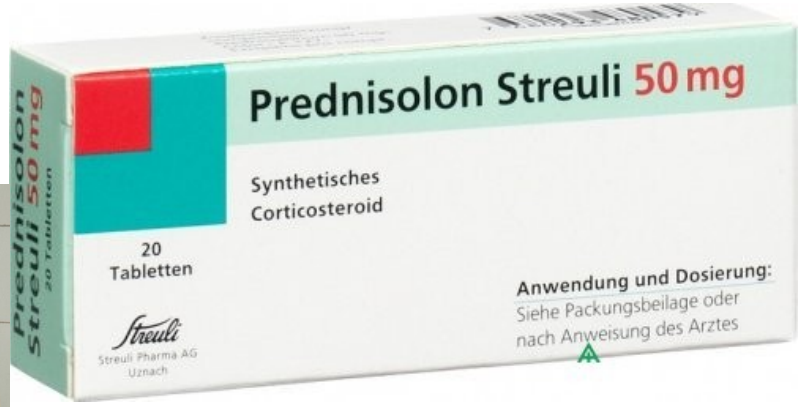
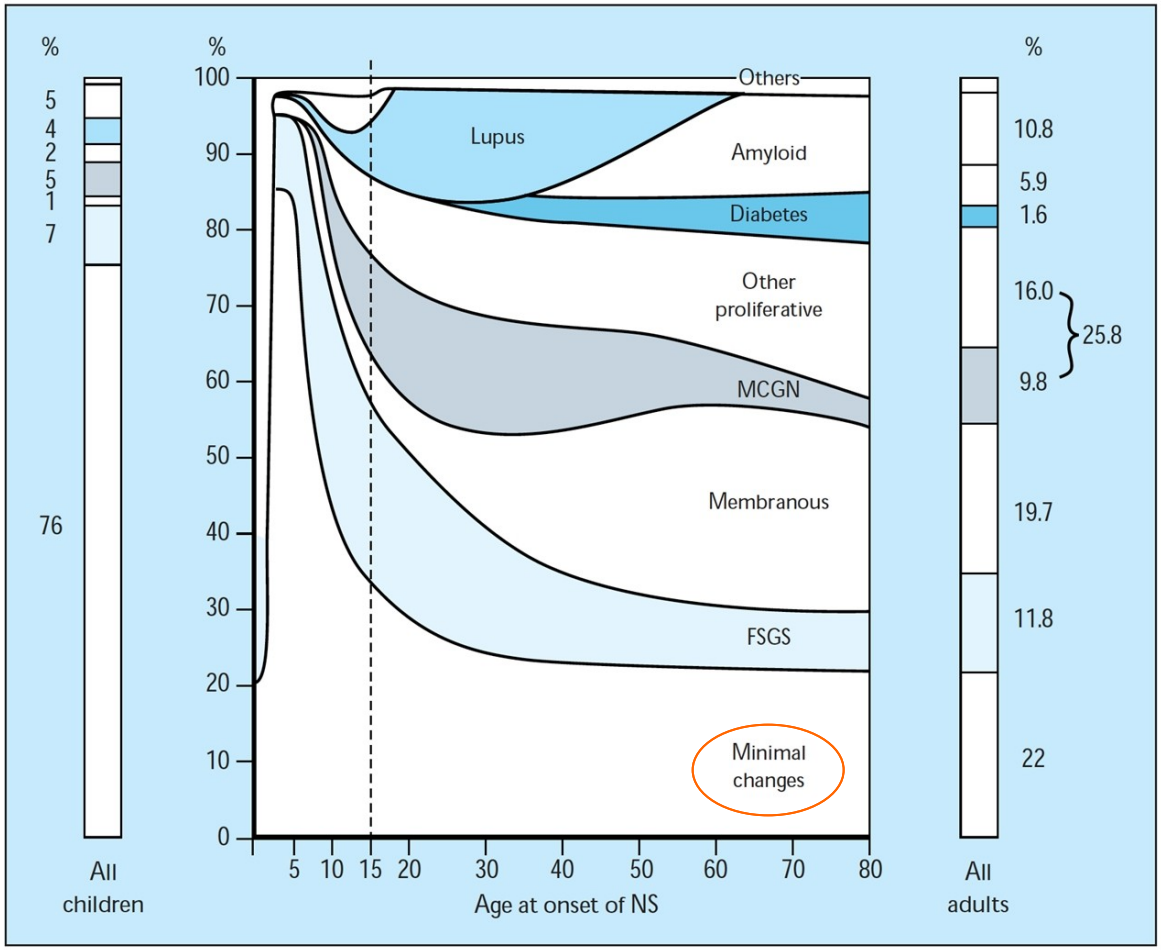
Behandeling nefrotisch syndroom bij kinderen

Themadag Specifieke Diagnoses
26-9-2015

A. Bouts, kindernefroloog,
Emma Kinderziekenhuis/AMC, Amsterdam



Nefrotisch syndroom op kinderleeftijd



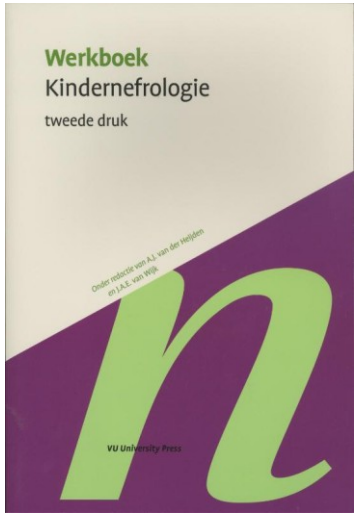
Nefrotisch syndroom op kinderleeftijd
minimal change?
atypisch beloop = indicatie voor overleg kindernefroloog

Eerste presentatie	Beloop
Leeftijd < 12 mnd of > 12 jaar	Steroid ongevoelig (SRNS)
Hypertensie	Frequent recidiverend NS (FRNS)
Verminderde nierfunctie	Steroid afhankelijk NS (SDNS)
Systemische ziekte (o.a. SLE)	Steroid toxiciteit
Verlaagd complement (C3/C4)	Bij overweging start steroid sparende medicatie
Nefritisch-Nefrotisch syndroom (hematurie, overvulling, verminderde nierfunctie)	

Initiële behandeling MCNS

- Eerste episode
  - Prednison 60 mg/m^2/dag ged. 6 wkn (max. 80 mg)
  - Prednison 40 mg/m^2 om de dag ged. 6 wkn

- Respons
  - Remissie 90-95%
  - “Steroid sensitive nephrotic syndrome” (SSNS)



Natuurlijk beloop MCNS

- Remissie na initiële behandeling: 90%
- Steroid resistent (SRNS)

- Recidiverend beloop: 60-90%
  - Frequent recidiverend (FRNS)
  - Steroid afhankelijk (SDNS)
  - Steroid resistent (SRNS)

Initiële behandeling MCNS

Supplementary Table 1. Currently reported prednisolone regimens for the first episode of childhood nephrotic syndrome.

Initial prednisolone regimen	Duration	Cumulative dose	Reported use
ISKDC: 4 weeks 60 mg/m^2 daily 4 weeks 40 mg/m^2 on 3 out of 7 days or on alternate days	8 weeks	2240 mg/m^2	Canada,[1] Nigeria,[2] South-Korea,[3] UK,[4] USA[5]
BAPN: 60 mg/m^2 daily until remission 4 weeks 40 mg/m^2 on 3 out of 7 days or on alternate days	Maximum 8 weeks	Maximum 2240 mg/m^2	UK[6]
APN : 6 weeks 60 mg/m^2 daily 6 weeks 40 mg/m^2 on alternate days	12 weeks	3360 mg/m^2	Canada,[1] Germany,[7] Japan,[8] The Netherlands,[9] Spain,[10] USA[5]
SNP: 4 weeks 60 mg/m^2 daily 8 weeks 60 mg/m^2 on alternate days 2 weeks 45 mg/m^2 on alternate days 2 weeks 30 mg/m^2 on alternate days 2 weeks 15 mg/m^2 on alternate days	18 weeks	3990 mg/ m^2	France[11]
Modifications of one or more of the regimens described above	4-24 weeks	uncertain	Australia,[12] Brazil,[13] Egypt,[14] India,[15] Poland,[16] Taiwan,[17] Turkey,[18] USA[5]

ISKDC, International Society of Kidney Disease in Children; APN, Arbeitsgemeinschaft für Pädiatrische Nephrologie; BAPN, British Association for Pediatric Nephrology; SNP, Société de Néphrologie Pédiatrique.

Teeninga N. JASN. 2013;24:149-159.

Initiële behandeling MCNS

KDIGO Glomerulonephritis Workgroup, 2012:

"3.1: Treatment of the initial episode of SSNS

3.1.1: We recommend that corticosteroid therapy (prednisone or prednisolone)[1] be given for at least 12 weeks. (*1B*)

3.1.1.1: We recommend that oral prednisone be administered as a single daily dose (*1B*) starting at 60 mg/m^2/day or 2 mg/kg/day to a maximum 60 mg/day. (*1D*)

3.1.1.2: We recommend that daily oral prednisone be given for 4–6 weeks (*1C*) followed by alternate-day medication as a single daily dose starting at 40 mg/m^2 or 1.5 mg/kg (maximum 40 mg on alternate days) (*1D*) and continued for 2–5 months with tapering of the dose. (*1B*)" (163).

- "Risk of relapse 30% reduced with 12 wks compared to 8 wks"

www.kdigo.org

Lombel RM. Ped Nephrol 2013;28:415-426

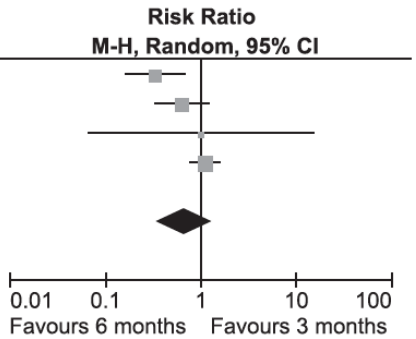
Initiële behandeling MCNS

> 3mnd prednison : geen voordeel

A

Study or Subgroup	6 months prednisolone Events	Total	3 months prednisolone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Gulati 2001	8	70	24	70	27.8%	0.33 [0.16, 0.69]	2002
Hiraoka 2003	10	36	15	34	29.9%	0.63 [0.33, 1.20]	2003
Mishra 2012	1	37	1	37	5.1%	1.00 [0.06, 15.40]	2012
Current study	32	64	28	62	37.1%	1.11 [0.77, 1.60]	2012
Total (95% CI)		**207**		**203**	**100.0%**	**0.67 [0.34, 1.29]**	
Total events	51		68				

Heterogeneity: Tau² = 0.27; Chi² = 9.64, df = 3 (P = 0.02); I² = 69%
Test for overall effect: Z = 1.20 (P = 0.23)



B

Study or Subgroup	6 months prednisolone Events	Total	3 months prednisolone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Hiraoka 2003	10	36	15	34	28.4%	0.63 [0.33, 1.20]	2003
Mishra 2012	1	37	1	37	1.8%	1.00 [0.06, 15.40]	2012
Current study	32	64	28	62	69.8%	1.11 [0.77, 1.60]	2012
Total (95% CI)		**137**		**133**	**100.0%**	**0.94 [0.65, 1.36]**	
Total events	43		44				

Heterogeneity: Tau² = 0.02; Chi² = 2.23, df = 2 (P = 0.33); I² = 10%
Test for overall effect: Z = 0.32 (P = 0.75)

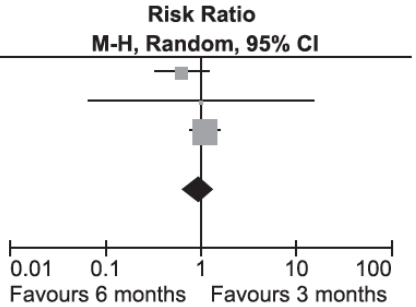
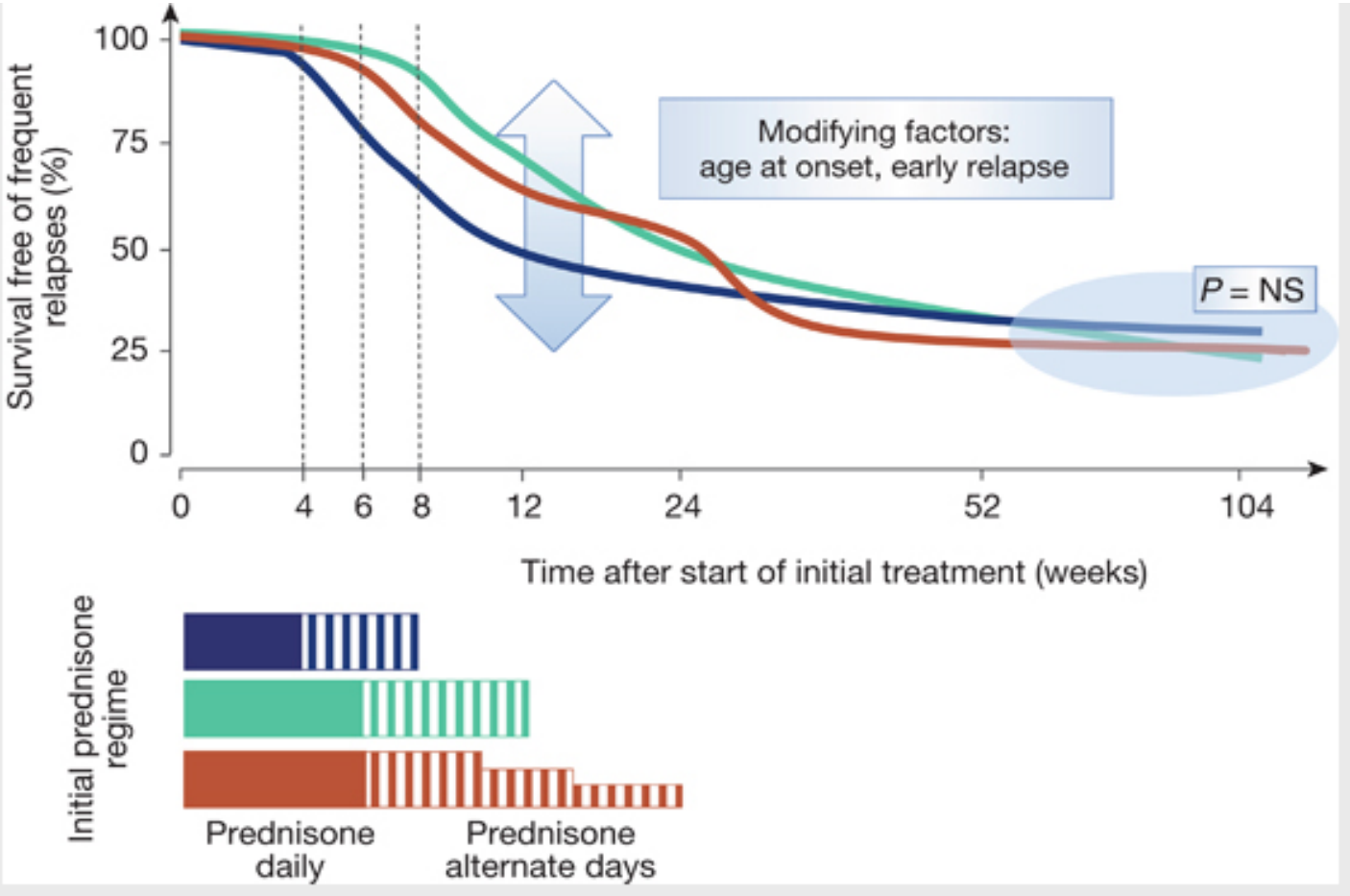


Figure 4. Meta-analyses of studies comparing 3 months of prednisolone to 6 months of prednisolone do not reveal a benefit of prolonged treatment duration. (A) All four available studies (B) Two fully published studies. In both analyses, numbers of FRNS of the current study correspond with numbers of strict FRNS. Analyses were performed with Review Manager (RevMan) version 5.1 for Windows (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2011).

Teeninga N. JASN. 2013;24:149-159.

Initiële behandeling MCNS



Hoyer PF. Kidney Int: 2015;87:17-19

Conclusie: Initiële behandeling MCNS

- Recidiverend beloop bij ±50% patiënten
- Langere duur initiële behandeling biedt geen extra voordeel (op de langere termijn)
- Klinisch beloop mogelijk afhankelijk van:
  - Leeftijd: jongere kinderen meer recidiverend beloop, meer steroid-afhankelijkheid
  - Tijd tot eerste terugval(?)
  - Geslacht

Hoyer PF. Kidney Int: 2015;87:17-19

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Nefritisch-Nefrotisch syndroom (hematurie, overvulling, verminderde nierfunctie)	

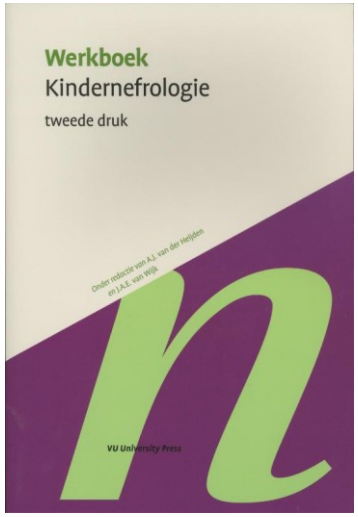
Risicofactoren voor frequente recidieven

- Vroegtijdig eerste recidief
- Korte tijd tussen 1e en 2e recidief
- Aantal recidieven in eerste 6 maanden
- Jonge leeftijd
- Jongens
- Initieel niet snel reageren
- Infectie bij debut
- Hematurie bij debut

Behandeling recidief / steroid afhankelijkheid

- Behandeling recidief
  - Prednison 60 mg/m^2/dag tot de urine 3 dgn vrij van eiwit is
  - Prednison 40 mg/m^2 o.d.d. ged. 6 wkn

- Behandeling FRNS & SDNS
  - Cyclofosfamide 3 mg/kg/dag ged. 8 wkn
  - Ciclosporine (geen dosisadvies)
  - Mycofenolaat mofetil (geen dosisadvies)



Behandeling recidief

KDIGO Glomerulonephritis Workgroup, 2012:

"3.2: Treatment of relapsing SSNS with corticosteroids

3.2.1: Corticosteroid therapy for children with infrequent relapses of SSNS:

3.2.1.1: We suggest that infrequent relapses of SSNS in children be treated with a single daily dose of prednisone 60 mg/m^2 or 2 mg/kg (maximum of 60 mg/day) until the child has been in complete remission for at least 3 days. (*2D*)

3.2.1.2: We suggest that, after achieving complete remission, children be given prednisone as a single dose on alternate days (40 mg/m^2 per dose or 1.5 mg/kg per dose: maximum 40 mg on alternate days) for at least 4 weeks. (*2C*)

- Pred 60 mg/m2 tot 3 dgn remissie
- 40 mg/m2 AD 4 weeks

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Lombel RM. Ped Nephrol 2013;28:415-426

Behandeling FRNS / SDNS

3.2.2: Corticosteroid therapy for frequently relapsing (FR) and steroid-dependent (SD) SSNS:

3.2.2.1: We suggest that relapses in children with FR or SD SSNS be treated with daily prednisone until the child has been in remission for at least 3 days, followed by alternate-day prednisone for at least 3 months. (*2C*)

3.2.2.2: We suggest that prednisone be given on alternate days in the lowest dose to maintain remission without major adverse effects in children with FR and SD SSNS. (*2D*)

3.2.2.3: We suggest that daily prednisone at the lowest dose be given to maintain remission without major adverse effects in children with SD SSNS where alternate-day prednisone therapy is not effective. (*2D*)

3.2.2.4: We suggest that daily prednisone be given during episodes of upper respiratory tract and other infections to reduce the risk for relapse in children with FR and SD SSNS already on alternate-day prednisone. (*2C*)" (164–165).

- Na remissie, pred odd 3 mnd, laagst mogelijke dosering
- Pred dagelijks als odd niet werkt
- Bij luchtweginfectie dgls pred

www.kdigo.org

Lombel RM. Ped Nephrol 2013;28:415-426

Bijwerkingen prednison

Cushing	Afbuigende lengtegroei
gewichtstoename	Spieratrofie
Osteoporose	Neuropsychiatrisch
Verminderde immuniteit / Infecties	Aseptisch botnecrose
Huid: striae, atrofie, ecchymosen	Acne
Verminderde glucose tolerantie / DM	Intracraniele drukverhoging
Verhoogd cholesterol	Thrombose
Cataract	
Zoutretentie / Hypertensie	

Original article

Arch Dis Child 2010 feb;95(2):146-9

Long-term steroid treatment and growth: a study in steroid-dependent nephrotic syndrome

Department of Nephrology, Great Ormond Street Hospital for Children, Great Ormond Street, London, UK

Jacob Simmonds, Nicholas Grundy, Richard Trompeter, Kjell Tullus

- Retrospective study 1993-2004
- SDNS
- N= 41
- Mean observation: 4.2 patients yrs
- Relapses: 0.25 per patient yr
- 21 periods steroid sparing treatment: levamisole, ciclosporin, cyclofosfamide

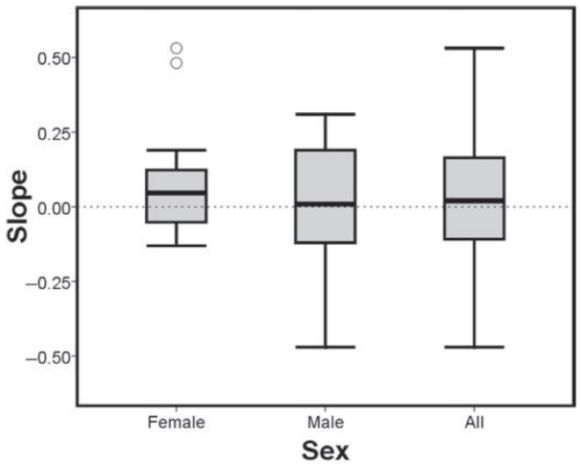


Figure 1 Change in height standard deviation score (SDS) velocity over the entire course of study, grouped by sex.

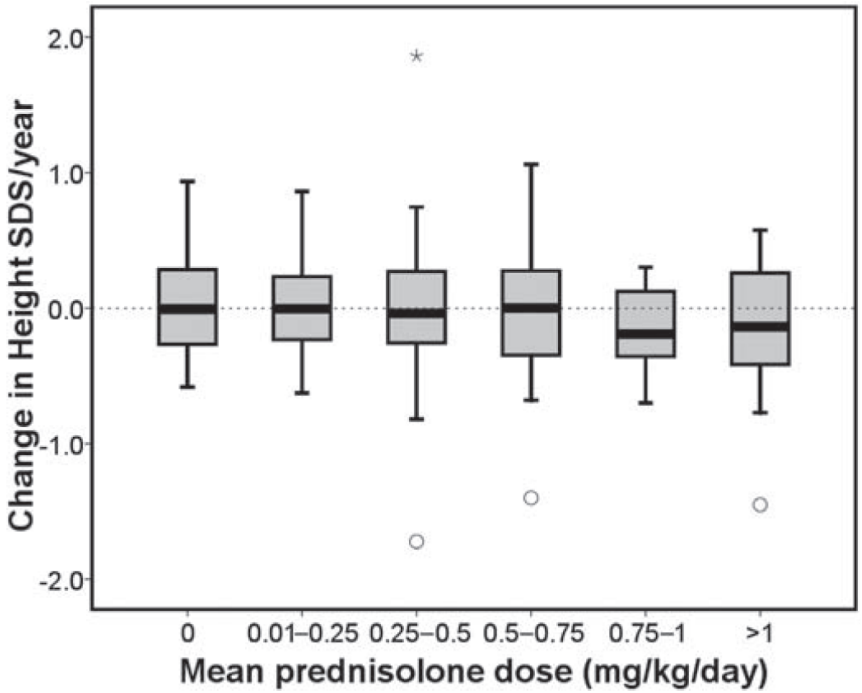


Figure 2 Six-month change in height standard deviation score (SDS)/year grouped by prednisolone dose (mg/kg/day).

Steroids

Nephrol Dial Transplant (2013) 28: 2099–2106
doi: 10.1093/ndt/gft090
Advance Access publication 2 May 2013

Prevention of steroid-induced low bone mineral density in children with renal diseases: a systematic review

Mariken P. Gruppen[1], Jean-Claude Davin[1], Michiel J. Oosterveld[1], Michiel F. Schreuder[2], Eiske M. Dorresteijn[3], Sharon P. Kramer[4] and Antonia H. Bouts[1]

[1]Department of Pediatric Nephrology, Emma Children's Hospital/Academic Medical Centre, Amsterdam, The Netherlands, [2]Department of Pediatric Nephrology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, [3]Department of Pediatric Nephrology, Erasmus MC-Sophia, Rotterdam, The Netherlands and [4]Cochrane Collaboration Centre, Academic Medical Centre, Amsterdam, The Netherlands

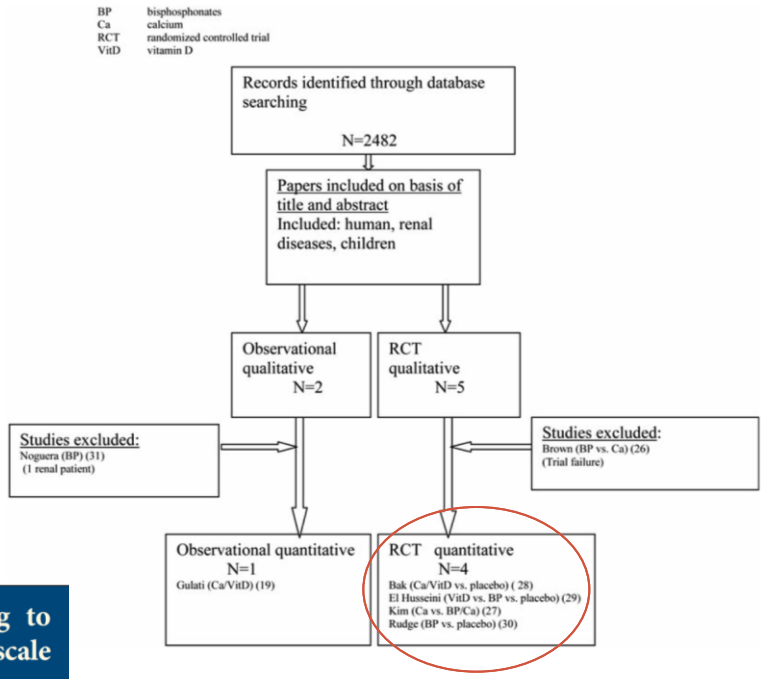


Table 2. Risk of bias Cochrane Collaboration's tool [23]

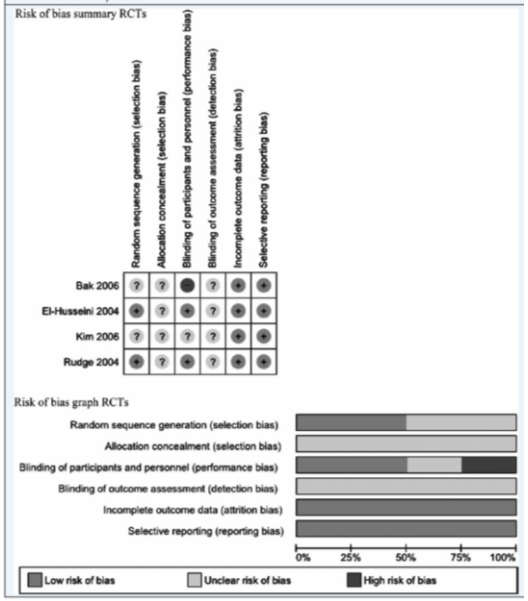


Table 3. Cohort star template according to the Newcastle–Ottawa quality assessment scale [25]

	Selection ★★★★	Comparability ★★	Outcome ★★★
Gulati *et al.* [19]	★★★	★	★★★

Conclusions:

- All studies reported significant improvement in BMD in treatment group compared to control group.
- According to GRADE, the quality of evidence of the effectiveness of Ca/vitD compared with placebo for the outcome BMD was classified as low

Ca/vitD advies

- Laagdrempelig starten
- Overweeg monitoring 25(OH)D spiegels, Ca,PTH

- Ca normale intake 30-75 mg/kg/dag
- <10 kg: 250 mg/dg; 10-40 kg 500 mg/dg; >40 kg 1000 mg/dg
- vitD (Devaron®, Divisun®): 400-800 IE/dg

- DXA scan?

Epidemiology and Pathophysiology of Nephrotic Syndrome–Associated Thromboembolic Disease

Bryce A. Kerlin,[†‡] Rose Ayoob,[§] and William E. Smoyer*[‡§]*

Clin J Am Soc Nephrol 7: 513–520, 2012.

- More common in adults (25%) than children (3%)
- Variation within type of NS:
  congenital NS, secondary NS, (vasculitis), membranous nephropathy (SLE)

Table 1. Summary of reported incidence of nephrotic syndrome–associated thromboembolism

Publication Year	Author	*N*	TE	%TE	Study Type	Notes
Childhood						
1973	Egli *et al.* (15)	3377	60	1.8	Retrospective	Probably only symptomatic TE
1984	Mahan *et al.* (23)	41	4	9.8	Retrospective	Only congenital nephrotic syndrome
1986	Hoyer *et al.* (17)	26	7	26.9*	Retrospective	V·Q evidence of PE
1987	Mehls *et al.* (24)	204	9	4.4	Retrospective	Primarily only symptomatic TE
1991	Tsau *et al.* (25)	193	2	1	Retrospective	Only symptomatic TE reported
1997	Schlegel (8)	360	11	3.0	Not stated	Primarily only symptomatic TE
2000	Citak *et al.*l (14)	49	2	4.1	Prospective	Only symptomatic TE reported
2000	Lilova *et al.* (19)	447	9	2.0	Retrospective	Only symptomatic TE reported
2001	Hamed *et al.* (16)	30	4	13.0	Retrospective	Only congenital nephrotic syndrome
2009	Kerlin *et al.* (2)	326	30	9.2	Retrospective	Only symptomatic TE reported; included secondary causes of NS
TOTAL		5053	141	2.8		

Behandeling recidief / steroid afhankelijkheid

- Zorgstandaard Nefrotisch Syndroom (www.zorgstandaarden.net)

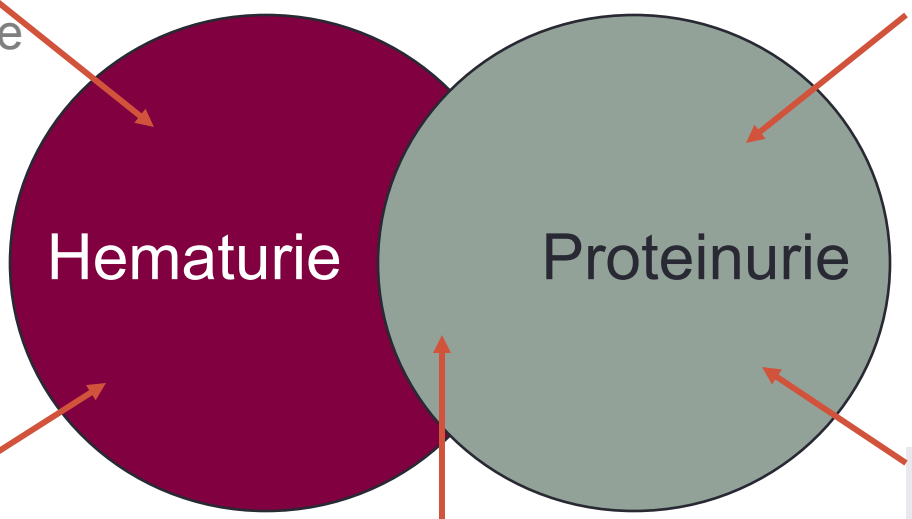
- Steroidafhankelijk NS & FRNS
  - Levamisol (Elmisol®)
  - Cyclofosfamide (Endoxan®)
  - Ciclosporine (Neoral®)
  - Tacrolimus (Prograft®)
  - Mycofenolaat mofetil (Cellcept®)
  - Rituximab (MabThera®)
  - Combinatie van bovenstaande

Zorgstandaarden
Zeldzame Aandoeningen

Indicaties voor nierbiopt

Fasen van renale macroscop. hematurie

Persisterende proteinurie > 1 J



Doofheid

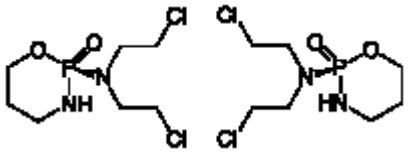
Familiaire

Nefropathie

Nefritisch syndroom/
Glomerulonefritis

Nefrotisch syndroom
- steroïd-resistentie
- oudere kinderen
- (1e levensjaar)
- systeemziekte

Cyclofosfamide



- Stikstofmosterdgassen; hecht alkyl groep aand DNA, en interfereert hierdoor aan DNA replicatie
- Bijwerkingen gerelateerd aan cumulatieve dosis, duur, leeftijd patient
- Significante bijwerkingen: haarverlies, beenmerg suppressie, infecties, verhoogd risico op maligniteit, verminderde vruchtbaarheid, hemorrhagische cystitis, gastro-intestinale klachten, mucositis, longfibrose
- Metabolisme beïnvloed door oa steroiden (cytochrome p450)
- Immunomodulatoire effecten: eliminatie T-regulatoire cellen (CD4+CD25+ T-cellen), inductie T-cel groei factoren zoals IFN.
- Gebruik voor NS sinds 1967. Minder effectief bij steroid afhankelijkheid dan FRNS.

Cyclofosfamide (Endoxan)

Nephrol Dial Transplant (2011) 26: 178–184
doi: 10.1093/ndt/gfq405
Advance Access publication 7 July 2010

Long-term effects of cyclophosphamide therapy in steroid-dependent or frequently relapsing idiopathic nephrotic syndrome

Benoît Cammas[1,4,*], Jérôme Harambat[1,*], Aurélia Bertholet-Thomas[2], François Bouissou[3], Denis Morin[4], Vincent Guigonis[5], Salih Bendeddouche[6], Nawel Afroukh-Hacini[7], Pierre Cochat[2], Brigitte Llanas[1], Stéphane Decramer[3] and Bruno Ranchin[2]

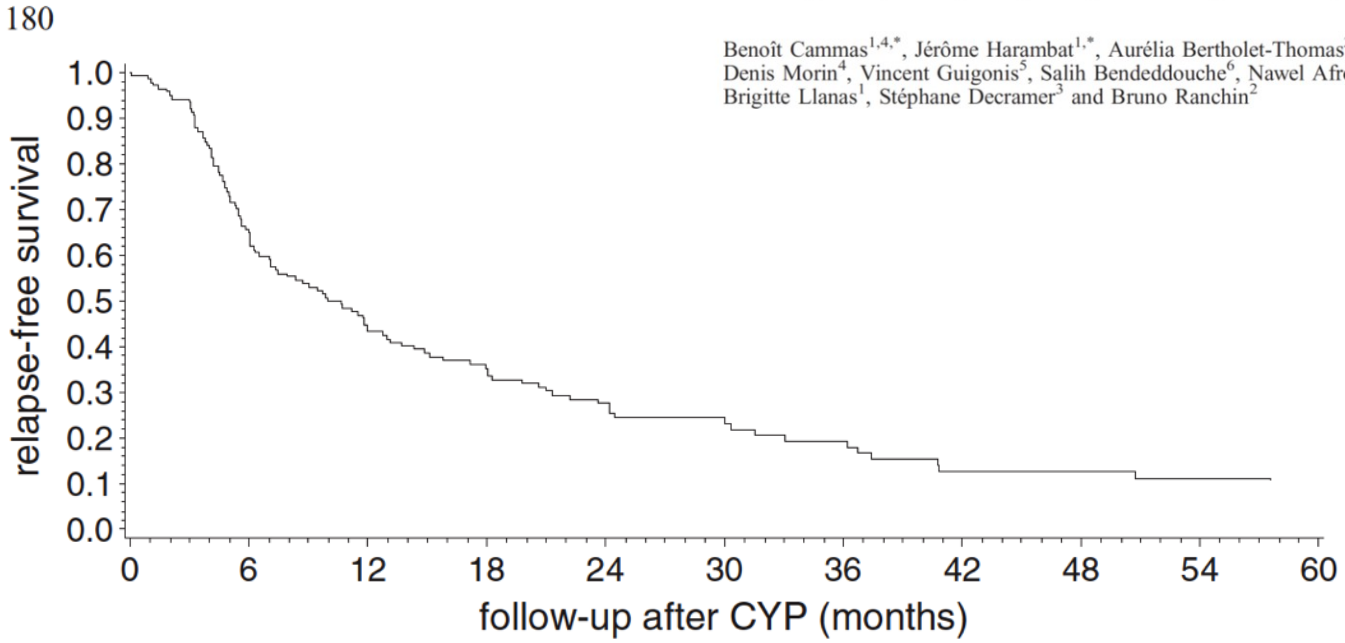
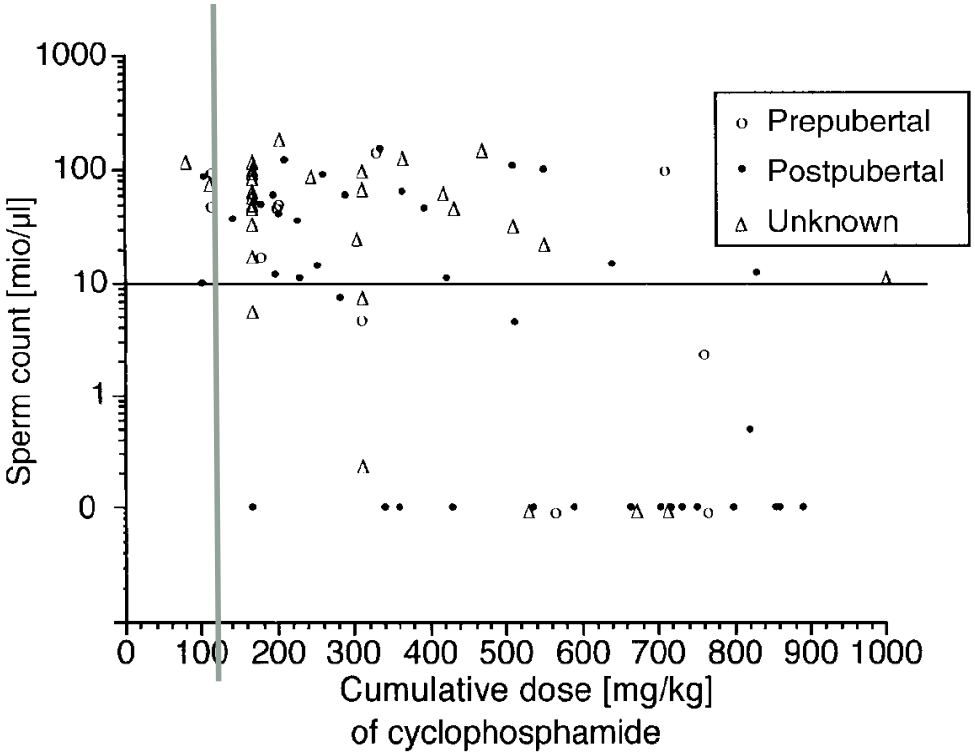


Fig. 1. Relapse-free survival after cyclophosphamide treatment.

Endoxan bijwerkingen

- Leukopenie – dosis afhankelijk
- Hemorrhagische cystitis –> hydratie++, Mesna?
- Misselijkheid
- Haarverlies
- (Fertiliteit)
- (Maligniteit)

- Gebruikelijk:
- 2.5 mg/kg x 8 weken



Latta et al, Ped Nephrol 2001

Cyclofosfamide vs. Levamisol

Table 4 Meta-analyses of randomized controlled trials of corticosteroid-sparing agents compared with prednisone and/or placebo in children with frequently relapsing or steroid-dependent steroid-sensitive nephrotic syndrome

Agent	RCTs[a] N	Patients N	Risk ratio of relapse (95 % CI[b])	Time of outcome (months)	Relative risk reduction
Cyclophosphamide	3	102	0.44 (0.26,0.73)	6–12	56 %
Chlorambucil	2	32	0.13 (0.03,0.57)	12	87 %
Levamisole	5	269	0.43 (0.27,0.68)	4–12	57 %
Mizoribine	1	197	Relapse rate ratio[c] 0.81 (0.61,1.05)	18	Not significant
Azathioprine	2	60	0.90 (0.59,1.38)	6	Not significant

[a] Randomized controlled trials

[b] Confidence intervals

[c] Relapse risk ratio = [total number of relapses ÷ observation period in treatment group] ÷ [total number of relapses ÷ observation period in control group]

Reproduced with permission from Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Workgroup. KDIGO Clinical Practice Guideline for Glomerulonephritis [8]

Lombel RM. Ped Nephrol 2013;28:415-426

Levamisol

Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children (Review)

Pravisitthikul N, Willis NS, Hodson EM, Craig JC

THE COCHRANE COLLABORATION®

Analysis 12.2. Comparison 12 Levamisole versus steroids or placebo or both, or no treatment, Outcome 2 Relapse at 6 to 12 months.

Review: Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children

Comparison: 12 Levamisole versus steroids or placebo or both, or no treatment

Outcome: 2 Relapse at 6 to 12 months

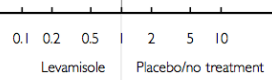
Study or subgroup	Levamisole n/N	Placebo/no treatment n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Abeyagunawardena 2006a	8/42	26/34		11.5 %	0.25 [0.13, 0.48]
Al-Saran 2006	14/34	24/24		14.5 %	0.42 [0.28, 0.63]
BAPN 1991	27/31	28/30		16.5 %	0.93 [0.79, 1.10]
Dayal 1994	9/22	10/14		12.1 %	0.57 [0.31, 1.05]
Rashid 1996	11/20	18/20		14.2 %	0.61 [0.40, 0.93]
Sural 2001	17/30	23/28		14.9 %	0.69 [0.48, 0.99]
Weiss 1993	15/16	16/18		16.3 %	1.05 [0.86, 1.30]
Total (95% CI)	**195**	**168**		**100.0 %**	**0.62 [0.42, 0.91]**

Total events: 101 (Levamisole), 145 (Placebo/no treatment)

Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 60.11$, df = 6 ($P<0.00001$); $I^2 = 90\%$

Test for overall effect: Z = 2.42 (P = 0.016)

Test for subgroup differences: Not applicable



- an ESPN supported trial -
www.levamisoletrial.com

- 1984: P Niaudet: Treatment of INS with Levamisole

Levamisole bijwerkingen

Table 2. Adverse effects of levamisole

	Adverse effects	Reference
Common	Nausea	(1,2)
	Vomiting	
	Abdominal cramping pain	
	Flu-like symptoms	
	Rashes	
Infrequent	Vasculitis	(2,3,10,12,16), our patient
	Agranulocytosis (defined as neutrophil <20%)	(1)
	Multifocal leukoencephalopathy	(1)
	Hypogammaglobulinemia	(13)
	Arthritis	
	Convulsion	
	Disulfiram-like reactions	(1)
	Myopathy	Our patient

Mode of action: restores cell-mediated immune function by activating T-cells, increasing neutrophil mobility, chemotaxis, and increasing the formation of anitbodies to antigen.
Immunosuppressive effect in diseases with T-cell overactivity
These paradoxical effects depend on dose administration and host genetic factors

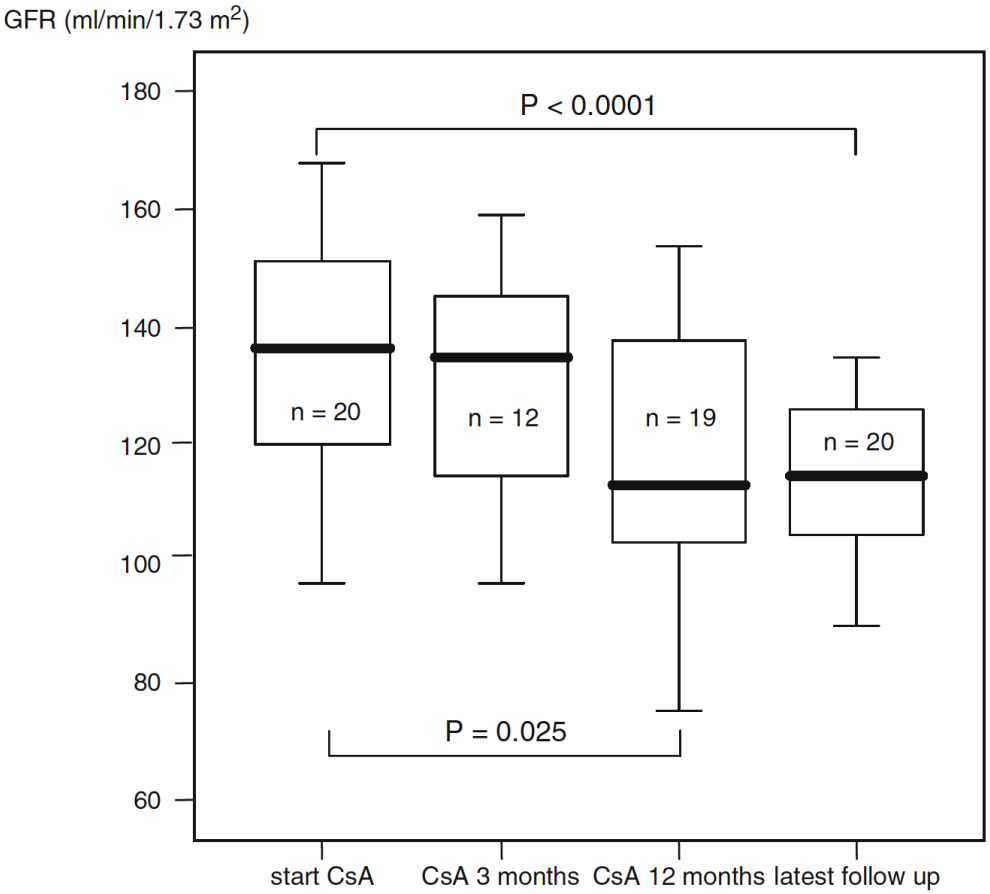
Calcineurine inhibitoren

- Cyclosporine (Neoral®) en Tacrolimus (Prograft®)

- Immuunsuppressief
- Stabilisieren podocytenstructuur
- 1e keuze bij focale sclerose
- Effectief, maar vaak recidief na afbouw

- Risico op nierschade:
  - Tubulointerstitiele fibrose
  - Vasculopathie (arteriolar hyalinosis)

Ciclosporine



Nefrotoxiciteit op lange termijn

Gemiddelde FU 5 jaar (max 10jr)

Neoral dosis ±130mg/m²/d

Histologisch géén afwijkingen

Kranz B. Pediatr Nephrol 2008;23:581-6.

Ciclosporine of tacrolimus

Table 5 Reported side effects in children with refractory nephrotic syndrome treated with CsA or TAC

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

Values are given as the number of patients

ALT/AST, Alanine/aspartate transaminase; CsA, cyclosporine A; TAC, tacrolimus

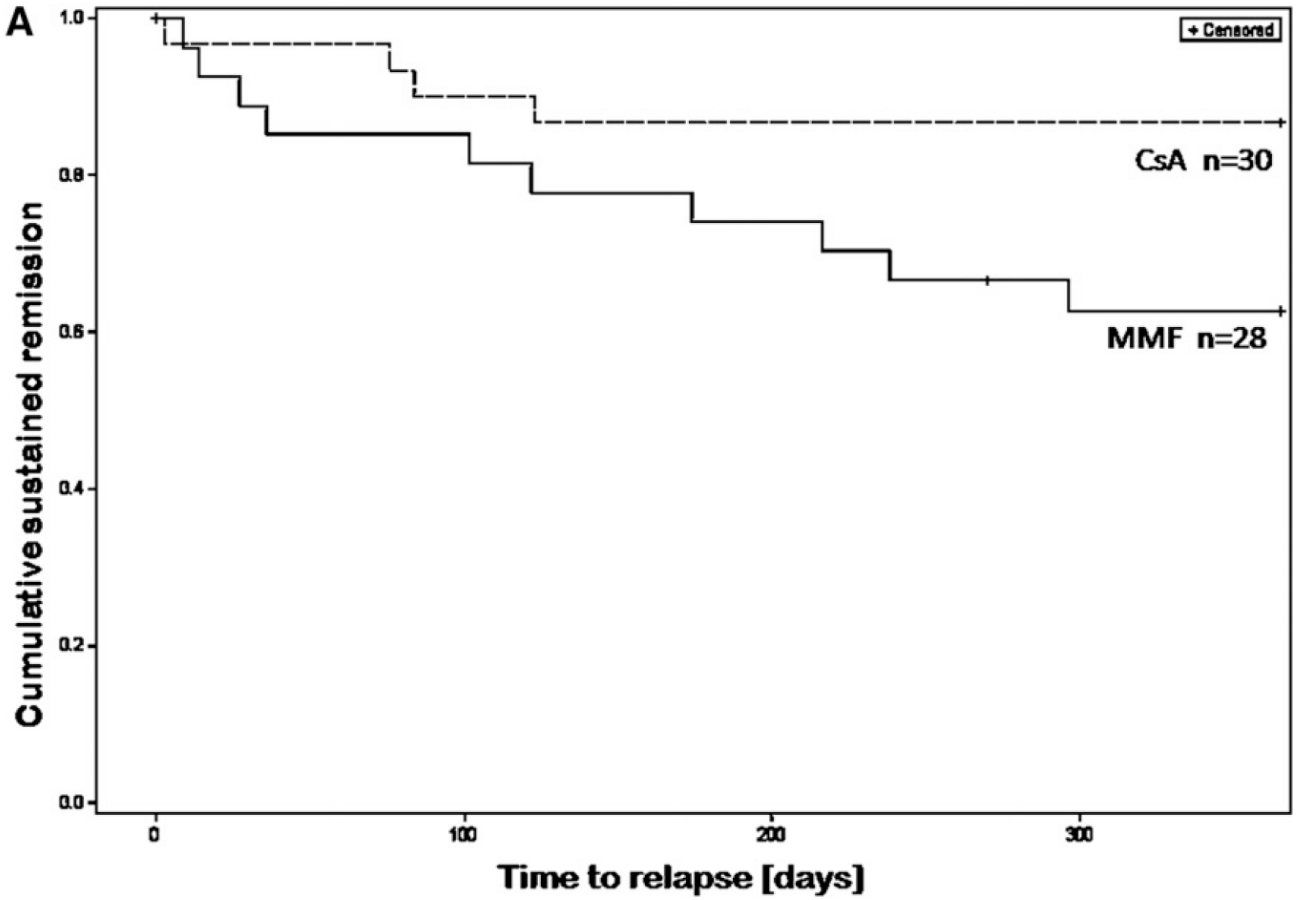
Bijwerkingen calcineurineremmers:
- Ciclosporine
- Tacrolimus

Wang W. Pediatr Nephrol. 2012;27:2073-2079

Mycofenolaat mofetil

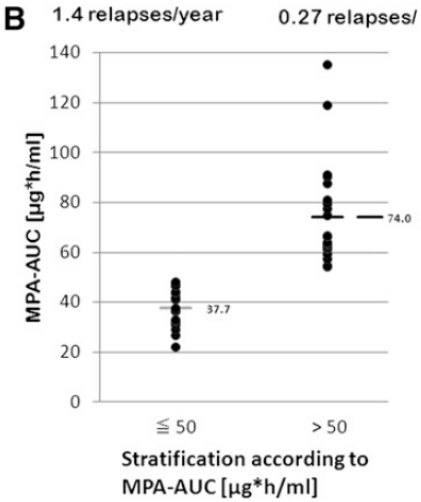
- Minder effectief dan calcineureremmers
- Bijwerkingen: gastrointestinale klachten, anemie en leukopenie, leverfunctie-stoornissen, geen nefrotoxiciteit

Mycofenolaat mofetil vs. ciclosporine



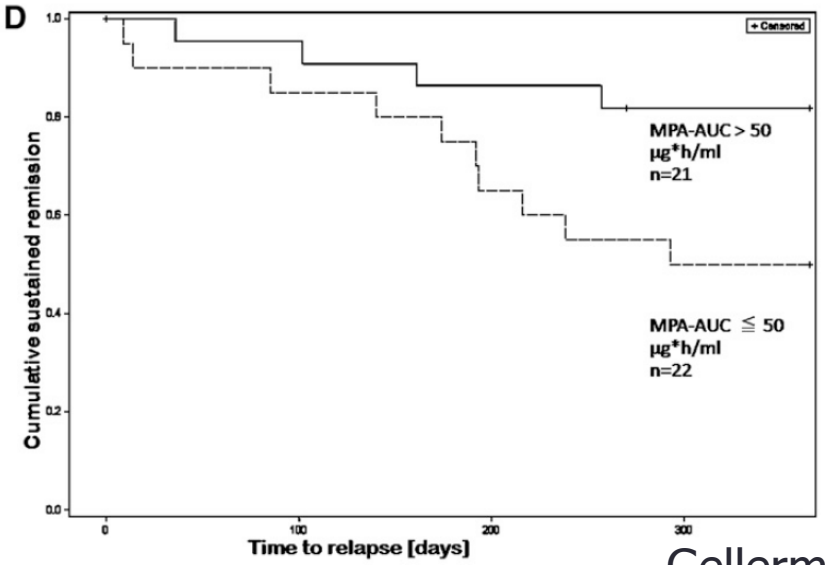
Gellerman J. J Am Soc Nephrol 2013;24:1689-1697

Mycofenolaat mofetil vs. ciclosporine



MPA-AUC [µg*h/ml]	≦ 50 [n=22]	> 50 [n=21]
Mean age [years]	10.1	9.86
MMF-Dosage [mg/m² /d]	1111	1030

Let op:
- Dosering
- Spiegelcontrole MMF



Gellerman J. J Am Soc Nephrol 2013;24:1689-1697

Rituximab

Pediatr Nephrol (2013) 28:1001–1009
DOI 10.1007/s00467-012-2260-3

REVIEW

Indications for use and safety of rituximab in childhood renal diseases

Kjell Tullus · Stephen D. Marks

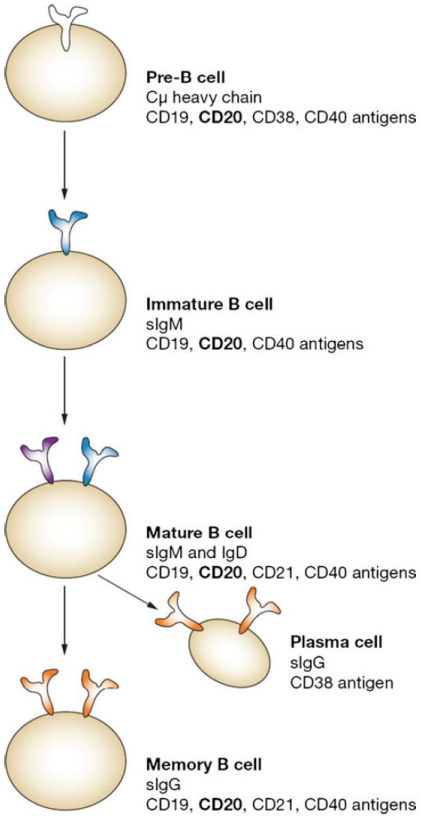
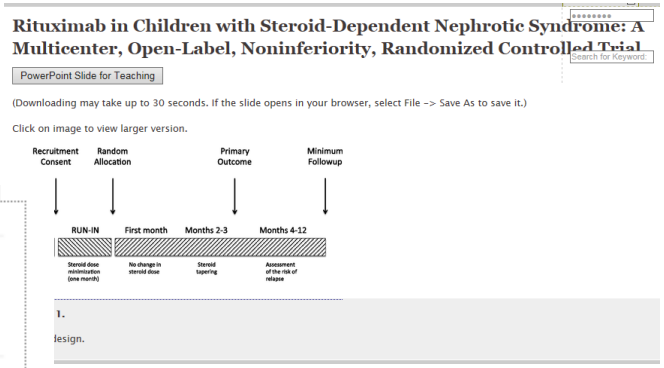


Fig. 1 B cell development and antigen expression. With permission from Salama and Pusey, Nature Clinical Practice Nephrology 2006;2:221–230

- B-cell depletion by antibody-dependent cell-mediated cytotoxicity, via binding IgG1 to B-cells to generate immune complexes that attract and bind FcyR-expressing effector cells
- Complement-dependent cytoxicity and direct signaling leading to apoptosis

Rituximab



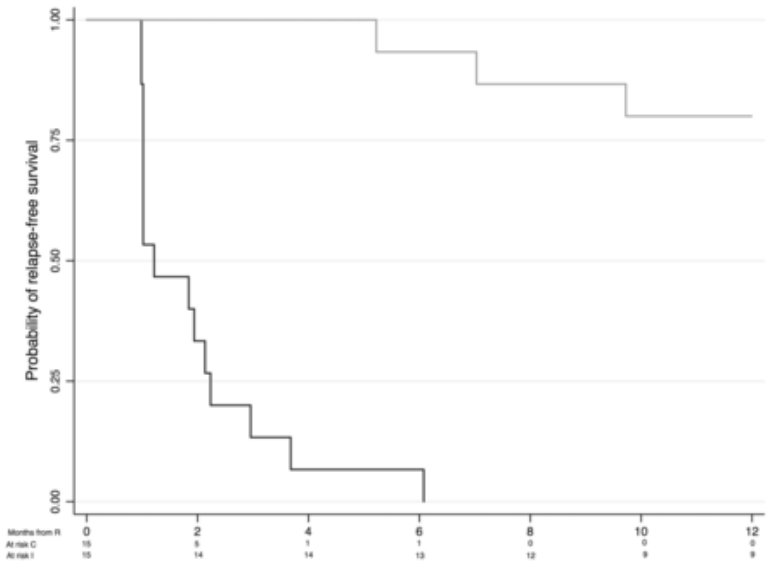


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Figure 5.

One-year relapse-free survival by treatment group in the prednisone (control; dark gray) and rituximab (intervention; light gray) groups. The risk of relapse was reduced by 98% in children treated with rituximab (hazard ratio, 0.02; 95% CI, 0.01 to 0.15). C, comparator group; I, intervention group; R, randomization.

- Effectief bij SDNS
- Ook bij SRNS?

Ravani P et al. J Am Soc Nephrol 2015;26(9):2259-66

Rituximab

Pediatr Nephrol (2013) 28:1001–1009
DOI 10.1007/s00467-012-2260-3

REVIEW

Indications for use and safety of rituximab in childhood renal diseases

Kjell Tullus · Stephen D. Marks

Table 2 Outcome in larger case series of rituximab treatment in children with steroid-dependent or frequently relapsing nephrotic syndrome

Author	Number of children	Full or partial response (*n*) (%)	Side-effects
Benz et al. [32]	1	1	None described
Guigonis et al. [33]	22	19 (85 %)	Five mild
			Four regarded as severe
			Atrial arrhythmia stopping spontaneously
			Malaise, transient bronchospasm
			Severe rotavirus gastroenteritis
			Transient neutropenia with gingivitis
Prytula et al. [34]	28	23 (82 %)	Data not separated on different diagnosis in the publication
			19 (27 %) of 70 showed side-effect
			Most common acute reaction to infusion one was a severe and life-threatening anaphylactic reaction
			Three severe infection
			Agranulocytosis with sepsis
			Two cases of pneumonia one of which with pseudomonas
Gulati et al. [35]	24	20 (83.3 %)	Three had mild infusion reactions
Kemper et al. [36]	37	26 (70.3 %)	No serious side-effects

Behandeling frequente recidieven / steroid afhankelijkheid

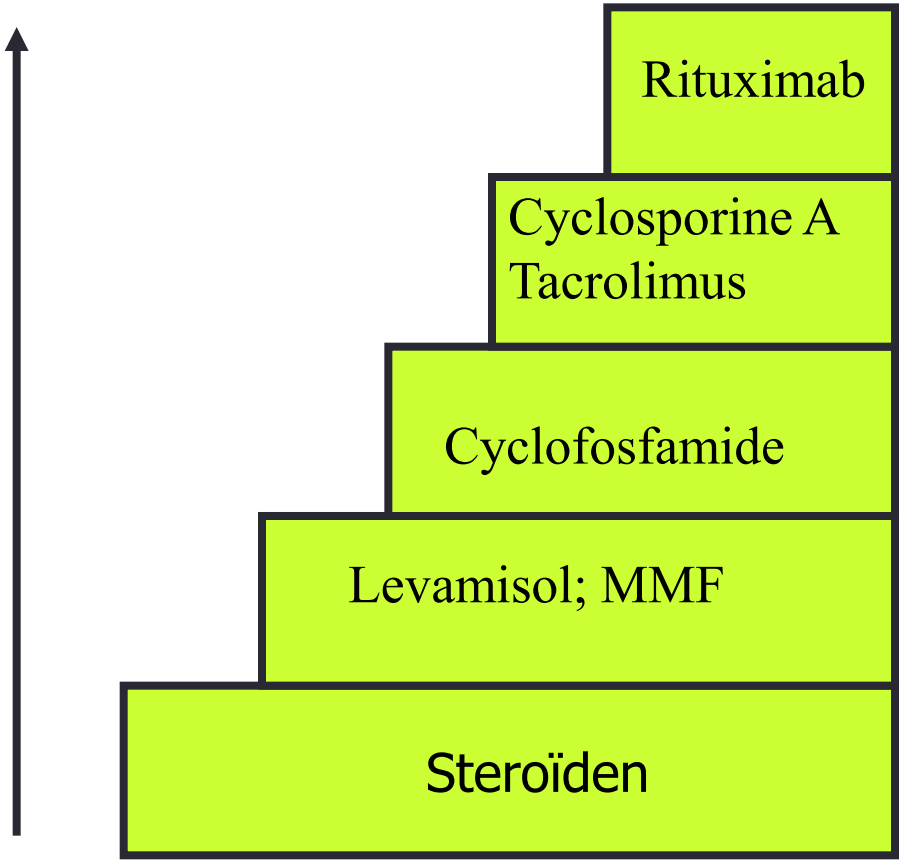
	Voor	Tegen
Levamisol	Weinig bijwerkingen, langdurige remissie, niet duur	Leukopenie, recidief na stop, beschikbaarheid
Mycofenolat mofetil (Cellcept®)	Langdurig remissie tijdens beh., niet nefrotoxisch	Myelosuppressief, recidief na stop, minder effectief dan ciclo/tacro
Ciclosporine A (Neoral®)	Langdurig remissie tijdens beh.	Recidief na stop, bijwerkingen (cosmetisch, nefrotoxisch)
Tacrolimus (Prograft®)	Langdurig remissie tijdens beh.	Recidief na stop, bijwerkingen (nefrotoxisch)
Cyclofosfamide (Endoxan®)	Langdurig remissie, relatief korte behandelduur, niet duur	Minder effectief in SDNS, myelosuppressief, lange termijn bijwerking (fertiliteit, maligniteit)
Rituximab (Mabthera®)	Langdurige remissie bij ernstig SD	Infusie-gerelateerde bijw., zeldzaam maar ernstige bijw (longfibrose, leukoencefalopathie)

Samenvattend

- Steroiden bij eerste presentatie
- Steroiden bij recidief
- Alternatieve middelen bij frequente recidieven / steroidafhankelijkheid en bijwerkingen van steroiden
- Volgorde? Bij voorkeur geen cyclofosfamide gezien bijwerkingen.
- Levamisol, MMF, CNI, Rituximab
- Combinatie van lage doseringen

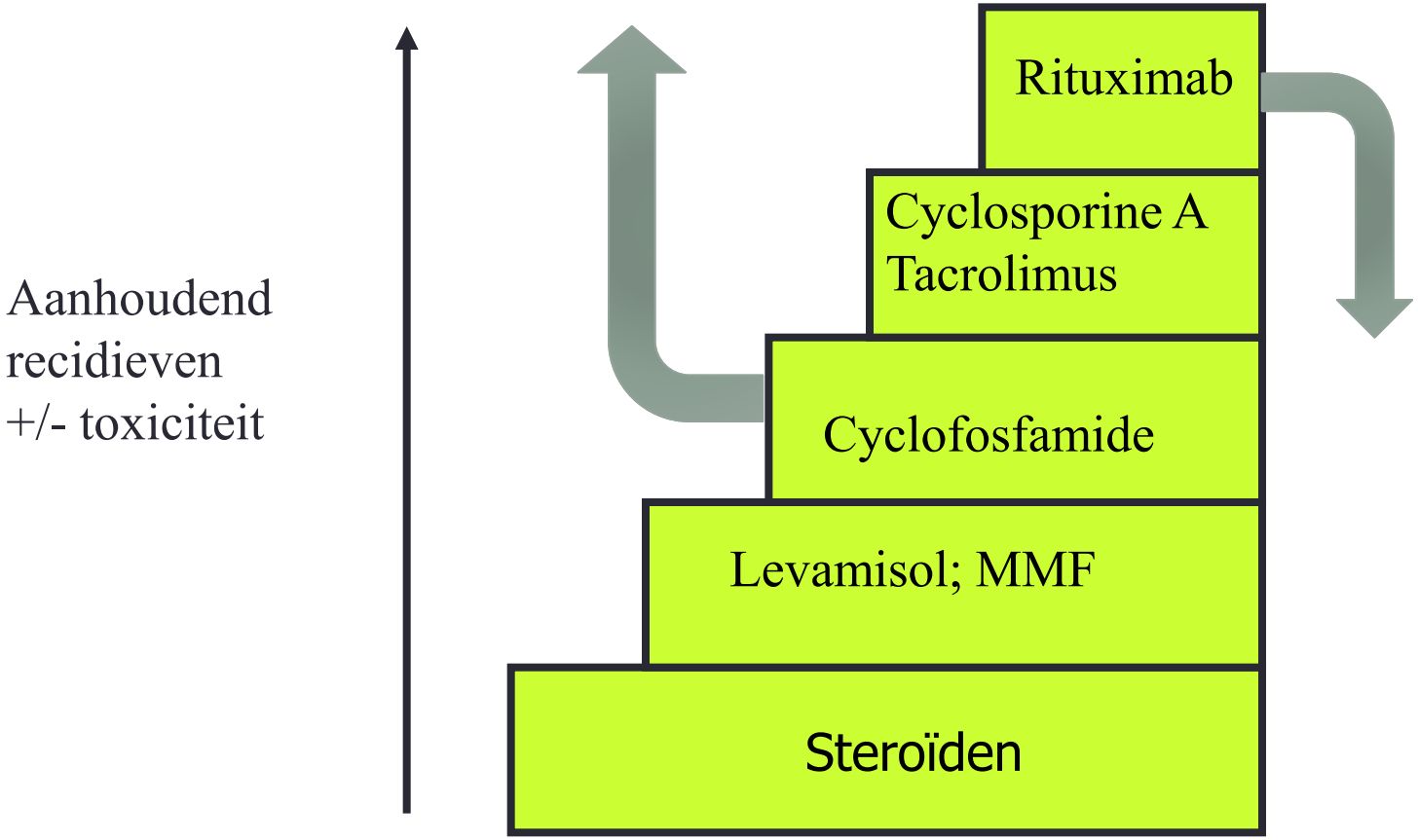
Steroidsparende therapie 2009

Aanhoudend
recidieven
+/- toxiciteit



C. Plank, Pediatric Nephrology Springmeeting 2009

Steroidsparende therapie 2014?



Follow-up kinderen met NS

- Lengte (groei), gewicht, bloeddruk
- Lab: nierfunctie, bloedbeeld, glucose, leverfunctie, Ca/vitD spiegels, PTH, CNI-spiegels, ANCA, B-cell subsets, IgG, urine sediment, eiwit/kreat
- Oogonderzoek
- Tandvlees controle
- KLIK (“thermometer” kwaliteit van leven in kaart)
- School
- Psychische bijwerkingen
- Huid onderzoek

Expertisecentrum nefrotisch syndrooom

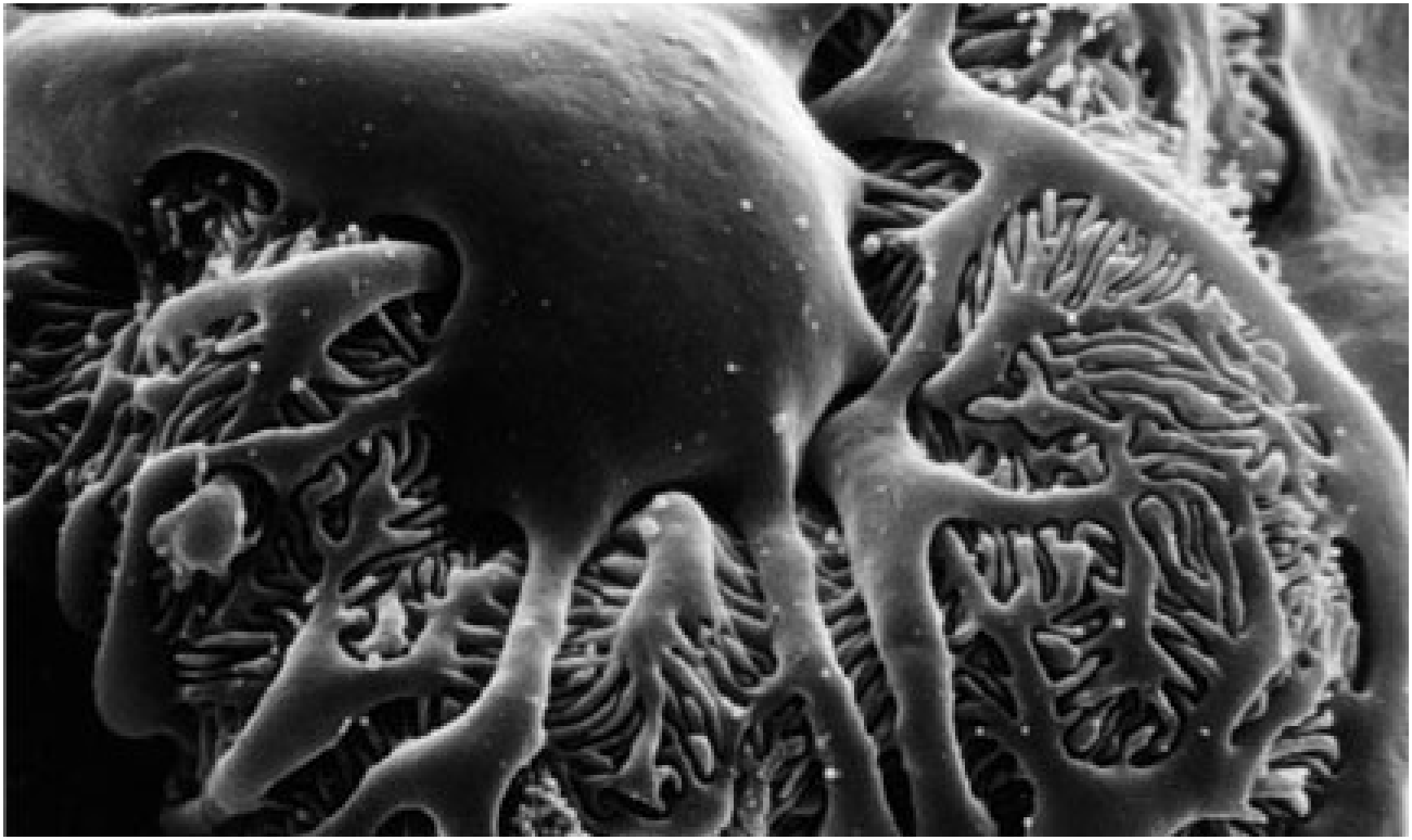
Criteria Expertisecentra
a) Is bekend met zowel de elementaire als meest recente wetenschappelijke ontwikkelingen t.a.v. o.a. diagnostiek, causale en/of symptomatische behandeling, primaire, secundaire en tertiaire preventieve maatregelen en/of specifieke psychosociale begeleiding van de patiëntengroep.
b) Deelt en dissemineert ervaring op het terrein van onderzoek en patiëntenzorg met andere expertisecentra en/of zorgprofessionals in de vorm van shared
c) Is *hét* kenniscentrum en fungeert als informatieloket/vraagbaak zorgverleners, patiënten en hun naasten als maatschappelijke
d) Levert hoog gespecialiseerde, complexe patiëntenzorg met een
e) Is in staat tot gespecialiseerde verrichtingen zoals operaties of diagnostiek en bijbehorende counseling.
f) Verricht kwalitatief hoogwaardig wetenschappelijk onderzoek publiceert daarover. Indien het expertisecentrum niet gevestig centrum, dient er een samenwerkingsverband te bestaan met e buitenlands academisch centrum.
g) Heeft aantoonbare buitenlandse contacten o.g.v. wetenschappelijk en klinisch en/of sociaal wetenschappelijk onderzoek.
h) Draagt zorg voor na-/bijscholing/opleiding van nieuwe experts en zorgverleners, alsmede voor adequate kennisoverdracht.
i) Staat garant voor de een continuüm van expertise en kennis bij zorgverleners gedurende het leven van de patiënt, zoals bij de transitie van kindergeneeskunde naar volwassenenzorg.
j) Initieert en draagt bij aan de ontwikkeling van zorgstandaarden/richtlijnen i.s.m. de relevante patiëntenorganisatie(s), en stemt deze af met vergelijkbare initiatieven in Europa/wereldwijd.
k) Verzamelt gegevens van patiënten in registraties en/of biobanken en deelt deze met andere expertisecentra in binnen- en buitenland.
l) Werkt samen met relevante patiëntenorganisatie(s).
m) Draagt zorg voor een minimum aantal patiënten om een optimaal kennis en ervaringsniveau te kunnen garanderen. Dit minimum aantal is afhankelijk van de prevalentie van de aandoening en de benodigde omvang van multidisciplinaire zorg.
n) Is bereid tot zowel het ondergaan, als het uitvoeren van visitatiebezoeken.
o) Garandeert continue bereikbaarheid (per e-mail/telefoon).
p) Heeft steun van de Raad van Bestuur op het terrein van erkenning van expertise, borging van financiële stabiliteit en continuïteit.

ZELDZAAM ZICHTBAAR!

Nierpatiënten Vereniging Nederland

NFU NEDERLANDSE FEDERATIE VAN UNIVERSITAIR MEDISCHE CENTRA

orphanet

VSOP

Dank voor uw aandacht