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The European Rare Kidney Disease Reference Network

Primary therapy of steroid-sensitive nephrotic syndrome

Lutz T. Weber & the Cologne Team of Pediatric Nephrology

Agenda

Introduction

- Definition
- Manifestation
- Pathophysiology

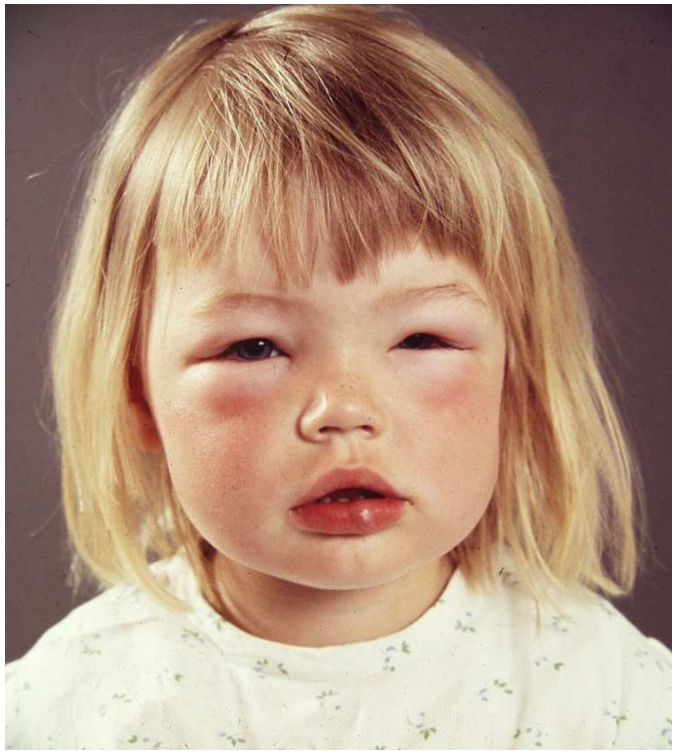
Primary Therapy

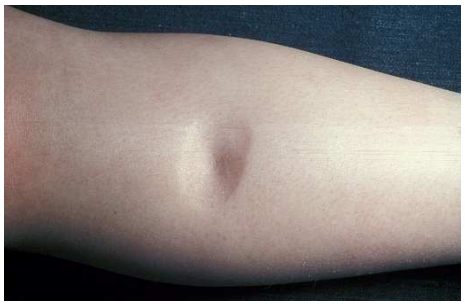
- Non-immunosuppressive Therapy
  Complications and Prophylaxis
- Immunosuppressive Therapy (Glucocorticoids (Steroids))

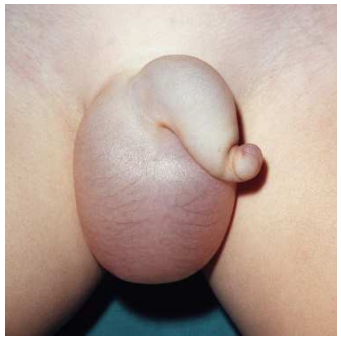
Perspective

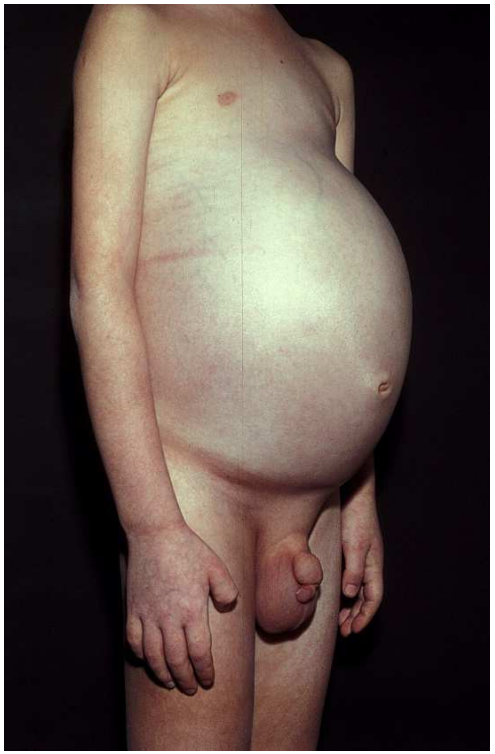
- INTENT Study
- LEARNS Study

Clinical Appearance









Benz MR & Weber LT, Monatsschr Kinderheilkd, 2012

Definition of Nephrotic Syndrome

– Heavy proteinuria (>1g/m^2xd)
– Hypoalbuminemia (<2,5 g/dL)

Characteristic:
– Edema
– Hypercholesterinemia, hypertriglyceridemia

Underlying condition

Primary nephrotic syndrome

Secondary nephrotic syndrome

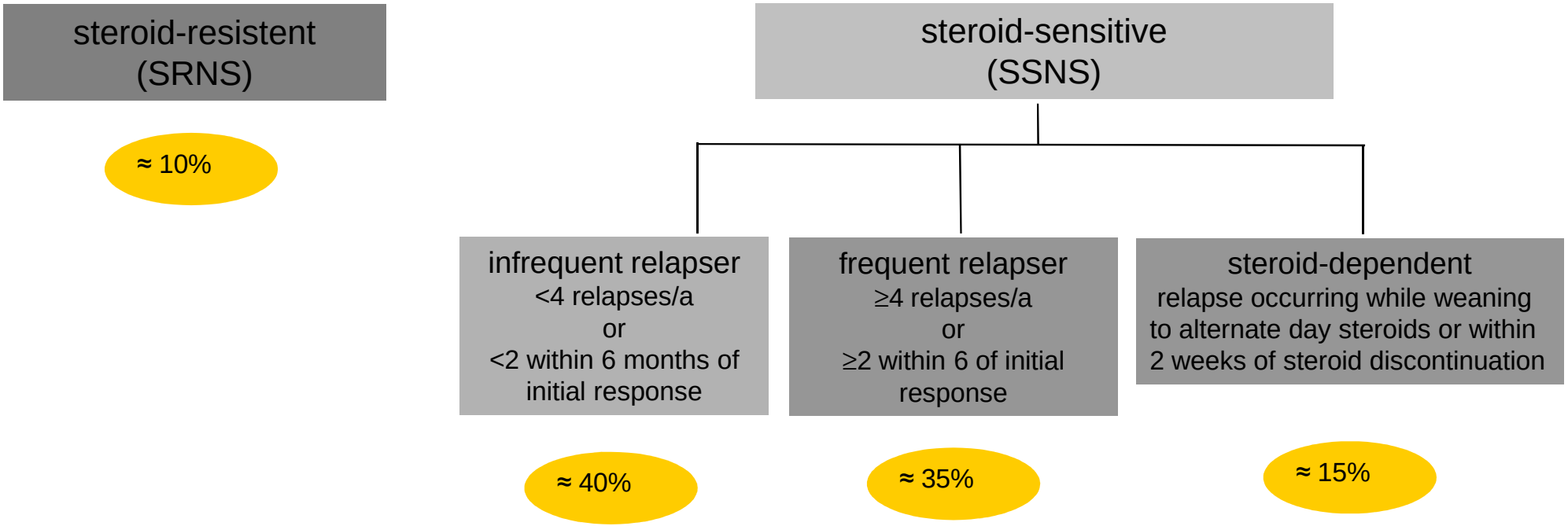
genetic
idiopathic

Panel 2: Causes of non-idiopathic childhood nephrotic syndrome (NS)

- Nephritic/nephrotic glomerular disorders
  - IgA nephropathy and Henoch–Schonlein purpura
  - Membranoproliferative glomerulonephritis
  - Lupus nephritis
  - Postinfectious glomerulonephritis
  - Immune complex mediated glomerulopathy
  - C1q nephropathy
- Thin basement membrane disease
- Membranous nephropathy
- Sickle-cell nephropathy
- Thrombotic microangiopathy
- Interstitial nephritis
- Infections associated with NS
  - Hepatitis B and C
  - HIV-1
  - Malaria
  - Syphilis
  - Toxoplasmosis
  - Varicella zoster
- Drugs associated with NS
  - Non-steroidal anti-inflammatory drugs
  - Bisphosphonates
  - D-penicillamine
  - Heavy metals (mercury and gold)
  - Lithium
  - Rifampicin
  - Sulfasalazine
- T-cell-related malignancy
  - Hodgkin's lymphoma
  - Thymoma
  - Leukaemia

Noone DG et al., Lancet, 2018

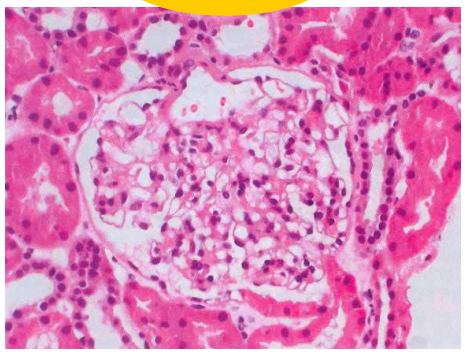
Idiopathic Nephrotic Syndrome
Clinical Manifestation



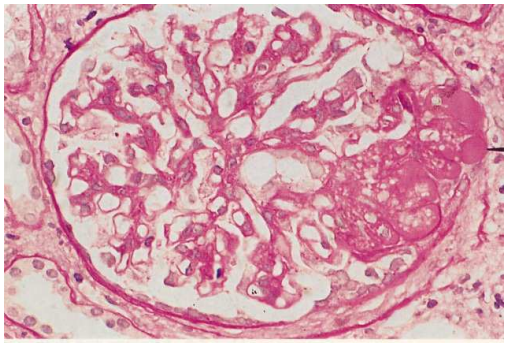
Idiopathic Nephrotic Syndrome
Histological Manifestation

Minimal change GN

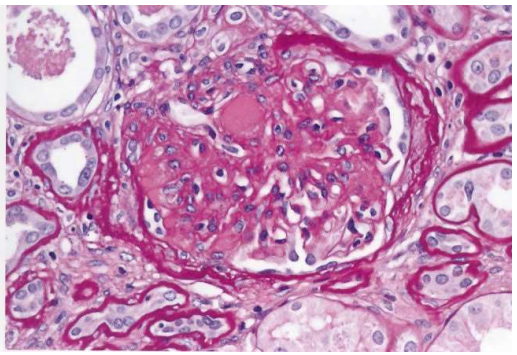
≈ 80%



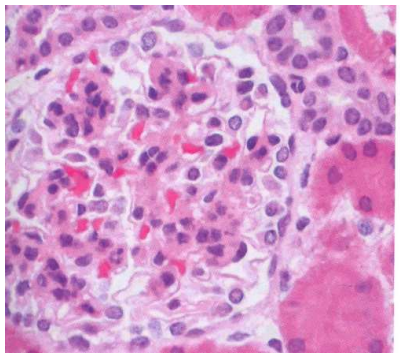
Focal segmental glomerulosclerosis (FSGS)



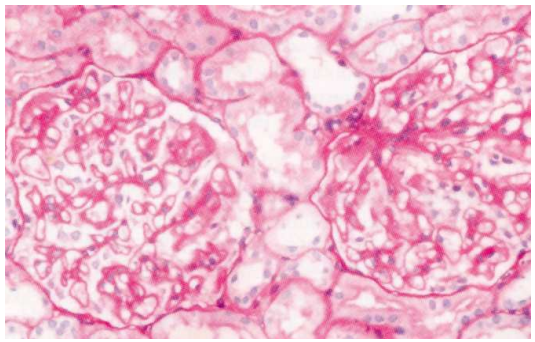
Diffuse mesangial sclerosis



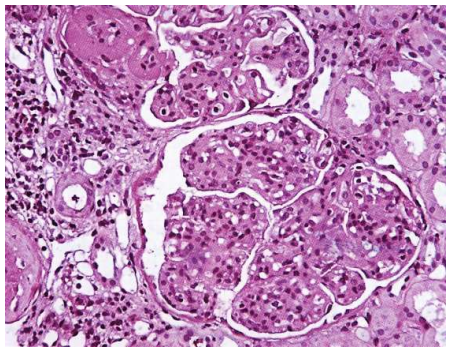
Mesangial proliferative GN



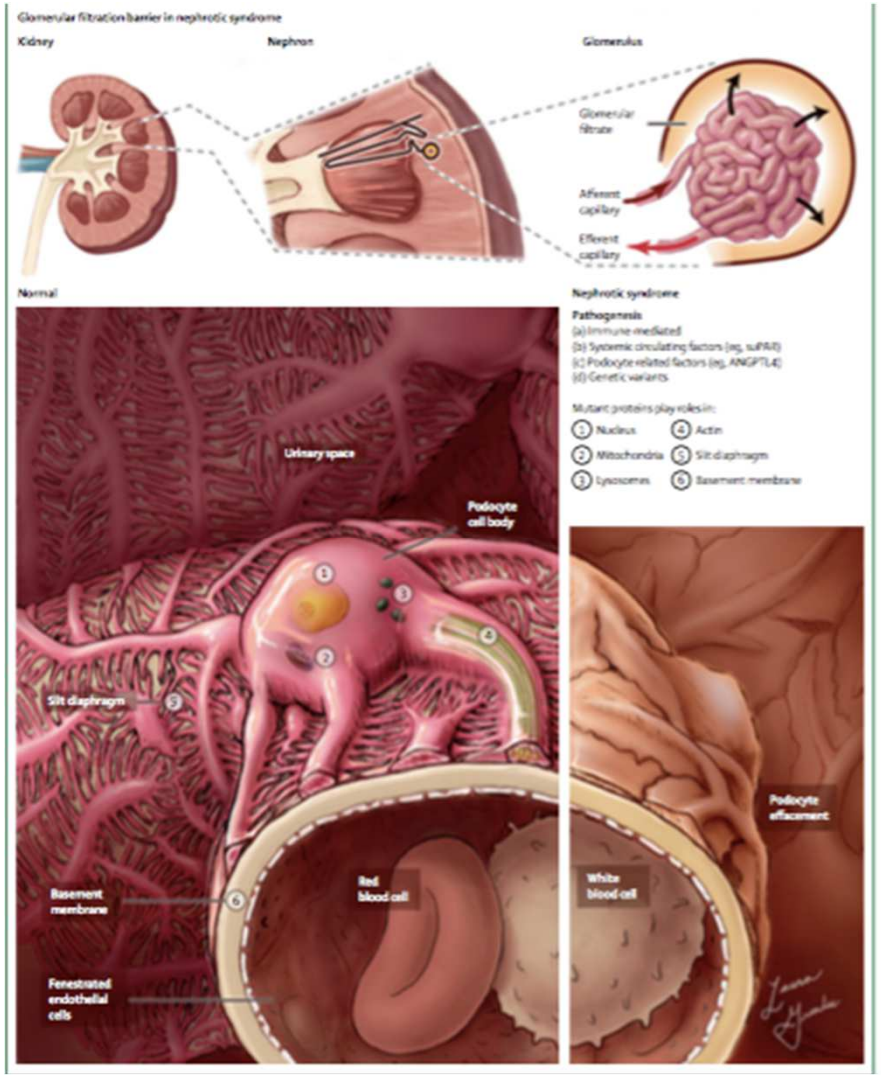
Membranous GN



Membranoproliferative GN

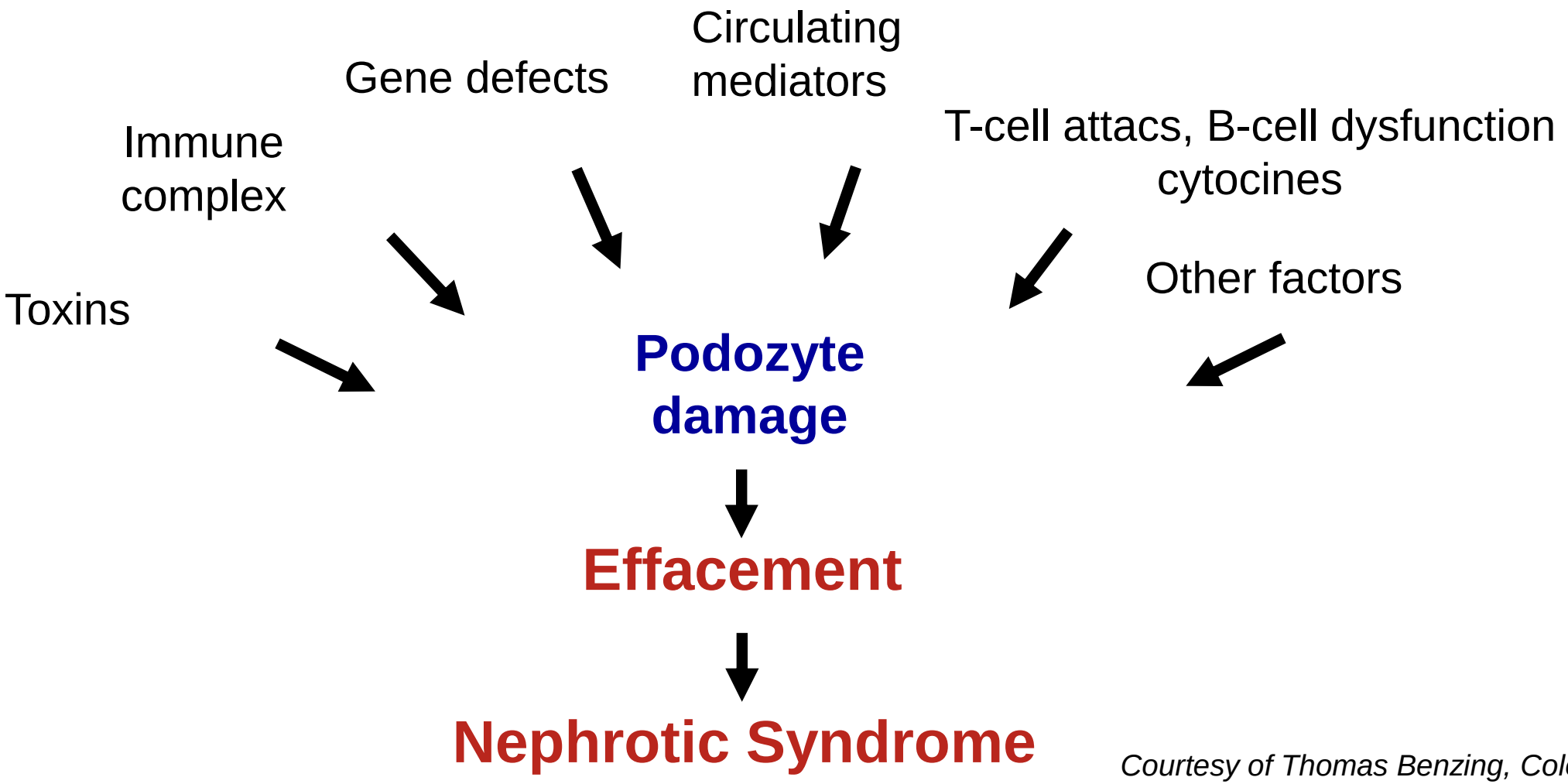


Pathophysiology



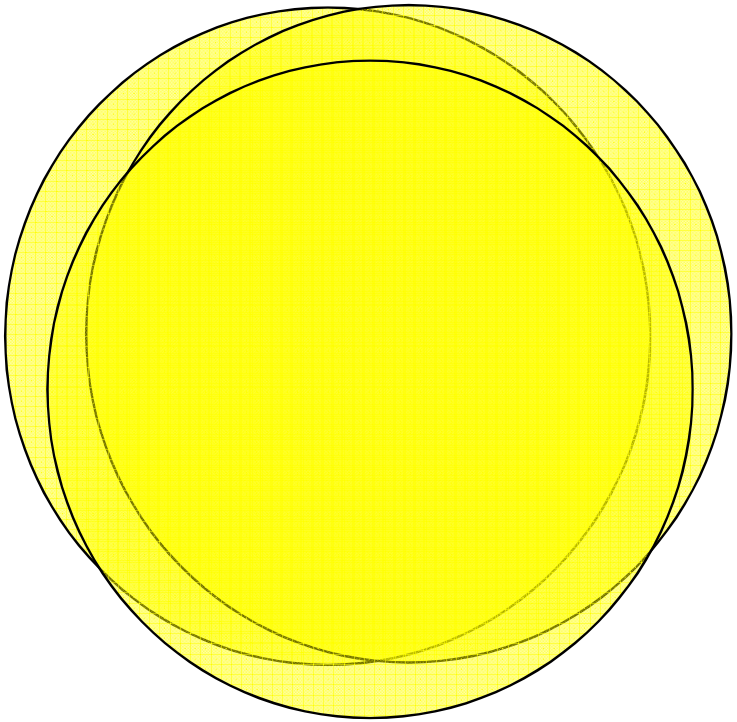
Noone DG et al., Lancet, 2018

Nephrotic Syndrome
A Disease of the Podocyte

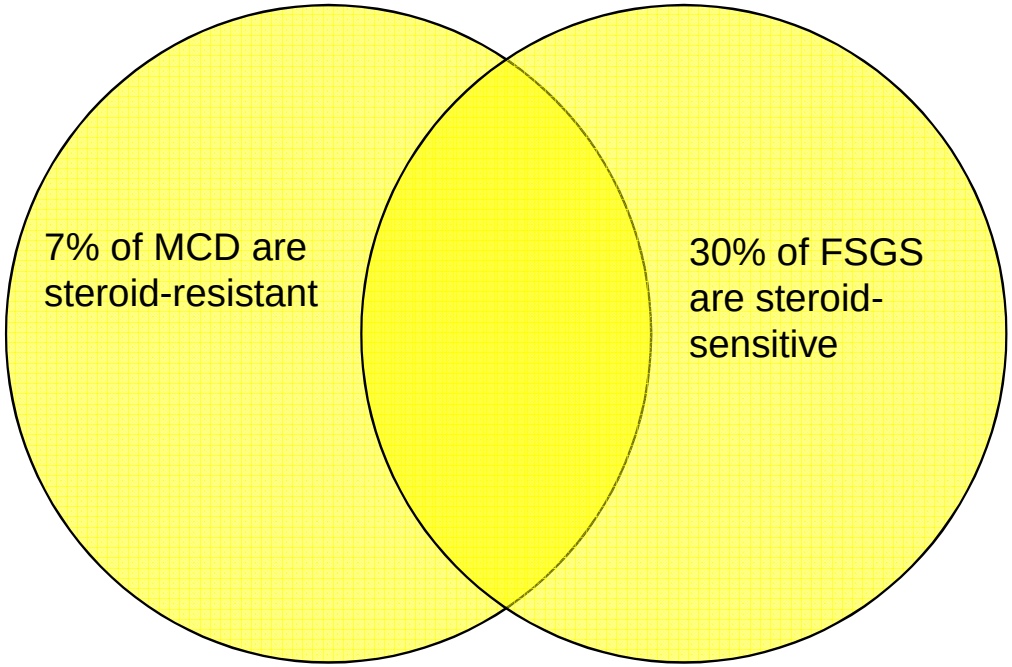


Courtesy of Thomas Benzing, Cologne

Idiopathic nephrotic syndrome ≠ MCD ≠ SSNS



SRNS ≠ FSGS



Primary Therapy

Treatment targets

symptomatic

- efficient
- no (little)side effects
- no relapse
- good prognosis

immunosuppressive

Proteinuria

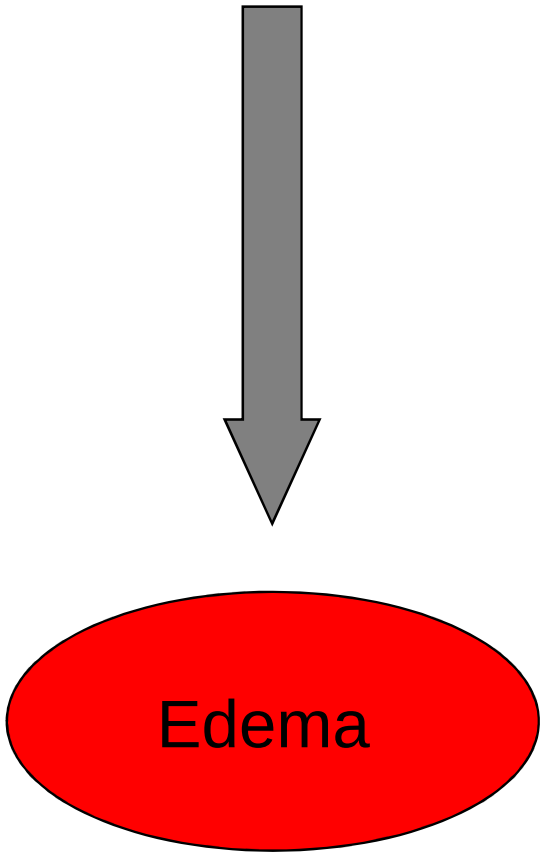
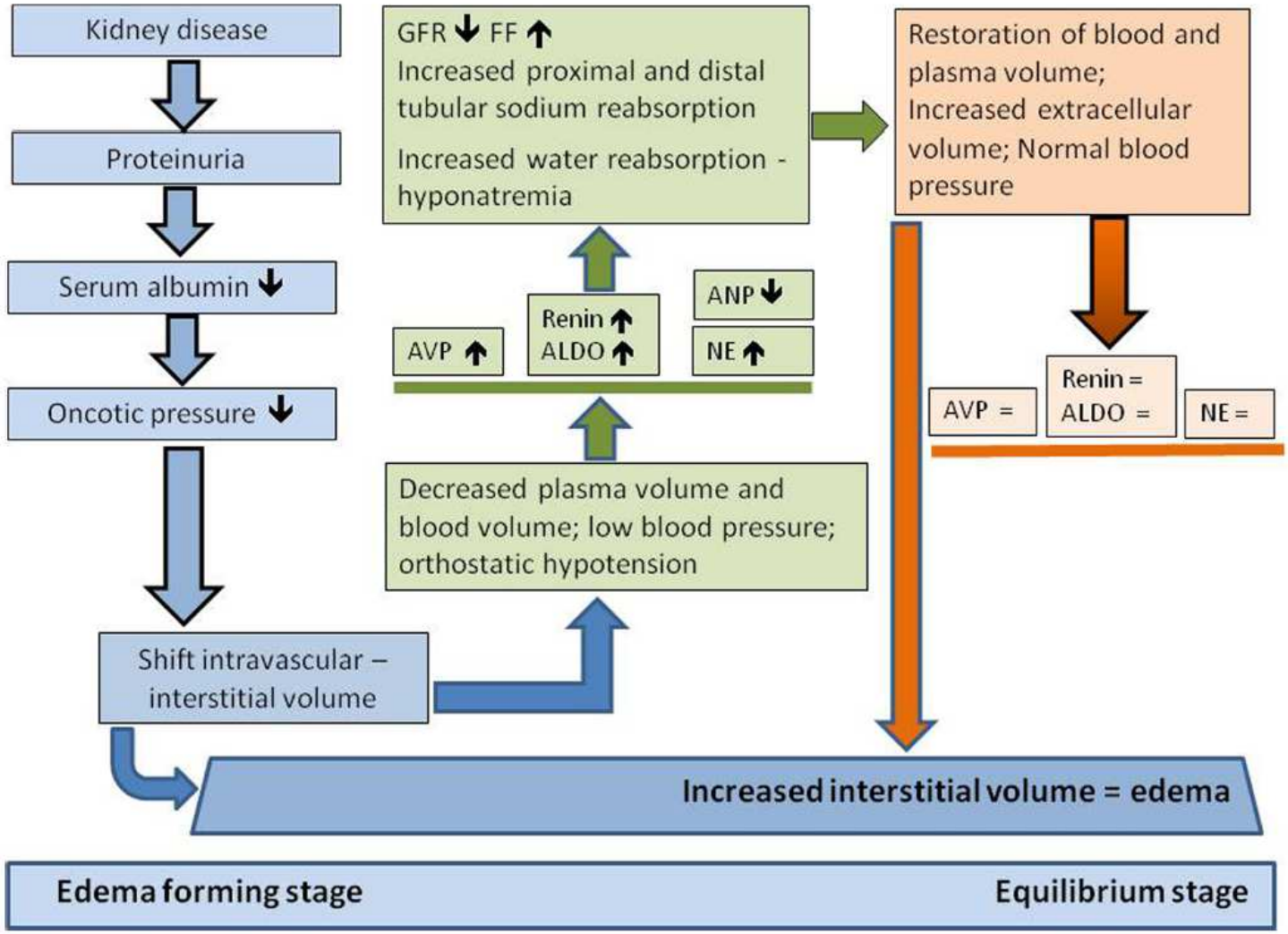
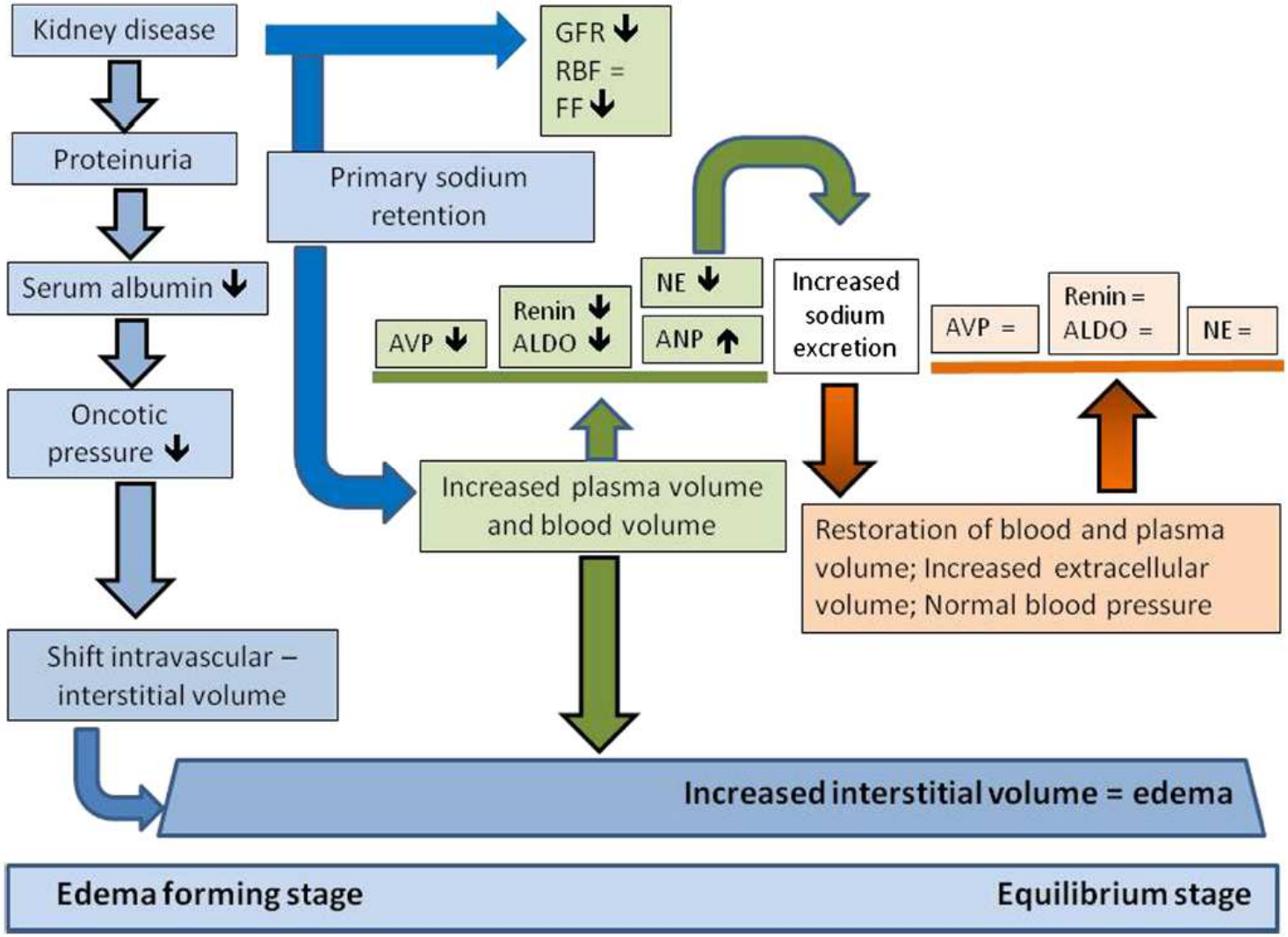


Fig. 1 The "Underfilling" theory of sodium retention in the nephrotic syndrome. *AVP* Arginine vasopressin, *ALDO* aldosterone, *ANP* atrial natriuretic peptide, *NE* norepinephrine, *GFR* glomerular filtration rate, *FF* filtration fraction. Reproduced with permission [3]



Cadnapaphornchai MA et al., Pediatr Nephrol, 2014

Fig. 3 The "Overfilling" theory of sodium retention in the nephrotic syndrome. Reproduced with permission [3]



Cadnapaphornchai MA et al., Pediatr Nephrol, 2014

Where are we?
Underfill or Overfill?

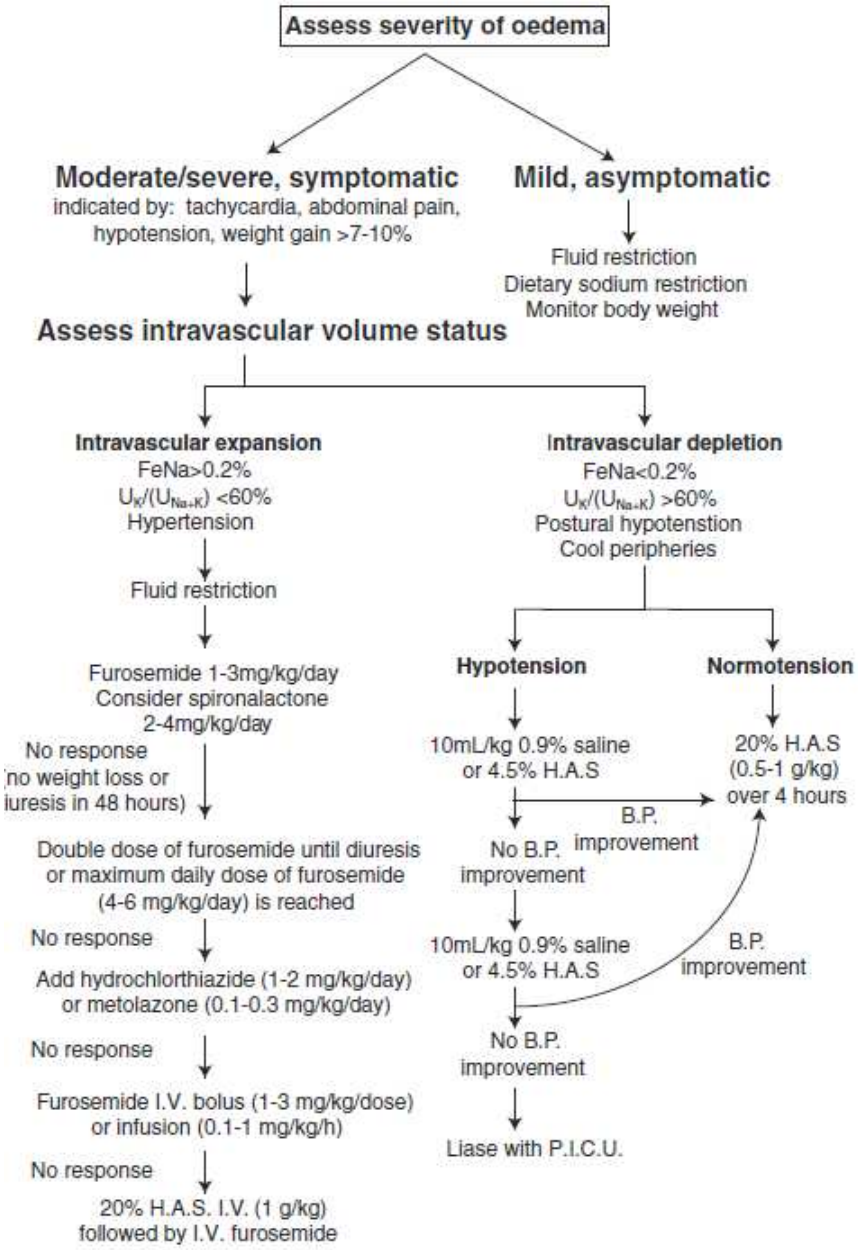
- FE_{Na}
- Tubular sodium/potassium-exchange

- Signs of intravascular hypovolemia
  - renin↑/ aldosterone↑
  - urine-sodium <10 mmol
  - FE_{Na} <0,2%
  - $(U_K)/(U_K + U_{Na})$ >60%

Table 1 Factors which help to differentiate overfill and underfill edema in nephrotic syndrome[a]

Factors	Overfill	Underfill
GFR <50 % of normal	+	–
GFR >75 % of normal	–	+
Serum albumin >2 g/dL	+	–
Serum albumin <2 g/dL	–	+
Minimal change histology	–	+
Hypertension	+	–
Postural hypotension	–	+

Kapur G et al., CJASN, 2009
Vande Walle JG et al., JASN, 1999
Vande Walle JG et al., Pediatr Nephrol, 2001
Cadnapaphornchai MA et al., Pediatr Nephrol, 2014



McCaffrey J et al., Pediatr Nephrol, 2015

Treatment of edema (increased total body water and –sodium)

- low sodium diet (<2 mmol/kg x d)
- (lymphatic drainage)

- **fluid restriction**
- **diuretics**

CAVE
in hypovolemia

- albumine 20% 2-5 ml/kg for (2-)4 h i.v.
  - 30-60 min thereafter 1-2 mg furosemide i.v.

Only indicated in treatment resistant, life threatening edema

CAVE
hypervolemia
(hypertension, pulmonary edema)

- (Hemofiltration)

Edema - Diuretics

- Furosemide
  - high proteine binding
    - NS: low serum albumine binding → short THL
    - NS: high tubular albumine binding→ reduced efficacy

  NS: higher doses: 2-5(-10) mg/kd x d

  CAVE ototoxicity due to high peak levels

  - administration every 6 h → maintainant infusion
  - combination with thiazide (1-2 mg/kg x d)

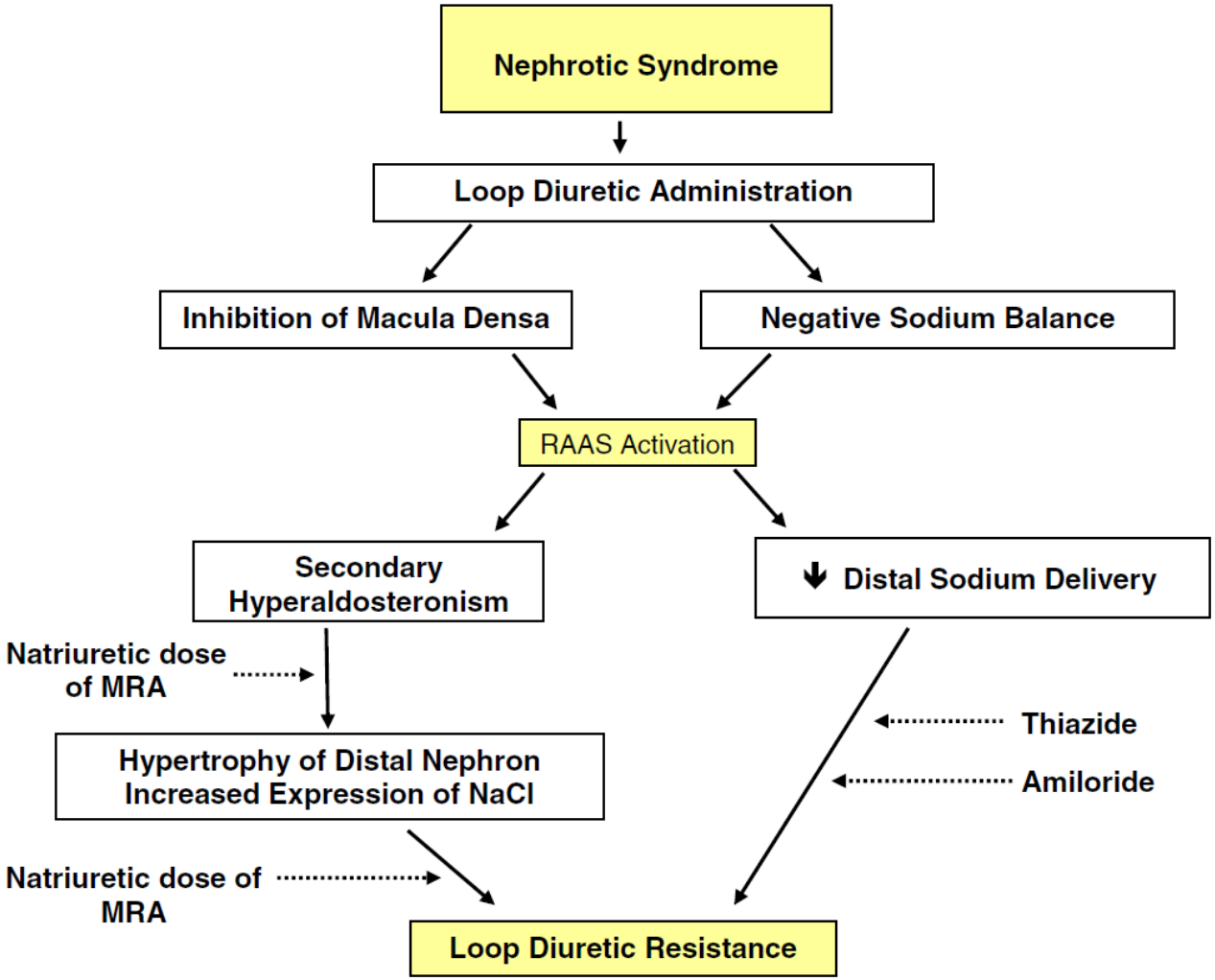
  CAVE hypokalemia

- Amiloride
  - blocks ENaC
  - combination

    (z.B. Diaphal® 40 mg Furosemide/ 5 mg Amiloride)
  - off licence in children

Deschenes G et al., Arch Pediatr, 2004

Mechanisms of Loop Diuretic Resistance in Nephrotic Syndrome



Cadnapaphornchai MA et al., Pediatr Nephrol, 2014

Nutrition – acute phase

- low sodium (<1-2 mmol/kg x d)
- proteine intake 100-140% of RDA
- avoid saturated fatty acids (hyperlipidemia)

- in high-dose glucocorticoid therapy
  - low intake of carbohydrates
  - low intake of fat

Important complications

- Hypovolemia (low oncotic pressure)

- Immune deficiency (altered cellular/humoral immunity, disturbances of the complement system)

- Risk of thromboembolic disease (imbalance of coagulation factors (high molecular weight procoagulants such as factor V and VIII ↑, low molecular weight anticoagulants such as antithrombin ↓; reactive thrombocytosis and platelet dysfunction (PCAP deficiency); hemoconcentration)

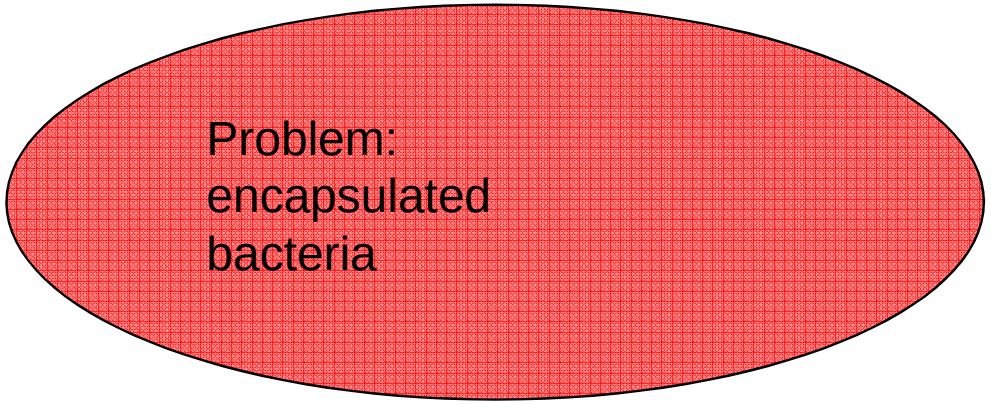
- Hypothyroidism (e.g. due to loss of thyroxine-binding globulin)

- Dyslipidemia
  (increased hepatic synthesis; reduced hepatic cholesterol uptake; altered metabolism)

Infections

- Sides of infection
  - cellulitis, pneumonia < 10 years, UTI > 10 years, peritonitis, (sepsis, osteomyelitis)
- Cause
  - IgG↓↓
  - abnormal T/B-cell-function
  - complement disturbancies,…

  + immunosuppressive therapy



- bacterial
  - *S. pneumoniae, Staphylococcus, HiB*,…

    (peritonitis, cellulitis,….)
- viral
  - Varicella-zoster virus, influenza virus….

Krensky AM et al., American Journal of Diseases of Children, 1982
McCaffrey et al., Pediatr Nephrol, 2015

Prophylaxis of infections

- Antibacterial prophylaxis controversial
  - Cave: resistancies
  - 110 children need to be treated for 1 year to avoid one episode of pneumococcal infection (McIntyre P et al., J Peadiatr Child Health, 1998)

- **Pneumococcal vaccination!**
- **Influenca vaccination!** (inactivated vaccine)

- VZV-exposure
  - Vaccinated?
  - Titer? (uncertain in proteinuria)
  - Passive varicella vaccination (within 4 (up to 10) days)
  - (Val)Aciclovir

Live vaccine in nephrotic syndrome?

Table I. Inclusion criteria for patients with nephrotic syndrome

1. Patients with nephrotic syndrome, aged ≥1 y
2. Negative or borderline antibody titer against 1 or more of measles, rubella, varicella, and mumps
3. Current treatment with 1 or 2 immunosuppressive agents (CsA, Tac, MMF, or MZR)
4. Normal cellular immunity
   $CD4^+$ cells ≥500/mm^3*
   Normal lymphocyte blast transformation by phytohemagglutinin (stimulation index ≥101.6)†
5. Serum IgG level‡ ≥300 mg/dL§
6. Recovery of normal B-cell count in patient with a history of rituximab treatment
7. No steroid use or prednisolone <1 mg/kg/d or <2 mg/kg/2 d
8. Trough levels of Tac¶ <10 ng/mL
9. Trough levels of CsA** <100 ng/mL
10. Remission of nephrotic syndrome for >6 mo
11. Difficulty discontinuing immunosuppressive agents due to relapse of nephrotic syndrome
12. Written informed consent obtained from patients or families

CsA, cyclosporine; *MMF*, mycophenolate mofetil; *MZR*, mizoribine; *Tac*, tacrolimus.
*Cutoff value was adapted from the Centers for Disease Control and Prevention recommendation,[21] which shows the CD4 lymphocyte counts under no evidence of immunosuppression.
†Cutoff value provided by the manufacturer.
‡Serum IgG level assessed as described previously.[22]
§Cutoff value determined as described previously,[23] which shows a 95% range of IgG level of patients aged 1 year.
The criteria in ‡ and § were established in July 2013,when we encountered a renal transplant recipient with chickenpox caused by a varicella vaccine strain, as indicated by her low cellular and humoral immunity (CD4 cell count of 511/mm^3, PHA stimulation index of 91.1, and serum IgG level of 208 mg/dL).
¶Tac level assessed as described previously.[24]
**The method of assessing CsA level was described by Morelle et al.[25].

Table IV. Seroconversion rates after the initial vaccination in this study

Variables	Measles	Rubella	Varicella	Mumps (Total)	Mumps (Torii strain)	Mumps (Hoshino strain)
Vaccinations, n	23	19	42	20	10	10
Seropositivity, n (%)	22 (95.7)	19 (100)	26 (61.9)	8 (40.0)	4 (40.0)	4 (40.0)
Vaccine failure, n (%)						
Borderline (±)	1 (4.3)	0 (0.0)	8 (19.0)	5 (25.0)	1 (10.0)	4 (40.0)
Negative (–)	0 (0.0)	0 (0.0)	8 (19.0)	7 (35.0)	5 (50.0)	2 (20.0)
Antibody titers after vaccination						
Mean ± SD	36.7 ± 72.6	29.8 ± 23.3	8.9 ± 11.9	3.5 ± 3.5	3.5 ± 4.4	3.6 ± 2.6
Median (range)	15.6 (3.2-329.0)	23.1 (4.6-80.2)	5.6 (<2.0-58.1)	3.5 (<2.0-11.2)	1.8 (<2.0-11.2)	3.6 (<2.0-8.1)

Table VI. Preservation of antibody 1 year after vaccination in seropositive patients

Antibody titer 2 mo after vaccination	Measles		Rubella		Varicella		Mumps	
	Patients, n	Positive antibody 1 y after vaccination, n (%)	Patients, n	Positive antibody 1 y after vaccination, n (%)	Patients, n	Positive antibody 1 y after vaccination, n (%)	Patients, n	Positive antibody 1 y after vaccination, n (%)
<10.0	3	1 (33.3)	3	2 (66.7)	17	11 (64.7)	7	1 (14.3)
≥10.0	15	14 (93.3)	14	14 (100.0)	13	12 (92.3)	3	1 (33.3)
Total	18	15 (83.3)	17	16 (94.1)	30	23 (76.7)	10	2 (20.0)

Kamei K et al., J Pediatr, 2018

Thrombembolic disease

- Second leading cause of mortality
- Venous and arterial
- Deep vein thrombosis, **sinus vein thrombosis**

Prophylaxis

- Mobilisation
- Screening for thrombophilia?
- low molecular weight heparin
  - e.g. enoxaparin: 1 mg/kg s.c. in 1 ED
  - AntiXa-level: 0.2-0.4 U/ml
  - CAVE:
    - not in anuria
    - when GFR≤ 40 ml/min x 1,73m^2 → AntiXa-level every 48 h
- no indication for
  - unfractinated heparine, cumarines

Antihypertensive Therapy

Target: Blood pressure < 90. percentile for age, sex and height

- **A**CE-Inhibitor/ **A**T1-Receptor antagonists
  - antiproteinuric, renoprotective
  - glomerular perfusion↓
    - Cave: Hypovolemia

- **D**iuretics (furosemide, thiazide, amiloride)
- **B**etablocker
- **C**alciumantagonists

Summary of Non-Immunosuppressive Therapy of Nephrotic Syndrome

Table 2 Summary of treatment strategies in different phases of idiopathic nephrotic syndrome

Treatment strategies	Nephrotic state	Remission under immunosuppressive therapy	Remission after discontinuation of immunosuppressive therapy
Prophylactic antibiotics	✗	✗	✗
Pneumococcal vaccine	✗	✗ (ideally)	✓
Influenza vaccine	✗	✗	✓
Varicella vaccine	✗	✗	✓
Thromboprophylaxis	✗	✗	✗
Consideration of fluid restriction/ diuretics/ albumin infusions	✓	✗	✗

McCaffrey J et al., Pediatr Nephrol, 2015

Published protocols for steroid treatment (prednisone or prednisolone) for initial presentation of idiopathic nephrotic syndrome

	International Study of Kidney Disease in Children (ISKDC)[61]	Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN)[2]	Haute Autorité de Santé (France)[62]	Italian Society for Pediatric Nephrology (SINePe)[63]	KDIGO Glomerulonephritis Guidelines[1]	Hospital for Sick Children (Toronto, Canada)[11]
Year of publication	1970	1988	2008	2017	2012	2016
Initial presentation						
Initial dose and duration	60 mg/m² per day × 4 weeks	60 mg/m² per day × 6 weeks (maximUm dose 80 mg)	60 mg/m² per day × 4 weeks (maximum dose 60 mg)	60 mg/m² per day × 6 weeks (maximum 60 mg in single or 2 divided doses)	60 mg/m² per day or 2 mg/kg per day × 4–6 weeks (maximum 60 mg)	60 mg/m² per day × 6 weeks (maximum 60 mg in single morning dose)
Subsequent dose and tapering	4 weeks of 40 mg/m² per alternate day but given on 3 consecutive days out of a week	40 mg/m² per alternate day × 6 weeks (maximum dose 60 mg)	60 mg/m² per alternate day × 8 weeks (maximum 60 mg) followed by a 15 mg/m² per alternate day × 15 days and continue to wean. In addition, 3 methylprednisolone pulses if proteinuria persists after 1 month of daily prednisone therapy	40 mg/m² per alternate day × 6 weeks (single dose; maximum 40 mg) without tapering	40 mg/m² per alternate day or 1·5 mg/kg/alternate day (maximum 40 mg) × 6–8 weeks (at least 12 weeks) and continued for 2–5 months with tapering	40 mg/m² per alternate day × 6 weeks (maximum 60 mg), 30 mg/m² per alternate day × 8 days (maximum 30 mg), 20 mg/m² per alternate day × 8 days (maximum 20 mg), 10 mg/m² per alternate day × 12 days (maximum 10 mg)

Noone DG et al., Lancet, 2018

Variability of Diagnostic Criteria and Treatment of Idiopathic Nephrotic Syndrome across European Countries

No.	Centers	Drug	Max. daily dose (mg/day)	Duration of daily dose (weeks)	Total duration (weeks)	Cumulative dose of steroids (mg/m^2)	Tapering	IVMP test
01	Spain—2	Prednisone	80	4	8	2240	No	Yes
02	UK—1	Prednisolone	60	4	8	2240	No	No
03	Russia—2	Prednisone	60	6	12	2500	Yes	No
04	Croatia—3	Prednisolone	80	4	14	2660	Yes	No
05	Croatia—2	Prednisolone	80	4	10	2760	No	No
06	Croatia—1	Prednisone	60	4	13	2780	Yes	Yes
07	Serbia—1	Prednisolone	60	4	8	2800	No	Yes
08	Spain—1	Prednisone	80	4	17	3000	Yes	Yes
09	Belgium—1	Prednisone	60	4	16	3010	Yes	Yes
10	Lithuania	Prednisone	60	4	12	3150	Yes	Yes
11	Turkey—4	Prednisolone	60	4	16	3185	Yes	No
12	Turkey—1	Prednisolone	60	4	20	3325	Yes	Yes
13	Denmark[a]	Prednisolone	80	6	12	3360	No	No
14	Germany[a]	Prednisone	60	6	12	3360	No	Yes
15	Italy—1	Prednisone	70	6	12	3360	Yes	Yes
16	Italy—3	Prednisone	60	6	12	3360	Yes	Yes
17	UK—2	Prednisolone	80	6	12	3360	No	No
18	Netherlands	Prednisolone	80	6	12	3360	No	No
19	Serbia—2	Prednisolone	80	6	12	3360	No	Yes
20	Belgium—2	Prednisolone	80	6	16	3555	Yes	Yes
21	Norway	Prednisolone	60	4	16	3570	Yes	Yes
22	Turkey—3	Prednisolone	60	4	12	3570	Yes	No
23	Turkey—2	Prednisone	60	4	18	3900	Yes	Yes
24	France[a]	Prednisone	60	4	18	3990	Yes	Yes
25	Italy—2	Prednisone	75	4	18	3990	Yes	Yes
26	Russia—1	Prednisone	60	6	18	3990	Yes	Yes
27	Greece	Prednisone	60	4	18	3990	Yes	Yes
28	Russia—3	Prednisolone	60	6	18	4095	Yes	Yes
29	Poland	Prednisone	60	4	24	4245	Yes	Yes

Centers and countries have been classified according to the cumulative dose of steroids

IVMP intravenous methylprednisolone

[a] Nationwide protocol adopted by all the centers

Deschênes G et al., Eur J Pediatr, 2017

Molecular basis of glucocorticoid efficacy

Genomic effects:

- Expression of proinflammatory and immune stimulating genes ↓
- Expression of antiinflammatory and immunosuppressive genes ↑

Non genomic effects:

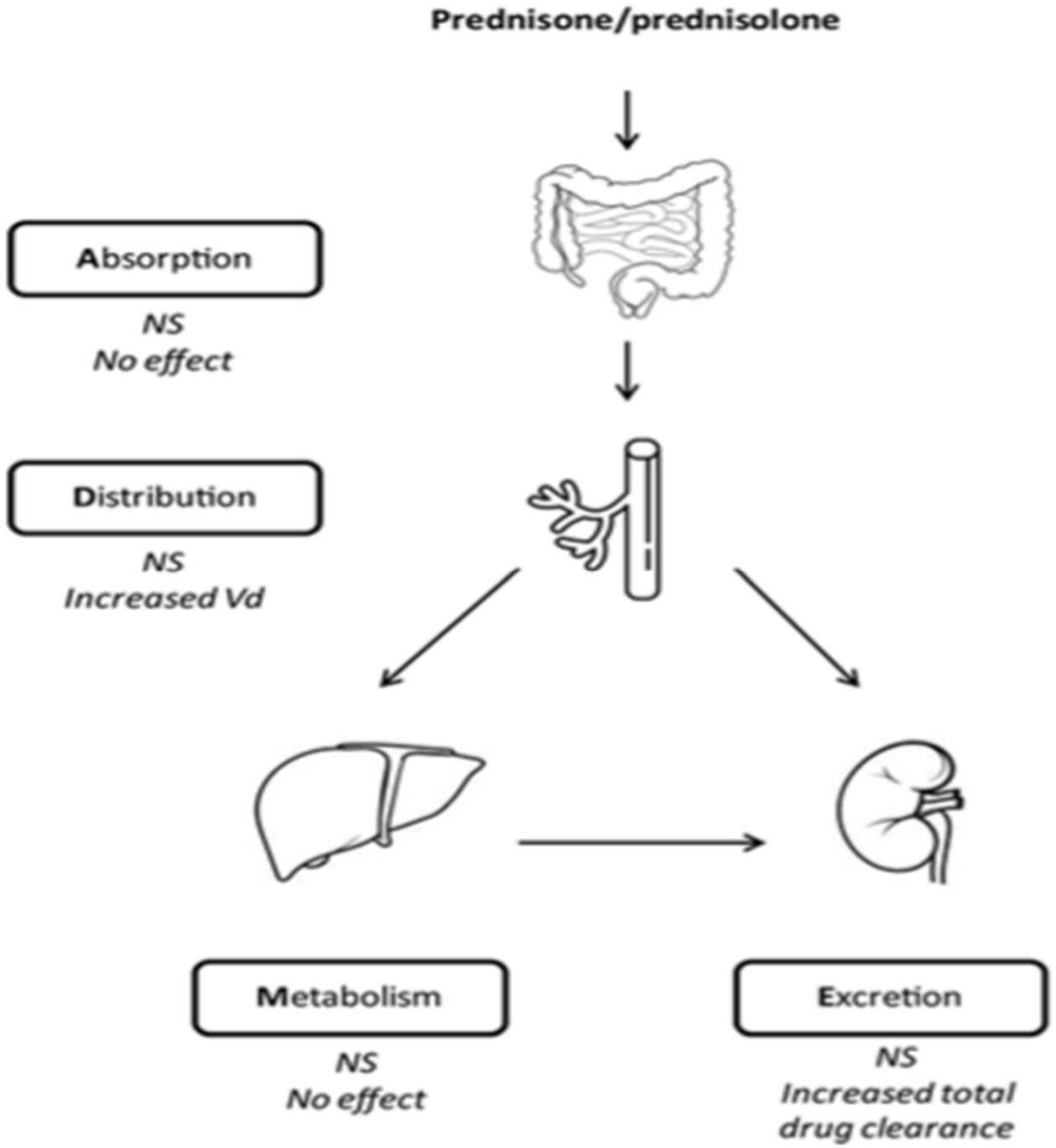
- Stabilization of membranes
- Regulation of membraneous ion channels

In nephrotic syndrome:

- Podocyte protection (repair mechanisms including Nephrin production)
- Stabilization of actin filaments in podocytes
- Decrease of apoptosis

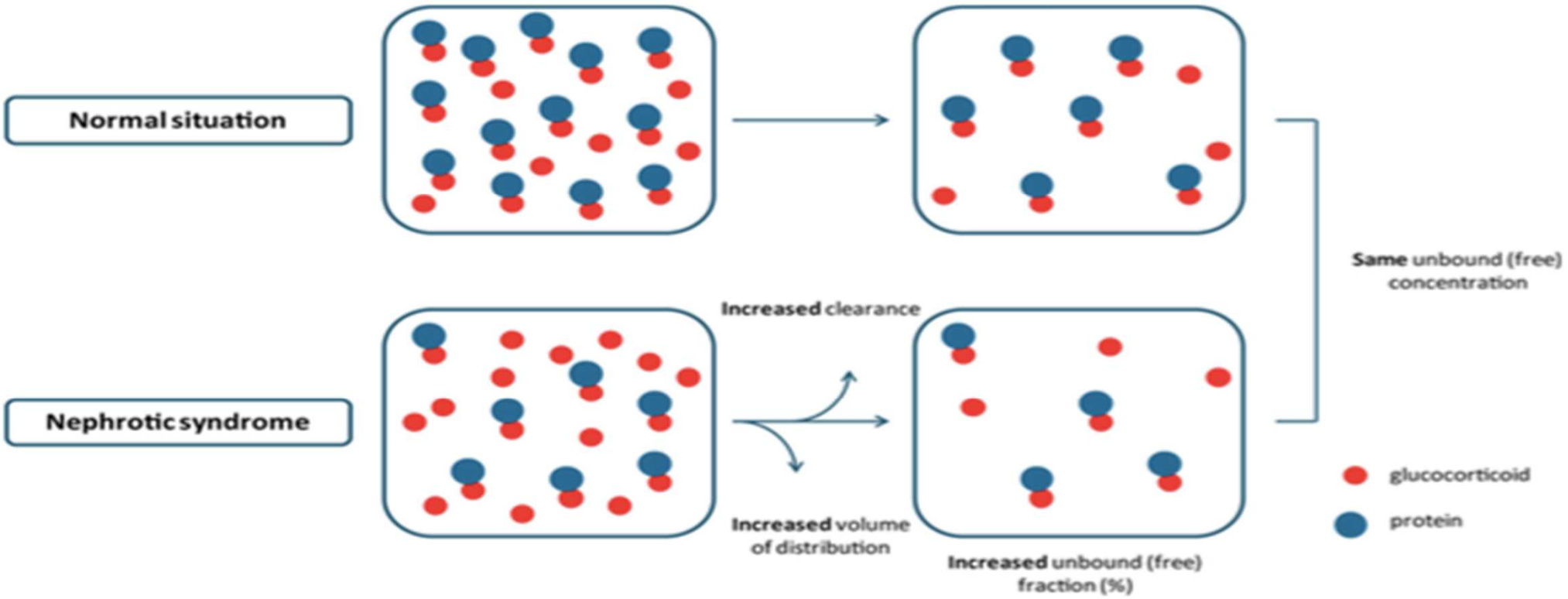
Schijvens AM et al., Pediatr Nephrology, 2019

ADME of steroids in nephrotic syndrome



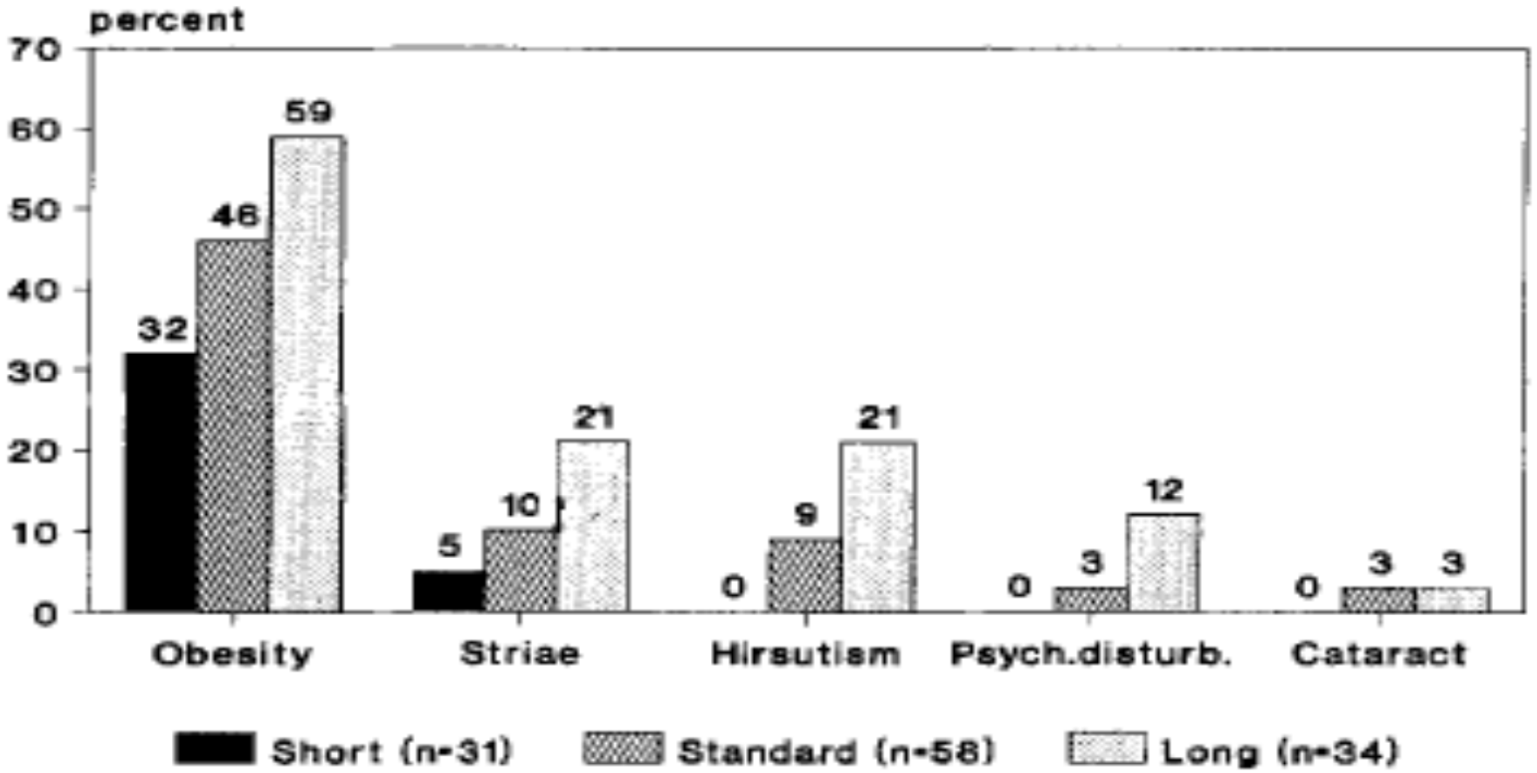
Schijvens AM et al., Pediatr Nephrology, 2019

Free glucocorticoid concentration remains unchanged in nephrotic syndrome



Schijvens AM et al., Pediatr Nephrology, 2019

APN-Study 6Wks/6Wks *versus* 4Wks/4Wks (ISKDC)



Ehrich and Brodehl, Eur J Pediatr, 1993

CLINICAL RESEARCH www.jasn.org

Extending Prednisolone Treatment Does Not Reduce Relapses in Childhood Nephrotic Syndrome

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

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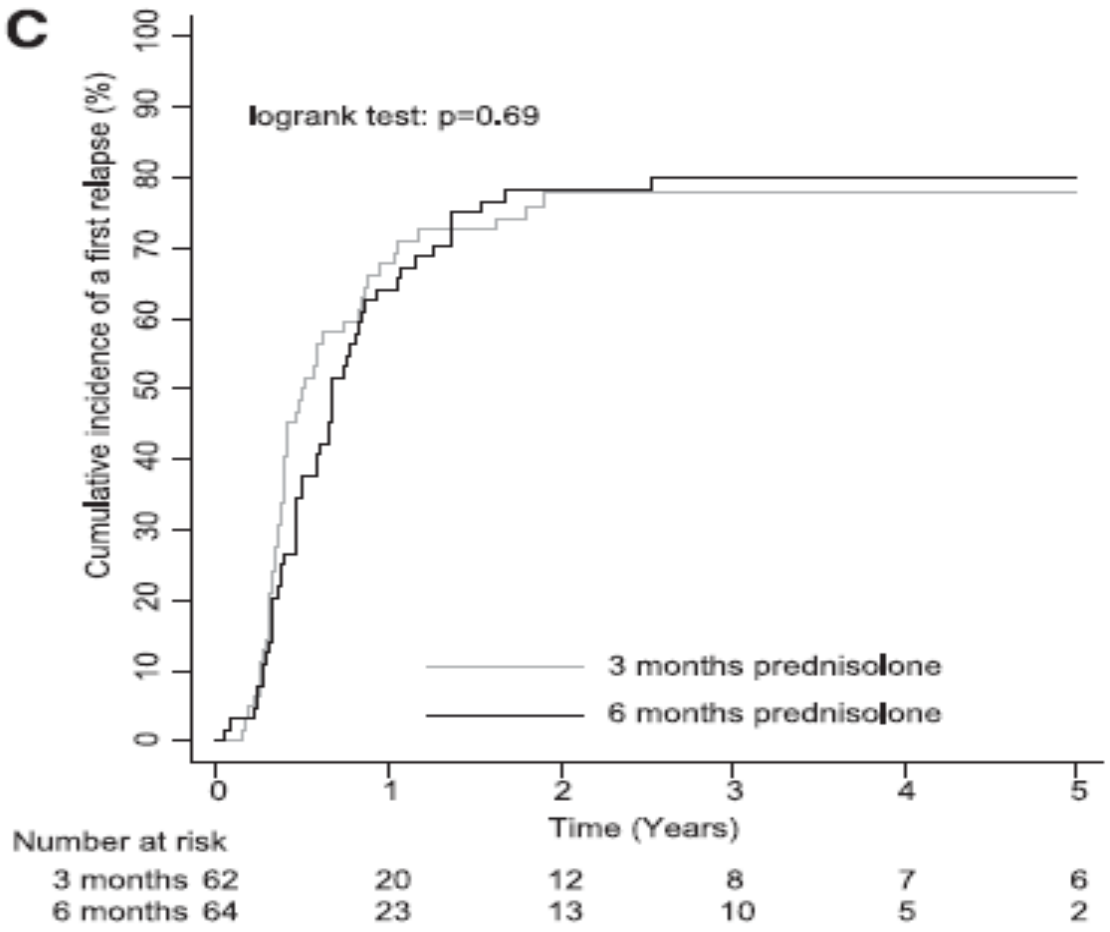
week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15-24	cumulative dose
3 months prednisolone	60 D		60 D				40 AD						placebo AD			3360
6 months prednisolone	60 D		50 D				40 AD				20 AD				10 AD	3320-3710

remission: switch to trial medication

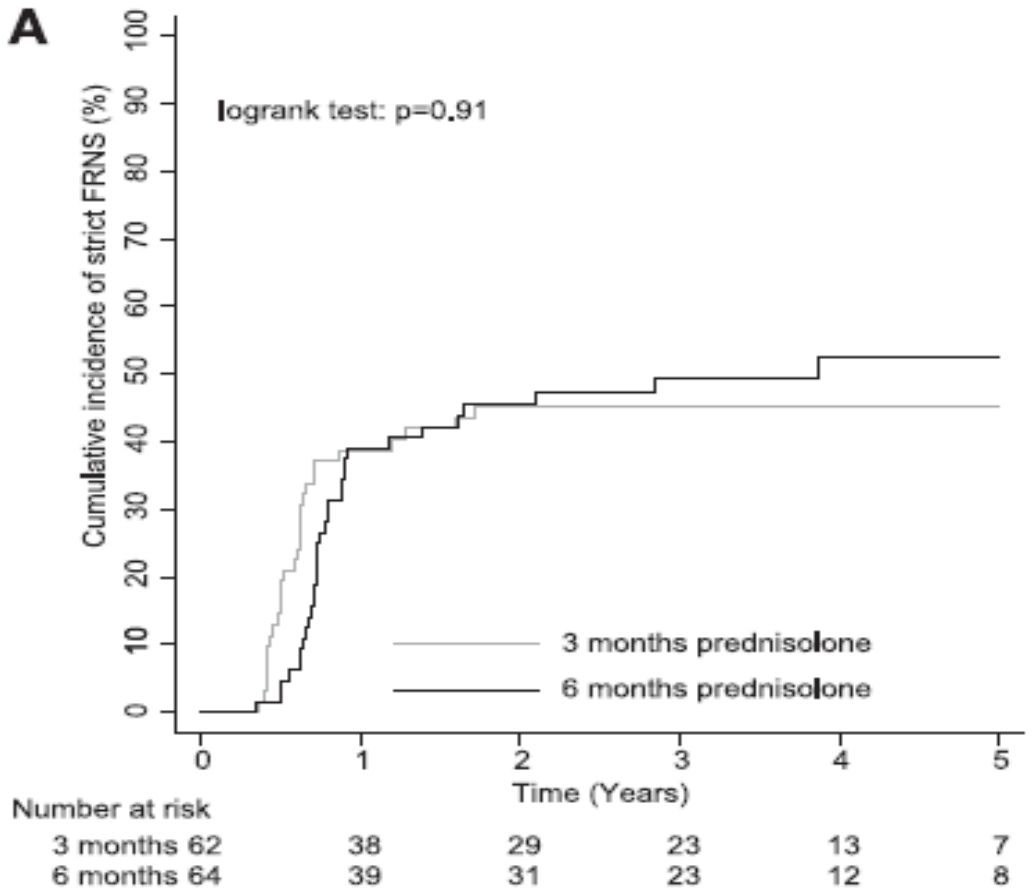
Teeninga et al., CJASN, 2013

Length of glucocorticoid treatment – no effect on relapse rate



Teeninga et al., CJASN, 2013

Length of glucocorticoid treatment – no effect on risk of FRNS



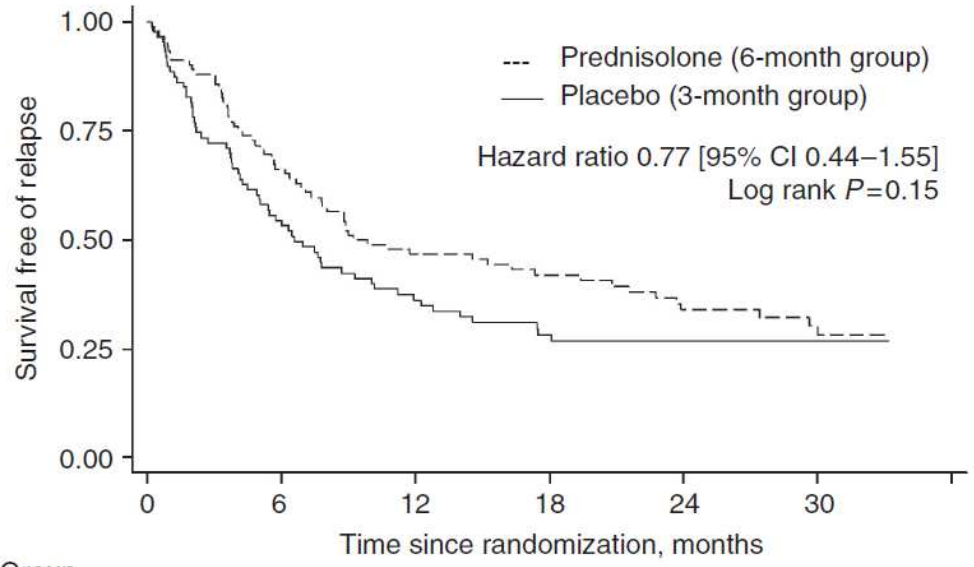
Teeninga et al., CJASN, 2013

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

Aditi Sinha[1], Abhijeet Saha[2], Manish Kumar[3], Sonia Sharma[1], Kamran Afzal[4], Amarjeet Mehta[5], Mani Kalaivani[6], Pankaj Hari[1] and Arvind Bagga[1]

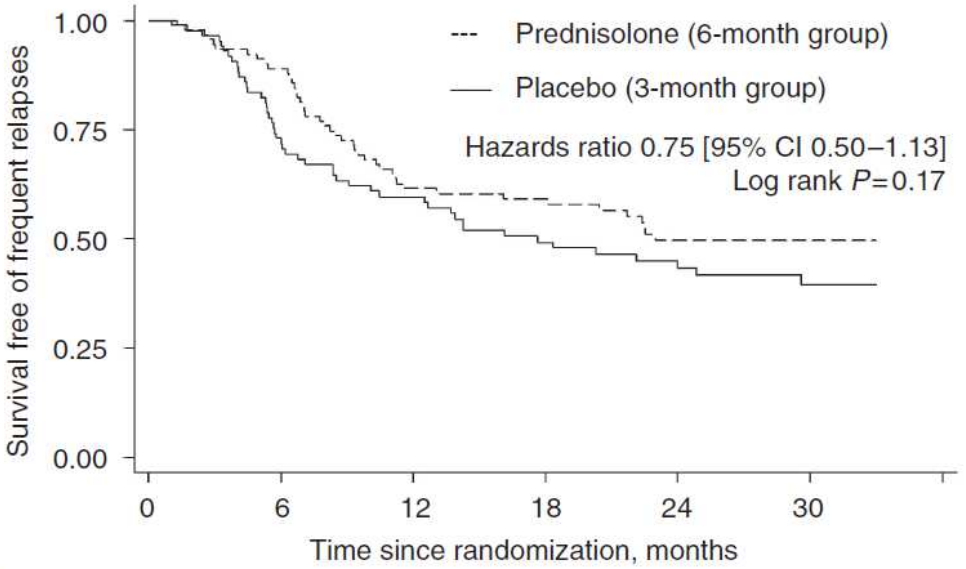
[1]Division of Nephrology, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India; [2]Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Ram Manohar Lohia Hospital, New Delhi, India; [3]Department of Pediatrics, Chacha Nehru Bal Chikitsalaya, New Delhi, India; [4]Department of Pediatrics, Jawaharlal Nehru Medical College, Aligarh, India; [5]Department of Pediatrics, Sawai Man Singh Medical College, Jaipur, India and [6]Department of Biostatistics, All India Institute of Medical Sciences, New Delhi, India

Kidney International, 2015



Group							
6-Month	92	61 (31)	43 (18)	35 (4)	25 (6)	15 (2)	cum. 3.530 mg/m^2
3-Month	88	47 (39)	30 (15)	20 (6)	17 (1)	12 (0)	cum. 2.792 mg/m^2

Figure 2 | Relapse-free survival. The proportions with sustained remission in patients treated for 6 months and 3 months were similar at 12 months (46.7 vs. 36.2%), at 24 months (34.1 vs. 26.8%), and at last follow-up (28.4 vs. 26.8%). The panel shows the number of patients at risk (number relapsed) at each time point.



Group						
6-Month	92	81 (10)	56 (25)	47 (2)	35 (7)	22 (0)
3-Month	88	62 (24)	49 (10)	36 (8)	30 (3)	18 (3)

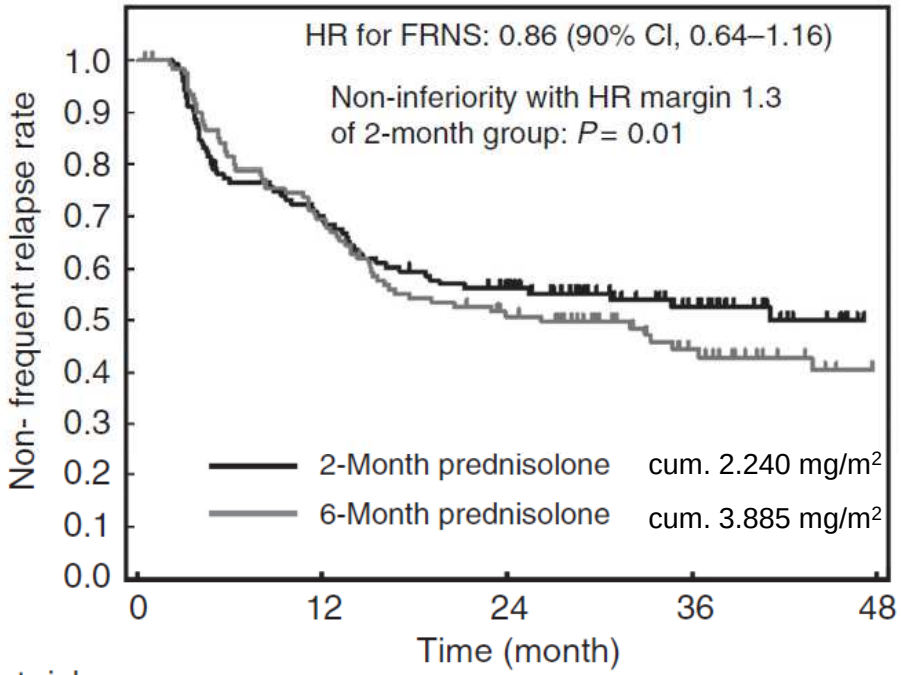
Figure 3 | Survival free of frequent relapses. Proportions of patients with frequent relapses in the 6-month and 3-month groups were 38.4 and 40.4% at 12 months, 50.4 and 56.5% at 24 months, and 50.4 and 60.4% at last follow-up. The panel shows the number of patients at risk (number with frequent relapses) at each time point.

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

Norishige Yoshikawa[1], Koichi Nakanishi[1], Mayumi Sako[2], Mari S. Oba[3], Rintaro Mori[4], Erika Ota[4], Kenji Ishikura[5], Hiroshi Hataya[5], Masataka Honda[5], Shuichi Ito[6], Yuko Shima[1], Hiroshi Kaito[7], Kandai Nozu[7], Hidefumi Nakamura[2], Takashi Igarashi[8], Yasuo Ohashi[9] and Kazumoto Iijima[7]; for the Japanese Study Group of Kidney Disease in Children[10]

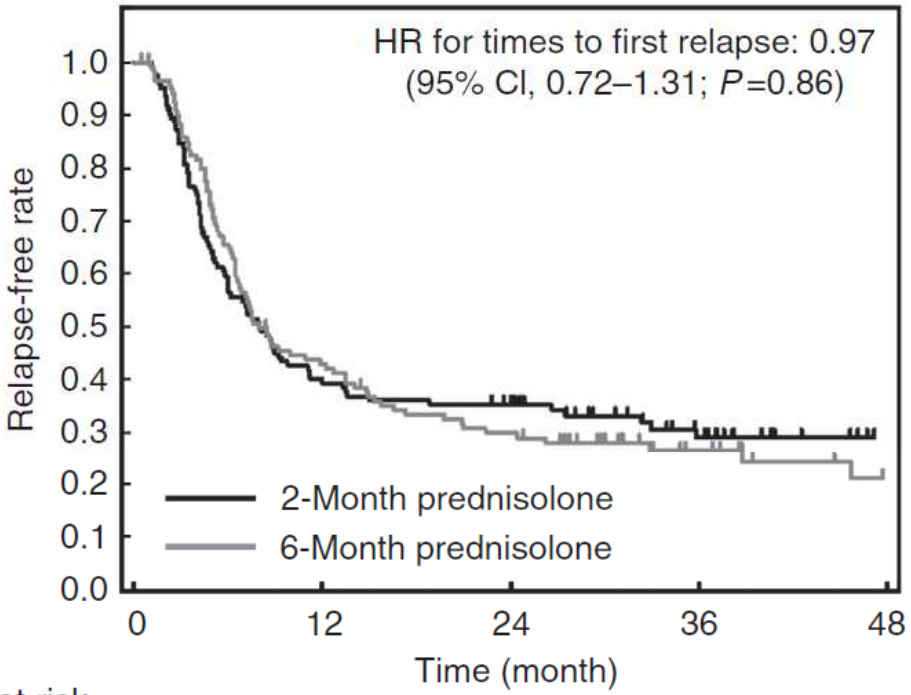
[1]Department of Pediatrics, Wakayama Medical University, Wakayama City, Japan; [2]Division for Clinical Trials, Clinical Research Center, National Center for Child Health and Development, Tokyo, Japan; [3]Department of Biostatistics and Epidemiology, Graduate School of Medicine, Yokohama City University, Yokohama, Japan; [4]Department of Health Policy, National Center for Child Health and Development, Tokyo, Japan; [5]Department of Nephrology, Tokyo Metropolitan Children's Medical Center, Tokyo, Japan; [6]Department of Nephrology and Rheumatology, National Center for Child Health and Development, Tokyo, Japan; [7]Department of Pediatrics, Kobe University Graduate School of Medicine, Kobe, Japan; [8]National Center for Child Health and Development, Tokyo, Japan and [9]Department of Biostatistics, School of Public Health, The University of Tokyo, Tokyo, Japan

Kidney International, 2015



Number at risk					
2-Month group	124	86	64	34	11
6-Month group	122	82	55	29	14

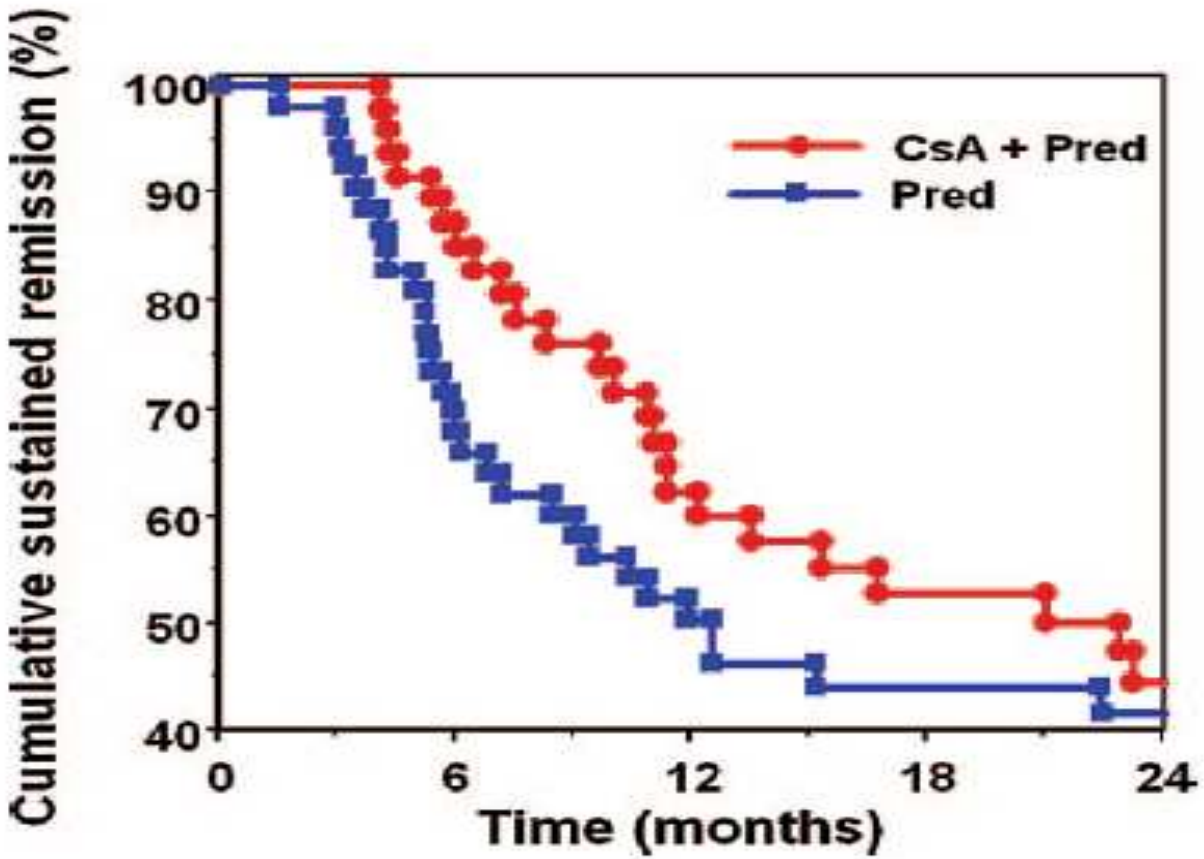
Figure 2 | Kaplan–Meier estimates of time to frequently relapsing nephrotic syndrome (FRNS). HR, hazard ratio.



Number at risk					
2-Month group	124	48	40	19	4
6-Month group	122	50	34	15	6

Figure 3 | Kaplan–Meier estimates of time to first relapse. HR, hazard ratio.

GPN-Study
6Wks/6Wks *versus* 6Wks/6Wks plus CsA



Hoyer and Brodehl, J Am Soc Nephrol, 2006

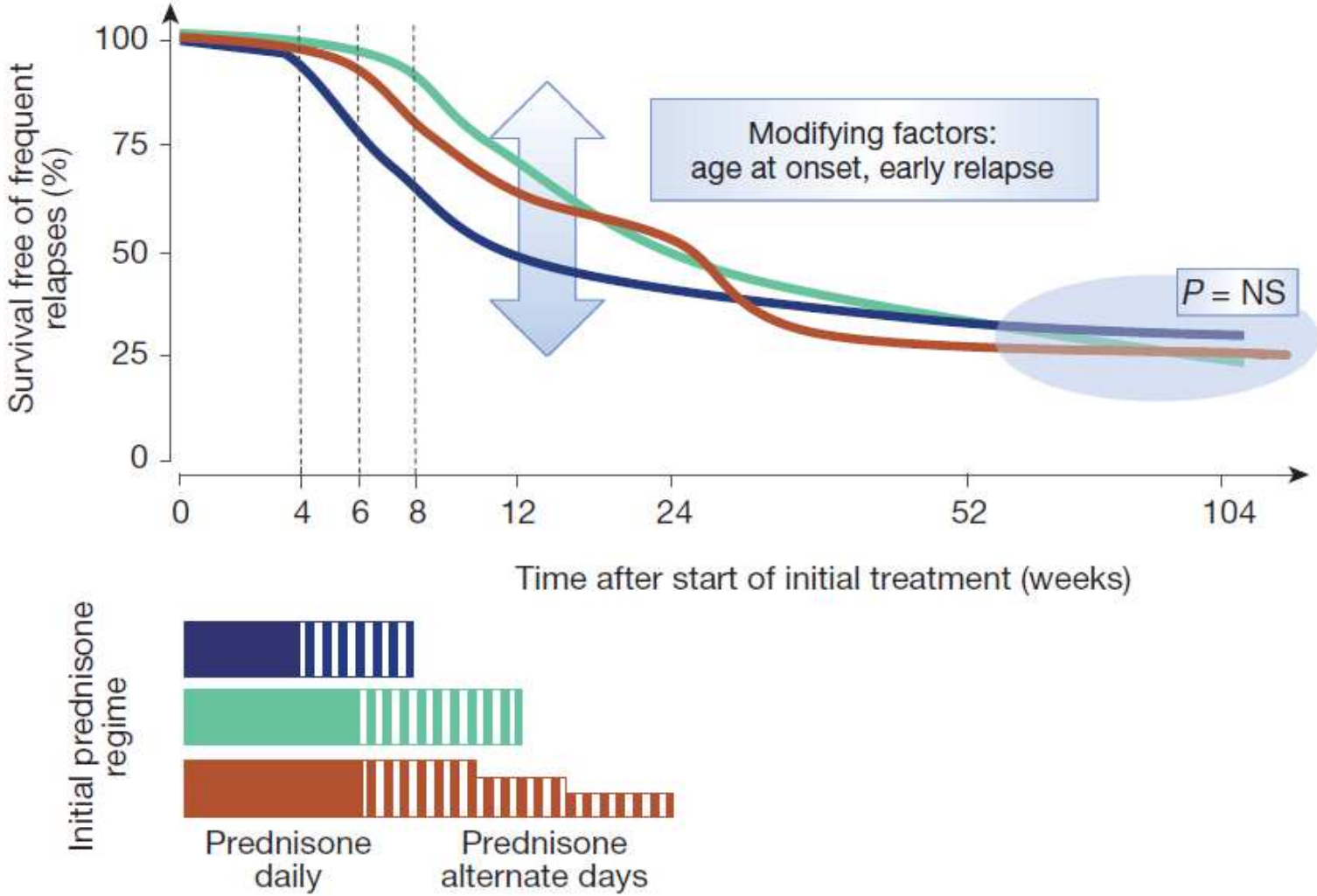


Figure 1 | Lack of effect of extending initial prednisone treatment on long-term freedom from frequent relapses. NS, not significant.

Hoyer PF, Kidney International, 2015

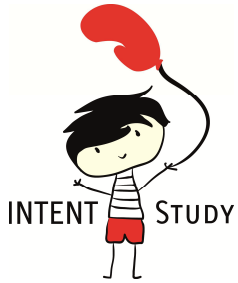
Findings

- Initial immunosuppressive therapy: Prednisone
- Problem: Prednisone associated side-effects
- Extension of initial glucocorticoid therapy has probably no impact on natural (long-term) course

Ehrich and Brodehl, 1993; Hoyer 2006, 2015

GPN
Gesellschaft für Pädiatrische Nephrologie

INTENT Study



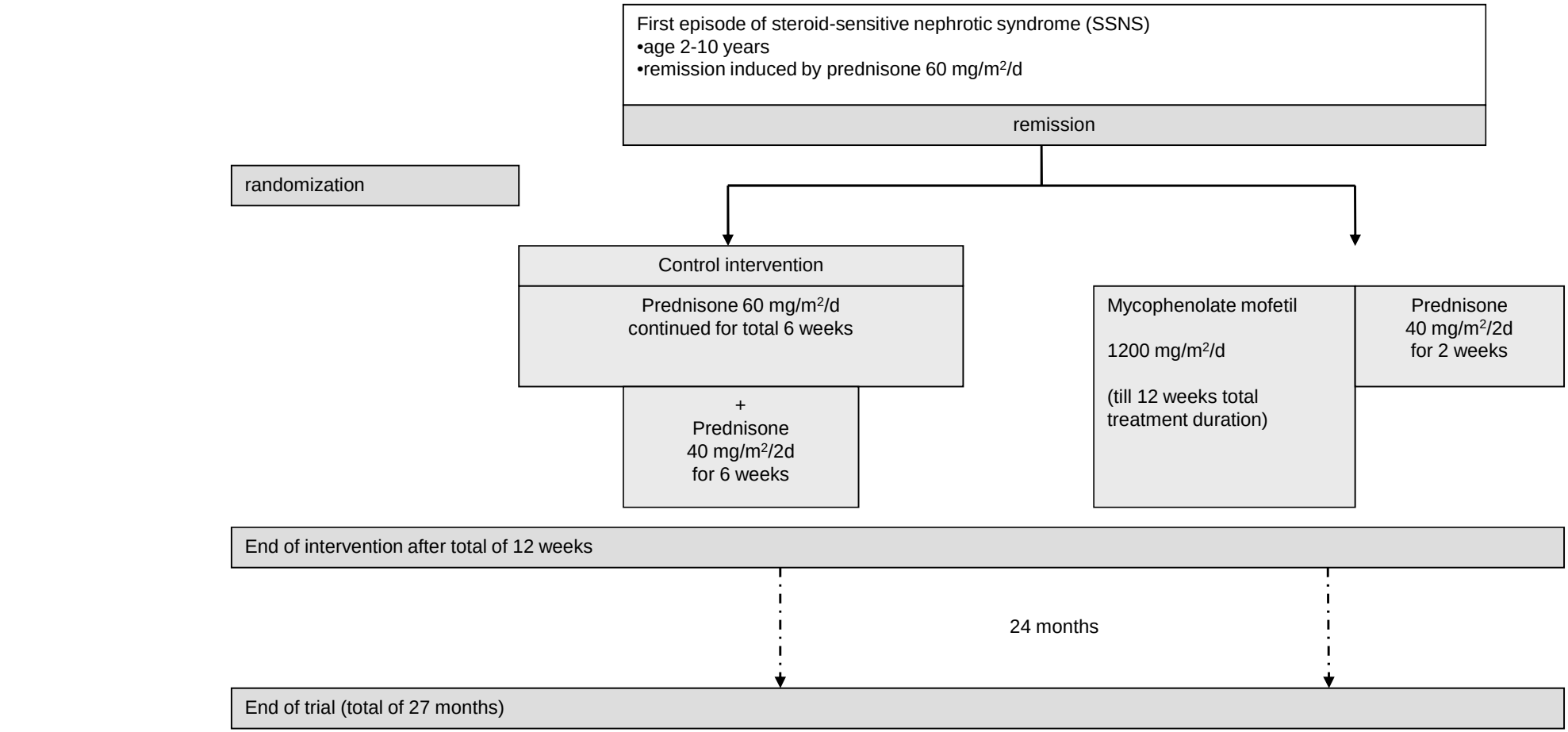
Initial treatment of idiopathic nephrotic syndrome in children with mycophenolate mofetil vs. prednisone: A randomized, controlled, multicenter trial

Bundesministerium
für Bildung
und Forschung

Protocol comittee

Jutta Gellermann, Uwe Querfeld	Berlin
Peter F. Hoyer	Essen
Dirk E. Müller-Wiefel, Markus Kemper	Hamburg
Dieter Haffner	Hannover
Burkhard Tönshoff	Heidelberg
Marcus R. Benz, Lutz T. Weber, Jörg Dötsch	Köln
Martin Konrad	Münster

Initial treatment of idiopathic nephrotic syndrome in children with mycophenolate mofetil vs. prednisone: A randomized, controlled, multicenter trial (INTENT Study) of GPN



Hypothesis

Initial therapy with Steroids and Mycophenolic Acid compared to standard therapy according to GPN shows

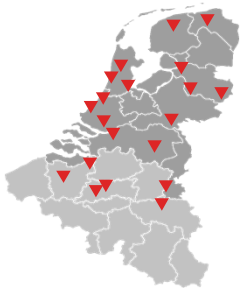
- less adverse events

- non-inferiority regarding maintenance of initial remissions within the first 24 months after onset

Prevention of relapses with levamisole as adjuvant therapy to corticosteroids in children with a first episode of idiopathic nephrotic syndrome (LEARNS).

International, multicentre, randomised, double blind, phase III, placebo-controlled clinical trial

The Netherlands: 15 centres
Belgium : 5 centres



Hypothesis

Combined treatment of children with a first episode of INS with steroids and levamisole will prevent relapses after the first episode of INS.

Primary objective

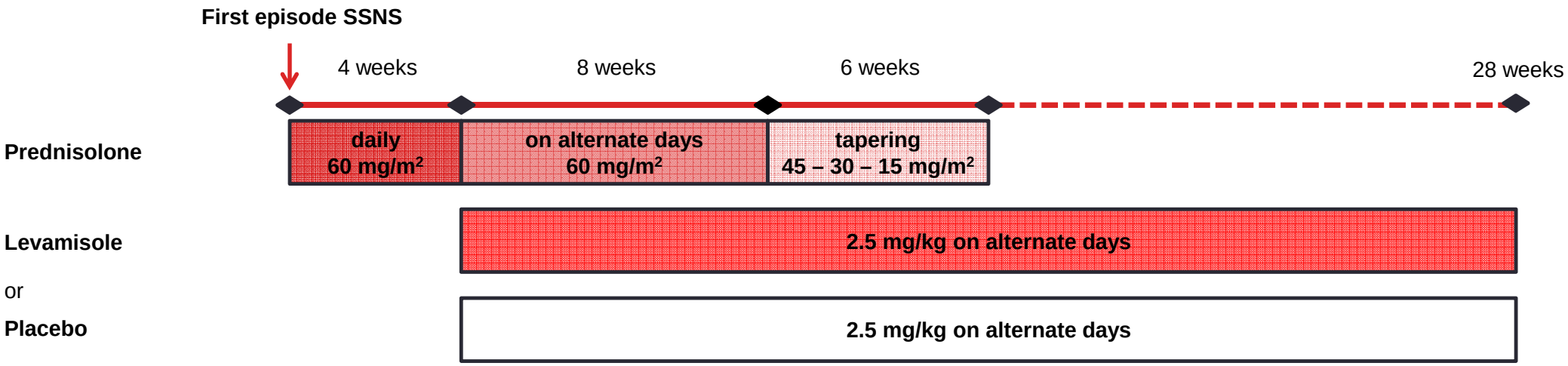
To investigate the efficacy and safety of additional levamisole in comparison with placebo of the first episode of SSNS in children (age 2-16 years) on the occurence of relapses <12 months.

Study treatment

Inclusion: Children (2-16 years) with a first episode of SSNS

Follow-up: 2 years after first presentation

Primary endpoint: Occurence of relapses at 1 year after first presentation



LEARNS learns@amsterdamumc.nl

Summary

- **Glucocorticoids are the fundament of treatment of idiopathic nephrotic syndrome in childhood.**

- **Primary response to steroids has prognostic significance.**

- **Nephrotic syndrome has significant morbidity (e.g. edema) and complications such as infections and thromboembolic events have to be regarded.**

- **Non-immunosuppressive therapy complies with individual needs.**

- **Overall prognosis of SSNS as for renal function is good. Most often, however, it has a relapsing course and patients´ life is filled with fear and sorrow.**

- **Intensity and length of primary glucocorticoid therapy has no impact on the natural course of the disease.**

- **Future studies investigate novel regimen of primary therapy, e.g. with reduced glucocorticoid exposure.**

ERKNet

The European Rare Kidney Disease Reference Network

Next webinar: Jun 04

” Monogenic Causes of Hypertension"

Rosa Vargas-Poussou, Paris (Necker), France.