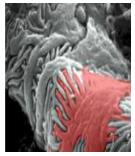
UniversityHospital Heidelberg

ERKNet
The European
Rare Kidney Disease
Reference Network



PodoNet

IPNA

Síndrome nefrótico, una visión actual

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Division of Pediatric Nephrology
Center for Pediatric and Adolescent Medicine
Heidelberg, Germany

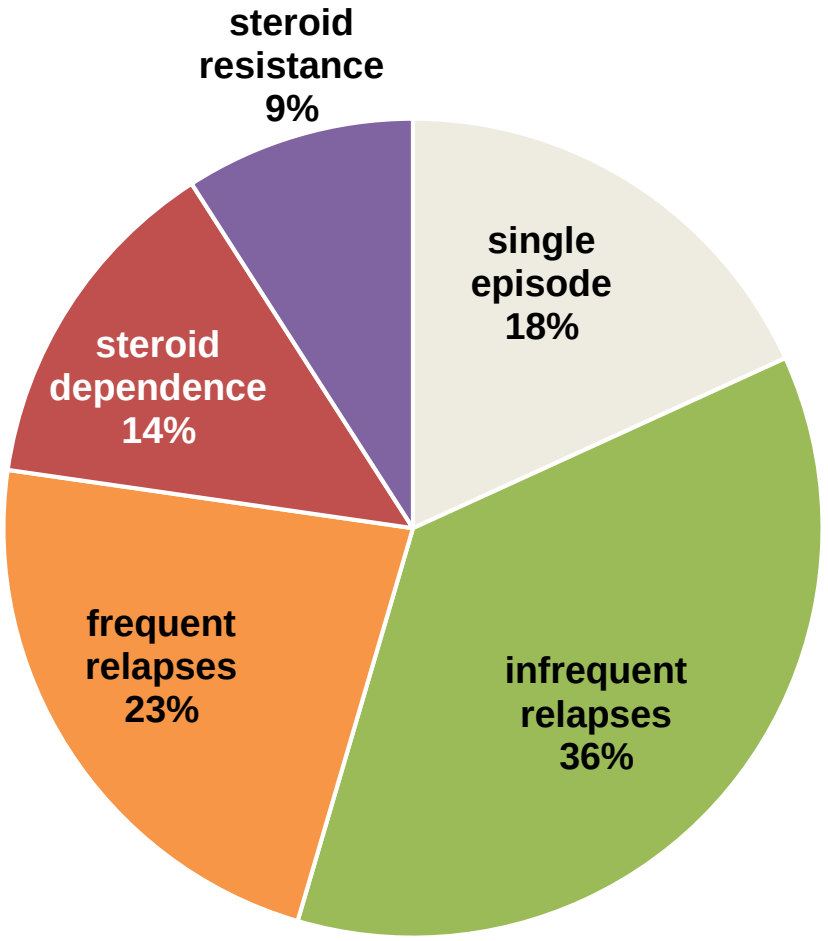
Idiopathic Nephrotic Syndrome

Most common chronic kidney disease in childhood: prevalence 1/7,000 among Caucasians, 1/1,200 among Asians

Good long-term prognosis of steroid sensitive forms

40% frequently relapsing/ steroid dependent phenotypes

FRNS/SDNS:
Significant 2° morbidity from steroid toxicity



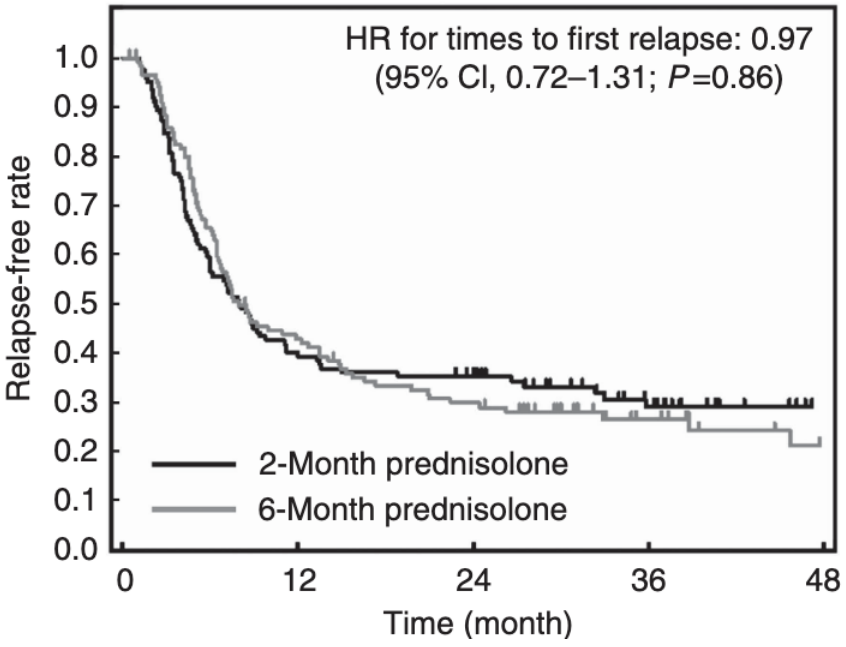
Practice of Steroid Therapy in SSNS

Lande *et al* Pediatr Nephrol 2000 14: 766-769

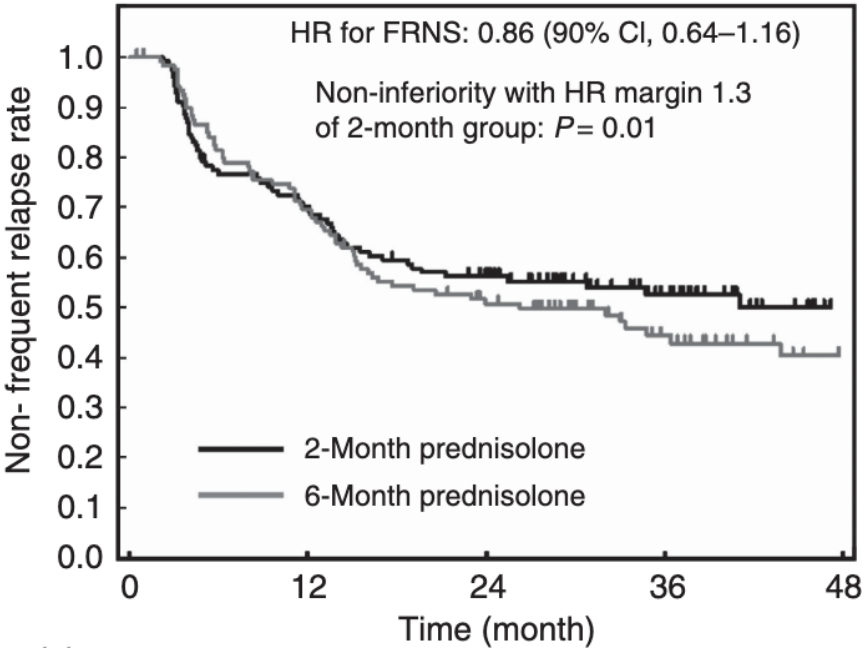
ISKDC Protocol (8 wks)	13%
APN Protocol (12 wks)	7%
ISKDC Protocol, then tapering	36%
APN Protocol, then tapering	14%
Start tapering steroids with remission	14%
Other	15%

A multicenter randomized trial indicates initial prednisolone treatment for childhood nephrotic syndrome for two months is not inferior to six-month treatment

Time to 1st relapse

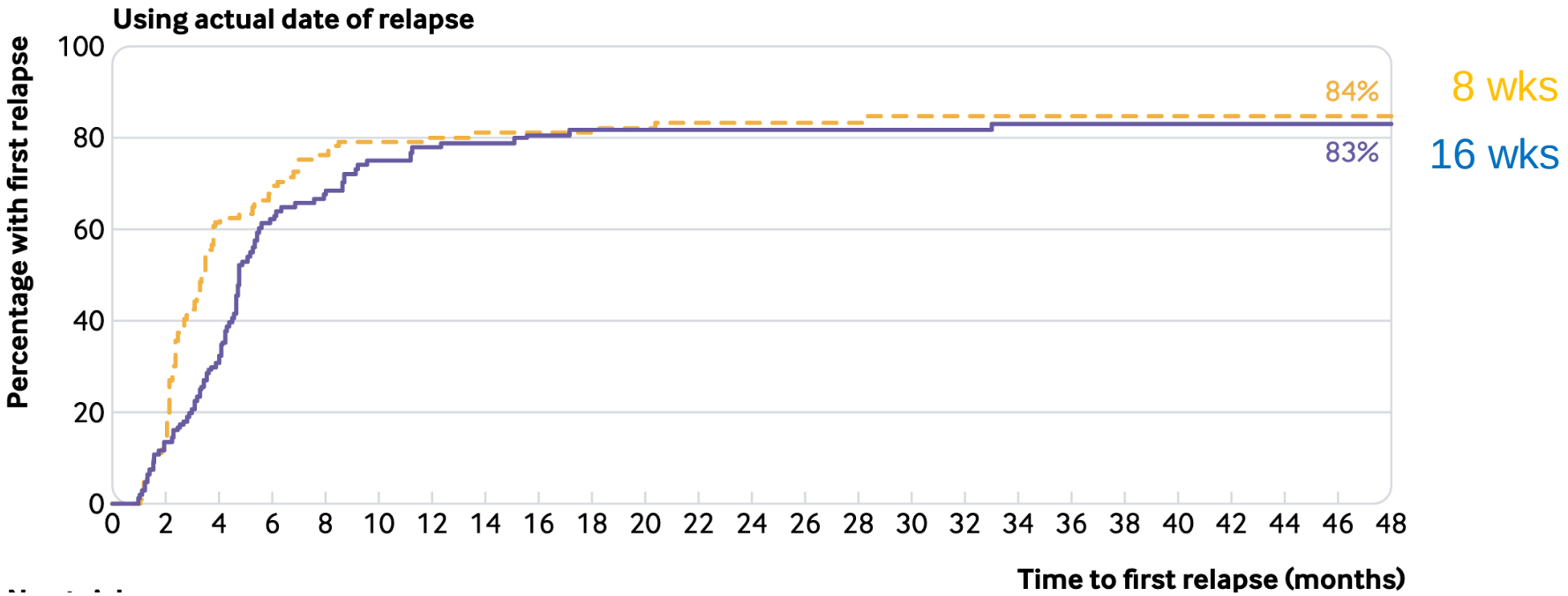


Time to FR status



Yoshikawa *et al* Kidney Int 2014

Long term tapering versus standard prednisolone treatment for first episode of childhood nephrotic syndrome: phase III randomised controlled trial and economic evaluation



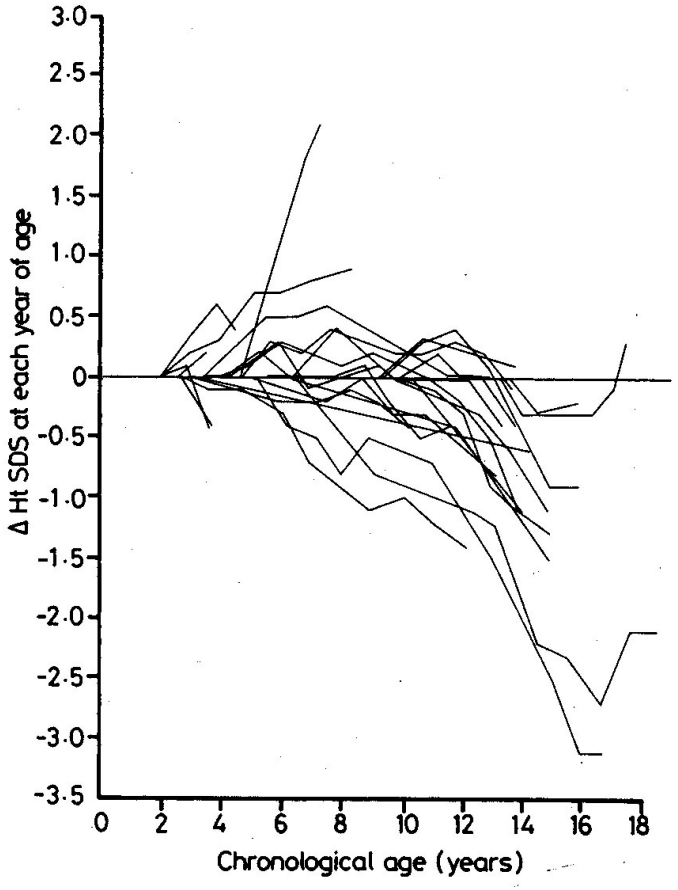
Webb *et al.* BMJ 2019

Management of Complicated Steroid Sensitive NS

Alternate-Day Maintenance Steroid Therapy

- Adverse effect rate lower than with equivalent daily dosing
- Taper to lowest effective maintenance dose
  - <0.5mg/kg/48h
  - May be continued over years
  - Try withdrawing therapy every 6 months

Long-term Growth Effects of Alternate-Day Maintenance Steroid Therapy



Rees *et al* Arch Dis Child. 1988; 63: 484-490

Relapse Prevention by Preemptive Steroid Therapy

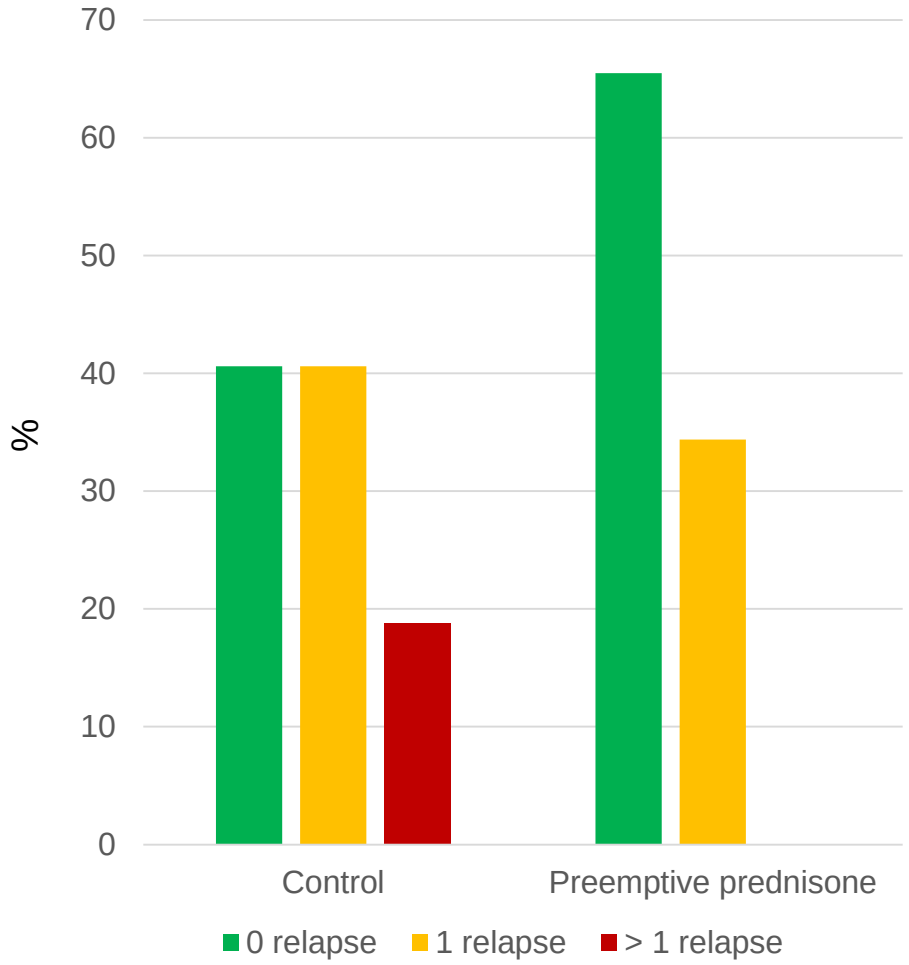
Double-blind placebo-controlled crossover trial

48 patients with idiopathic NS who had been receiving corticosteroid therapy for a minimum of 3 months.

At URTI onset:

- Group A: 5 days daily prednisone at 0.5 mg/kg
- Group B: 5 days placebo

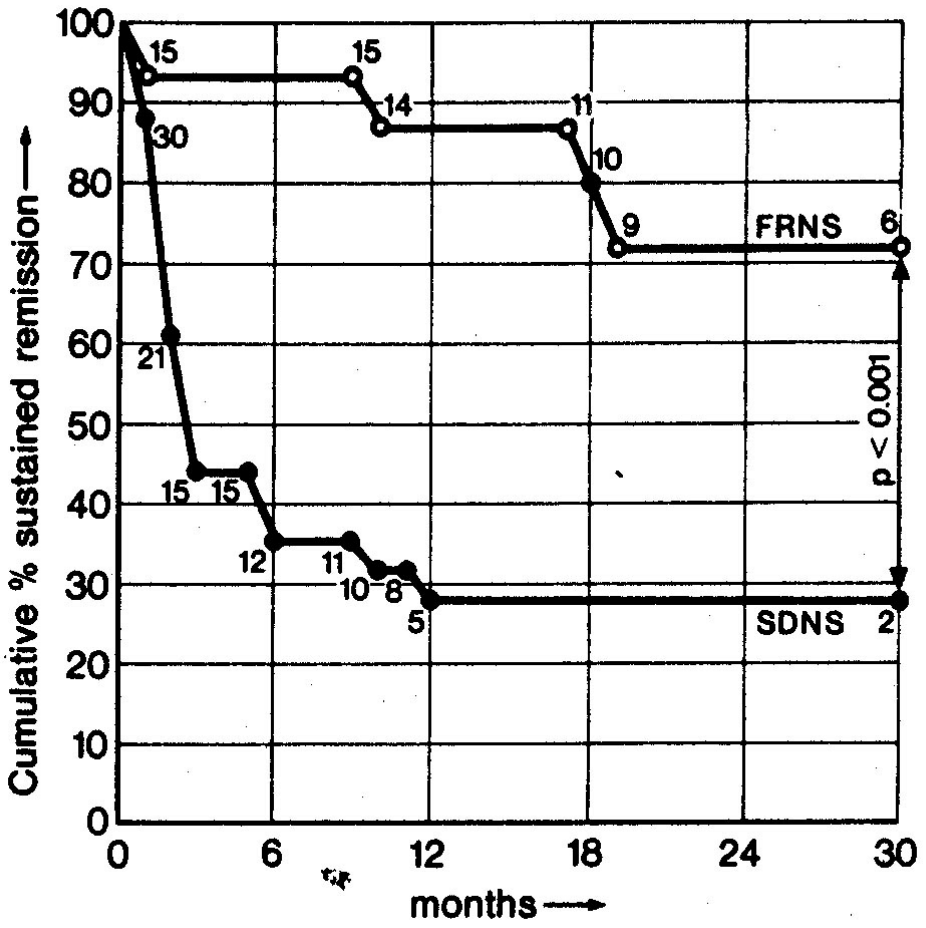
Follow up: 1 year, then cross-over



Abeyagunawardena *et al*. Pediatr Nephrol 2017

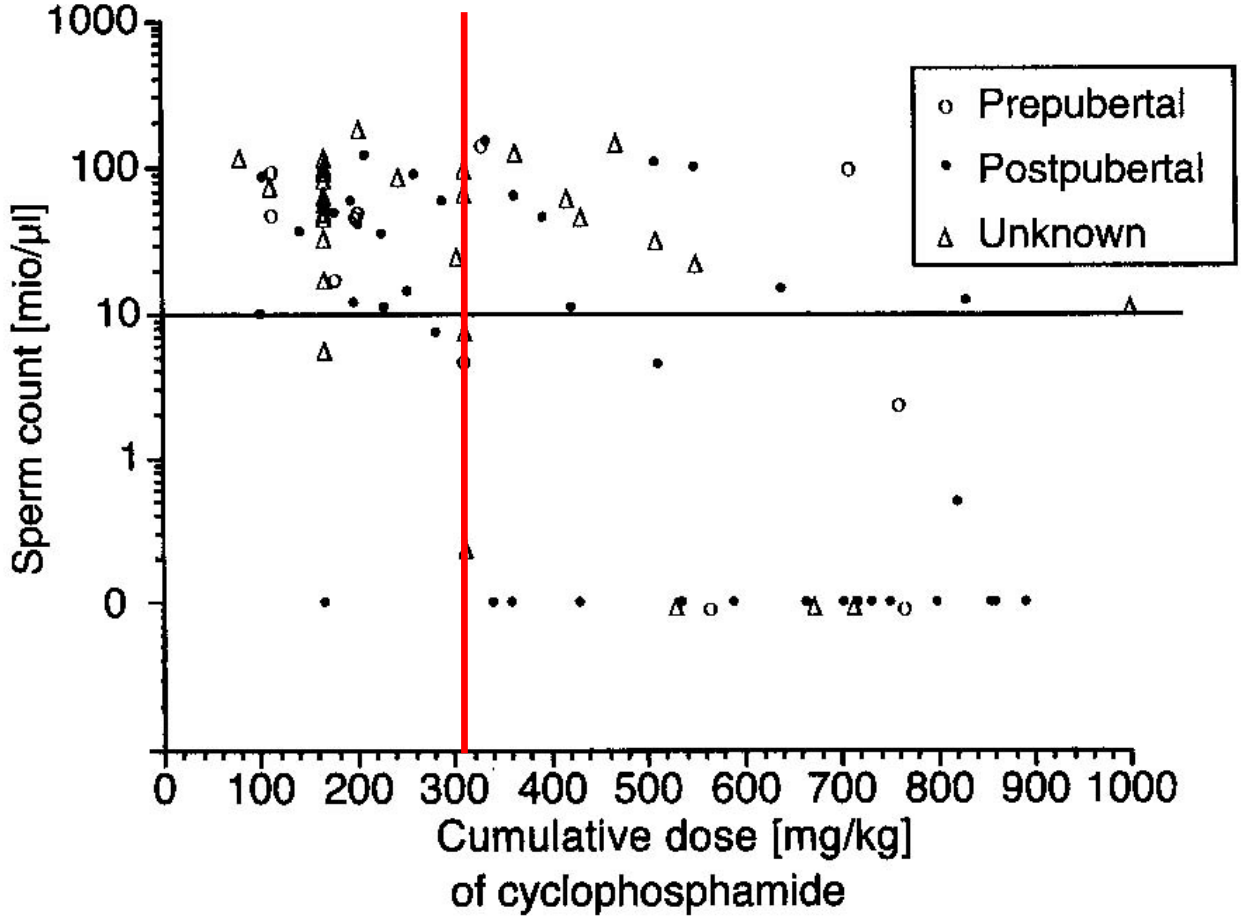
Steroid Sparing by Alkylating Agents

- Cyclophosphamide, Chlorambucil
- Inhibit DNA transcription by alkylation of purine bases
- Cytotoxic and immunosuppressive
- Induction of long-term remission by 2 to 3 months administration possible



APN New Engl J Med. 1982; 306: 451-454

Cyclophosphamide and Fertility



Latta *et al* Pediatr Nephrol. 2001; 16: 271-282

Alkylating Agents and Malignancy

Meta-analysis:

38 studies of cytotoxic therapy of children with steroid-sensitive NS

14 malignancies after 1573 therapy cycles in 1504 children (~1%)

9 hematological disorders

5 solid tumors

Latta *et al* Pediatr Nephrol. 2001; 16: 271-282

Calcineurin Inhibitors (CsA, Tacrolimus)

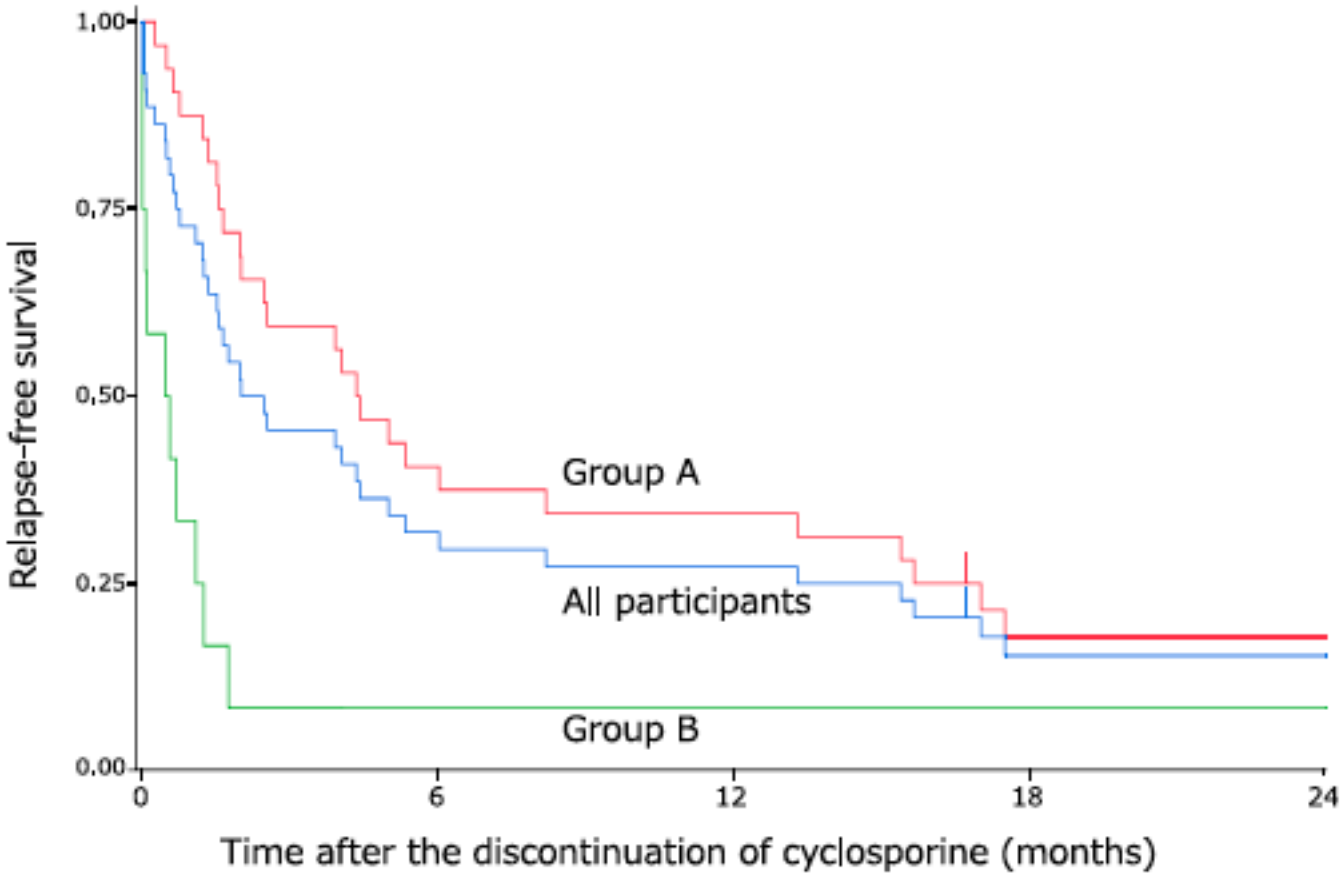
- **CsA efficacy equivalent to alkylating agents**
  RR 0.91 (0.55-1.48)

- **Tacrolimus:** similar efficacy as Ciclosporin A

- **Dose dependent efficacy**
  Sustained remission rate (CsA): 50% vs. 15% @ 4.8 vs. 2.5 mg/kg/d

- **High post-withdrawal relapse risk** (CsA): 84% (60% FRNS/SDNS)

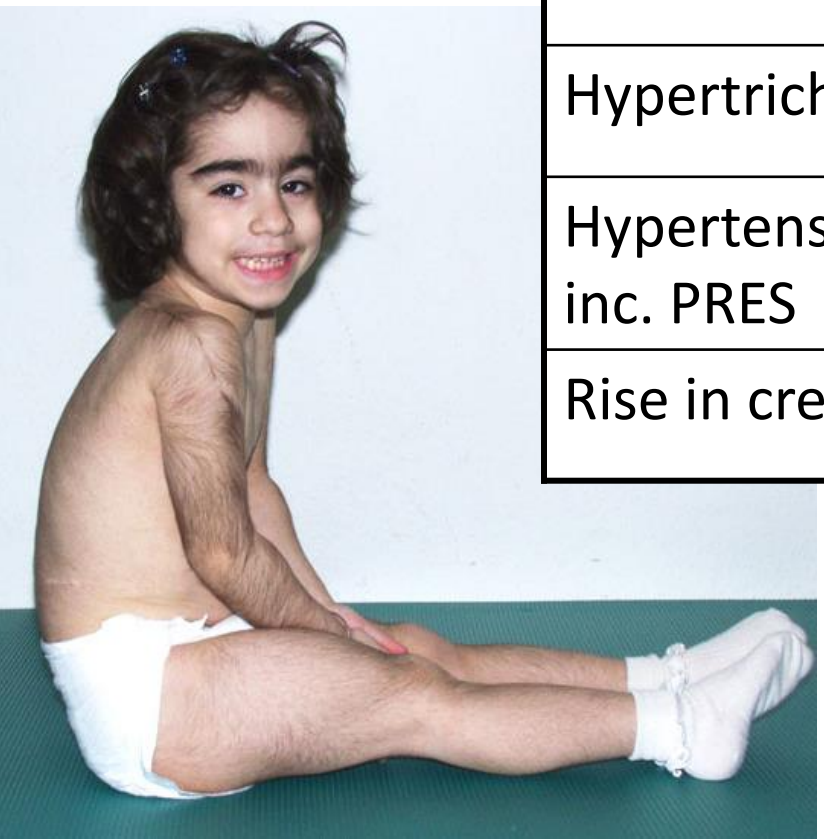
Post-Discontinuation Relapse Rate after 2-yr CsA Therapy



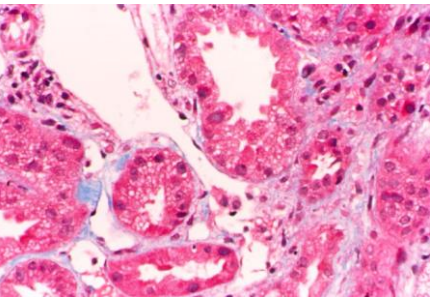
Ishikura et al. cJASN 2012

Cyclosporin A: Side Effects

Durkan A *et al*. Cochrane database of systematic reviews 2005



	Incidence
Gingival hyperplasia	23%
Hypertrichosis	27%
Hypertension inc. PRES	13%
Rise in creatinine	10%



Calcineurin Inhibitor Nephrotoxicity

- **Acute:** Microvascular thrombosis,
  endothelial and mycoyte necrosis
  Isometric vacuolation of PTEC
  Acute tubular necrosis
- **Chronic:** Nodular hyaline arteriopathy
  Striped interstitial fibrosis, tubular atrophy
- **Incidence:** 30-40% @ 1 yr, 80% @ 4yrs
- **Reversibility**: Vascular yes, tubulointerstitial no
- **Risk factors**: Duration of exposure
  > 1 month nephrotic range proteinuria
  Higher CsA levels
  RAS inhibitor co-treatment

Management of CNI-Dependent NS

- **Tacrolimus** preferred due to side effect profile
- Explore and maintain minimal CNI dose required to maintain remission
- Consider discontinuation after 2 years of treatment
- Consider combination with MMF to spare dosage

Adverse events	CsA (n=24)	TAC (n=50)	P
Nephrotoxicity	4	0	0.002
ALT/AST elevation	5	8	0.61
Gastrointestinal symptoms	5	11	0.91
Transient hypertension	3	12	0.23
Glucose intolerance and diabetes	0	1	0.37
Early-stage cataract	0	2	0.21
Hirsutism	8	0	<0.001
Psychiatric symptoms	0	2	0.21
Severe infections	9	15	0.52
Nutritional anemia	0	2	0.21

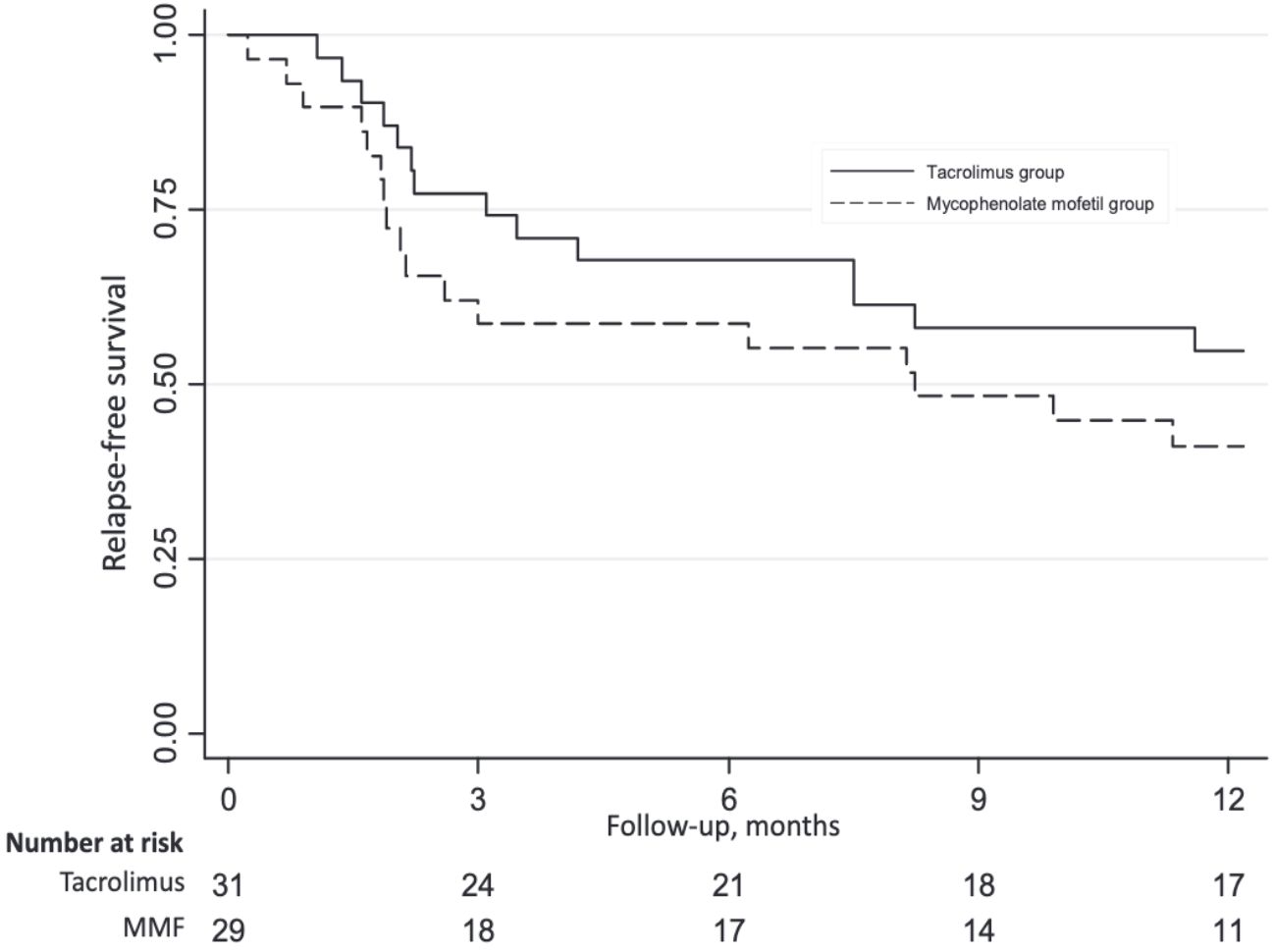
Wang et al. Pediatr Nephrol 2012

Mycophenolate Mofetil (MMF)

- Inhibits purine synthesis in B and T lymphocytes
- Non-nephrotoxic
- Non-gonadotoxic
- 10-15% gastrointestinal intolerance
- Reduces relapse rate by 50-75%
  Complete steroid withdrawal in 50% of pts

Mycophenolate mofetil is inferior to tacrolimus in sustaining remission in children with idiopathic steroid-resistant nephrotic syndrome

see

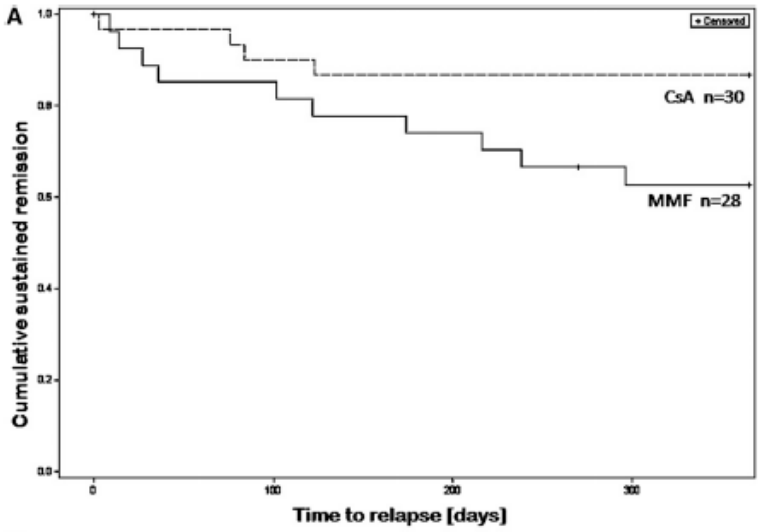


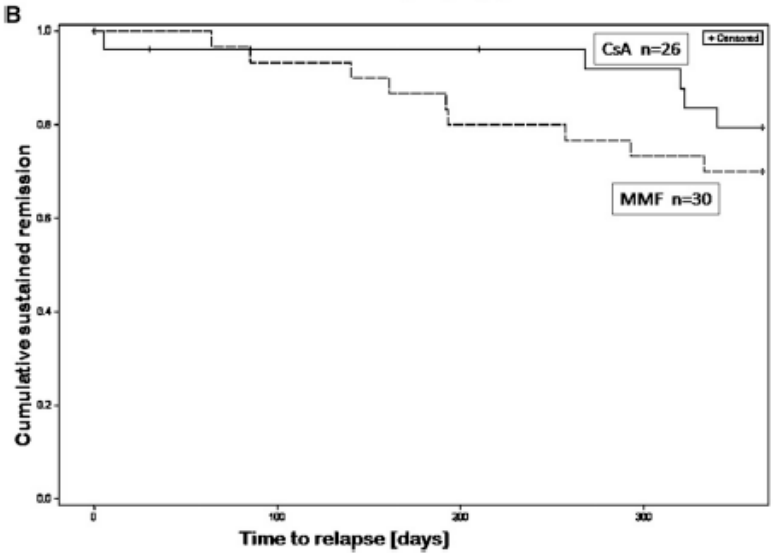
Tacrolimus

MMF

Sinha *et al.* Kidney Int 2017

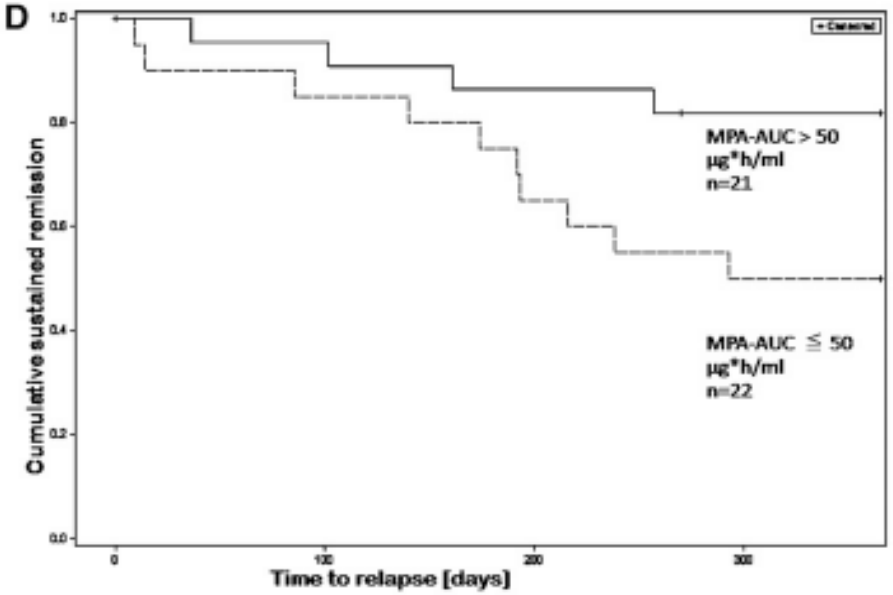
CsA vs. MMF in Frequently Relapsing NS





12-month cross-over trial
60 children with FRNS
Less effective than CsA
Efficacy may be optimized by TDM

MMF-AUC predicted relapse



Gellermann et al. JASN 2013

A Role for Levamisole in Idiopathic NS?

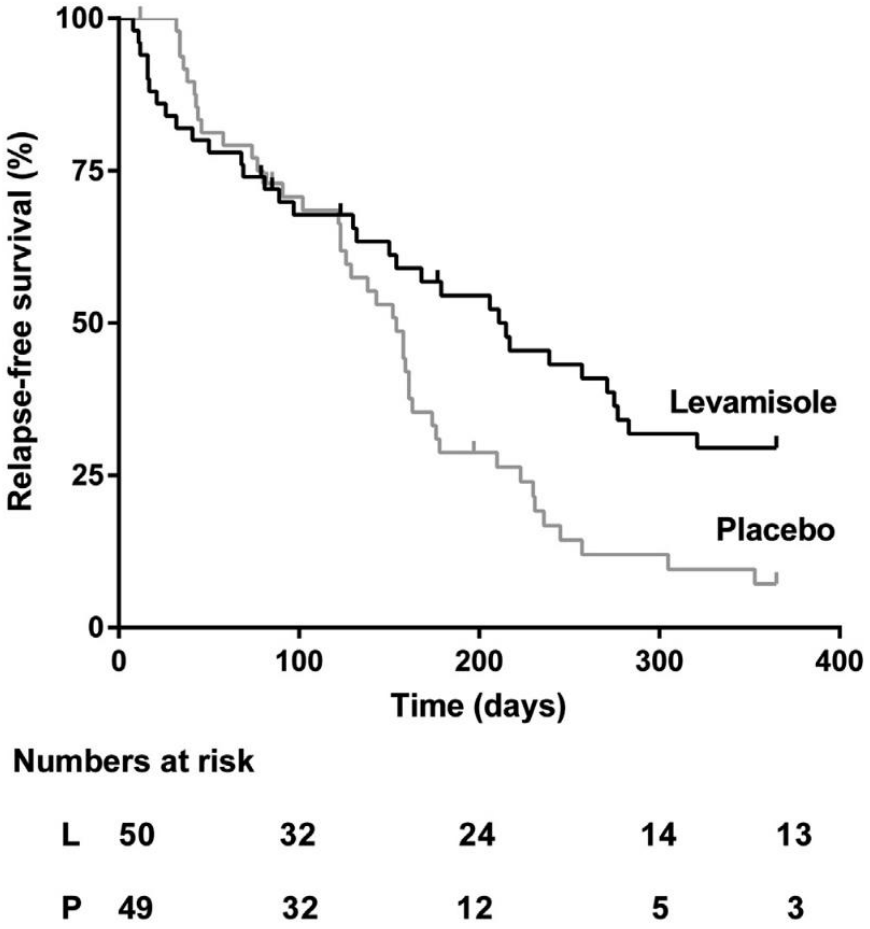


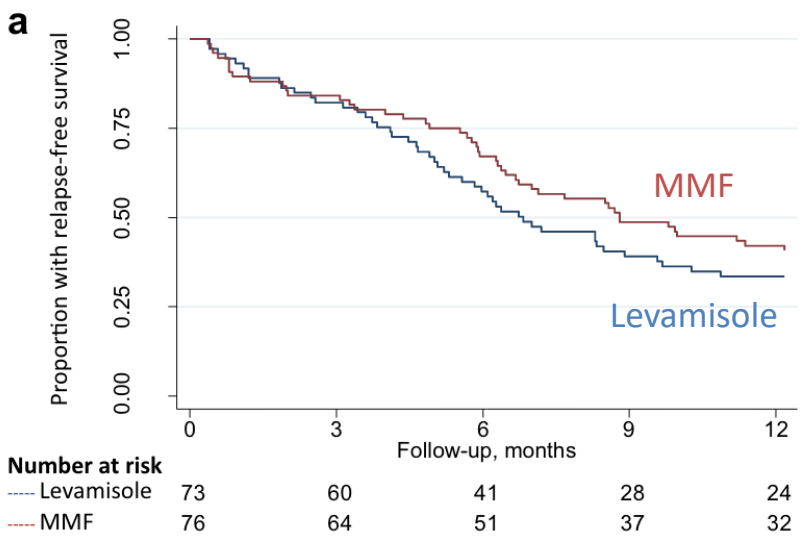
Table 4 | Most frequently encountered SAEs in the safety population

	Levamisole (*n/N*)	Placebo (*n/N*)
AEs		
At least 1 AE[a]	29/50	19/50
Cough	6/50	6/50
Nasopharyngitis	8/50	10/50
Pyrexia	10/50	6/50
Neutropenia (1000–1500/μl)	3/50	3/50
SAEs		
Neutropenia (500–1000/μl)	4/50	1/50
Neutropenia (<500/μl)	1/50	
Hospitalization[b]	3/50[a]	0/50
Reduced GFR	1/50	0/50
Arthritis/ANCA+	1/50	0/50

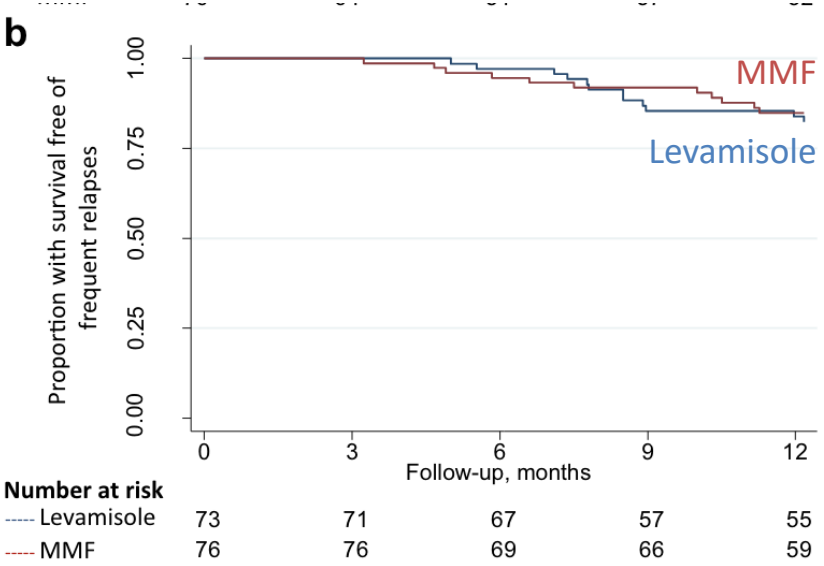
Gruppen et al. Kidney Int 2017

Levamisole is as efficacious as MMF in Reducing Relapse Frequency in Children with FRNS

Relapse-free survival

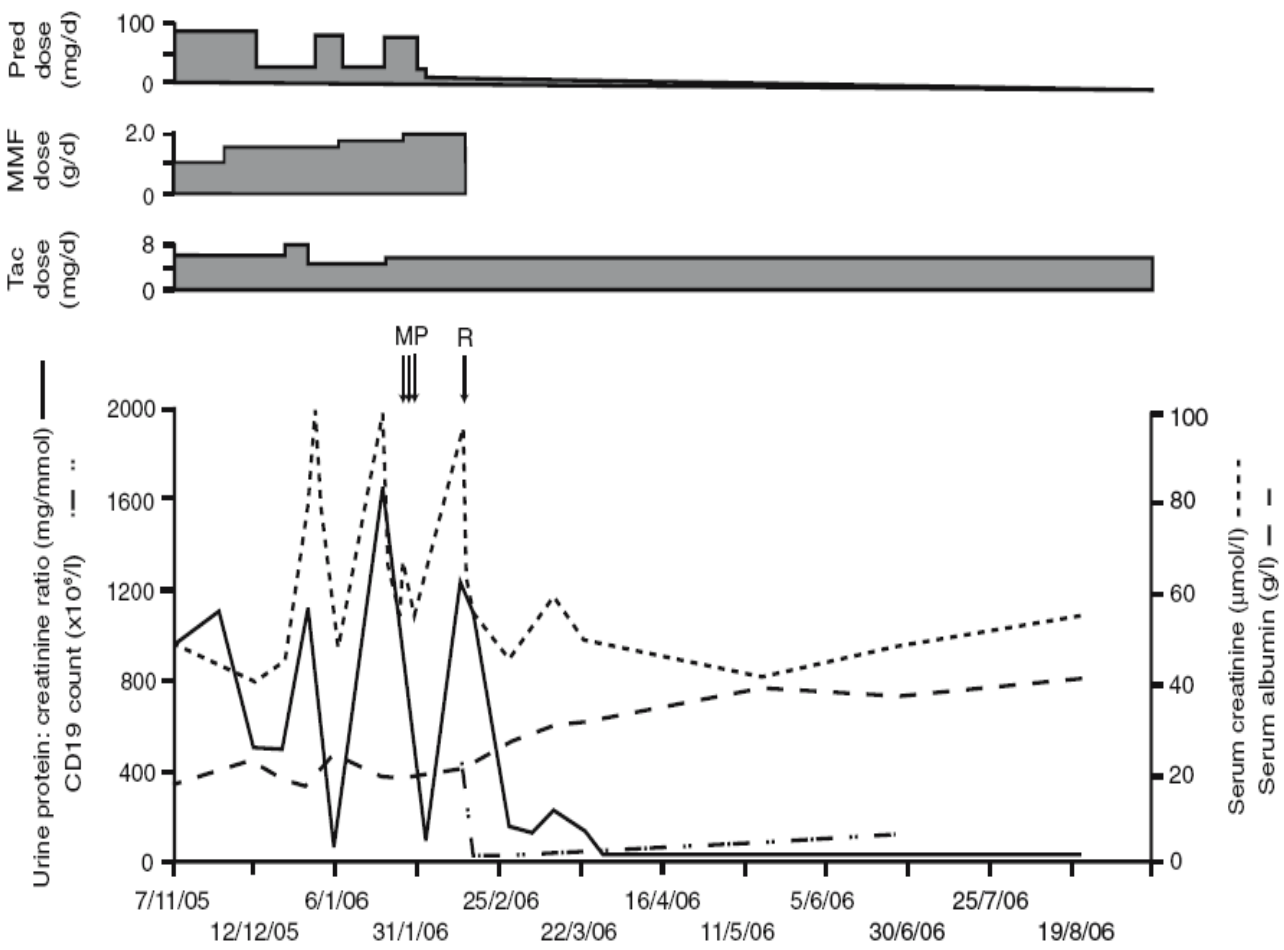


Frequent relapse-free survival



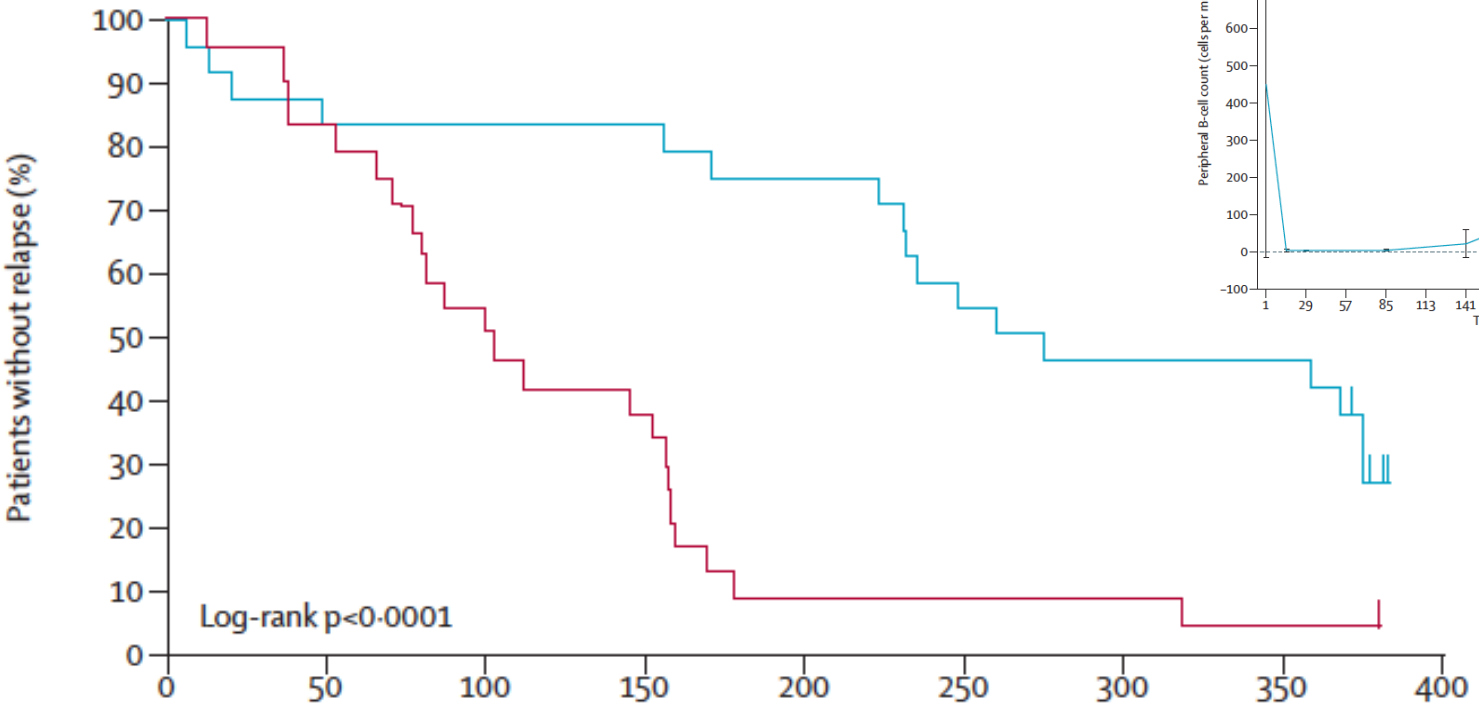
Sinha et al. Kidney Int 2019

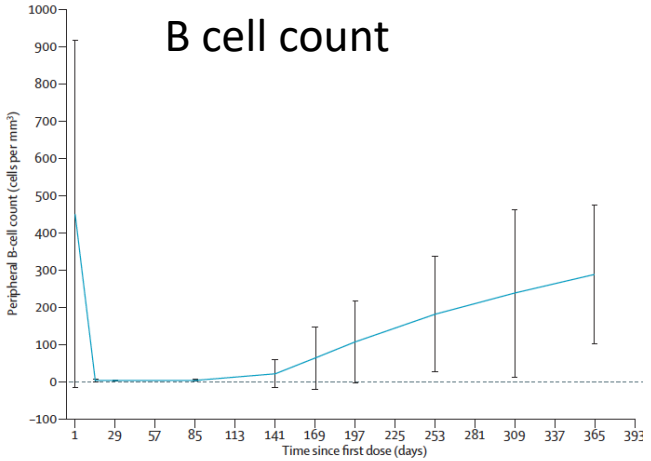
B-Cell Depleting Therapy: Rituximab



Smith. Pediatr Nephrol 2007; 22: 893-8

Rituximab vs. Placebo in SDNS





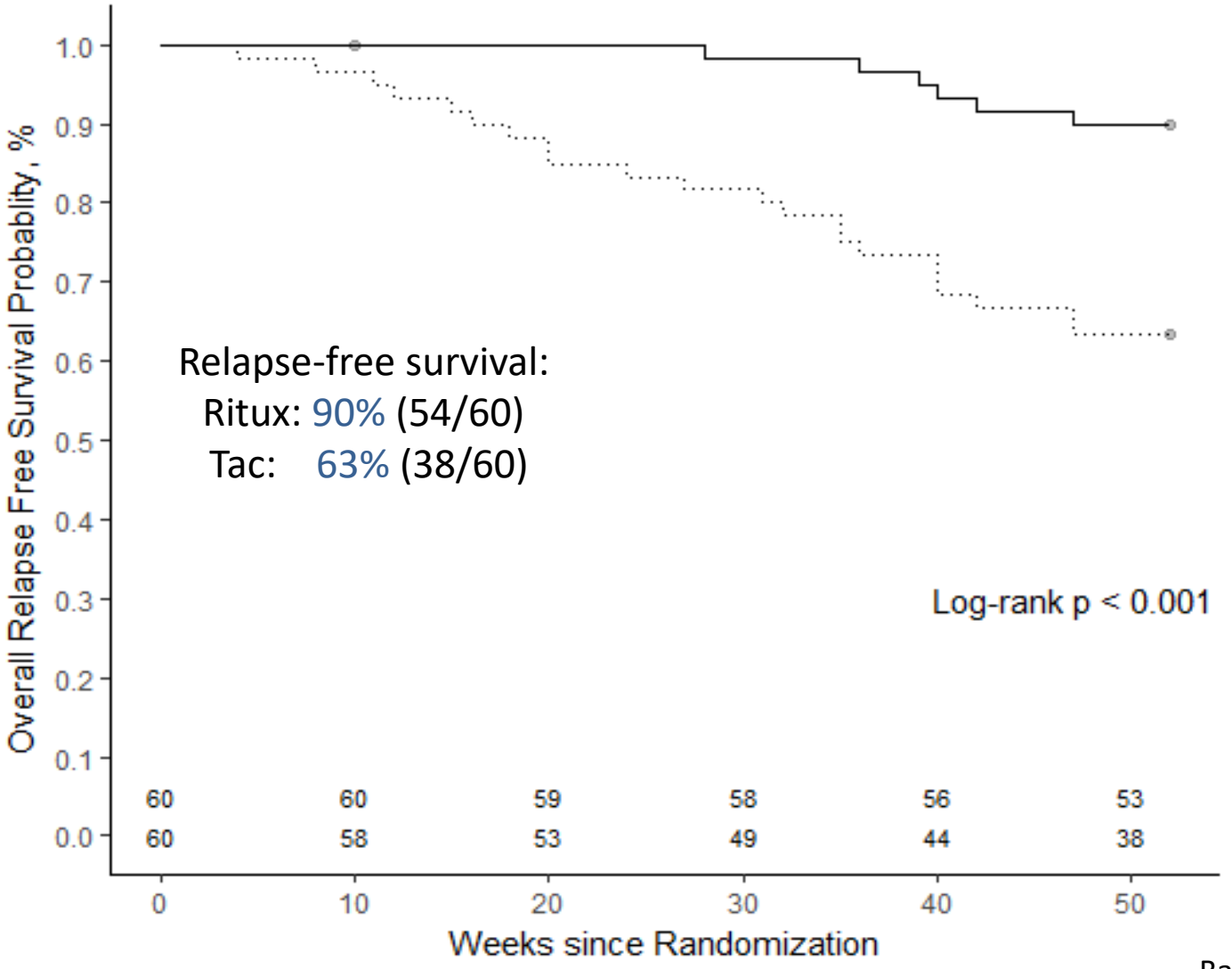
Median relapse-free period:

Rituximab:	267 (223-374) days
Placebo:	101 (70-155) days
Hazard ratio:	0.27 (0.14-0.53), p<0.0001

Iijima et al. Lancet 2014

Rituximab vs. Tacrolimus

RITURNS



Basu JAMA Pediatr 2018

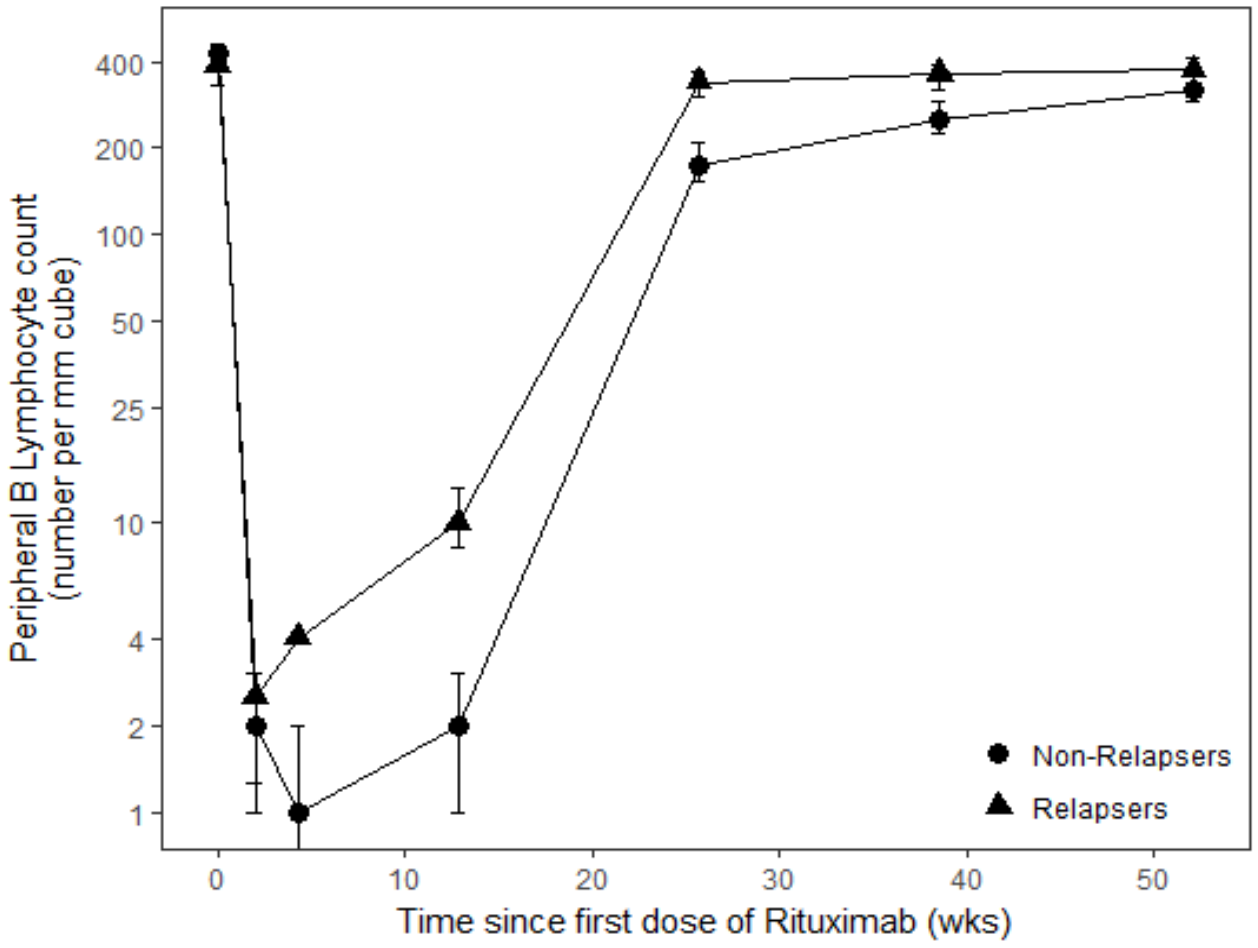
Steroid Exposure

RITURNS

	Tacrolimus	Rituximab	Mean difference/ Odds ratio [95% CI]	p
Pts off steroids at month 12 (%)	46/58 (79.3)	55/59 (93.2)	3.59 [1.1; 11.9]	0.029
Cumulative prednisolone dose in study year (mg/kg)	86.3 ± 58.0	25.8 ± 27.8	60.5 [43.9; 77.1]	<0.001
Change in cumulative prednisolone dose from pre-study year (mg/kg)	-161 ± 68	-213 ± 49	52.5 [30.8; 74.2]	<0.001
Prednisolone dose at month 12 (mg/kg/ad)	0.62 ± 1.33	0.19 ± 0.76	0.43 [0; 0.8]	0.036
12-month change in prednisolone dose (mg/kg/ad)	-0.70 1.32	-1.12 ±0.74	0.42 [0; 0.8]	0.038

Post Rituximab B-Lymphocyte Recovery and NS Relapse

RITURNS

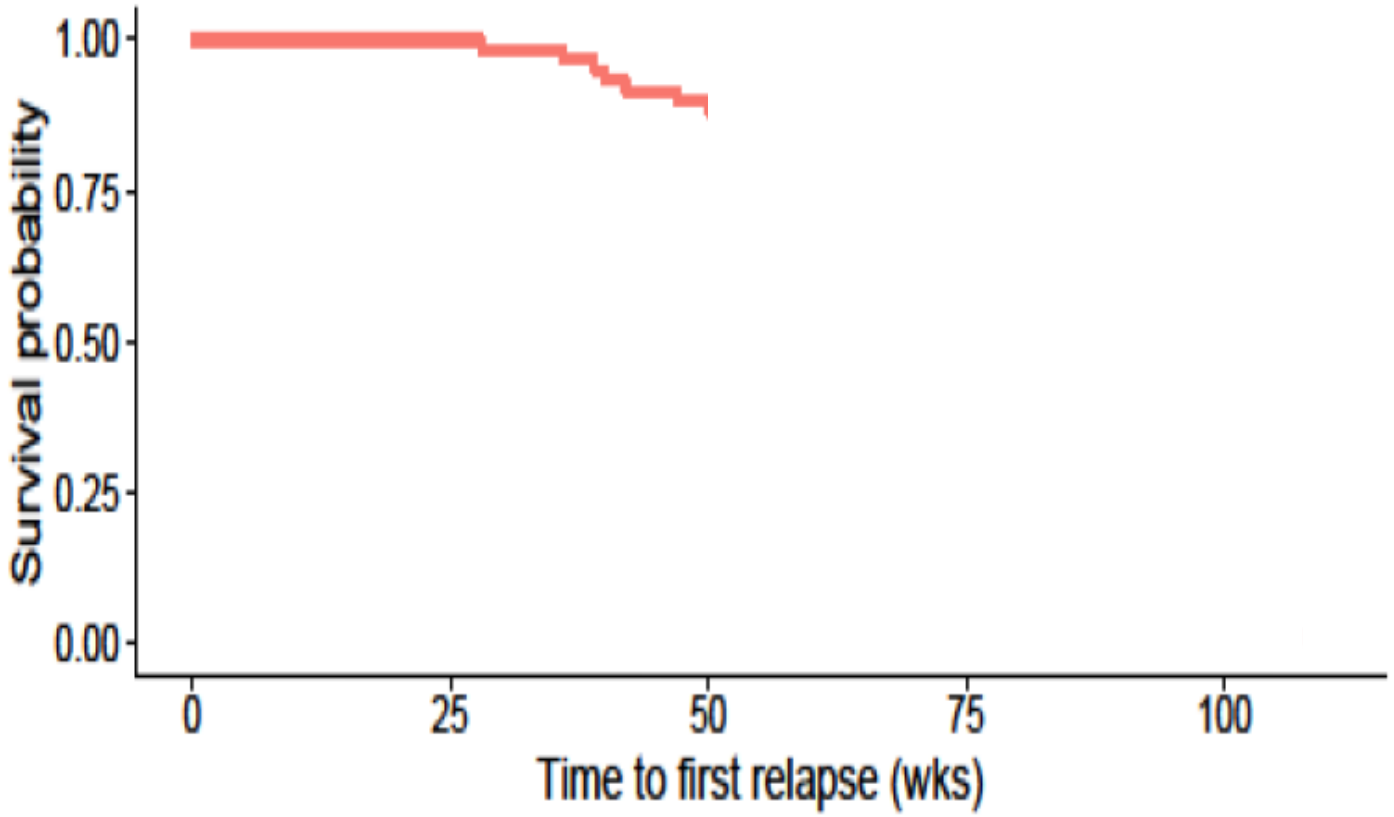


Basu JAMA Pediatr 2018

Post-Rituximab Follow-up

RITURNS

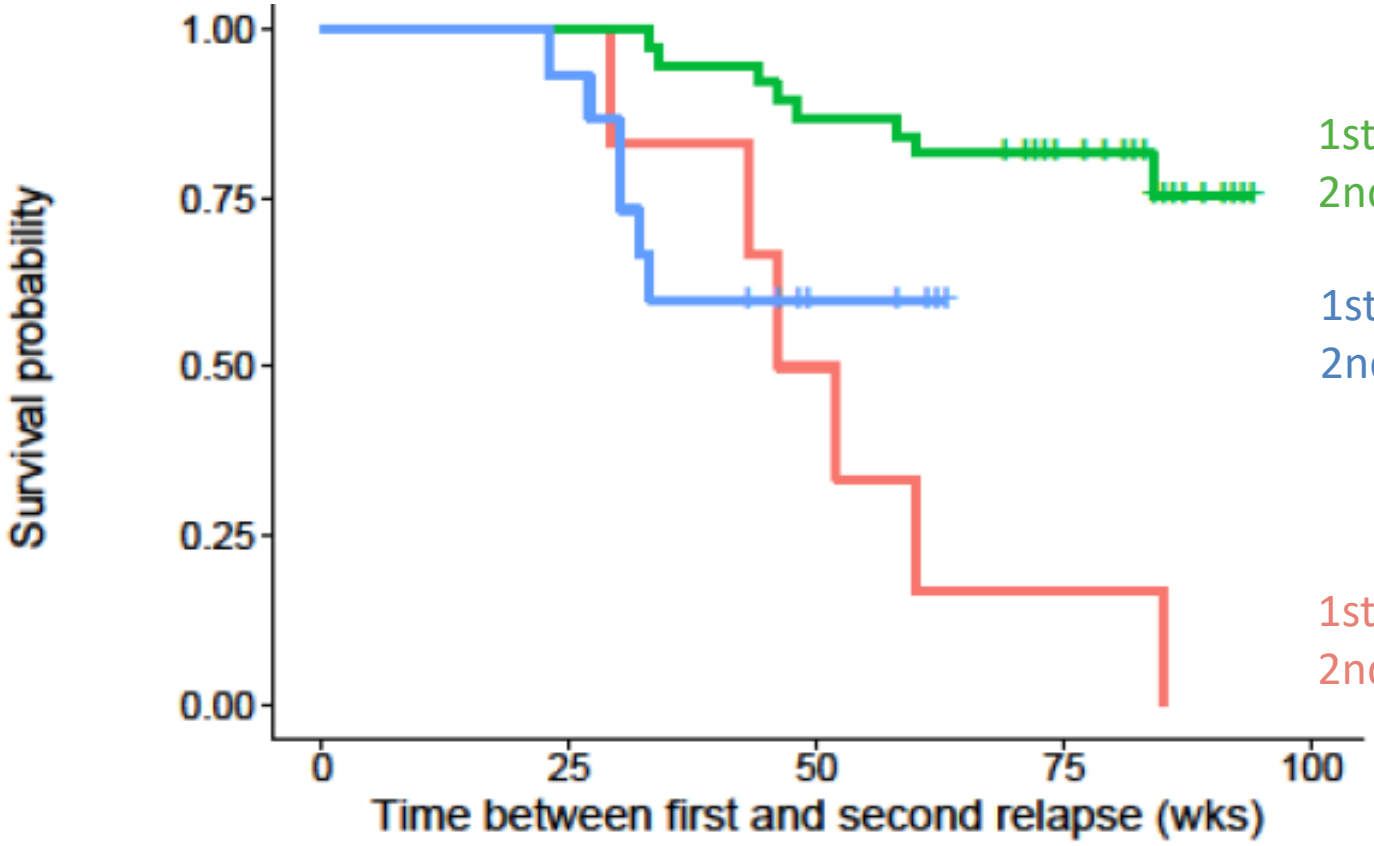
Time to first relapse



Post-Rituximab Follow-up

RITURNS

Time from first to second relapse



1st rel. 52-80 wks
2nd Ritux + MMF

1st rel. >80 wks
2nd Ritux

1st rel. <52wks
2nd Ritux @ 52 wks

Rituximab: Safety Aspects

Acute adverse effects

- Bronchospasm, hypotension, fever, arthralgia

Reported late adverse effects

- Pulmonary fibrosis
- *Pneumocystis jiroveci* pneumonia
- Bacterial pneumonia
- Myocarditis requiring heart transplantation
- Existing hypogammaglobulinaemia may be prolonged
- Multifocal leucoencephalopathy due to JC polyomavirus (reported in 57 SLE patients)

Adverse Events

RITURNS

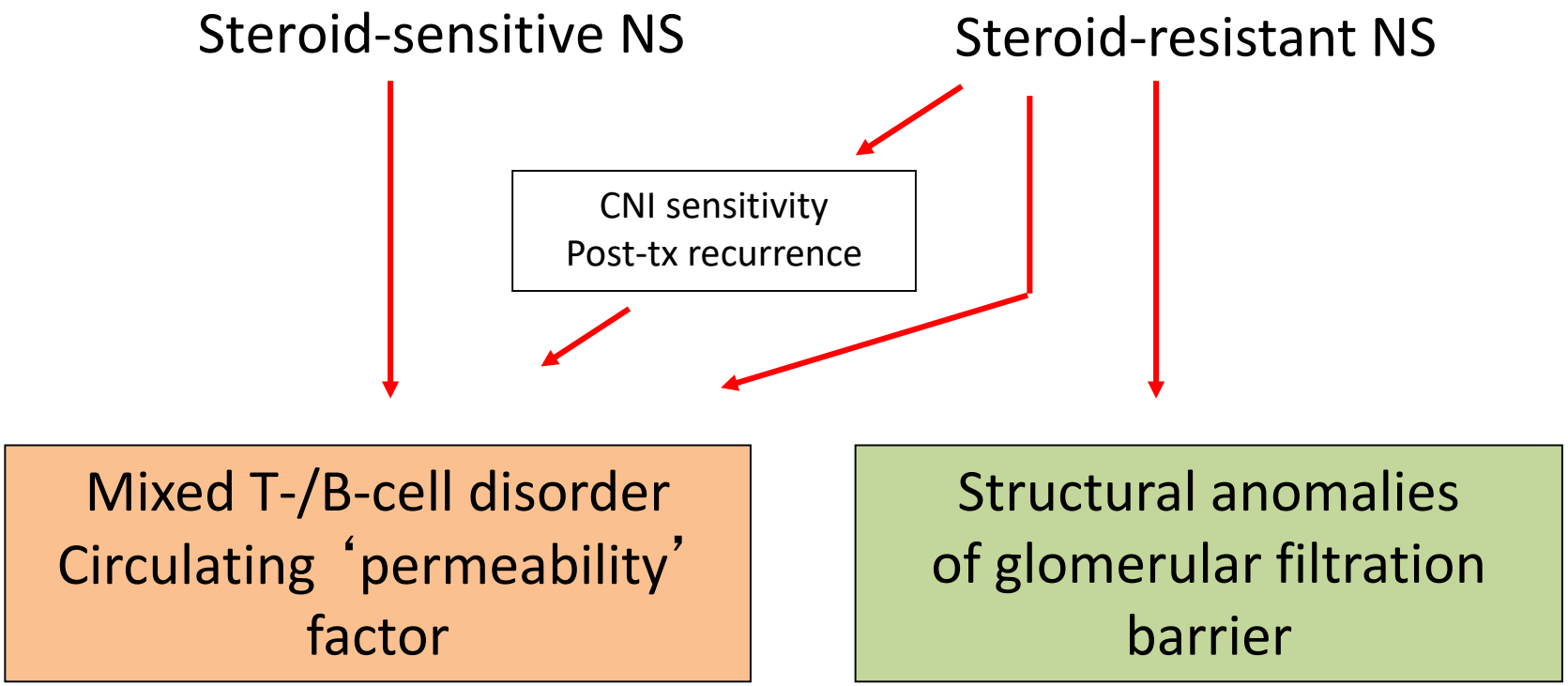
	Tacrolimus group *(n=60)*	Rituximab group *(n=60)*
Number of any adverse events	145	123
Patients with at least one adverse event	47	41
Number of Grade 1 adverse events	87	95
Number of Grade 2 adverse events	**51**	**24**
Number of Grade 3 adverse events	7	4

23 transfusion reactions with Rituximab, most mild and transient

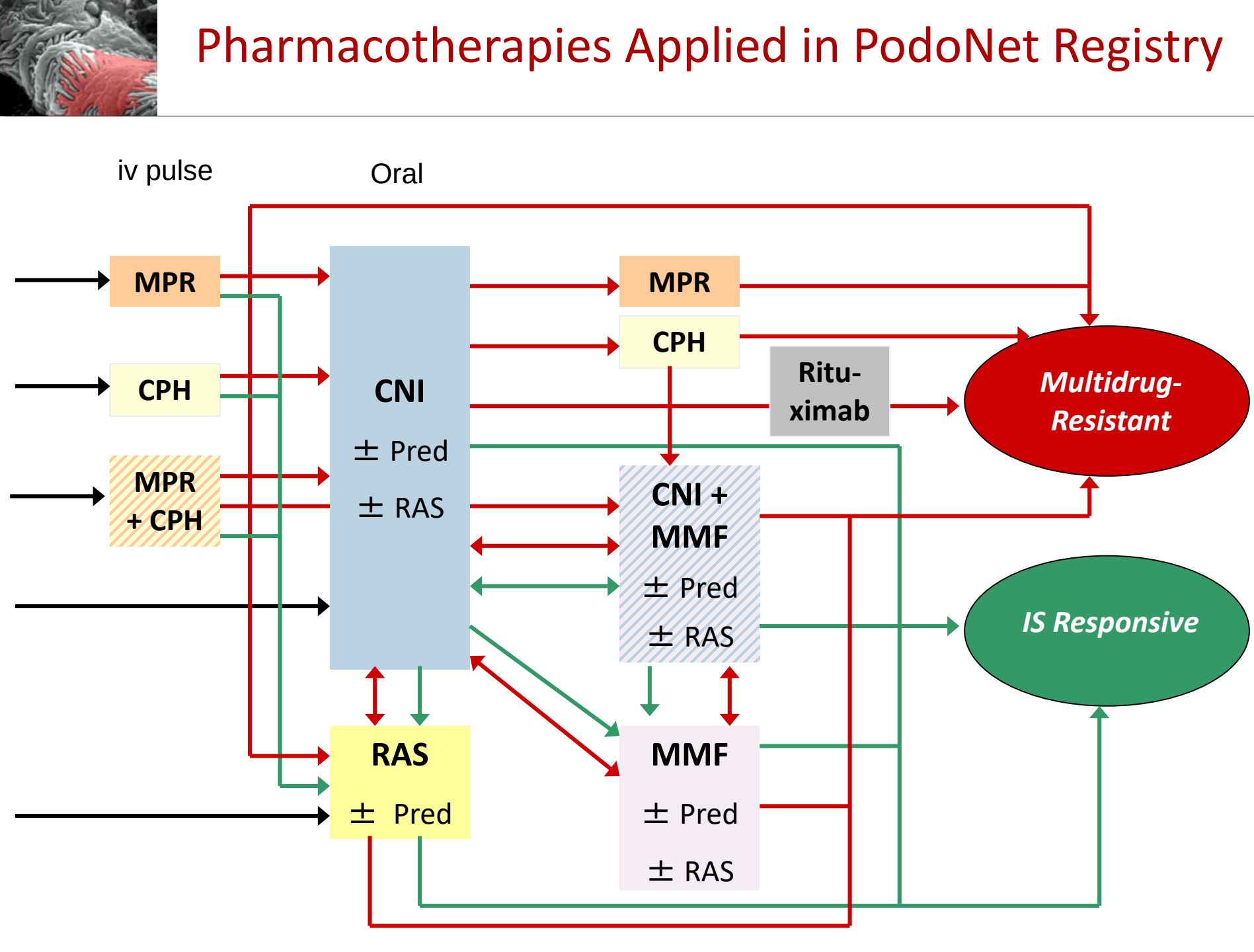
Basu JAMA Pediatr 2018

Management of Steroid Resistant NS

‘Idiopathic’ Nephrotic Syndrome

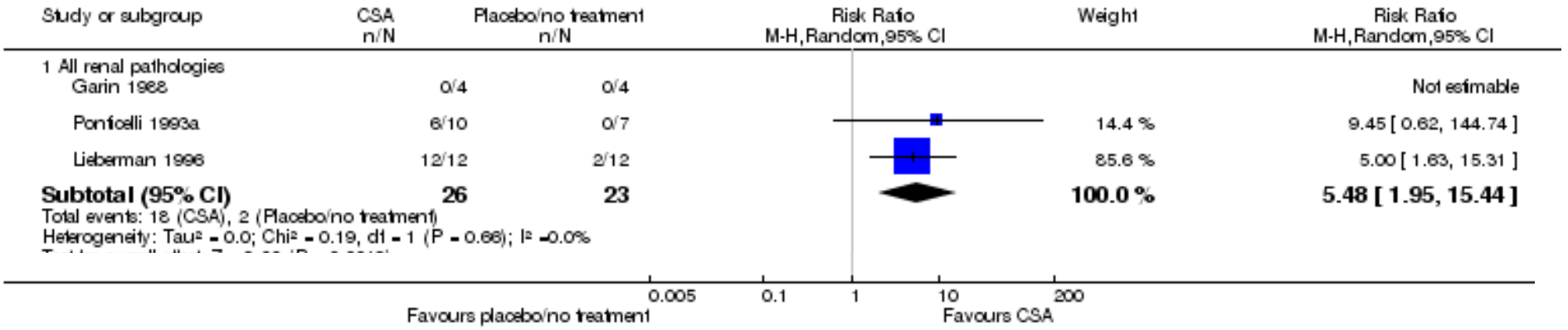


Pharmacotherapies Applied in PodoNet Registry

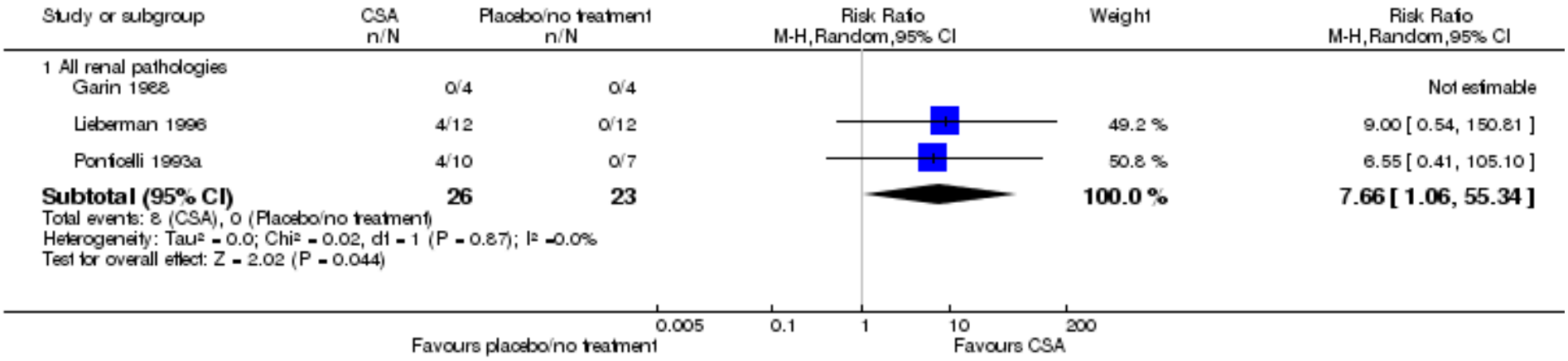


Induction of SRNS Remission by CsA: Controlled Trial Results

Complete or partial remission

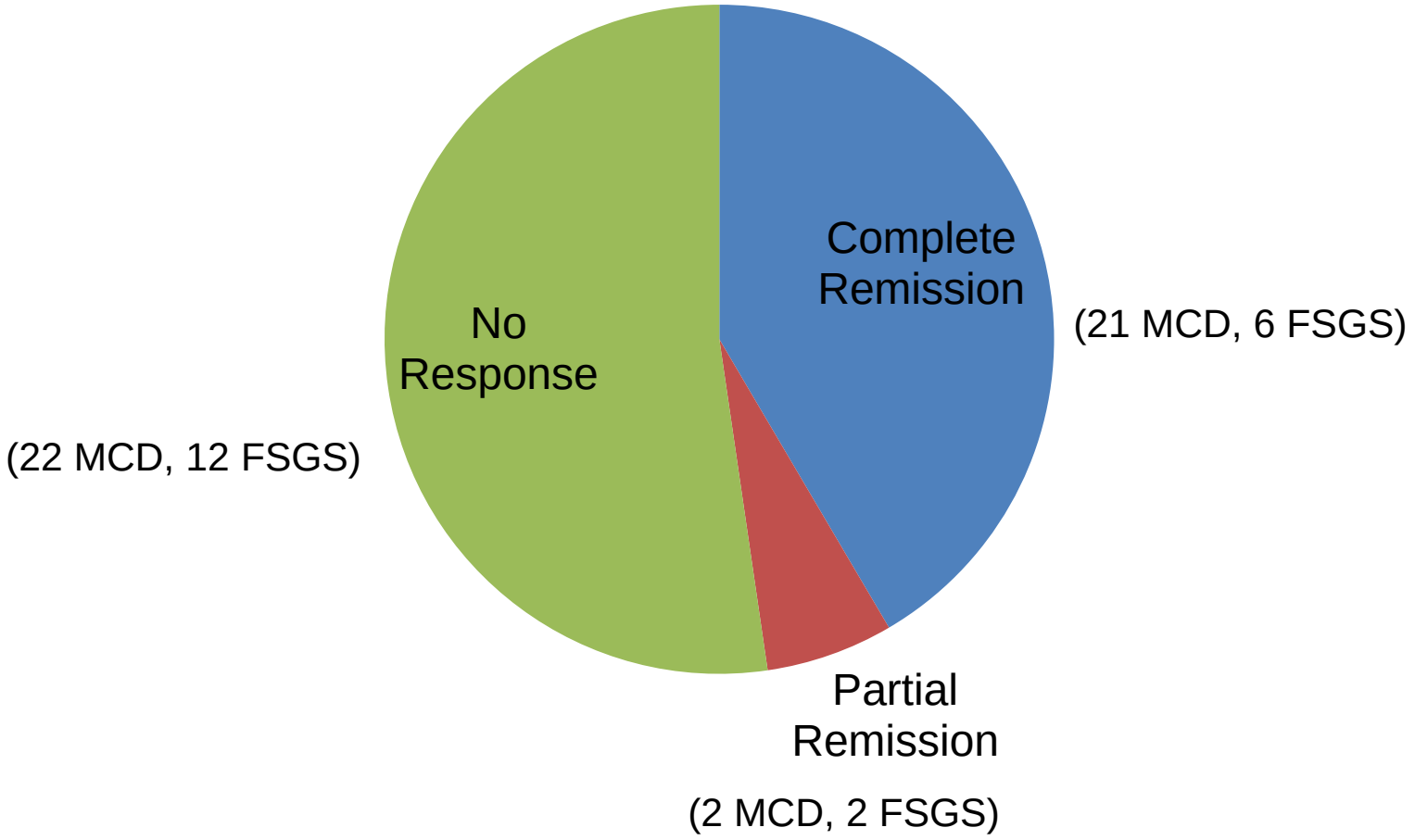


Complete remission



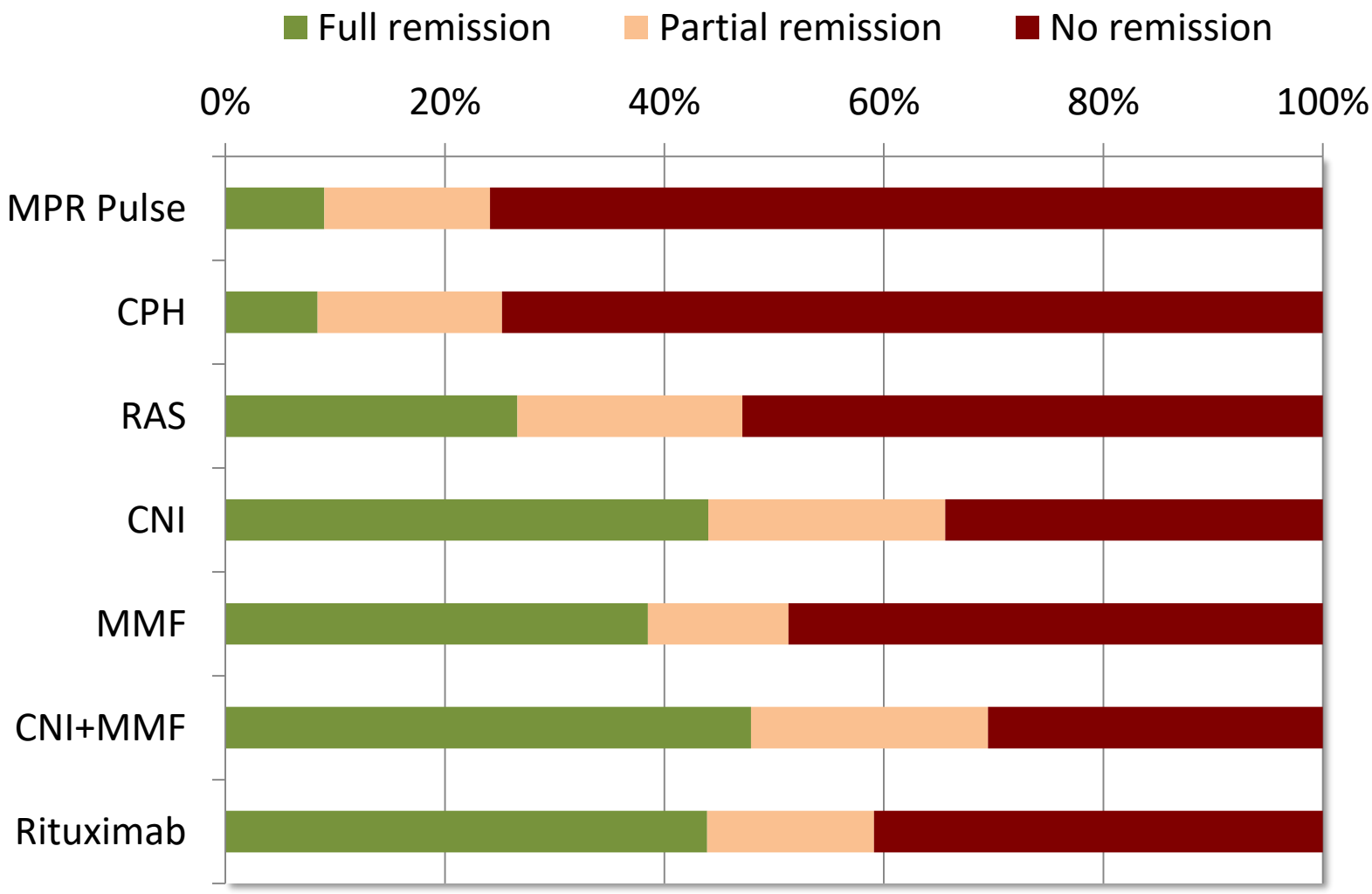
Hodson et al. Cochrane Reviews 2016

Steroid Resistant NS: Efficacy of Cyclosporin A and Prednisone

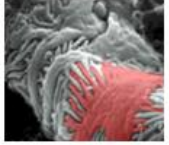


Niaudet, J Pediatr 1994;125:981

Efficacy of Treatment Protocols



Trautmann et al. cJASN 2015



PodoNet

Clinical, Genetic and Experimental Research into Hereditary Diseases of the Podocyte

Genetic diagnosis made in 333 of 1,294 SRNS subjects (25.7%)

Mutation detection rate:

41% of familial cases

36% of sporadic but consanguineous cases

19% of sporadic, non-consanguineous cases

GENE	CLASSIFICATION
NPHS1	1st line SRNS gene
NPHS2	1st line SRNS gene
WT1	1st line SRNS gene ; syndromic gene
INF2	well-acknowledged causative gene
PLCE1	well-acknowledged causative gene
TRPC6	well-acknowledged causative gene
CD2AP	well-acknowledged causative gene
ACTN4	well-acknowledged causative gene
COQ2	syndromic gene
COQ6	syndromic gene
LAMB2	syndromic gene
LMX1B	syndromic gene
SMARCAL1	syndromic gene
ADCK4	novel gene proposed in a few recent studies
ARHGDIA	novel gene proposed in a few recent studies
ITGA3	novel gene proposed in a few recent studies
MYO1E	novel gene proposed in a few recent studies
MYH9	novel gene proposed in a few recent studies
PTPRO	novel gene proposed in a few recent studies
C14ORF142	novel gene proposed in a few recent studies
CD151	novel gene proposed in a few recent studies
EMP2	novel gene proposed in a few recent studies
PDSS2	novel gene proposed in a few recent studies
SCARB2	novel gene proposed in a few recent studies
ARHGAP24	candidate gene
KANK2	candidate gene
ITGB4	candidate gene
MAGI2	candidate gene
MPDZ	candidate gene
TTC21B	candidate gene
mt-TL1	candidate gene

Podocytopathy Genes

Cytoskeleton proteins

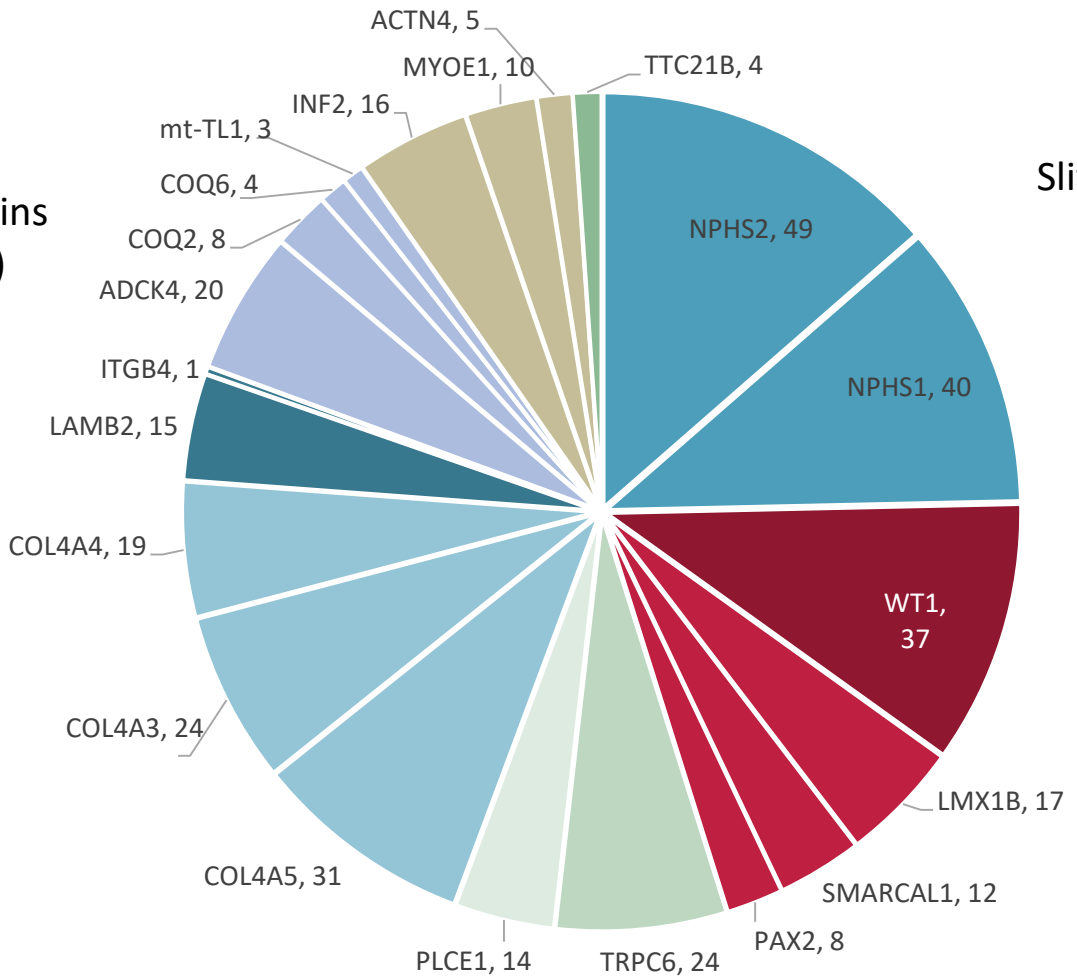
Slit diaphragm

Transcription factors

Signaling proteins

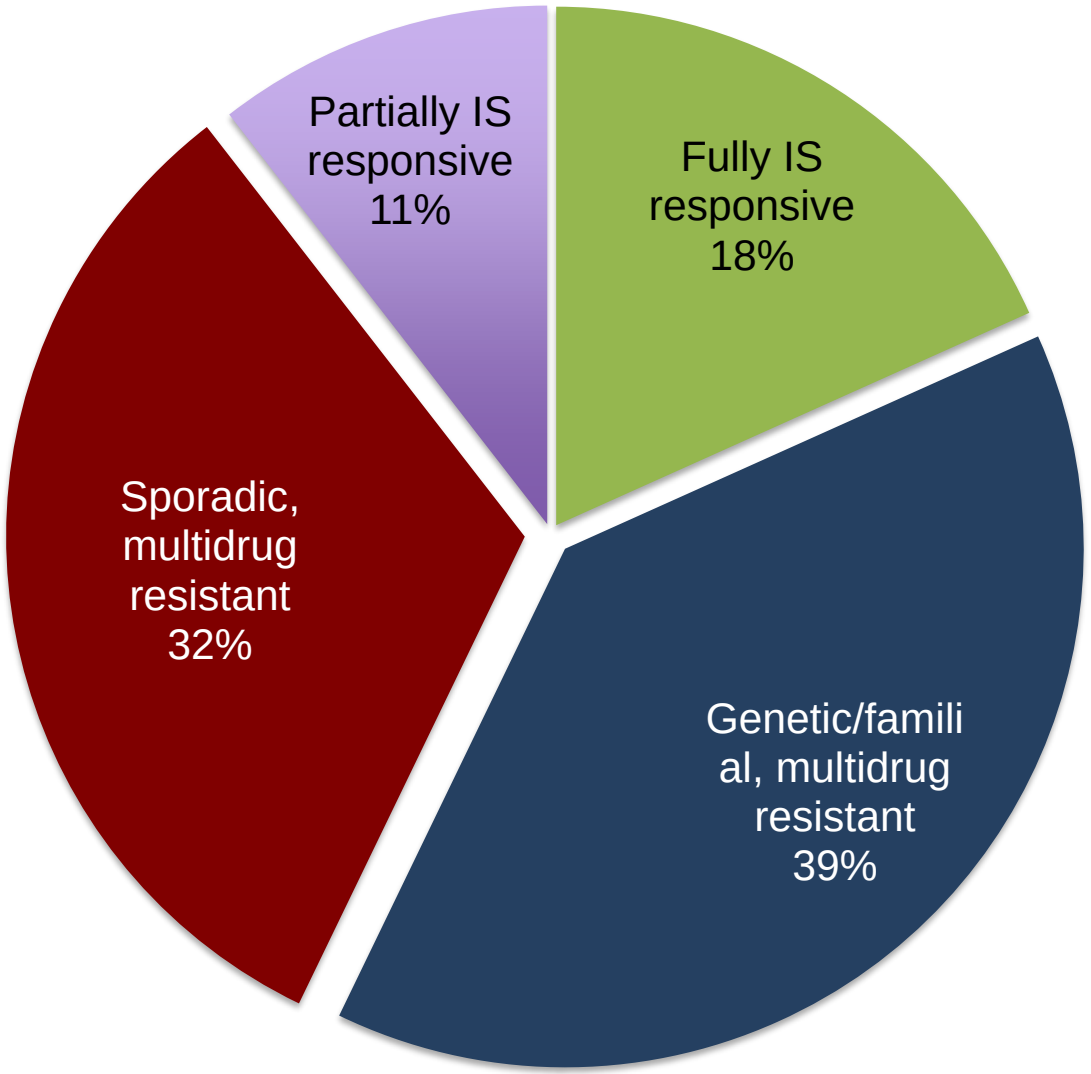
Basement membrane proteins

Mitochondrial proteins (CoQ10 synthase)

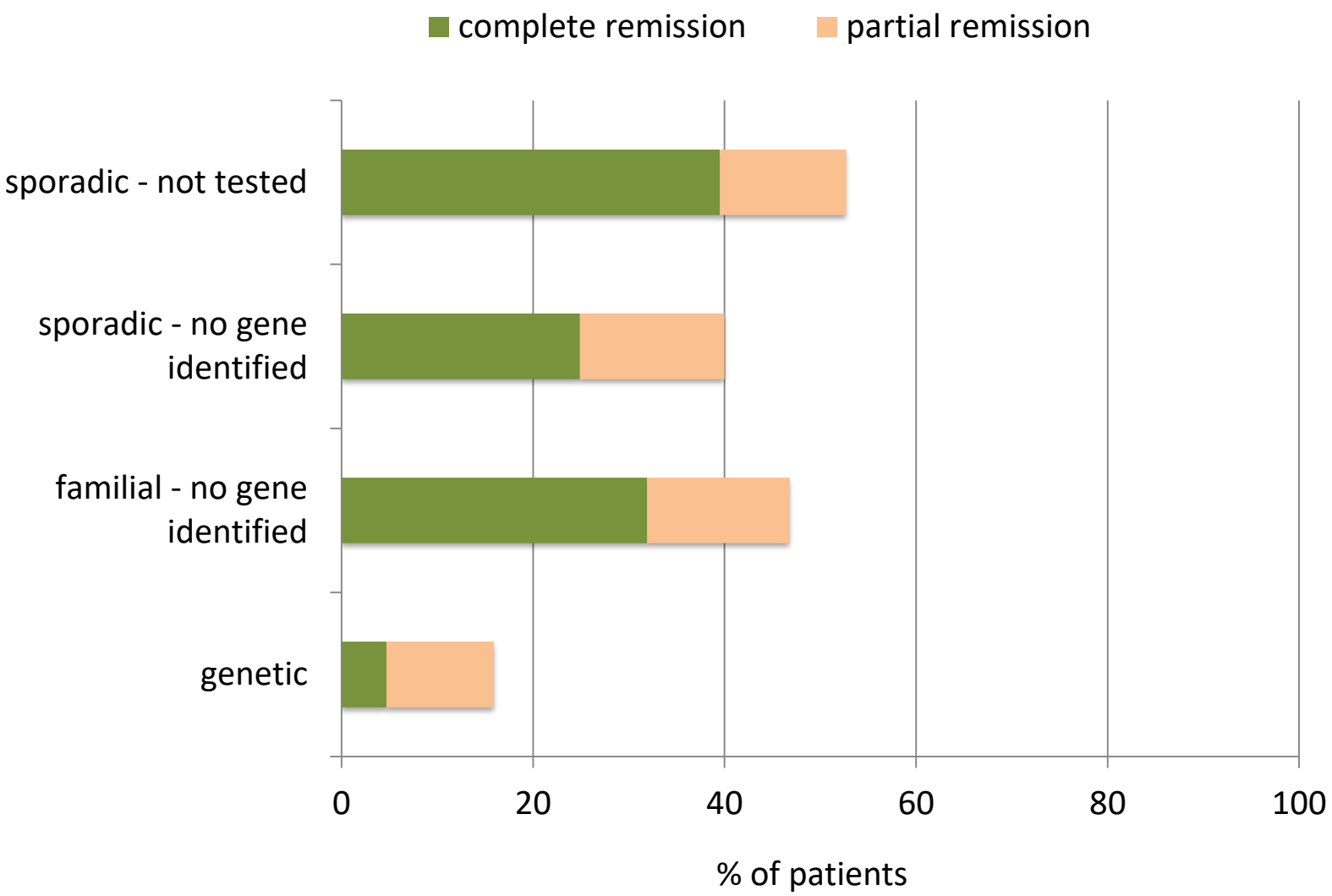


Distribution of SRNS Subtypes

n=899



Response to Intensified Immunosuppression by Genetic Status



Proposed IPNA Clinical Practice Recommendation

- No proteinuria remission after 4 weeks standard prednisone treatment:

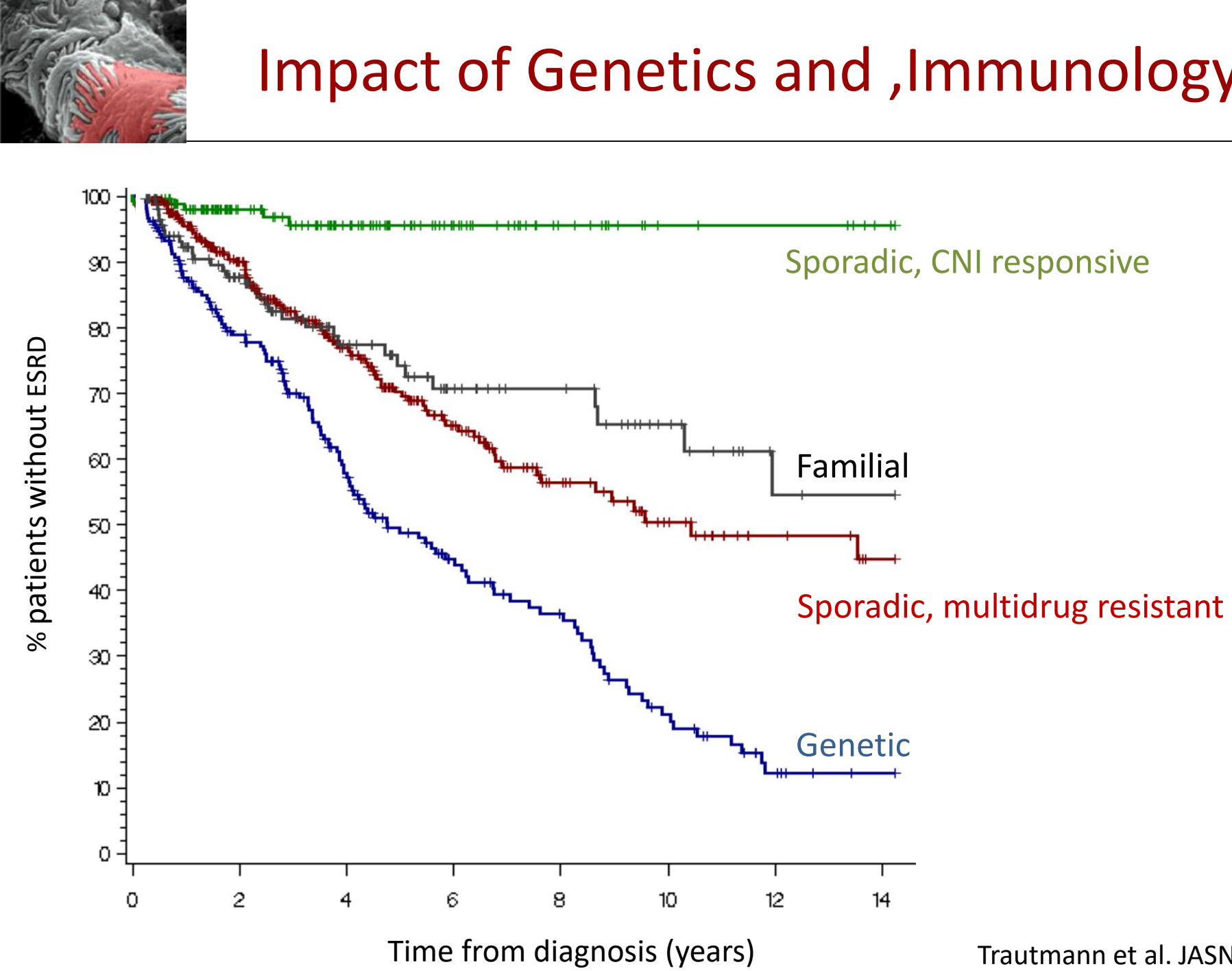
2-week „confirmation phase“:

- Establish ACE/ARB therapy at highest tolerated dose
- Consider 3 MPR iv pulses
- Initiate NGS gene panel diagnostics
- Organize kidney biopsy

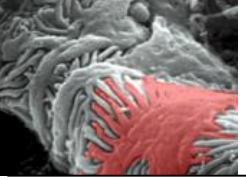
If full remission not obtained at week 6:

- **Diagnosis of SRNS**
- Administer calcineurin inhibitor for 6 months
- Wean oral steroids within 3 months

Impact of Genetics and ‚Immunology‘



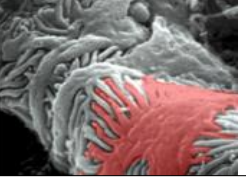
Trautmann et al. JASN 2017



Risk Factors for Renal Survival

Extended Cox analysis **adjusted for genetic disease**

	Hazard Ratio	p
Age at disease onset		
< 5 years	2.448	<0.0001
≥ 5 years	0.754	0.43
CKD stage at disease onset (ref: CKD 1)		
CKD 2	1.035	0.85
CKD 3	2.029	0.0005
CKD 4	7.068	<0.0001
Histological diagnosis (ref: MCN)		
DMS	6.493	<0.0001
FSGS	1.993	0.0009
MesPGN	0.990	0.97
Response to intensified IS (ref: no remission)		
Complete remission	0.098	<0.0001
Partial remission	0.554	0.12



Disease Recurrence in **PodoNet** Registry Cohort

1766 patients
with primary SRNS

260 transplant recipients

233 with recurrence information

Recurrence	Yes n=37	No n=196
idiopathic	29	76
genetic	4	103
unknown	4	17

Idiopathic
n=105
(49.5%)

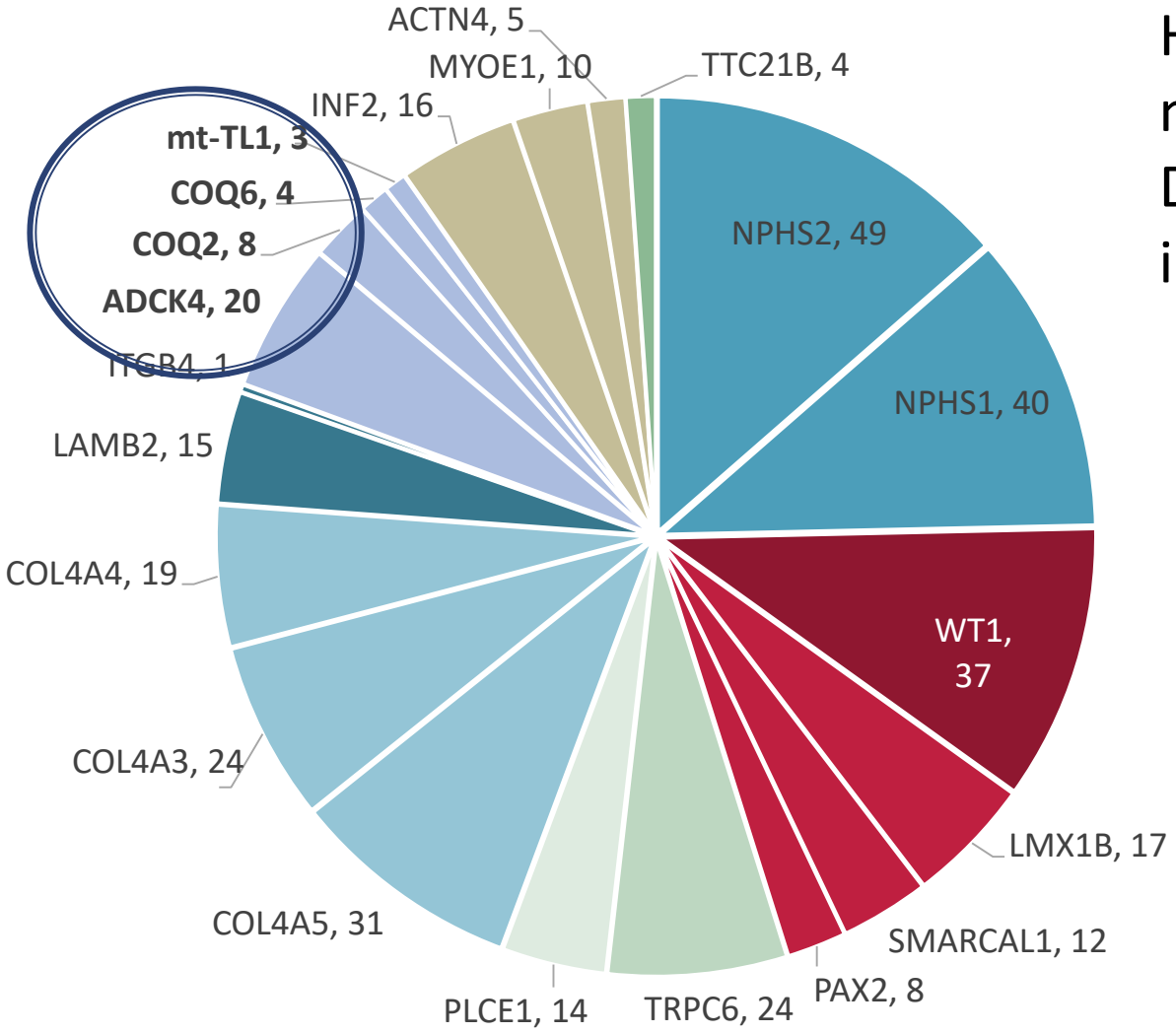
Recurrence rate
27.6%

Recurrence rate
15.8 %

Genetic
n=107
(50.5%)

Recurrence rate
3.7 %

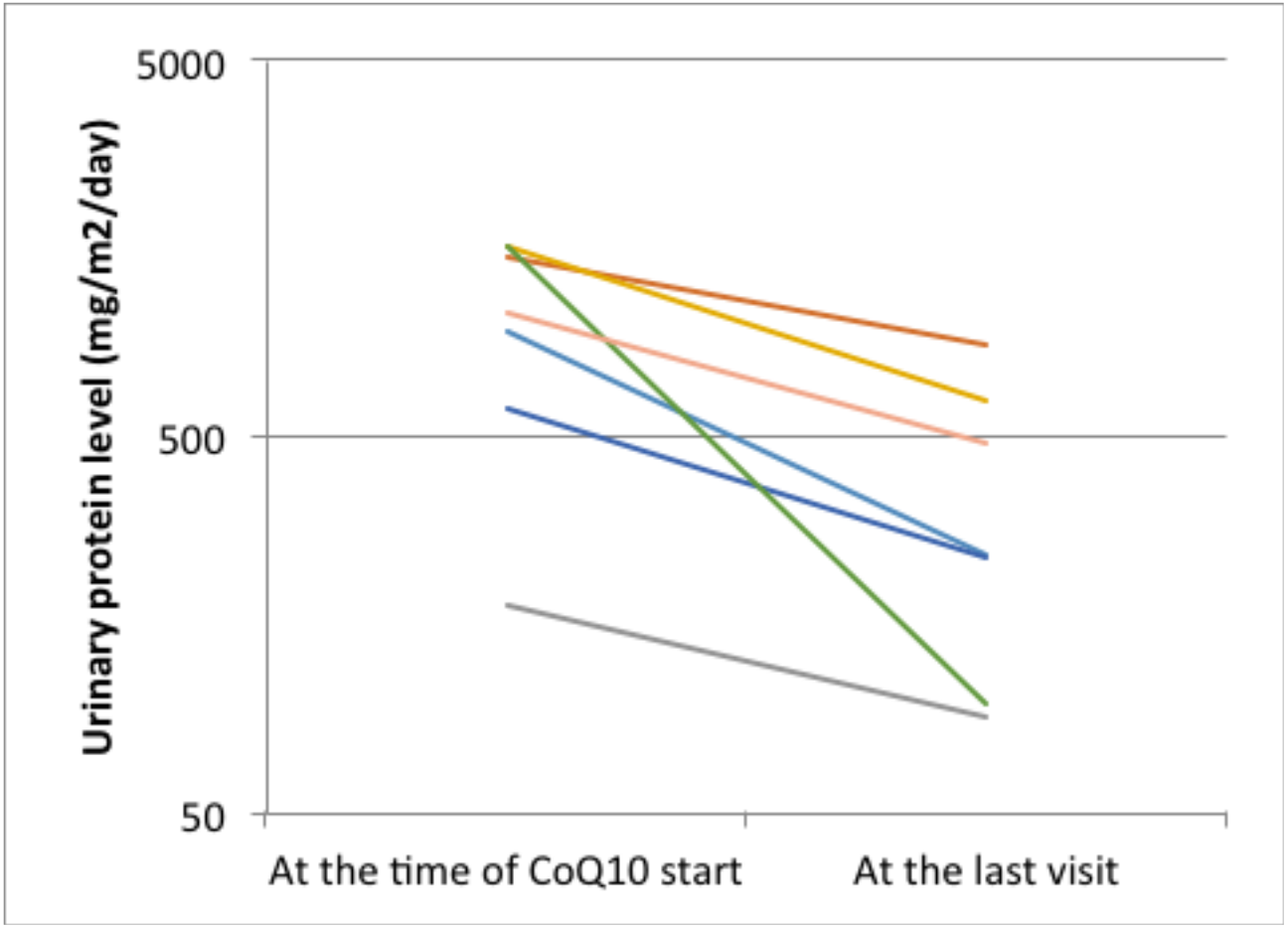
Genetic Causes of SRNS: NGS Panel Results



Hereditary mitochondriopathies:
Disease cause
in 2% of all,
10% of confirmed hereditary SRNS cases

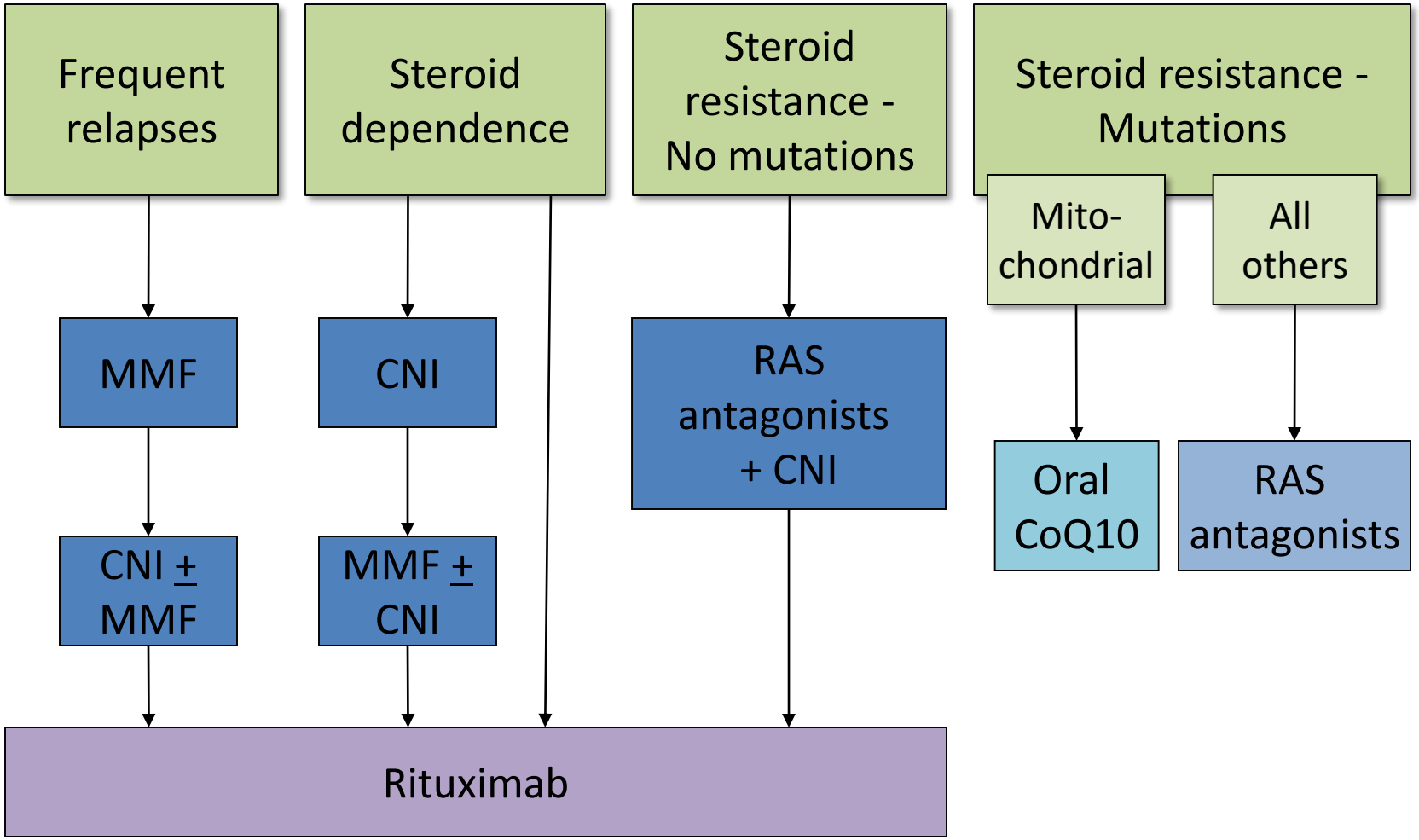
Oral CoQ10 Supplementation in ADCK4 Glomerulopathy

8 children, mean treatment duration 8 (2-12) months



Atmaca et al. PN 2017

Rational Therapeutic Options in Complicated Nephrotic Syndrome



Experimental Options in Multidrug Resistant NS Nephrotic Syndrome

Ofatumumab (CD20 antibody) - efficacious in Rituximab resistant patients ?

Abatacept (B7-1 antibody)

- early positive experience in adults, not confirmed in later studies

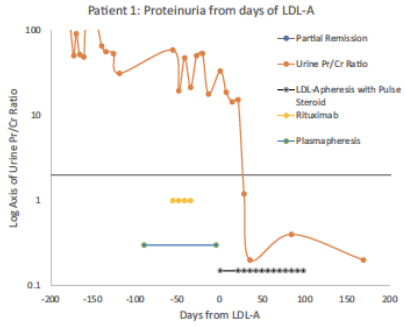
Oral galactose - anecdotal responsiveness – RCT ongoing

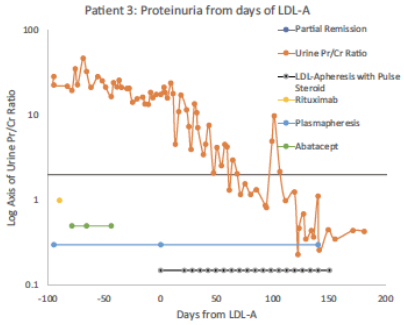
Plasmapheresis / plasma exchange / immunoadsorption

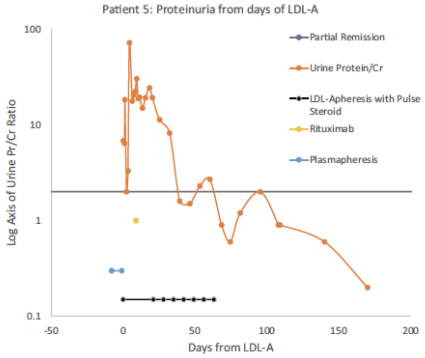
Established in post-transplant disease recurrence,
little evidence in multidrug resistant NS

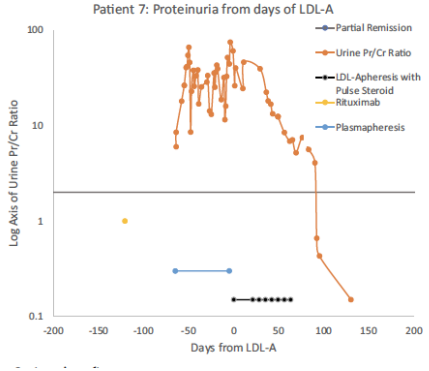
LDL apheresis ?

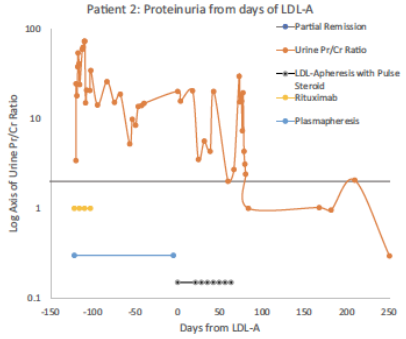
LDL apheresis combined with steroid pulse therapy in children with post-transplant NS recurrence

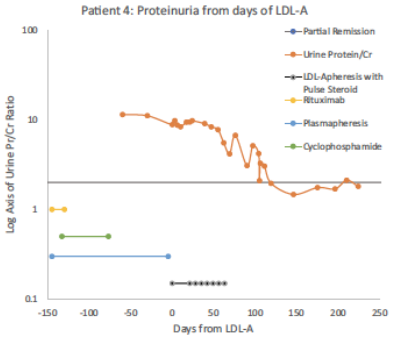


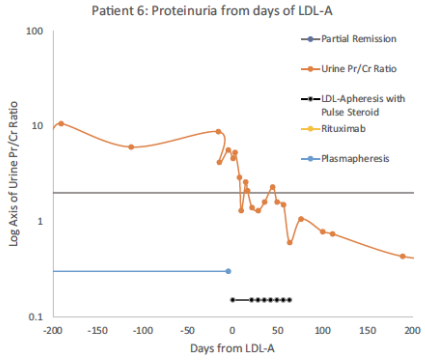












Thank you !

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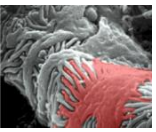

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