (Haef, 1999)</td>
<td>34</td>
<td>1.8</td>
</tr>
<tr>
<td>France (Simon, 1994)</td>
<td>63</td>
<td>25-31</td>
</tr>
<tr>
<td>Spain (Rivera, 2002)</td>
<td>39</td>
<td>-</td>
</tr>
<tr>
<td>Romania (Covic, 2006)</td>
<td>39</td>
<td>-</td>
</tr>
<tr>
<td>Kentucky (Wyatt, 1998)</td>
<td>86</td>
<td>5.4</td>
</tr>
</tbody>
</table>
I. IgA nephropathy – mesangioproliferative glomerulonefritis
IgA nephropathy
IgA nephropathy
IgA nephropathy
IgA nephropathy – clinical features

1. the most common glomerulonephritis in Europe (20-40% out of all primary GN)

2. typical clinical presentation:
   - asymptomatic microscopic hematuria or
   - episodes of parainfectious macroscopic hematuria
   - young males

3. outcome of untreated IgA nephropathy is not benign – at least 20% of pts develop ESRD during 20 years
IgA nephropathy – negative prognostic factors

a. clinical
- hypertension
- proteinuria (> 1 g/24 hrs)
- decreased GFR at presentation

b. histologic
- glomerulosclerosis
- interstitial fibrosis
- vascular sclerosis
Renal outcome in IgAN
Pathogenesis of IgAN

Roos and van Kooten, , Kidney Int., 2007, 71: 1089 - 1090

Mucosal pathogen exposure

Inadequate clearance by mucosal immunity

Dysregulation of mucosal immunity

- Secretory IgA
- Polymeric IgA
- Degalactosylated IgA

Enhancement of systemic IgA production

BONE MARROW

Serum IgA

CIRCULATION

Binding to mesangial IgA receptor

MESANGIUM

Activation of mesangial cells
- Complement activation
- Inflammation

Renal injury
Hinge region of human IgA1 and IgA2

Pathogenesis of IgAN


- Glomerular deposition
- Glomerular injury
- Alterations of urinary proteome
IgA nephropathy - treatment

1. optimal control of blood pressure using ACEI and/or AIIA
2. fish oil in pts with slowly progressive renal insufficiency
3. corticosteroids in proteinuric pts with normal or only slightly decreased RF
4. cytotoxics in pts with progressive renal insufficiency
Therapy of IgAN using ACE-inhibitors - RCT

1. 44 pts with biopsy proven IgAN, Pu > 0.5 g/d and Scr < 132 μmol randomized to either enalapril or control of hypertension without ACEI
2. primary endpoint - 50% increase of Scr, mean FU 76 months
3. primary endpoint reached by 13% of enalapril-treated pts compared to 57% of pts in the control group (p<0.05)
4. PU decreased significantly in pts treated by enalapril and tended to increase in the control group
The effect of fish oil on renal function in IgAN
Strippoli et al., Am J Kidney Dis, 2003, 41: 1129 - 1139

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (95%CI Random)</th>
<th>Weight %</th>
<th>RR (95%CI Random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bennett</td>
<td>2 / 17</td>
<td>2 / 20</td>
<td></td>
<td>26.2</td>
<td>1.18 [0.18, 7.48]</td>
</tr>
<tr>
<td>Donadio</td>
<td>3 / 55</td>
<td>14 / 51</td>
<td></td>
<td>33.7</td>
<td>0.20 [0.06, 0.85]</td>
</tr>
<tr>
<td>Petterson</td>
<td>11 / 15</td>
<td>9 / 17</td>
<td></td>
<td>40.1</td>
<td>1.39 [0.81, 2.38]</td>
</tr>
<tr>
<td>Total(95%CI)</td>
<td>16 / 87</td>
<td>25 / 88</td>
<td></td>
<td>100.0</td>
<td>0.69 [0.15, 3.21]</td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square=11.18 df=2 p=0.0037
Test for overall effect z=-0.47 p=0.6
The effect of steroids on renal function in IgAN
Strippoli et al., Am J Kidney Dis, 2003, 41: 1129 - 1139

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (95% CI Random)</th>
<th>Weight %</th>
<th>RR (95% CI Random)</th>
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</thead>
<tbody>
<tr>
<td>Pozzi</td>
<td>10 / 43</td>
<td>23 / 43</td>
<td></td>
<td>49.7</td>
<td>0.43 [0.24, 0.60]</td>
</tr>
<tr>
<td>Lai</td>
<td>9 / 17</td>
<td>10 / 17</td>
<td></td>
<td>50.3</td>
<td>0.90 [0.49, 1.64]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>18 / 60</td>
<td>33 / 60</td>
<td></td>
<td>100.0</td>
<td>0.63 [0.30, 1.31]</td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square = 2.95 df = 1 p = 0.086
Test for overall effect z = -1.25 p = 0.2

Fig 2. Effect of steroids on renal function in patients with IgA nephropathy. Weighted mean follow-up, 48 months. Studies are sorted by weight.
Corticosteroids in IgAN: long-term outcome

1. secondary analysis of multicentric RCT - 86 pts with IgAN treated 6 m with MP and Pred or only by symptomatic treatment

2. 10-yr renal survival significantly better in pts treated by steroids (97% vs. 53%, p=0.0003)

3. PU decreased in pts who did not reach the doubling of Scr and increased in pts with progressive renal insufficiency
The effect of cytotoxics on renal function in IgAN
Strippoli et al., Am J Kidney Dis, 2003, 41: 1129 - 1139

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (95%CI Random)</th>
<th>Weight %</th>
<th>RR (95%CI Random)</th>
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</thead>
<tbody>
<tr>
<td>Yoshioka</td>
<td>0 / 40</td>
<td>1 / 34</td>
<td></td>
<td>3.1</td>
<td>0.28[0.21, 0.67]</td>
</tr>
<tr>
<td>Walker</td>
<td>1 / 25</td>
<td>2 / 27</td>
<td></td>
<td>5.7</td>
<td>0.54[0.35, 0.85]</td>
</tr>
<tr>
<td>Woo</td>
<td>6 / 39</td>
<td>9 / 54</td>
<td></td>
<td>36.7</td>
<td>0.56[0.23, 1.47]</td>
</tr>
<tr>
<td>Ballardie</td>
<td>5 / 19</td>
<td>18 / 19</td>
<td></td>
<td>54.4</td>
<td>0.26[0.13, 0.59]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>12 / 123</td>
<td>30 / 114</td>
<td></td>
<td>100.0</td>
<td>0.38[0.22, 0.66]</td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square = 1.59, df = 3, p = 0.86
Test for overall effect z = -3.40, p = 0.0007
Rate of GFR loss in pts with progressive IgAN treated 2-yrs by CS and cytotoxics (CPH→AZA)

Renal outcome in pts with progressive IgAN treated by prednisolone and cytotoxics
Relative efficacy of IgAN treatment options

Evidence-based recommendations in IgAN
Floege, Nephrol Dial Transplant, 2003, 18: 241 - 245

1. in pts with PU < 1.5 g/d and normal GFR steroids may decrease Pu, but their long-term effect remains uncertain

2. in pts with PU 1 – 3.5 g/d and preserved renal function - 6-months treatment with corticosteroids

3. in pts with progressive renal insufficiency insuficiencí and Scr < 250 μmol/l - treatment with corticosteroids and cytotoxics
Algorithm of recommended treatment options in IgAN

Ballardie, JASN, 2007, 18: 2806 - 2809
II. Podocytopathies

Damage to the glomerular capillary wall resulting in:

1. nephrotic selective proteinuria
   - minimal change disease
2. nephrotic non-selective proteinuria with microscopic hematuria
   - focal segmental glomerulosclerosis
   - idiopathic membranous nephropathy
Podocytopathies

Damage to the podocyte caused by:
1. antipodocyte antibodies
   - membranous nephropathy

2. Genetic, viral, toxic and immunologic mechanisms
   - focal segmental glomerulosclerosis
   - minimal change disease
IIa. Membranous nephropathy
Membranous nephropathy

Stage I

Stage II

Stage III

Stage IV
Membranous nephropathy
Membranous nephropathy
Membranous nephropathy
Membranous nephropathy
Membranous nephropathy

1. Secondary – planted antigens?
   - infections
     (hepatitis B, syphilis, malaria)
   - drugs
     (organic gold, penicillamine, NSAID)
   - neoplasms
     (carcinomas, e.g. Colon, lung, or stomach, and lymphomas)
   - systemic lupus erythematosus

2. Idiopathic – antibodies directed to podocyte antigens?
Idiopathic membranous nephropathy

1. very common - 15-25% of adult nephrotic syndrome
2. Nephrotic proteinuria in about 80% of pts
3. Microscopic hematuria common
4. Hypertension and chronic renal failure are uncommon at presentation, but may develop during follow-up
Pathogenesis of IMN

1. Experimental model of IMN – Heymann’s nephritis in rats
   - antibodies against megalin
     (not expressed by human podocytes)

2. Antenatal membranous nephropathy in a child of a woman with truncating mutations of MME (metallomembrane endopeptidase) gene
   - alloimmunisation against NEP

3. Common IMN – supposedly antibodies against other podocyte proteins
Natural course of idiopathic membranous nephropathy

1. Spontaneous remission may develop in about one third of patients
2. Nephrotic syndrome persists in another third of patients
3. Only 20-30% of patients progress to ESRD during 20-30 years of follow up
High incidence of remission in untreated membranous nephropathy

Mosconi et al., NEJM, 1993
Outcome of nephrotic vs. non-nephrotic pts with IMN

A- renal survival

B-renal and patient death
Treatment of IMN
Corticosteroids vs. placebo in adults with IMN

<table>
<thead>
<tr>
<th>Study</th>
<th>No of pts</th>
<th>Duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSAINS, 1979</td>
<td>72</td>
<td>8-12 w</td>
<td>more CR and PR RF preserved</td>
</tr>
<tr>
<td>Cameron, 1990</td>
<td>107</td>
<td>8 w</td>
<td>no difference</td>
</tr>
<tr>
<td>Cattran, 1989</td>
<td>158</td>
<td>6 mo</td>
<td>no difference</td>
</tr>
</tbody>
</table>
Conservative vs. IS treatment in IMN


Retrospective study - 20 pts conservative (CON), 19 pts - CS and CHLB (IST)

At the end of FU:

CON: 65% dialyzed, 10% advanced RF, 25% death

IST: 58% stable renal function, 38% CR or PR

IST - better 4-year (90% vs. 55%) and 7-year renal survival (90% vs. 20%)
Serum creatinine in progressive IMN on conservative vs. immunosuppressive treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>No of pts</th>
<th>Duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ponticelli, 1984</td>
<td>67</td>
<td>6 mo</td>
<td>more CR and PR</td>
</tr>
<tr>
<td>MP+CAB vs ST</td>
<td></td>
<td></td>
<td>(23/30 vs. 9/30)</td>
</tr>
<tr>
<td>Ponticelli, 1992</td>
<td>92</td>
<td>6 mo</td>
<td>earlier remission</td>
</tr>
<tr>
<td>MP+CAB vs MP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ponticelli, 1995</td>
<td>67</td>
<td>10 year FU</td>
<td>better renal surv.</td>
</tr>
<tr>
<td>MP+CAB vs ST</td>
<td></td>
<td></td>
<td>(0.92 vs. 0.60)</td>
</tr>
</tbody>
</table>
Efficacy of different regimens in membranous nephropathy

Ponticelli et al., NEJM, 1992
Other kinds of treatment

1. cyclosporine A  
   a/ in progressive MGN  
   b/ in steroid-resistant MGN
2. tacrolimus
3. mycophenolate mofetil
4. rituximab
5. IVIG
1.a/ Cyclosporine in progressive IMN
Cattran et al., Kidney Int., 1995, 47: 1130 - 1135

- 64 pts followed without treatment for 12 m
- 17 pts - decline of GFR (> 8 ml/min/yr and persistent nephrotic PU)
were randomized to 12-m:
1. CyA (9 pts) or 2. placebo (8 pts)

Proteinuria and rate of decline of GFR decreased only in CyA
Cyclosporine in progressive IMN

*Catrnan et al., Kidney Int., 1995, 47: 1130 - 1135*

<table>
<thead>
<tr>
<th>PU (g/day)</th>
<th>before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>CyA</td>
<td>11.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Placebo</td>
<td>12.8</td>
<td>9.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GFR (ml/min/m)</th>
<th>before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>CyA</td>
<td>-2.4</td>
<td>-0.7</td>
</tr>
<tr>
<td>Placebo</td>
<td>-2.2</td>
<td>-2.1</td>
</tr>
</tbody>
</table>
1.b/ Cyclosporine in steroid-resistant MN

51 pts still nephrotic on high-dose CS for 8 weeks

Randomized to 26 w of:
1) CyA and low-dose CS,
2) placebo and low dose CS

Mean follow-up was 78 weeks
% Remission of NS in pts with steroid-resistant MN treated by CyA
(26-w treatment)
2. Tacrolimus monotherapy in MN: a randomized controlled trial

*Praga et al., Kidney Int., 2007, 71: 924 - 930*

48 pts with biopsy proven MN randomized to tacrolimus monotherapy (12 months) or placebo

<table>
<thead>
<tr>
<th>% RR</th>
<th>6 m</th>
<th>12 m</th>
<th>18 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tc</td>
<td>58%</td>
<td>82%</td>
<td>94%</td>
</tr>
<tr>
<td>Placebo</td>
<td>10%</td>
<td>24%</td>
<td>35%</td>
</tr>
</tbody>
</table>

↑ 50% SCr in 6 pts in placebo and only 1 pt in Tc group
3. Mycophenolate mofetil in IMN: compared with a historic group treated with CPH

Branten et al., AJKD., 2007, 50: 248 - 256

32 pts with IMN treated 1 yr by MMF (2g/day) compared with 32 historical controls treated also 1 yr by CPH (1.5 mg/kg/day), the steroid regimen the same in both limbs

<table>
<thead>
<tr>
<th></th>
<th>PU</th>
<th>MMF</th>
<th>Cr</th>
<th>CPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 m</td>
<td>8.4</td>
<td>1.4 g/24h</td>
<td>159</td>
<td>115 umol/l</td>
</tr>
<tr>
<td>12 m</td>
<td>124 umol/l</td>
<td>159</td>
<td>115 umol/l</td>
<td></td>
</tr>
</tbody>
</table>

69
4. a Rituximab in IMN, who can benefit from the treatment

Remuzzi et al., Lancet, 2002, 360: 923 – 924,
Ruggenenti et al., CJASN, 2006, 1: 738 – 748.

8 pts with IMN treated with RTX (375 mg/m2)
- PU decreased during 4 m from 8.6 to 3.8 g/24h
- Therapy was not effective in pts with tubular atrophy and interstitial fibrosis
4. Rituximab in IMN, comparison of standard and B-cell titrated regimen

Cravedi et al., CJASN, 2007, 2: 932 - 937

12 new incident IMN pts treated by B-cell driven RTX compared to 24 historical controls (standard RTX protocol – 4x 375 mg/m2)
Immunosuppressive treatment for IMN: a systematic review


1. Systematic review of RCT in IMN in adults with NS followed for at least 6 months

2. Four therapeutic studies identified: steroids alone, alkylating agents, calcineurin inhibitors, antiproliferative agents

3. With the exception of a beneficial effect of alkylating agents on complete remission no positive influence of IST on the outcome of the patients with IMN was documented
Treatment of IMN - current recommendations

1. **Corticosteroids should not be used as sole therapy**

2. **Azathioprine is not effective in reversing or stabilizing progressive renal insufficiency**

3. **Cytotoxics induce prolonged remission of nephrotic syndrome and improve renal survival, their use should be reserved for patients with progressive disease**

4. **Cyclosporine seems to be effective in progressive renal insufficiency**

5. **New drugs – tacrolimus, MMF, rituximab should be reserved pro refractory pts**
Guidelines for the treatment of IMN


Asymptomatic proteinuria
(<4 g/day + normal renal function)

- Spontaneous remission

Maintain blood pressure ≤130/80 mmHg using ACEI; continue to monitor proteinuria and renal function

Moderate proteinuria
(≥4 to <8 g/day)

- ACEI, dietary protein restriction, maintain BP ≤130/80 mmHg, observe for 6 months

- Persistent nephrotic range proteinuria **

- Italian regimen using * chlorambucil or cyclophosphamide *

- Consider cyclosporine if Italian regimen is poorly tolerated or fails *

Heavy proteinuria ≥8 g/day with or without renal insufficiency

- ACEI, dietary protein restriction, maintain BP ≤130/80 mmHg, observe for 6 months

- Persistent heavy proteinuria and/or decreasing function **

- Consider cyclosporine *

- Consider modified Italian regimen if cyclosporine is poorly tolerated or fails
IIb. Minimal change disease
Minimal change disease
Minimal change disease
MCD – clinical presentation

1. nephrotic syndrome with selective proteinuria

2. uncommon: hematuria, hypertension and reduced renal function
Minimal change disease-prevalence among nephrotic patients

Children - 85 – 95%
Young adults - 50%
Adults > 40 years - 20 – 25%
Classification of patients with minimal change disease based on response to corticosteroids

1. **Steroid responsive (sensitive)**
   
   develop complete remission of proteinuria within 8 – 12 weeks of treatment
   (in adults remission should develop within 16 weeks)

2. **Steroid dependent**
   
   develop relapse during tapering of steroids or within 2 weeks after cessation of therapy

3. **Steroid resistant**
   
   fail to respond to steroid treatment at all
Clinical course of MCD in children

1. Remission - 90%
   a. no relapses - 20%
   b. infrequent relapses - 40%
   c. frequent relapses and steroid dependent - 30%

2. Resistance to steroids - 10%
   a. response to alternative treatment - 8%
   b. refractory to any kind of treatment - 2%

In adults, initial response rate is lower, relapses and steroid dependence are less frequent
Steroid induced remission in nephrotic syndrome

Nolasco et al., Kidney Int., 1986
Therapy of MCD in children – current recommendations

1. Initially course of prednisone 60 mg/m² for 4-6 weeks with 40 mg/m² every alternate day for another 4-6 weeks

2. Relapses treated in a similar way, but tapering of prednisone starts when urine becomes protein free

3. Frequent relapsers and steroid dependent patients treated either by cyclophosphamide 2 mg/kg/day for 8 weeks or by cyclosporine 5 mg/kg/day for 6-12 months

4. Treatment of steroid resistant patients is usually unsatisfactory
Therapy of MCD – modifications in adults

1. Initially course of prednisone 1 mg/kg for 8-16 weeks or for one week after remission is achieved, then several weeks (one month) 1 mg/kg on alternate days, thereafter corticosteroids are slowly tapered during several months.

2. Relapses treated in a similar way.

3. Frequent relapsers and steroid dependent patients treated either by CPH 2 mg/kg/day for 8 weeks or by CyA 5 mg/kg/day for 6-12 months.

4. Treatment of steroid resistant patients is usually unsatisfactory.
IIc. Focal segmental

glomerulosclerosis
Etiology of FSGS

1. Primary FSGS
   a. classical variant
   b. glomerular tip lesion
   c. collapsing glomerulopathy

2. Secondary FSGS
   a. healing focal lesions (FSGN)
   b. hyperfiltration in residual nephrons
      - agenesis of one kidney
      - vesicoureteral reflux
      - morbid obesity
   c. damage to epithelial cells
      - HIV nephropathy
      - heroin nephropathy
Mild FSGS
Moderate FSGS
Tip lesion in early FSGS
Collapsing FSGS
Classification of FSGS

1. Immunologic
   mechanisms not yet identified

2. Viral FSGS
   a. HIV
   b. hepatitis C
   c. parvovirus B19

3. Toxic FSGS
   a. heroin
   b. pamidronate

4. Genetic FSGS
   a. podocin
   b. α-actinin
   c. TRPC6
   d. PLCE1
   e. CD2AP
Proposed taxonomy of the podocytopathies

Pathogenesis of primary FSGS

1. Circulating permeability factors
   a. immunoglobulin, or Ig-like molecule
   b. protein of MW about 30-50 kDa
   c. factor inhibiting inducible NO synthase in mesangial cells (hemopexin)

2. Deficient inhibitors of permeability factors lost in urine
   apolipoproteins of HDL complex
   (e.g. apo J, apo E₂ and apo E₄)

3. Late onset congenital FSGS
   deficiency of podocyte proteins
   (podocin, α-actinin, CD2AP, et al.)
Efficacy of plasma exchange in primary FSGS
Mitwalli et al., NDT, 1998
## Identified nonsyndromic FSGS/NS genes

<table>
<thead>
<tr>
<th>Disease</th>
<th>Locus</th>
<th>Inherit.</th>
<th>Gene</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital NS</td>
<td>19q13.1</td>
<td>AR</td>
<td>NPHS1</td>
<td>Nephrin</td>
</tr>
<tr>
<td>SRNS</td>
<td>1q25-32</td>
<td>AR</td>
<td>NPHS2</td>
<td>Podocin</td>
</tr>
<tr>
<td>FSGS1</td>
<td>19q13</td>
<td>AD</td>
<td>ACTN4</td>
<td>α-actinin</td>
</tr>
<tr>
<td>FSGS2</td>
<td>11q21-22</td>
<td>AD</td>
<td>FSGS2</td>
<td>TRPC6</td>
</tr>
<tr>
<td>FSGS3</td>
<td>6q</td>
<td>AD, AR</td>
<td>FSGS3</td>
<td>CD2AP</td>
</tr>
<tr>
<td>DMS</td>
<td>10q23.32-24.1</td>
<td>AR</td>
<td>NPHS3</td>
<td>PLCE1</td>
</tr>
<tr>
<td>SSNS1</td>
<td>2p</td>
<td>AR</td>
<td>SSNS1</td>
<td>unknown</td>
</tr>
</tbody>
</table>
FSGS – clinical presentation

1. Asymptomatic proteinuria or full blown nephrotic syndrome
2. Hypertension, microscopic hematuria and decreased renal function common
3. Slowly progressive disease – 50% 10-year renal survival
4. Sclerosis of segments of glomerular tuft
Cumulative renal survival in FSGS
Korbet, NDT, 1999, 14 (Suppl. 3): 68 - 73

a/ according to base-line proteinurie
Cumulative renal survival in FSGS
Korbet, NDT, 1999, 14 (Suppl. 3): 68 - 73

b/ according to base-line renal function
Cumulative renal survival in FSGS

Korbet, NDT, 1999, 14 (Suppl. 3): 68 - 73

c/ according to remission
Immunosuppressive treatment of FSGS

1. corticosteroids
2. cyclosporin A
3. novel drugs
   - tacrolimus
   - mycophenolate mofetil
   - rituximab
### 1. Corticosteroids in adults with FSGS

*Franceschini et al., Seminars in Nephrology, 2003, 23: 229 - 233*

<table>
<thead>
<tr>
<th>Study</th>
<th>No of pts</th>
<th>Duration</th>
<th>CR</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggarwal, 1993</td>
<td>38</td>
<td>6 mo</td>
<td>31%</td>
<td>NA</td>
</tr>
<tr>
<td>Rydel, 1995</td>
<td>30</td>
<td>5.5 mo</td>
<td>33%</td>
<td>67%</td>
</tr>
<tr>
<td>Cattran, 1998</td>
<td>17</td>
<td>5-6 mo</td>
<td>47%</td>
<td>25%</td>
</tr>
<tr>
<td>Ponticelli, 1999</td>
<td>53</td>
<td>6 mo</td>
<td>40%</td>
<td>40%</td>
</tr>
<tr>
<td>Chitalia, 1999</td>
<td>28</td>
<td>3 mo</td>
<td>21%</td>
<td>NA</td>
</tr>
</tbody>
</table>
2a. Treatment of steroid-resistant pts with idiopathic nephrotic syndrome with cyclosporine

Ponticelli et al., Kidney Int., 1993, 43: 1377 - 1384

45 nephrotic pts (24 adults 21 children) with MCD (13 pts) or FSGS (32 pts) resistant to the 6 week treatment with PRED treated 6 m: 1) CyA, 2) symptomatic treatment

Remission during 1 yr of FU in 13/22 on CyA and 3/19 on symptomatic treatment

PU decreased in CyA (6th m) to about 45%, no change of PU on symptomatic treatment
Proteinuria in steroid-resistant pts with INS treated by CyA or symptomatic treatment

Ponticelli et al., Kidney Int., 1993, 43: 1377 - 1384

[Graph showing proteinuria levels over time with standard deviations indicated by error bars.]
2b. Treatment of steroid-resistant FSGS with CyA


49 adult FSGS resistant to 8 w Pred treated for 26 w:
→ A. CyA and low-dose CS or
→ B. placebo and low-dose CS
FU at least 200 w

**Results:**
26 w:

PR and CR - CyA 70%, placebo 4%

78 w:

Relapse - 40%, resp. 60% of responding pts
50% CCr decreased in 25% CyA pts, in 52% placebo pts
Remission of NS in steroid-resistant pts with FSGS treated by CyA or placebo

Cattran et al., Kidney Int., 1999, 56: 2220 - 2226
3a. Treatment of FSGS in adult with tacrolimus monotherapy


6 naive FSGS nephrotic pts treated by tacrolimus
- all in remission after 6.5 months
- Pu 11.0 vs 2.8 g/day

5 FSGS pts in remission on CyA with worsening RF switched to tacrolimus
- Pu further improved, slightly improved RF
3b. Mycophenolate mofetil in FSGS
*Cattran et al., Clin. Nephrol., 2004, 62: 405 - 411*

18 FSGS pts resistant to CS (75% also to CPH or CyA) switched to MMF

6 m: substantial improvement of Pu in 44% (8/18)

1 yr post treatment, Improvement sustained in 50% (4/8), no pt CR

No deterioration of RF during treatment, 3 pts progressed to CRF during FU
Mycophenolate mofetil in FSGS
Segarra et al., NDT, 2007, 22: 1351 - 1360

Among 98 pts with primary GN 22 pts with FSGS treated by MMF

CR in 2 pts, PR in 10 pts, response rate 54%

Median time to response 150 days
3c. Rituximab and FSGS
Ahmed and Wong., NDT, 2008, 23: 11 - 17

Only case reports both in post-transplant FSGS and FSGS in native kidneys (3 children)

Overall success rate in FSGS 8/12 and 7/7 in MCD.
Treatment of primary FSGS – current recommendations

1. Response to corticosteroids may increase from only 10-30% up to 60% with longer treatment with higher dose (60 mg/m² at least 3 months, patients should be considered steroid resistant after 6 months)

2. Cyclosporine may reduce proteinuria and lower the risk of progression to ESRD even in steroid resistant patients, treatment should be long (at least 6 months), relapses after cyclosporine withdrawal are common

3. Cytotoxics remain only second-line therapy, the evidence for their effect in steroid resistant patients is not conclusive

4. Newer drugs – tacrolimus, sirolimus, MMF, rituximab should be reserved only for refractory pts
Podocytes and slit diaphragms
Glomerular capillary wall

Electronoptic view of the slit diaphragm
Slit diaphragm in congenital nephrotic syndrome (D)
Nephrin and slit diaphragm
Components of the slit diaphragm protein complex
Mutations of podocyte proteins in FSGS
Major causes of podocyte effacement

1. Slit diaphragm and its lipid raft
   nephrin, podocin, TRPC6, CD2AP
2. Podocyte cytoskeleton
   \( \alpha \)-actinin
3. Adhesion of podocyte to GBM
   \( \beta \)-dystroglycan, \( \beta 1 \)-integrins
4. Loss of podocyte electronegative charge
   podocalyxin
Conclusions - podocytopenies

1. recent progress in the podocyte biology may result in the elucidation of the pathogenesis of the common acquired podocytopenies

2. direct effect of different drugs on podocytes may change the current paradigm that the reduction of proteinuria is exerted either by the immunosuppressive or hemodynamic effect

3. better understanding of the podocyte biology may lead to the discovery of new drugs aimed at preservation of the glomerular capillary wall
Summary of therapy of GN

1. Drugs and procedures with relatively well defined indications

   - corticosteroids
   - cytotoxics (CPH, chlorambucil)
   - cyclosporine
   - symptomatic treatment
     - (ACEI, AIIA, and other antihypertensives, NSAIDS
     - lipid lowering drugs)
Summary of therapy of GN – cont´

2. Drugs and procedures with limited experience and not well defined indications

   mycophenolate mofetil
   tacrolimus
   rapamycin
   intravenous immunoglobulins
   monoclonal antibodies (e.g. infliximab, rituximab)
   soluble cytokine receptors (e.g. etanercept)
   plasma exchange
   immunoadsorption
Conclusions – primary GN

1. Patients with primary GN endangered by:
   a. complications of nephrotic syndrome
   b. progression to ESRF

2. Urinary findings are important, but renal biopsy remains essential for diagnosis, treatment and assessment of outcome

3. primary GN treatable diseases,
   pts should be treated according to available evidence

4. further progress in treatment depends on better understanding of their pathogenesis