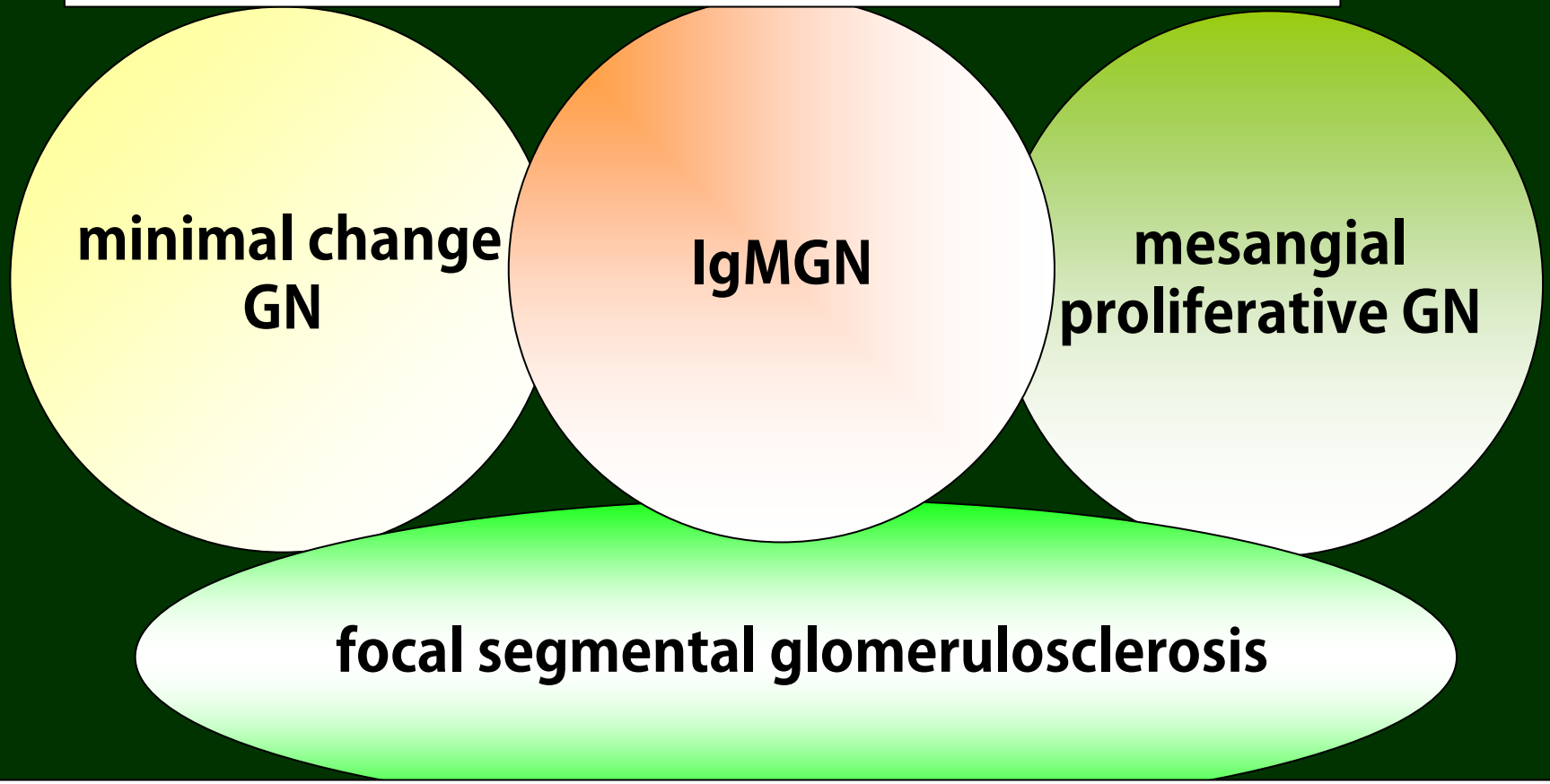
Budapest
August 26, 2008

Treatment of difficult cases of nephrotic syndrome

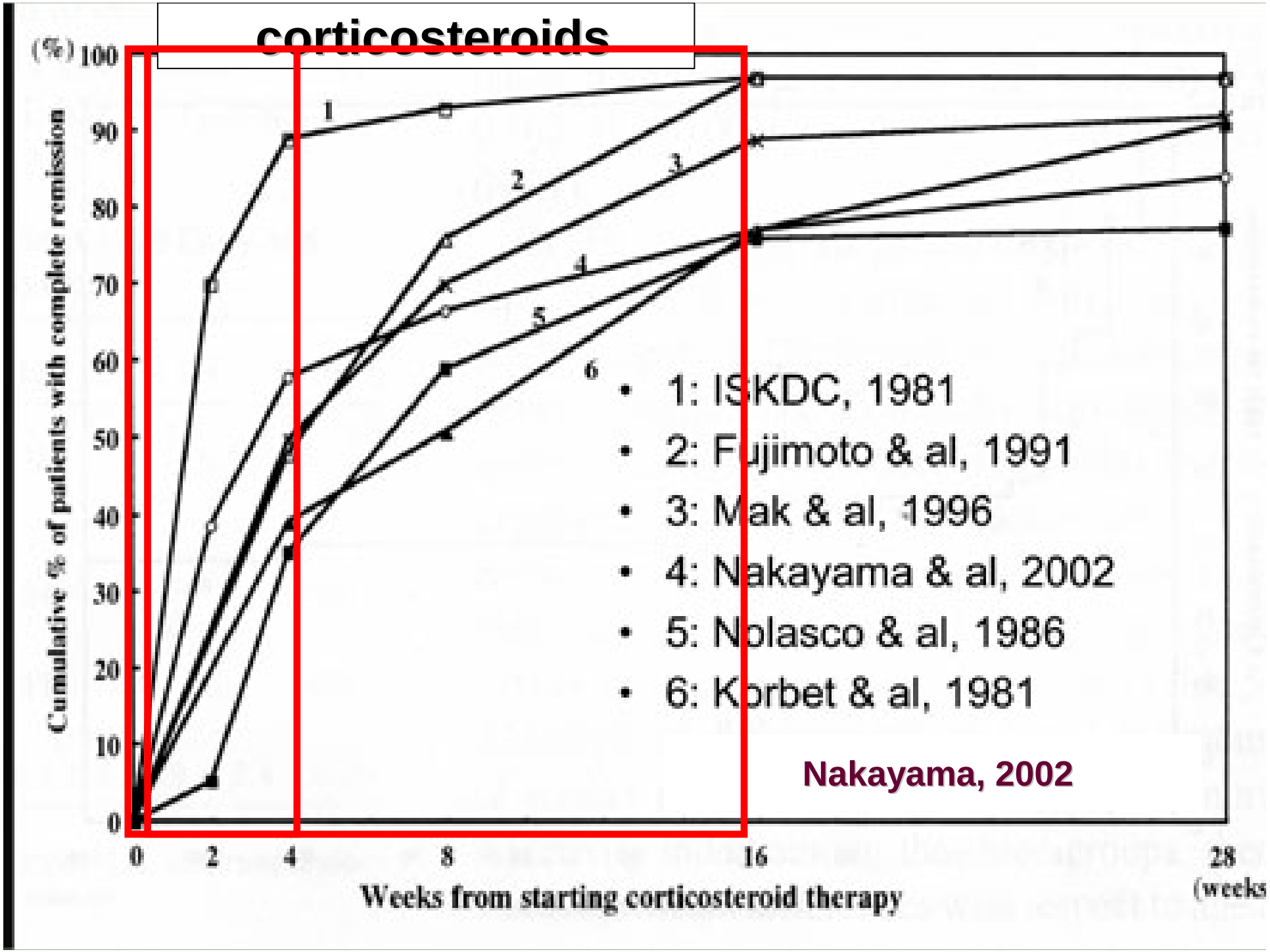
Rosanna Coppo
Regina Margherita University Hospital
Turin,
Italy

Idiopathic Nephrotic Syndrome



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

Meyrier A, 2005 Exp Opin Pharmacother


corticosteroids
(%)
Cumulative % of patients with complete remission
100
90
80
70
60
50
40
30
20
10
0
1
2
3
4
5
6
0
2
4
8
16
28
(weeks
Weeks from starting corticosteroid therapy
• 1: ISKDC, 1981
• 2: Fujimoto & al, 1991
• 3: Mak & al, 1996
• 4: Nakayama & al, 2002
• 5: Nolasco & al, 1986
• 6: Korbet & al, 1981
Nakayama, 2002

Cochrane Renal Group 2004 :CD001533

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

	Complete Remission	Partial Remission	Failure
Steroid Dependent	52%	24%	24%
Steroid Resistant	15%	10%	75%

2006

Cochrane Database Syst Rev 2006: CD003594
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

Treatment of steroid-resistant NS with

Cytotoxic Drugs

EBM Recommendations

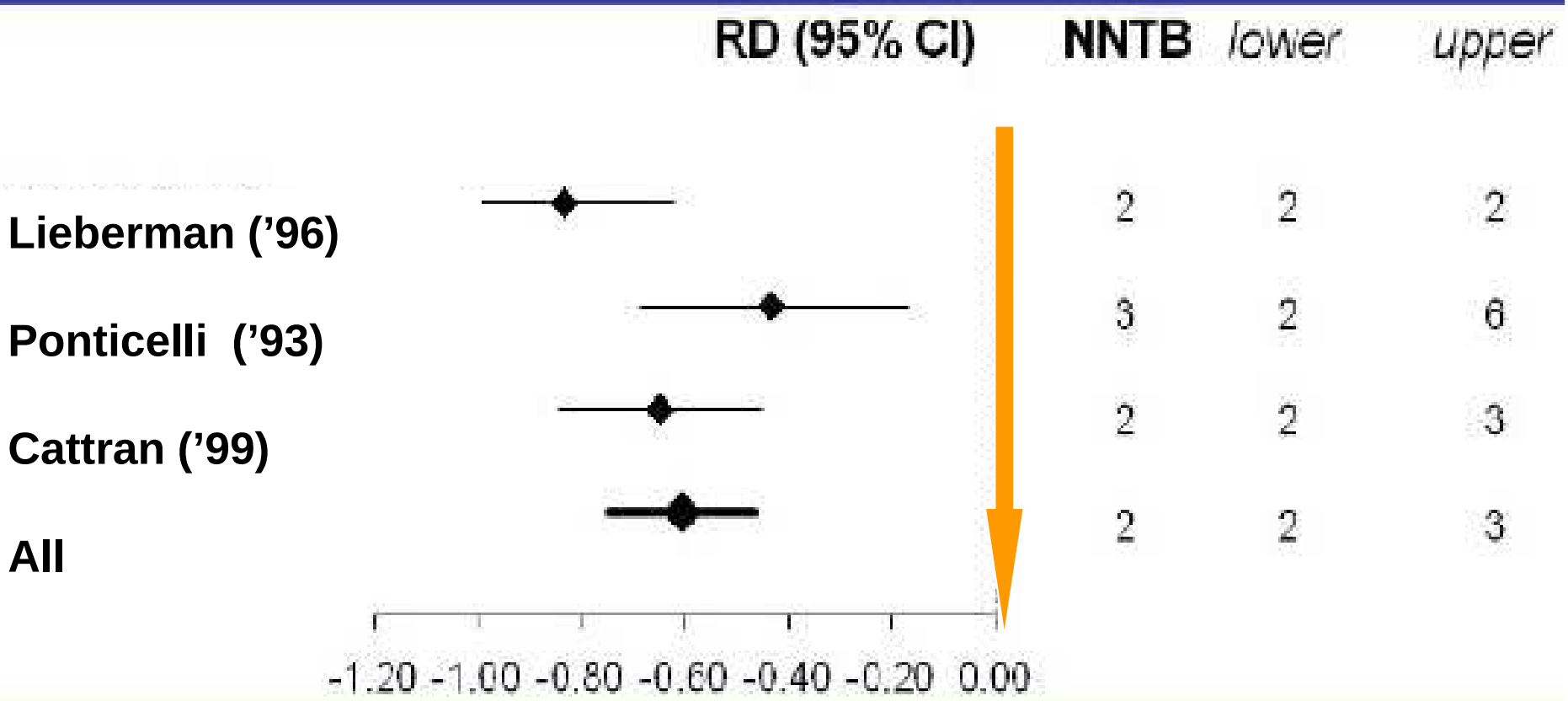
Treatment	L of Ev	Grade	Comments
Oral cyclophosphamide (12 weeks)	4 (MCGL)	D	Possible benefit from pooled case series; small numbers in RCTs- uncertain benefit
	1 (FSGS)	A	No benefit
IV cyclophosphamide (500 mg/m2, monthly for 6 months)	2 (MCGL)	B	Advantage over oral cyclophosphamide, but small numbers
	4 (FSGS)	D	Possible benefits, short FU to ESRF

Treatment and outcome of children and adults with idiopathic steroid-resistant NS

ALKYLATING AGENTS

CYCLOSPORIN

Cyclosporin A in steroid-resistant NS in adults RCTs metanalysis



Ravani P, 2005

2006

Cochrane Database Syst Rev 2006: CD003594

Interventions for idiopathic steroid-resistant NS in children

3 RCTs: 49 children:

RR of persistent NS

Cyclosporin (CyA) vs PL

RR 0.64 (0.47-0.88)

Treatment of steroid-resistant NS

Cyclosporin A

Evidence-based recommendations

Treatment	Level of evidence	Grade	Comments
MCGL Cyclosporin (at least 6 months)	4	D	Possible benefit from pooled case series; no significant benefit in RCT – small numbers
FSGS Cyclosporin (at least 6 months)	1	A	Beneficial

Treatment and outcome of children and adults with idiopathic steroid-resistant NS

ALKYLATING AGENTS

CYCLOSPORIN

ANGIOTENSIN ANTAGONISTS

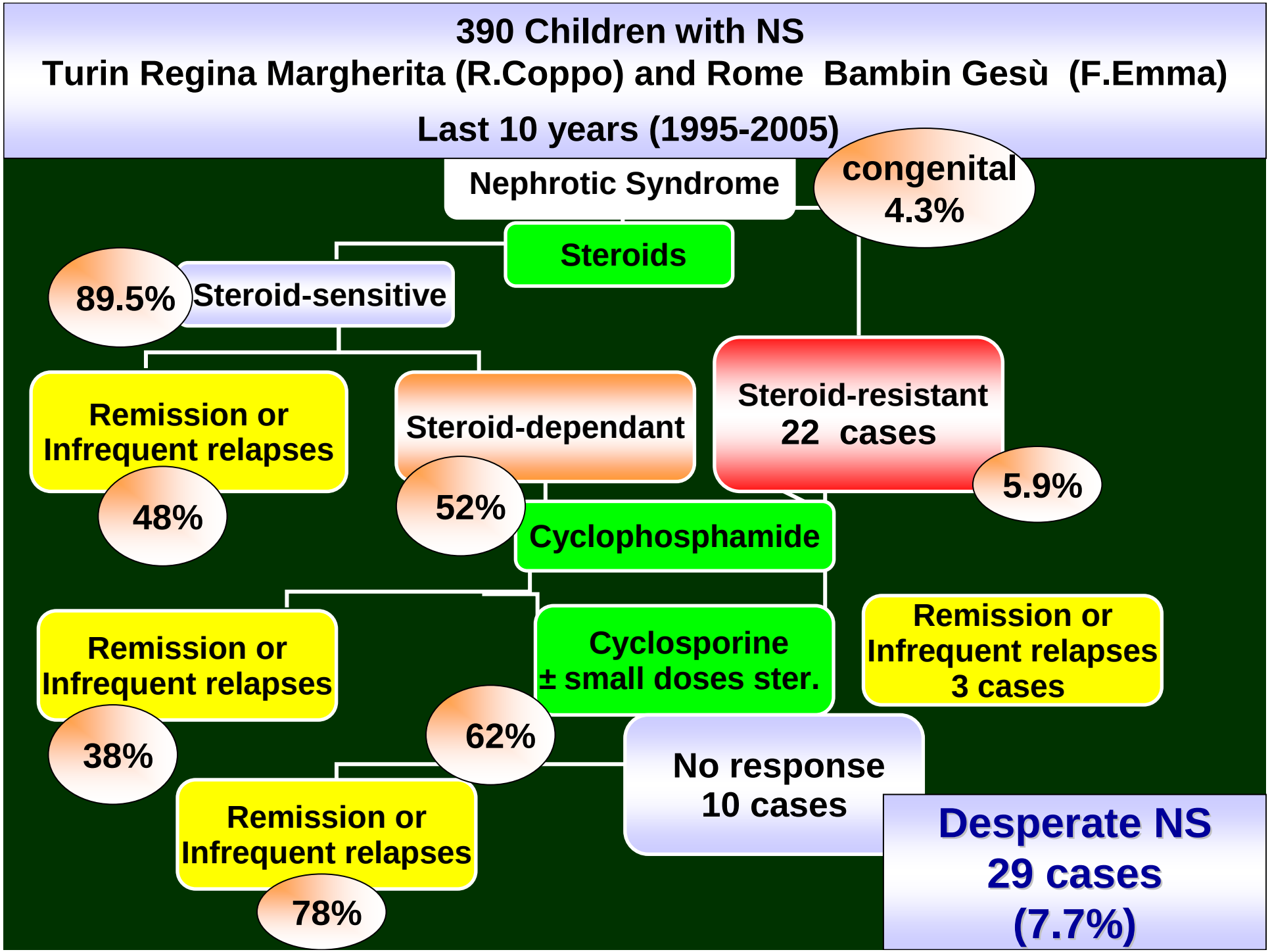
Treatment of steroid-resistant FSGS:

ACE-inhibitors

Evidence-based recommendations

Treatment	L of Ev	Grade	Comments
High dose Enalapril and Fosinopril	3	C	Useful in reducing proteinuria

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


390 Children with NS
Turin Regina Margherita (R.Coppo) and Rome Bambin Gesù (F.Emma)
Last 10 years (1995-2005)
Nephrotic Syndrome
congenital
4.3%
Steroids
89.5%
Steroid-sensitive
Remission or
Infrequent relapses
48%
Steroid-dependant
52%
Steroid-resistant
22 cases
5.9%
Cyclophosphamide
Remission or
Infrequent relapses
38%
Cyclosporine
± small doses ster.
62%
Remission or
Infrequent relapses
3 cases
No response
10 cases
Remission or
Infrequent relapses
78%
Desperate NS
29 cases
(7.7%)

"Desperate"cases of nephrotic syndrome no sustained remission after

STEROIDS
8 weeks in children
6 months in adults

ALKYLATING AGENTS
8-12 weeks

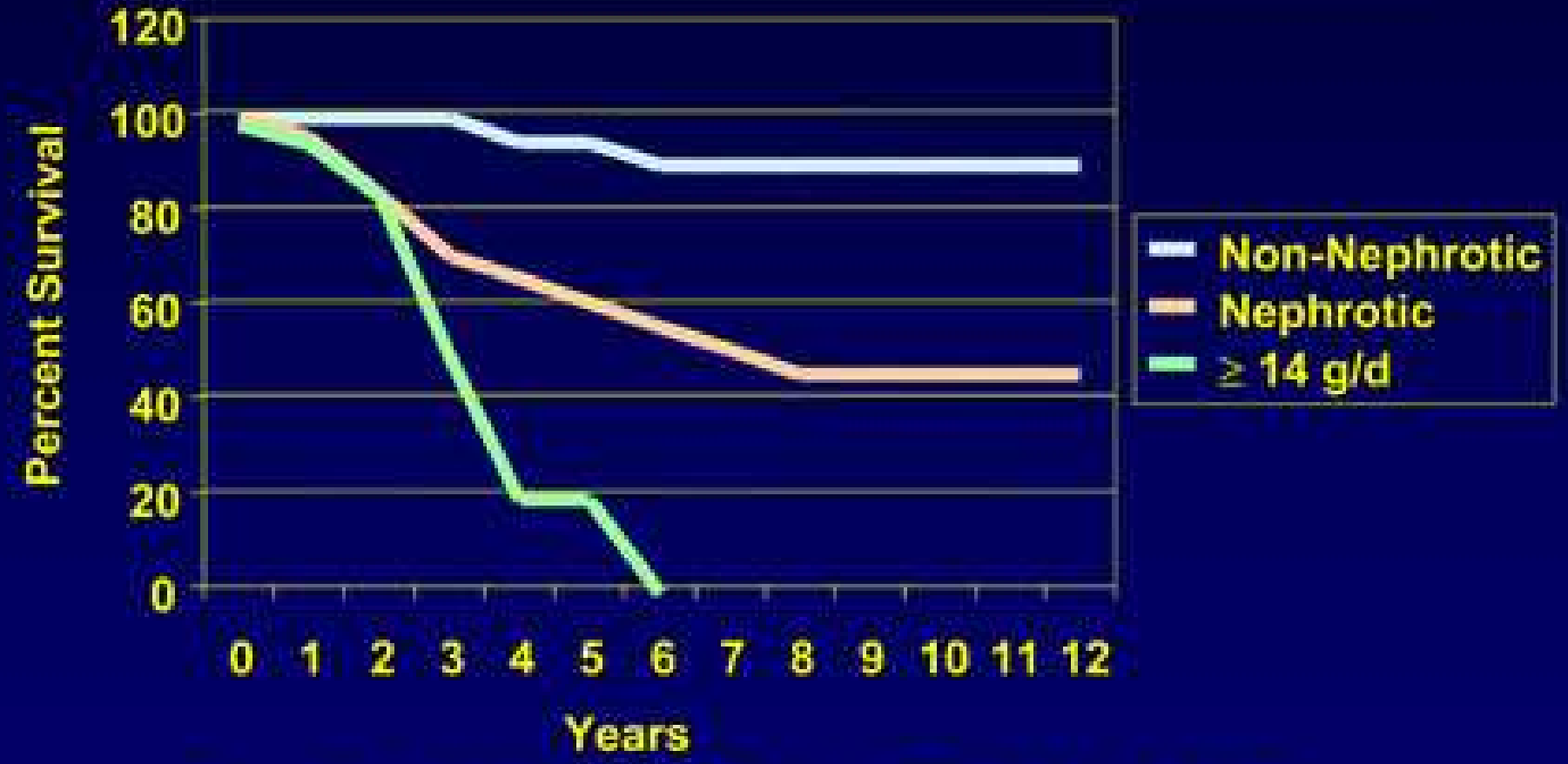
CYCLOSPORIN
6 months

ANGIOTENSIN ANTAGONISTS

rescue therapy?

Cumulative Percentage Renal Survival in Primary FSGS

for non-nephrotic patients, nephrotic patients, and patients with massive proteinuria



Source: Korbet, S.M. *Nephrol Dial Transplant* (1999) 14 (Suppl 3): 68-73

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, 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

Methylprednisolone pulses

Evidence-Based recommendations

Treatment	Level of evidence	Grade	Comments
IV methylprednisolone (3-6 months)	5 (MCGL)	D	Possible benefit, small numbers in case series
IV methylprednisolone (6-12 months) with alkylating agents	4 (FSGS)	D	Possible benefit

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

Ponticelli C, et al Am J Kid Dis 2006; 2: 233-240

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

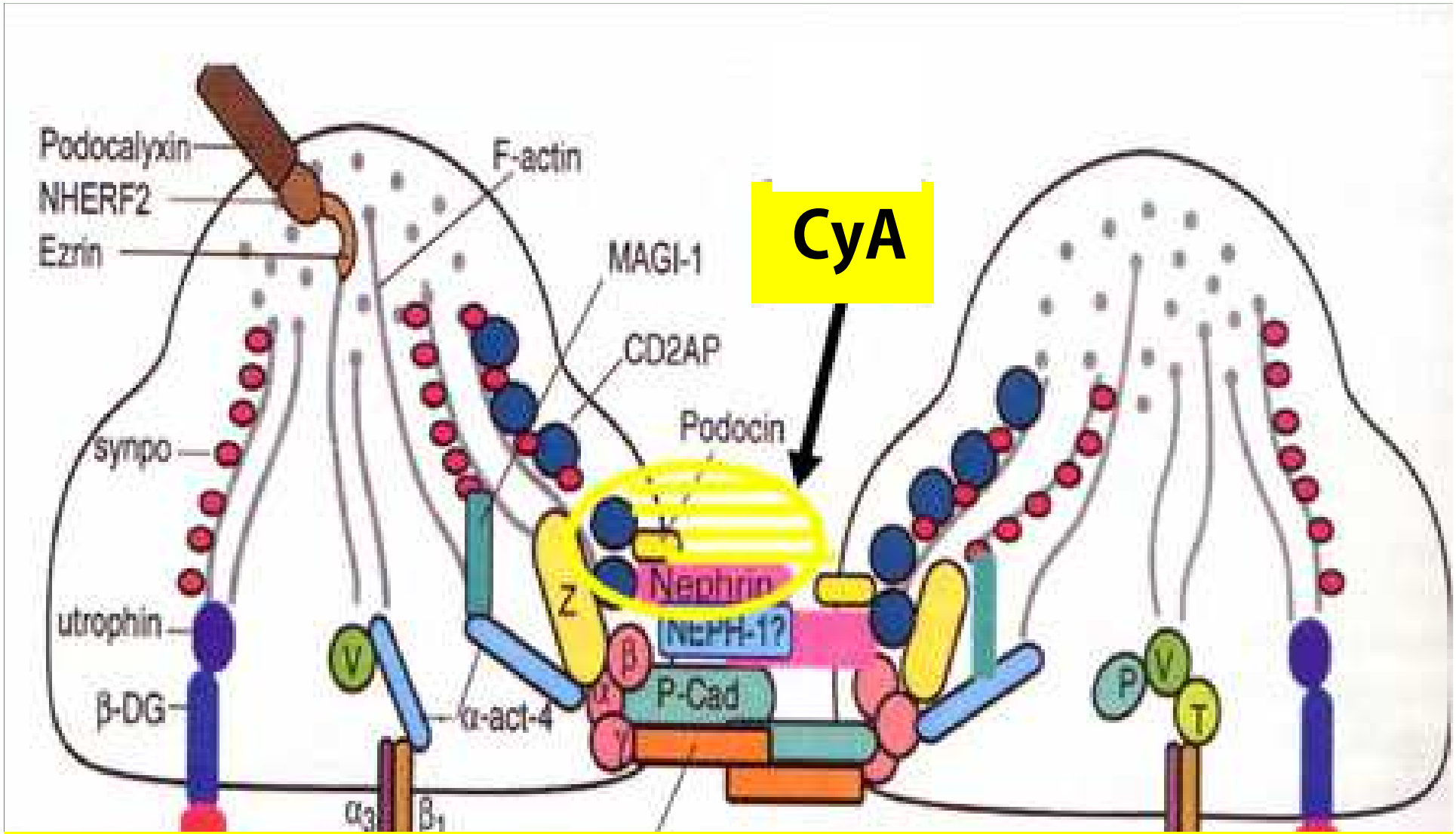
Meyrier 2005 ASN

Proteinuria reduction in 6/6,

but progression to CKD was not modified.

Physico-chemical effect

instead of immune-effect?



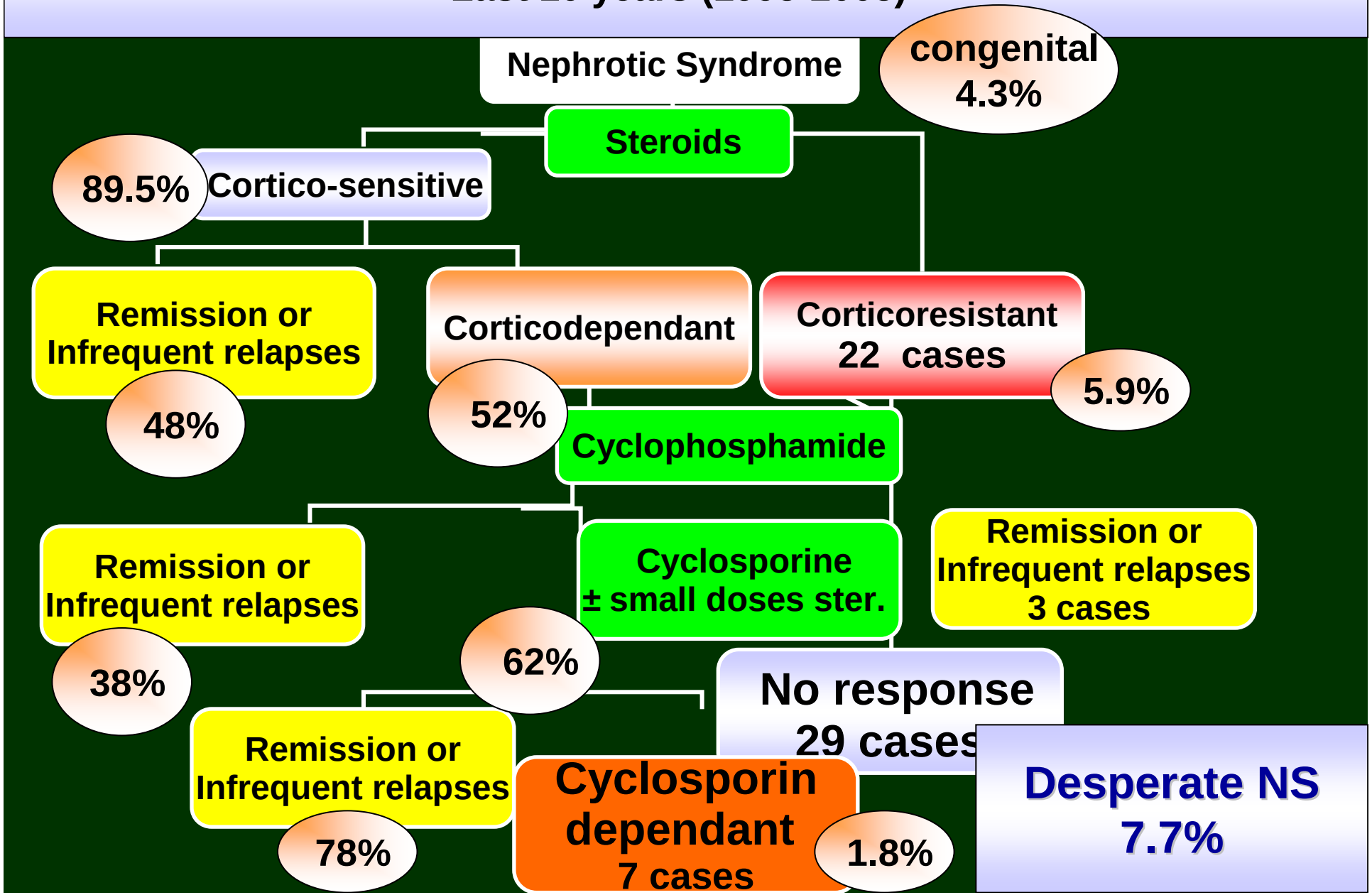
Meyrier's hypothesis:
ACTH and CyA are lipophilic and bind to a lipidic complex associated to the slit diaphragm, limiting the protein leak

steroid, cytotoxic and cyclosporin resistant desperate NS: rescue therapy

- Steroid therapy : different doses, different forms
- Cyclosporin therapy over sevaral years

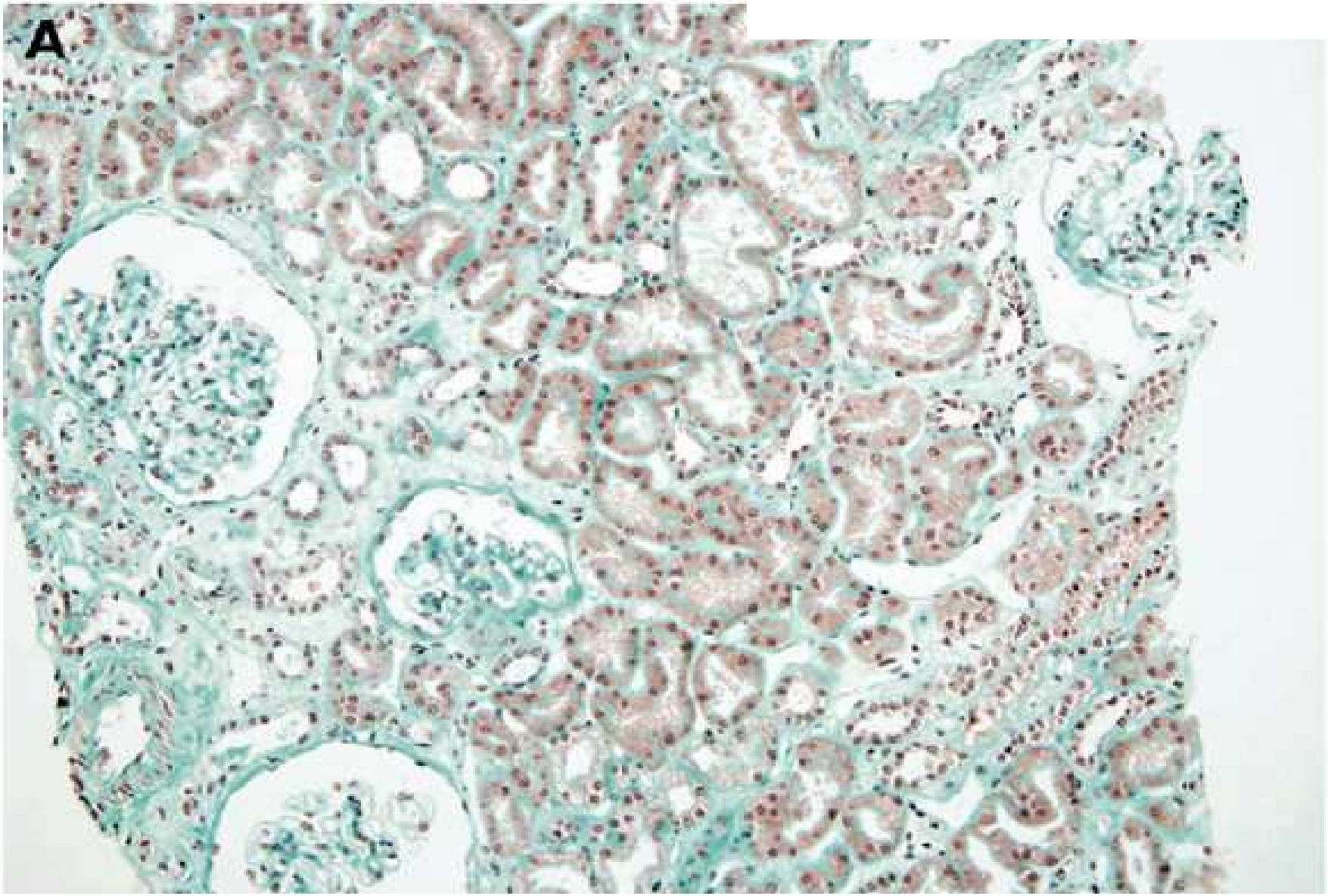
390 cases of Children with NS Turin and Rome Center

Last 10 years (1995-2005)



An example of CyA nephrotoxicity.

Francois H, et al
Am J Kidney Dis. 2007;49:158-61.



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

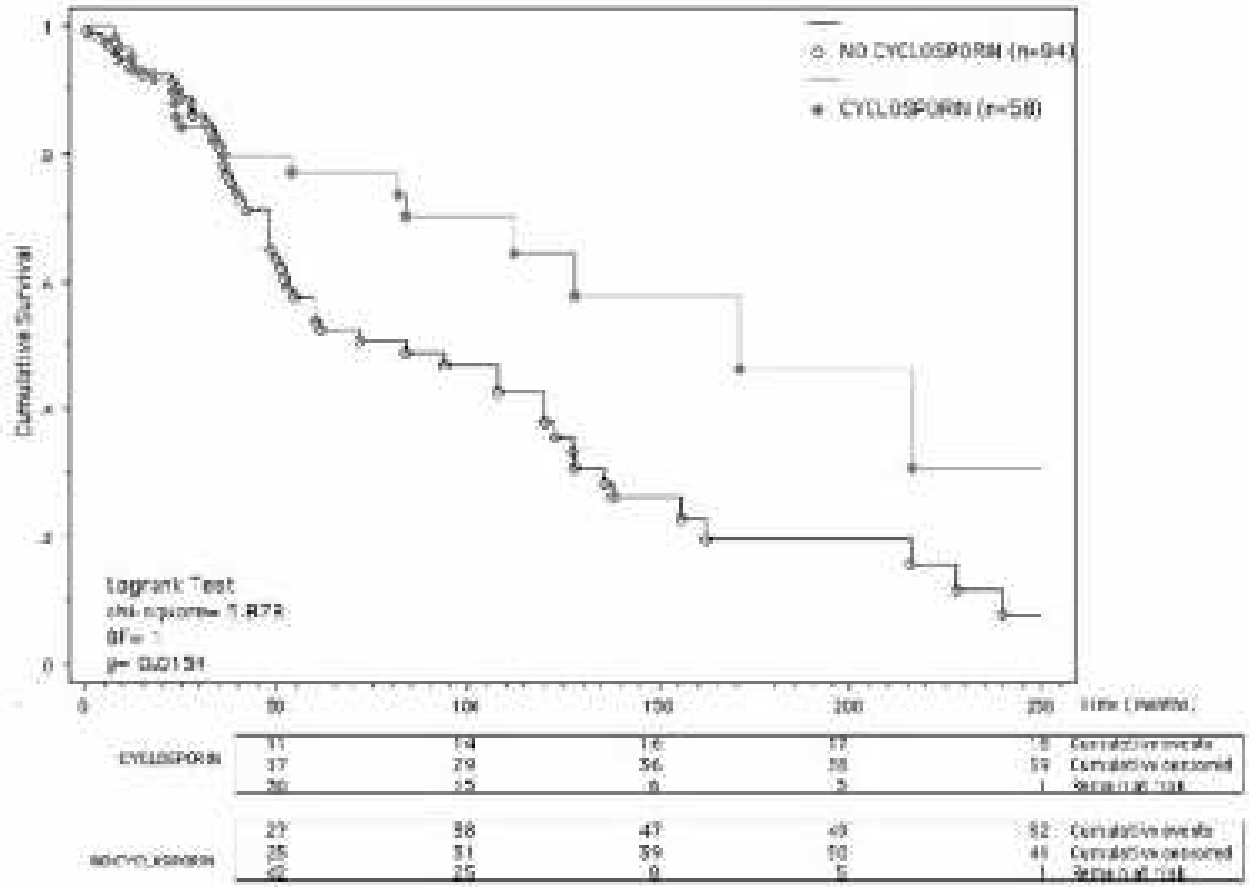
NS treated with CyA

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

TACROLIMUS

Segarra A, *NDT 2002; 17:6*

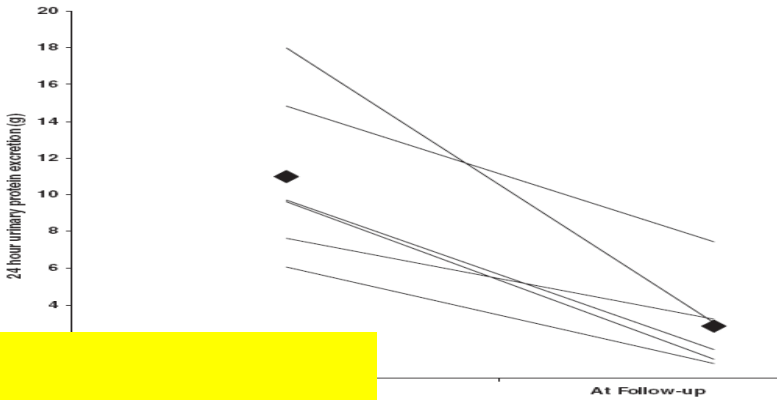
NS steroid and/or cyclosporin dependent/resistant

Total remission in 100% of CyA-dependent cases

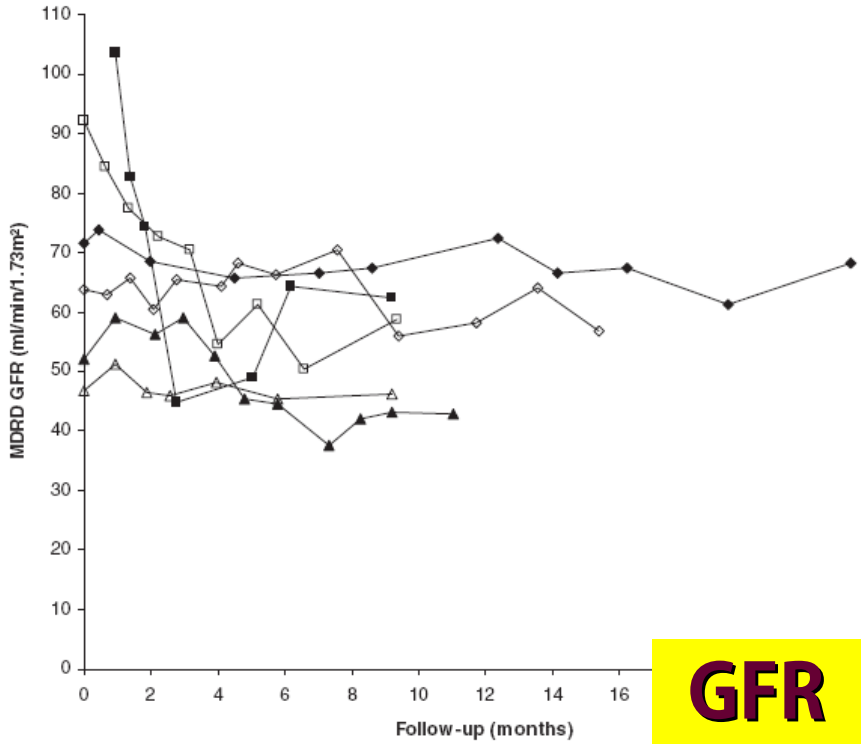
15% of primary CyA-resistant

TAC monotherapy in steroid-dependent NS

Duncan M et al, NDT 2004; 19:3062



proteinuira



GFR

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

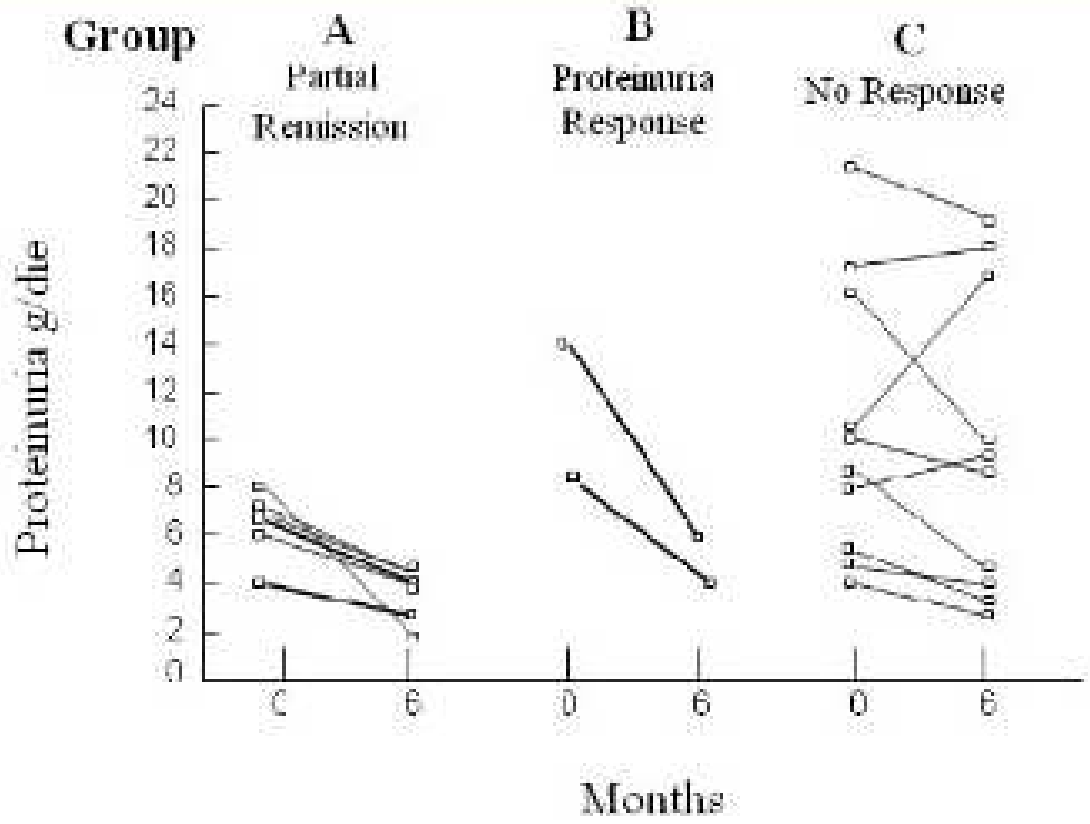
Reduced dose of P assumed from 0.7 to 0.3 mg/Kg/day $p<0.0001$.

After withdrowal 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

Author	N cases	Regimen	Efficacy
Day CJ (Wolverhampt, UK, NDT 2002)	7 adults	MMF (1 gx2)	Complete remission 6/7 1/7 partial r.
Montané (Miami, US, Ped Nephrol 2003)	9 childr.	MP pulses (15 mg/kg/week x 4-8) ACE-i/ARB MMF (250-500 mg/m2)	Proteinuria (6-24 months) 72% below baseline p<0.01
Mendizabal S (Spain, Ped Nephrol 2005)	27 5 SRNS	no response to CP and CyA MMF (1200 mg/m2)	1/5 remission Relapse after withdrawal.
Ulinski (Lyon, Ped Nephrol 2005)	9 4SRNS	CyA with GFR impairment: 2g/1.73 m2	0/4 remissions

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

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 Immunoadsorbance on A Protein
± cyclophosfamide:
70% reduction in proteinuria

Lyon and Miami Protocol

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

Encouraging results

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

- mainteined GFR for about a mean of 4 years.
- Temporay remission in 2 children.
- Patients which did not respond needed dialysis after 1-2 years.

Treatment of steroid-resistant FSGS: Evidence-based recommendations

Treatment	L of Ev	Grade	Comments
Mycophenolate mofetil	6	D	Case reports
Tacrolimus	6	D	Case reports
Plasmapheresis	6	D	Anedoctal reports

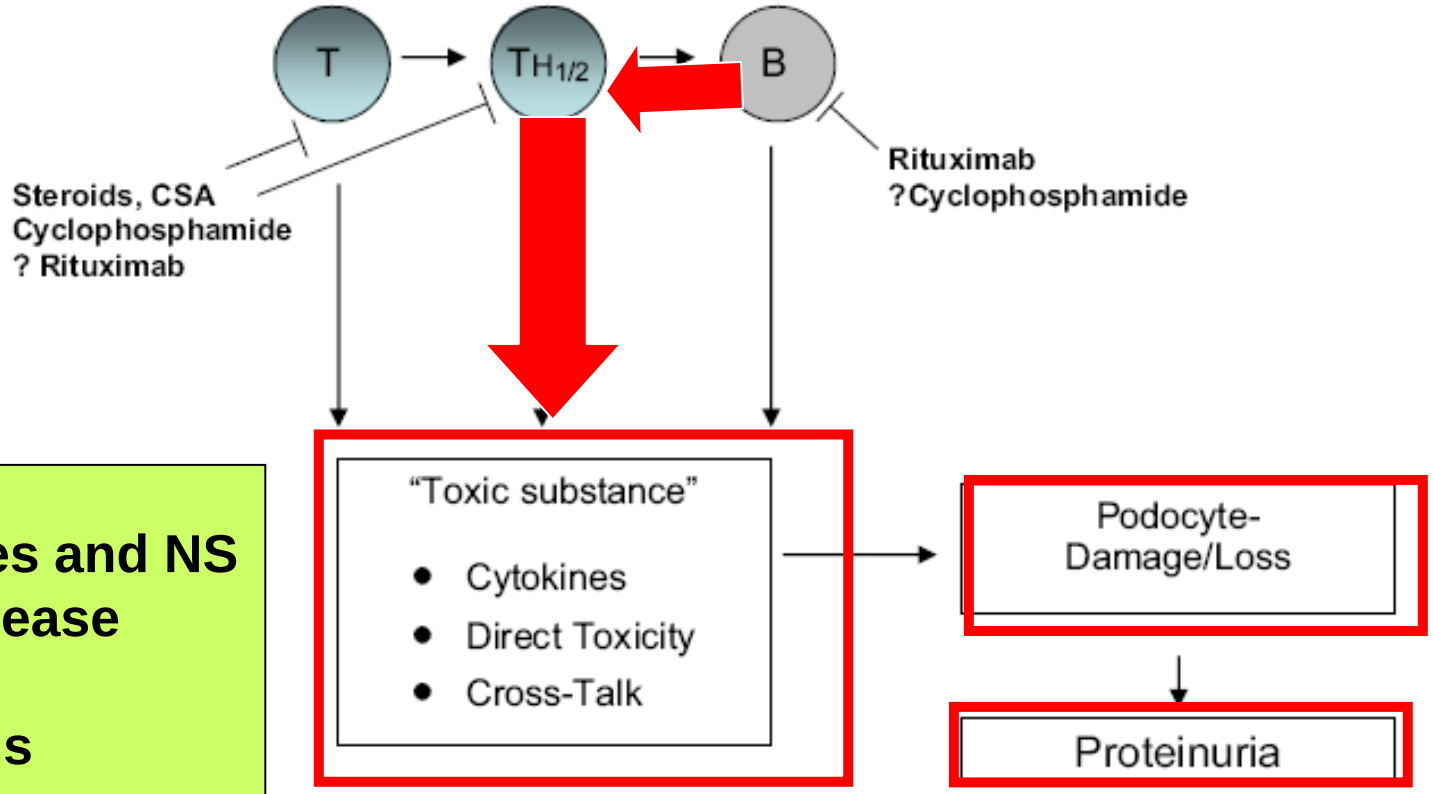
Steroid-, cytotoxic- and cyclosporin- resistant NS:
sporadic case reports of
rescue therapy

B cells
as new target
for NS treatment?

Anti-CD 20
chimeric MoAb
Rituximab

B and T collaboration

PF (Ig part?)
B cells activated in relapse



T lymphocytes and NS
Hodgkin's disease
Allergy
Viral infections
In vitro evidences
Shaloub's hypothesis:
permeabilizing
T lymphokine

Anti-CD20 monoclonal antibodies (Rituximab)

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

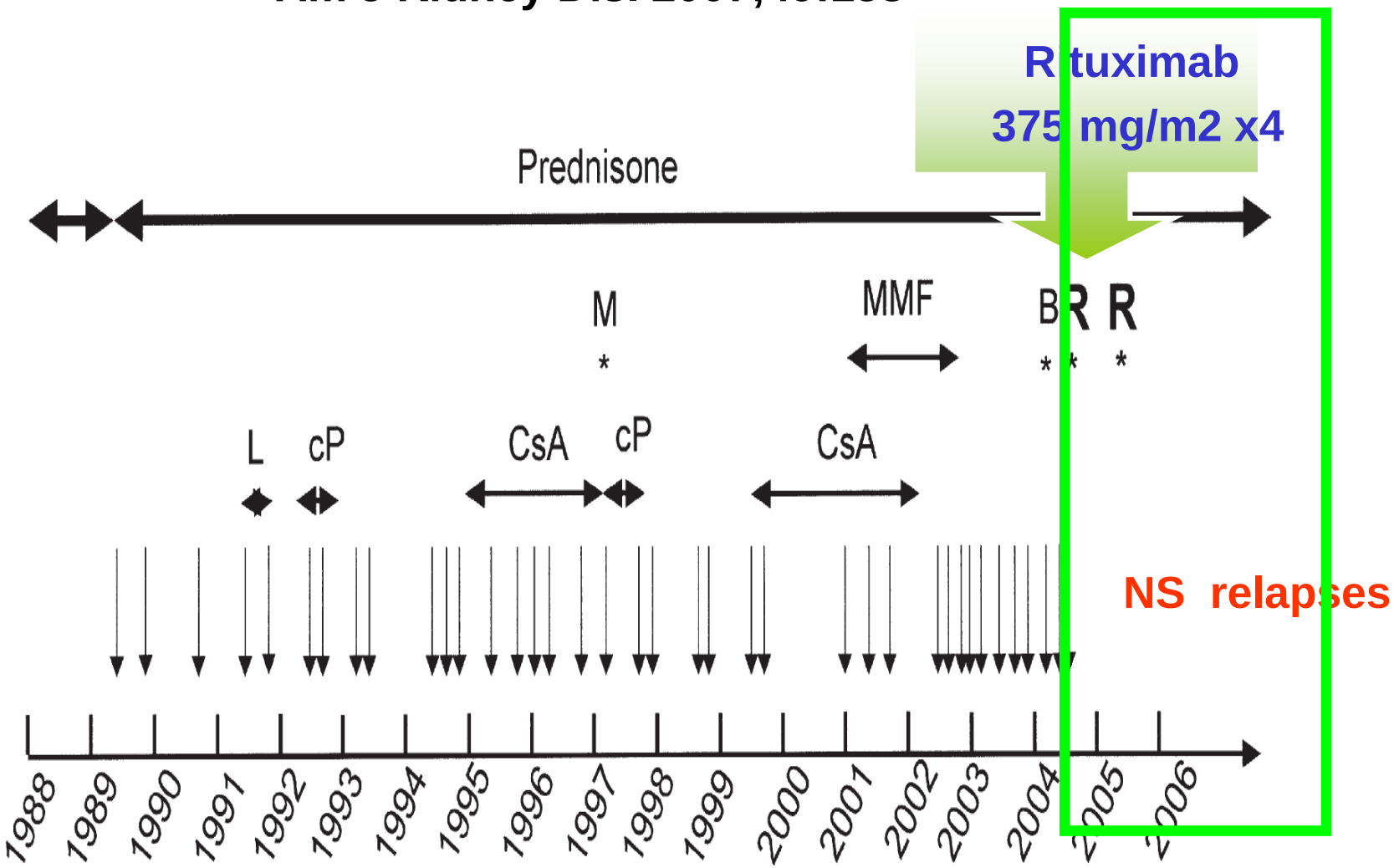
A case of steroid dependent NS, treated with Rituximab because of thrombocytopenic purpura (375 mg/m2 /week x4 weeks)

(Benz, Pediatr Nephrol 2004)

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

(Nozu, Pediatr Nephrol 2005, 20, 1660)

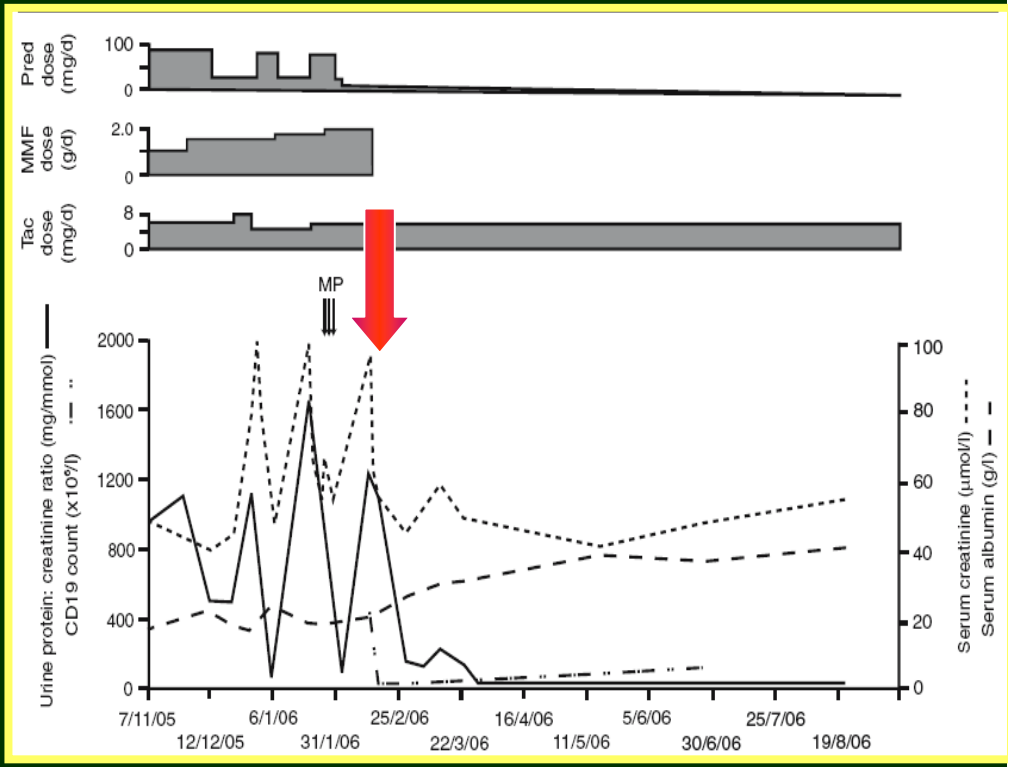
Francois H, Daugas E, Bensman A, Ronco P.
Unexpected efficacy of rituximab in multirelapsing minimal change nephrotic syndrome in the adult
Am J Kidney Dis. 2007;49:158-61.



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

Pediatr Nephrol (2007) 22:893–898

10 cases have been successfully treated with 4 doses of Rituximab (375 mg/m2/week)



Pediatr Nephrol (2008) 23:3–7
DOI 10.1007/s00467-007-0596-x

EDITORIAL COMMENTARY

Rituximab: is replacement of cyclophosphamide and calcineurin inhibitors in steroid-dependent nephrotic syndrome possible?

Jörg Dötsch · Dirk. E. Müller-Wiefel · Markus J. Kemper

Pediatr Nephrol (2008) 23:1269–1279
DOI 10.1007/s00467-008-0814-1

ORIGINAL ARTICLE

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 withrawal**

- **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

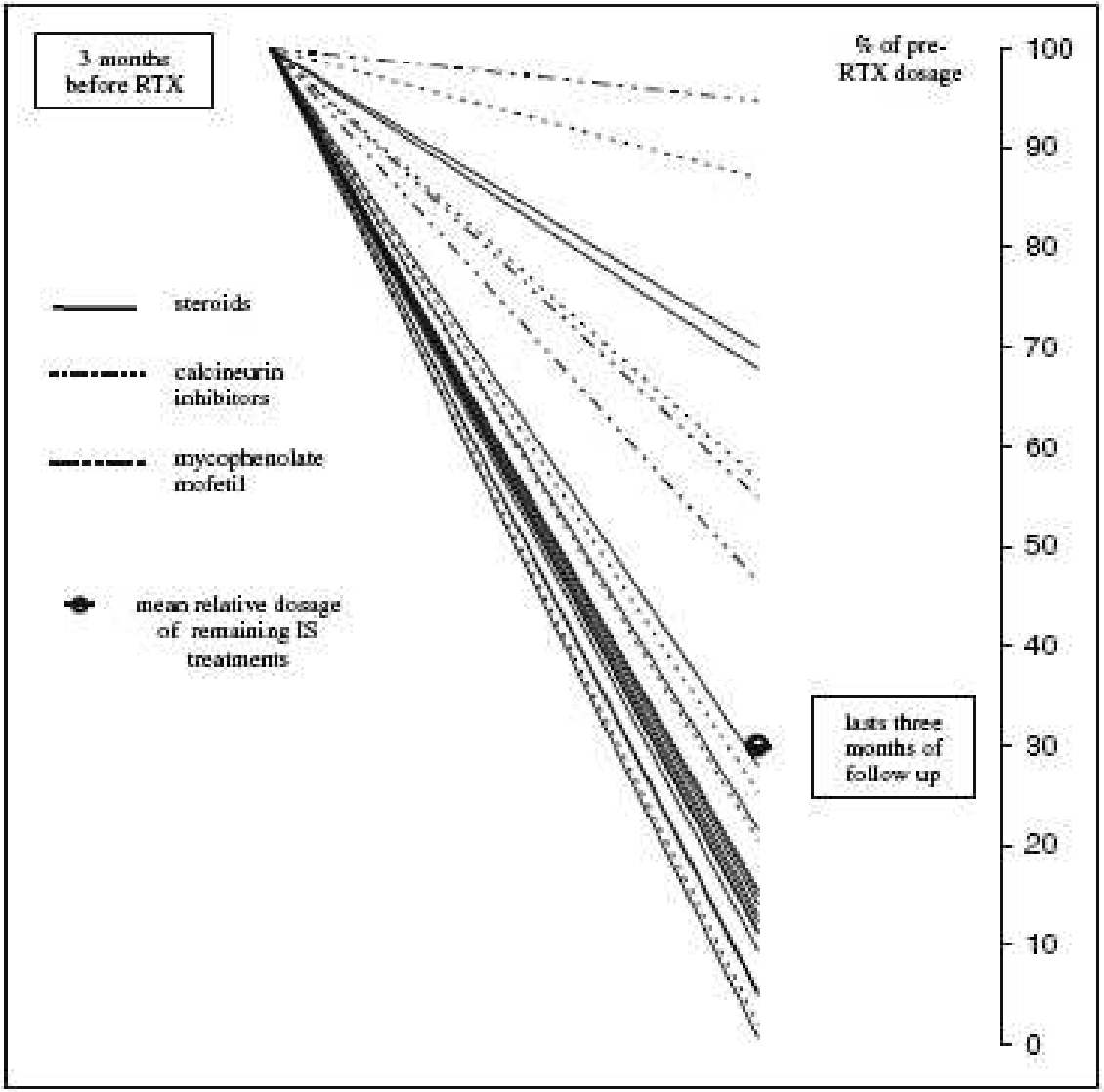
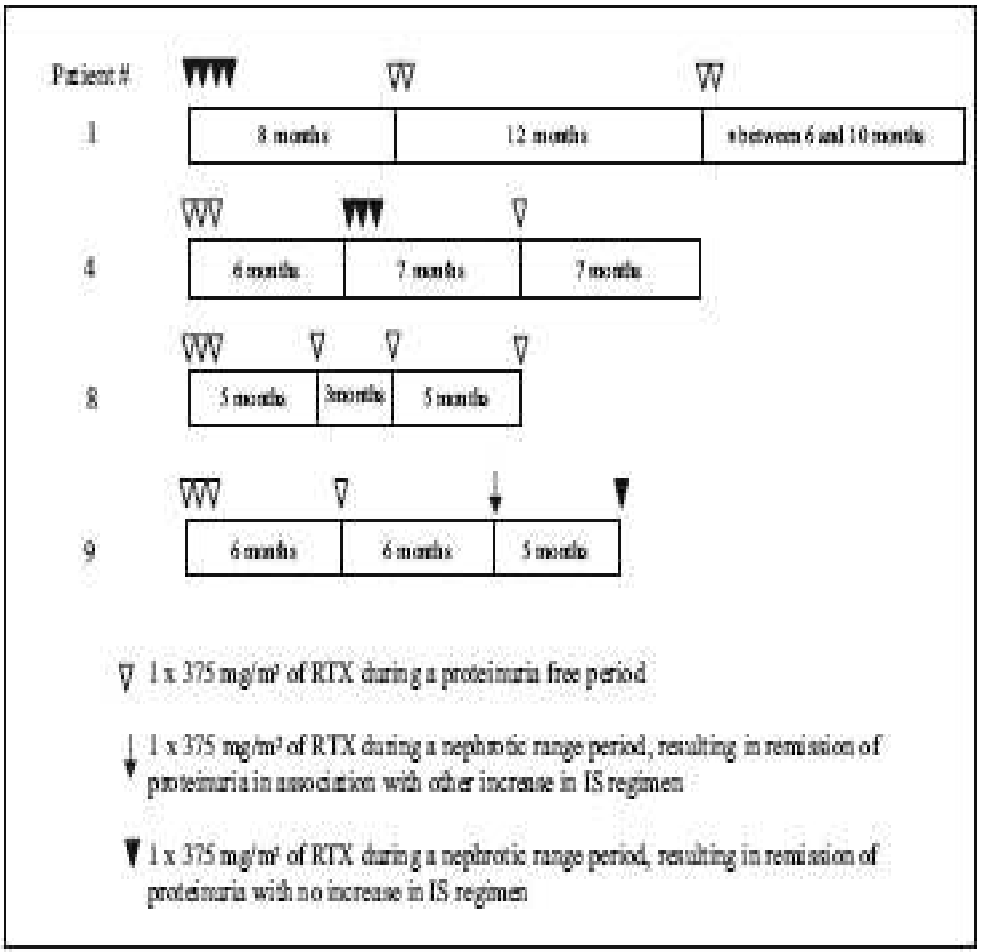


Fig. 2 Relative decrease of remaining immunosuppressive treatments (IST) in the 14 rituximab (RTX)-responsive patients who still receive IST at the end of follow-up. For each IS agent still given at the end of the follow-up, the percent of dosage reduction was calculated as the ratio of average dosage 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

Fig. 3 Duration of B-cell depletion after each rituximab (RTX) course according to RTX dosage and proteinuric status at the time of RTX infusion. ☒Only data from patients with three courses or more of RTX are presented. *No CD19 determination was performed between the sixth and tenth months



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)

Nephrol Dial Transplant (2008) 23: 11–17
doi: 10.1093/ndt/gfm683
Advance Access publication 9 December 2007

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

Pediatr Nephrol (2008) 23:3–7
DOI 10.1007/s00467-007-0596-x

EDITORIAL COMMENTARY

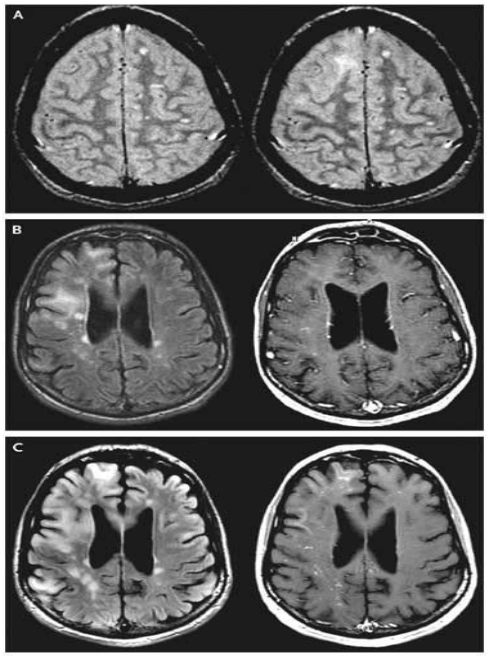
Rituximab: is replacement of cyclophosphamide and calcineurin inhibitors in steroid-dependent nephrotic syndrome possible?

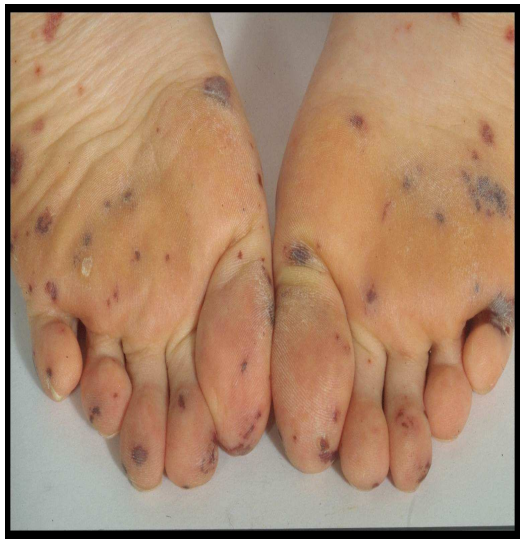
Jörg Dötsch · Dirk. E. Müller-Wiefel · Markus J. Kemper

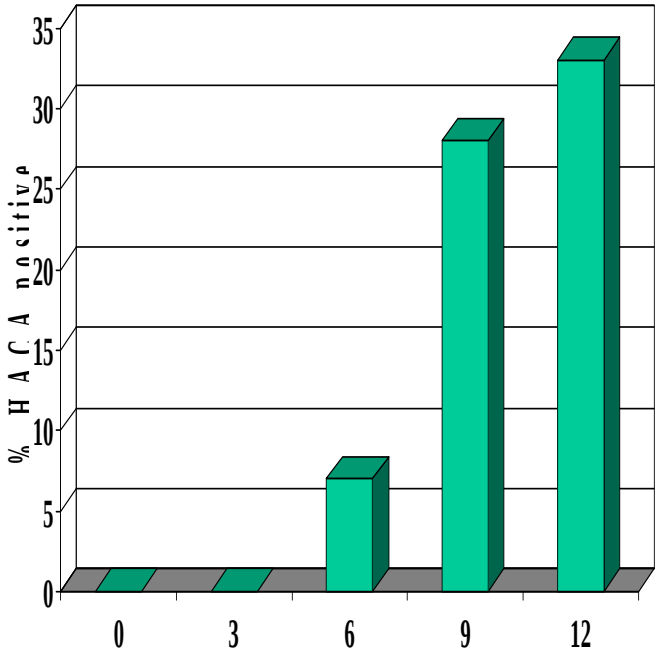
Rituximab used in > 500.000 subjects

Toxicity, adverse events:

- **2 cases of leukoencephalitis in SLE treated with multiple drugs , including Rituximab**
- **Allergic reactions, anti chymeric Antibodies.**







Pediatr Nephrol (2007) 22:158–160
DOI 10.1007/s00467-006-0260-x

LETTER TO THE EDITORS

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

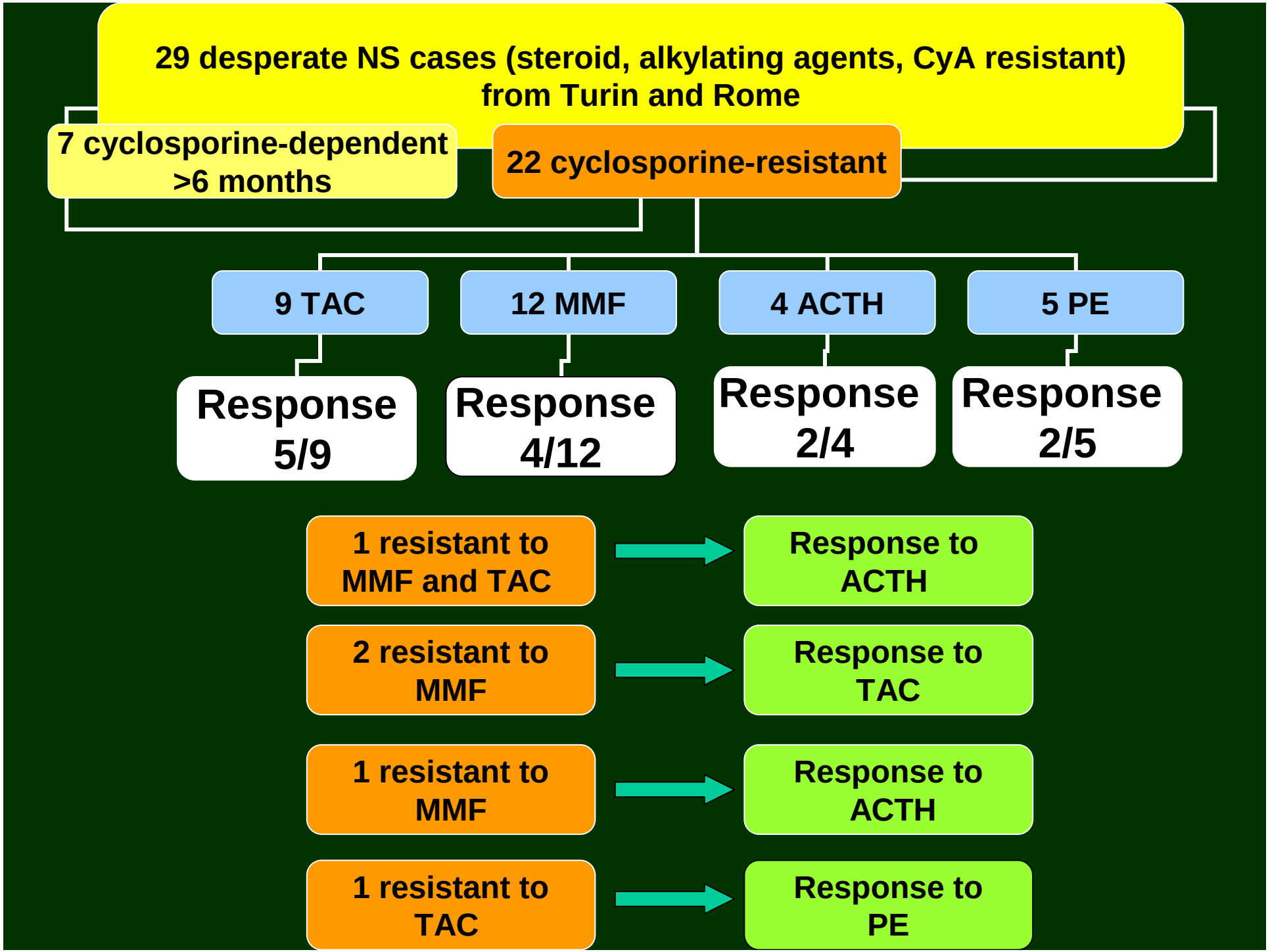
Stephen D. Marks · Mary McGraw

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
12 MMF
4 ACTH
5 PE
Response 5/9
Response 4/12
Response 2/4
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