Steroid-dependent nephrotic syndrome in children

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Definition

- **Nephrotic syndrome (NS)** – urinary albumin loss at the level of 3,5 g/1,73 m²/24h or 40 mg/m²/hour or 50 mg/kg/24 h with the consequent hypoalbuminemia <25 g/l, hyperlipidemia and edema.

- **Steroid-sensitive NS** – the one with a remission of proteinuria within 6 weeks of standard prednisone/prednisolone regimen of 2 mg/kg or 60 mg/m² daily
Epidemiology of NS in childhood

- Annual incidence – 2-7 cases per 100,000
- Prevalence – 12-16/100,000

Pathogenesis of idiopathic NS. Still unclear

• Schalhoub hypothesis (1974): T-lymphocytes dysfunction leading to some cytokine production (IL-8?, sIL-2R?) capable to inhibit lymphocyte proliferation and to increase GBM permeability due to charge selectivity loss.

• Later on – dysfunction of podocytes with albumin loss via slit diaphragm disorganized by circulating factor (IL-4?, IL-13?, other?)
NS Pathogenesis

• NF-κB – promotes IL-13, TNF-α and other cytokines synthesis
• B-lymphocytes regulate T-lymphocytes function via CD80 protein (Rituximab induced remission)
• Potential role for soluble urokinase receptors (suPAR)?
### Table 1. Partial List of Proposed Humoral Mediators of Glomerular Permeability in Idiopathic Nephrotic Syndromes

<table>
<thead>
<tr>
<th>Candidate Factor</th>
<th>Major Findings</th>
<th>Example References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permeability factors from T cells</td>
<td>Stimulation of T cells from nephrotic individuals releases substance(s) that induce vascular permeability in guinea pigs; secreted products of a T-cell hybridoma from MCD individual induces proteinuria when injected into rats</td>
<td>11, 22</td>
</tr>
<tr>
<td>Hemopexin</td>
<td>Present in normal and MCD plasma; proteinuria after injection into rats with decreased nephron expression in rat glomeruli</td>
<td>23-25</td>
</tr>
<tr>
<td>IL-13</td>
<td>Overexpression in rats produces features of nephrotic syndrome without histologic changes</td>
<td>26</td>
</tr>
<tr>
<td>CLC-1</td>
<td>Present in FSGS plasma; induces permeability in isolated glomeruli; decreases nephron expression ex vivo and in vitro</td>
<td>27</td>
</tr>
<tr>
<td>Angptl4</td>
<td>Induced in multiple rodent proteinuric models; podocyte transgenic rats develop proteinuria</td>
<td>27</td>
</tr>
<tr>
<td>suPAR</td>
<td>Induced in FSGS, but not MCD, patient sera; transgenic mice develop FSGS and proteinuria</td>
<td>6</td>
</tr>
</tbody>
</table>

**Note:** Other proposed mediators include vascular endothelial growth factor, heparinase, sialidase, and C-mip (intracellular protein).

Abbreviations: Angptl4, angiopoietin-like 4; CLC-1, cardiotrophin-like cytokine 1 (also known as CLCF1); FSGS, focal segmental glomerulosclerosis; IL-13, interleukin 13; MCD, minimal change disease; suPAR, soluble urokinase plasminogen activator receptor.
Circulating urokinase receptors (suPAR)

Pollak M, Nature Medicine 2011
Circulating urokinase receptors (suPAR)
suPAR does not differ in genetic and non-genetic NS

Wei et al, JASN 2012
T and B-cell interaction

B-cells present an antigen to T-cells. T-cells induce B-cells to produce antibodies.
Symptomatic approach to NS

• Infection: bacterial, viral (*Varicella Zoster*), fungal (*Candida*). Early antibiotics, acyclovir or antifungals. Vaccination in the remission not on cytotoxic drugs.

• Treatment and prophylaxis of thromboses. Mobilisation, heparin or antiplatelet therapy if Salb<20 g/l

• Mineral metabolism correction (vit.D 2000-4000 IU, calcium up to 500 mg/day)

• Edema treatment (i/v 20% albumin, furosemide up to 10 mg/kg)

• Diet with normal protein content, salt restriction
Evaluation of intravascular volume (J. Van de Walle)

- Underfill Uk/(Uk+Una)=74±21%
- Normal Uk/(Uk+Una)=38±18%
- Overfill Uk/(Uk+Una)=37±18%
Prednisolone/prednisone dosage regimen in NS

• Standard dose 2 mg/kg or 60 mg/m² per day
• In daily course the dose divided into 2 or three equal parts every 8 – 12 hours
• In alternate day course the dose decreased to 40 mg/m² in a single morning dose
• In case of prolonged treatment prednisolone may be substituted to methylprednisolone to decrease mineralocorticoid action
Pathology of NS in children (ISKDC, 1981)

Number of patients

- MCN
- FSGS
- MPGN
- DMP
- RPGN
- MGN
- Other

Steroid sensitive
Steroid resistant
Clinical course of NS and steroid response

**Steroid sensitive** – remission on 4 weeks course of prednisolone
2 mg/kg or 60 mg/ m²

- *Non-relapsing* (20-30%)
- *Infrequently relapsing* - less than 3 relapses per year
- *Frequently relapsing* - 2 or more relapses in 6 months (up to 50%)
- *Steroid-dependent* - relapse on reduction of Prednisone dosage or < 2 weeks after its cessation
- *Late response* - remission after 4 weeks of prednisolone
- *Secondary resistant* – absence of remission during next prednisolone course after initial response

**Steroid resistant**
Initial therapy of first episode

- Duration of treatment is probably more important than cumulative dose of steroid
  
  *Elisabeth M Hodson, John F Knight, Narelle S Willis, Jonathan C Craig*

- Corticosteroid therapy in nephrotic syndrome: a meta-analysis of randomised controlled trials
  
  *Arch Dis Child 2000;83:45-51*

- APN Nephrotic Syndrome Study VIII: 12 weeks pred ± CsA ® no difference in 2 years except of delayed first relapse (*P.Hoyer*)
Efficacy and length of initial therapy

Initial steroid treatment

- Long remission
- Rare relapses
- Frequent relapses
Initial course duration and remissions in NS

Treatment of relapse

- Same as first episode if infrequent
- Prednisolone/prednisone 2 mg/kg or 60 mg/m$^2$ until 3 days of proteinuria absent, then the same dose on alternate days for 6-8 weeks, then taper (APN)
- Recommended total duration of steroids – 4-5 months
Side effects of steroids

- Obesity/Cushing syndrome
- Arterial hypertension
- Cataract
- GI ulcers
- Osteoporosis
- Poor growth
- Psychoses
Mechanism of immunosuppressive agents
Frequently relapsing and steroid dependent NS

- Minimal steroid dose sufficient to prevent relapses. Side effects control
- Alkylating agents: cyclophosphamide 2 mg/kg or chlorambucil 0.2 mg/kg during 8-12 weeks with alternate day pred
- Cyclosporine A 3-6 mg/kg (C0-80-150 ng/ml, C2- 800-1200 ng/ml)
- Levamisole 2.5 mg/kg every other day (watch neutropenia!)
- MMF
- Rituximab
- ACTH???
Alkylating agents

• Maintain remission in 1 year in 67-93%, in 5 years in 36-66% (70-s 80-s XX century, ISKDC)

• 12-weeks of Cyph better than 8 weeks (67% and 30% remissions in 2 years (APN, Arch Dis Child 1987; 62:1102)

• Cyph is more efficient in frequent relapsers than in steroid dependent (APN, N Engl J Med 1982; 306: 451)

• Gonadotoxicity threshold for Cyph - 250 mg/kg, Chlbc – 10 mg/kg (Bogdanovich, 1991)
Levamisole 2.5 mg/kg every other day

- Remission after 112 days in 14 patients on Levamisole and 4 pts on placebo (total number – 61 patient). Relapse in first 3 months after Levamisole discontinued. (British Assoc Ped Nephr, Lancet 1991; 337:155)

- Significant decrease in number of relapses and prednisone doses in 43 SDNS pts treated with Levamisole during 6-12 months. (Bagga A. et al, Pediatr Nephrol 1997; 11:415-7)
Mechanism of calcineurin inhibitors
Cyclosporin A in nephrotic syndrome. First reports

• First used in adults in 1986

• First used in children in 1988
CsA in FRNS and SDNS

• Indicated in steroid toxicity
• Used in doses 4-6 mg/kg or 100-150 mg/m²
• Goal concentration in a whole blood 70-150 ng/ml before or 700-1000 ng/ml 2 hours after
• Multiple evidences of efficacy in maintaining remission and steroid sparing effect (Gregory, 1996; Mahmoud, 2005; Inoue, 1999; Hoyer, 2006; Ignatova, 2003)
• Disadvantages: CsA dependency, CsA toxicity
CsA (Sandimmune Neoral®) in FRNS and SDNS (NCZD experience)

Patients and methods:
• 78 children 2-17 y.o.; m/f-60:18. Remission on steroids
• History of NS 46 ± 37 month
• Normal GFR
• CsA doses 3,6 (3,2; 4,3) mg/kg/day
• C₀ 109,0 (66,9; 147,7) ng/ml
• C₂ 896,9 (603,0; 1026,0) ng/ml

M. Matveeva, 2012
Efficacy of CsA in SDNS (n=78)

- Complete cessation of Prednisone with remission > 6 months: 61 (78%)
- No relapse: 33 (42%)
- Reduction of relapses and prednisone dosage: 36 (46%)
- No effect: 9 (12%)
Prednisolone dose and number of relapses in children treated with CsA
CsA (Sandimmune Neoral®) in FRNS and SDNS. Causes of discontinuation

• CsA discontinued in 20 children

  – GFR decrease 50% or more - 5 (6%)
  – Long remission - 7 (9%)
  – No effect - 7 (9%)
  – Biopsy data - 1 (1.3%)

MMF added - 11 (14%)
CsA (Sandimmune Neoral®) in FRNS and SDNS. Biopsy

- Kidney biopsy – in 15 (19%) after 25 (24; 31) months of CsA

Results:
- Signs of nephrotoxicity – y 6 (40%) patients, in 4 (66,7%) of them elevation of creatinine reported
CsA (Sandimmune Neoral®) in FRNS and SDNS. Results 2

• Average prednisolone dose decreased from 1,4 to 0,4 mg/kg/48h
• Frequency of relapses decreased from 2 (1,5; 3) to 0,7 (0,5; 1) per patient per year
• GFR decrease >30% - in 15 children (19%): in 5 (6%)– CsA stopped after 19 (10; 38) months
MMF in children with NS

- 33 children with FRNS and normal GFR
- MMF 600 mg/m² x 2 per day (up to 1000 mg)
- Prednisolone tapered in 16 weeks
- 24 (75%) maintained remission for 6 months on MMF
- Frequency of relapses down from 1 in 2 months to 1 in 14.7 months
- In 8 – remission after cessation of MMF
- In 8 – relapse on MMF

MMF in children with NS

- 21 child with SDNS
- MMF during $1,0 \pm 0,5$ years
- Relapses decrease from $0,8 \pm 0,41$ to $0,47 \pm 0,43$ per month ($p<0,02$) – 40%
- Low incidence of side effects and good tolerance

Switch from CsA to MMF – to avoid nephrotoxicity

- 9 children with SD/SRNS and cyclosporine toxicity
- Increasing doses of MMF up to 1g/1,73 m² x bid, stop CsA and tapering steroids
- After 9 months remission maintained without serious side effects
- GFR increased from 76,9 ± 4,8 to 119,9 ± 5,9 ml/min, prednisolone decreased from 0,85 to 0,29 mg/kg/day

Rituximab

• Monoclonal antibodies against CD20
• Side effects: fever, chills, infection
• Rituximab was also successfully used in MGN, FSGS and recurrent GN in the graft (Ahmed MS, Wong CF; NDT 2008; 23: 11-17)
### Rituximab in steroid dependent NS

<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Histology</th>
<th>Age (years)</th>
<th>Dosage</th>
<th>Follow-up (months)</th>
<th>response (relapses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benz et al. 2004</td>
<td>1</td>
<td>FSGS</td>
<td>15</td>
<td>375 mg/m² № 4 (1 x/week)</td>
<td>12</td>
<td>FR³</td>
</tr>
<tr>
<td>Gilbert et al. 2006</td>
<td>1</td>
<td>MC</td>
<td>15</td>
<td>375 mg/m² № 4 (1 x/week)</td>
<td>16</td>
<td>FR³ (1 – after 9 months)</td>
</tr>
<tr>
<td>Hofstra et al. 2007</td>
<td>1</td>
<td>MC</td>
<td>13</td>
<td>1 g № 2 (1 x/2 week)</td>
<td>4</td>
<td>FR³</td>
</tr>
</tbody>
</table>

**Immunosuppressive treatment (before RTX):** Prednisone, Cyclophosphamide, CsA, tacrolimus, MMF

**FR** – full remission

³ no proteinuria before starting the treatment
### Rituximab in steroid dependent NS

<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Histology</th>
<th>Age (years)</th>
<th>Dosages</th>
<th>Follow-up (months)</th>
<th>Response (relapses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al. 2007</td>
<td>1</td>
<td>MC</td>
<td>13</td>
<td>375 mg/m² № 1</td>
<td>6</td>
<td>FR&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bagga et al. 2007</td>
<td>5</td>
<td>MC (2) FSGS (3)</td>
<td>3 - 16</td>
<td>375 mg/m² № 4 (1 x/week)</td>
<td>3,5-14,5</td>
<td>FR - 4 (1) Frequent relapse-1</td>
</tr>
<tr>
<td>Nakayama et al. 2008</td>
<td>2</td>
<td>FSGS</td>
<td>10; 15</td>
<td>375 mg/m² № 1</td>
<td>8 ; 15</td>
<td>FR - 2 (1–after 8 months)</td>
</tr>
<tr>
<td>Peters et al. 2007</td>
<td>2</td>
<td>FSGS</td>
<td>15; 20</td>
<td>1 g № 2 (1 x/2 week)</td>
<td>7; 10</td>
<td>FR</td>
</tr>
<tr>
<td>Suri et al. 2008</td>
<td>1</td>
<td>FSGS</td>
<td>1</td>
<td>375 mg/m² № 4 (1 x/week)</td>
<td>3</td>
<td>FR</td>
</tr>
</tbody>
</table>

Immunosuppressive therapy (before RTX): prednisone, iv – MP, CPH, CsA, Tacrolimus, MMF  
FR – full remission, <sup>a</sup> no proteinuria before starting the treatment
### Rituximab in children with refractory SDNS

<table>
<thead>
<tr>
<th>N</th>
<th>I course</th>
<th>Duration of follow-up after 1st course (months)</th>
<th>Relapses before RTX N/ (n/year)</th>
<th>Relapses after 1st course 6 months N</th>
<th>Relapses after 1st course 12 months N</th>
<th>Prednisone before RTX mg/kg/day</th>
<th>Prednisone after 1st course 6 months mg/kg/day</th>
<th>Prednisone after 1st course 12 months mg/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>375 x 4</td>
<td>12</td>
<td>18 (3.0)</td>
<td>0.0</td>
<td>2.0</td>
<td>0.78</td>
<td>- (second course) -</td>
<td>- (second course) -</td>
</tr>
<tr>
<td>2</td>
<td>375 x 4</td>
<td>12</td>
<td>14 (1.8)</td>
<td>0.0</td>
<td>0.0</td>
<td>0.37</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>375 x 4</td>
<td>12</td>
<td>17 (2.7)</td>
<td>0.0</td>
<td>0.0</td>
<td>0.64</td>
<td>0.09</td>
<td>0.05</td>
</tr>
<tr>
<td>4</td>
<td>375 x 4</td>
<td>12</td>
<td>37 (3.7)</td>
<td>0.0</td>
<td>0.0</td>
<td>0.32</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>5</td>
<td>375 x 1</td>
<td>12</td>
<td>10 (1.8)</td>
<td>0.0</td>
<td>0.0</td>
<td>0.38</td>
<td>0.10</td>
<td>0.04</td>
</tr>
<tr>
<td>6</td>
<td>375 x 2</td>
<td>6</td>
<td>6 (6.0)</td>
<td>0.0</td>
<td>no data</td>
<td>0.75</td>
<td>0.25</td>
<td>no data</td>
</tr>
<tr>
<td>7</td>
<td>375 x 2</td>
<td>6</td>
<td>12 (4.2)</td>
<td>0.0</td>
<td>no data</td>
<td>0.50</td>
<td>-</td>
<td>no data</td>
</tr>
<tr>
<td>8</td>
<td>375 x 2</td>
<td>6</td>
<td>20 (2.5)</td>
<td>0.0</td>
<td>no data</td>
<td>0.46</td>
<td>0.12</td>
<td>no data</td>
</tr>
<tr>
<td>9</td>
<td>375 x 2</td>
<td>6</td>
<td>18 (3.2)</td>
<td>0.0</td>
<td>no data</td>
<td>0.35</td>
<td>-</td>
<td>no data</td>
</tr>
<tr>
<td>Med. Min. Max.</td>
<td></td>
<td></td>
<td>17.0 (3.0) 6.0 (1.8) 37.0 (6.0)</td>
<td></td>
<td></td>
<td>0.46 0.32 0.78</td>
<td></td>
<td>0.10 0.04 0.04</td>
</tr>
</tbody>
</table>
Efficacy and safety of Rituximab in children with refractory SDNS (meta-analysis)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lijima K 2014</td>
<td>-1.31</td>
<td>0.34</td>
<td>31.4%</td>
<td>0.27 [0.14, 0.53]</td>
<td></td>
</tr>
<tr>
<td>Magnasco A 2011</td>
<td>0.07</td>
<td>0.82</td>
<td>11.7%</td>
<td>1.07 [0.21, 5.35]</td>
<td></td>
</tr>
<tr>
<td>Ravani P 2011</td>
<td>-0.95</td>
<td>0.28</td>
<td>35.4%</td>
<td>0.39 [0.22, 0.67]</td>
<td></td>
</tr>
<tr>
<td>Sinha A 2012</td>
<td>0.12</td>
<td>0.52</td>
<td>21.4%</td>
<td>1.13 [0.41, 3.12]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td><strong>0.49 [0.26, 0.92]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.22; Chi² = 6.69, df = 3 (P = 0.08); I² = 55%
Test for overall effect: Z = 2.21 (P = 0.03)

Zhao et al. 2015; *Scientific Reports* 5, Article number: 8219
Prognosis in SDNS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Adulthood relapsers (n = 14)</th>
<th>Adulthood non-relapsers (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No steroid-dependency</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>Steroid-dependency</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>One course of cytotoxic treatment</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>≥ 2 courses of cytotoxic treatment</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>