IDIOPATHIC STEROID RESISTANT NEPHROTIC SYNDROME IN CHILDREN

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CASE DEFINITION OF NS IN CHILDREN

- **Heavy proteinuria:**
  - 3+/4+ on urinary dipsticks analysis
  - urine albumin excretion (>40mg/m^2 per hour or 50mg/kg per day)
  - random spot urine protein: creatinine ratio >2 [mg/mg]
- **Hypoalbuminaemia** serum albumin <2.5mg/dL)
- **Hyperlipidaemia** (serum cholesterol >200mg/dl or 6.5mmol/L)
- **Supportive criteria**

↑α2 globulin

± Oedema

*Gipson DS, Massengill SF, Yao L, et al. Pediatrics 2009; **124**(2): 747-57.*
*Hogg RJ, Furth S, Lemley KV, et al. Pediatrics 2003; **111**(6 Pt 1): 1416-21.*

Introduction

- 80% of children are steroid sensitive (SS).
- 50-60% of SS group have frequent relapses or develop steroid dependency.
- Common histological types: MCD, Mes Prolif, FSGS.

EPIDEMIOLOGY

- Incidence varies with race, age and geography.
- Annual incidence ±2 - 2.7 per 100 000 in USA.
- Cumulative prevalence of 16 per 100 000.
- Six folder greater in Asian than European children.
- Peak age of onset of idiopathic NS 1 - 6 years.

cont...

NS IN AFRICA

1970s → Racial differences

Whites
Indians → Pattern of disease similar to industrialised countries

Blacks → Distinct differences

DISTINCTIVE FEATURES OF NS IN BLACK SA CHILDREN

- Paucity of MCD.
- Majority are steroid resistant.
- Often find an identifiable cause (e.g. HIV, HBV, Syphilis, Strep.)
- Malaria and schistosomal nephropathy rare.
- Congenital syphilis and CMV important in newborns.
- HIV nephropathy seen from 2001 but now on the decline.

CASE DEFINITION OF SRNS

ISKDC (International Study of Kidney Disease in Children)

- Failure to achieve remission following 8 weeks of the standard oral prednisone regime (ISKDC - 60mg/m^2 daily for 4 weeks followed by 40mg/m^2 on alternate days for 4 weeks).

ISKDC (1981) Kidney Int 20(6):765-771

OTHER REPORTED DEFINITIONS

- Above followed by three to five doses of intravenous methylprednisolone.

Murnagham K et al. Acta Pediatr Scand 73(6): 733-739

PREDICTORS OF STEROID RESISTANCE

Clinical

- Hypertension (50 – 60% likehood)
- Haematuria (30%)
- Hypertension + Haematuria (20%)
- Age of presentation (<1yr or > 8yrs)
- Black race

Laboratory

- Elevated plasma creatinine
- Massive proteinuria (> 10g/day)
- Selectivity index >0.2
- Tubular proteinuria (increased excretion of $\beta_2$microglobulin, retinol-binding protein, lysozyme).

Histology

- Tubulointerstitial disease on renal biopsy or collapsing FSGS and percentage sclerosed glomeruli >50% carry a worse prognosis.

J Lab Clinic Med (1997) 129(1):47 - 52

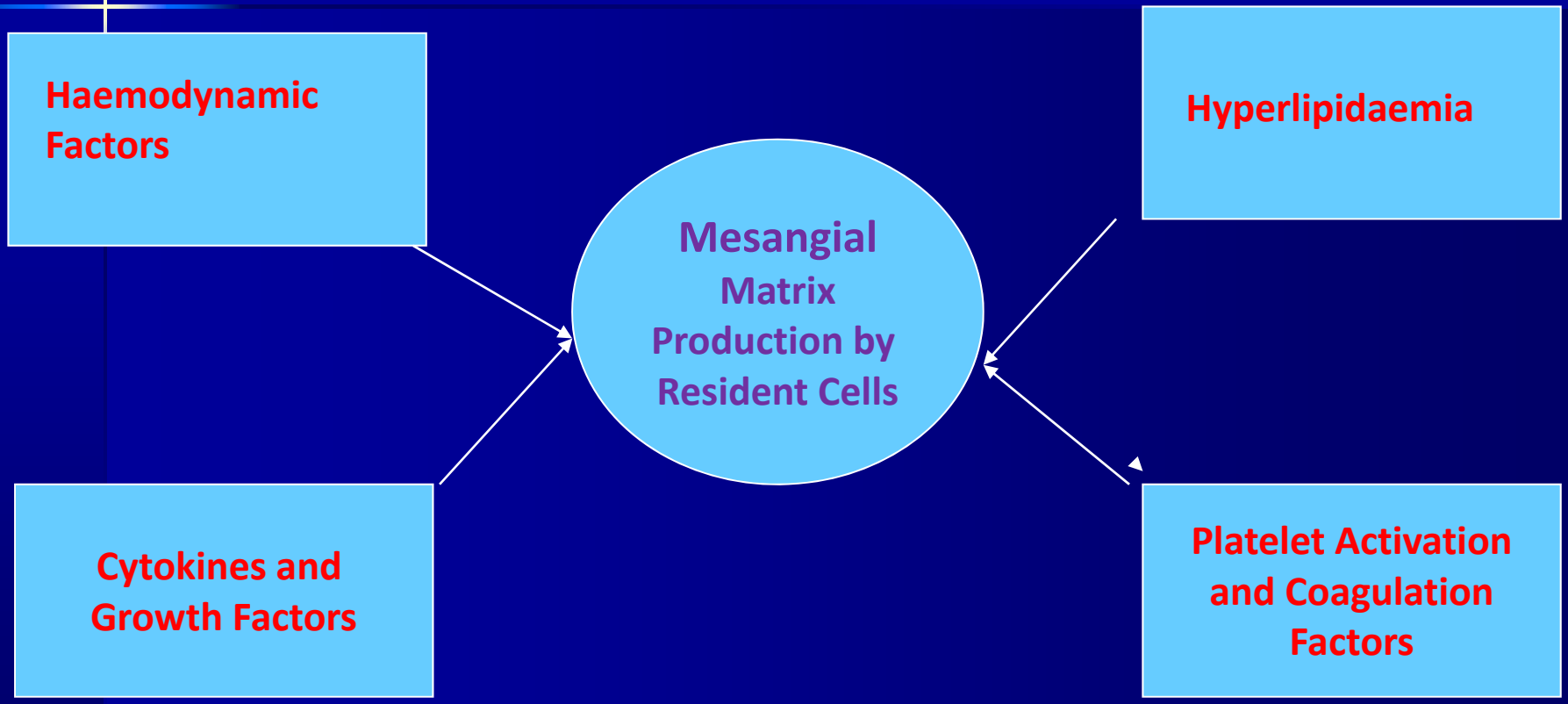
CHARACTERISTICS OF SRNS

- Clinically and genetically a heterogenous disease.
- Many cases are also resistant to additional immunosuppressive agents.
- Carries the highest risk for extra-renal complications.
- Progression to ESRD in 50% of children if untreated.
- ± 25-40% of FSGS with SRNS develop recurrence of primary disease if transplanted.
- Approximately 75% of patients exhibit renal histological features of FSGS however 20% demonstrate minimal change disease.
- Family cases of SRNS described suggest the presence of monogenic variants.

Pediatr Nephrol 2004; 28: 557-573

J Am Soc Nephrol 2004; 15: 722-732

PATHOGENESIS OF GLOMERULOSCLEROSIS IN SRNS



Kidney Int 1995; 47: 559-561

PATHOGENESIS OF FSGS ……*cont .*

- **Circulatory permeability factor implicated in the pathogenesis of primary FSGS.**
- **Soluble urokinase-type plasminogen activator receptor (su*PAR*) is implicated as a biomarker and possible contributing factor in the development of FSGS.**

Jefferson JA, et. al Kidney Int, 2013,84(2);235

Evidence for ‘circulating‘ component of permeability factor in FSGS.

- FSGS can occur very rapidly after kidney Tx (30 % of cases in adults, >50 % in children).
- Recurrence of FSGS can be prevented or delayed in high-risk patients with pre-Tx plasmapheresis.
- Injection of plasma or plasma fractions from patients with FSGS in rats causes proteinuria.
- Sera from patients with FSGS increases albumin permeability in an isolated glomerulus model *ex vivo*.
- A transient FSGS has been transmitted to a newborn from a mother with FSGS.

McCathy EJ, et. al, Clin J am soc. Nephrol 2010;5:2115

WHAT ARE THE GENETIC MECHANISMS LEADING TO STEROID RESISTANCE?

- Precise mechanism remains elusive.
- Specific genetic mutations:

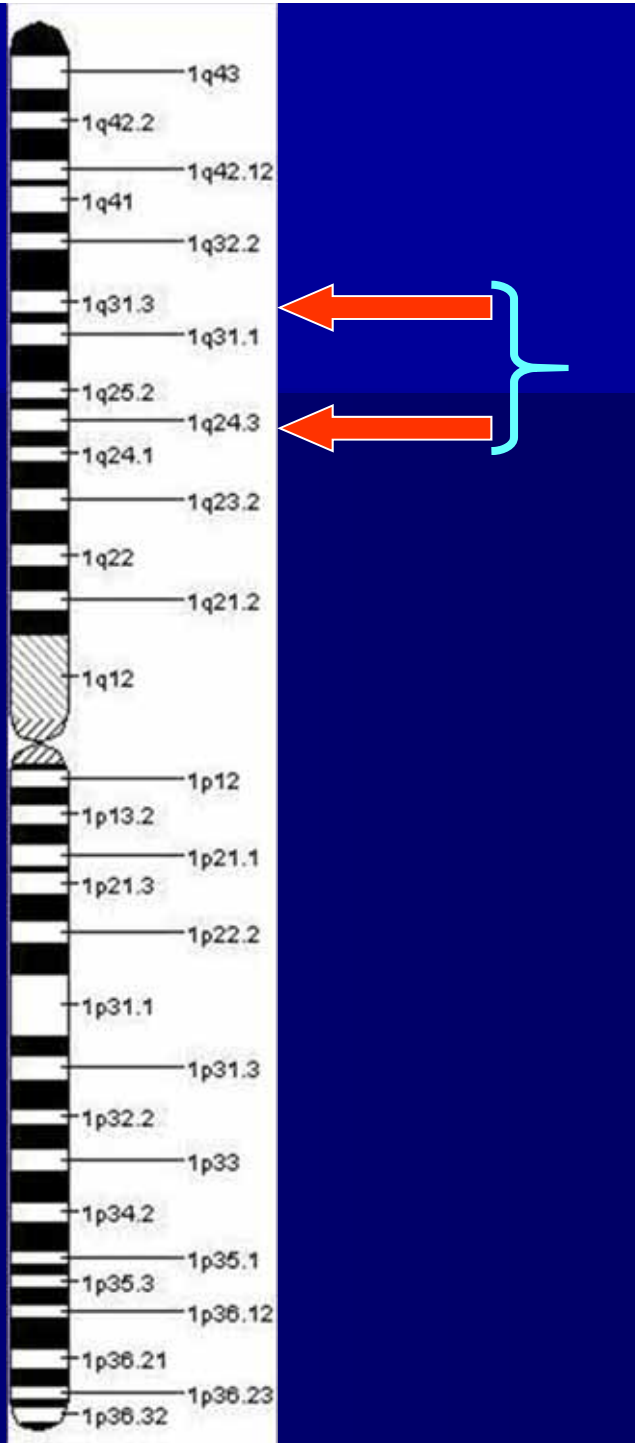
NPHS1	-	Nephrin
NPHS2	-	Podocin
ACTN4	-	Alpha-Actinin-4
CD2AP	-	CD2 associated protein
WT1	-	Transcription factor (Denys-Drash and Frasier syndrome)
TRPC6	-	Canonical Transient Receptor Potential Cation 6
INF2	-	Formin Family of actin regulating proteins
MYH9/APOL1	-	Chromosome 22 – variants associated with FSGS and HIV nephropathy in African-Americans

- All proteins are integral components of the GBM.

Pediatr Nephrol 1999; 19: 1313-1318

Nat Genet 2008; 40: 1185

- The NPHS2 gene has been mapped on chromosome 1 at position 1q25-q31.
- Encodes for a 383 amino acid protein called podocin, which is expressed in podocytes.
- Podocin is an integral membrane protein located at the slit diaphragm of the glomerular permeability barrier.
- This gene is mutated in patient with SRNS and more specifically in patients presenting with FSGS.



NPHS2 MUTATIONS IN SRNS

- Reported in the following group of idiopathic SRNS:
  - Autosomal recessive inheritance in FSGS
  - Congenital or infantile NS
  - Adolescents and adults with familial FSGS
  - Sporadic SRNS
- Encodes a 383-amino acid protein called podocin.
- This is a lipid raft-associated protein exclusively expressed in the podocytes at the foot processes.
- Ruf et al reported that none of the children mutations in sporadic SRNS with *NPSH2* mutations responded to cyclosporine or cyclophosphamide treatment.
- Higher rate of recurrence of proteinuria in patients with SR FSGS and a single heterozygous *NPHS2* mutations.
- Therefore testing for this mutation is important in living donor transplantation when the donor is carrying a heterozygous *NPHS2* mutation. The kidney may be at increased risk for late onset FSGS and the donor with one kidney may be at risk of developing FSGS.

Ruf et al. J Am Soc Nephrol 2004; 15: 722-732

Genetic mutations of NPHS2 gene in SRNS

- **Israeli-Arab** – **55% showed NPHS2 mutations**
- **Chinese study** – **4% and 15.9%**
- **Turkish** – **13.3% and 27.4%**
- **Japanese** – **1 of 13 with congenital NS displayed NPHS2 mutation**

- **Korean**
- **Japanese**
- **Israeli-Jewish**
- **African American**

– **no NPHS2 mutations found**

– **no disease causing mutations in NPHS2 and WT1 genes**

Berdeli A et al. Pediatr Nephrol 2007; 22(12): 2031-40.
Chernin G et al. Pediatric Nephrol 2008; 23(9): 1455-60.

Limitations of Genetic Testing Using NPHS2

- 80% children SSNS.
- Only 20% have SRNS due to NPHS2 mutations.
- Gene locus will identify only 5% of cases
- There are other yet to be identified genes responsible for higher proportion of cases of SRNS.

COMPLICATIONS

- Renal impairment
- Anasarca
- Infections (includes primary peritonitis)
- Malnutrition and growth retardation
- Hypertension
- Thrombotic complications (e.g. renal vein thrombosis)
- Hypovolaemic shock
- Accelerated arteriosclerosis
- Secondary immunodeficiency
- Side effects of drug therapy

TREATMENT OF SRNS

SYMPTOMATIC TREATMENT

- **Diet**
  - salt restriction (no added salt)
  - reduction of saturated fat intake (<30% of total calorie intake)
  - complex carbohydrates
  - protein intake 130 – 140% (2 – 2.5g/kg) of the normal daily allowance according to statural age.
- **Hypovolaemia** - albumin or plasma infusions
- **Control of oedema** - diuretics with albumin infusions.
- **Prevention of thromboemboli**
  - warfarin
  - aspirin
  - heparin
- **Hypertension** - anti hypertensive drugs
- **Infections and immunisation** - antimicrobials and vaccines

IMMUNOSUPRESSIVE THERAPY

Second line agents

- Alkylating agents
  - Cyclophosphamide
  - Chlorambucil
- Levamisole

Intensive therapy

- Cyclosporine
- Pulses dose Methylprednisolone
- Pulse dose cyclophosphamide

New agents

- Tacrolimus (Prograf®)
- MMF (Cellcept®)
- Monoclonal antibodies (e.g. rituximab, ocrelizumab, ofatumumab)

Cyclosporine

- Remission rates range from 20-38% (CR 31% and PR 38% during 6 mths Rx) .
- Relapses follow tapering of treatment or when treatment discontinued (±70%).
- Prolonged use associated with chronic nephrotoxicity (tubulointerstitial lesions with striped interstitial fibrosis and groups of atropic tubules)
- Other adverse effects:
  - hyperkalaemia, HPT, hypertrichosis, gum hypertrophy, hypermagnesaemia, bone marrow suppression, nausea and vomiting.

Garin EH et al. Am J Dis Child (1988);142:985

Ponticelli et al. Kidney Int (1993);43:1377

EFFECT OF COMBINATION WITH STEROIDS ON REMISSION RATE IN PATIENTS WITH STEROID-RESISTANT NEPHROTIC SYNDROME

	Complete remission	Partial remission	Failure
CsA monotherapy (n=123)	14%	12%	74%
CsA + Steroids (n=103	24%	24%	52%

Lieberman KV et al. (1996): J Am Soc Nephrol;7:56

Impact of the National Institute of Health Focal Segmental Glomerulosclerosis (NIH FSGS) clinical trial on the treatment of steroid-resistant FSGS

Nephrol Dial Transplant (2013) 28: 527-534

Aim

To compare cyclosporine (CSA) with combined mycophenolate mofetil (MMF) and oral pulsed dexamethasone (DEX).

Study Design

- Multicentre, open-labelled, randomised study in the USA.
- All enrolled patients were treated with low-dose prednisone (0.3mg/kg on alternate days) x 6 months.
- All were treated with lisinopril (or, if intolerant losartan) at the maximally tolerated dose.
- CSA dosage was adjusted to target a 12-h trough level of 100 – 250mg/mL.
- MMF was dosed at 25-36mg/kg/day up to 2g/day, in 2 divided doses.
- DEX pulses were given weekly for the first 8 weeks, then biweekly until week 26, then every 4 weeks through week 50.
- N = 138 of an original 500.

Inclusion criteria

- Patients with biopsy-proven FSGS.
- Age 2–40 years.
- eGFR >40mL/min/1.73m^2.
- Urinary protein – to – creatinine ratio (Up/c) >1g/g, sustained over two visits.
- Steroid resistance (Up/c > 1g/g despite a minimum of 4 weeks of high dose steroids).

Exclusion criteria

- Steroid sensitive or dependant patients.
- Obese patients to limit the presence of obesity-associated FSGS.
- Secondary causes of FSGS.

Summary of results

- While no differences were statistically significant, point estimates for each level of the primary outcome favoured CSA.
- Proteinuria decreased in both groups, but to a greater extent in the CSA group.
- CSA group experienced a greater decline in eGFR at week 26.
- Adverse event rates were similar in the two groups.

Discussion

- Largest randomised trial ever carried out for SR–FSGS.
- Among the largest trial for any glomerular disease outside of diabetic nephropathy or lupus nephritis.
- Strong representation from racial and ethnic minorities.
- Large paediatric FSGS population with two-thirds of patients <18 years of age.
- The strength of the study was the centralised biopsy review.

- Response to treatment was moderate.
  - ~40% in both groups achieved complete or partial remission after 1 year.
  - only 60% of these (24% of the total) were still in remission 6 months later.
- This highlights the morbidity and treatment resistance of FSGS.
- Study was largely underpowered, raising the possibility of a substantial type II (beta) error.
- Special consideration should be given to MMF–DEX in patients with baseline-impaired GFR or in those who become dependent on immunosuppression to maintain remission.

TACROLIMUS

- Macrolide antibiotic isolated from fungus *Streptomycin tsukubgensis.*
- Selective inhibitory action on CD4 T-helper lymphocytes.
- More potent agent in cytokine suppression compared to cyclosporine.
- Also has a variety of effects on cellular functions, and intracellular signaling events not seen with cyclosporine.
- Precise mechanism of action in decreasing proteinuria needs to be defined – possibly due to increased expression of synaptopodin, which in turn stabilises the contractile apparatus of podocyte foot processes.

MYCOPHENOLATE MOFETIL

- Highly selective, non competitive inhibitor of inosine monophosphate dehyrdrogenase, the rate limiting enzyme in de novo biosynthesis of guanosine nucleotides.
- Prodrug of MPA.
- Strongly inhibits both T- and B-lymphocyte proliferation.
- Used treatment of allograft rejection, SLE, vasculitis, IgA nephropathy, MN.

USE OF MMF IN PAEDIATRIC NS

- Best responses obtained in children with SDNS.
- Success rate in treating SRNS less gratifying.
- Paediatric dosage not yet established.
- Suggested dose 15 – 25 mg/kg p.o bid.

Ped Nephrol (2007); 22: 2059-2065

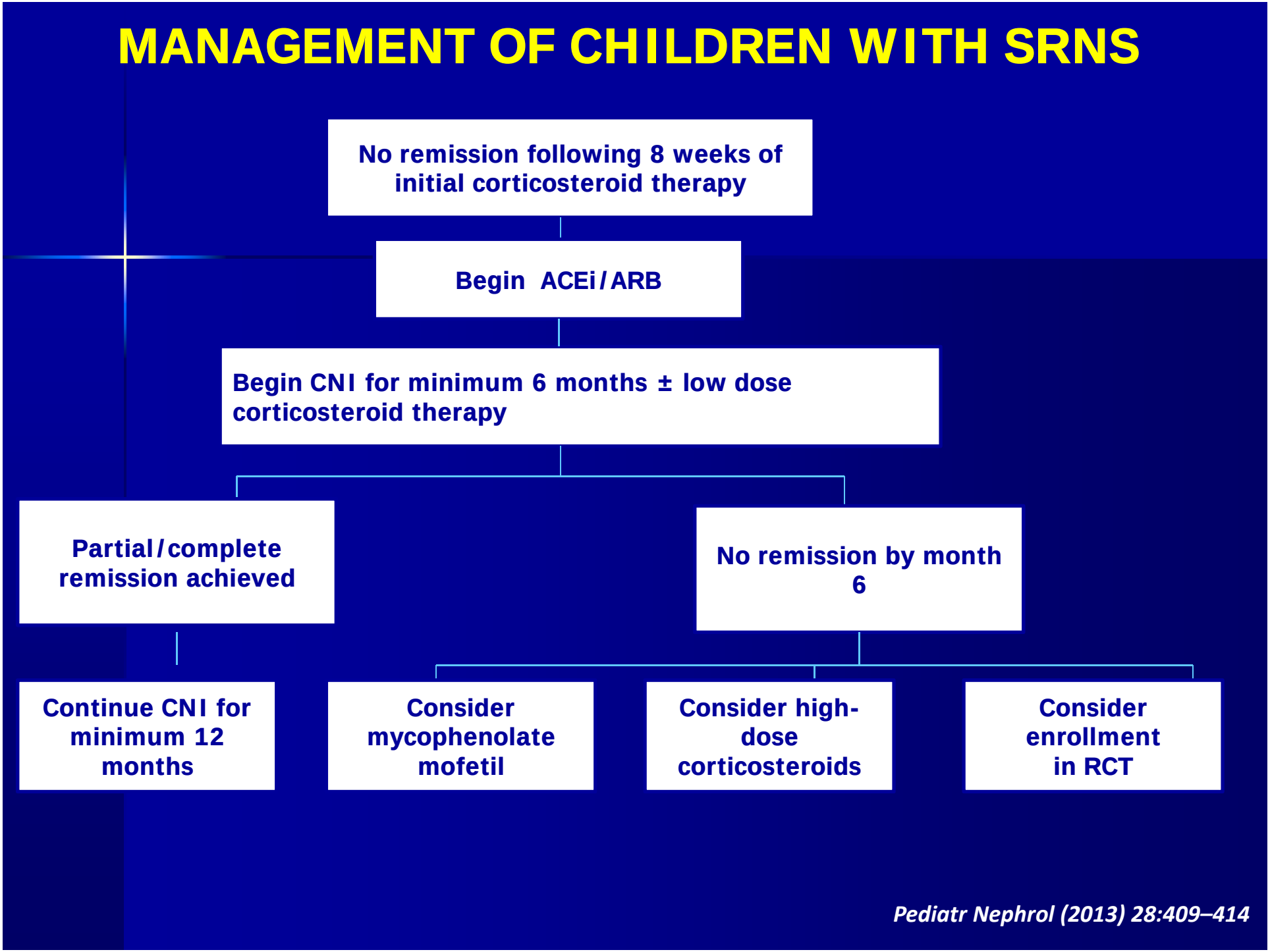
Randomized controlled trials in steroid-resistant nephrotic syndrome

Author	No.	Intervention	Control	Duration (months)	Remission complete or partial	RR for remission	Conclusion
Lieberman and Tejani 1996	24	Cyclosporine	Placebo	6	12 (100 %) vs. 2 (17 %)	5.00 (1.63–15.31)	Remission cyclosporine > placebo
Ponticelli et al. 1993	17[a]	Cyclosporine	Supportive therapy	12 [b]	6 (60 %) vs. 0 (0 %)	9.45 (0.62–144.74)	Remission cyclosporine > control
Garin et al. 1988	8	Cyclosporine	None		2 0 (0 %) vs. 0 (0 %)	0 (0.0–0.0)	No sig. Difference
Choudhry et al. 2009	41	Tacrolimus + prednisone	Cyclosporine + prednisone[c]	2	12 18 (86 %) vs. 15(75 %)	1.14 (0.84–1.55)	No significant difference
Gipson et al. 2011	138	Cyclosporine	MMF[d] + dexamethasone	12	33 (45.8 %) vs. 22(33 %)	1.35 (0.90–2.10)	No significant Difference
ISKDC 1974	31	CPA + prednisone	Prednisone	12	3 10 (56 %) vs 16(46 %)	1.20 (0.59–) 2.47	No significant difference
Tarshish et al. 1996	53	CPA + prednisone	Prednisone	CPA 3	16 (50%) vs Prednisone 12	0.88 (0.53–1.45)	No significant difference

RR risk ratio for remission; a Children; b 6 months full dose followed by taper 25 % every 2 months; c prednisone given on alternate days;
d mycophenolate mofetil; e cyclophosphamide

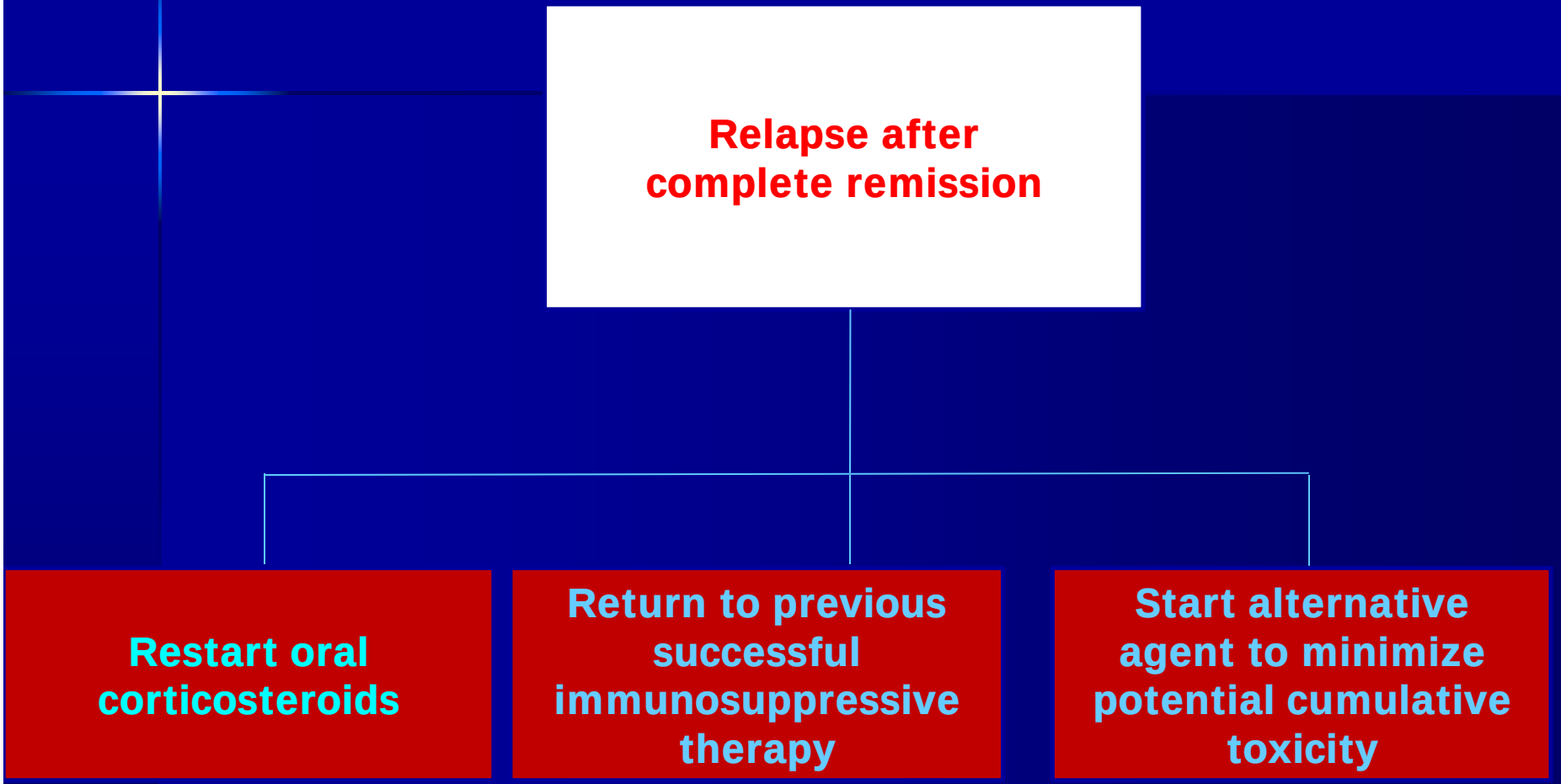
KDIGO Clinical Practice Guidelines for GN Kidney Int 2012; (2): 139

MANAGEMENT OF CHILDREN WITH SRNS



Pediatr Nephrol (2013) 28:409–414

MANAGEMENT OF CHILDREN WITH SRNS WHO RELAPSE



Pediatr Nephrol (2013) 28:409–414

RECOMMENDATIONS OF THE KDIGO GLOMERULONEPHRITIS WORKGROUP, 2012

- Recommend using a CNI as initial therapy for children with SRNS.
- CNI therapy be continued for a minimum of 6 months and then stopped if a partial or complete remission of proteinuria not achieved.
- If achieved – continue for 12 months.
- Low-dose corticosteroid therapy be combined with CNI therapy.
- For failed CNI therapy consider MMF, high dose corticosteroids or a combination of these agents.
- Cyclophosphamide should not be used unless no other Rx works.
- ACEi or ARBs should be used in all children with SRNS.

NB. Guideline does not include routine evaluation for genetic mutations.

Optimal drug levels for SRNS are not yet established.

Based on case series, complete or partial remissions less common in the presence of NS associated with podocin mutations.

MANAGEMENT OF SRNS IN DEVELOPING COUNTRIES

- Major consideration cost.
- Compliance.
- Many still use pulse methlyprednisolone in combination with oral cyclophosphamide and low dose oral steroids.
- IV cyclophosphamide with MP and oral steroids used in some centres.

Mendoza, S.A., et al.,. Pediatr Nephrol, 1990. 4(4): p. 303-7)
Adhikari, M et al. Pediatr Nephrol, 1997. 11(4): p. 423-8.

RITUXIMAB

- Rituximab is a chimeric anti-CD20 (anti B-cell) monoclonal antibody.
- This antibody efficiently eliminates B cells, as the CD20 antigen is expressed early in B-cell ontogeny but is absent in mature plasma cells.
- Has been reported to be beneficial in patients with SRNS in a limited number of small case series.

Nakayama M et al Pediatr Nephrol 2008; 23: 481
Bagga A et al N Engl J Med 2007; 356: 2751

OTHER AGENTS

- Vincristine
- Azathioprine
- Sirolimus
- Mizoribine
- Immunoglobulin infusions

ADJUCTIVE THERAPY

- ACEI and ARBs
- Lipid lowering agents (statins)
- Vitamin and mineral supplementation
- Anti-thrombotic agents
- CKD (stage III – IV) - ESRD therapy including RRT


Thank You