Emma Kinderziekenhuis
Amsterdam UMC

Themadag Zeldzame Nierziekten
Nefrotisch Syndroom

Nefrotisch syndroom: Nieuwe Inzichten

A Bouts | 8 nov 2025

Nefrotisch syndroom

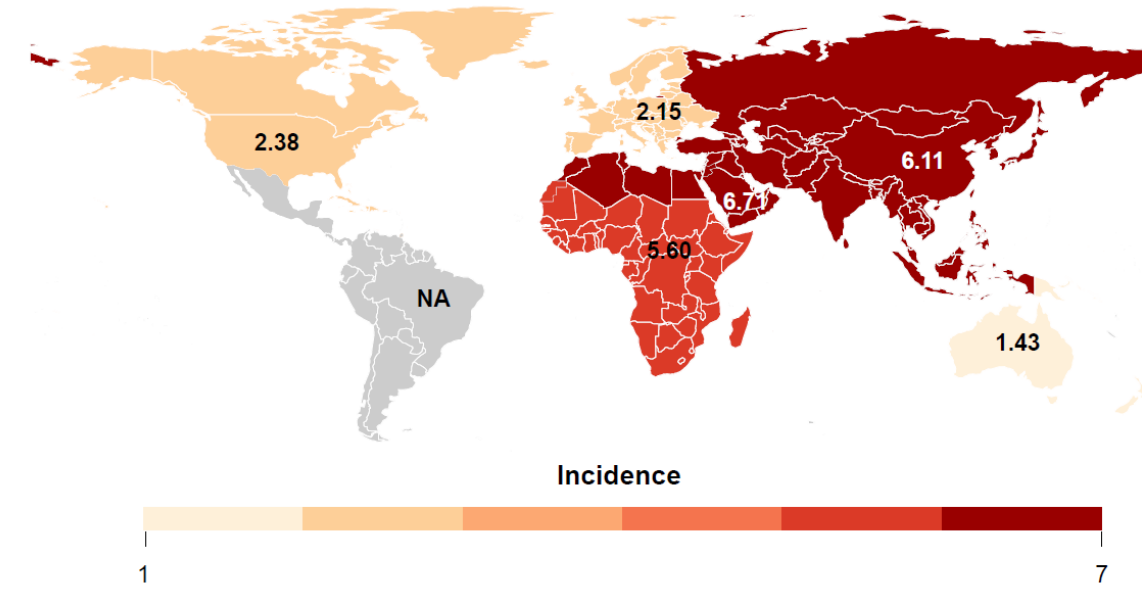
1. Vochtophopingen - Oedemen
2. Massaal eiwitverlies via urine – nefrotische range proteinurie
3. Verlaagd eiwit in bloed – hypoalbuminemie
4. Verhoogd vetgehalte in bloed - hypercholesterolemie

Incidence and Relapse of Idiopathic Nephrotic Syndrome: Meta-analysis

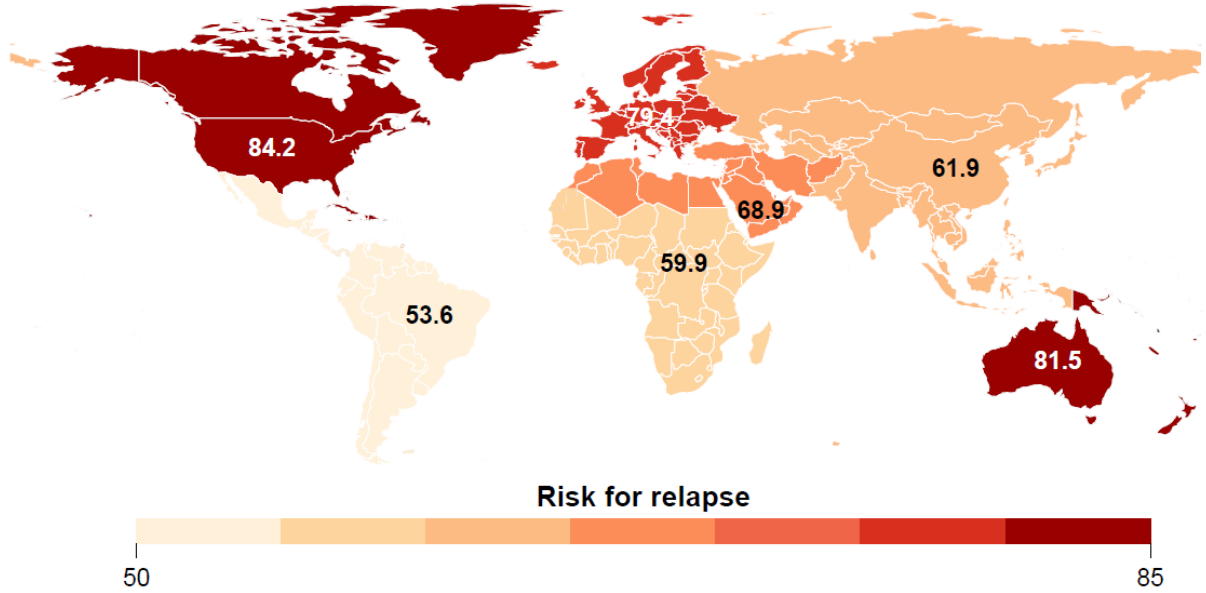
Floor Veltkamp, MD, Leonie R. Rensma, BSc, Antonia H. M. Bouts, MD, PhD, on behalf of the LEARNS consortium

In Nederland 40-50 kinderen met eerste presentatie NS

A. Incidence of INS per 100,000 children per year



B. Risk for relapse (%) of INS

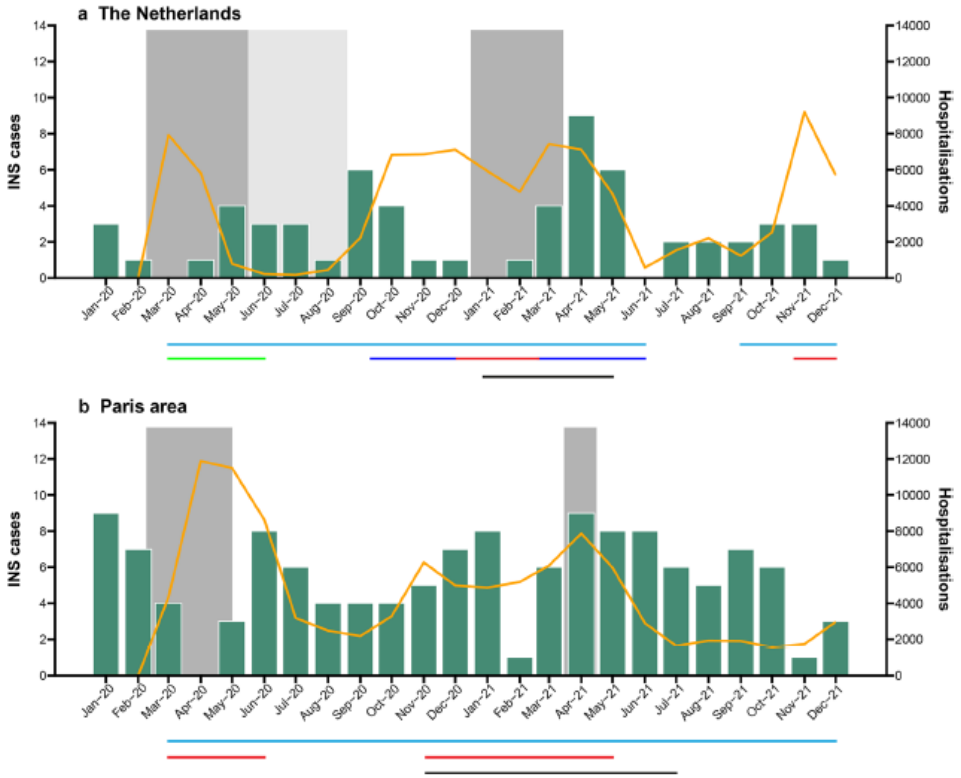


Incidentie = aantal nieuwe patiënten per jaar
Overall **incidentie** = **2.92** (95% PI 2.20–3.64)
Hoger in niets-Westerse landen
Stabiel over de tijd

Recidief = terugval
Overall recidief = **71.9%** (95% PI 38.8-95.5)
Hoger in Westerse landen
Daling (-21%) over de tijd

Veltkamp et al. Pediatrics 2021

COVID Pandemie



Pediatric Nephrology
https://doi.org/10.1007/s00467-023-06006-9

ORIGINAL ARTICLE

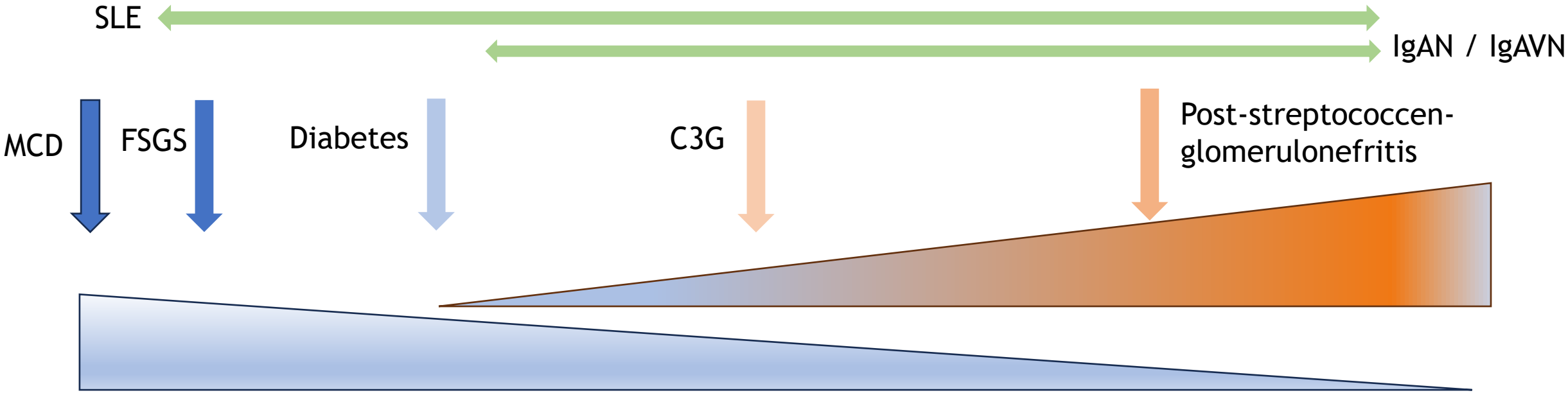
Incidence of idiopathic nephrotic syndrome during the Covid-19 pandemic in the Paris area (France) and in the Netherlands

Floor Veltkamp[1] · Victoire Thenot[2] · Carlijn Mussies[1] · Bas van Lieshout[1] · Hessel Peters-Sengers[3,4] · Jesper Kers[5,6,7] · Djera H. Khan[4] · Julien Hogan[2] · Sandrine Florquin[4] · Antonia H. M. Bouts[1] · Claire Dossier[2] on behalf of the NEPHROVIR network, the LEARNS consortium

- Tijdens lockdown minder presentaties kinderen met 1e episode nefrotisch syndroom
- Conclusie: afname infecties door lockdown maatregel waardoor minder nefrotisch syndroom.

Veltkamp et al. Pediatric Nephrology 2023

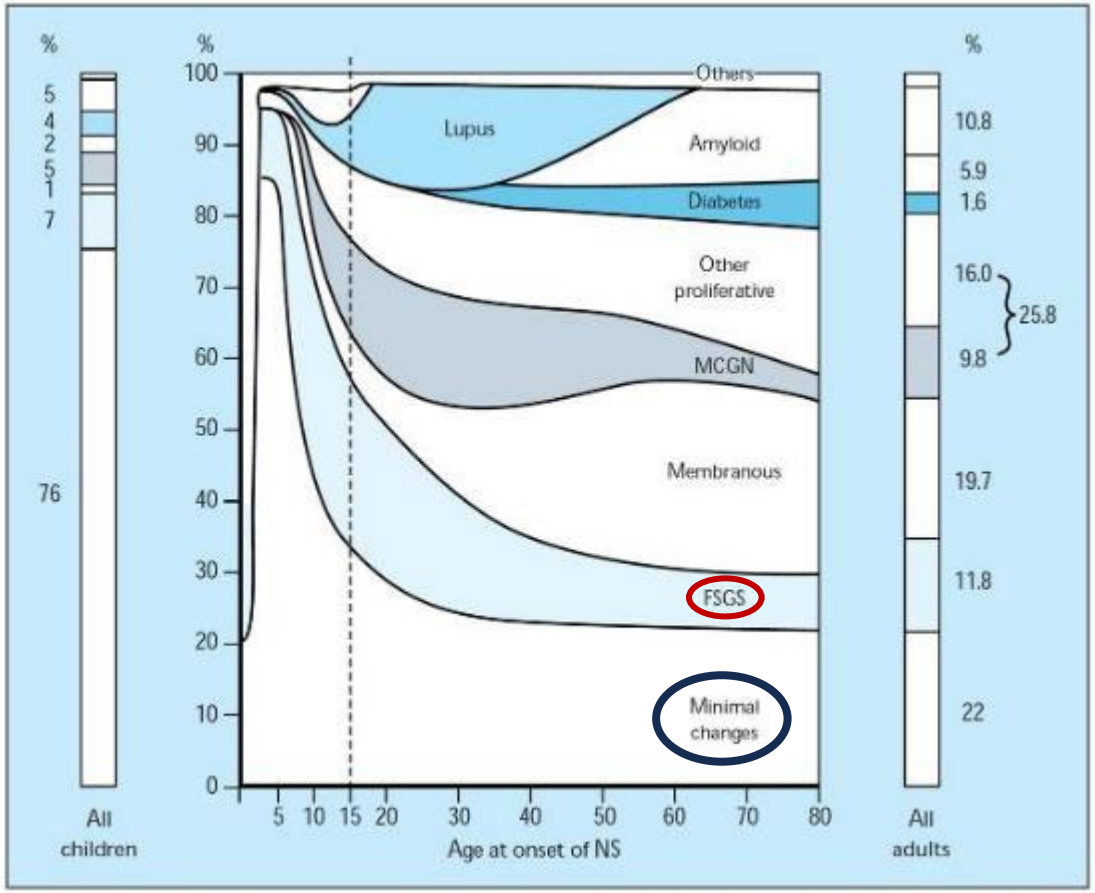
Nefrotisch of Nefritisch?



Nefrotisch syndroom
proteinurie > 200 mg/mmol
Hypoalbuminemie < 30 g/L
oedemen
hypercholesterolemie
ondervulling

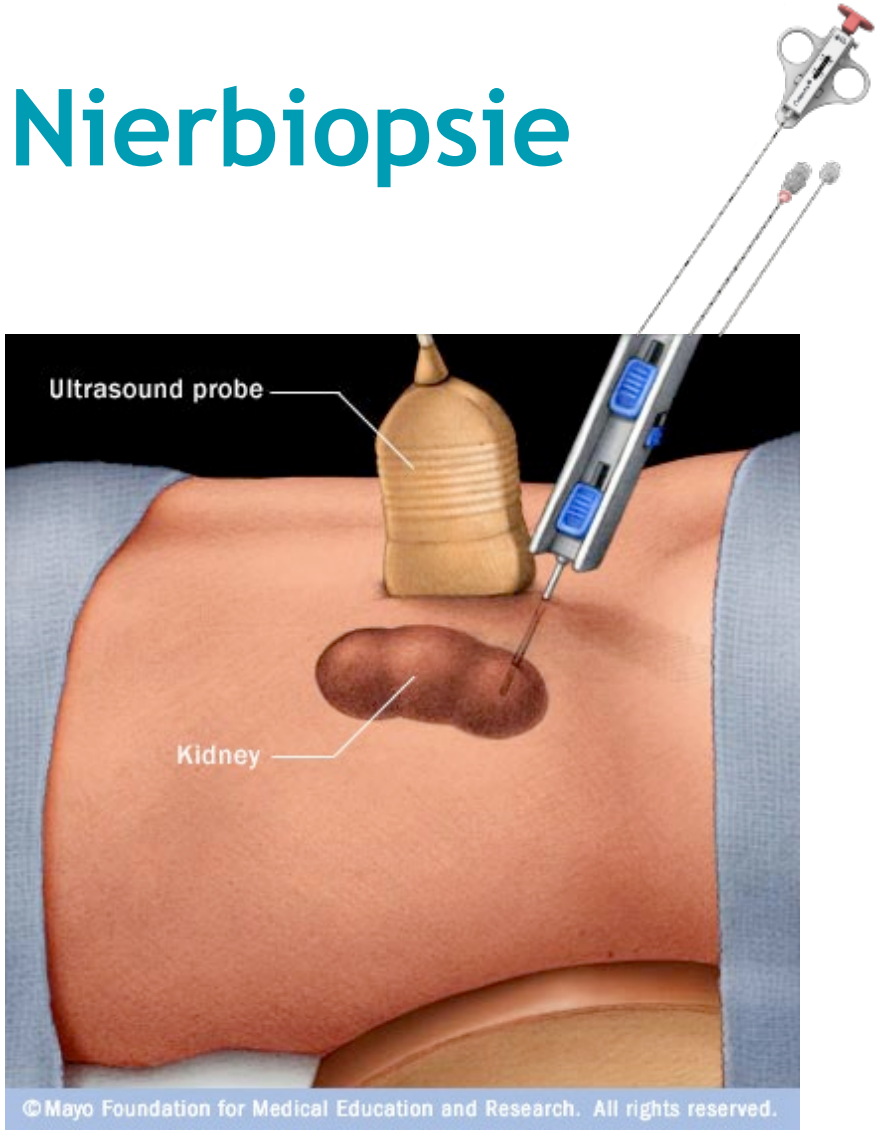
Nefritisch syndroom
Bloed in urine - hematurie
oedemen
Hoge bloeddruk - hypertensie
Weinig plassen

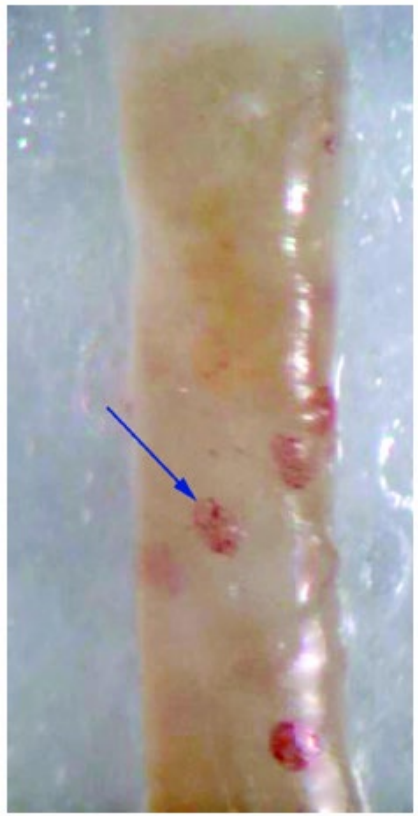
Oorzaken Nefrotisch Syndroom



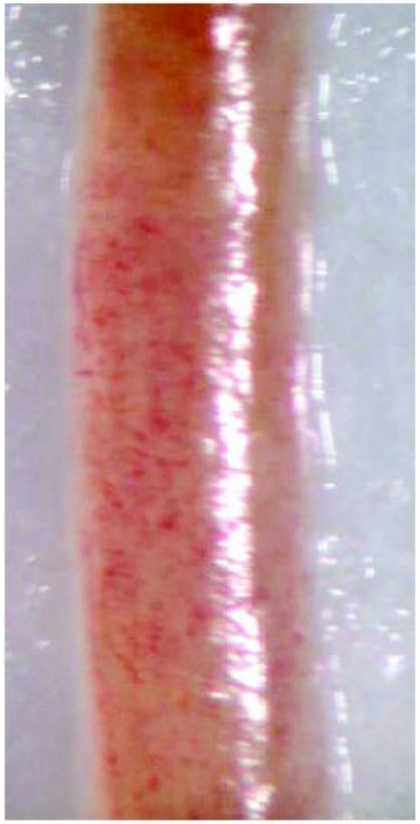
- Leeftijd < 3 maanden = congenitaal nefrotisch syndroom = genetisch
- Leeftijd 3 maanden – 1 jaar = infantiel nefrotisch syndroom
- >2 jaar = meestal minimal changes (MCD)
- > 12 jaar vaker FSGS (focale segmentale glomerulosclerose)
- MCD en FSGS diagnose wordt gesteld met Nierbiopt = histologische diagnose!

Nierbiopsie



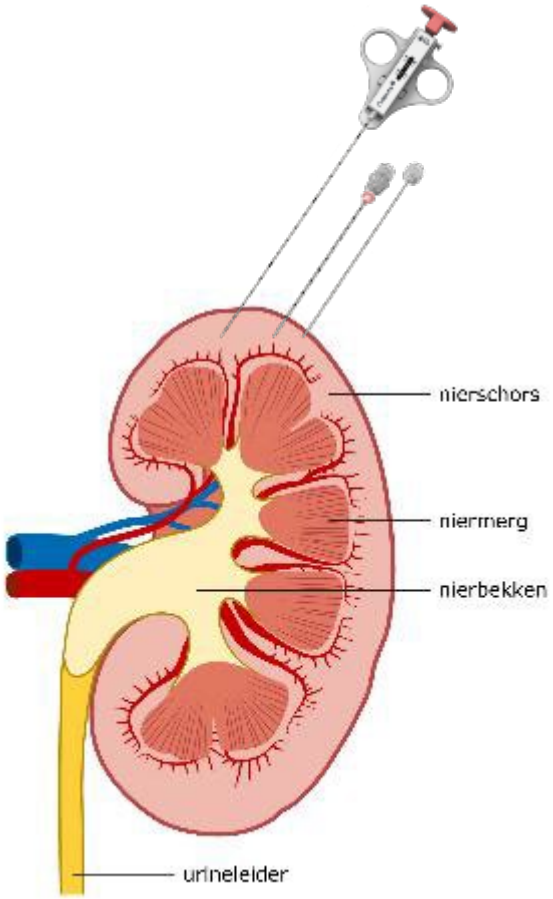


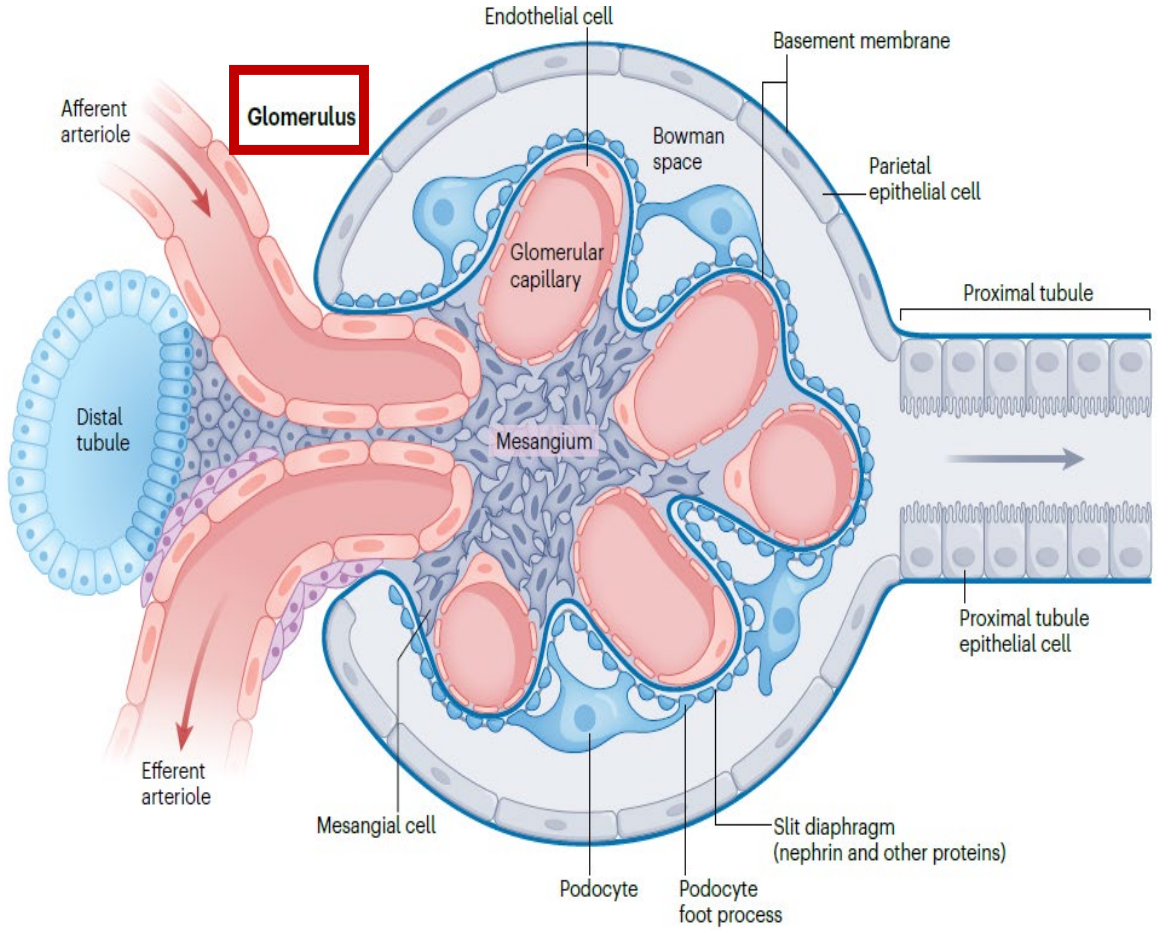
Schors



Merg

In de nier

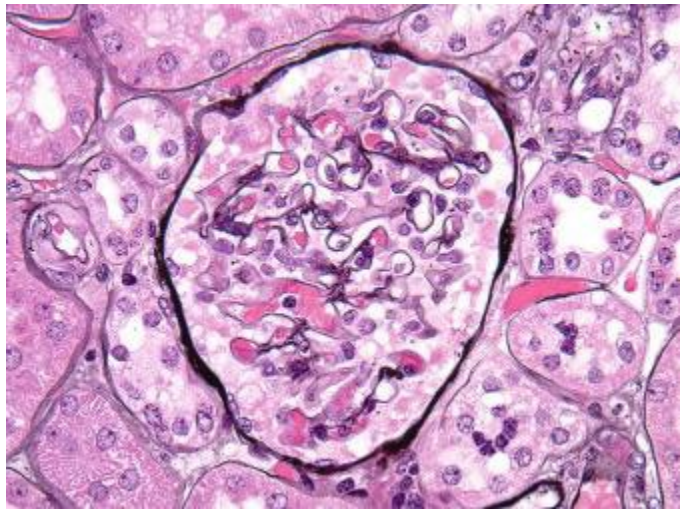

nierschors
niermerg
nierbekken
urineleider


Endothelial cell
Basement membrane
Afferent arteriole
Glomerulus
Bowman space
Parietal epithelial cell
Glomerular capillary
Proximal tubule
Distal tubule
Mesangium
Proximal tubule epithelial cell
Efferent arteriole
Mesangial cell
Slit diaphragm (nephrin and other proteins)
Podocyte
Podocyte foot process

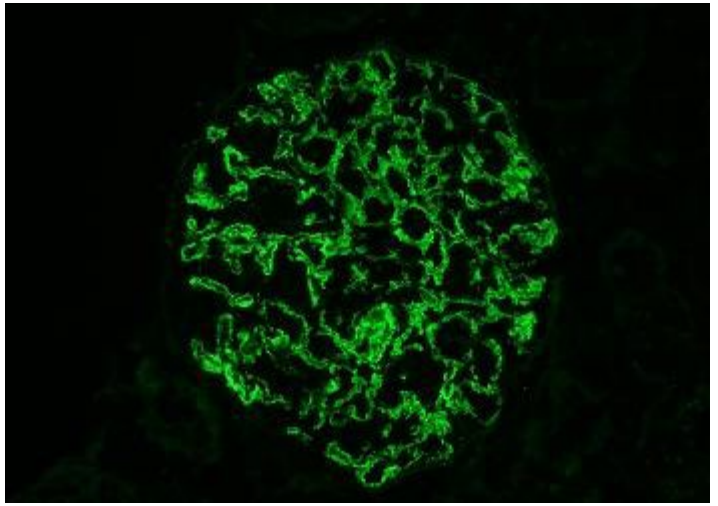
Beoordeling nierbiopt

1. Lichtmicroscopie
2. Immuunfluroescentie
3. Electronen microscopie

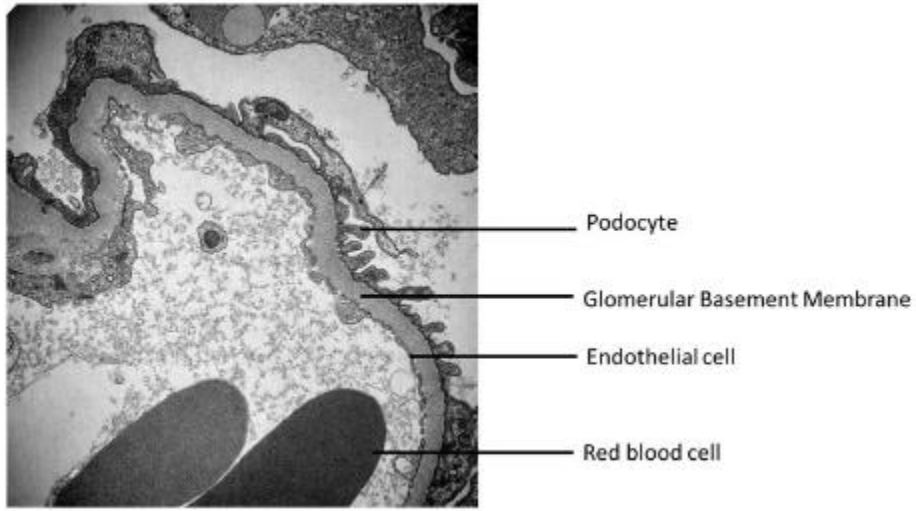
1



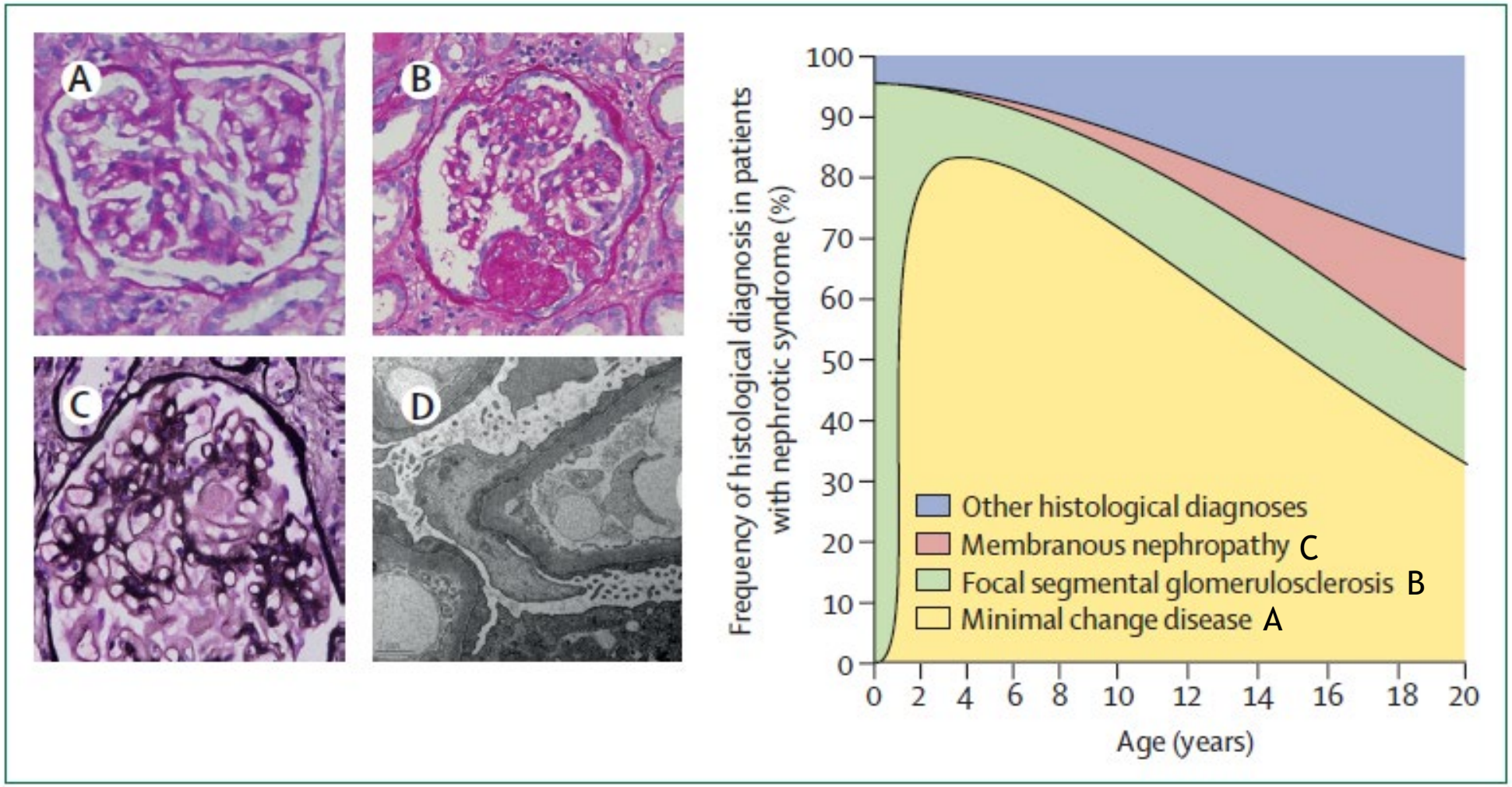
2



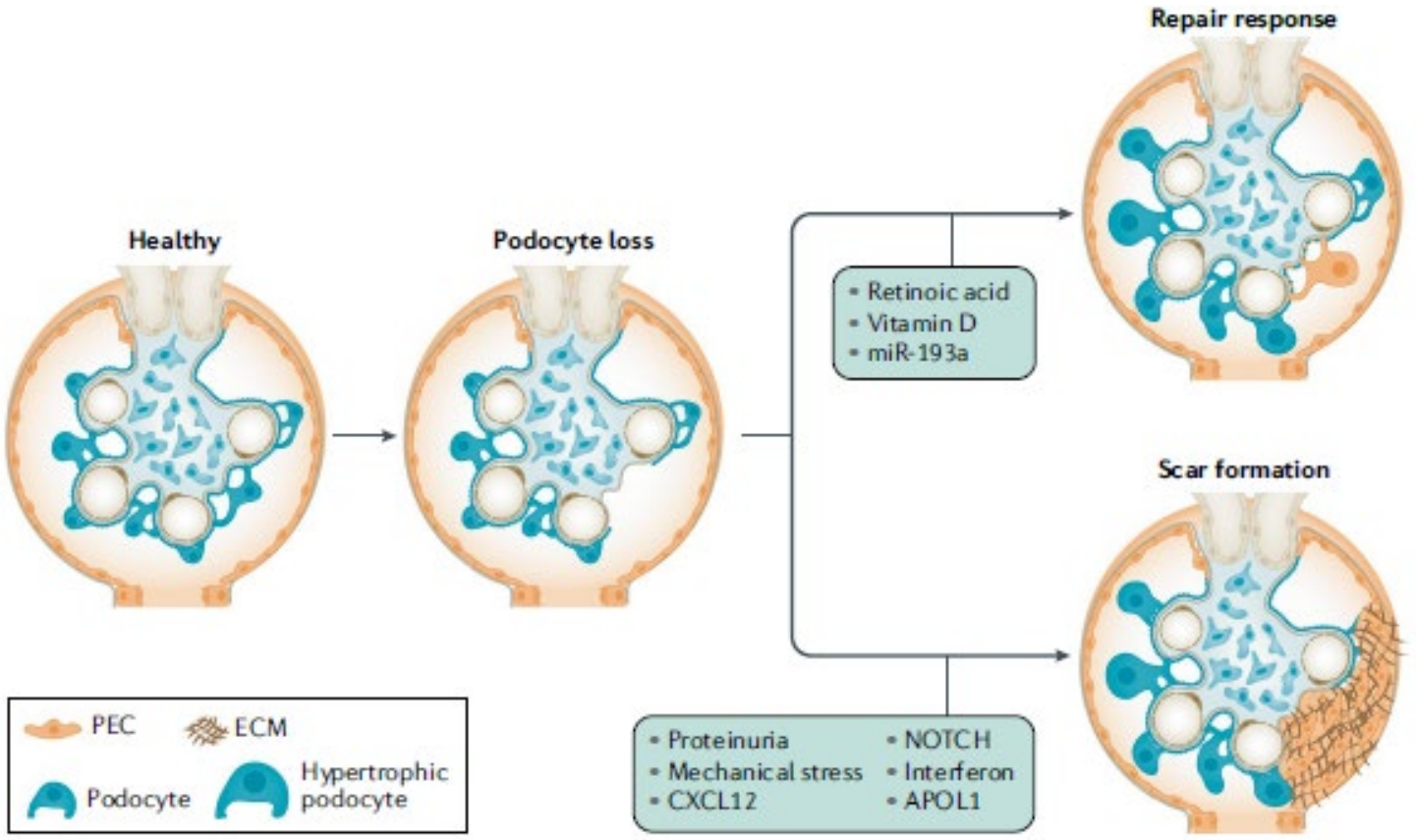
3



Weefselonderzoek - Histologie



Podocyt - loss - repair



Kopp et al.,| Nature Reviews 2020

Indeling nefrotisch syndroom bij kinderen; respons op behandeling

- Prednisolon-gevoelig = steroid-sensitief nefrotisch syndroom (SSNS) = 85%

  → urine eiwitvrij < 4 weken na start prednisolon 60 mg/m2/dag

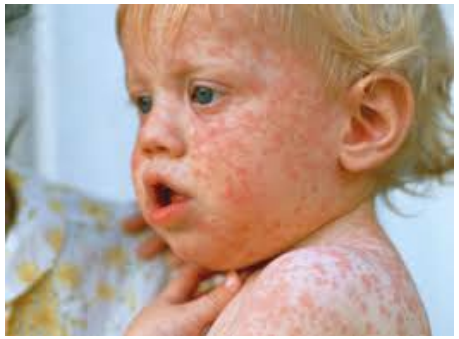
- Niet-prednisolon gevoelig = steroid- resistent nefrotisch syndroom (SRNS) =15%

  → urine niet eiwitvrij (geen remissie bereikt) < 4 weken prednisolon

Trautman et al| IPNA guideline SSNS I PedNeph 2022

Inzicht in nefrotisch syndroom = gebaseerd op klinische bevindingen

- Remissie na mazelen – mazelen onderdrukt T-cel afweer.
- Remissie NS bij patiënten met Hodgkin lymfoom na Rituximab
- Respons op behandeling met T- and B-cel gerichte medicijnen
- Associatie met allergie
- Geen immuuncomplex ziekte want geen neerslagen in nierbiopt.
- Snel recidief na niertransplantatie: circulerende factor?



MEASLES IN THE NEPHROTIC SYNDROME

ARTHUR H. ROSENBLUM, M.D., HERMAN B. LANDER, M.D., AND RALPH M. FISHER, M.D.
CHICAGO, ILL.

DURING the recent measles epidemic in the Chicago area in the winters of 1947 and 1948 we were privileged to observe the effects of the disease on seven patients with the nephrotic syndrome. Six of these patients were studied at the Children's Division of the Cook County Hospital and one at the Sarah Morris Hospital of Michael Reese Hospital.

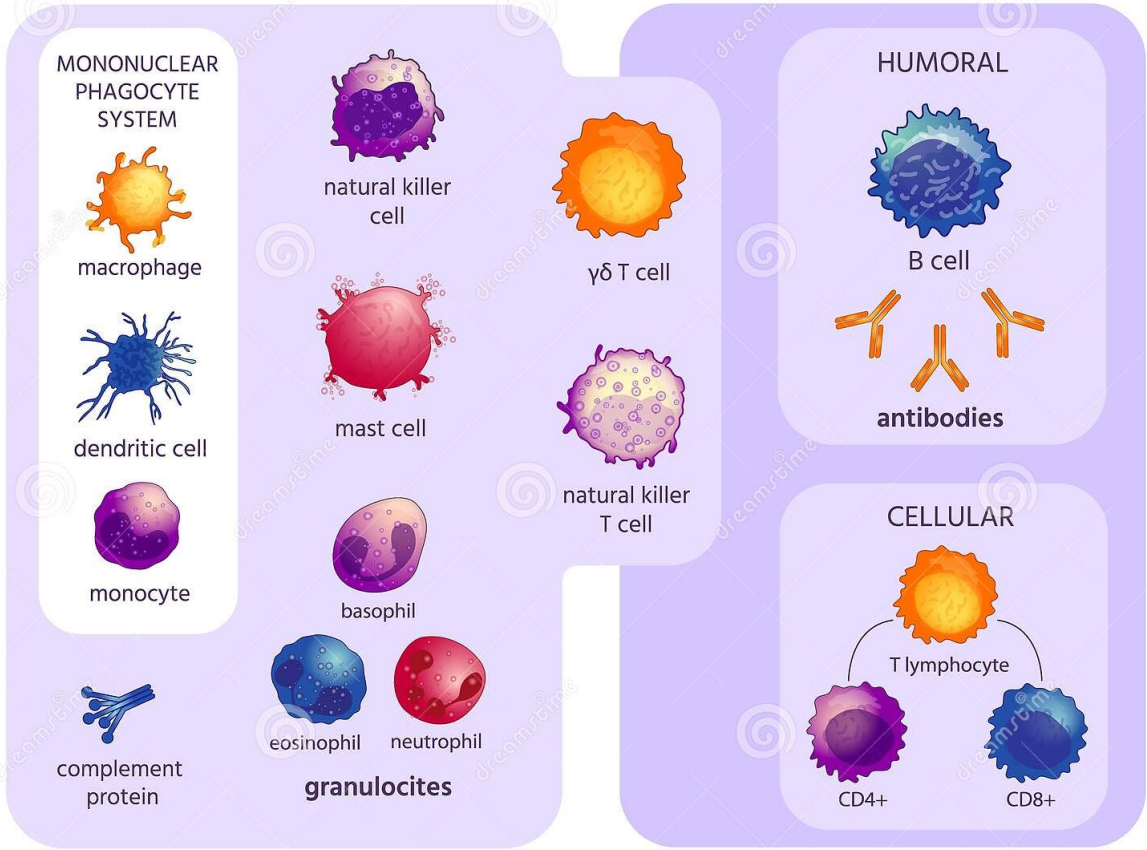
IMMUNITY

INNATE = aangeboren

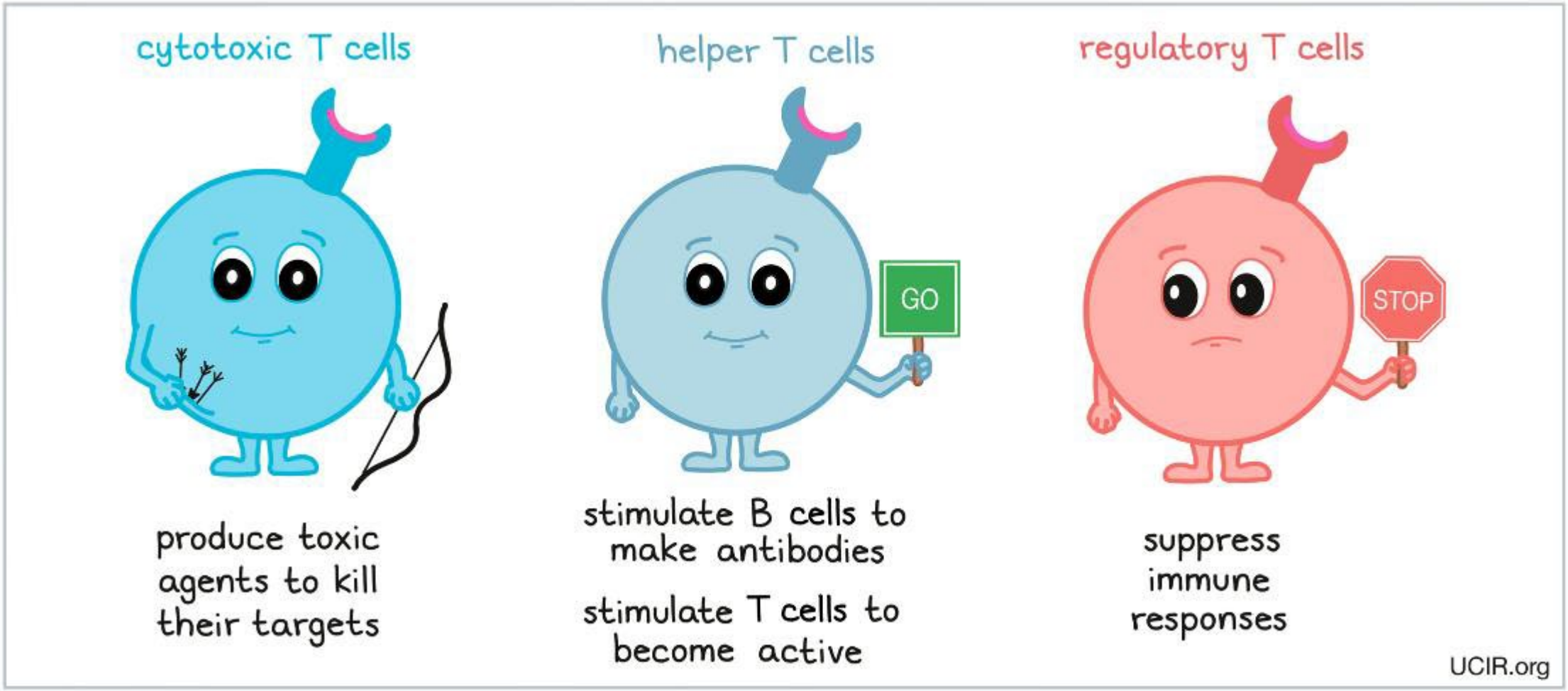
NONSPECIFIC
fast response (0-4 hours)

ADAPTIVE = verworven

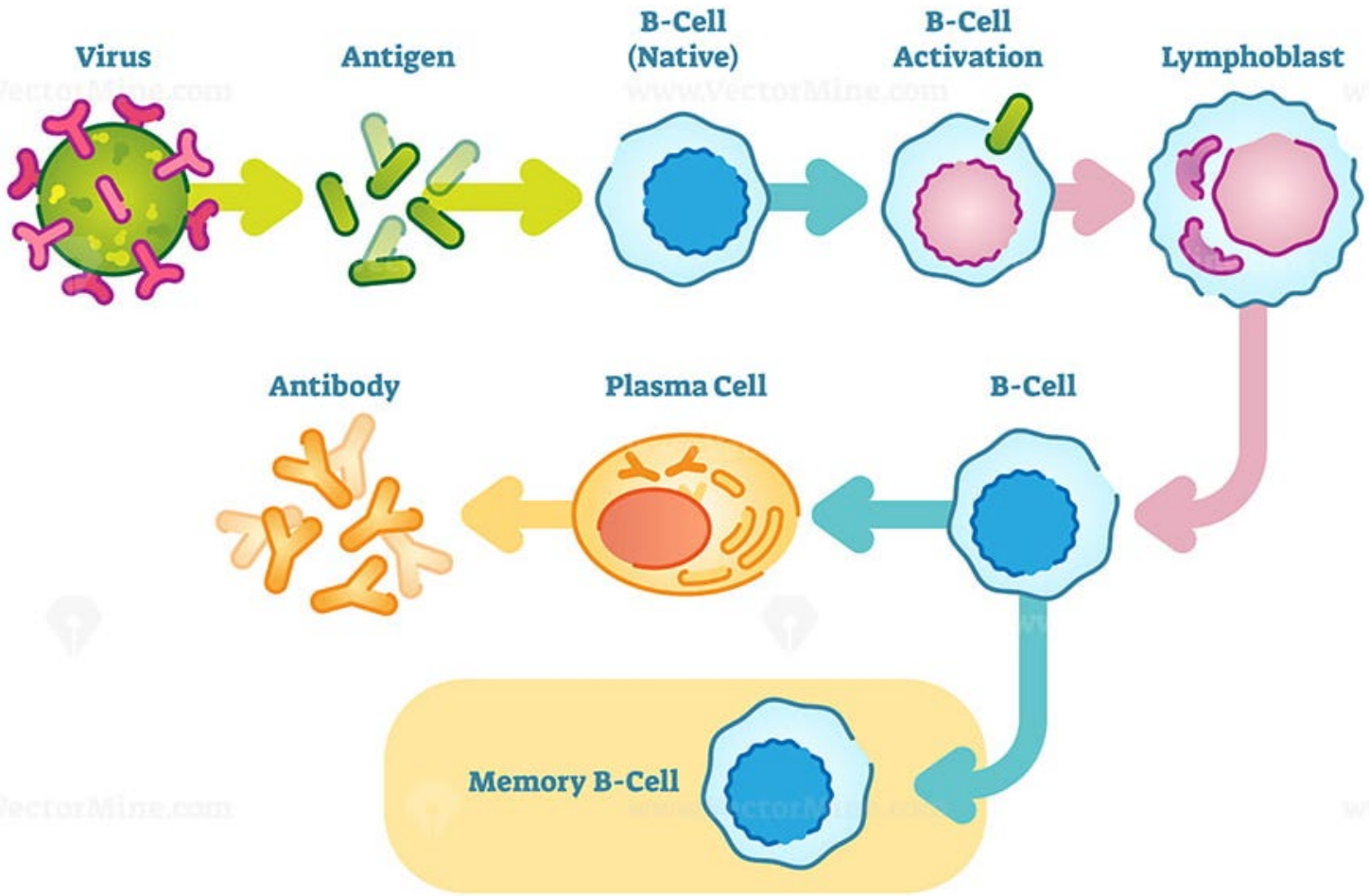
SPECIFIC
slow response (4-14 days)



T-cellen

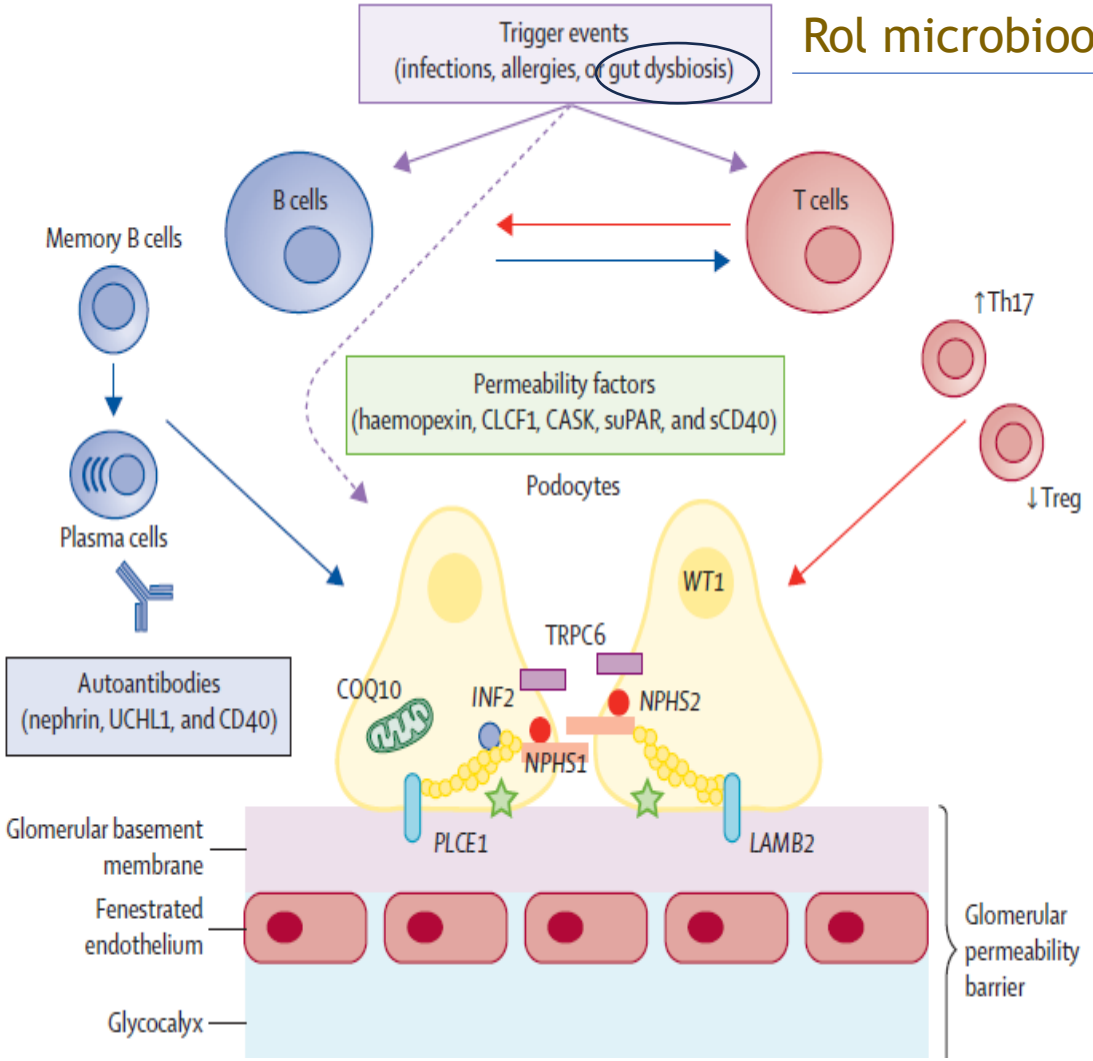

cytotoxic T cells
helper T cells
regulatory T cells
GO
STOP
produce toxic agents to kill their targets
stimulate B cells to make antibodies
stimulate T cells to become active
suppress immune responses
UCIR.org

B-cellen


Virus
Antigen
B-Cell (Native)
B-Cell Activation
Lymphoblast
Antibody
Plasma Cell
B-Cell
Memory B-Cell

Immuun factoren bij kinderen met NS

Welke circulerende factor??



Contents lists available at ScienceDirect

Pediatrics & Neonatology

journal homepage: www.pediatr-neonatol.com

Review Article

Gut dysbiosis as a susceptibility factor in childhood idiopathic nephrotic syndrome

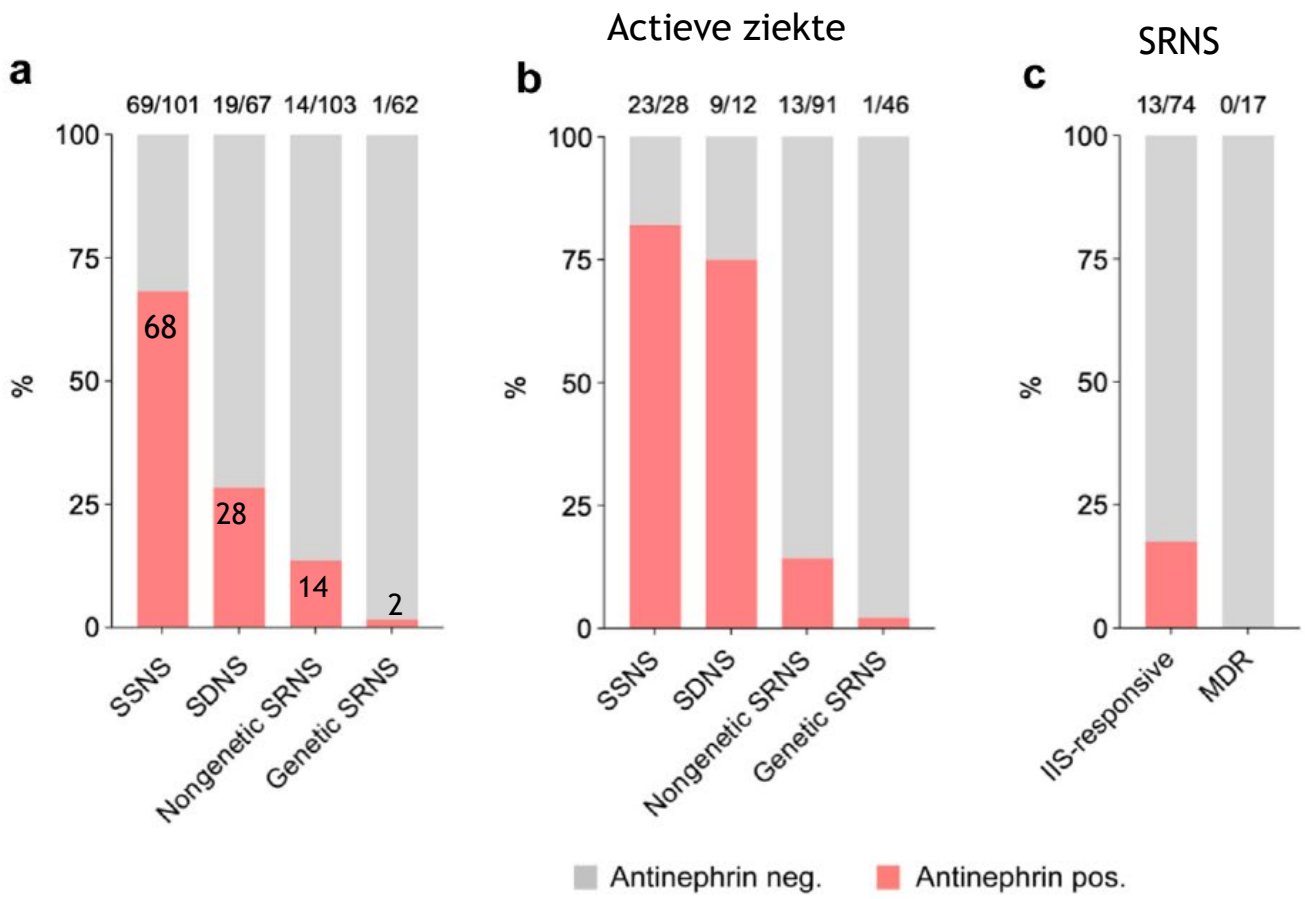
Kazunari Kaneko

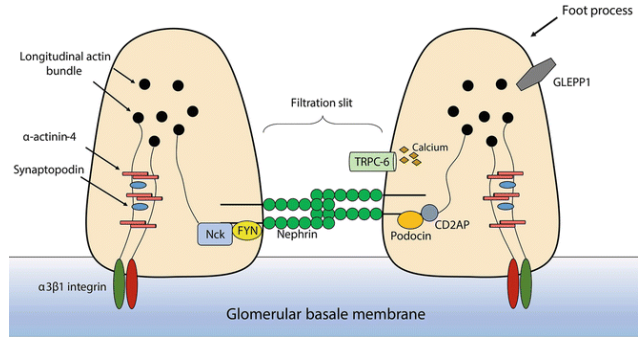
Department of Pediatrics, Kansai Medical University, 2-5-1, Shin-machi, Hirakata, Osaka, 573 1010, Japan

Vivarelli et al| Lancet 2023

Anti-podocyt antistoffen: anti-nefrine

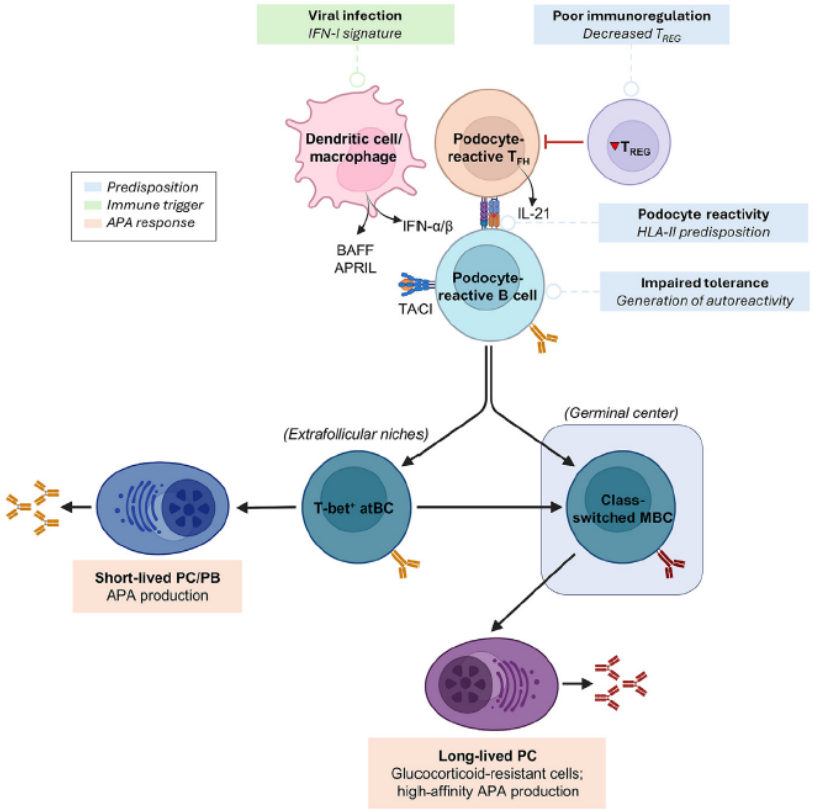
101 kinderen





Hengel et al.| Kidney Int 2025

Auto-immuun theorie nefrotisch syndroom

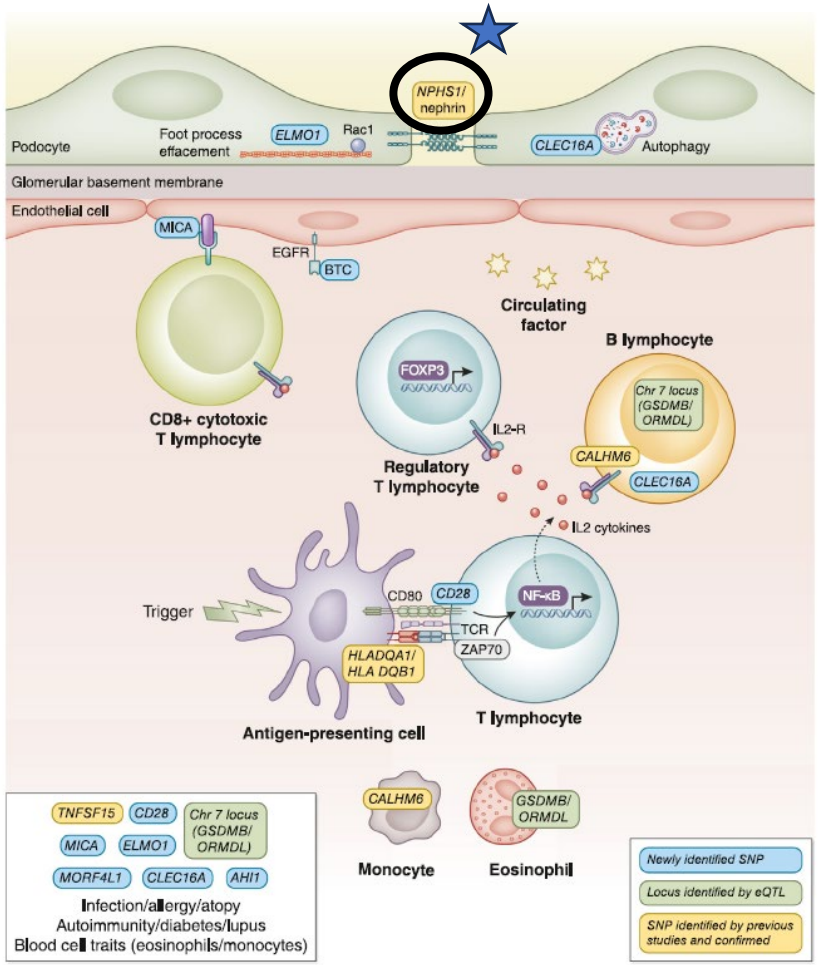


- Door virale infecties en slechte immuunregulatie (Treg) worden APAs (anti-podocyten antistoffen) gemaakt.
- Genetische predispositie
- Verminderde tolerantie

Niet-immuun factoren SSNS

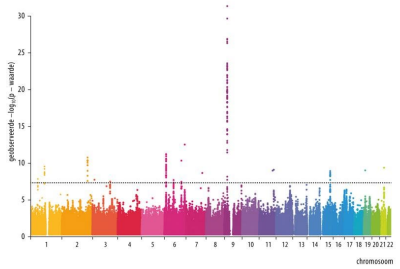
- 3% van kinderen met NS hebben broer/zus met NS
- Niet monogenetisch = ziekte wordt niet veroorzaakt door fout in 1 gen.
- Genetische vatbaarheid?
- Genezing in puberteit bij deel van kinderen met SSNS (effect hormonen?)

Niet-immuun factoren SSNS in kinderen



- GWAS =

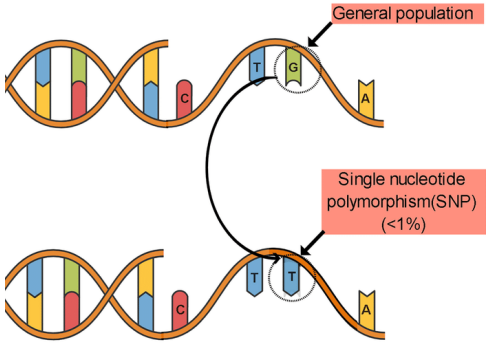
  genome wide association studies



Verband zoeken tussen genetische variaties (SNPs) en ziekte

- SNPs =

Single nucleotide polymorphism



★ NPHS1 SNP relatie met anti-nefrine antistoffen?

Boyer et al| Kidney International 2024
Barry et al I Nature Communications 2023

Standaard behandeling nefrotisch syndroom

1e episode

Prednisolon

12 wk (60 mg/m2/dag 6 wk, 40 mg/m2/odd 6 wk)

Alternatieve schema's:

8 wk (Amerikaanse schema)

18 wk (Franse schema)

Recidiverend NS

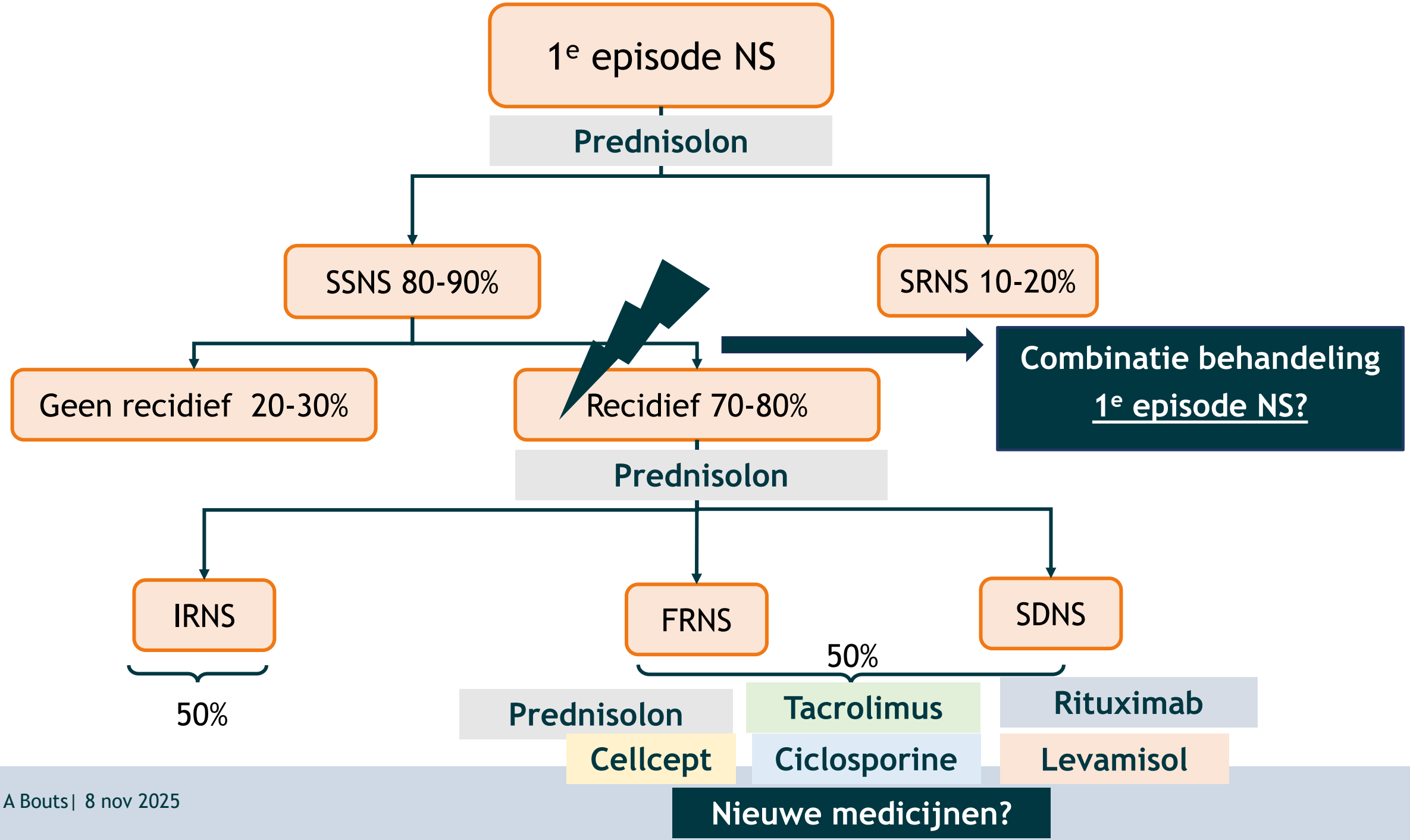
Frequent recidiverend (FRNS),

Prednisolon afhankelijk (SDNS)

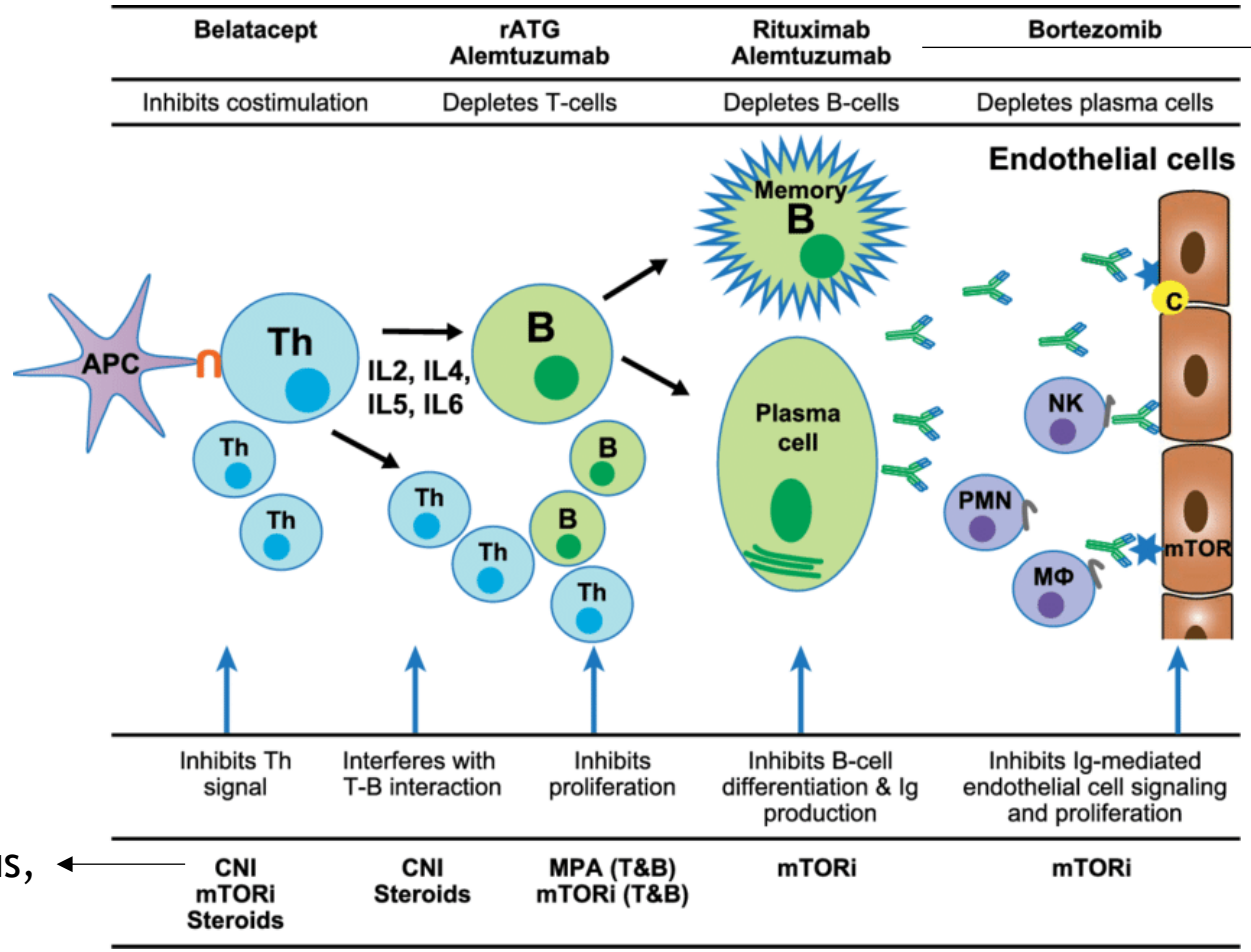
Prednisolon (60 mg/m2/dag tot eiwitvrij, 40 mg/m2/odd 4 wk)

Prednisolon-sparend medicijn

Wanneer start?

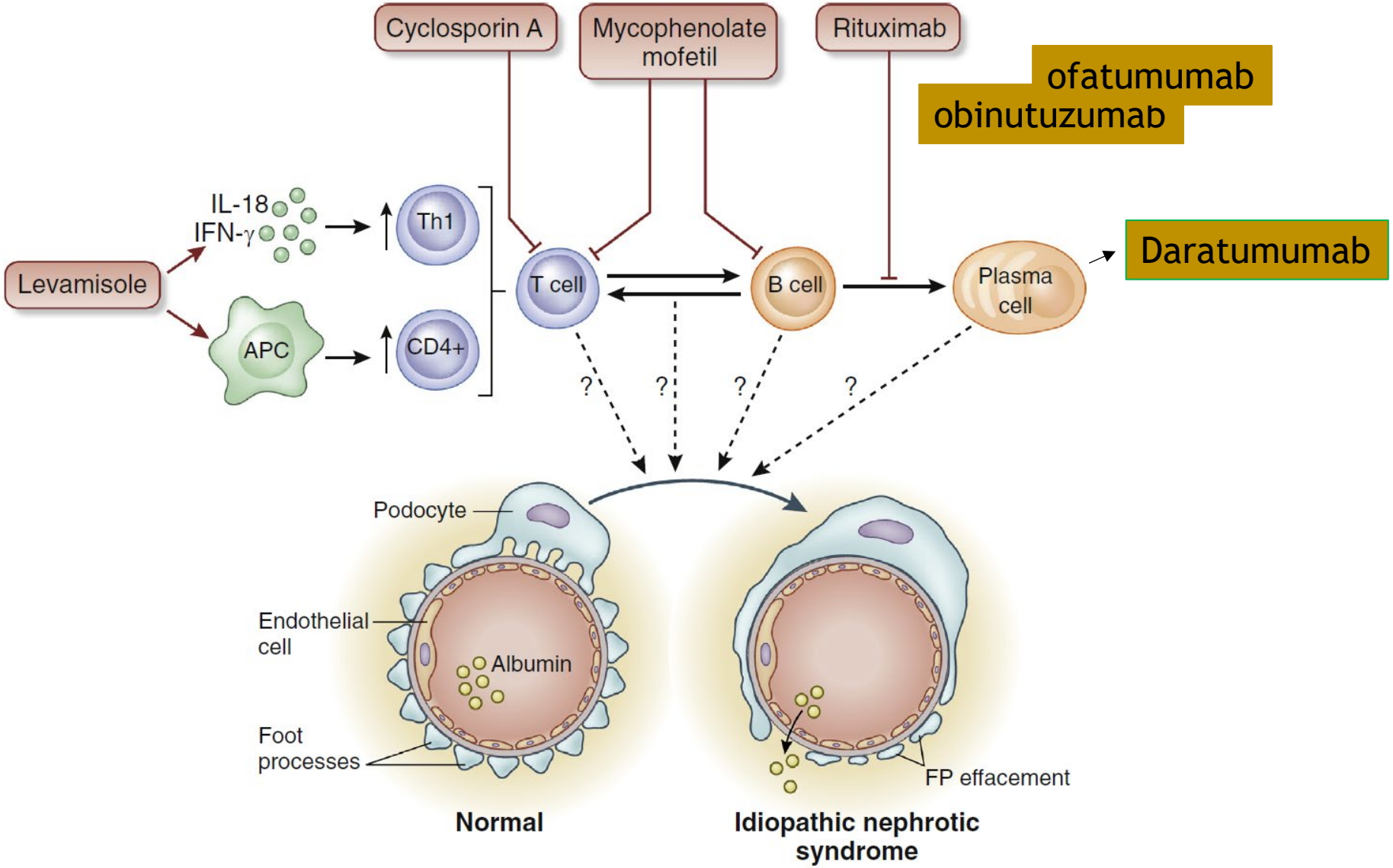

1e episode NS
Prednisolon
SSNS 80-90%
SRNS 10-20%
Geen recidief 20-30%
Recidief 70-80%
Combinatie behandeling
1e episode NS?
Prednisolon
IRNS
FRNS
SDNS
50%
50%
Prednisolon
Tacrolimus
Rituximab
Cellcept
Ciclosporine
Levamisol
Nieuwe medicijnen?

Aangrijpingspunten van immuunsuppressiva



Anti-plasmacel: Daratumumab
Anti-CD20:
- Obinutuzumab
- Ofatumumab

CNI = tacrolimus, ciclosporine



Vivarelli et al| Kidney Int 2019

Studies 1e episode nefrotisch syndroom

- NEPHROVIR-3
- LEARNS

- INTENT

Open access Protocol

BMJ Open

Initial treatment of steroid-sensitive idiopathic nephrotic syndrome in children with mycophenolate mofetil *versus* prednisone: protocol for a randomised, controlled, multicentre trial (INTENT study)

Rasmus Ehren,[1] Marcus R Benz,[1] Jorg Doetsch,[1] Alexander Fichtner,[2] Jutta Gellermann,[3] Dieter Haffner,[4] Britta Höcker,[2] Peter F Hoyer,[5] Bärbel Kästner,[6] Markus J Kemper,[7] Martin Konrad,[8] Steffen Luntz,[6] Uwe Querfeld,[3] Anja Sander,[9] Burkhard Toenshoff,[2] Lutz T Weber,[1] on behalf of the Gesellschaft für Pädiatrische Nephrologie (GPN)

Open access Protocol

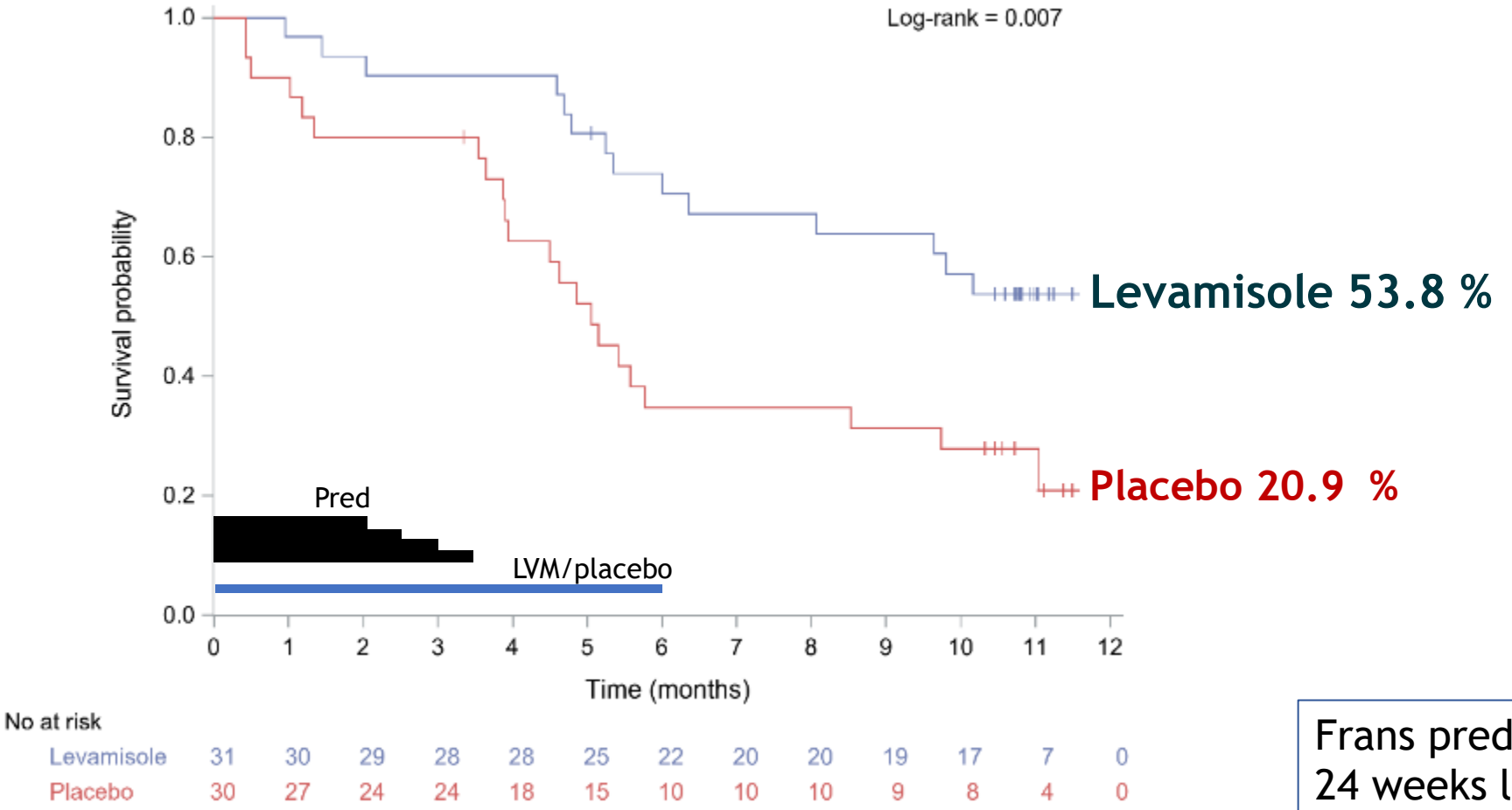
BMJ Open

Prevention of relapses with levamisole as adjuvant therapy in children with a first episode of idiopathic nephrotic syndrome: study protocol for a double blind, randomised placebo-controlled trial (the LEARNS study)

Floor Veltkamp,[1] Djera H Khan,[2] Christa Reefman,[1] Susan Veissi,[3] Hedy A van Oers,[4] Elena Levtchenko,[5] Ron A A Mathôt,[6] Sandrine Florquin,[2] Joanna A E van Wijk,[7] Michiel F Schreuder,[3] Lotte Haverman,[4] Antonia H M Bouts[1]

Prednisolon alleen = niet genoeg!?

NEPHROVIR-3 : Recidief-vrij curve



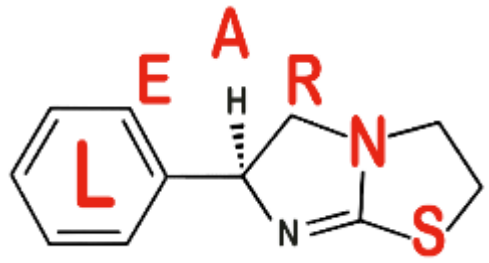
Levamisole 53.8 %

Placebo 20.9 %

>30% minder recidief na 1 jaar

Frans prednisolon schema
24 weeks levamisol 2.5 mg/kg/ad

Dossier C, Not yet published



LEARNS RCT – einde inclusie – niet gedeblindeerd

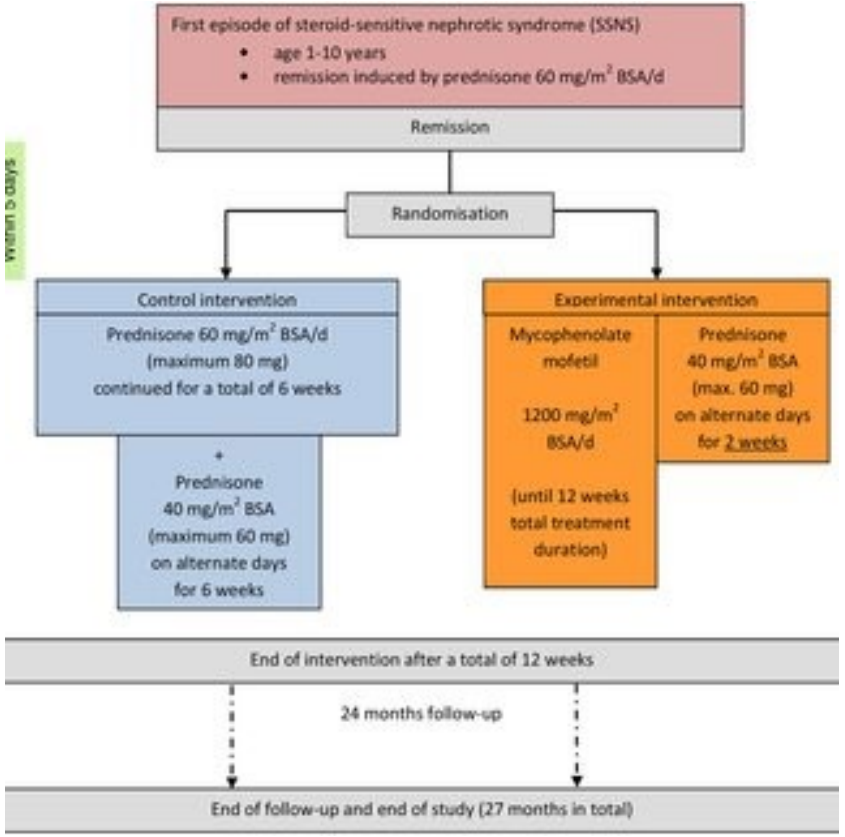
- 86 patients geïncludeerd
- 5 lost to follow-up
- 79 patienten minimaal 1 jaar vervolgd: 50 (63,3%) recidief-vrij op 1 jaar
- 63 patienten 2 jaar vervolgd:

  50 (63,3%) recidief-vrij op 1 jaar

  26 (41,3%) recidief-vrij op 2 jaar

INTENT

- 12 wk prednisolon versus 2 wk prednisolon
  na remissie + Cellcept 12 wk



- Recidief 1 jaar Cellcept arm 79,1%
- Recidief 1 jaar prednisolon arm 74,8%

Conclusie:

1. beide armen gelijke uitkomst
2. Voordeel van minder prednisolon tav bijwerkingen

Kinderen met frequent recidiverend (FRNS) en prednisolon afhankelijk (SDNS) nefrotisch syndroom

Levamisol bij kinderen met FRNS/SDNS

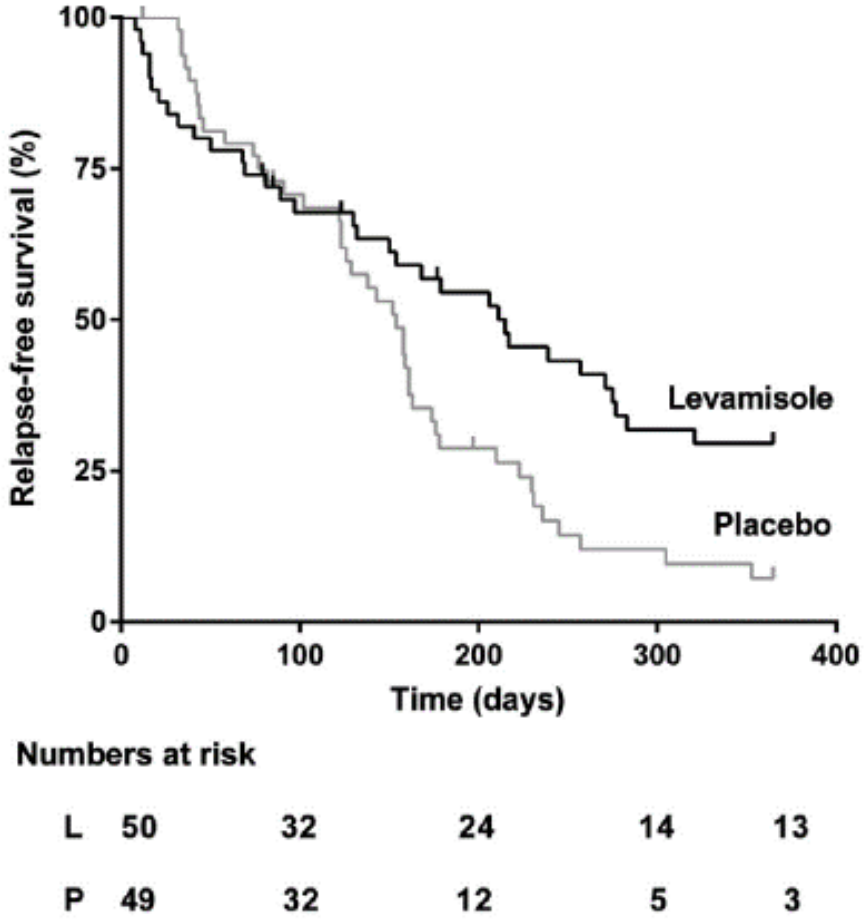
Dosering: 2.5 mg/kg om de dag, 1 jaar

Minder recidieven

- Zonder recidief na 1 jaar
  - Levamisol: 26%
  - Placebo: 6%

Belangrijkste bijwerking:

- Daling witte bloedcellen (neutropenie):
  14% (vs 8% in placebo)



20% verschil

Gruppen et al. Kidney Int (2018)

An open label non-inferiority randomized controlled trial evaluated alternate day prednisolone given daily during infections vs. levamisole in frequently relapsing nephrotic syndrome.

kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Methods and cohort

Open label RCT

Steroid sensitive NS

160 patients; 2-18 years old

Frequent relapses; steroid threshold ≤1 mg/kg

No significant steroid toxicity

Stratified for: Age </>4 years, steroid dependence

75% boys

17.5% steroid dependent

Median age 4.3 years

Disease duration 1.2 years

1 year follow up

CTRI/2015/07/006002

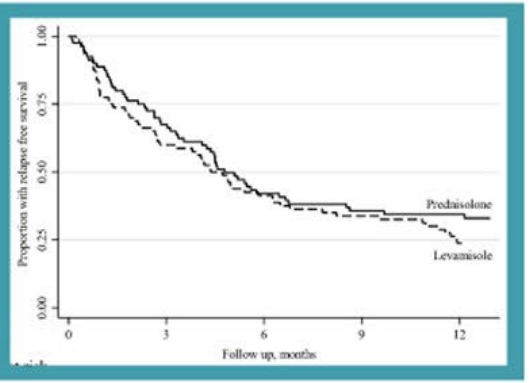
Intervention

Prednisolone at 0.5-0.7 mg/kg on alternate days; daily during infections, for 1 year

Intervention outcomes	% (95% CI)
Frequent relapses	40 (30-51)*
Sustained remission	34 (24-45)
Treatment failure	41 (31-52)*
Relapses per year	1.8 (1.8-2.1)
Prednisolone, mg/kg/d	0.42 (0.29, 0.59)*

*$P < 0.05$

Survival free of relapse



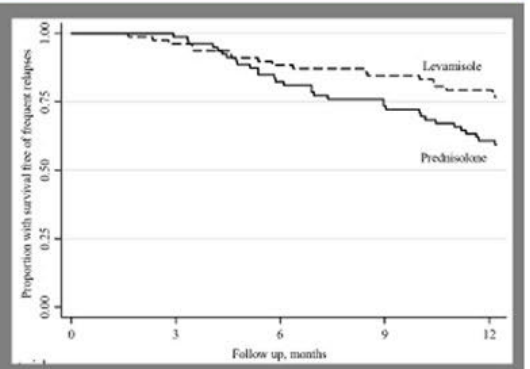
Control

Oral levamisole at 2-2.5 mg/kg on alternate days, for 1 year

Prednisolone tapered over 3-mo

Control outcomes	% (95% CI)
Frequent relapses	23 (15-33)*
Sustained remission	24 (16-34)
Treatment failure	25 (17-36)*
Relapses per year	1.6 (1.3-1.9)
Prednisolone, mg/kg/d	0.28 (0.14, 0.46)*

Survival free of frequent relapses

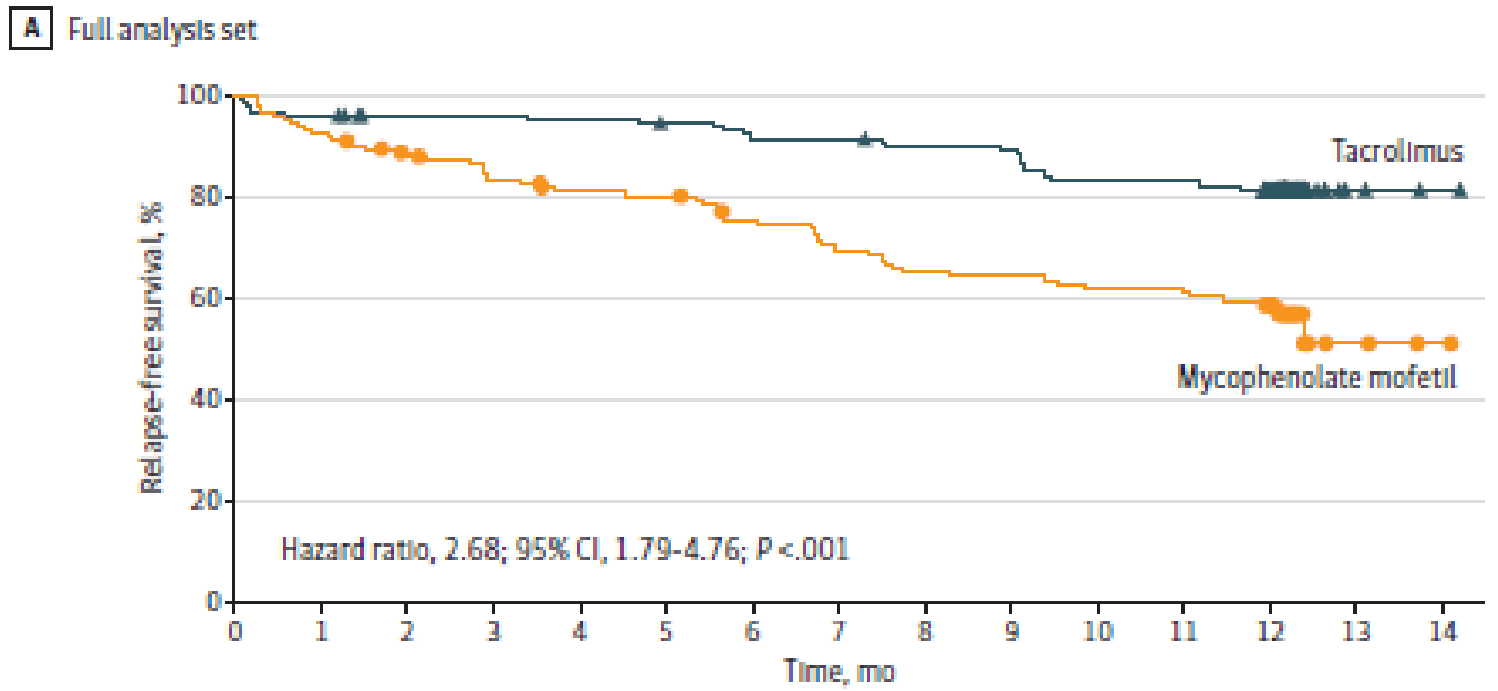


Sinha, 2023

CONCLUSION **Alternate-day prednisolone was not non-inferior to levamisole in preventing frequent relapses; the latter was more steroid-sparing. Both therapies were similarly effective in other outcome measures.**

Cellcept of tacrolimus voor FRNS/SDNS

Figure 2. One-Year Relapse-Free Survival



No. at risk

Tacrolimus	135	130	126	126	125	123	119	119	116	115	107	107	99	3	1
Mycophenolate mofetil	135	125	117	109	104	103	95	87	82	81	78	77	70	3	1

23% verschil

Efficacy and safety of rituximab *vs.* tacrolimus in difficult-to-treat steroid-sensitive nephrotic syndrome: an open label pilot RCT

Graphical Abstract

HYPOTHESIS: RTX is not inferior to TAC in sustaining remission for 1 year in patients with difficult-to-treat nephrotic syndrome

DESIGN AND OUTCOMES

Pilot open label RCT

RTX 375 mg/m² IV x 2 doses (n=21)

TAC 0.1-0.2 mg/kg orally daily (n=20)

Steroid sensitive NS

3–18 years old

Frequent relapses

Failed ≥2 agents

Significant steroid toxicity

CTRI/2018/11/016342

1 yr follow up

Baseline features similar

83% boys

73% steroid-dependent

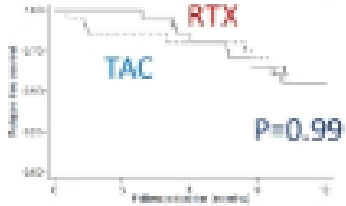
Disease for >5 years

80% had failed 3 agents

	Frequent relapses*	Prednisone (mg/kg/day)	Incidence of relapses
Sustained remission			
11 (55%)	7 (35%)	0.11	0.85 per yr
11 (55%)	1 (5%)	0.11	0.52 per yr

* ≥3 relapses in 1-yr or ≥2 in 6-months

Time to relapse similar



Frequent relapses: RTX > TAC

Adverse events

Infusion related; **diarrhea**

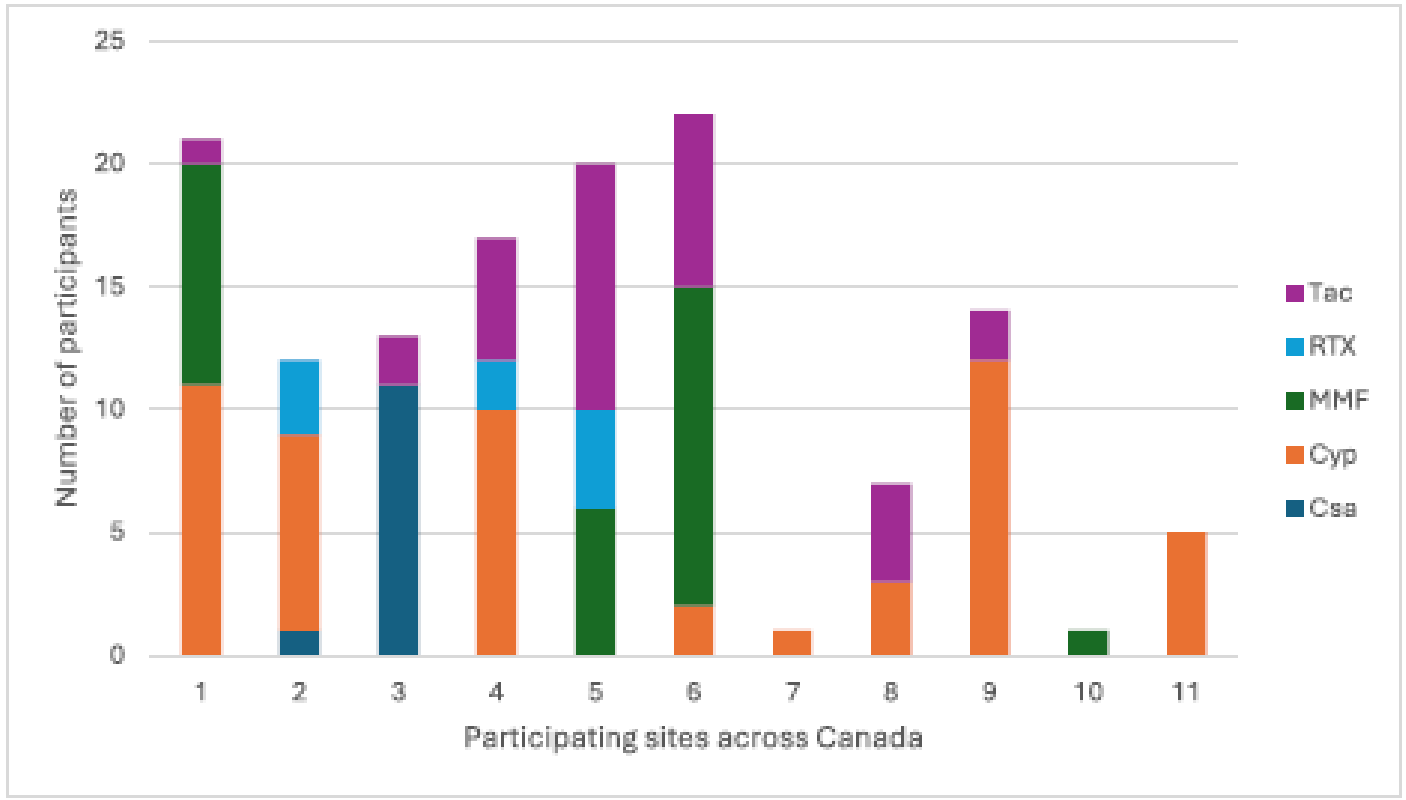
CONCLUSIONS: Rituximab and tacrolimus similarly sustained remission in more than half the patients with difficult-to-treat steroid-sensitive NS, but noninferiority of rituximab was not demonstrated.

Fewer patients on tacrolimus relapsed frequently.

Mathew et al. 2022

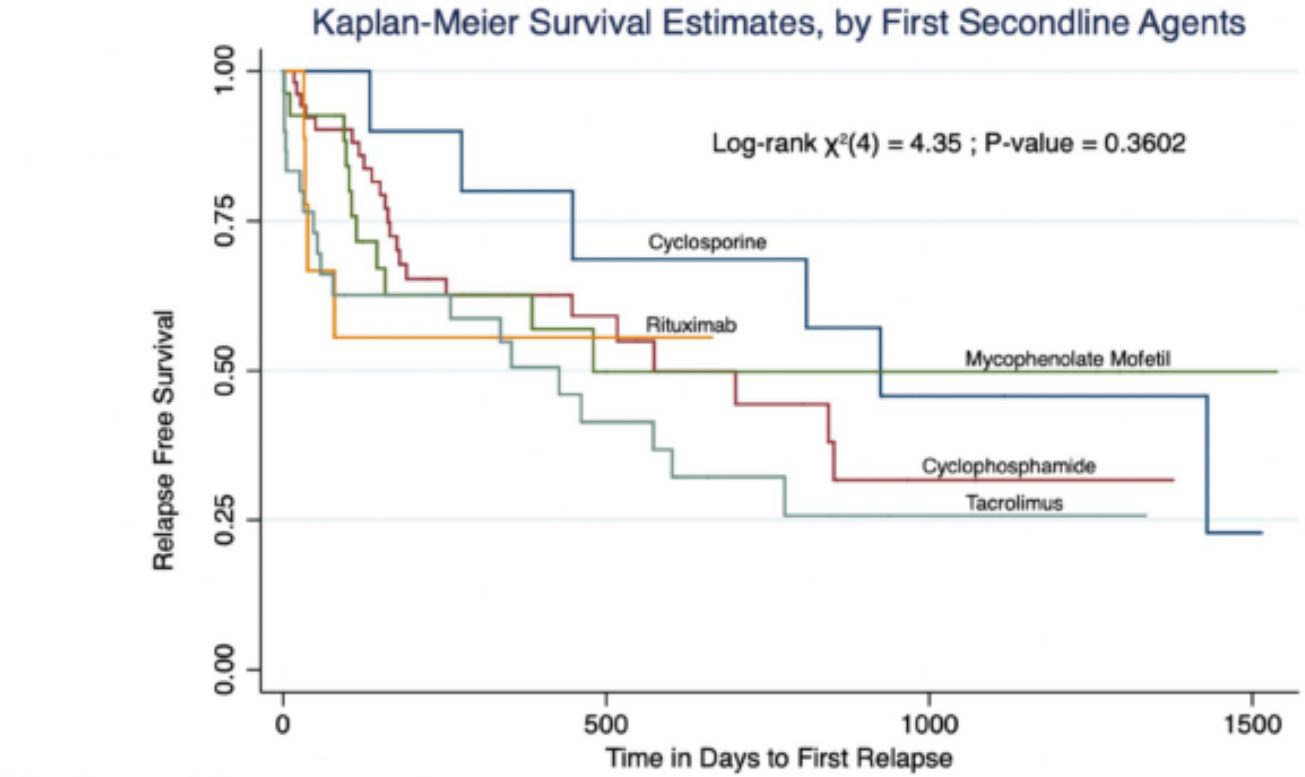
Pediatric Nephrology
Journal of the
IPNA International Pediatric Nephrology Association

Variaties in gebruik prednisolon-sparende medicijnen bij kinderen met SSNS



Tacrolimus
Rituximab
Cellcept
Cyclofosfamide
ciclosporine

Behandeling en tijd tot recidief



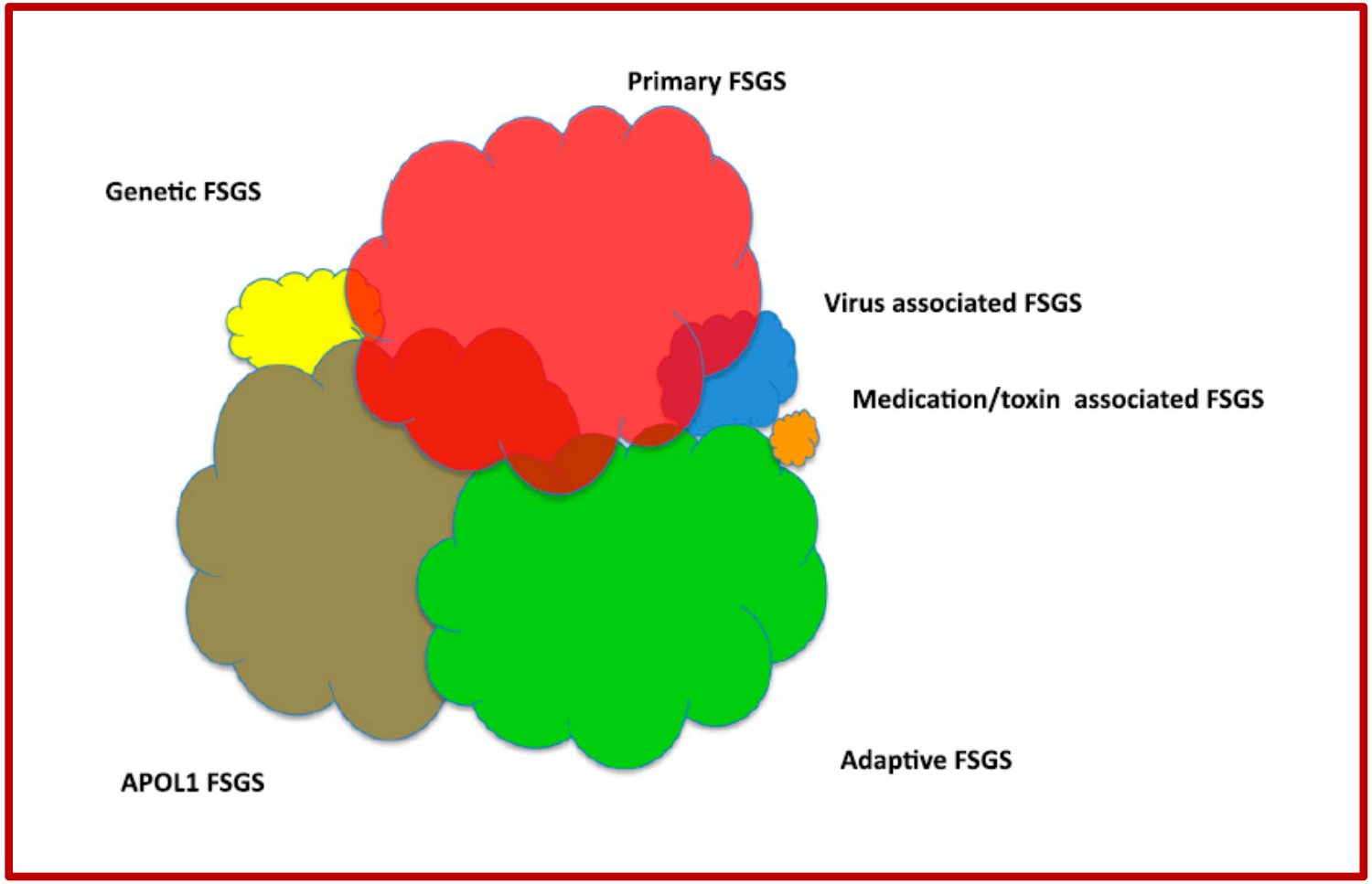
Number at risk

Cyclosporine:	11	6	3	1
Cyclophosphamide:	52	14	3	0
Mycophenolate Mofetil:	27	7	5	1
Rituximab:	9	1	0	0
Tacrolimus:	30	9	2	0

Prednisolon-resistent nefrotisch syndroom

- In biopt vaker FSGS
- Genetisch?
- Immunologisch?

☐ Nefrotisch syndroom (NPHS) / focale segmentele glomerulosclerose (FSGS) (NEF11v23.1; 106 genen)

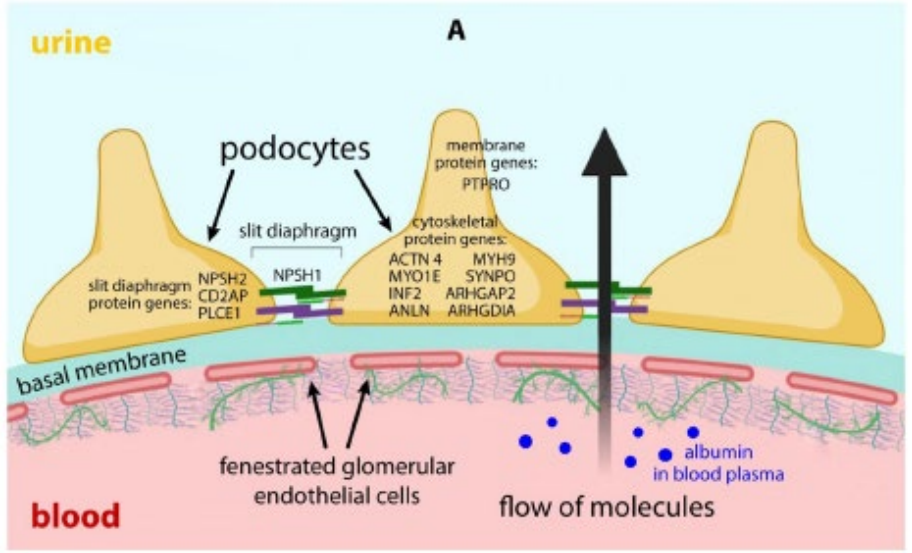


Genetische vorm van SRNS / FSGS

Gene Panel

NPHS1	ACTN4
NPHS2	INF2
WT1	ADCK4
LAMB2	COQ2
PLCE1	COQ6
TRPC6	LMX1B
	APOL1

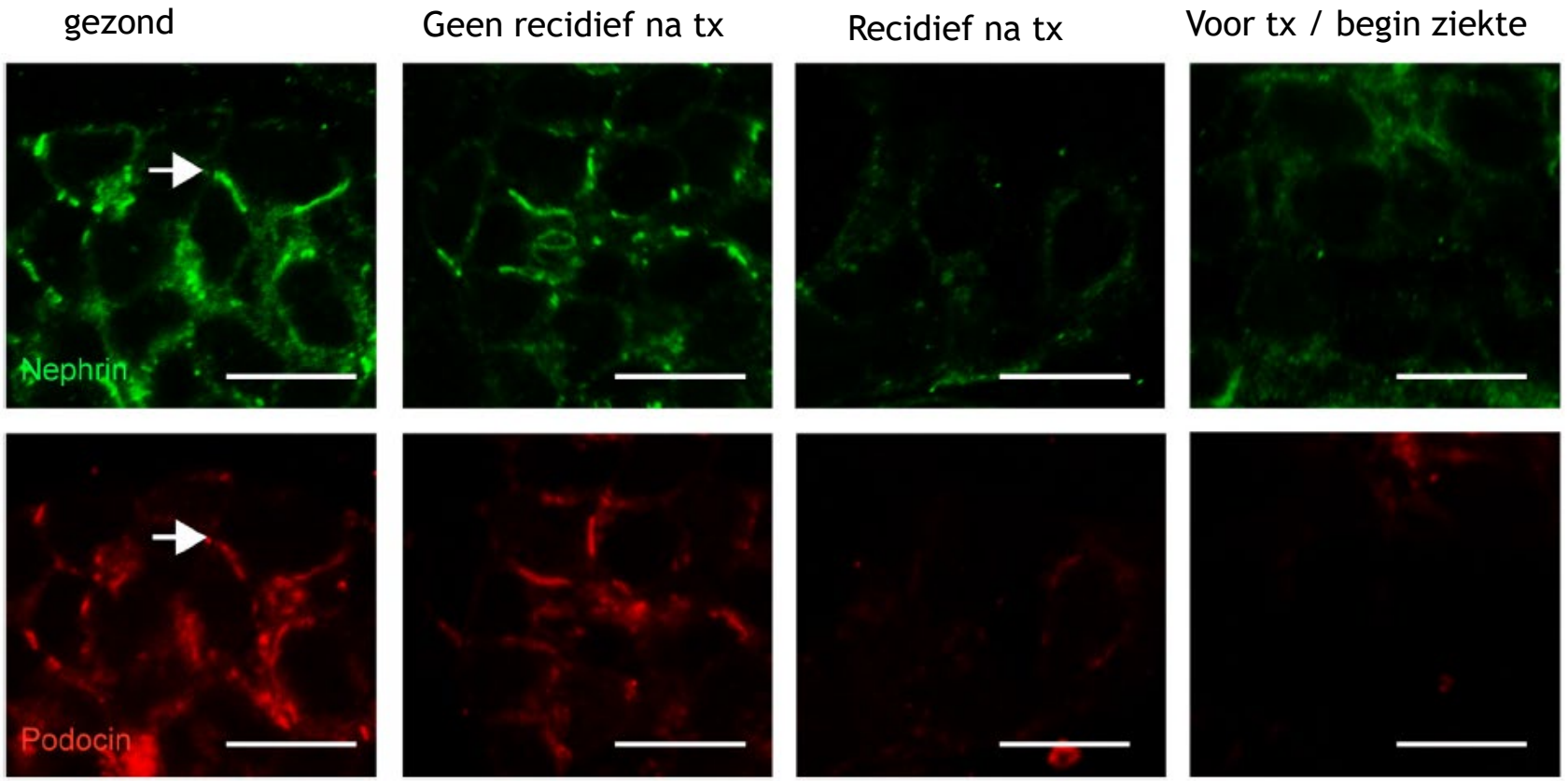
Leeftijd presentatie NS	Kans genetische afw
0-3 maanden	70-85%
4-12 maanden	40-45%
13 maanden – 6 jaar	25%
7-12 jaar	18%
>12 jaar	10%



Circulerende factor zoeken met organoids

(gemaakt uit pluripotente stamcellen)

Organoids behandeld met plasma van:



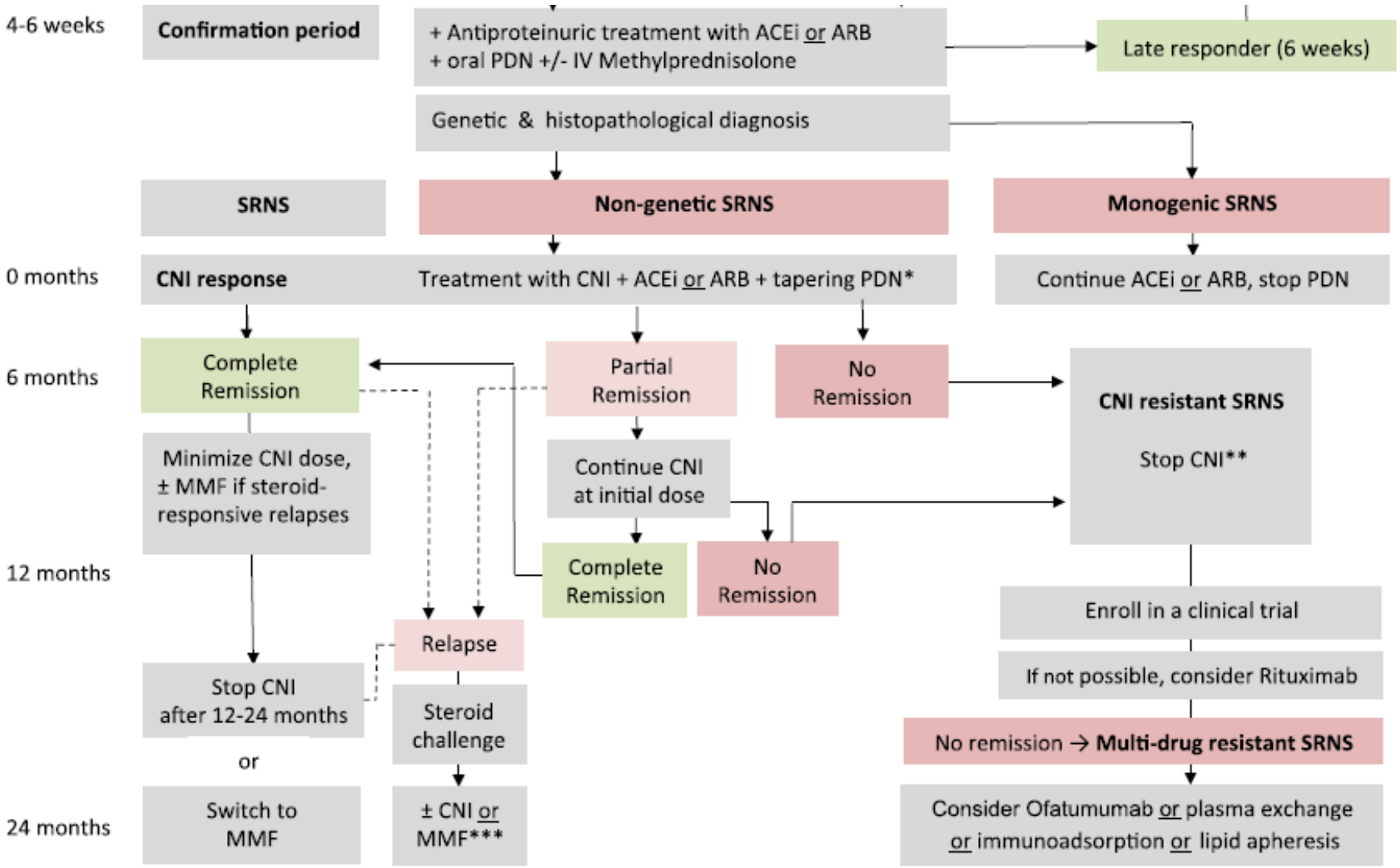
Geen bewijs voor anti-nefrine antistoffen!

Behandeling prednisolon-resistent NS

Volgens IPNA richtlijn:

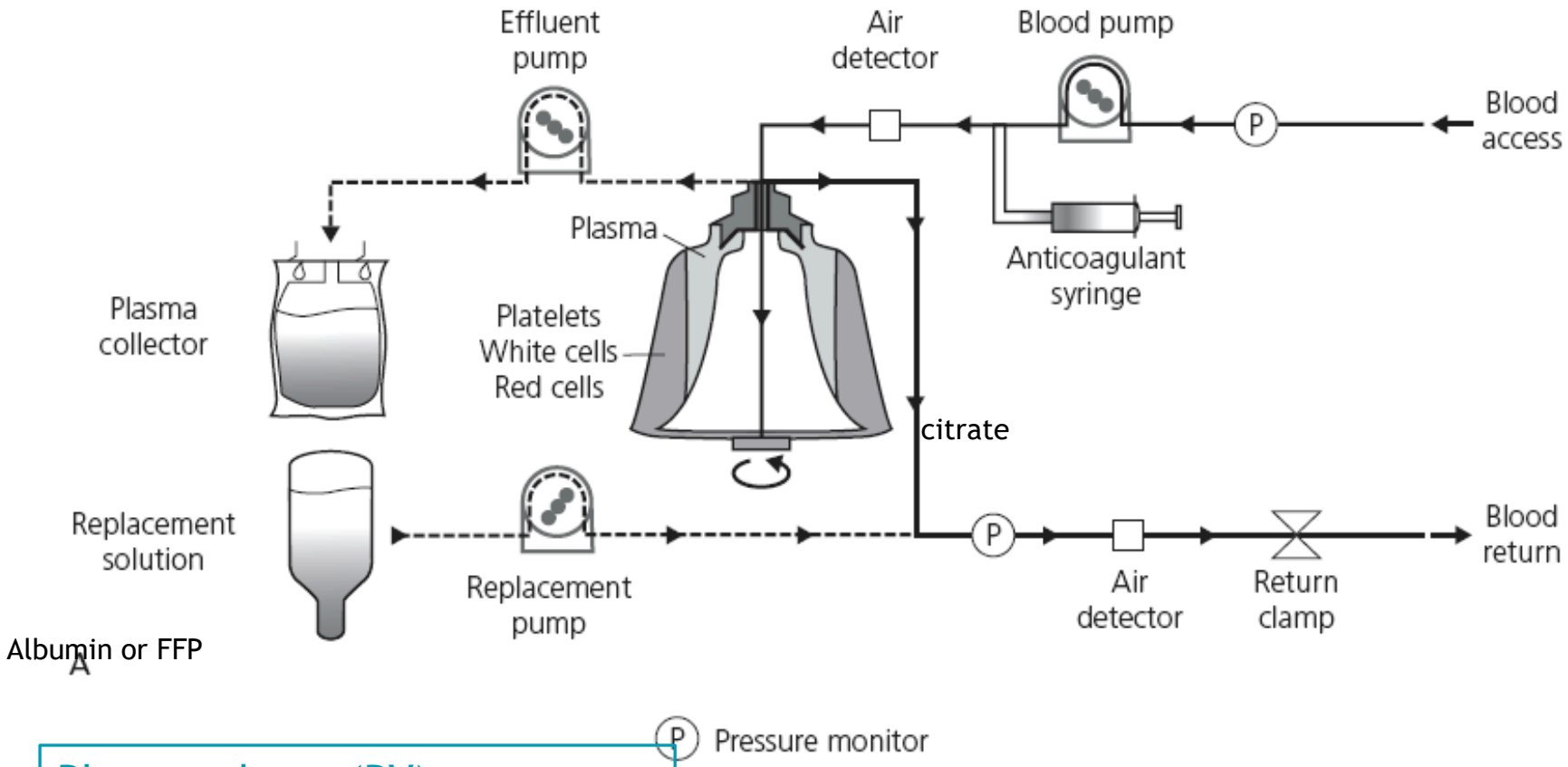
- Nierbiopt en DNA onderzoek
- 3 x pulse methylprednisolon via infuus
- Tacrolimus
- Prednisolon afbouw tot stop
- ACE-remmer zoals enalapril of lisinopril en/of ARB zoals losartan

IPNA richtlijn



Trautman et al.| Ped Neph 2020

Plasmaferese-centrifuge

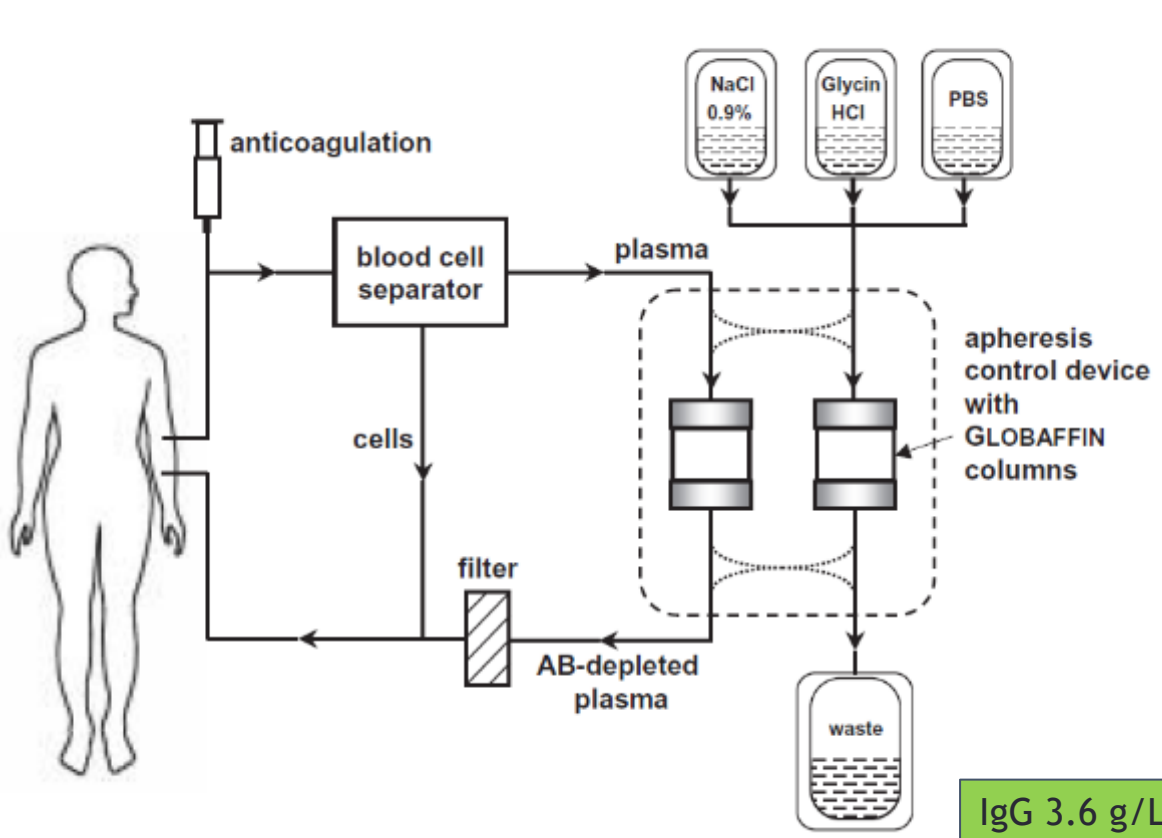


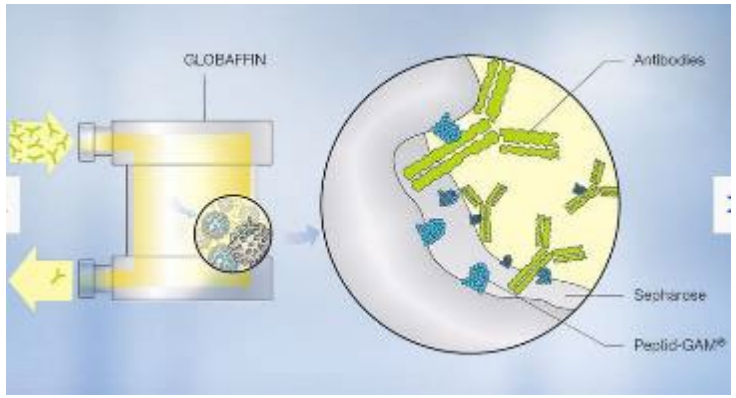
Plasmavolume (PV)
- PV = gew x 0.065 x (1-ht)
- 1-1.5 x PV
- 75% verwijdering = 1.4 PV

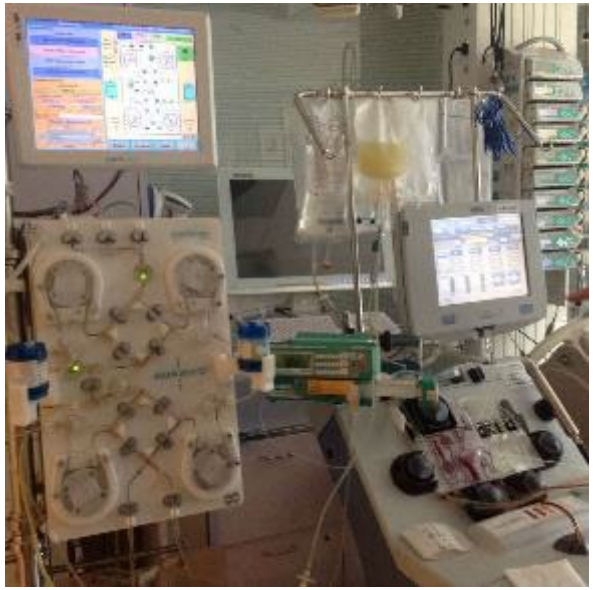
Voordelen: eenvoudige techniek, single-needle, sneller dan P-filtratie

Nadelen: groot extracorporeel volume, trombocytopenie, hypocalciemie

Plasmaferese - dubbele filtratie - immunoadsorptie



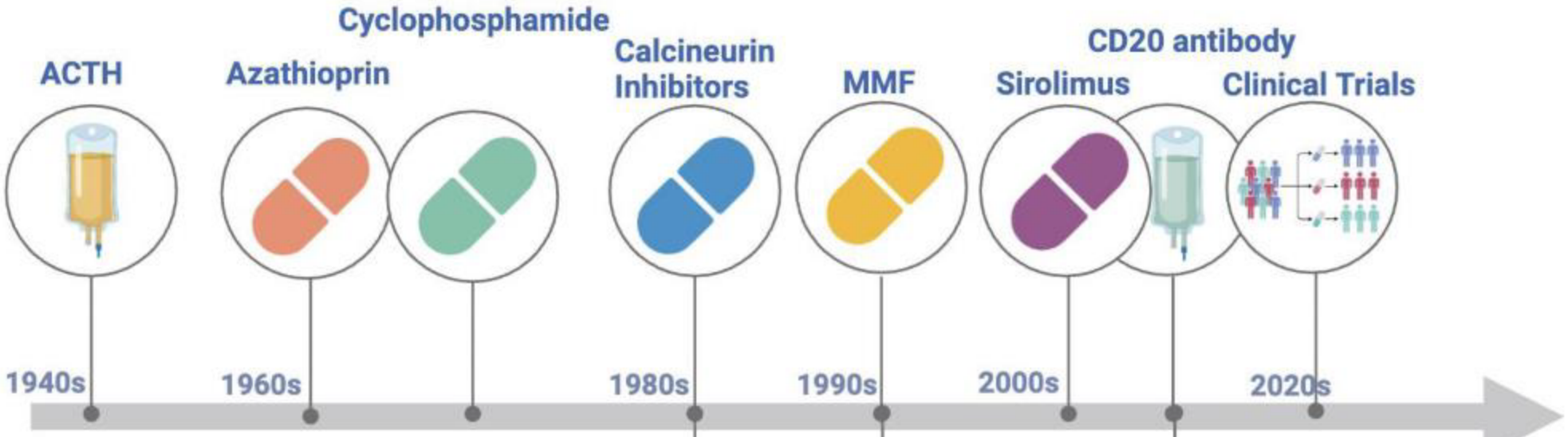




IgG 3.6 g/L
IgA 0 g/L
IgM 0.03 g/L

Voordelen: alleen Ig verwijderen
Nadelen: langere behandelduur, kosten

Timeline of treatment in FSGS



ACTH:
Has showed benefits in proteinuria reduction in adults.
Has showed no effects in children.

Azathioprin:
May reduce proteinuria but no evidence in adults.

Has no evidence of being superior compared to corticosteroid in children.

Cyclophosphamide:
Is infective in adults and children.

Calcineurin inhibitors:
Have shown widespread use and effectiveness. Discerning superiority between CNI remains elusive from historical data.

MMF:
Demonstrates proteinuria reduction in adults.
Promise data in children by sparing corticosteroid use.

Sirolimus:
No efficacy in FSGS

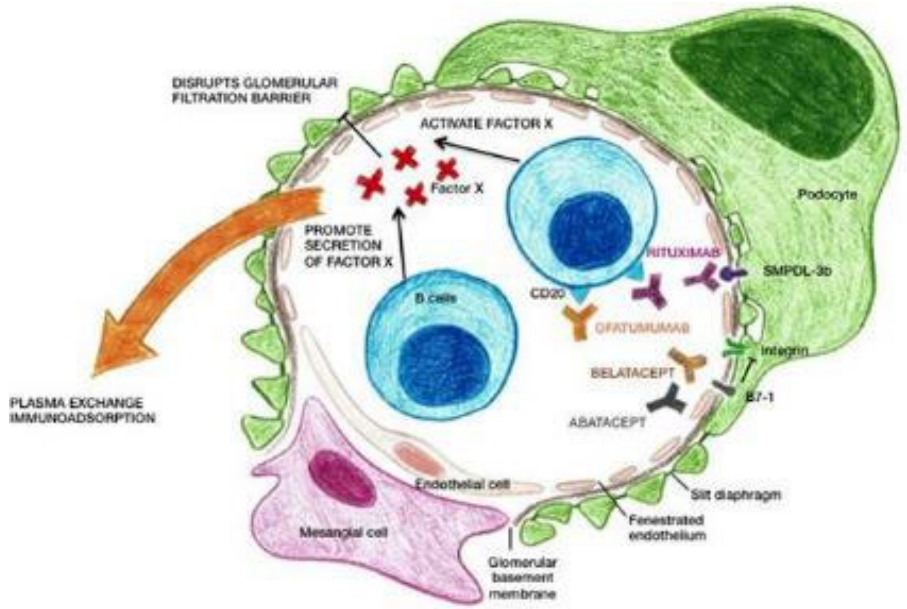
Rituximab:
Has limited evidence

Clinical Trials
Sparsentan, Atrasentan, TRPC5 channel modulators, SLIT2 antagonists, APOL1 inhibitors, and other promising interventions.

MATCH
Novel approach by providing participants with results of biomarker analyses

Mishra et al.| Kidney Medicine 2024

Prognose FSGS



- Eind stadium nierfalen als niet in remissie
- Dialyse
- Niertransplantatie
- Risico op recidief primaire ziekte na niertransplantatie

Nieuwe inzichten behandeling SRNS / FSGS en recidief na niertransplantatie

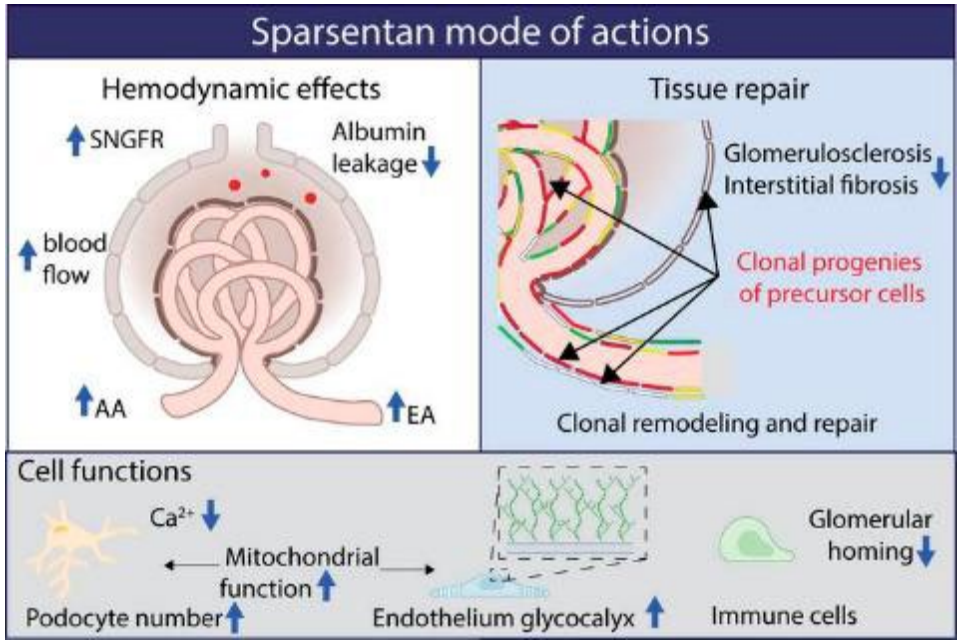
als geen effect tacrolimus, Cellcept, ACEi, ARB

Plasmaferese, plasmafiltratie, immunoadsorptie, LDL-ferese

Anti-CD20 mAb (Rituximab, ofatumumab, obinutuzumab)

Anti-CD38 (daratumumab)

Studies (RCTs): sparsentan (Eppik), …




B-cell