STEROID RESISTANT NEPHROTIC SYNDROME

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G.Deschenes
THE WEIGHT OF THE DIFFERENT FORMS OF IDIOPATHIC NEPHROTIC SYNDROME

Patients < 16 yrs, Paris area 12 million residents Dec 2007 - May 2010

190 "primary" NS

188 idiopathic

174 steroid sensitive (93%)

37 No relapse (20%)

138 Relapsers (73%)

14 steroid resistant (7%)

90 steroid dependent (48%)

G.Deschences
Genetic vs idiopathic SRNS age distribution

n = 1174 patients

Trautmann & the Podonet consortium 2015
G.Deschenes
DEFINITION #1

- **Persistence**
  - Proteinuria > 0.25 g/mmol
  - hypoalbuminemia <30 g/L

- **following**
  - 4 to 8 weeks of oral prednisone or prednisolone at 60 mg/m²/d

- **WITHOUT IVMP test**

- **UK, GERMANY and 4/14 isolated centers in europe**
  *(NSWG query 2014)*
DEFINITION #2

- **Persistence**
  - Proteinuria > 0.25 g/mmol
  - hypoalbuminemia <30 g/L
- **following**
  - 4 to 8 weeks of oral prednisone or prednisolone at 60 mg/m²/d
- **AND**
  - IV methyl prednisolone
  - 3 x 1 g/1,73m²
- **France & 17/24 isolated centers in europe**
  *(NSWG query 2013)*

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THE SPECTRUM OF IDIOPATHIC SRNS

• Resistant to oral prednisone or to oral+IV prednisone that responds to calcineurin antagonists
• Resistant to the association of prednisone and calcineurin antagonists that reccurs on a renal graft
• All resistant forms with a negative genetic testing

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PREVALENCE AT THE FIRST FLARE

<table>
<thead>
<tr>
<th>Séries</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Franche-Comté</td>
<td>4</td>
</tr>
<tr>
<td>Paris area</td>
<td>7</td>
</tr>
<tr>
<td>Aquitaine</td>
<td>10</td>
</tr>
<tr>
<td>Yorkshire</td>
<td>12</td>
</tr>
<tr>
<td>ISKDC-2013</td>
<td>13</td>
</tr>
<tr>
<td>Iran</td>
<td>13</td>
</tr>
<tr>
<td>New Zealand</td>
<td>19</td>
</tr>
</tbody>
</table>

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LATE OR SECONDARY STEROID RESISTANCE

Srivastava 1986

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LATE OR SECONDARY STEROID RESISTANCE

N = 29 (10F/19M)
Age 4.3±3.4 years

<table>
<thead>
<tr>
<th></th>
<th>median</th>
<th>range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial delay of response to</td>
<td>14 days</td>
<td>4-56</td>
</tr>
<tr>
<td>steroid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delay of late resistance</td>
<td>19 months</td>
<td>2-170</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Complete remission</th>
<th>Partial remission</th>
<th>Nephrotic proteinuria</th>
<th>ESRD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>14</td>
<td>6</td>
<td>6</td>
<td>3</td>
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</table>

Straatmann 2013
G.Deschenes
## HISTOLOGY

<table>
<thead>
<tr>
<th>Study</th>
<th>Minimal change disease</th>
<th>Focal segmental glomerulosclerosis</th>
<th>Diffuse mesangial proliferation</th>
<th>TOTAL</th>
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<tbody>
<tr>
<td>Habib 1971</td>
<td>32</td>
<td>31</td>
<td>nd</td>
<td>63</td>
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<tr>
<td>Mekhali 2009</td>
<td>35</td>
<td>33</td>
<td>10</td>
<td>78</td>
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<tr>
<td>Gulati 2012</td>
<td>78</td>
<td>43</td>
<td>10</td>
<td>131</td>
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<td>Zagury 2013</td>
<td>53</td>
<td>74</td>
<td>9</td>
<td>133</td>
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<tr>
<td><strong>TOTAL</strong></td>
<td><strong>198</strong></td>
<td><strong>181</strong></td>
<td>-</td>
<td><strong>379</strong></td>
</tr>
</tbody>
</table>
RENAL SURVIVAL

Ingulli & Tejani 1991

N = 57 children
28 primary SRNS
29 secondary SRNS

G.Deschesnes
CYCLOSPORINE-PREDNISONE

Ponticelli 1993

<table>
<thead>
<tr>
<th></th>
<th>Complete remission</th>
<th>Partial remission</th>
<th>Failure</th>
<th>Total</th>
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<tr>
<td>MCD</td>
<td>21</td>
<td>2</td>
<td>22</td>
<td>45</td>
</tr>
<tr>
<td>FSGS</td>
<td>6</td>
<td>2</td>
<td>12</td>
<td>20</td>
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<tr>
<td>Total</td>
<td>27</td>
<td>4</td>
<td>34</td>
<td>65</td>
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Niaudet 1994
G.Deschenes
PRED-CYCLOSPORINE vs PRED-TACROLIMUS
probability of non-response

Choudhry 2009

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PREDNISONE + CALCINEURIN ANTAGONISTS
probability of non-response
Robert-Debré series

N = 69 patients

weeks
probability of non response
0 10 20 30 40 50
0%
20%
40%
60%
80%
100%

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CYCLOPHOSPHAMIDE vs TACROLIMUS
all patients under prednisone

Gulati 2012
THE PLACE OF ANTIPROTEASOMES

saquinavir

Patient 6

prednisone (mg/kg/m)
plasma exchange
ACTH
rituximab
tacrolimus (mg/kg/d)

saquinavir (mg/kg/d)

disease onset

2005 2008 2009 2010

Coppo 2012

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RENAL SURVIVAL

78 children – 45 primary – 33 late or secondary

remission after cyclosporine: 45%

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Mekahli 2009
RENAL SURVIVAL
according to renal histology

Mekahli 2009

Zagury 2013

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RENAL SURVIVAL
according to initial or late resistance

Mekahli 2009
Zagury 2013

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THE MAIN FACTOR OF PROGNOSIS IS THE RESPONSE TO CYCLOSPORINE

\[ N = 136 \text{ children} \\
114 \text{ primary SRNS} \\
22 \text{ secondary SRNS} \]
Robert-Debré Series

N = 68/69 patients resistant to 4 wks+3MP

GENDER

F 32
M 37

STEROID RESISTANCE

LATE 12
PRIMARY 57

initial renal histology

<table>
<thead>
<tr>
<th>Description</th>
<th>Count</th>
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<tbody>
<tr>
<td>Minimal change</td>
<td>30</td>
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<tr>
<td>Focal and segmental</td>
<td>35</td>
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<tr>
<td>Glomerulosclerosis</td>
<td></td>
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<tr>
<td>No biopsy</td>
<td>4</td>
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</table>

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# Robert-Debré Series

Global outcome and duration of immunosuppression

<table>
<thead>
<tr>
<th>Duration of immunosuppression</th>
<th>n</th>
<th>median</th>
<th>IQ</th>
<th>range</th>
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</thead>
<tbody>
<tr>
<td>in patients in remission after IS withdrawal</td>
<td>32</td>
<td>39 mths</td>
<td>22-67</td>
<td>14-196</td>
</tr>
<tr>
<td>in patients in remission under IS treatment</td>
<td>18</td>
<td>41 mths</td>
<td>30-80</td>
<td>15-221</td>
</tr>
<tr>
<td>in patients with partial remission despite IS treatment</td>
<td>5</td>
<td>52 mths</td>
<td>na</td>
<td>18-162</td>
</tr>
<tr>
<td>Delay of ESRD</td>
<td>12</td>
<td>8 mths</td>
<td>5-21</td>
<td>1-32</td>
</tr>
<tr>
<td>DEATH/lost of follow-up</td>
<td>1+1</td>
<td></td>
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</table>
# Robert-Debré Series

\[ N = 69 \]

## 1\textsuperscript{st} line treatment

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<th>Treatment</th>
<th>Count</th>
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<tbody>
<tr>
<td>PRED+CYCLO</td>
<td>60</td>
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<tr>
<td>PRED+FK</td>
<td>9</td>
</tr>
<tr>
<td>SWITCH CYCLO-TO-FK</td>
<td>15</td>
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</tbody>
</table>

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## RESULTS

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Remission after withdrawal of 1\textsuperscript{st} line treatment</td>
<td>16 (24%)</td>
</tr>
<tr>
<td><strong>Duration of 1st line treatment</strong></td>
<td>Med=27</td>
</tr>
<tr>
<td></td>
<td>IQ = 17-54</td>
</tr>
<tr>
<td><strong>Number of patients treated ≤ 18 months</strong></td>
<td>6</td>
</tr>
<tr>
<td><strong>Initial response to 1st line treatment</strong></td>
<td>2-9 weeks</td>
</tr>
<tr>
<td>Residual treatment with ACEi-ARA2</td>
<td>5</td>
</tr>
<tr>
<td>Patients in remission still in the 1\textsuperscript{st} line treatment</td>
<td>5</td>
</tr>
<tr>
<td>Progression to ESRD under the 1\textsuperscript{st} line treatment</td>
<td>9</td>
</tr>
</tbody>
</table>

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# Robert-Debré Series

**N = 67**

## 2nd line treatment and beyond

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Count</th>
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<tbody>
<tr>
<td>RITUXIMAB</td>
<td>28</td>
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<tr>
<td>Cyclophosphamide or chlorambucil</td>
<td>10</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>9</td>
</tr>
<tr>
<td>IV cyclosporine</td>
<td>5</td>
</tr>
<tr>
<td>IVIG</td>
<td>5</td>
</tr>
<tr>
<td>Plasma exchanges</td>
<td>5</td>
</tr>
<tr>
<td>Immunoabsorption + IV immunoglobulins</td>
<td>6</td>
</tr>
</tbody>
</table>
## RESULTS

<table>
<thead>
<tr>
<th>Description</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission after withdrawal of the additional treatment</td>
<td>16 (24%)</td>
</tr>
<tr>
<td>Total duration of treatment</td>
<td>Med = 63, IQ= 32-98</td>
</tr>
<tr>
<td>Residual treatment with ACEi-ARA2</td>
<td>2</td>
</tr>
<tr>
<td>Remission still under additional treatment</td>
<td>13</td>
</tr>
<tr>
<td>Full range proteinuria under or after additional treatment</td>
<td>5</td>
</tr>
<tr>
<td>Progression to ESRD despite an additional treatment</td>
<td>3</td>
</tr>
</tbody>
</table>
A PLACE OF ANTIPROTEASES?

saquinavir

Patient 6

- prednisone (mg/kg/m)
- plasma exchange
- ACTH
- rituximab
- tacrolimus (mg/kg/d)
- saquinavir (mg/kg/d)

Disease onset

2005

2008

2009

2010

Coppo 2012

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B CELL DEPLETION BY RITUXIMAB

failure in multiresistant patients

RTX = rituximab+prednisone+cyclosporine/tacrolimus
STD = prednisone+cyclosporine/tacrolimus

M1
M0
M2
M3

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proteinuria

Dose of prednisone

Dose of cyclosporin or tacro (in% of STD)

month

RTX
STD

RTX
STD

RTX
STD

RTX
STD

Magnasco 2012
RECURRENCE AFTER RENAL GRAFT

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Fig. 1—Clinical course of case 1.

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HISTOLOGY

not a recurrence of FSGS but a recurrence of SRNS

- **RECURRENT Ellison 2009**
  - 35 patients
  - 42 grafts

- **Primary histology**
  - MCD 5 pts
  - FSGS 30 pts

<table>
<thead>
<tr>
<th>Graft histology</th>
<th>MCD</th>
<th>FSGS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M1</strong></td>
<td>30/31</td>
<td>1/31</td>
</tr>
<tr>
<td><strong>M3</strong></td>
<td>28/39</td>
<td>11/39</td>
</tr>
<tr>
<td><strong>M12</strong></td>
<td>22/36</td>
<td>14/36</td>
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</table>

Canaud 2009

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# Plasma Exchanges

<table>
<thead>
<tr>
<th></th>
<th><strong>Ohta 2001</strong></th>
<th><strong>Pardon 2006</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Recurrence</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Remission</td>
<td>1/4</td>
<td>4/9</td>
</tr>
</tbody>
</table>
# HIGH DOSE CYCLOSPORINE

<table>
<thead>
<tr>
<th></th>
<th>Salomon 2003</th>
<th>Raafat 2004</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of grafts</strong></td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td><strong>Route</strong></td>
<td>IV</td>
<td>ORAL</td>
</tr>
<tr>
<td><strong>Doses (mg/kg/d)</strong></td>
<td>3</td>
<td>8-25</td>
</tr>
<tr>
<td><strong>Trough level (ng/mL)</strong></td>
<td>250-350</td>
<td>200-1000</td>
</tr>
<tr>
<td><strong>Plasma exchanges</strong></td>
<td>0/12</td>
<td>7/16</td>
</tr>
<tr>
<td><strong>Remission</strong></td>
<td>11/12</td>
<td>13/16</td>
</tr>
<tr>
<td><strong>Graft failure</strong></td>
<td>3/12</td>
<td>3/16</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction (patients)</td>
<td>14/14</td>
</tr>
<tr>
<td>Pred-aza/mmf (patients)</td>
<td>14/14</td>
</tr>
<tr>
<td>Cyclosporine IV (patients)</td>
<td>11/14</td>
</tr>
<tr>
<td>Cyclosporine IV (days)</td>
<td>17-58</td>
</tr>
<tr>
<td>Cyclosporine (dose)</td>
<td>57-200 mg/kg</td>
</tr>
<tr>
<td>Cyclophosphamide (patients)</td>
<td>14/14</td>
</tr>
<tr>
<td>Plasma exchanges (n)</td>
<td>11-34</td>
</tr>
<tr>
<td>Remission M3</td>
<td>11/14</td>
</tr>
<tr>
<td>Graft failure</td>
<td>4/14</td>
</tr>
</tbody>
</table>
RITUXIMAB
+ PLASMA EXCHANGES
+ CYCLOPHOSPHAMIDE

Hristea 2001

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RITUXIMAB + PLASMA EXCHANGES
1 success

Grenda 2011
G. Deschenes
RITUXIMAB + PLASMA EXCHANGES
2 success + 2 failures

Yabu 2008
G. Deschenes
RITUXIMAB
prevention of recurrence in 2\textsuperscript{nd} graft

- 4 adult patients
  - Failure of 1st graft due to recurrence
  - 2\textsuperscript{nd} graft
    - Rituximab at day 0 in 2 pts
    - Rituximab at day 7 in 2 pts
  - No recurrence in 4 pts
  - Follow-up 12-54 months

Audard, 2012

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IMMUNOGLOBULINS
IMMUNOADSORPTION
IN MULTIRESISTANT
NEPHROTIC SYNDROME

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G.Deschenes
Speculated view of the physiopathology

**VIRUS**

- Proteinuria
- Foot process effacement

**B cells**

- IgG-IgM

**Plasma cells**

- IgG-IgM

**PODOCYTE**

- Proteinuria
- Foot process effacement

**Auto-antibodies**

**GBM**

**DQA1**

**DQB1**

- Cyclophosphamide
- Rituximab
- High dose steroids

- Immunoabsorption
- IViG

- Cyclophosphamide
- IViG

- G.Deschenes
**Protein A immunoadsorption**
- 8 patients 16 to 60 years of age
- Initial disease
  - ✔ Steroid resistant MCNS: 4
  - ✔ Steroid resistant FSGS: 2
  - ✔ Primary NS: 2
- 3-6 sessions

_Dental 1994_

---

**Therasorb® immunoadsorption**
- 4 patients
- Initial disease
  - ✔ Steroid resistant MCNS: 3
  - ✔ Steroid resistant FSGS: 1
- 5 sessions

_Dental 1998_
RECURRENCE ON RENAL GRAFT

_correlation between proteinuria and IgS level_

Dantal 1998

G.Deschenes
1. Secondary steroid resistance
2. Multidrug resistance to mycophenolate tacrolimus & rituximab
3. IA treatment in 07-2012
4. Stop tacrolimus in 01-2013
5. Last follow up in aug-2015
Pu = 0.1 g/L
TREATMENT OF MULTIRESISTANT FORMS
a robert-debré series

- **Immunoadsorption of Ig**
  - Adsorber Therasorb
  - 4-5 session/week x 2 weeks
- **Polyclonal IVIg substitution**
  - 0.5 g/L
  - plasma IgG before the session: 12-15 g/L
- **Tacrolimus**
  - Trough level around 10 ng/mL
- **Rituximab after session #10**

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<table>
<thead>
<tr>
<th>#</th>
<th>AGE yrs</th>
<th>sex</th>
<th>TYPE</th>
<th>TREATMENT</th>
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<tbody>
<tr>
<td>1</td>
<td>16</td>
<td>M</td>
<td>FSGS</td>
<td>Secondary steroid resistant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PRED, Cyc A, MMF, RTX</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>M</td>
<td>MCD</td>
<td>Primary steroid resistant</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>PRED, Cyc A, FK, Galactose</td>
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<tr>
<td>3</td>
<td>9</td>
<td>M</td>
<td>MCD</td>
<td>Primary steroid resistant</td>
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<td>PRED, Cyc A, FK</td>
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<td>F</td>
<td>MCD</td>
<td>Primary steroid resistant</td>
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<td></td>
<td></td>
<td>PRED, Cyc A, MMF, FK, RTX, levamisole</td>
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<tr>
<td>5</td>
<td>5</td>
<td>F</td>
<td>FSGS</td>
<td>Primary steroid resistant</td>
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<td></td>
<td></td>
<td>PRED, Cyc A, FK</td>
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<td>6</td>
<td>18</td>
<td>F</td>
<td>ND</td>
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<td>PRED, CPO, MMF, Cyc A, FK, levamisole</td>
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<td>7</td>
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<td>M</td>
<td>MCD</td>
<td>Secondary steroid resistant</td>
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<td>PRED, Cyc A, MMF, FK</td>
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<td>MCD</td>
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<td>PRED, FK, Cyc A</td>
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<td>10</td>
<td>20</td>
<td>F</td>
<td>FSGS</td>
<td>Recurrence after KT</td>
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<tr>
<td>11</td>
<td>12</td>
<td>F</td>
<td>FSGS</td>
<td>Recurrence after KT</td>
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<tr>
<td>12</td>
<td>12</td>
<td>M</td>
<td>FSGS</td>
<td>Recurrence after KT</td>
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<tr>
<td>13</td>
<td>19</td>
<td>M</td>
<td>FSGS</td>
<td>Recurrence after KT</td>
</tr>
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<td>M</td>
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<td>F</td>
<td>FSGS</td>
<td>Recurrence after KT</td>
</tr>
<tr>
<td>17</td>
<td>16</td>
<td>F</td>
<td>ND</td>
<td>Recurrence after KT</td>
</tr>
</tbody>
</table>

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## RESULTS

<table>
<thead>
<tr>
<th></th>
<th>Primary kidneys</th>
<th>Post graft</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Remission</strong></td>
<td>8/9</td>
<td>8/8</td>
</tr>
<tr>
<td><strong>Sessions</strong></td>
<td>388</td>
<td>301</td>
</tr>
<tr>
<td><strong>N session/patient</strong></td>
<td>23(18-113)</td>
<td>12(7-181)</td>
</tr>
<tr>
<td><strong>IgG extraction</strong></td>
<td>66(28-85)</td>
<td>75(18-90)</td>
</tr>
<tr>
<td><strong>Plasma IgG before session in g/L</strong></td>
<td>13.2(1.3-24.2)</td>
<td>8.5(1.5-23.5)</td>
</tr>
<tr>
<td><strong>Tacrolimus – trough level in ng/mL</strong></td>
<td>10.5</td>
<td>7.2</td>
</tr>
<tr>
<td><strong>Remission without drugs</strong></td>
<td>4/9</td>
<td>5/8*</td>
</tr>
<tr>
<td><strong>Dependency to immunoadsorption</strong></td>
<td>3/9</td>
<td>3/8</td>
</tr>
<tr>
<td><strong>Failure</strong></td>
<td>1/9</td>
<td>0/8</td>
</tr>
</tbody>
</table>

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* Otherwise the prevention of rejection
LEVEL OF PROTEINURIA
(10 first sessions)

N = 16 patients

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TO SUMMARIZE

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RECOMMENDATIONS
KDIGO 2013

No remission following 8 weeks of initial corticosteroid therapy

Begin ACEi/ARB

Begin CNI for minimum 6 months

Partial/complete remission achieved
- Continue CNI for minimum 12 months

No remission by month 6
- Consider mycophenolate mofetil
- Consider high-dose corticosteroids
- Consider enrollment in RCT

Relapse after complete remission
- Restart oral corticosteroids
- Return to previous successful immunosuppressive therapy
- Start alternative agent to minimize potential cumulative toxicity

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SUGGESTIONS

STEROID RESISTANCE

- Prednisone + calcineurin antagonists
- Genetic screening

Remission at 3 months
- Try to stop early: Rituximab
- Treat during 18 months
- Nephrotic proteinuria at 3 months = multiresistance
- Stop & Recovery
- Immunoadsorption
- IV immunoglobulins
- Tacrolimus
- Rituximab

ACEi or ARA2 if residual proteinuria or in case of treatment failure
CLINICAL CASE : ONSET

• **24/12/2012**
  – Edema
  – Proteinuria 7.7 g/L
  – Serum Albumin 11.4 g/L
  – Start prednisone
    **25/12/2012**

• **28/01/2013**
  – Proteinuria 1.13 g/jour
  – Serum Albumin 26 g/L

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CLINICAL CASE : ONSET

• 24/12/2012
  – Edema
  – Proteinuria 7.7 g/L
  – Serum Albumin 11.4 g/L
  – Start prednisone 25/12/2012

• 28/01/2013
  – Proteinuria 1.13 g/jour
  – Serum Albumin 26 g/L

• IV methylprednisolone
  – 28/01, 30/01, 01/02
  – 1 g/1.73m²

• 08/02/2013
  – Proteinuria 1.69 g/day
  – Serum Albumin 20.3 g/L
  – Histology MCD
• 24/12/2012
  – Edema
  – Proteinuria 7.7 g/L
  – Serum Albumin 11.4 g/L
  – Start prednisone 25/12/2012

• 28/01/2013
  – Proteinuria 1.13 g/jour
  – Serum Albumin 26 g/L

• IV methylprednisolone
  – 28/01, 30/01, 01/02
  – 1 g/1.73m²

• 08/02/2013
  – Proteinuria 1.69 g/day
  – Serum Albumin 20.3 g/L
  – Histology MCD
  – Start tacrolimus 5 mg/day

• Remission 11/03/2014
  – Proteinuria = 0.18 g/L
  – Serum Albumin = 27.5 g/L
  – Weight 16 kg
varicella

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