Second-Line Therapy in MCD
(Steroid Dependent/Resistant Nephrotic Syndrome)
Nephrology Grand Rounds
Tuesday March 29th, 2011
Steroid Response
Steroid Dependent/Resistant Nephrotic Syndrome (SDNS/SRNS)
Relapses Rates
Steroid Sparing Regimens in SDNS/SRNS
- Alkylating Agents
  - Cyclophosphamide (CYC)
  - Chlorambucil
- Calcineurin Inhibitors
  - Cyclosporine (CSA)
  - Tacrolimus (TAC)
- Mycophenolate Mofetil (MMF)
- Rituximab (RTX)
Most common form of nephrotic syndrome (NS) in children.

In children younger than 10 years, MCD makes up to 90% of all cases of NS.

In adolescents above the age of 10, MCD accounts for 50% of NS cases.

In adults, MCD accounts for 10–15% of primary NS cases.
Glucocorticoids
## Steroid Dependence/Resistance

<table>
<thead>
<tr>
<th>Term</th>
<th>Adult</th>
<th>Pediatric $^{14,15}$</th>
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</thead>
<tbody>
<tr>
<td>Relapse</td>
<td>Proteinuria $\geq 3.5 \text{ g day}^{-1}$ occurring after complete remission has been obtained for $\geq 1$ month</td>
<td>Albu-stix 3+ or proteinuria $&gt; 40 \text{ mg m}^{-2} \text{ h}^{-1}$ occurring on 3 days within 1 week</td>
</tr>
<tr>
<td>Frequently relapsing</td>
<td>2+ relapses within 6 months</td>
<td>2+ relapses within 6 months</td>
</tr>
<tr>
<td>Complete remission</td>
<td>Reduction of proteinuria to $\leq 0.20 \text{ g day}^{-1}$ and serum albumin $&gt; 35 \text{ g l}^{-1}$</td>
<td>$&lt; 4 \text{ mg m}^{-2} \text{ h}^{-1}$ on at least 3 occasions within 7 days serum albumin $&gt; 35 \text{ g l}^{-1}$</td>
</tr>
<tr>
<td>Partial remission</td>
<td>Reduction of proteinuria to between $0.21 \text{ g day}^{-1}$ and $3.4 \text{ g day}^{-1}$ and 3.4 g day$^{-1}$ decrease in proteinuria of $\geq 50%$ from baseline</td>
<td>Disappearance of edema. Increase in serum albumin $&gt; 35 \text{ g l}^{-1}$ and persisting proteinuria $&gt; 4 \text{ mg m}^{-2} \text{ h}^{-1}$ or $&gt; 100 \text{ mg m}^{-2} \text{ day}^{-1}$</td>
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<tr>
<td>Steroid-resistant</td>
<td>Persistence of proteinuria despite prednisone therapy 1 mg kg$^{-1}$ day$^{-1}$ $\times$ 4 months</td>
<td>Persistence of proteinuria despite prednisone therapy 60 mg m$^{-2}$ $\times$ 4 weeks$^a$</td>
</tr>
<tr>
<td>Steroid-dependent—NS recurs when stop or decrease treatment</td>
<td>Two consecutive relapses occurring during therapy or within 14 days of completing steroid therapy$^{16}$</td>
<td>Two relapses of proteinuria within 14 days after stopping or during alternate day steroid therapy</td>
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NS, nephrotic syndrome.

$^a$Or persistence of proteinuria despite prednisone therapy 60 mg m$^{-2}$ $\times$ 4 weeks and three methylprednisolone pulses.
# Steroid Response

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<tr>
<th>Study</th>
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<tr>
<td><strong>Number of Patients</strong></td>
<td>40</td>
<td>89</td>
<td>51</td>
<td>33</td>
<td>62</td>
<td>95</td>
<td>401</td>
</tr>
<tr>
<td><strong>CR + PR</strong></td>
<td>98%</td>
<td>91%</td>
<td>92%</td>
<td>97%</td>
<td>98%</td>
<td>92%</td>
<td>95%</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>91%</td>
<td>78%</td>
<td>76%</td>
<td>97%</td>
<td>93%</td>
<td>75%</td>
<td>95%</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>7%</td>
<td>13%</td>
<td>16%</td>
<td>5%</td>
<td>17%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Steroid Resistance</strong></td>
<td>2%</td>
<td>9%</td>
<td>8%</td>
<td>3%</td>
<td>2%</td>
<td>8%</td>
<td>5%</td>
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</table>
Glucocorticoid therapy remains the mainstay of treatment with CR in 75–97% of MCD adults.

Only one RCT in adults with MCD that compared prednisone (PRED) with supportive therapy (n=31).
- 75 % of PRED treated pts had remission to <1g/day of proteinuria within 6 mo.
- In the untreated group, 50% were in remission at 18 mo and approximately 70% at 3 yrs.

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</tr>
<tr>
<td>Total Relapses</td>
<td>65%</td>
<td>76%</td>
<td>70%</td>
<td>37%</td>
<td>62%</td>
<td>73%</td>
<td>71%</td>
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<tr>
<td>Frequent-relapsers</td>
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<tr>
<td></td>
<td>16%</td>
<td></td>
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<td></td>
<td></td>
<td>44%</td>
</tr>
<tr>
<td>Steroid-dependent</td>
<td>40%</td>
<td>14%</td>
<td>50%</td>
<td>10%</td>
<td></td>
<td></td>
<td>18%</td>
</tr>
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</table>
Steroid Sparing Regimens

- Adverse side effects of longstanding steroids has prompted the use of other immunomodulating agents.
- The data on steroid sparing regimens in SDMCD, FRMCD or SRMCD is mostly based on retrospective reviews and prospective observational cohort studies.
- Furthermore, these studies are mainly in the conducted in the pediatric “idiopathic” NS population (includes MCD, FSGS and occasionally membranous pts).
Cyclophosphamide
Prospective control trial of 30 children with FRNS randomized to PRED vs PRED + CYC (8 wk course, 3mg/kg/d).
Retrospective review of 89 adult MCD pts from 1963–1982 (mean f/u of 7.5 yrs).

CYC was used in 36 pts:
- 2 as initial treatment
- 11 for steroid resistance
- 23 for relapses

Nolasco et al. KI, 1986.
Remission of proteinuria with CYC was similar to PRED alone, 70% remitting in 16 wks.

Fig. 3. Time to complete loss of proteinuria in 36 adult-onset nephrotic patients with minimal changes treated with cyclophosphamide. Symbols are: all the patients (-----); (----) those treated concomitantly with prednisone ($N=11$); and (●—●) those treated with cyclophosphamide alone ($N=25$).
**CYC Remission Rates**

Fig. 4. Stability of response to cyclophosphamide in 28 patients who lost proteinuria completely following treatment with cyclophosphamide (○—○), compared with 55 patients who lost proteinuria completely following corticosteroid treatment (....). The response following cyclophosphamide is significantly more stable.

Nolasco et al. KI, 1986.
Multicenter retrospective study, reviewed 143 children with SDNS and FRNS treated with CYC and followed over a 15–yr period.
Use of alkylating agents has been associated with bone marrow suppression, hemorrhagic cystitis, alopecia, sterility and increased risk of malignancy.

These side effects have prompted the investigation of other steroid sparing regimens.
Cyclosporine
Forty children with SDNS and signs of steroid toxicity were randomly assigned to receive either:
- CSA (6 mg/kg, for 3 mo followed by tapering doses over the next 3 mo) or
- Chlorambucil (0.2mg/kg cumulative dose of 8 mg/kg over 40 d).

Randomization occurred after remission of proteinuria with PRED (subsequently tapered off in 3 mo).
Of the 20 pts treated with CSA:
- 4 relapsed before or on discontinuation of PRED,
- 7 relapsed when the initial dose of CSA was tapered, and
- 8 after withdrawal of CSA.

Of the 20 pts treated with chlorambucil:
- 14 relapsed (at a mean of 7 mo post–Rx),
- 6 were still in remission 27–49 mo post–Rx.

The remission rate at 3 yrs was 30% after a course of chlorambucil compared with only 5% after a 3-month course of CSA.
Open, prospective, randomized, multicenter trial in 73 pts with SDNS or FRNS (adults and children).

Randomized to either:
- 8 wks of CYC (2.5mg/kg/d) or
- 9 months of CSA (5mg/kg/d), then tapered off by mo 12.

F/u for 2 yrs.
At 9 mo, CSA (74% CR, 14% PR) vs CYC (64% CR, 4% PR), but not statistically significant.

At 2 yrs, 25% of CSA pts (50% adults and 20% children) and 63% of CYC (40% adults and 68% children) were relapse-free.
The mean dose of PRED per year was significantly less ($P<0.001$) in both groups for the experimental year than for the year before randomization.
The mean number of relapses per year was significantly less \((P < 0.001)\) in both groups for the experimental year than for the year before randomization.
Later the same year, Ponticelli reported another RCT of CSA, but this time the study population was steroid resistant (SRNS, biopsies showing MCD or FSGS).

45 SRNS pts randomly assigned to:
- Supportive therapy (n=19) or
- CSA (5mg/kg/d for adults, 6mg/kg/d for children, for 6 mo then tapered off by 25% every 2 mo until complete discontinuation).

During the 1st year, 59% of CSA pts vs 16% of controls attained remissions (CR + PR), however, with tapering of CSA, proteinuria trended towards baseline values.
Tacrolimus
Experience is much more limited with tacrolimus use, and no studies have shown a benefit over CSA in the treatment of SDNS, FRNS or SRNS.
Prospective cohort study of SDMCD adults.

Pts were either given TAC (n=12) or pulse CYC (n=26) in combination with oral PRED (0.5 mg/kg/day) for 24 wks.

Mean follow-up after treatment was 23.0 mo
TAC vs CYC – Li et al.
61.5% CYC pts vs 72.7% TAC pts ($P = 0.683$) successfully withdrew from steroids for $> 2$ wks.

For CR pts, maintained remission post-Tx was:
- 70% for CYC and 60% for TAC at 24-wk and
- 60% for CYC and 50% for TAC at final f/u ($23.0 \pm 10$ mo).

No significant difference in sustained remissions or relapse rate between the two groups.
TAC vs CYC – Li et al.

Li et al. NDT, 2008.
Mycophenolate Mofetil
## MMF

<table>
<thead>
<tr>
<th>Author/Year Country (Reference Number)</th>
<th>Patients Studied</th>
<th>Dosage of MMF and Length of Follow-up</th>
<th>Results of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barletta et al./2003/United States (2)</td>
<td>10 children with CsA-dependent NS and 4 with SDNS; 8 of 10 CsA-dependent patients had interstitial fibrosis</td>
<td>800 to 1200 mg/m² d; all patients had previously received a 12-wk course of cyclophosphamide</td>
<td>Significant reduction in frequency of relapses after start of MMF in both CsA-dependent and SDNS patients</td>
</tr>
<tr>
<td>Bagga et al./2003/India (3)</td>
<td>19 children (aged 3 to 11 yr) with SDNS that was associated with MCNS in 10 and FSGS in 3 patients</td>
<td>29 (21 to 33) mg/kg per d in 2 doses for 11.8 mo; patients then followed for 17 mo after MMF prescribed</td>
<td>Decrease in number of relapses while on MMF; relapse rate was higher after MMF was stopped; no serious adverse events</td>
</tr>
<tr>
<td>Gellermann et al./2004/Germany (4)</td>
<td>7 children (median age 12.7 yr [9 to 16 yr]) who had SDNS and signs of nephrotoxicity after long courses of CsA therapy</td>
<td>Initial dose 500 mg/m² twice daily; dosage was adjusted to give trough MPA level of 1.5 to 4.5 mg/ml; duration of therapy 25 (15 to 39) mo</td>
<td>6 of 7 patients were maintained in remission while on MMF; GFR rose after patients were switched from CsA; no leukopenia or gastrointestinal adverse effects</td>
</tr>
<tr>
<td>Novak et al./2005/United States (5)</td>
<td>21 children (aged 2 to 17 yr at time of MMF therapy)</td>
<td>600 mg/m² twice daily (maximum dosage 1 g twice daily); duration of prescription 1.0 ± 0.7 yr</td>
<td>Relapse rate fell from 0.89 to 0.55 relapses per month while on MMF; one patient developed diarrhea but stayed on MMF</td>
</tr>
<tr>
<td>Ulininski et al./2005/France (6)</td>
<td>9 children (3 to 16 yr) with CsA-dependent NS or SRNS and CsA nephrotoxicity were switched from CsA to MMF</td>
<td>Up to 1 g/1.73 m² twice daily for 261 ± 183 d</td>
<td>SDNS patients stayed in remission; SRNS had no change in level of proteinuria; GFR increased from 76 ± 5 to 119 ± 6 ml/min per 1.73 m²; no adverse events</td>
</tr>
<tr>
<td>Pecoraro et al./2005/Italy (7) (abstract)</td>
<td>12 children with SDNS (mean age 8.7 yr) with renal biopsy showing FSGS in 2 and MCNS in 10</td>
<td>27.8 mg/kg per d for mean of 24 mo was given after NS remission was induced with steroids; plasma trough level of MPA was 3.6 ± 1.2 μg/ml</td>
<td>Nine of 12 patients achieved a sustained remission; 10 of 12 stayed in remission on MMF; no adverse events</td>
</tr>
</tbody>
</table>
26 children (21 SDNS/5 SRNS, MCD/FSGS), who received sequential Tx with CYC and CSA.
Median age of NS onset was 2.8 yrs and median age of MMF Tx was 11.4 yrs.
Study to assessed Tx efficacy at 6 mo.
In 5 pts with SRNS, only 1 achieved CR.
In the patients with SDNS, steroid sparing was achieved in 75% and 45% remained in remission on MMF monotherapy.
Withdrawal of MMF resulted in immediate relapse in 47%.
Multicenter, prospective, open-label study (SDNS = 6, FRNS = 27).

All pts were in remission at the time of study entry.

Received MMF 600 mg/m2 BID (max 1g BID) for 6 mo.

A tapering dosage of PRED QOD was given during the first 16 wk of MMF therapy.
MMF – Hogg et al.

- 75% of pts stayed in remission throughout the 6 mo of MMF therapy (25% relapsed).

- The relapse rate in these pts improved from one episode every 2 mo before MMF to one every 14.7 mo after MMF.

- Eight pts stayed in remission during the post-MMF period (f/u of 18–30 mo), whereas 16 relapsed shortly after stopping MMF.

Hogg et al. CJASN, 2006.
Rituximab
22 pts (ages 6–22 yrs) with SDNS or steroid-resistant but CSA-sensitive idiopathic nephrotic syndrome (SRCySNS) were treated with 2–4 infusions of RTX.

All pts were given RTX concurrently with one to three of the following drugs: steroids, CSA, TAC, and/or MMF.
Patient with severe SDNS or SRCySNS fulfilling criteria for inclusion in the study

- For proteinuric patients: Induce a remission with conventional IS treatments (if possible)

- Start RTX in association with at least one other IS treatment

- 2* to 4* weekly infusions of 375mg/m² RTX
  * left to the clinician decision

- Taper IS treatment, from the fourth RTX infusion (or before) starting with the less well-tolerated treatment
  **Goal:** at the 6th month after the first RTX infusion, the IS dosages must be below the usual relapse threshold for the patient

- No relapse of proteinuria before reappearance of CD19 cells despite IS tapering below the usual threshold

- Continue RTX therapy until 18 months of complete B cell depletion. (additional infusion of RTX as soon as CD19 cells are positive)

- Discontinue RTX therapy

RTX – Guigonis et al.

- RTX induced a complete B–cell depletion (by CD19 count) in all pts irrespective of the proteinuric status.

- The complete B–cell depletion obtained after the first course of RTX lasted from 2–11 mo (median 6 mo).

- Duration of RTX effect was not related to either the nephrotic status or the total RTX dose.
Remission was induced in 3 of 7 nephrotic patients at the time of RTX treatment.

One or more immunosuppressives could be withdrawn in 19 pts (85%), without relapse of proteinuria and without increasing other immunosuppressives.

Relative decrease in the remaining immunosuppressives in the 14 pts who responded to RTX.
RTX – Guigonis et al.

No relapse of proteinuria was recorded during the B–cell depletion period.

Relapses occurred in three pts when CD19+ cell counts were btw 54–273 cells/mm² (3–7% of total lymphocyte count).

RTX was unsuccessful in three pts (B cell depleted, but remained nephrotic).
Pts with SRNS (n=33) or SDNS (n=24), not responding to medications or showing calcineurin inhibitor toxicity, treated with 2–4 doses of RTX, and followed >12 mo.

Mean ages of SRNS and SDNS were 12.7 and 11.7, respectively.
Six mo after RTX in SRNS pts:
- 9 (27.2%) pts showed CR,
- 7 (21.2%) had PR, and
- 17 (51.5%) had no response.

At 21.5 mo, remission was sustained in 15 pts (CR=7, PR=8).

Of 24 pts with SDNS remission was sustained in:
- 20 (83.3%) at 12 mo and
- 17 (71%) at f/u of 16.8 mo.

The mean difference in relapses before and 12 mo after RTX was 3.9 episodes/pt per yr.
Kaplan–Meier curve showing the remission rates in pts with SDNS.

International Cyclosporine Workshop Recommendations

Treatment of Adult Idiopathic Glomerular Disease Associated with Nephrotic Syndrome
Figure 2 | Algorithm for the use of cyclosporin in the treatment of minimal change disease in adults.

Thank You