Sindrome nefrosica corticosensibile

Francesco Emma

Division of Nephrology and Dialysis
Bambino Gesù Children's Hospital, IRCCS - Rome, Italy

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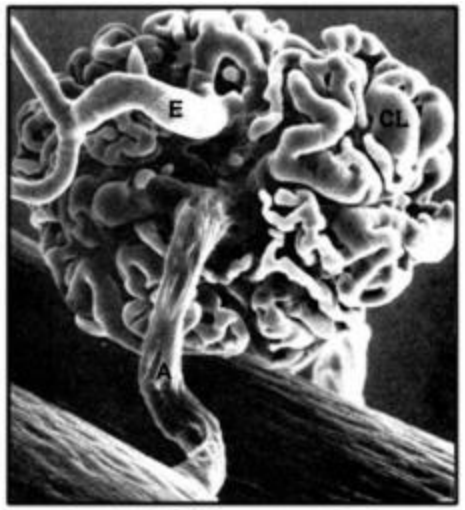
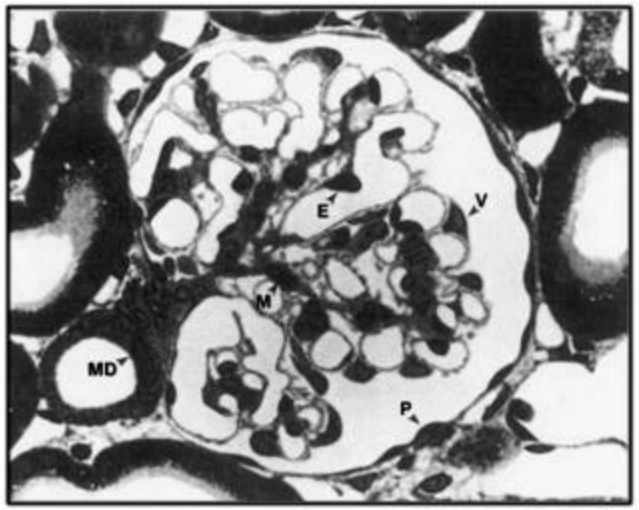
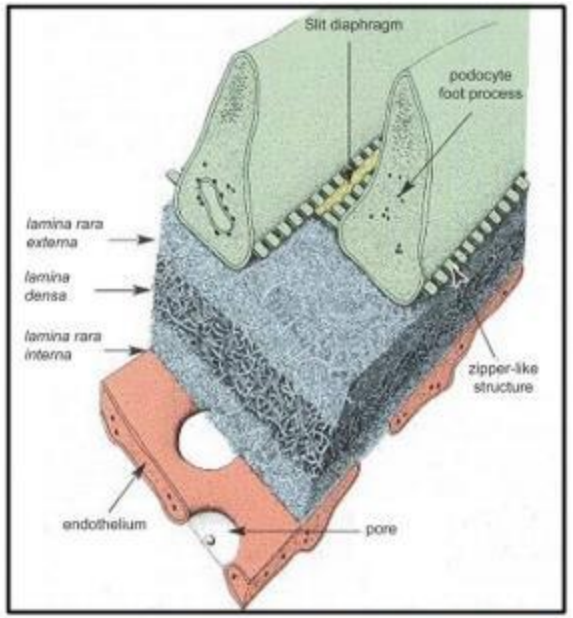
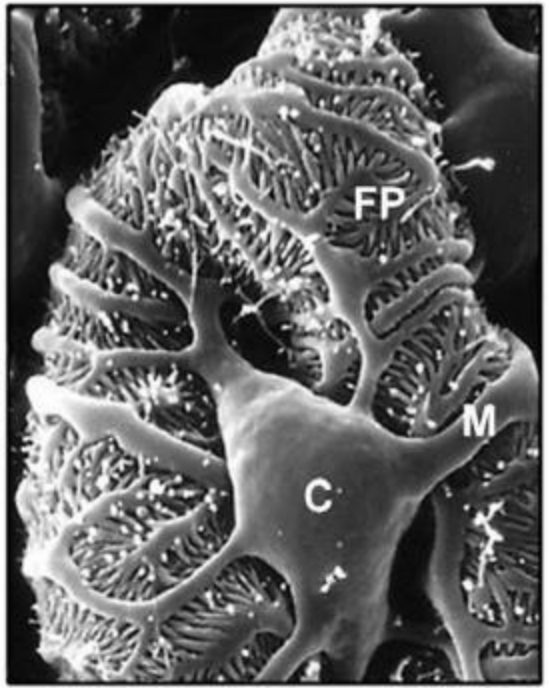
OSPEDALE PEDIATRICO

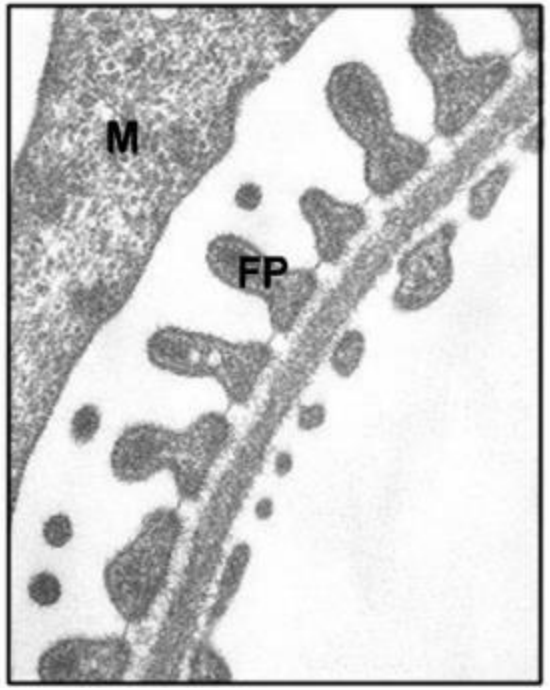
Il glomerulo

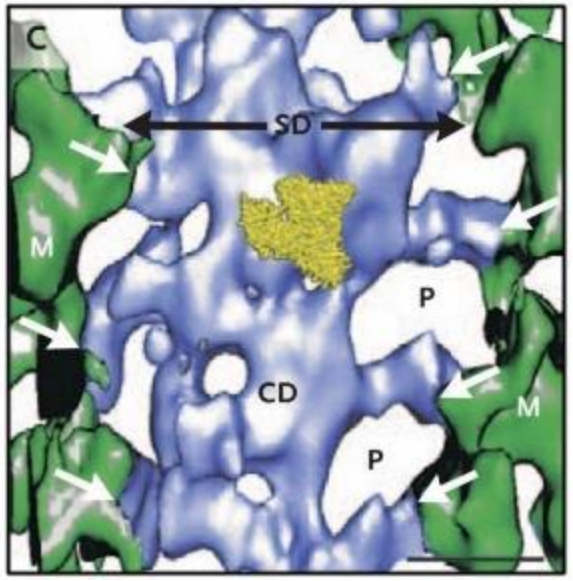






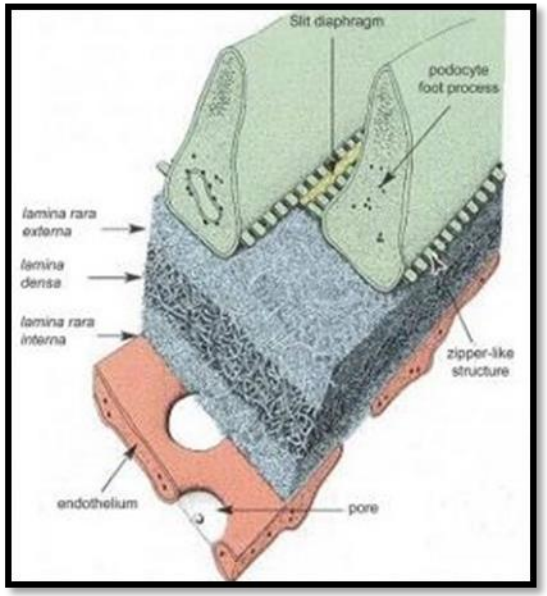


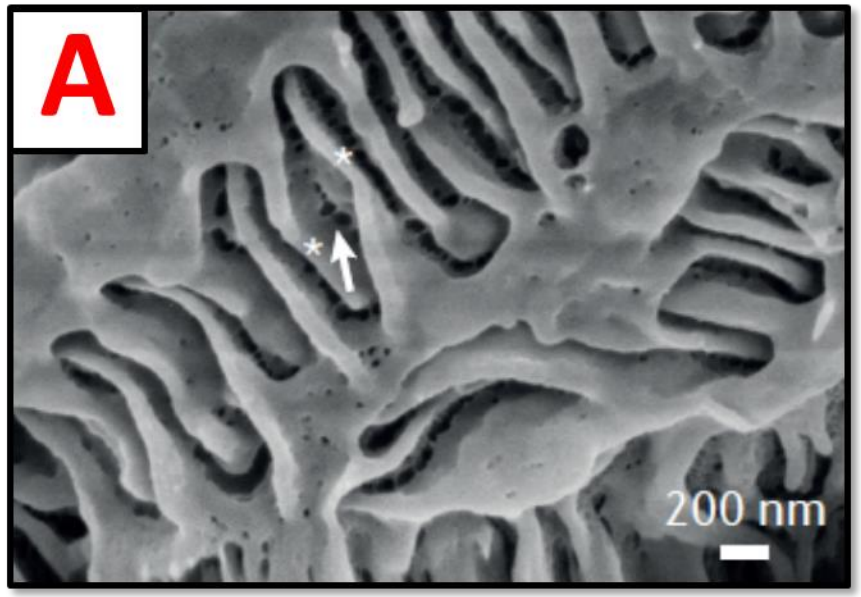


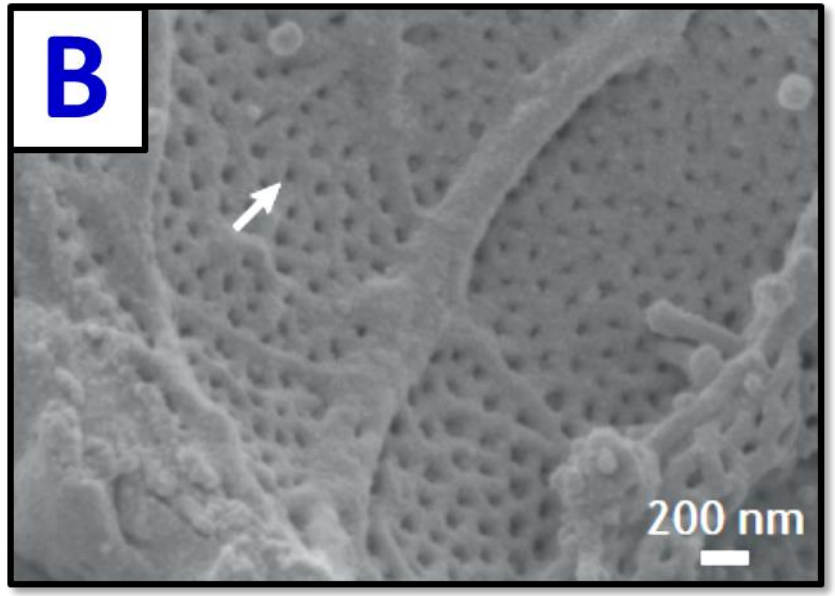


Il glomerulo

A







B

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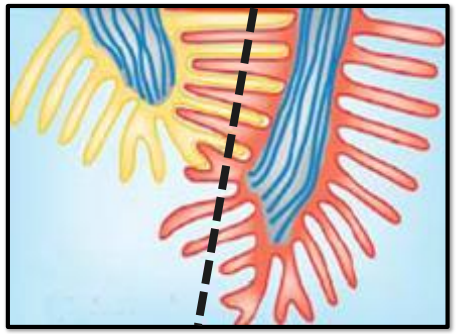
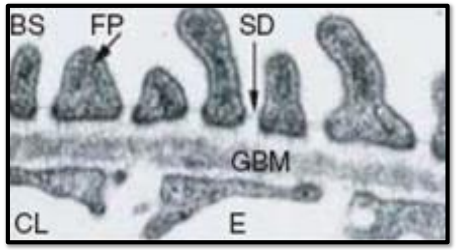
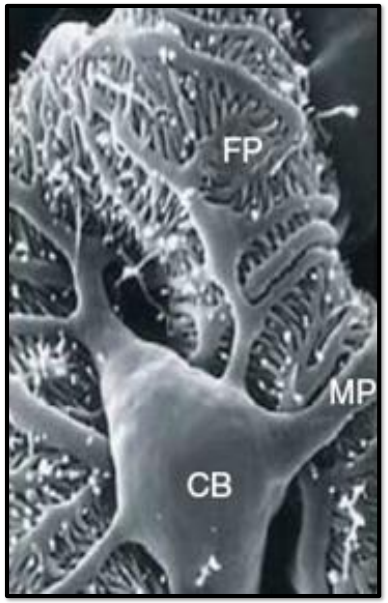
Perico et al, Nat Rev Nephrol 2016

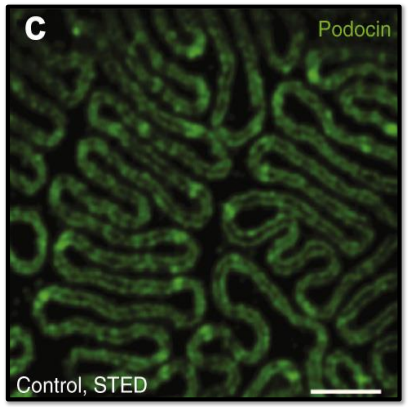
Fusione dei pedicelli

Normal

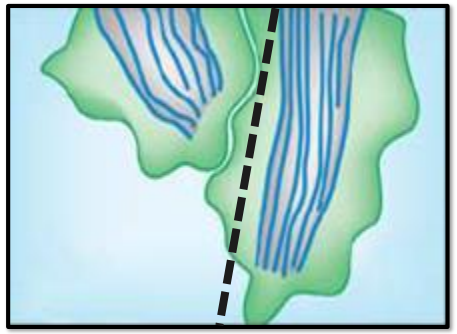


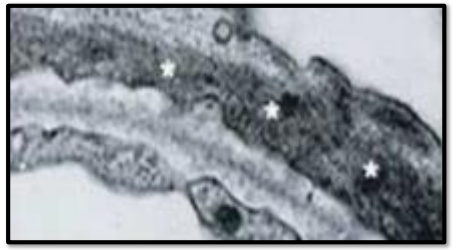


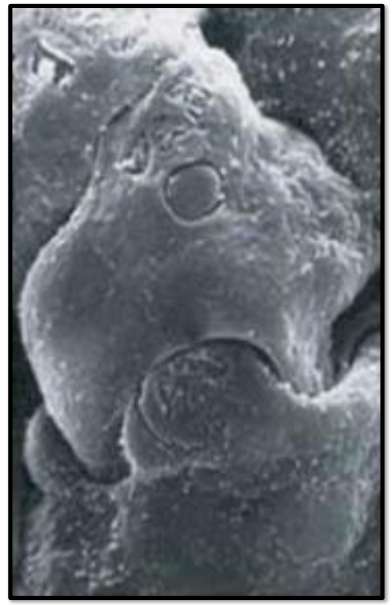


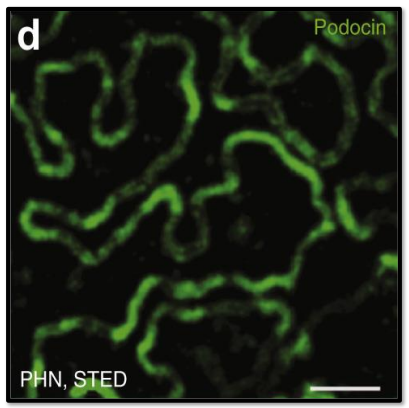


Nephrotic syndrome









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Definizioni

Sindrome nefrosica

- edemi
- proteinuria importante (>40 mg/m^2/h)
- ipoalbuminemia (<2.5 g/dl)

Remissione

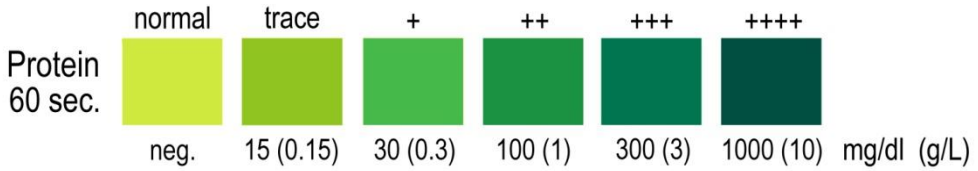
- riduzione marcata della proteinuria (<4 mg/m^2/h o stick urine negativo)
- risoluzione degli edemi
- normalizzazione dell'albumina sierica (≥3.5 g/dl)

Ricaduta

- ricomparsa di proteinuria marcata (>40 mg/m^2/h)
- stick urine positivo (≥3+ per 3 giorni or pos. per 7 giorni)
- ± edemi

ISKDC, J Pediatr, 1981 - Niaudet P, Pediatric Nephrology, 2004

Stix urinario



Definizioni…

Steroid Sensitive Nephrotic Syndrome (SSNS)

Responsta al PDN (60mg/m²/24h) in 4-6 settimane

Steroid Resistant Nephrotic Syndrome (SRNS)

Assenza di responsta al PDN (60mg/m²/24h) in 4-6 settimane ± boli di MP

Multi-Drug Resistant Nephrotic Syndrome (MDRNS)

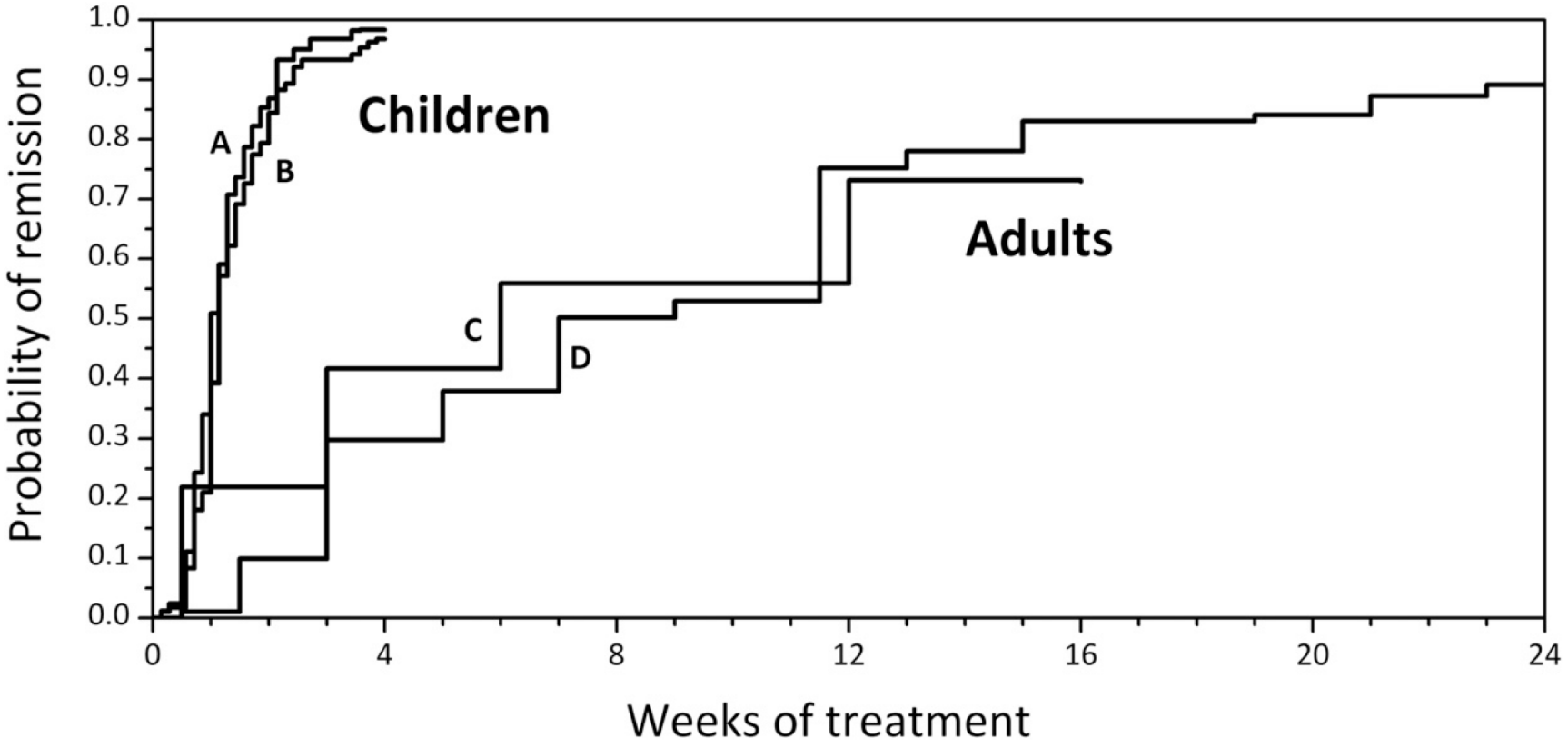
Mal definita, assenza di risposta a farmaci di seconda linea in:

- 6 mesi (remissione oarziale)

- 24 mesi (remissione complete)

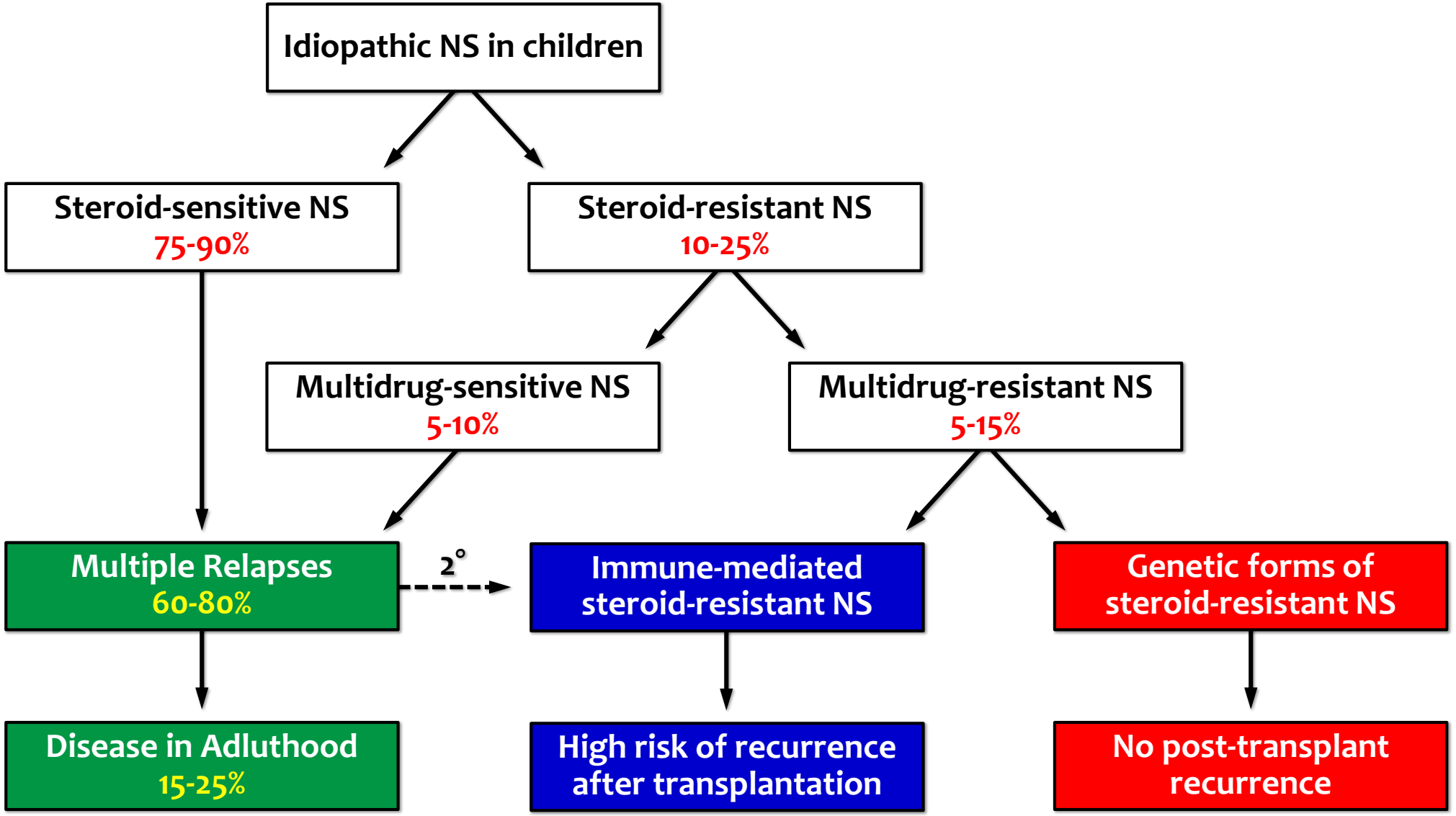
ISKDC J Pediatr 1981, Niaudet P Pediatric Nephrology, Philadelphia, 2004, Ehrich, Nephrol Dial Transpl 2011

Time to remission in children and adults



Vivarelli et al, CJASN 2016

Idiopathic nephrotic syndrome in children



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Patogenesi della syndrome nefrosica cortico-sensibile

"E' ironico che come medici riusciamo a trattare con successo malattie di cui non comprendiamo la patogenesi.

Questo è il caso della sindrome nefrosica a lesioni minime, la più comune causa di nefrosi in età pediatrica".

Bambino Gesù
OSPEDALE PEDIATRICO

Cunard and Kelly, Editorial JASN 2002

Rischi di bias negli studi clinici

THE COCHRANE COLLABORATION®

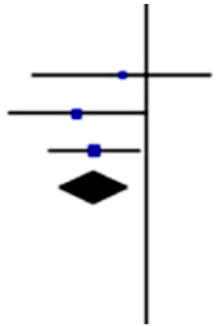
A. Randomizzazione casuale
B. Allocazione in cieco
C. Condotta dello studio in doppio cieco
D. Analisi dei risultati in cieco
E. Dati di esito incompleti
F. Descrizione selettiva dei risultati
G. Altri bias

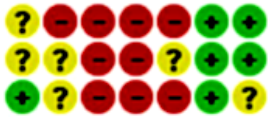
Rischio di bias:

+ basso
? incerto
- elevato

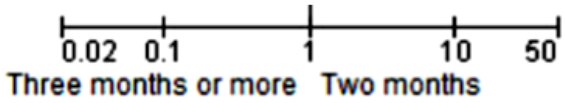
Initial therapy for INS in children : 2 months vs ≥3 months

Study or Subgroup	Three months or more Events	Total	Two months Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
1.5.2 High or unclear risk of bias for allocation bias								
Norero 1996	3	29	4	27	6.5%	0.70 [0.17, 2.84]		
Ueda 1988	3	17	15	29	9.9%	0.34 [0.12, 1.01]		
Jayantha 2002a	8	48	26	70	18.5%	0.45 [0.22, 0.91]		
Subtotal (95% CI)		**94**		**126**	**34.9%**	**0.45 [0.26, 0.77]**		
Total events	14		45					
Heterogeneity: Tau² = 0.00; Chi² = 0.63, df = 2 (P = 0.73); I² = 0%								
Test for overall effect: Z = 2.90 (P = 0.004)								





Heterogeneity: Tau² = 0.08; Chi² = 7.80, df = 5 (P = 0.17); I² = 36%
Test for overall effect: Z = 1.94 (P = 0.05)
Test for subgroup differences: Chi² = 5.30, df = 1 (P = 0.02), I² = 81.1%



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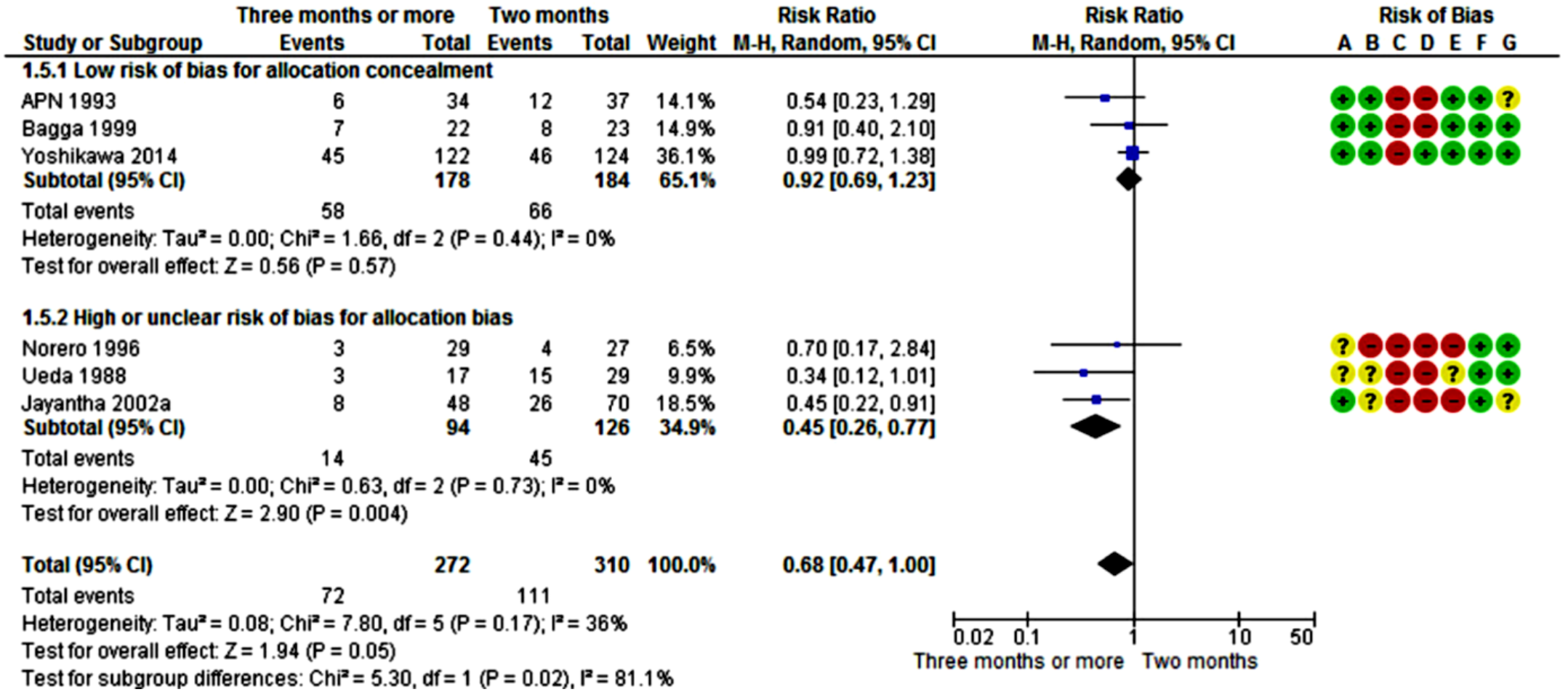
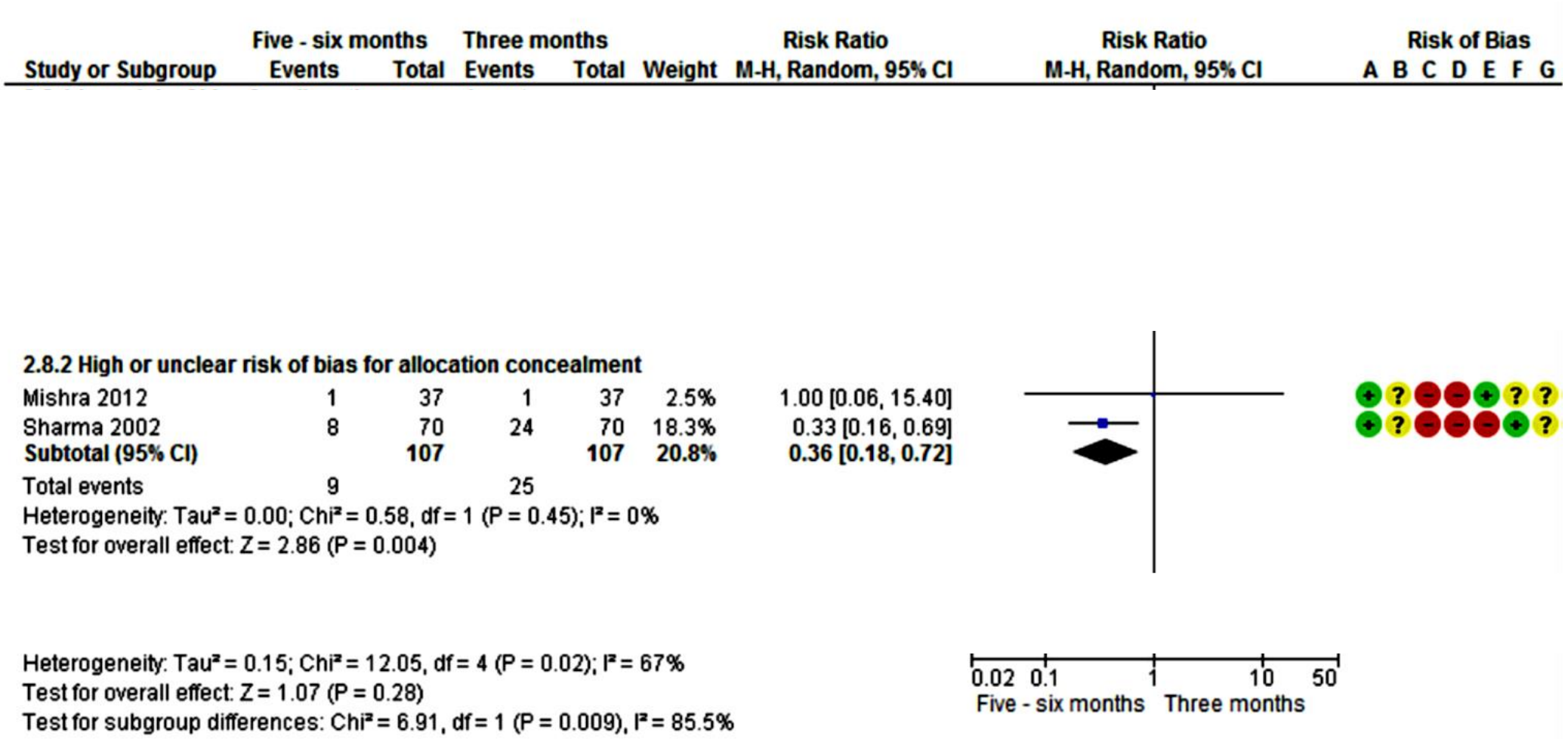
Initial therapy for INS in children : 2 months vs ≥3 months



THE COCHRANE COLLABORATION®

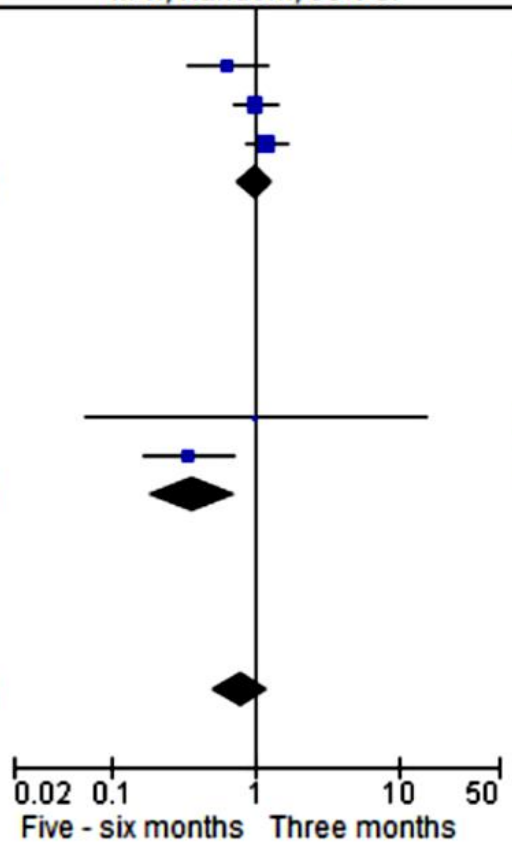
Initial therapy for INS in children: 3 months vs 5-6 months

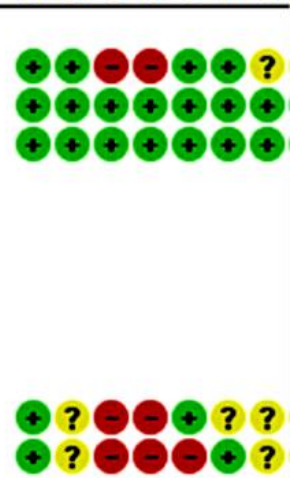


THE COCHRANE COLLABORATION®

Initial therapy for INS in children: 3 months vs 5-6 months

Study or Subgroup	Five - six months Events	Total	Three months Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.8.1 Low risk of bias for allocation concealment						
Hiraoka 2003	10	36	15	34	20.4%	0.63 [0.33, 1.20]
Sinha 2014	36	92	35	89	28.8%	1.00 [0.69, 1.43]
Teeninga 2013	38	64	31	62	30.0%	1.19 [0.86, 1.64]
Subtotal (95% CI)		**192**		**185**	**79.2%**	**1.00 [0.74, 1.34]**
Total events	84		81			
Heterogeneity: Tau² = 0.02; Chi² = 3.06, df = 2 (P = 0.22); I² = 35%						
Test for overall effect: Z = 0.02 (P = 0.98)						
2.8.2 High or unclear risk of bias for allocation concealment						
Mishra 2012	1	37	1	37	2.5%	1.00 [0.06, 15.40]
Sharma 2002	8	70	24	70	18.3%	0.33 [0.16, 0.69]
Subtotal (95% CI)		**107**		**107**	**20.8%**	**0.36 [0.18, 0.72]**
Total events	9		25			
Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 1 (P = 0.45); I² = 0%						
Test for overall effect: Z = 2.86 (P = 0.004)						
Total (95% CI)		**299**		**292**	**100.0%**	**0.78 [0.50, 1.22]**
Total events	93		106			
Heterogeneity: Tau² = 0.15; Chi² = 12.05, df = 4 (P = 0.02); I² = 67%						
Test for overall effect: Z = 1.07 (P = 0.28)						
Test for subgroup differences: Chi² = 6.91, df = 1 (P = 0.009), I² = 85.5%						





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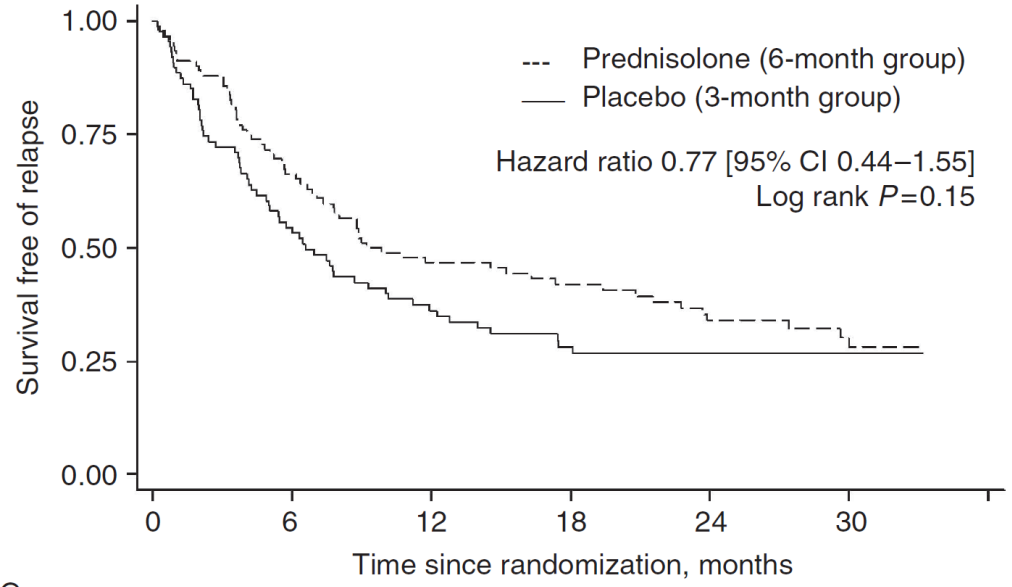
Evolution according to the initial therapy 3 vs 6 months

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]



Group						
6-Month	92	61 (31)	43 (18)	35 (4)	25 (6)	15 (2)
3-Month	88	47 (39)	30 (15)	20 (6)	17 (1)	12 (0)

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%).

Kidney International (2015)

PDN therapy at onset has no impact on long-term outcome

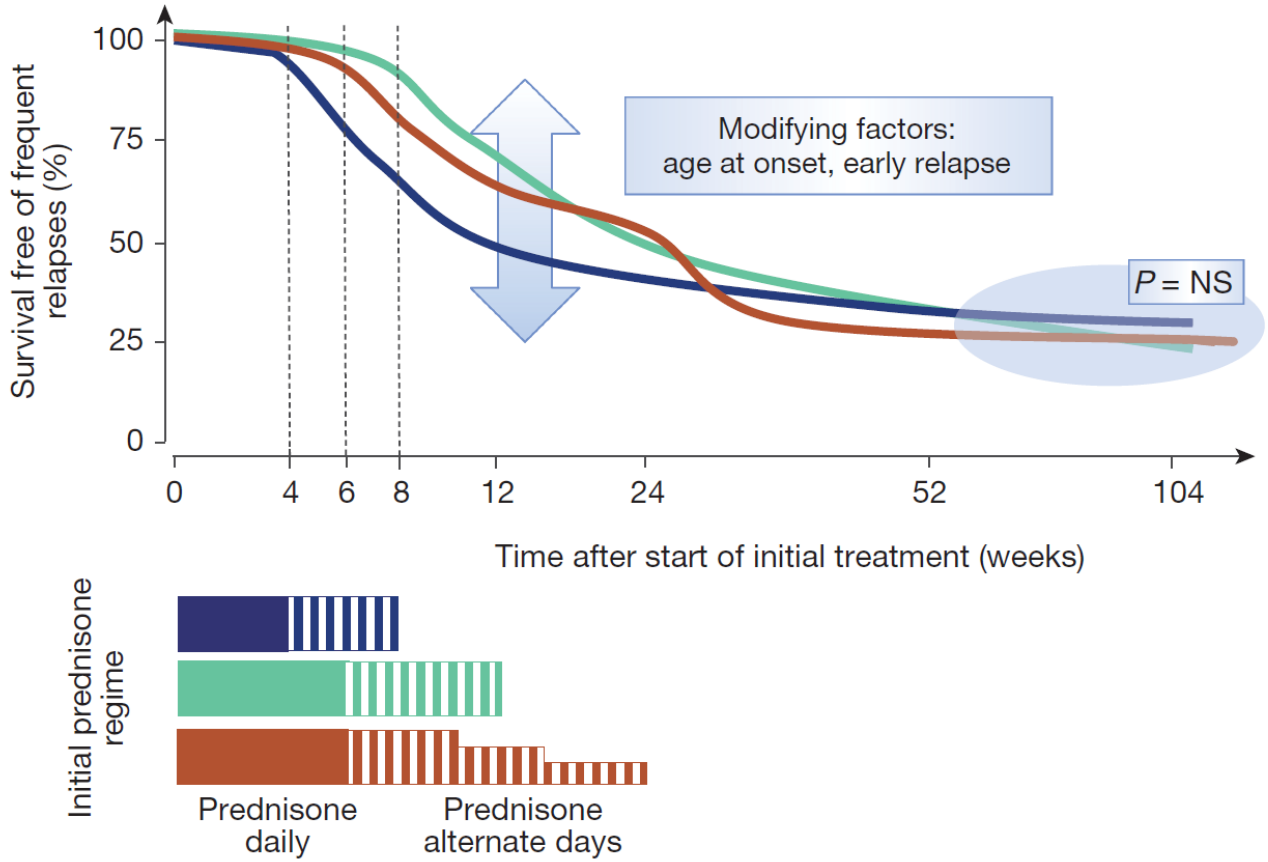


Figure 1 | Lack of effect of extending initial prednisone treatment on long-term freedom from frequent relapses. NS, not significant.

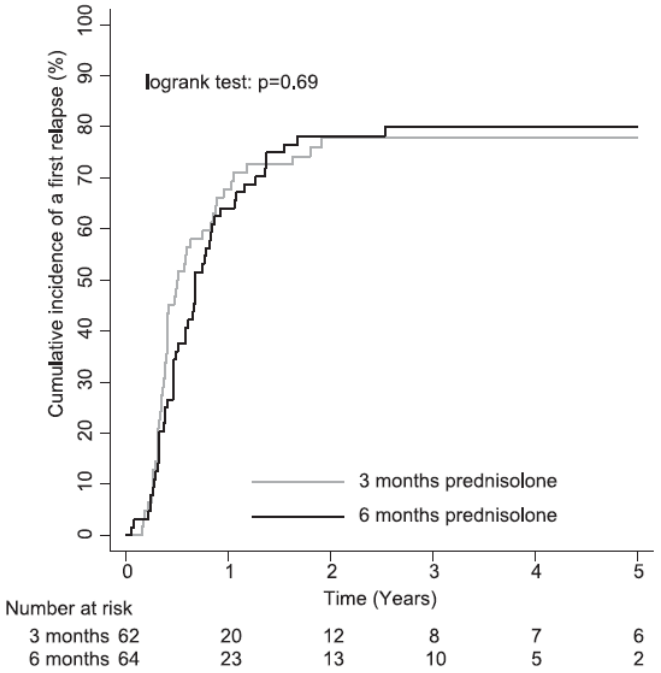
Hoyer P. Kidney Int 2015

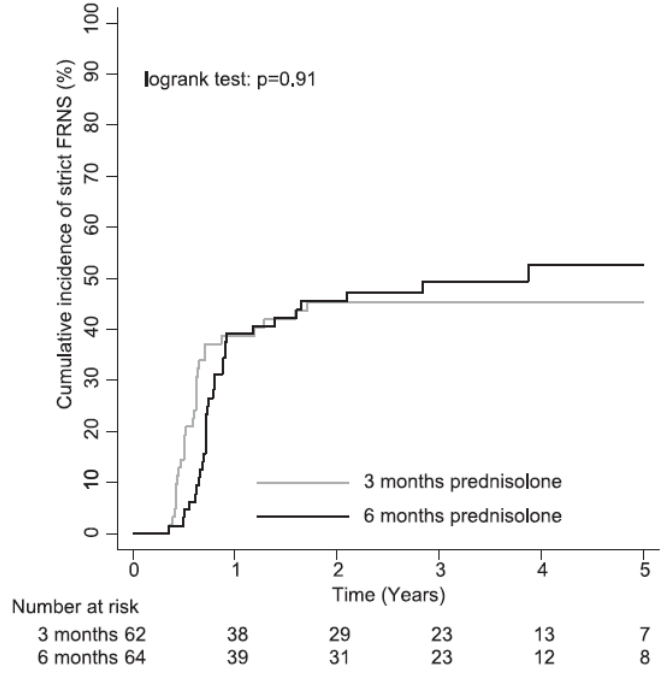
PDN tapering or not?

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*

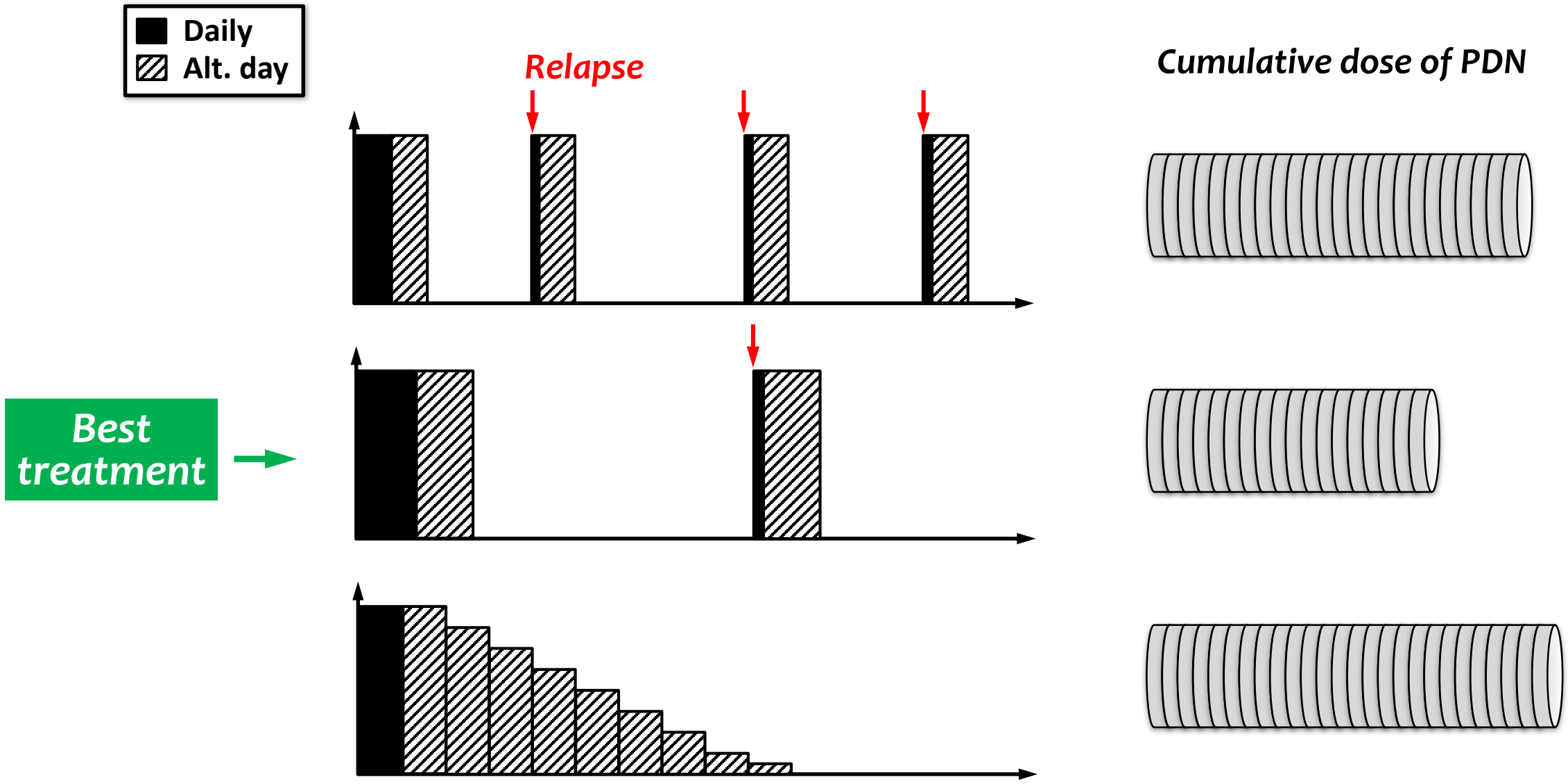
week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15-24	cumulative dose
3 months prednisolone	60 D		60 D				40 AD						placebo AD			3360
6 months prednisolone	60 D		50 D				40 AD				20 AD				10 AD	3320-3710





Teeninga et al, JASN 2012

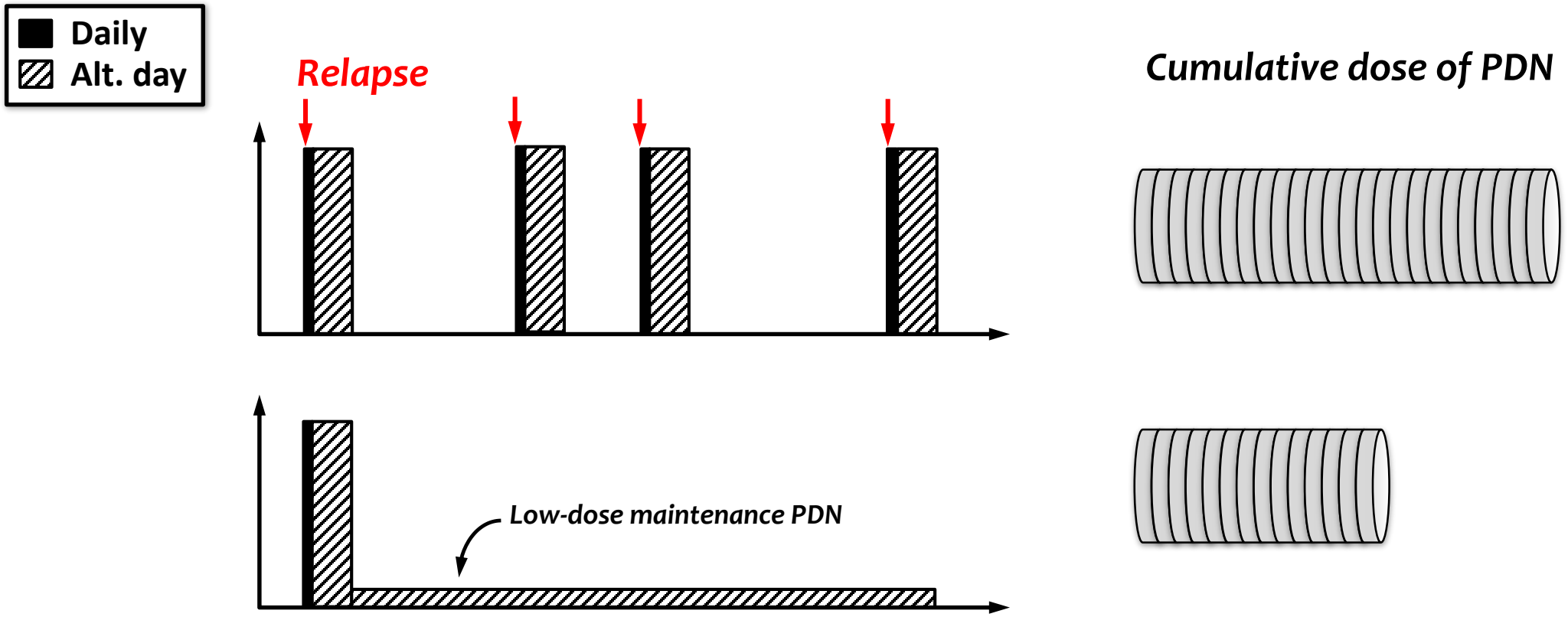
Principles of steroid treatment



Quanto conta il trattamento del primo episodio?

- Le evidenze scientifiche non suggeriscono che il decorso della malattia sia influenzato dal trattamento dell'episodio iniziale
- La tossicità della terapia è in gran parte secondaria a cicli ripetuti di steroidi
- Per comprendere se la malattia è più o meno severa, è necessario trattare tutti bambini con lo stesso protocollo

Principles of steroid treatment



Patients need to relapse less than twice/year to have advantage in stopping PDN

In caso di virosi è utile aumentare lo steroide

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

Ashima Gulati, Aditi Sinha,* Vishnubhatla Sreenivas,† Aparna Math,* Pankaj Hari,* and Arvind Bagga**

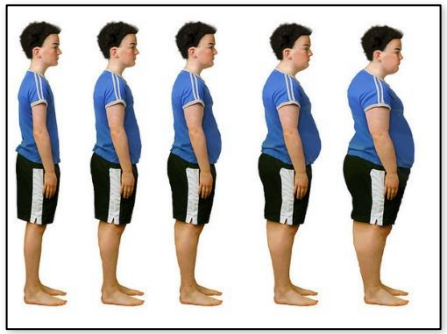
Clin J Am Soc Nephrol 6: 63–69, 2011.

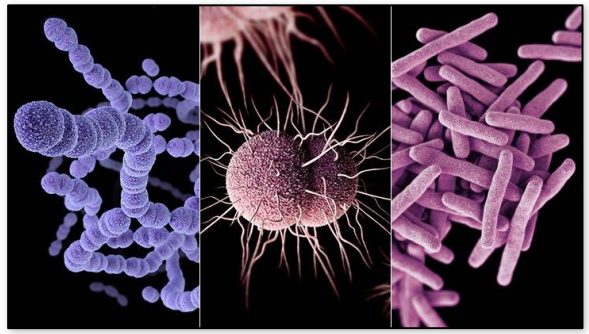
100 pz. con SNCSFR in terapia steroidea discontinua prolungata

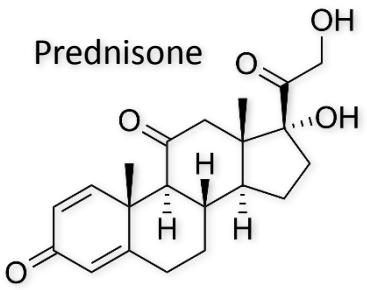
- ✓ **Gruppo A: continuava la dose abituale a giorni alterni**
- ✓ **Gruppo B: assumeva la stessa dose tutti i giorni per 7 giorni**

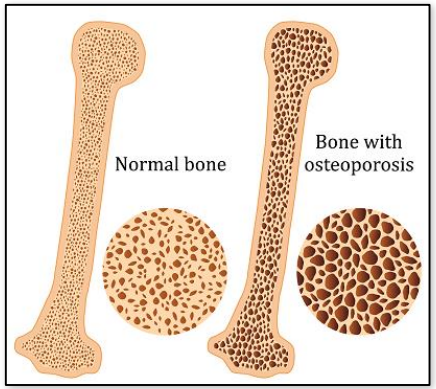
La somministrazione quotidiana di steroide durante la virosi respiratoria intercorrente produceva una riduzione del 59% nella frequenza di recidive

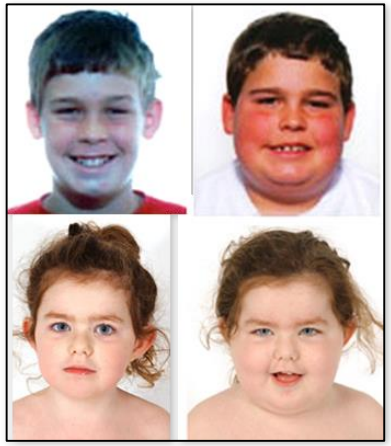
Tossicità steroidea

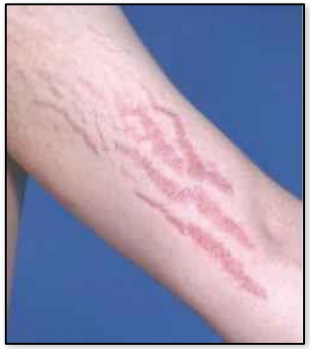


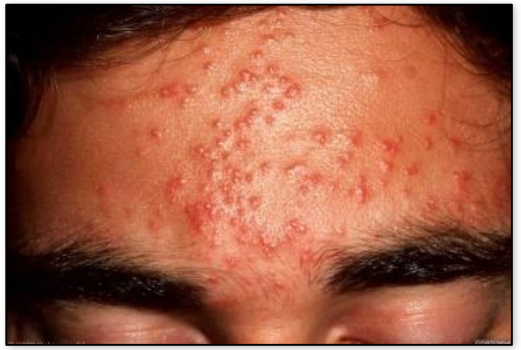












Farmaci di risparmio steroideo

Farmaco	Efficacia	Indicazione	Commenti
Inibitori di calcineurina CsA, FK506	+++++	SDNS	Tossicità renale / ipertensione
Acido micofenolico	++++	FRNS/SDNS	Spesso efficace solo a dosaggi elevate (> 600 mg/m²)
Levamisolo	+++	FRNS	Solo 1 studio condotto in maniera ottimale
Ciclofosfamide	+++	?	Nei casi molto severi, spesso meno efficace
Rituximab	buona	?	Incertezze su: dosaggio ottimale, numero massimo di dosi, effetti secondari a lungo termine

Ciclosporina A

Patient Characteristics	Units	Value	N
Age at CsA initiation	years	6.5 [2.2 - 14.2]	53
Duration of NS before CsA	years	1.1 [0.4 - 11.2]	53
Number of relapses before CsA	rel/years	2.3 [1.6 - 5.2]	53
Number of relapses on CsA	rel/years	0.5 [0.0 - 3.0]	53
CsA dosage mg/kg /d	mg/Kg/d	4.2 ±1.2	53
Off PDN after 1 year	N (%)	27 (51%)	53

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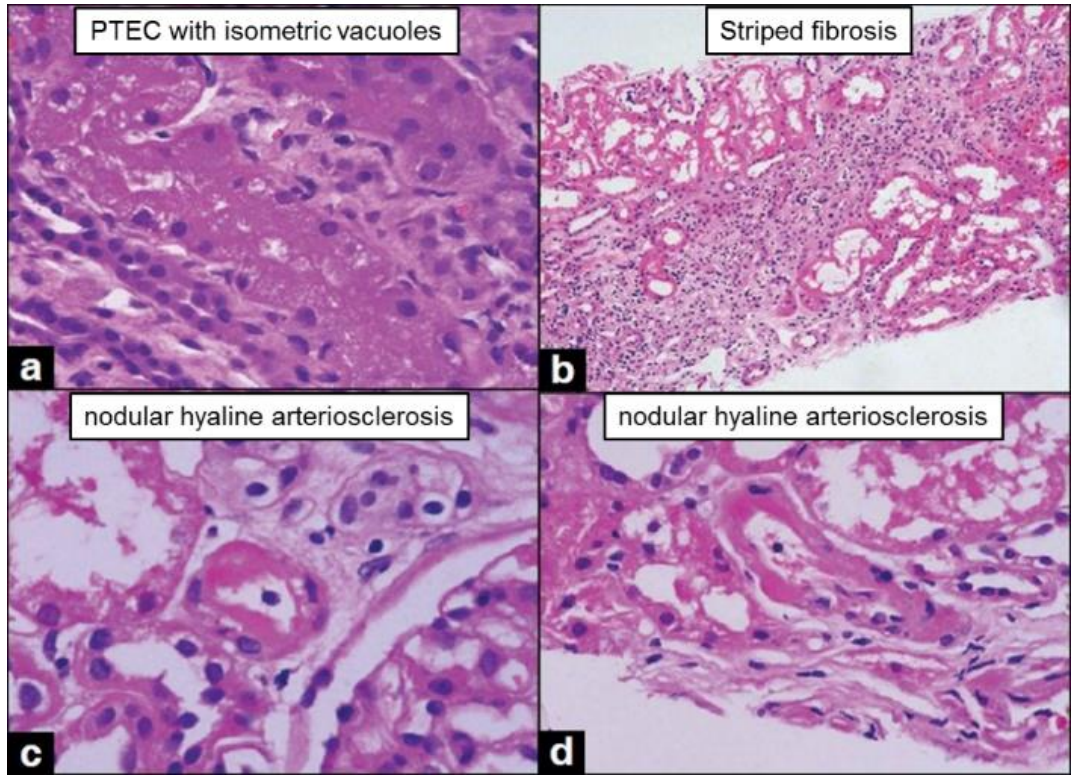
Kengne-Wafo et al, Clin J Am Soc Nephrol, 2009

Ciclosporina A: effetti secondari

- Ipertensione arteriosa
- Immunosoppressione
- Monitoraggio dei livelli
- Tossicità renale



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FK506

- Forse più potente
- Meno ipertensione
- Altri effetti secondari
- Difficile aumentare le dosi nei casi difficili

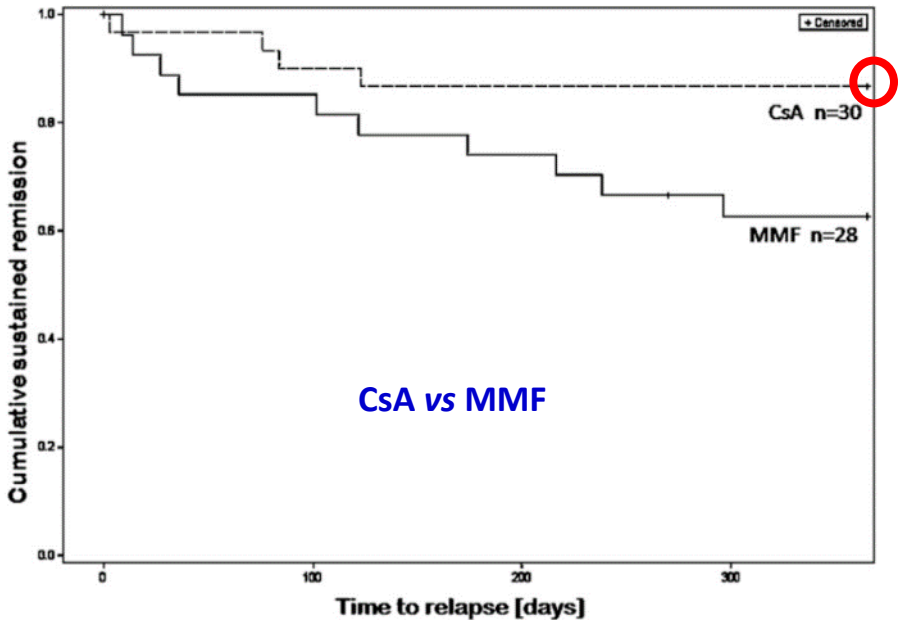
MMF

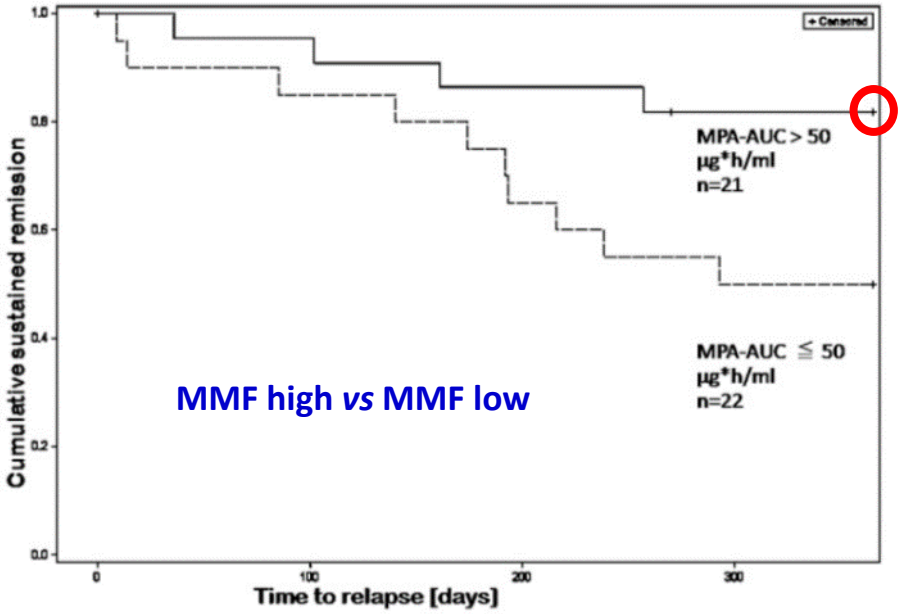
- Non nefrotossico
- Immunosoppressivo
- Effetti secondari soprattutto gastro-enterici ed ematologici
- Teratogenico
- Difficile farmacocinetica

MMF vs CsA

Mycophenolate Mofetil versus Cyclosporin A in Children with Frequently Relapsing Nephrotic Syndrome

Jutta Gellermann,* Lutz Weber,† Lars Pape,‡ Burkhard Tönshoff,§ Peter Hoyer,‖ and Uwe Querfeld,* for the Gesellschaft für Pädiatrische Nephrologie (GPN)





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Gellermann et al, JASN 2013

Levamisolo

- Un solo studio prospettico
- Funziona nelle forme meno gravi
- Pochi effetti secondari
- In 5% dei casi, rash, vasculite, artralgie (ANCA pos)

Rituximab

- Sicuramente efficace
- Consente di ridurre altri immunosoppressori
- Forse più efficace nei pazienti più grandi
- Dosaggio ottimale non ben definite
- Reazioni allergiche
- Rari casi di infezioni e/o lesioni polmonari devastanti
- Possibile Perdita della memoria immunitaria

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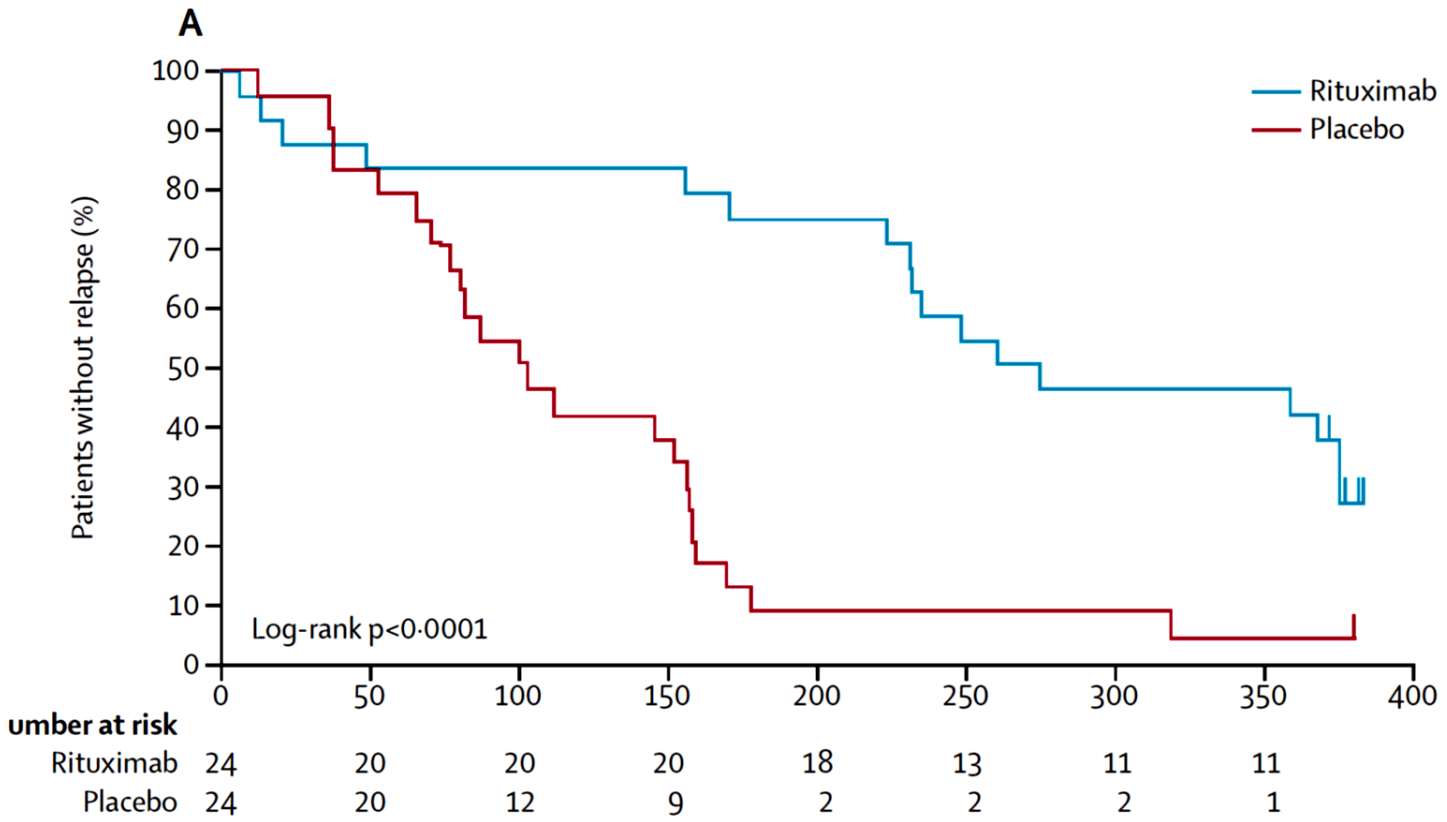
Guigonis et al *Pediatr Nephrol* 2008, Kamei et al *Pediatr Nephrol* 2009, Prytula et al *Pediatr Nephrol* 2011, Filler et al *Pediatr Nephrol* 2010, Gulati et al *Clin J Am Soc Nephrol* 2010, Kemper et al *Pediatr Nephrol* 2007, Kemper et al *Nephrol Dial Transpl* 2012, Ravani et al *Clin J Am Soc Nephrol* 2011, Ravani et al *Kidney Int* 2013, Ruggenenti et al, *J Am Soc Nephrol* 2014, Iijima *Lancet* 2014, Ravani et al *J Am Soc Nephrol* 2015

Rituximab



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Iijima et al, Lancet 2014

Ciclofosfamide

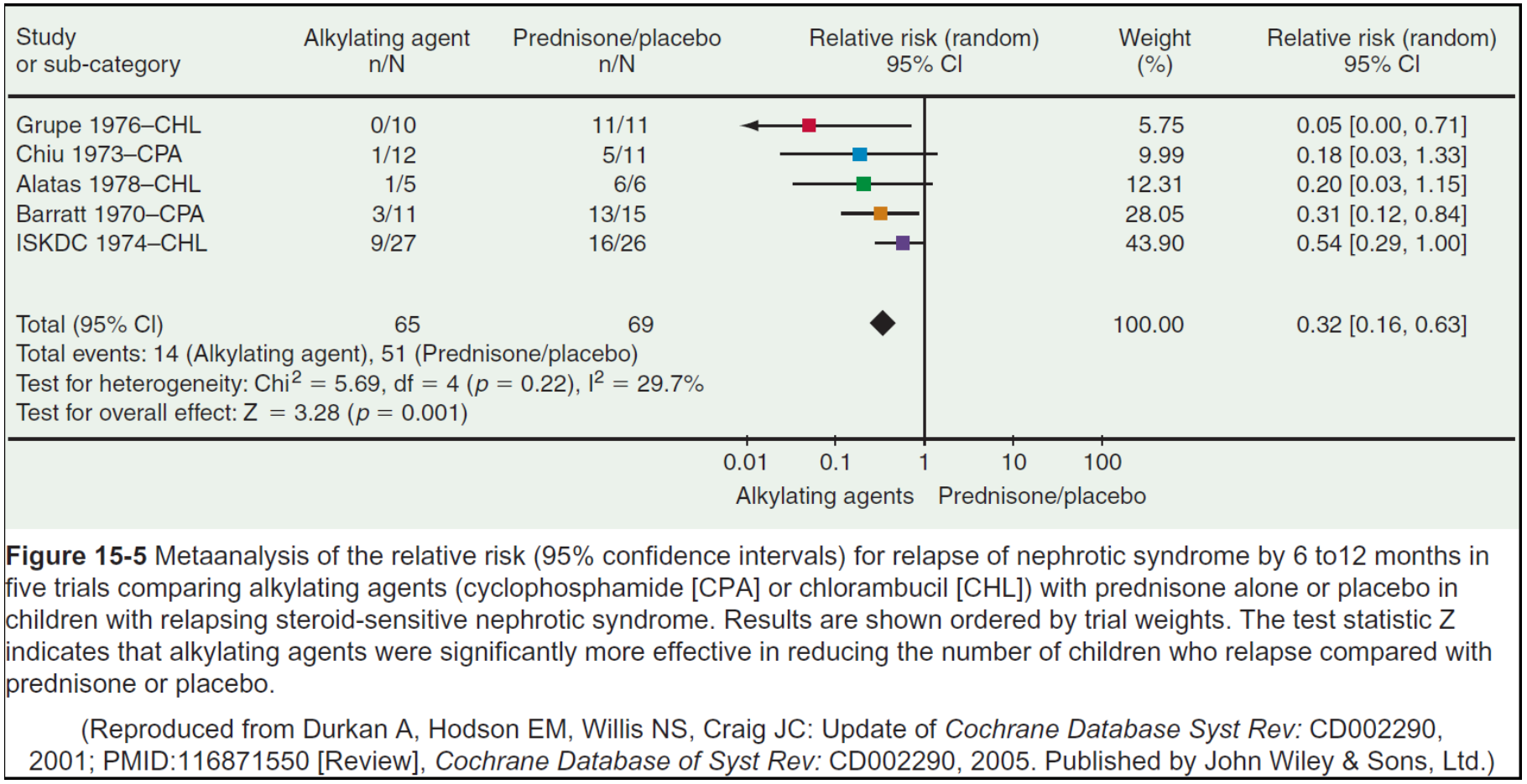

Figure 15-5 Metaanalysis of the relative risk (95% confidence intervals) for relapse of nephrotic syndrome by 6 to12 months in five trials comparing alkylating agents (cyclophosphamide [CPA] or chlorambucil [CHL]) with prednisone alone or placebo in children with relapsing steroid-sensitive nephrotic syndrome. Results are shown ordered by trial weights. The test statistic Z indicates that alkylating agents were significantly more effective in reducing the number of children who relapse compared with prednisone or placebo.

(Reproduced from Durkan A, Hodson EM, Willis NS, Craig JC: Update of *Cochrane Database Syst Rev:* CD002290, 2001; PMID:116871550 [Review], *Cochrane Database of Syst Rev:* CD002290, 2005. Published by John Wiley & Sons, Ltd.)

Funziona meglio nei pazienti con forme non troppo gravi

Kemer et al, Pediatr Nephrol 2000 - Zaguri et al, Pediatr Nephrol 2011

Baudoin et al, Pediatr Nephrol 2012 - Bagga et al, Am J Kidney Dis 2003

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Thank you

francesco.emma@opbg.net