THẬN NHI
HỘI NGHỊ THẬN HỌC THẾ GIỚI ÚC 4/2019

PGS TS VŨ HUY TRỤ

- HC THẬN HƯ
- IgA VASCULITIS (HENOCH SCHONLEIN)

1. HC THẬN HƯ :

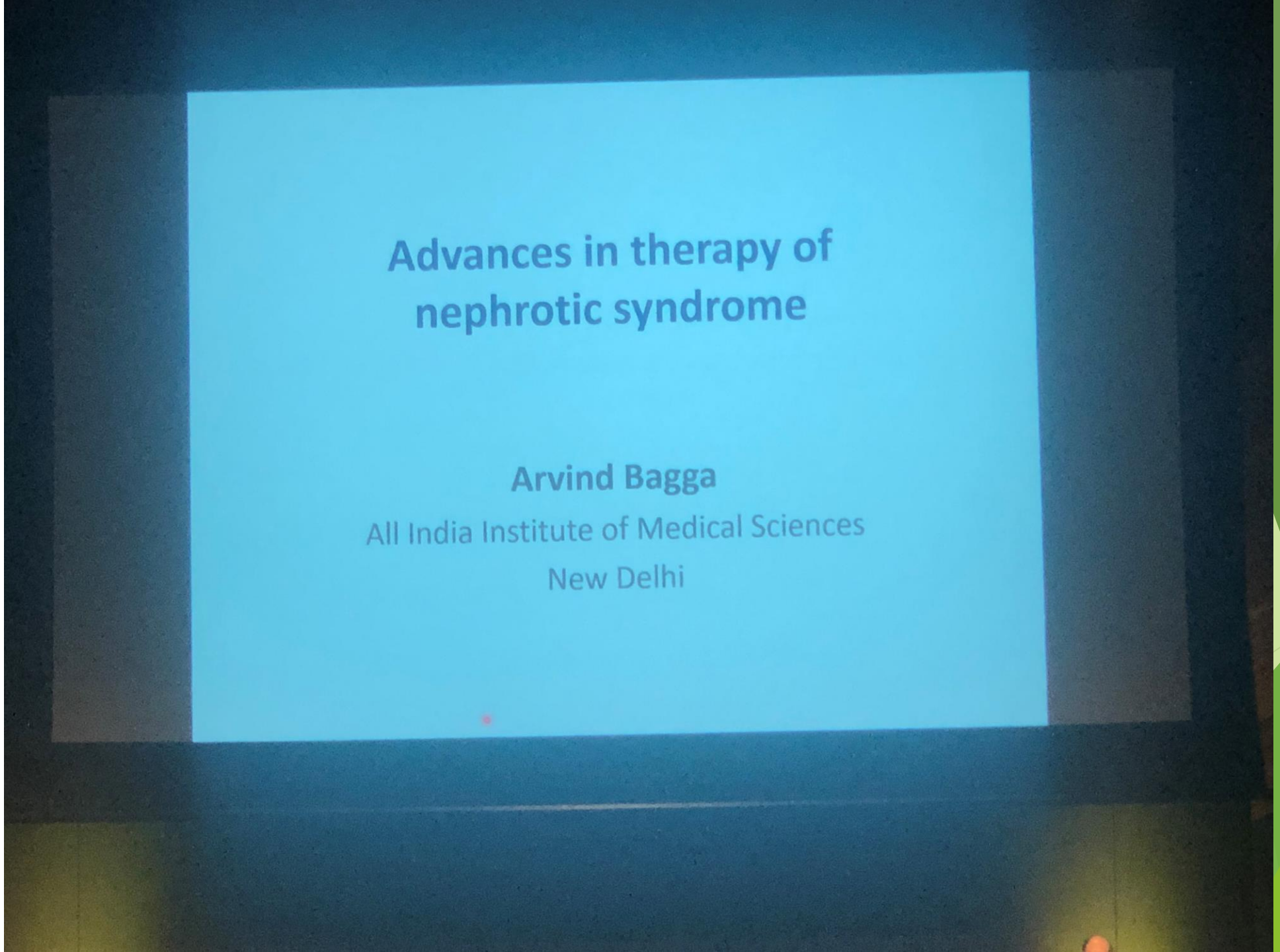
1.1. TIÊU CHẨN CHẨN ĐOÁN :

Hội chứng thận hư (HCTH) là một hội chứng lâm sàng bao gồm:

- Tiểu đạm > 50mg/kg/ngày hay > 1g/m^2/ngày (hay > 40mg/m^2/giờ) hay protein/creatinine > 2 mg/mg
- Albumine máu < 25g/l, đạm máu < 55g/l
- Tăng lipid máu (cholesterol> 2,2g/l).
- Phù

2. NHẮC LẠI CƠ CHẾ BỊNH SINH :

3. ĐIỀU TRỊ :


Advances in therapy of nephrotic syndrome
Arvind Bagga
All India Institute of Medical Sciences
New Delhi

3.1 . ĐIỀU TRỊ LẦN ĐẦU :

Regimens for steroid treatment of first episode of SSNS

- ISKDC regimen 1966
  - Prednisolone at 60mg/m^2/day (max 80mg) for 4 weeks
  - Prednisolone at 40mg/m^2/day (max 60mg) for 3 of 7 days for 4 weeks
- APN regimen 1979
  - Prednisolone at 60mg/m^2/day (max 80mg) for 4 weeks
  - Prednisolone at 40mg/m^2/day (max 60mg) given on alternate mornings for 4 weeks
- APN regimen 1993
  - Prednisolone at 60mg/m^2/day (max 80mg) for 6 weeks
  - Prednisolone at 40mg/m^2/day (max 60mg)

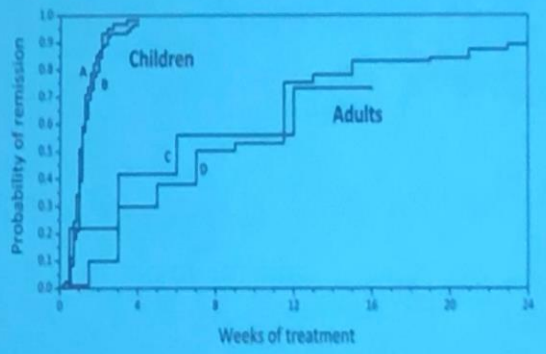
  on alternate mornings for 6 weeks

Steroid sensitive nephrotic syndrome

	US, 2009	India, 2019	France, 2008*	KDIGO, 2012	Italy, 2017
Initial episode	Daily 6 w; Alt day 6 w	Daily 6 w; alt day 6 w	Daily 4 w; alt day 8 w; taper; duration 18 w	Daily 4-6 w; Alt day 4-6 w; taper	Daily 6 w; Alt day 6 w
Relapse	Daily till remission; alt day 4 w	Daily till remission; alt day 4 w	Daily till remission; alt day 4 w; taper 12 w	Daily till remission; alt day 4 w	Daily till remission; alt. day 4 w
Long-term prednisone	2-3 m	9-18 m alt; daily in infection	12-18 m	≥ 3 m alt d; daily in infection	NA
FR; dependence	FR CPA 12 w MMF 1-2 y CyA/Tac 2-5 y Dependence CyA/Tac MMF CPA	Lev 1-2 y CPA 12 w MMF 1-2 y CyA/Tac 1-2 y RTX	Lev CPA CyA MMF	CPA 8-12 w Chlorambucil 8 w Lev ≥ 1 y CyA, Tac ≥ 1 y MMF ≥ 1 y Rituximab	NA

CPA cyclophosphamide, CyA cyclosporine, FR frequent relapses, Lev levamisole, Tac tacrolimus, w weeks, y years

Predniso(lo)ne for the first episode



ISKDC: 60 mg/m²/d *x* 4-wk; 40 mg/m²/alternate day *x* 4-wk

Kidney International 2000; Pediatr Nephrol 2011;26:2167

Cochrane 2000; Update 2007..... *studies were inadequate*

Minimum 3 months; extending better

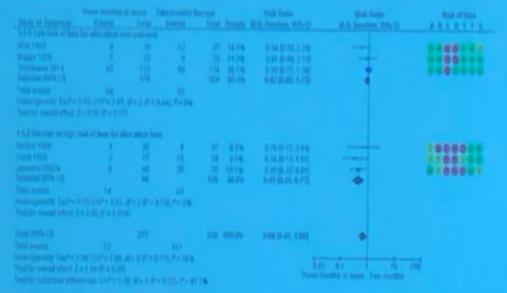
9 RCT Prednisolone for **3–6,** compared to **2** months

Reduce risk of relapse by 27-43%; frequent relapses by 33-45%

KDIGO 2012 Daily 4–6 wk; alternate-day 2–5 months


No difference in frequent relapses with extended initial therapy >2-3 months
3 months vs. 2 months
3 months or longer
2 months
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
APN 1993 6 34 12 37 7.9% 0.54 [0.23, 1.29]
Bagga 1999 7 22 8 23 8.4% 0.91 [0.40, 2.10]
Jayantha 2002a 8 48 26 70 10.7% 0.45 [0.22, 0.91]
Norero 1996 3 29 4 27 3.5% 0.70 [0.17, 2.84]
Paul 2014 20 47 14 46 14.6% 1.40 [0.81, 2.42]
Ueda 1988 3 17 15 29 5.5% 0.34 [0.12, 1.01]
Webb 2017 60 114 55 109 26.4% 1.04 [0.81, 1.35]
Yoshikawa 2014 45 122 46 124 23.1% 0.99 [0.72, 1.38]
Total (95% CI) 433 465 100.0% 0.86 [0.65, 1.13]
Total events 152 180
Heterogeneity: Tau² = 0.08; Chi² = 12.50, df = 7 (P = 0.09); I² = 44%
Test for overall effect: Z = 1.09 (P = 0.28)
0.01 0.1 1 10 100
Favours [experimental] Favours [control]
5-6 months vs. 3 months
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Hiraoka 2003 10 36 15 34 21.5% 0.63 [0.33, 1.20]
Mishra 2012 1 37 1 37 3.2% 1.00 [0.06, 15.40]
Sharma 2000 8 70 24 70 19.7% 0.33 [0.16, 0.69]
Sinha 2014 36 92 25 88 26.7% 1.39 [0.92, 2.12]
Teeninga 2013 38 64 31 62 28.8% 1.19 [0.86, 1.64]
Total (95% CI) 299 292 100.0% 0.84 [0.50, 1.40]
Total events 93 96
Heterogeneity: Tau² = 0.21; Chi² = 14.67, df = 4 (P = 0.005); I² = 73%
Test for overall effect: Z = 0.67 (P = 0.50)
0.01 0.1 1 10 100
Favours [experimental] Favours [control]

RCTs on initial therapy: Bias influences 'effect size'



2 vs. 3+ months

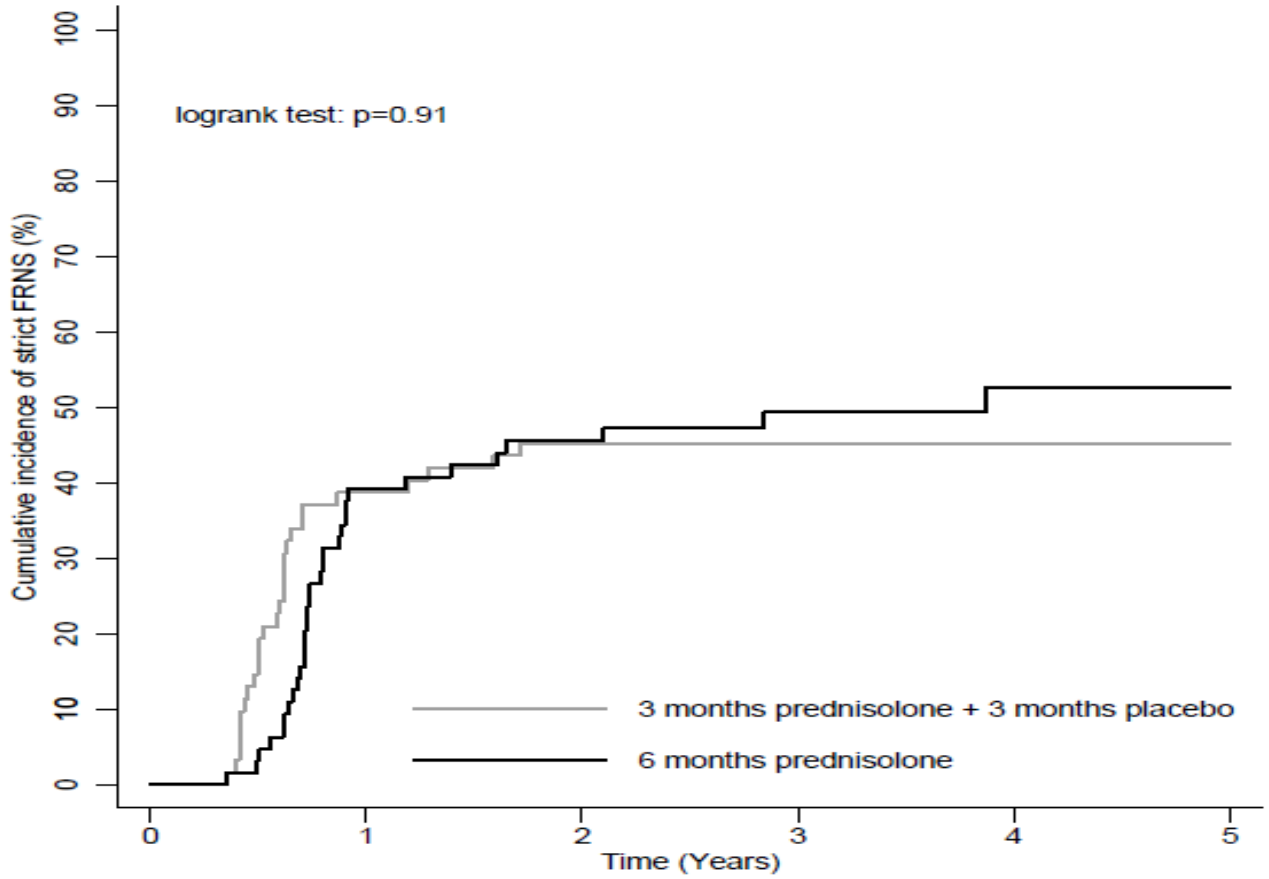
3 vs. 5-6 months

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Courtesy, J Craig

Initial episode: 4-6 wk daily; 4-6 wk alternate day

DUTCH : Increased duration of prednisolone does not reduce risk of frequently relapsing SSNS- dose not duration is the factor



Teeninga et al. JASN 2013

J Am Soc Nephrol 24: 149–159, 2013

CLINICAL RESEARCH www.jasn.org

Extending Prednisolone Treatment Does Not Reduce Relapses in Childhood Nephrotic Syndrome

Nynke Teeninga,* Joana E. Kist-van Holthe,† Nienke van Rijswijk,* Nienke I. de Mos,‡ Wim C.J. Hop,§ Jack F.M. Wetzels,‖ Albert J. van der Heijden,* and Jeroen Nauta*

150 children with NS

- 3 months of prednisolone followed by 3 months of placebo

or

- 6 months of prednisolone

median follow-up 47 months.

Both groups received equal cumulative doses of prednisolone (3360 mg/m2)

Relapses

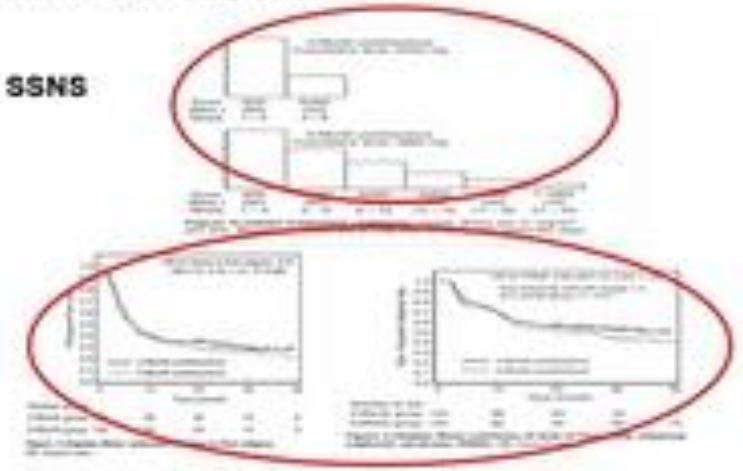
- 77% of patients on prednisolone 3 months
- 80% of patients on prednisolone 6 months
- frequent relapses (45% versus 50%).

JAPAN

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

255 children with initial episode of SSNS
2 - or 6-months of prednisolone

Time to frequent relapses
Time to first relapse
similar in both groups



Extending initial prednisolone treatment in a randomized control trial from 3 to 6 months did not significantly influence the course of illness in children with steroid-sensitive nephrotic syndrome.

Sinha A, Bagga A et al Kidney Int. 2015;87:217-24

181 children
3 months of standard therapy,
tapering prednisolone for 3 months or placebo for 3 months

No difference in
Number of relapses at 1 year,
sustained remission,
frequent relapses

Extending initial steroid treatment from 3 to 6 months does not influence the course of SSNS in children.

Steroid sensitive nephrotic syndrome

	US, 2009	India, 2019	France, 2008*	KDIGO, 2012	Italy, 2017
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Relapse	Daily till remission; alt day 4 w	Daily till remission; alt day 4 w	Daily till remission; alt day 4 w; taper 12 w	Daily till remission; alt day 4 w	Daily till remission; alt. day 4 w
Long-term prednisone	2-3 m	9-18 m alt; daily in infection	12-18 m	≥ 3 m alt d; daily in infection	NA
FR; dependence	FR CPA 12 w MMF 1-2 y CyA/Tac 2-5 y Dependence CyA/Tac MMF CPA	Lev 1-2 y CPA 12 w MMF 1-2 y CyA/Tac 1-2 y RTX	Lev CPA CyA MMF	CPA 8-12 w Chlorambucil 8 w Lev ≥ 1 y CyA, Tac ≥ 1 y MMF ≥ 1 y Rituximab	NA

CPA cyclophosphamide, CyA cyclosporine, FR frequent relapses, Lev levamisole, Tac tacrolimus, w weeks, y years

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CPA cyclophosphamide, CyA cyclosporine, FR frequent relapses, Lev levamisole, Tac tacrolimus, w weeks, y years

So what do we do about steroids now for first presentation?

- Generally agreed, give a 3 month course not a 6 month course
- No national consensus in Australia yet :
- 2 suggested protocols:
- 1. 60 mg/m2/day (max 80 mg) for 4wk then reduce to 40 mg/m2/on alternate days (max 60mg) for 4 wk then wean over 4-6 wk
  or
- 2. 60 mg/m2/day (max 80 mg) for 6 wk then reduce to 40 mg/m2/on alternate days (max 60mg) for 6 wk then stop or Taper over 12 wk

4.2 ĐIỀU TRỊ TÁI PHÁT

4.2.1 Tái phát lần đầu:

Prednisone 2mg/kg/ngày cho đến khi đạm niệu (-) 3 ngày liên tiếp, tối thiểu 14 ngày .

Sau đó: Prednisone 1,5 mg/kg/cách ngày, trong 4 tuần.

Sau o : giảm dần

ĐIỀU TRỊ TÁI PHÁT

4.2.2 Tái phát thường xuyên, hoặc lệ thuộc corticoid:

Prednisone 2mg/kg/ngày cho đến khi đạm niệu (-) 3 ngày liên tiếp

Sau đó : Prednisone 1,5 mg/kg/ cách ngày, trong 4 tuần

Tiếp theo giảm liều dần, rồi duy trì: 0,1- 0,5mg/kg/cách ngày trong 3-12th

TPTX : 3-6th

Phụ thuộc : 9-12th

Effective steroid sparing agents for SSNS

Cyclophosphamide	2 mg/kg/day	8-12 weeks
Chlorambucil	0.1-0.2 mg/kg/day	8-12 weeks
Levamisole	2.5 mg/kg on alt days	12 months or more
Cyclosporin*	4-5 mg/kg/day in 2 doses	12 months or more
Tacrolimus*	0.1 mg/kg/day in 2 doses	12 months or more
Mycophenolate mofetil	1200 mg/m^2/day in 2 doses	12 months or more
Rituximab	375 mg/m^2 per dose	?once /once yearly as required

* Starting dose; monitor levels

4.3 ĐIỀU TRỊ THỂ KHÁNG CORTICOID :

Thể kháng corticoid:

- sinh thiết thận

Managing relapses

~80% have relapses; 50% frequent, dependence

Relapse PDN 60 mg/m^2/d till protein free for 3-5 days; 40 mg/m^2 alternate-d for 4 weeks, stop

Low-dose prednisolone for relapses

Great Ormond Street Hospital. Pediatr Nephrol 2017;32:99

87 relapses (57 patients): Prednisolone 1 mg/kg/d

70% relapses responded within **one-wk**

No effect on frequency of later relapses, QoL

Single center RCT: Lower dose works well

ESPN 2017. Tel Aviv University

30 patients randomized prednisone **1-**, **1.5-**, **2** mg/kg/d

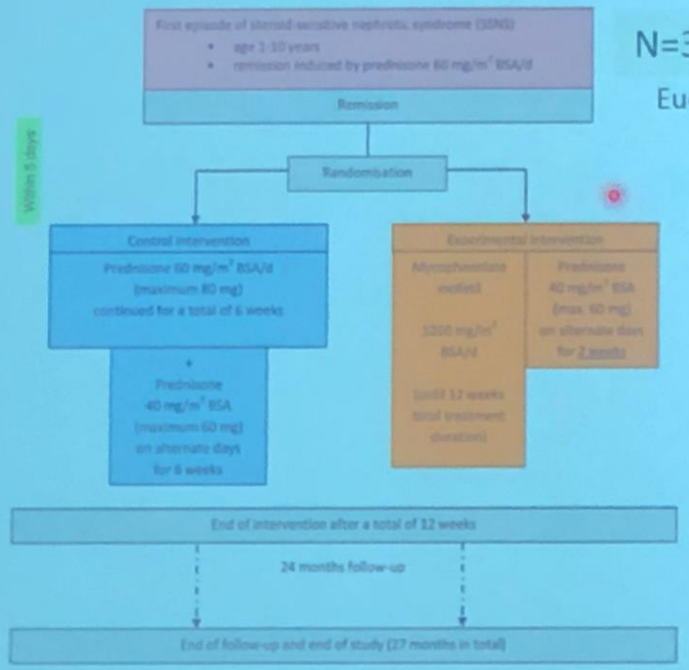
Time to response **8±2.7**; **9.5±2.3**; & **7.1±1.3** days

RCT: Reduced duration of alternate-d therapy from 4 wk to 2 wk **did not influence** subsequent course CTRI 2015/06/009277

Current studies

Duration of initial therapy in the young CTRI/2015/06/005939 (India, US)

Initial therapy with MMF *vs.* prednisone: **INTENT**



N=340; non-inferiority design, open label

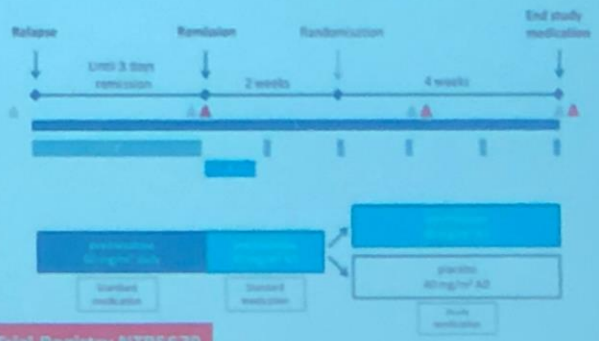
EudraCT2014-001991-76

Duration of therapy for relapse

REducing **STE**roids in **R**elapsing **N**ephrotic syndrome (RESTERN) – Dutch double blind, RCT

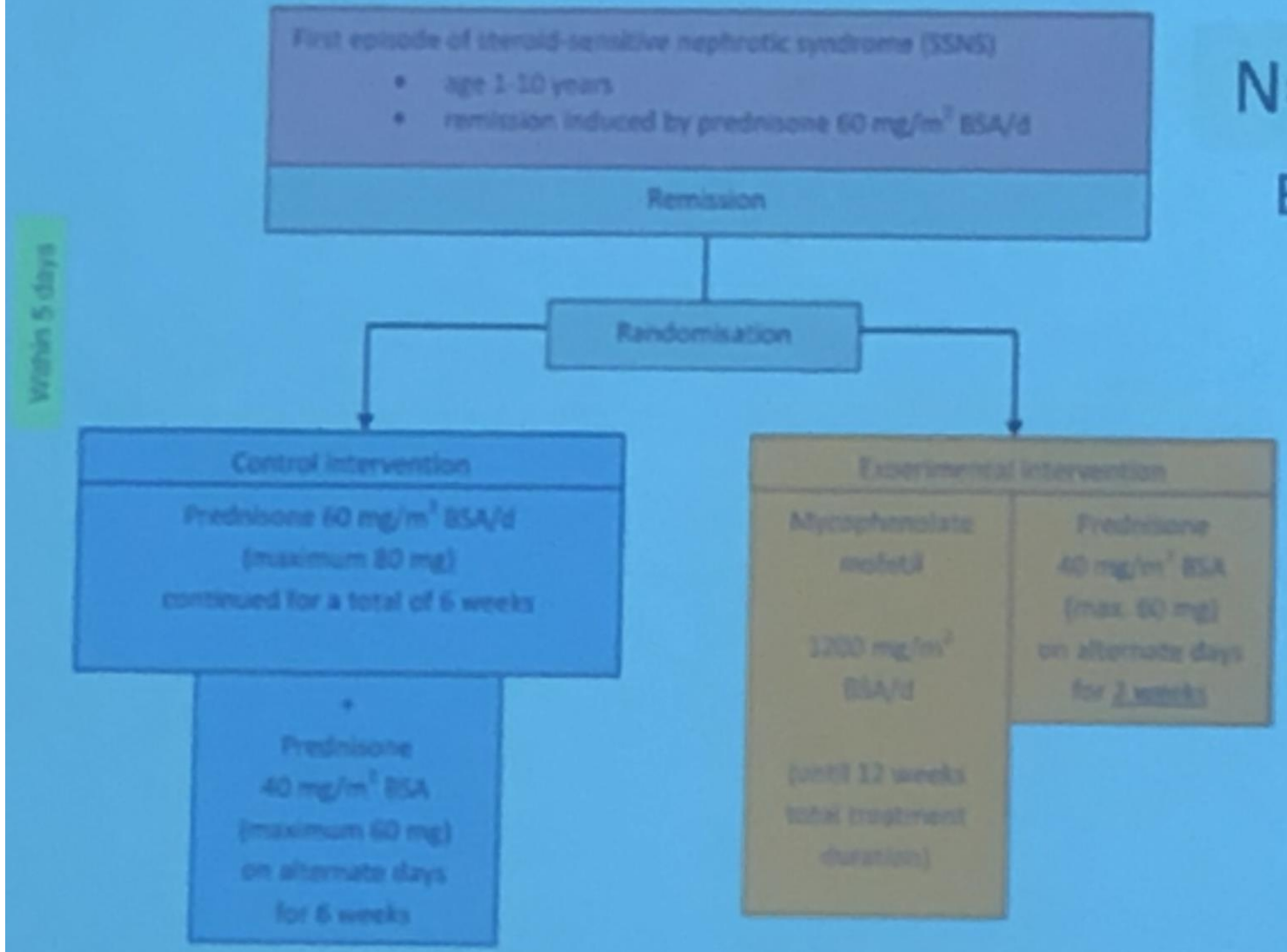
144 subjects (1-18 yr) receive 2-wk vs. 6-wk

Relapses, frequent relapses, dependence



Dutch Trial Registry NTR5670

Initial therapy with MMF *vs.* prednisor



N=340; non-ir

EudraCT2014-0

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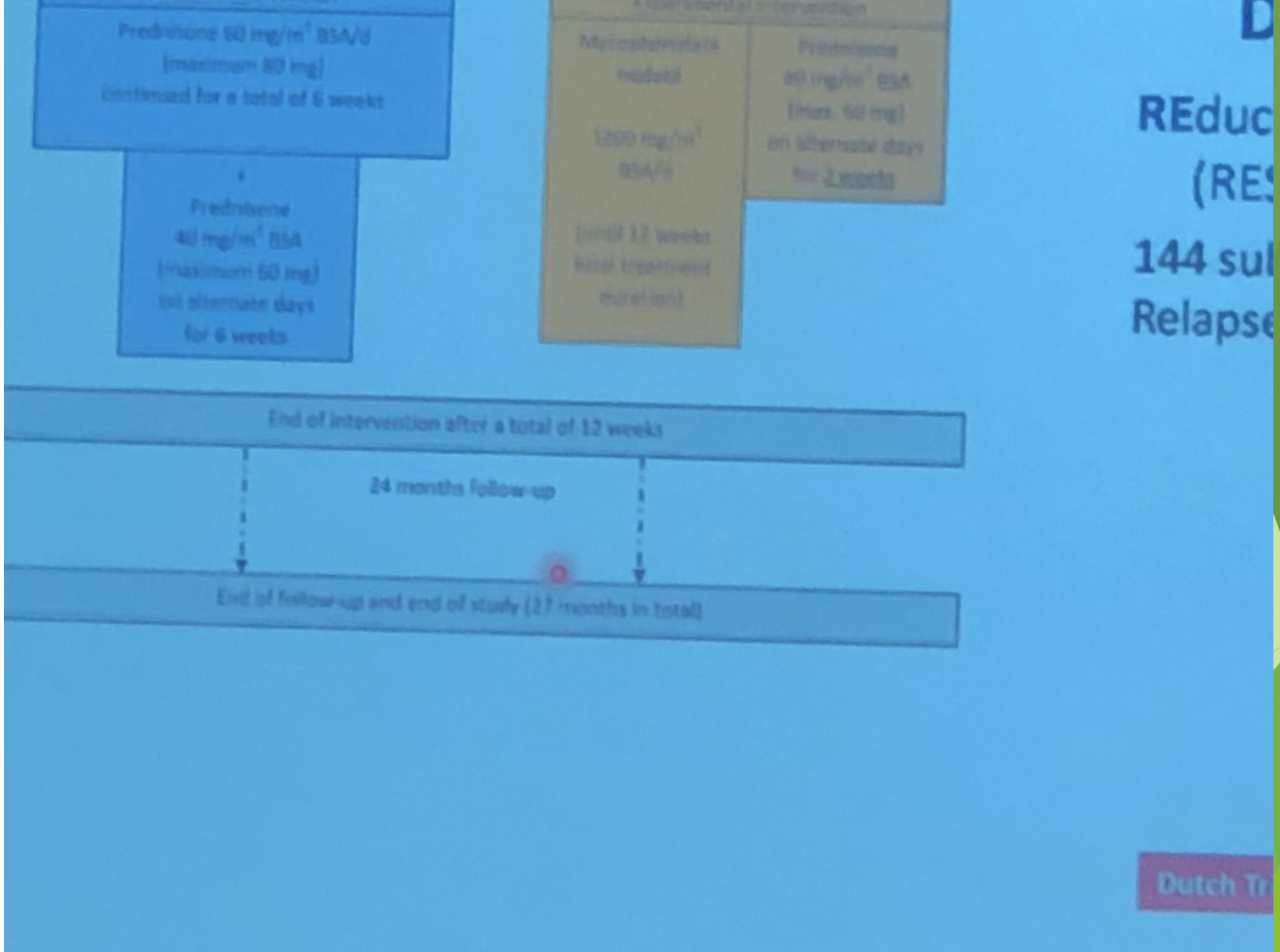
Relaps


Prednisone 60 mg/m² BSA/d
(maximum 80 mg)
continued for a total of 6 weeks
+
Prednisone
40 mg/m² BSA
(maximum 60 mg)
on alternate days
for 6 weeks
Mycophenolate
mofetil
1200 mg/m²
BSA/d
Prednisone
40 mg/m² BSA
(max. 60 mg)
on alternate days
for 2 weeks
End of intervention after a total of 12 weeks
24 months follow-up
End of follow-up and end of study (27 months in total)
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Relapse
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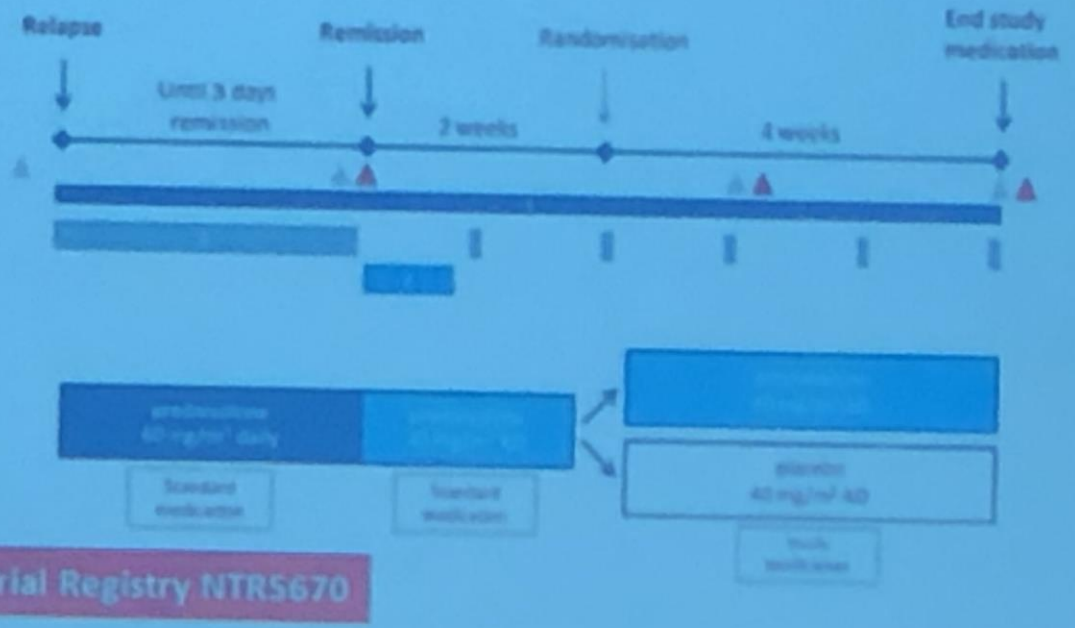
Duration of therapy for relapse

REducing **STE**roids in **R**elapsing **N**ephrotic syndrome (RESTERN) – Dutch double blind, RCT

144 subjects (1-18 yr) receive 2-wk vs. 6-wk

Relapses, frequent relapses, dependence



Dutch Trial Registry NTR5670

Long-term alternate day steroids

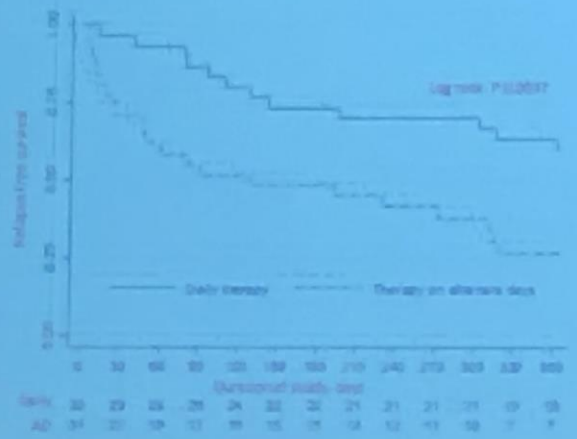
ISPN: 0.5-0.7 mg/kg, with taper for 9-18 months

Low dose daily prednisone 0.25 mg/kg (*x* 18 months) Pediatr Nephrol 1992

Low dose daily *vs.* alternate day prednisone in frequently relapsing nephrotic syndrome (RCT; N=62)

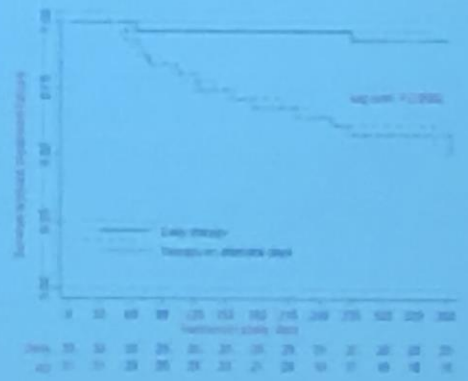
Daily dose reduce further?

Time to first relapse



Time to treatment failure

frequent relapses; steroid toxicity



Daily Corticosteroids Reduce Infection-associated Relapses in Frequently Relapsing Nephrotic Syndrome: A Randomized Controlled Trial

60% (RR 0.4; 0.3,0.6)

Clin J Am Soc Nephrol 2011; 6: 63-9

Pediatr Nephrol (2017) 32:1377–1382
DOI 10.1007/s00467-017-3645-5

ORIGINAL ARTICLE

Short courses of daily prednisolone during upper respiratory tract infections reduce relapse frequency in childhood nephrotic syndrome

N=33 patients; 0.5 mg/kg/d *x* 5 days

P=0.014

PREDNOS 2

N=300; placebo-controlled, multicenter
6-days daily prednisolone during URTI

KDIGO: Suggest use of daily prednisone during URTI in patients with frequent relapses 2B

A randomized clinical trial indicates that levamisole increases the time to relapse in children with steroid-sensitive idiopathic nephrotic syndrome

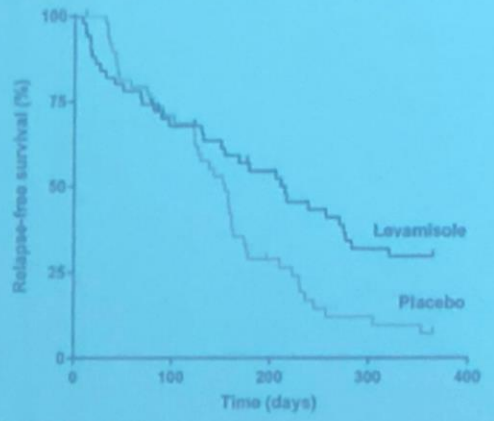
Kidney International (2018); 93: 510-18

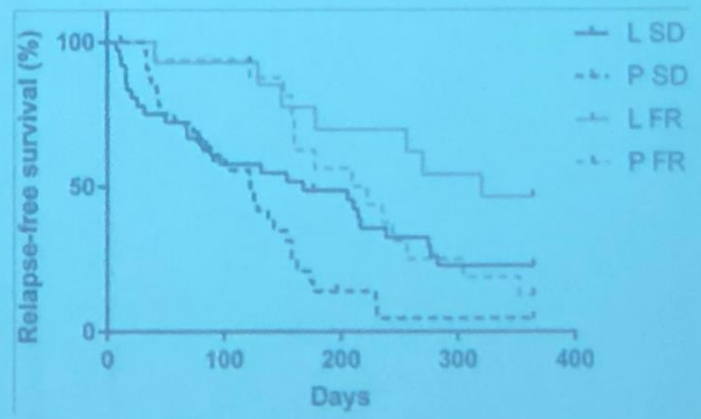
Placebo-controlled, double blind RCT (n=99)

Reduced risk of relapse: Levamisole (HR 0.22; 0.11–0.43)

Sustained remission @ 1-yr: 6% placebo; 26% levamisole

~8% asymptomatic reversible moderate neutropenia





Satisfactory results in frequent relapsers

Mycophenolate mofetil for 12 months 2C

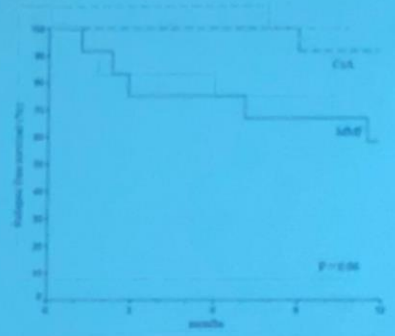
	Duration; mg/m²/d	Relapses (annual)
Barletta '03 [14]*	12 mo; 1000	Pre 2.9; during MMF 1.1; P 0.01
Geller '04 [7]*	25 mo; 1000	No relapse during treatment (5)
Mendizábal '05 [21]*	8 mo; 1250	Steroid sparing (15); remission (9); relapse (7) on withdrawal
Novak '05 [21]	12 mo; 1200	Pre 9.6; MMF 5.6; P 0.02
Al-Akash '05 [11]	12 mo; 1000	Pre 4.7; MMF 1; P 0.01
Hogg '06 [33]	6 mo; 1200	Pre 6-8.1; MMF 0.5-1; P 0.05 80% remission during therapy
Fujinaga '07 [12]*	11 mo; 1220	Pre 2.7; MMF 0.6; P 0.01 CsA, steroid sparing
AIIMS '07 [42]	14 mo; 800	62% reduced relapses; 50% steroid dose; P 0.001; Failure 12%

[n, retrospective]; [n, prospective]; *CsA

MMF more effective in young Dehoux, et al. Pediatr Nephrol (2016) 31:2095-2101

96 children; MMF dose 1063-1100 mg/m²/day for ~32 months

MMF inferior to CsA for frequent relapsers

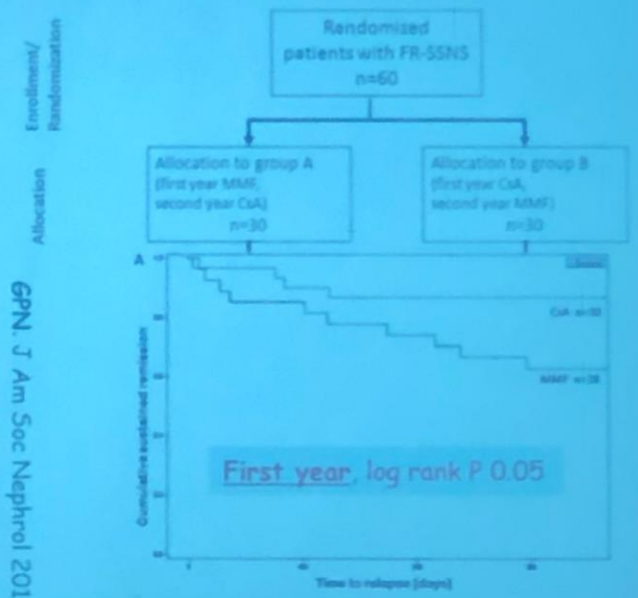


Dorresteyn. Ped Neph 2008

N=24

MMF preserves GFR

Lower relapse free survival;
0.8/yr vs. 0.08/yr



GPN. J Am Soc Nephrol 2013

CsA sustained remission 85%

MMF remission 64% (P=0.06)

High MPA levels better

eGFR better with MMF

MMF is not superior to levamisole in children with frequently relapsing or steroid dependent nephrotic syndrome

CTRI/2012/02/002394

207 patients assessed

Stratified for steroid dependence

Children, 6-18 years old
84% boys
28% steroid dependent

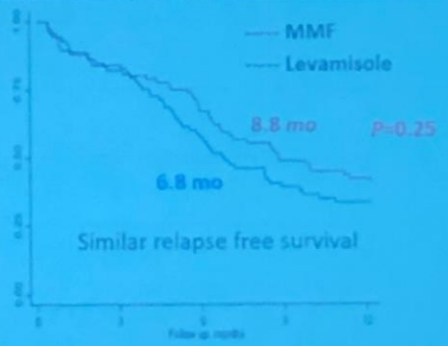
149 randomized

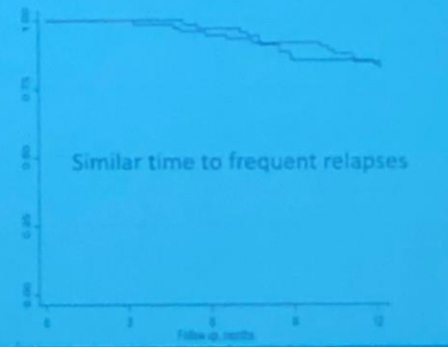
Intention to treat analysis

76 received MMF

73 received levamisole

Incident relapses, person-yr	1.1 [0.3, 1.3]	1.3 [1.1, 1.7]
Sustained remission, %	40.8 [30.4, 52.0]	34.2 [4.4, 45.7]
Frequent relapses, %	14.5 [8.1, 24.3]	16.4 [9.5, 26.7]
Treatment failure, %	15.8 [9.1, 25.8]	20.6 [2.8, 31.3]





Relative relapse rates similar in subgroups for sex, age & disease severity

CONCLUSION:

MMF not superior to levamisole in reducing frequency of relapses or likelihood of remission in children with frequent relapses

ISN kidney INTERNATIONAL

KI (2019) https://doi.org/10.1016/j.kint.2018.08.039

MMF exposure & control of relapses

Study	Mean relapses/yr
AIIMS (2019) MMF group 750-1000 mg/m^2	1.05
Gellerman (2013) MMF group	0.75
Low MPA exposure (AUC_{0-12} <50 µg.h/ml)	1.40
High MPA exposure (AUC_{0-12} >50 µg.h/ml)	0.27
Hackl (2016)	
Low MPA exposure (AUC_{0-12} <45 µg.h/ml)	1.06
High MPA exposure (AUC_{0-12} >45 µg.h/ml)	0.17

KI 2019; JASN 2013; Ther Drug Monitor 2016

High MPA clearance in hypoalbuminemia; high cholesterol, triglycerides

Rituximab effective in sensitive nephrotic syndrome

CJASN ePress. Published on August 26, 2010 as doi: 10.2215/CJN.03470410

Efficacy and Safety of Treatment with Rituximab for Difficult Steroid-Resistant and -Dependent Nephrotic Syndrome: Multicentric Report

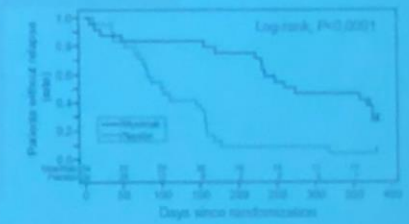
Ashima Gulati,* Aditi Sinha,* Stanley C. Jordan,† Pankaj Hari,* Amit K. Dinda,‡ Sonika Sharma,§ Rajendra N. Srivastava,* Asha Moudgil,‖ and Arvind Bagga*

Japan Research Group Lancet 2014; 384:1273–81 **[n=48]**

Rituximab or placebo q weekly for 4 weeks

Relapse free period longer in RTX

[median 267 vs. 101 days; HR 0.27; 0.1–0.5]



Efficacy and safety of rituximab in children with difficult-to-treat nephrotic syndrome NDT 2015

Steroid dependence (101); **CNI dependent steroid resistance** (34)

Relapse rates 82% & 71% **lower**

Remission: 16 *vs.* 10 months; P <0.0001

Sustaining rituximab response

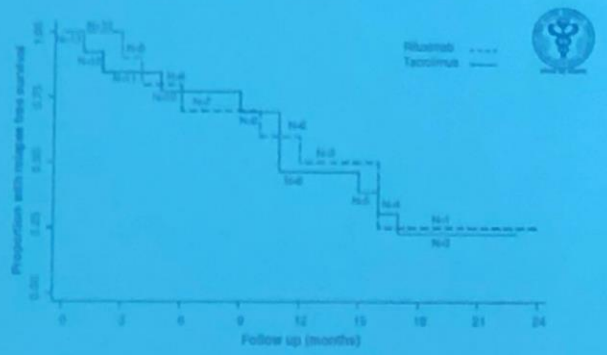
Add MMF following therapy JSKDC07; UMIN000014347

Repeat doses of RTX q 6-12 months

Sellier-Leclerc. Pediatr Nephrol 2010; 25:1109 Kimata et al. Am J Nephrol 2013; 38:483

NCT03899103: MMF *vs.* repeat doses of RTX

Short-term efficacy of rituximab versus tacrolimus in steroid-dependent nephrotic syndrome



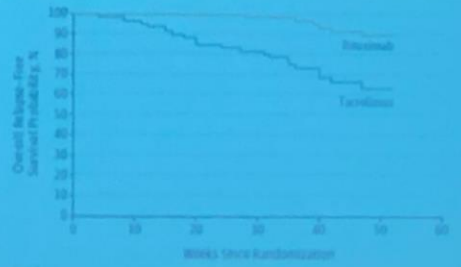
Similar at 6, 12 & 18 months

Pediatr Nephrol
DOI 10.1007/s00467-011-1997-4

RTX *vs.* Tacrolimus for dependence

120 children; 2 doses RTX *vs.* 1-yr Tac

RTX: higher relapse-free survival than Tac (90%, 63%; OR 5.2; 1.9-14.1)



JAMA Pediatr 2018;172(8):757-764

Rituximab dose and maintenance immunosuppression (mIS) in FR/SDNS

Design

Retrospective cohort

511 children

11 centres

Intervention

Rituximab doses
- Low (375mg/m²)
- Med (750mg/m²)
- High (1125-1500mg/m²)

± mIS (IS at relapse or given ≥ 6 months)

OUTCOME Median relapse-free survival

Without mIS	Low dose	8.5 months	⇧ Relapse Risk
	Med dose	12.7 months	
	High dose	14.3 months	
With mIS	Low dose	14.0 months	Similar Relapse Risk
	Med dose	10.9 months	
	High dose	12.0 months	

CONCLUSION Children receiving low-dose rituximab without mIS had the shortest relapse-free survival. Both rituximab dose and mIS have important effects on long-term control of FR/SDNS.

Abstract at WCN 2019. Eugene Chan, et al

4.3 ĐIỀU TRỊ THỂ KHÁNG CORTICOID :

Thể kháng corticoid:

- sinh thiết thận

MCNS, MESP-GN, FSGS :

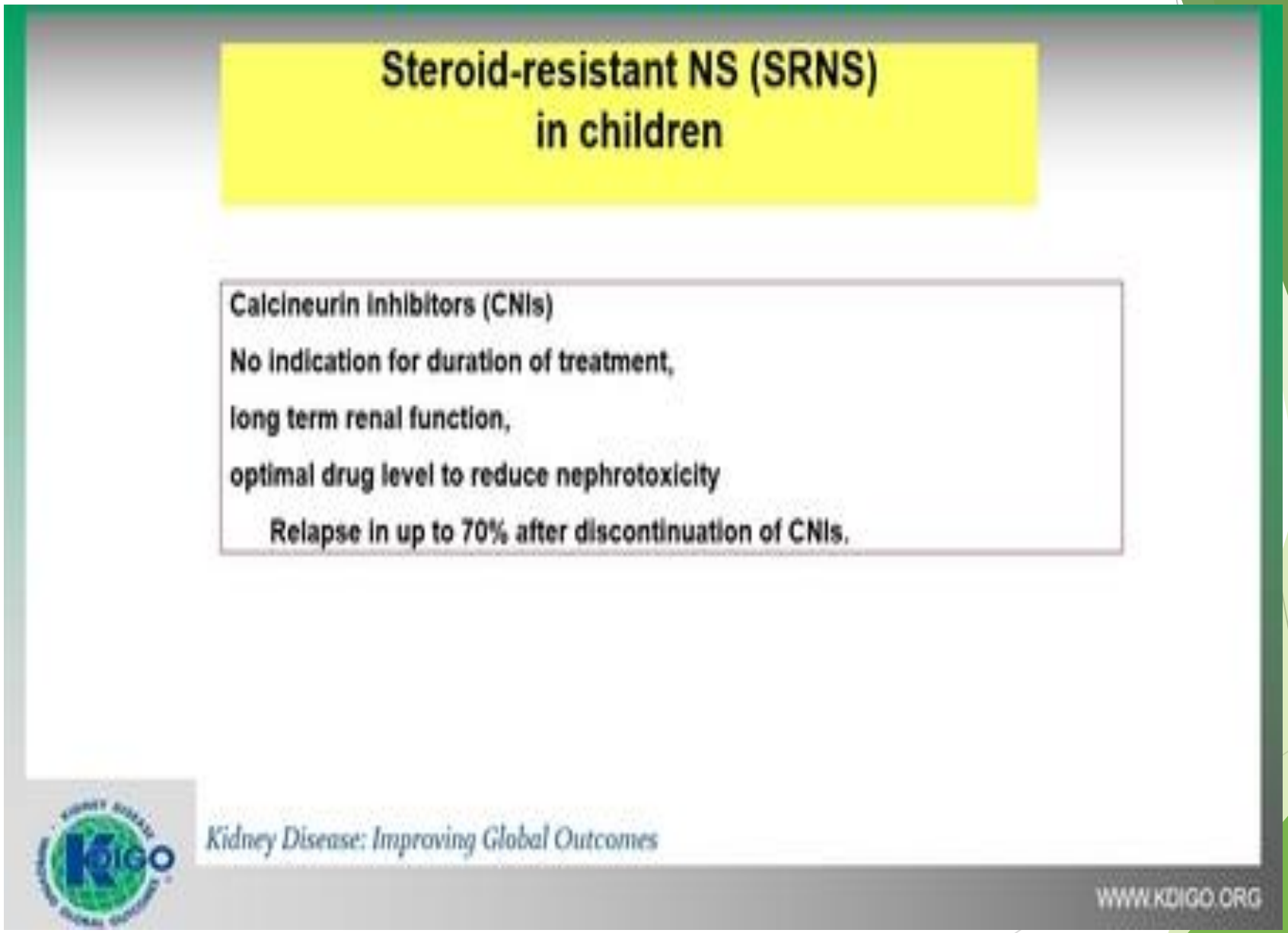
Cylosporine: 5mg/kg/ngày

hay Tacrolimus 0,15 mg /kg chia 2

+ Prednisone:

1mg/kg/ng 1 th

1mg/kg/cách ngày x 5 tháng


Steroid-resistant NS (SRNS)
in children
Calcineurin inhibitors (CNIs)
No indication for duration of treatment,
long term renal function,
optimal drug level to reduce nephrotoxicity
Relapse in up to 70% after discontinuation of CNIs.
Kidney Disease: Improving Global Outcomes
WWW.KDIGO.ORG

Spectrum of Steroid-Resistant and Congenital Nephrotic Syndrome in Children: The PodoNet Registry Cohort

- FSGS (56%), MCD (21%), mesangioproliferative GN (12%).
- A genetic disease in 24% (most common: NPHS2, WT1, and NPHS1).

- Calcineurin inhibitors and rituximab yielded 40-45% complete remission.

- RAS inhibition was associated with complete remission in 25% and partial remission in 20%

- A genetic diagnosis but not the histopathologic type was strongly predictive of intensified immunosuppressive therapy responsiveness.

to be considered in the next KDIGO edition

Is rituximab useful for steroid resistance?

Resistance to calcineurin inhibitors 20-30%

Author (publication year)	Number of patients	Patients of remission[a]	Patients of CR	Patients of PR
Case reports[b] [17–29]	13	10 (76.9%)	10 (76.9%)	0 (0.0%)
Bagga et al. (2007) [30]	33	16 (48.5%)	9 (27.3%)	7 (21.2%)
Gulati et al. (2010) [31]				
Prytula et al. (2010) [32]	27	18 (66.7%)	6 (22.2%)	12 (44.4%)
Kari et al. (2011) [33]	4	1 (25.0%)	1 (25.0%)	0 (0.0%)
Ito et al. (2013) [34]	19	12 (63.2%)	6 (31.6%)	6 (31.6%)
Kamei et al. (2014) [35]	10	8 (80.0%)	7 (70.0%)	10 (10.0%)
Sinha et al. (2015) [36]	58	17 (29.3%)	7 (12.1%)	10 (17.2%)
Basu et al. (2015) [37]	24	16 (66.7%)	5 (20.8%)	11 (45.8%)
Hoseini et al. (2018) [38]	30	17 (56.7%)	14 (46.7%)	3 (10.0%)
Magnasco et al. (2012) [39]	16	3 (18.8%)	NA	NA
Total	234	118 (50.4%)	65 (29.8%)[c]	50 (22.9%)[c]

Overall response <40%

91/234 from New Delhi

JASN 2012; 23: 1117–1124

Resistance to steroids and calcineurin inhibitors					
Magnasco et al. (2012)[39]	31	Open-label randomized controlled trial; 15 months	Rituximab 2 doses, 2 weeks apart, with prednisolone and tacrolimus or ciclosporin (n=16) vs prednisolone and tacrolimus or ciclosporin (n=15)	8.5 ± 4.4 vs 7.3 ± 3.7	No difference in proteinuria at 3 months ($P=0.77$). Similar proportions of patients with initial and delayed-onset steroid-resistant nephrotic syndrome responded in both groups

Remission: Initial resistance 54/123 (**44%**); late 45/78 (**58%**)

Remission: **FSGS** 54/130 (**42%**); **minimal change** 49/77 (**64%**)

Pediatric Nephrology doi.org/10.1007/s00467-018-4166-1

Not promising yet, ...

ACTH: Effective in membranous nephropathy, FSGS

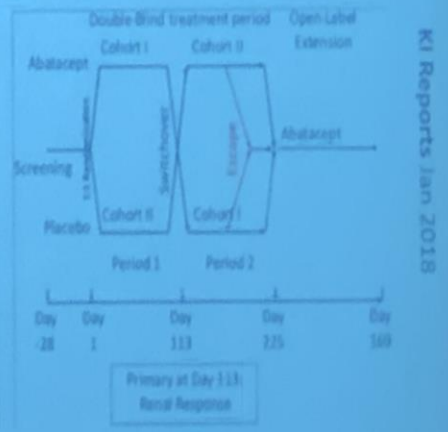
ATLANTIS (NCT02132195) CJASN 2018; 13 (12): 1859-65

RCT (China, NCT02972346); 3-12 yr for SDNS/SRNS

Abatacept (CTLA-4-Ig) Binds to CD80; inhibits T cell activation

Remission (Yu 2013); not replicated in 24/25

RCT; n=90 MCD, FSGS (NCT02592798)



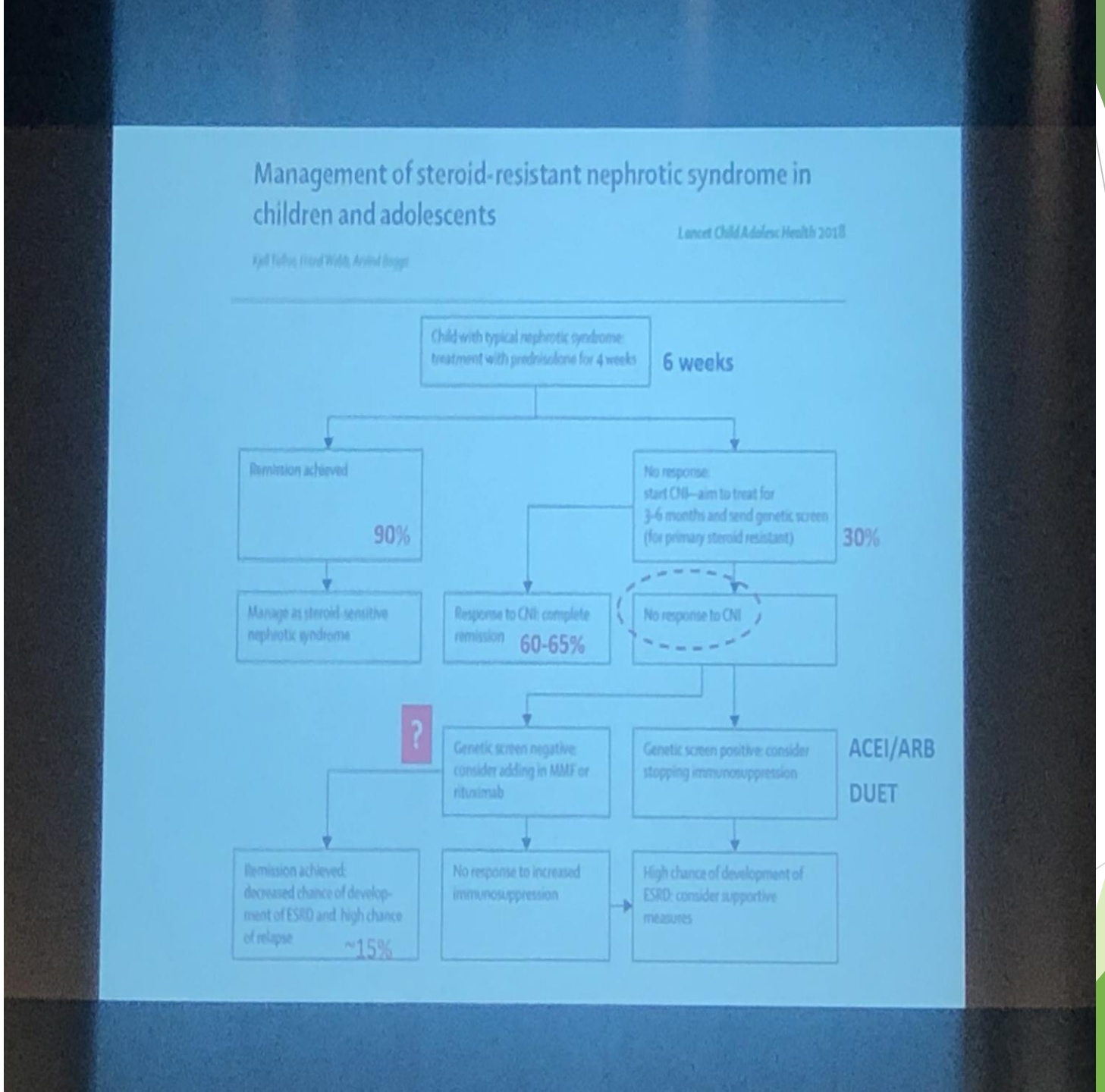
KI Reports Jan 2018

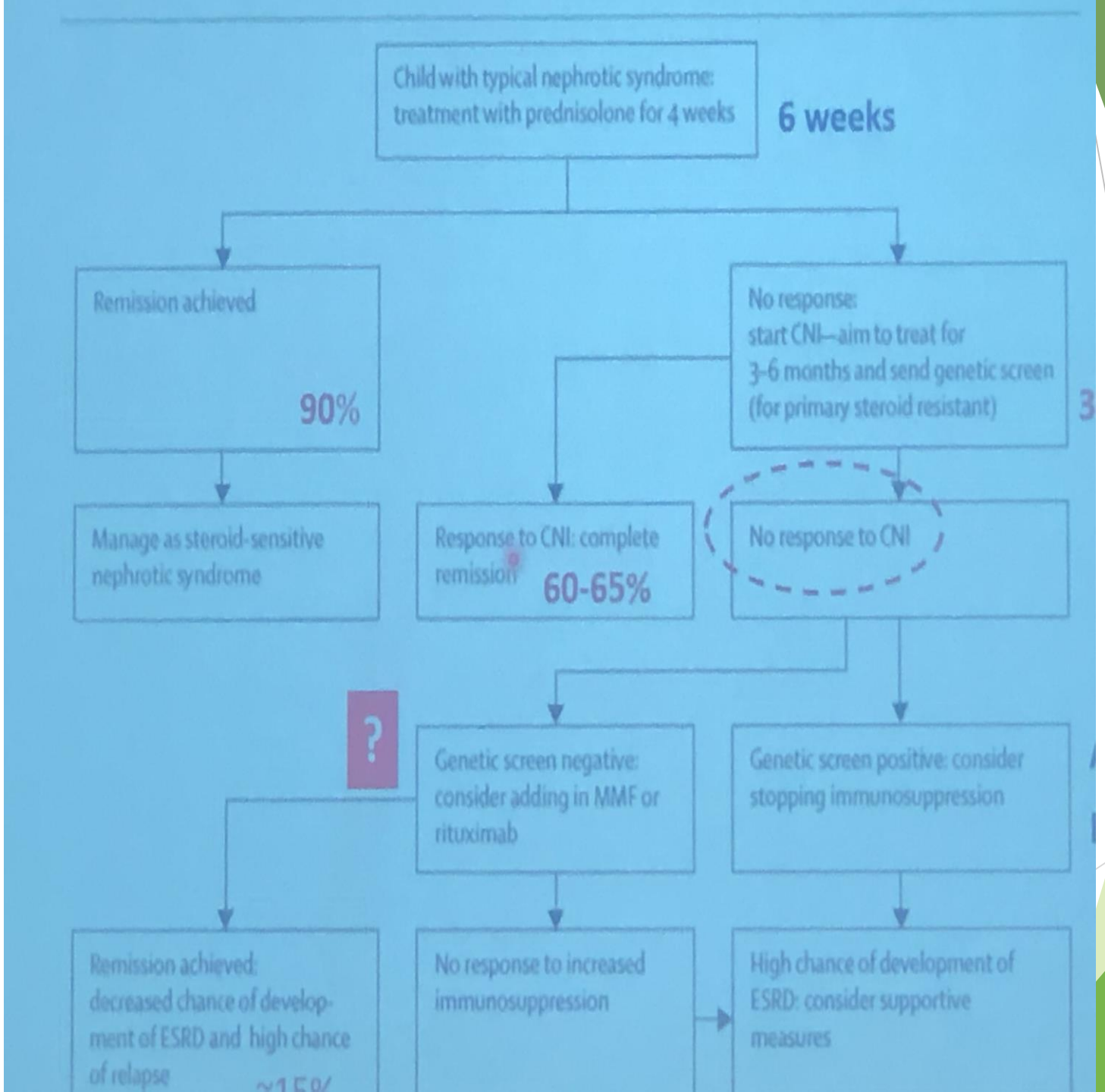
Adalimumab: TNF-α monoclonal

FONT I: 4/10 had 50% reduced proteinuria

FONT II: 0/7 any reduction in proteinuria

BMC Nephrol 2015


Management of steroid-resistant nephrotic syndrome in children and adolescents
Lancet Child Adolesc Health 2018
Child with typical nephrotic syndrome: treatment with prednisolone for 4 weeks
6 weeks
Remission achieved
90%
No response: start CNI—aim to treat for 3-6 months and send genetic screen (for primary steroid resistant)
30%
Manage as steroid-sensitive nephrotic syndrome
Response to CNI: complete remission
60-65%
No response to CNI
?
Genetic screen negative: consider adding in MMF or rituximab
Genetic screen positive: consider stopping immunosuppression
ACEI/ARB
DUET
Remission achieved: decreased chance of development of ESRD and high chance of relapse
~15%
No response to increased immunosuppression
High chance of development of ESRD: consider supportive measures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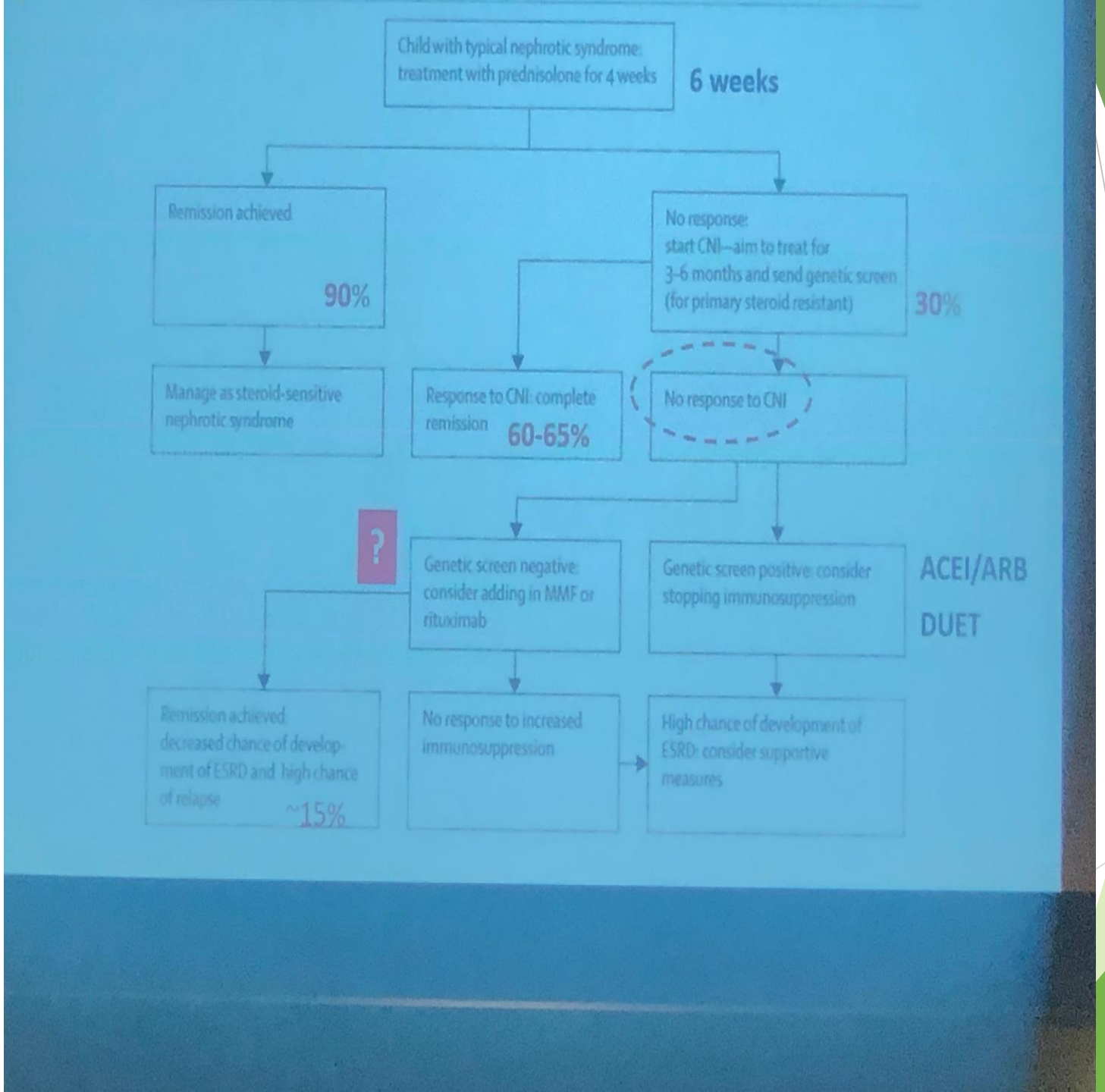
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High chance of development of ESRD: consider supportive measures

2. IgA VASCULITIS (HENOCH SCHONLEIN)

2.1. TÊN GỌI :

IgA VASCULITIS (HENOCH SCHONLEIN)

RHEUMATOLOGY

Original article

doi:10.1093/rheumatology/kez041

European consensus-based recommendations for diagnosis and treatment of immunoglobulin A vasculitis—the SHARE initiative

Seza Ozen[1], Stephen D. Marks[2], Paul Brogan[2], Noortje Groot [3,4,5], Nienke de Graeff[3], Tadej Avcin[6], Brigitte Bader-Meunier[7], Pavla Dolezalova[8], Brian M. Feldman[9], Isabelle Kone-Paut[10], Pekka Lahdenne[11], Liza McCann[5], Clarissa Pilkington[2], Angelo Ravelli[12], Annet van Royen[3], Yosef Uziel[13], Bas Vastert[3], Nico Wulffraat[3], Sylvia Kamphuis[4] and Michael W. Beresford [5,14]

Abstract

Objectives. IgA vasculitis (IgAV, formerly known as Henoch–Schönlein purpura) is the most common cause of systemic vasculitis in childhood. To date, there are no internationally agreed, evidence-based guidelines concerning the appropriate diagnosis and treatment of IgAV in children. Accordingly, treatment regimens differ widely. The European initiative SHARE (Single Hub and Access point for paediatric Rheumatology in Europe) aims to optimize care for children with rheumatic diseases. The aim therefore

Rheumatology key messages

- IgA vasculitis is the most common cause of systemic vasculitis in childhood.
- These are the first international, evidence-based recommendations concerning the management of childhood IgA vasculitis.
- All IgA vasculitis patients need to be proactively investigated for renal involvement, at diagnosis and throughout follow-up.

Number	Recommendations: Diagnosis	LoE	SoR
Classification criteria			
1.	The EULAR/PRINTO/PReS-endorsed Ankara 2008 criteria should be used to classify IgAV (formerly known as HSP) [26]	2A	B
Use of biopsy			
2.	A skin biopsy including specific immunofluorescence staining for IgA should be performed in case of atypical rash and/or to exclude alternative diagnoses; skin biopsy is not needed in a patient with the typical purpuric skin rash on lower limbs and buttocks	4	D
3.	Absence of IgA immunofluorescence staining on biopsy does not exclude the diagnosis of IgAV	3	C
Renal work-up			
4.	Renal involvement should be investigated using eGFR and urinalysis (haematuria and UP:UC ratio or UA:UC ratio)	2B	C
5.	A paediatric nephrologist should be consulted if an IgAV patient has moderate proteinuria[a] and/or impaired GFR[b]	4	D
6.	A renal biopsy should be performed if an IgAV patient has severe proteinuria (>250 mg/mmol for at least 4 weeks; although shorter duration of severe proteinuria is also a relative indication for biopsy), persistent moderate (100–250 mg/mmol) proteinuria[c] or impaired GFR[b]	2A	
Imaging			
7.	In severe abdominal pain, an US should be performed by an ultrasonographer with paediatric expertise to exclude intestinal intussusception	4	D

[a]Moderate proteinuria: UP:UC ratio 100–250 mg/mmol in an early morning urine sample. [b]Impaired GFR: <80 ml/min/1.73 m^2. [c]Persistent proteinuria, defined as per severity—see Table 2 for full definitions; note, for severe proteinuria >250 mg/mmol, renal biopsy may also be considered before 4 weeks (relative indication for biopsy), and persistence >4 weeks at this level is regarded as an absolute indication for renal biopsy. SHARE: Single Hub and Access point for paediatric Rheumatology in Europe; LoE: level of evidence; 1A: meta-analysis of cohort studies; 1B: meta-analysis of case–control studies; 2A: cohort studies; 2B: case–control studies; 3: non-comparative descriptive studies; 4: expert opinion [22]; SoR: strength of recommendation: A: based on level 1 evidence; B: based on level 2 or extrapolated from level 1; C: based on level 3 or extrapolated from level 1 or 2; D: based on level 4 or extrapolated from level 3 or 4 expert opinion [19]; HSP: Henoch-Schönlein purpura; IgAV: IgA vasculitis; PReS: Paediatric Rheumatology European Society; UP:UC: urine protein:urine creatinine ratio; UA:UC: urine albumin:urine creatinine ratio; eGFR, estimated glomerular filtration rate.

Severity of IgAV nephritis	Definition
Mild	Normal GFR[a] and mild[b] or moderate[c] proteinuria
Moderate	<50% crescents on renal biopsy and impaired GFR[d] or severe persistent proteinuria[e] [44]
Severe	>50% crescents on renal biopsy and impaired GFR[c] or severe persistent proteinuria[e] [44]
Persistent proteinuria [43]	• UP:UC ratio >250 mg/mmol for 4 weeks[e] [44] • UP:UC ratio >100 mg/mmol for 3 months • UP:UC ratio >50 mg/mmol for 6 months

[a]Normal GFR: >80 ml/min/1.73 m^2. [b]Mild proteinuria: UP:UC ratio <100 mg/mmol (in an early morning urine sample). [c]Moderate proteinuria: UP:UC ratio 100–250 mg/mmol (in an early morning urine sample). [d]Impaired GFR: <80 ml/min/1.73 m^2. [e]Severe persistent proteinuria: >250 mg/mmol for at least 4 weeks. Note: for those that use different units, these conversions can be used to determine equivalent cut-off scores: 1 g/day of proteinuria (in 24 h urine collection) = UP:UC (early morning UP:UC ratio) of 100 mg/mmol = UA:UC (early morning UA:UC ratio) of 70 mg/mmol. This approximates to urine dipstick testing for proteinuria of 150 mg/dl but does not replace laboratory UP:UC or UA:UC. IgAV: IgA vasculitis; GFR: glomerular filtration rate; UP:UC: urine protein:urine creatinine ratio; UP:UC: urine albumin:urine creatinine ratio.

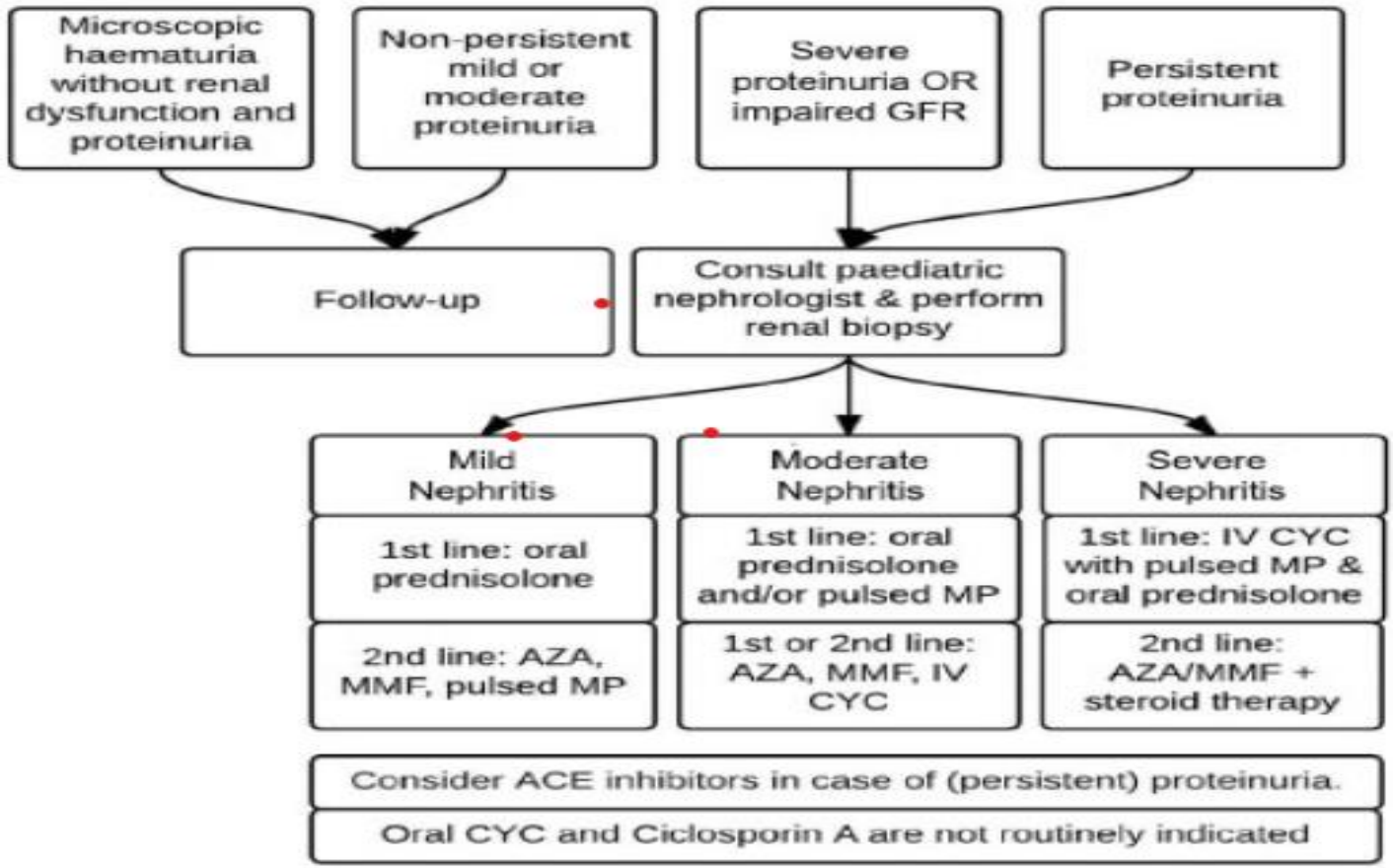
TABLE 3 SHARE recommendations for the treatment of IgAV

Number	Recommendations: Treatment	LoE	SoR
Analgesia			
1.	Adequate analgesia should be prescribed for IgAV-associated arthropathy[a]	4	D
2.	NSAIDs are not contraindicated if renal function is normal in IgAV	4	D
3.	Adequate analgesia should be prescribed for IgAV-associated abdominal pain	4	D
Use of CS			
4.	CS treatment is indicated in case of: • Orchitis • Cerebral vasculitis • Pulmonary haemorrhage • Other severe organ- or life-threatening vasculitis manifestations	4	D
5.	In patients with severe abdominal pain and/or rectal bleeding (in whom intestinal intussusception has been excluded), CS treatment could be considered	4	D
6.	The dose of oral CS (prednisolone/prednisone) should be 1–2 mg/kg/day	4	D
7.	If CS are indicated, pulsed i.v. methylprednisolone (e.g. 10–30 mg/kg with a maximum of 1 g/day on three consecutive days) may be considered for severe cases	4	D
8.	Prophylactic CS treatment to prevent the development of IgAV-associated nephritis is not indicated	1B	A
IgAV nephritis			
9.	When starting treatment of IgAV nephritis, a paediatric nephrologist should be consulted	4	D
10.	In the absence of robust data for evidence supporting the treatment of nephritis, a randomized controlled trial for the treatment of IgAV nephritis is urgently needed	4	D
11.	ACE inhibitors should be considered in IgAV nephritis to prevent/limit secondary glomerular injury for patients with persistent proteinuria	4	D
12.	Oral prednisolone should be used as first-line treatment in patients with mild IgAV nephritis	4	D
13.	AZA, MMF and/or pulsed methylprednisolone can be used as second-line treatment in patients with IgAV nephritis following renal biopsy	4	D
14.	Oral prednisolone and/or pulsed methylprednisolone should be used as first-line treatment in patients with moderate IgAV nephritis	4	D
15.	AZA, MMF or i.v. CYC may be used in the first- or second-line treatment of moderate IgAV nephritis	4	D
16.	Ciclosporin or oral CYC cannot be routinely recommended in moderate IgAV nephritis	4	D

14.	Oral prednisolone and/or pulsed methylprednisolone should be used as first-line treatment in patients with moderate IgAV nephritis	4	D
15.	AZA, MMF or i.v. CYC may be used in the first- or second-line treatment of moderate IgAV nephritis	4	D
16.	Ciclosporin or oral CYC cannot be routinely recommended in moderate IgAV nephritis	4	D
17.	As in other severe systemic small vessel vasculitides, i.v. CYC with pulsed methylprednisolone and/or oral prednisolone are recommended as first-line treatment in patients with severe IgAV nephritis	4	D
18.	In combination with steroid therapy, AZA and MMF may be used as maintenance treatment in patients with severe IgAV nephritis	4	D
19.	One treatment approach for IgAV nephritis is listed below in Fig. 1	4	D

[a]Adequate fluid intake is essential when taking NSAIDs. SHARE: Single Hub and Access point for paediatric Rheumatology in Europe; LoE: level of evidence; 1A: meta-analysis of randomized controlled trials; 1B: randomized controlled study; 2A: controlled study without randomization; 2B: quasi-experimental study; 3: descriptive study; 4: expert opinion [20]; SoR: strength of recommendation; A: based on level 1 evidence; B: based on level 2 or extrapolated from level 1; C: based on level 3 or extrapolated from level 1 or 2; D: based on level 4 or extrapolated from level 3 or 4 expert opinion [17]; IgAV: IgA vasculitis; ACE: angiotensin-converting enzyme.

FIG. 1 Guideline for the management of IgA vasculitis-associated nephritis



For definitions of severity of proteinuria, see Table2. For IgA vasculitis-associated crescentic glomerulonephritis,