Treatment of difficult cases of nephrotic syndrome
Idiopathic Nephrotic Syndrome

- minimal change GN
- IgMGN
- mesangial proliferative GN

focal segmental glomerulosclerosis

The best prognostic feature of MCGN and FSGS in both children and adults is the response to steroids

Meyrier A, 2005 Exp Opin Pharmacother
Treatment of first episode of NS with prednisone

2 months vs >3 months (19 RCTs)

**Results**

RR of relapse at 12-24 months: 0.70 (0.58-0.84 CI)

inverse relationship between duration and risk of relapse \( (R^2 0.56; \ P=0.03) \)

**Conclusion:**

The 1st episode of NS should be treated at least for 3 months with increasing benefit up to 7 months.
Steroid-Resistant Nephrotic Syndrome

Definition

Children
6 weeks of prednisone 2 mg/Kg/day
( + 3 e.v. pulses MP 10 mg/Kg)

Adults
4-6 months of prednisone 1 mg/Kg/day
Treatment of children and adults with idiopathic steroid-resistant NS

ALKYLATING AGENTS
The results of alkylating agents in nephrotic FSGS are disappointing

**ADULTS**  
*Meyrier 2003*

<table>
<thead>
<tr>
<th></th>
<th>Complete Remission</th>
<th>Partial Remission</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid Dependent</td>
<td>52%</td>
<td>24%</td>
<td>24%</td>
</tr>
<tr>
<td>Steroid Resistant</td>
<td>15%</td>
<td>10%</td>
<td>75%</td>
</tr>
</tbody>
</table>
Interventions for idiopathic steroid-resistant NS in children

9 RCTs involving 225 children: RR of persistent NS

- Oral Cyclophosphamide+P vs Prednisone: RR 1.01 (0.74-1.36)
- IV CPA vs oral CPA: RR 0.09 (0.01-1.39)
- Azathioprine+P vs Prednisone: RR 1.01 (0.77-1.32)

no significant effect on RR of persistent NS at the meta-analysis
<table>
<thead>
<tr>
<th>Treatment</th>
<th>L of Ev</th>
<th>Grade</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cyclophosphamide (12 weeks)</td>
<td>4 (MCGL)</td>
<td>D</td>
<td>Possible benefit from pooled case series; small numbers in RCTs- uncertain benefit</td>
</tr>
<tr>
<td>IV cyclophosphamide (500 mg/m2, monthly for 6 months)</td>
<td>2 (MCGL)</td>
<td>B</td>
<td>Advantage over oral cyclophosphamide, but small numbers</td>
</tr>
<tr>
<td></td>
<td>4 (FSGS)</td>
<td>D</td>
<td>Possible benefits, short FU to ESRF</td>
</tr>
</tbody>
</table>
Treatment and outcome of children and adults with idiopathic steroid-resistant NS

ALKYLATING AGENTS

CYCLOSPORIN
Cyclosporin A in steroid-resistant NS in adults

RCTs metaanalysis

Lieberman ('96)
Ponticelli ('93)
Cattran ('99)
All
Interventions for idiopathic steroid-resistant NS in children

3 RCTs: 49 children:

Cyclosporin (CyA) vs PL

RR of persistent NS

RR 0.64 (0.47-0.88)
## Treatment of steroid-resistant NS

### Cyclosporin A

**Evidence-based recommendations**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Level of evidence</th>
<th>Grade</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCGL Cyclosporin (at least 6 months)</td>
<td>4</td>
<td>D</td>
<td><strong>Possible benefit</strong> from pooled case series; no significant benefit in RCT – small numbers</td>
</tr>
<tr>
<td>FSGS Cyclosporin (at least 6 months)</td>
<td>1</td>
<td>A</td>
<td><strong>Beneficial</strong></td>
</tr>
</tbody>
</table>
Treatment and outcome of children and adults with idiopathic steroid-resistant NS

ALKYLATING AGENTS

CYCLOSPORIN

ANGIOTENSIN ANTAGONISTS
Treatment of steroid-resistant FSGS:

ACE-inhibitors

Evidence-based recommendations

<table>
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<tr>
<th>Treatment</th>
<th>L of Ev</th>
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</tr>
</thead>
<tbody>
<tr>
<td>High dose Enalapril and Fosinopril</td>
<td>3</td>
<td>C</td>
<td>Useful in reducing proteinuria</td>
</tr>
</tbody>
</table>

- ACE-I (fosinopril) after 12 weeks proteinuria reduction by 1 g/day (-1.21 to -0.69)
Nephrotic Syndrome

Steroid-sensitive

- 89.5%
- Remission or infrequent relapses

Steroid-resistant

- 22 cases
- Remission or infrequent relapses
- Steroid-dependant
  - 52%
  - Cyclophosphamide
    - 48%
    - Remission or infrequent relapses
    - 38%
    - Remission or infrequent relapses
  - 62%
  - Cyclosporine ± small doses ster.
    - 3 cases
    - Remission or infrequent relapses
  - 78%
  - Remission or infrequent relapses

Remission or infrequent relapses

Steroids

No response

- 10 cases

Desperate NS

- 29 cases (7.7%)

390 Children with NS
Turin Regina Margherita (R.Coppo) and Rome Bambin Gesù (F.Emma)
Last 10 years (1995-2005)
“Desperate” cases of nephrotic syndrome no sustained remission after

STEROIDS
8 weeks in children
6 months in adults

ALKYLATING AGENTS
8-12 weeks

CYCLOSPORIN
6 months

ANGIOTENSIN ANTAGONISTS

rescue therapy?
Cumulative Percentage Renal Survival in Primary FSGS
for non-nephrotic patients, nephrotic patients, and patients with massive proteinuria

Evidence Based Medicine and rare disease

Rare diseases and the assessment of intervention: what sorts of clinical trials can we use?
Wilken B, Inherit Metab Dis. 2001;24:291

Problems with finding evidence for rare events.
Kozma CM: Pharmaceutical Outcomes USA. Manag Care Interface. 2004;1:45-6
Steroid therapy: different doses, different forms

steroid, cytotoxic and cyclosporin resistant
desperate NS:
rescue therapy

- Steroid therapy: different doses, different forms
High IV steroid doses to improve the effect

Methylprednisolone pulses (10-30 mg/kg) in children

Mendoza: on alternate day for 2 weeks
(1995) 2 times/week for 4 weeks
1/week for 6 weeks
1/month for 24-48 months

Waldo: on alternate day for 2 weeks
(1998) 1/week for 6 weeks
1/month for 24 months

Favourable results: remission in up to 70%
Progression to ESRF halted
### Treatment of steroid-resistant NS

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<tbody>
<tr>
<td>IV methylprednisolone (3-6 months)</td>
<td>5 (MCGL)</td>
<td>D</td>
<td>Possible benefit, small numbers in case series</td>
</tr>
<tr>
<td>IV methylprednisolone (6-12 months)</td>
<td>4 (FSGS)</td>
<td>D</td>
<td>Possible benefit</td>
</tr>
<tr>
<td>with alkylating agents</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Other ways to achieve steroid effects: ACTH

ACTH

*Used in 1950’, because it does not inhibit surrenal glands, then substituted by oral steroids*

*Used to treat dislipidemia in membranous GN proteinuria was found to decrease*  
(Berg A, Kidney Int 1999)

**ACTH induced improvement in the nephrotic syndrome**

Berg NDT 2004, 19:1305-1307

23 cases of various GN
0.5 mg/week until 1 mg/3 times a week:
  in mean 25 µg / Kg / week:
General anti-proteinuric effect.
One case progressed to ESRF
RCT

ACTH in membranous GN

MP pulses + Cyclophosphamide or Chlorambucil versus ACTH from onset 2 mg / week for 1 year

Total or partial remissions:
MP+ Ctx: 15 / 16 versus ACTH :14 / 15
Proteinuria and cholesterol significantly reduced in both arms

the effect of ACTH is not lesser then MP pulses + Ctx
ACTH in 6 cases of FSGS that did not respond to traditional therapy
Meyrier 2005 ASN

Proteinuria reduction in 6/6, but progression to CKD was not modified.
Physico-chemical effect instead of immune-effect?
Meyrier’s hypothesis: ACTH and CyA are lipophilic and bind to a lipidic complex associated to the slit diaphragm, limiting the protein leak.
steroid, cytotoxic and cyclosporin resistant
desperate NS: 
rescue therapy

- Steroid therapy: different doses, different forms
- Cyclosporin therapy over several years
390 cases of Children with NS Turin and Rome Center
Last 10 years (1995-2005)

Nephrotic Syndrome

- Cortico-sensitive
  - Steroids
    - Remission or Infrequent relapses
      - 89.5%
    - Corticodependant
      - 48%
    - Cyclophosphamide
      - 52%
    - Cyclosporine ± small doses ster.
      - 62%
    - No response
      - 38%

- Corticoresistant
  - 22 cases
  - 5.9%

- Congenital
  - 4.3%

- Steroids
  - 390 cases of Children with NS Turin and Rome Center
  - 89.5% Cortico-sensitive
  - 4.3% Congenital
  - 52% Corticodependant
  - 5.9% Corticoresistant
  - 38% Remission or Infrequent relapses
  - 78% Cyclosporine dependant
  - 1.8% Desperate NS

Desperate NS 7.7%
An example of CyA nephrotoxicity.

Francois H, et al
Cyclosporin-dependent NS: not truly “desperate cases”

Renal tolerability of CyA is reasonably good when the dosage is low

Meyrier A, Expert Opin Pharm 2005
Long Term CyA treatment in SRNS
GE-ITALIAN STUDY Adult and Children
Ghiggeri 2004

• 55 steroid –resistant NS treated with CyA
NS remission (partial or total): 20 patients
Mean follow-up: 81 months

Renal biopsy after 5 years of treatment:
no tubular or interstitial fibrosis
SRNS: CsA Sensitivity is The Major Factor Influencing Long-term Renal Outcome

Ghiggeri GM, 2004
Effective and safe treatment with cyclosporine in nephrotic children: a prospective RCT
Ishikura K et al. Kidney Int. 2008;73:1167-73

Children with SDNS:
CyA for 6 months: TL 80-100 ng/ml

Over the next 18 mo.

Group A) TL 60-80 ng/ml
Group B) fixed dose 2.5 mg/Kg.

2 years after, higher rate of sustained remission in Group A, while TL < 40 ng/ml were not protective for relapse.
Steroid-, cytotoxic- and cyclosporin-resistant desperate NS: rescue therapy

- Steroid therapy: different doses, different forms
- Cyclosporin late response late and sustained effect, cyclosporin dependancy, risk of toxicity
- Other calcineurin-inhibitors: Tacrolimus
NS steroid and/or cyclosporin dependent/resistant
Total remission in 100% of CyA-dependent cases
15% of primary CyA-resistant

TAC monotherapy in steroid-dependent NS
Duncan M et al, NDT 2004; 19:3062
**TACROLIMUS**

**TAC in pediatric NS resistant to traditional therapies**

Loeffeler K (Canada) Ped Nephrol 2004; 19:281-7

*Total remission in 81% (0.6-5.5 months)*

*Partial remission in 13%*

**TAC in steroid-resistant and steroid-dependent NS**

Westhoff TH (Germany) Clin Nephrol 2006; 65:393-400

*Prospective RCT 10 children*

*Complete remission in 50%*

*Partial remission in 40%*

**TAC in steroid-dependent and cyclosporin dependent NS**

Sinha MD (UK), NDT 2006; 21:1848-542

*Retrospective analysis of 10 children treated with CyA*

*no difference in benefits of TAC vs continuing CyA*
Tacrolimus as a steroid-sparing agent for adults with steroid-dependent minimal change nephrotic syndrome
Li X, NDT 2008;23:1919-25

Adults with SDNS:
TAC (target 4-8 ng/ml) or
CPA 750 mg/m²/month
for 24 weeks
together with P 0.5 mg/Kg/day

complete remission: 90% TAC; 77% CPA (faster with TAC)
Similar remission rate after 2 years.
Steroid-, cytotoxic- and cyclosporin-resistant desperate NS: rescue therapy

- Steroid therapy: different doses, different forms
- Cyclosporin late response late and sustained effect, cyclosporin dependancy, risk of toxicity
- Other calcineurin-inhibitors: Tacrolimus
- Other purine synthesis inhibitors: Mycophenolate
MMF and prednisone in steroid-dependent NS

Bagga A Am J Kidney Dis 2003

19 Children previously treated with P, oral CP, and still cortico-dependent NS:
MMF 30 mg/Kg/day for 2 years associated with low tapering doses of Prednisone. FU: 18 months

Frequence of relapses from 6.6 to 2 each year p<0.0001:
MMF was effective as steroid-sparing agent

75% reduction of relapses
Reduced dose of P assumed from 0.7 to 0.3 mg/Kg/day p<0.0001.
After withdrawal relapse in 68% of the cases
No significant side effects.
MMF in FSGS: D. Cattran, 2004
18 cases steroid and CyA resistant:: Decrease in proteinuria in 44%
Relapse at MMF withdrawal in 50%.
# MMF in steroid-resistant NS

<table>
<thead>
<tr>
<th>Author</th>
<th>N cases</th>
<th>Regimen</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day CJ (Wolverhampt, UK, NDT 2002)</td>
<td>7 adults</td>
<td>MMF (1 gx2)</td>
<td>Complete remission 6/7 1/7 partial r.</td>
</tr>
<tr>
<td>Montané (Miami, US, Ped Nephrol 2003)</td>
<td>9 chldr.</td>
<td>MP pulses (15 mg/kg/week x 4-8) ACE-i/ARB MMF (250-500 mg/m2)</td>
<td>Proteinuria (6-24 months) 72% below baseline p&lt;0.01</td>
</tr>
<tr>
<td>Mendizabal S (Spain, Ped Nephrol 2005)</td>
<td>27 5 SRNS</td>
<td>no response to CP and CyA MMF (1200 mg/m2)</td>
<td>1/5 remission Relapse after withdrawal.</td>
</tr>
<tr>
<td>Ulinski (Lyon, Ped Nephrol 2005)</td>
<td>9 4SRNS</td>
<td>CyA with GFR impairment: 2g/1.73 m2</td>
<td>0/4 remissions</td>
</tr>
</tbody>
</table>
Steroid-, cytotoxic- and cyclosporin-resistant desperate NS:
rescue therapy
sporadic case reports

Permeability factor (PF)
V. Savin 1993

PF is a small anionic protein that binds to Prot A and has analogies with Immunoglobulins
Plasmapheresis and protein A immunoadsorption

Dantal et al (N Engl, 1994)
In native and in recurrent FSGS in grafted kidneys:

- Effect often limited in time, with relapse at withdrawal
- Some cases benefit from continued, chronic treatment:
  - High cost / often limited benefits
  - In cases with antiproteinuric response the progression to ESRF is only partially limited
New therapeutical approaches to NS recurrence on transplanted kidney

Plasmapheresis or Immunoabsorbance on A Protein + cyclophosphamide: 70% reduction in proteinuria

Lyon and Miami Protocol

Encouraging results

Cyclosporin A e.v.
3 mg/kg/day until 40 days after Tx:
82% remission up to 9 years.
Kidney survival at 5 years: 70%

Paris Protocol
Combined therapy with LDL apheresis and Prednisone for pediatric FSGS resistant to traditional activities.  

Hattori  
M Am J Kid Dis  2003

- In 11 children with GSFS, steroid and cyclosporin-resistant  
- LDL-Apheresis 2/weeks for 2 weeks, then 1/week for 6 weeks.  
- Prednisone 1 mg/Kg /day

Total remission in 5/11 within 4 weeks: a valuable addition to other options

- maintained GFR for about a mean of 4 years.  
- Temporary remission in 2 children.  
- Patients which did not respond needed dialysis after 1-2 years.
## Treatment of steroid-resistant FSGS: Evidence-based recommendations

<table>
<thead>
<tr>
<th>Treatment</th>
<th>L of Ev</th>
<th>Grade</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Mycophenolate mofetil</td>
<td>6</td>
<td>D</td>
<td>Case reports</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>6</td>
<td>D</td>
<td>Case reports</td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>6</td>
<td>D</td>
<td>Anecdotal reports</td>
</tr>
</tbody>
</table>
Steroid-, cytotoxic- and cyclosporin- resistant NS: sporadic case reports of rescue therapy

B cells as new target for NS treatment?

Anti-CD 20 chimeric MoAb Rituximab
T lymphocytes and NS Hodgkin’s disease
Allergy
Viral infections
In vitro evidences
Shaloub’s hypothesis: permeabilizing T lymphokine

B and T collaboration

PF (Ig part?)
B cells activated in relapse

Steroids, CSA
Cyclophosphamide
Rituximab

“Toxic substance”
- Cytokines
- Direct Toxicity
- Cross-Talk

Podocyte-Damage/Loss

Proteinuria
Rituximab is a chimeric mouse-human monoclonal antibody directed against the B cells-specific antigen CD20, which selectively and profoundly depletes B lymphocytes and has been widely used to treat B cell lymphomas.
A case of steroid dependent NS, treated with Rituximab because of thrombocytopenic purpura (375 mg/m2 /week x 4 weeks)

(Benz, Pediatr Nephrol 2004)

A case of PTLD treated with Rituximab; concomitant recurrent FSGS and SN disappeared

(Nozu, Pediatr Nephrol 2005, 20, 1660)

Rituximab 375 mg/m² x 4

Prednisone

L cP M * MMF CS A cP CS A

NS relapses
Is there a role for rituximab in the treatment of idiopathic childhood nephrotic syndrome?

10 cases have been successfully treated with 4 doses of Rituximab (375 mg/m²/week)
Rituximab: is replacement of cyclophosphamide and calcineurin inhibitors in steroid-dependent nephrotic syndrome possible?

Jörg Dötsch • Dirk. E. Müller-Wiefel • Markus J. Kemper
Rituximab treatment for severe steroid- or cyclosporine-dependent nephrotic syndrome: a multicentric series of 22 cases

Vincent Guigonis • Aymeric Dallocchio • Véronique Baudouin • Maud Dehennault • Caroline Hachon-Le Camus • Mickael Afanetti • Jaap Groothoff • Brigitte Llanas • Patrick Niaudet • Hubert Nivet • Natacha Raynaud • Sophie Taque • Pierre Ronco • François Bouissou
22 patients 6-22 y.o.
Median disease duration 11 years (3-16)
(7/22 were nephrotic)

- Steroid-resistant or
- Recurrence in spite of alkylating agents and 1 month of MMF
- Response to calcineurine inhibitors (for more than 3 years) but toxic effects and relapses on withdrawal

- 2-4 weekly infusions of 375 mg/m2 RTX

- If CD19 cells reappear repeat RTX
Results

- RTX induced a complete B cell depletion, lasting 2-11 months (median 6 months)
- Remission was induced in 4/7 NS
- Always effective in 15/15 proteinuria-free patients
- In 19/22 (85%) one or more concomitant immunosuppressive treatment was stopped
- Duration of RTX effect was not related to either nephrotic status of RTX dose
Fig. 2 Relative decrease of remaining immunosuppressive treatments (IST) in the 14 rituximab (RTX)-responsive patients who still receive IST at the end of follow-up. For each IS agent still given at the end of the follow-up, the percent of dosage reduction was calculated as the ratio of average dosage during the last 3 months of follow-up to the average dosage during the last 3 months before RTX therapy.
RTX was repeated in 12 patients who responded, when CD19 count was >1% of total lymphocytes.
Relapses

• none during B-cell depletion
• 4 relapses after 7-17 months (CD19 count 3-7%)

Failure of RTX therapy

• in 3 patients, nephrotic at treatment, receiving 4 doses, in spite of good CD19 depletion

Adverse effects

• In 10/22, mild (cutaneous eruptions, abdominal pain, headache, neutropenia, hypogammaglobulinemia in 8 cases)
Rituximab and nephrotic syndrome: a new therapeutic hope?

Muhammad Shahed Ahmed and Christopher F. Wong

Department of Nephrology, Aintree University Hospital Foundation Trust, Lower Lane, Liverpool L9 7AL, UK
Rituximab used in > 500,000 subjects

Toxicity, adverse events:

- 2 cases of leukoencephalitis in SLE treated with multiple drugs, including Rituximab

- Allergic reactions, anti chymeric Antibodies.
LETTER TO THE EDITORS

Does rituximab treat recurrent focal segmental glomerulosclerosis post-renal transplantation?

Stephen D. Marks • Mary McGraw

Good outcome
2 pediatric cases with PTLD
2 adult cases

No response
2 adult cases (3 and 10 months after Tx)
2 pediatric cases (4 months and 7 years after Tx
R.Coppo ERA-EDTA 2008)
Steroid-, cytotoxic- and cyclosporin-resistant desperate NS:
rescue therapy:
sporadic case reports

- Sirolimus in 6 FSGS reduced GFR in 5/6 and increased proteinuria: trial stopped.
- Mizoribine pulse therapy: 10 mg/kg: effective in CyA dependent SRNS to spare or discontinue CyA.
- Ketokonazole 50 mg in association with CyA: sparing effect.
- Antioxidants?
- Statins? collateral benefits for CV risk
29 desperate NS cases (steroid, alkylating agents, CyA resistant) from Turin and Rome

7 cyclosporine-dependent >6 months

22 cyclosporine-resistant

9 TAC
Response 5/9

12 MMF
Response 4/12

4 ACTH
Response 2/4

5 PE
Response 2/5

1 resistant to MMF and TAC
Response to ACTH

2 resistant to MMF
Response to TAC

1 resistant to MMF
Response to ACTH

1 resistant to TAC
Response to PE
A rescue therapy may be tried even in desperate NS

no feature is predictive of individual response

the research is open to new approaches