

# Le news sulla sindrome nefrosica

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**Pediatri a confronto.**

**Il territorio, l'ospedale e l'Università  
si incontrano**

Splendid Hotel La Torre (Mondello) Palermo 15 - 16 ottobre 2021

15  
1869  
2019



**Bambino Gesù**  
OSPEDALE PEDIATRICO

# Rischi di bias negli studi clinici



- 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

# Terapia iniziale per SNCS: confronto 3 vs 5-6 mesi di PDN

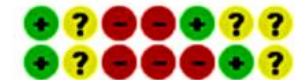
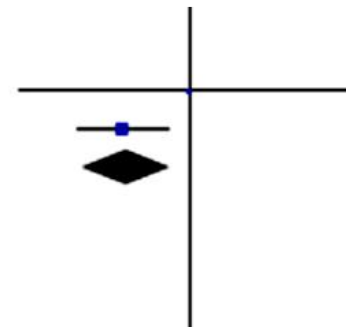
Study or Subgroup	Five - six months		Three months		Weight	Risk Ratio	Risk Ratio	Risk of Bias						
	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI	A	B	C	D	E	F	G

## 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]											
<b>Subtotal (95% CI)</b>		<b>107</b>		<b>107</b>	<b>20.8%</b>	<b>0.36 [0.18, 0.72]</b>											
Total events	9		25														

Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 0.58, df = 1 (P = 0.45); I<sup>2</sup> = 0%  
 Test for overall effect: Z = 2.86 (P = 0.004)

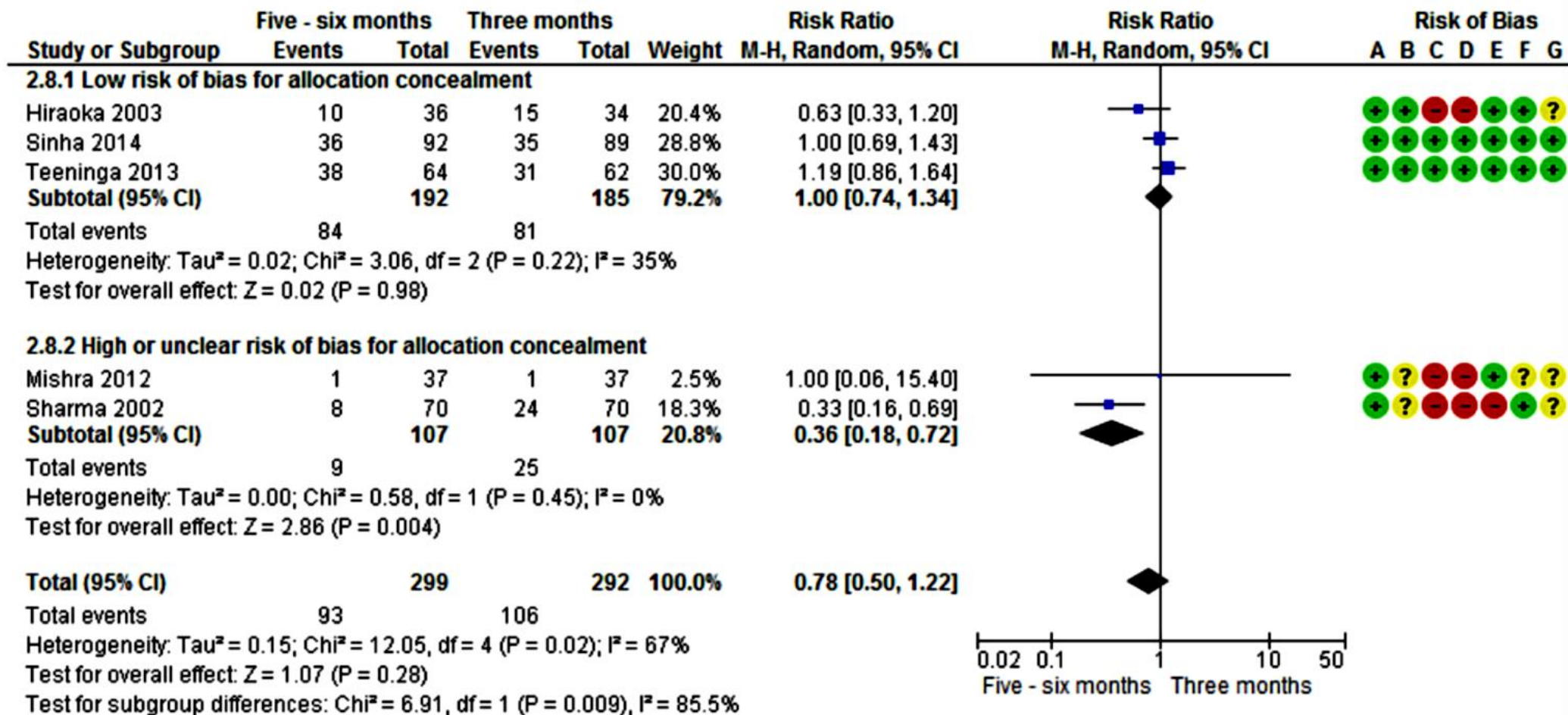
1.00 [0.06, 15.40]  
 0.33 [0.16, 0.69]  
 0.36 [0.18, 0.72]



Heterogeneity: Tau<sup>2</sup> = 0.15; Chi<sup>2</sup> = 12.05, df = 4 (P = 0.02); I<sup>2</sup> = 67%  
 Test for overall effect: Z = 1.07 (P = 0.28)  
 Test for subgroup differences: Chi<sup>2</sup> = 6.91, df = 1 (P = 0.009), I<sup>2</sup> = 85.5%

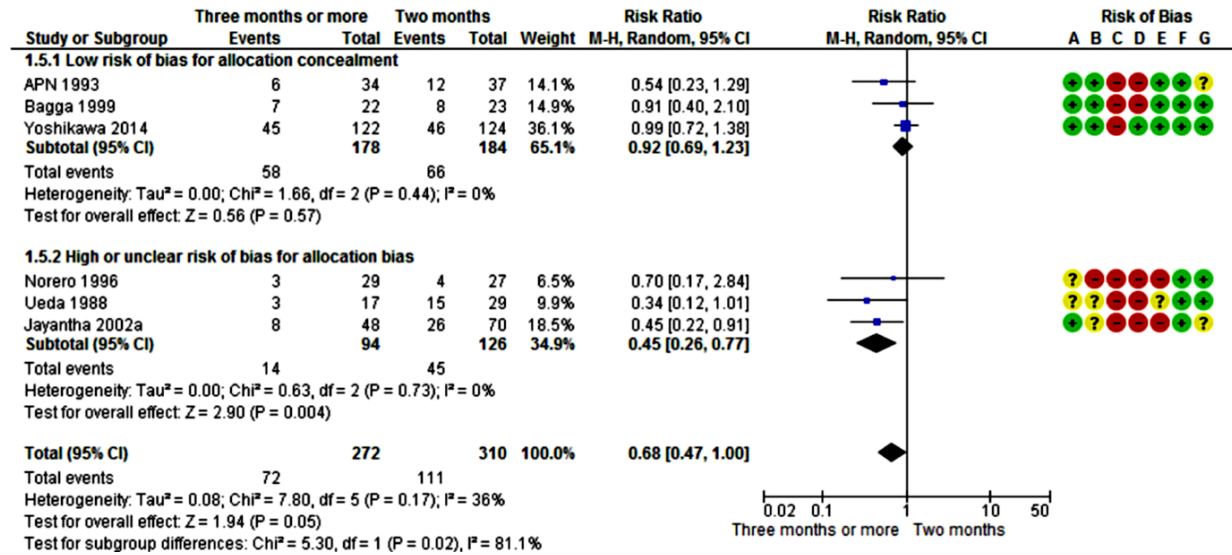
0.02 0.1 1 10 50  
 Five - six months Three months

# Terapia iniziale per SNCS: confronto 3 vs 5-6 mesi di PDN

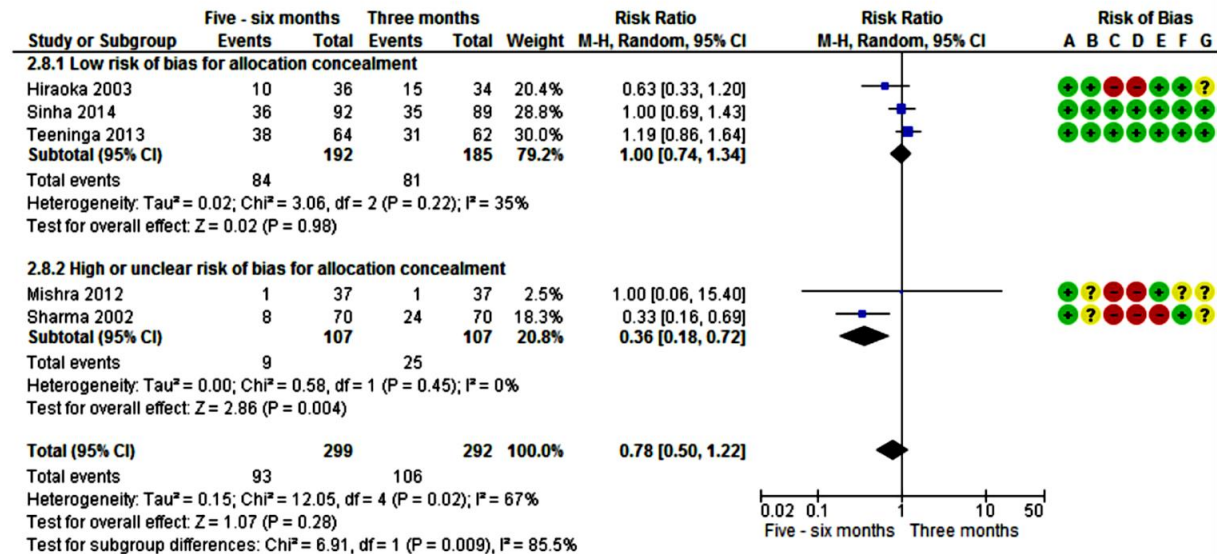


# Initial therapy for INS in children

## 2 vs. ≥3 months



## 3 vs. 5-6 months



# Protocolli di trattamento all'esordio

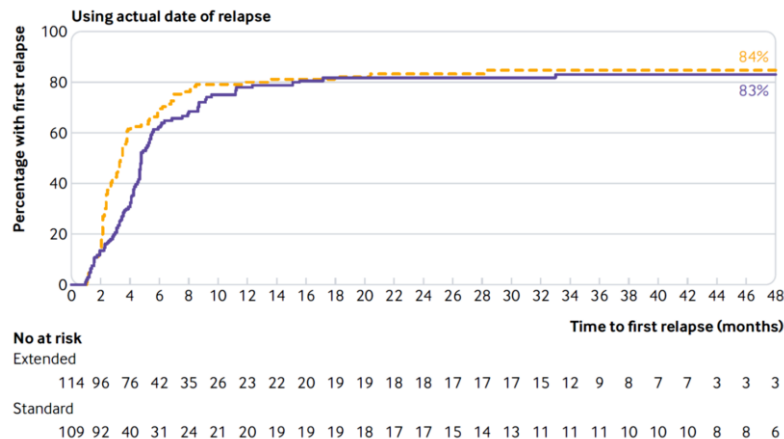
	International Study of Kidney Disease in Children (ISKDC) <sup>61</sup>	Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN) <sup>2</sup>	Haute Autorité de Santé (France) <sup>62</sup>	Italian Society for Pediatric Nephrology (SINePe) <sup>63</sup>	KDIGO Glomerulonephritis Guidelines <sup>1</sup>	Hospital for Sick Children (Toronto, Canada) <sup>11</sup>
Year of publication	1970	1988	2008	2017	2012	2016
Initial dose and duration	60 mg/m <sup>2</sup> per day × 4 weeks	60 mg/m <sup>2</sup> per day × 6 weeks (maximum dose 80 mg)	60 mg/m <sup>2</sup> per day × 4 weeks (maximum dose 60 mg)	60 mg/m <sup>2</sup> per day × 6 weeks (maximum 60 mg in single or 2 divided doses)	60 mg/m <sup>2</sup> per day or 2 mg/kg per day × 4–6 weeks (maximum 60 mg)	60 mg/m <sup>2</sup> per day × 6 weeks (maximum 60 mg in single morning dose)
Subsequent dose and tapering	4 weeks of 40 mg/m <sup>2</sup> per alternate day but given on 3 consecutive days out of a week	40 mg/m <sup>2</sup> per alternate day × 6 weeks (maximum dose 60 mg)	60 mg/m <sup>2</sup> per alternate day × 8 weeks (maximum 60 mg) followed by a 15 mg/m <sup>2</sup> 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/m <sup>2</sup> per alternate day × 6 weeks (single dose; maximum 40 mg) without tapering	40 mg/m <sup>2</sup> 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/m <sup>2</sup> per alternate day × 6 weeks (maximum 60 mg), 30 mg/m <sup>2</sup> per alternate day × 8 days (maximum 30 mg), 20 mg/m <sup>2</sup> per alternate day × 8 days (maximum 20 mg), 10 mg/m <sup>2</sup> per alternate day × 12 days (maximum 10 mg)

# La durata del primo trattamento è influente sul decorso della malattia

## 2 vs. 4 months

Long term tapering versus standard prednisolone treatment for first episode of childhood nephrotic syndrome: phase III randomised controlled trial and economic evaluation

Nicholas J A Webb,<sup>1,2</sup> Rebecca L Woolley,<sup>3</sup> Tosin Lambe,<sup>4</sup> Emma Frew,<sup>4</sup> Elizabeth A Brettell,<sup>3</sup> Emma N Barsoum,<sup>3</sup> Richard S Trompeter,<sup>5</sup> Carole Cummins,<sup>6</sup> Jonathan J Deeks,<sup>3,7</sup> Keith Wheatley,<sup>8</sup> Natalie J Ives,<sup>3</sup> On behalf of the PREDNOS Collaborative Group

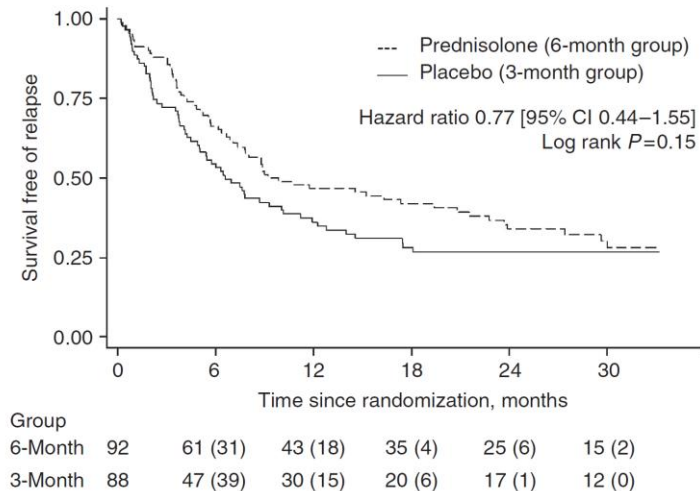


Webb et al, BMJ 2019

## 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<sup>1</sup>, Abhijeet Saha<sup>2</sup>, Manish Kumar<sup>3</sup>, Sonia Sharma<sup>1</sup>, Kamran Afzal<sup>4</sup>, Amarjeet Mehta<sup>5</sup>, Mani Kalaivani<sup>6</sup>, Pankaj Hari<sup>1</sup> and Arvind Bagga<sup>1</sup>

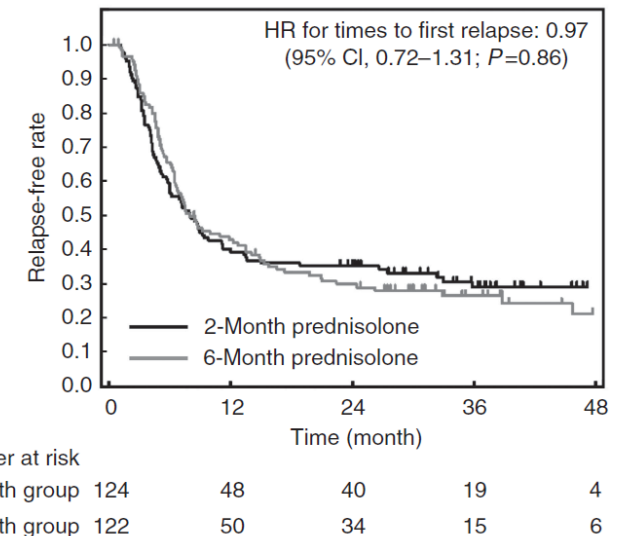


Sinha et al, Kidney Int 2015

## 2 vs. 6 months

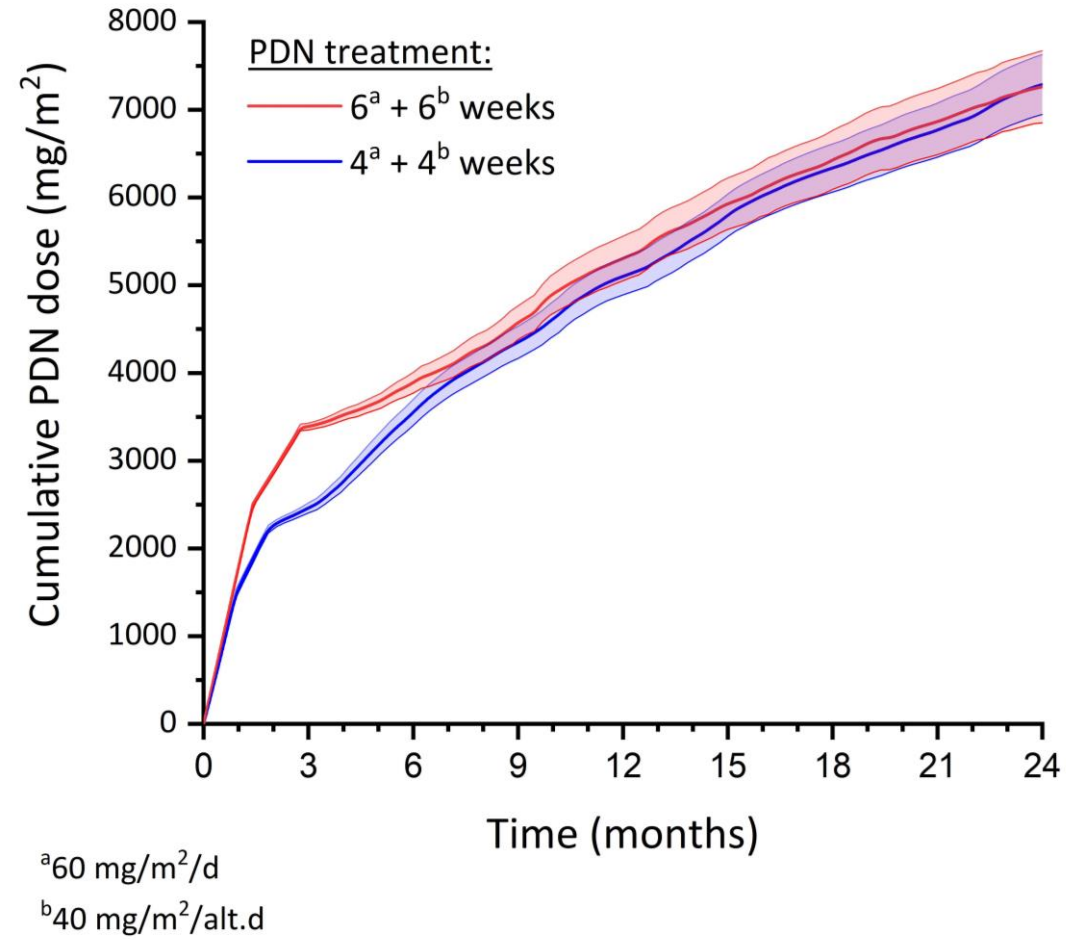
A multicenter randomized trial indicates initial prednisolone treatment for childhood nephrotic syndrome for two months is not inferior to six-month treatment

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



Yoshikawa et al, Kidney Int 2015

# La durata del primo trattamento è influente sul decorso della malattia



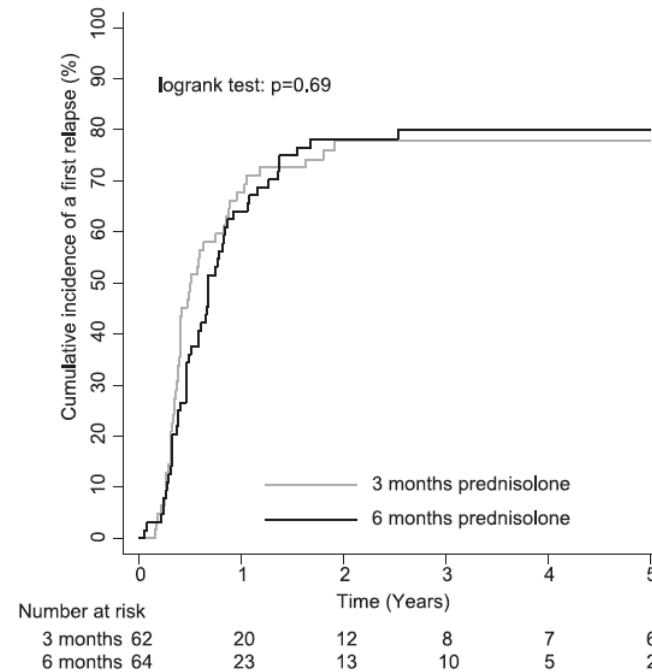


# Decalaggio del PDN all'esordio

## Extending Prednisolone Treatment Does Not Reduce Relapses in Childhood Nephrotic Syndrome

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

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



# Protocolli di trattamento delle recidive

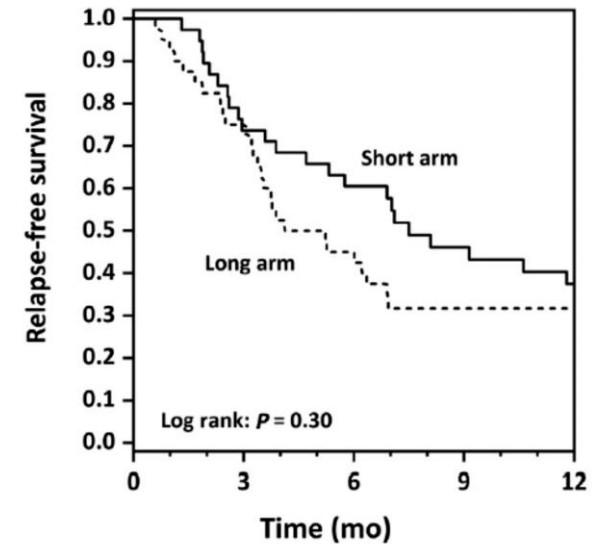
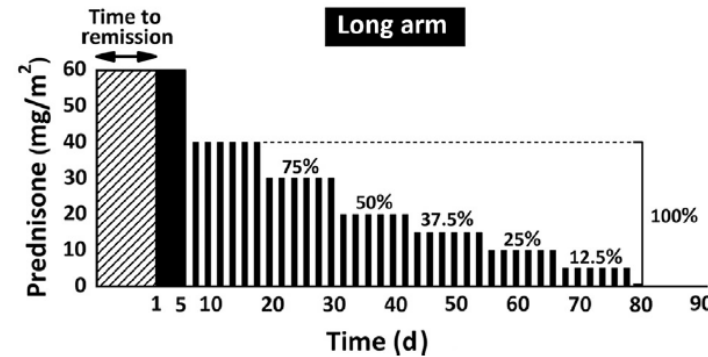
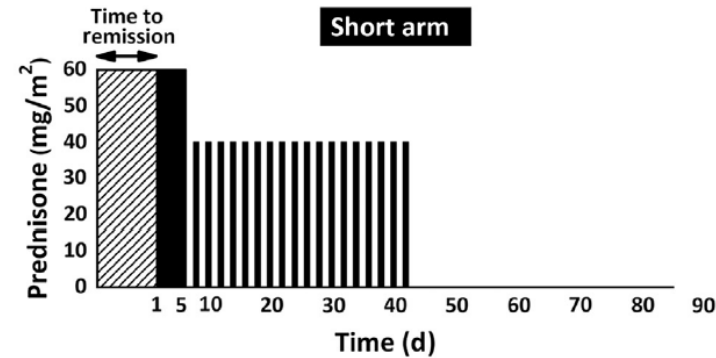
	International Study of Kidney Disease in Children (ISKDC) <sup>61</sup>	Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN) <sup>2</sup>	Haute Autorité de Santé (France) <sup>62</sup>	Italian Society for Pediatric Nephrology (SINePe) <sup>63</sup>	KDIGO Glomerulonephritis Guidelines <sup>1</sup>	Hospital for Sick Children (Toronto, Canada) <sup>11</sup>
Year of publication	1970	1988	2008	2017	2012	2016
Starting dose and duration	..	..	60 mg/m <sup>2</sup> per day until urine protein is negative for 6 days	60 mg/m <sup>2</sup> (max 60 mg in a single or 2 divided doses) until urine protein is negative for 5 days	60 mg/m <sup>2</sup> per day or 2.0 mg/kg per day (maximum of 60 mg/day) until urine is negative for 3 days	60 mg/m <sup>2</sup> per day until urinary protein is trace or negative for 5 consecutive days
Follow-up dose and duration	..	..	60 mg/m <sup>2</sup> per alternate day × 4 weeks, 45 mg/m <sup>2</sup> per alternate day × 4 weeks, 30 mg/m <sup>2</sup> per alternate day × 4 weeks, 15 mg/m <sup>2</sup> per alternate day × 4 weeks	40 mg/m <sup>2</sup> per alternate day (max 40 mg) × 4 weeks	40 mg/m <sup>2</sup> or 1.5 mg/kg/alternate day (maximum 40 mg) × 4 weeks (minimum)	60 mg/m <sup>2</sup> per alternate day × 8 days (maximum 60 mg/day), 50 mg/m <sup>2</sup> per alternate day × 8 days (maximum 50 mg/day), 40 mg/m <sup>2</sup> per alternate day × 8 days (maximum 40 mg/day), 30 mg/m <sup>2</sup> per alternate day × 8 days (maximum 30 mg/day), 20 mg/m <sup>2</sup> /alternate day × 8 days (maximum 20 mg/day), 10 mg/m <sup>2</sup> per alternate day × 8 days (maximum 10 mg/day)

# Decalaggio del PDN per il trattamento delle ricadute

Results of the PROPINE randomized controlled study suggest tapering of prednisone treatment for relapses of steroid sensitive nephrotic syndrome is not necessary in children

Antonio Gargiulo<sup>1</sup>, Laura Massella<sup>1</sup>, Barbara Ruggiero<sup>1</sup>, Lucilla Ravà<sup>2</sup>, Marta Ciofi degli Atti<sup>2</sup>, Marco Materassi<sup>3</sup>, Francesca Lugani<sup>4</sup>, Elisa Benetti<sup>5</sup>, William Morello<sup>6</sup>, Daniela Molino<sup>7</sup>, Francesca Mattozzi<sup>8</sup>, Marco Pennesi<sup>9</sup>, Silvio Maringhini<sup>10</sup>, Andrea Pasini<sup>11</sup>, Bruno Gianoglio<sup>8</sup>, Carmine Pecoraro<sup>7</sup>, Giovanni Montini<sup>6,12</sup>, Luisa Murer<sup>5</sup>, Gian Marco Ghiggeri<sup>4</sup>, Paola Romagnani<sup>3</sup>, Marina Vivarelli<sup>1</sup> and Francesco Emma<sup>1</sup>

Outcome			P value
Cumulative PDN dose, mg/m <sup>2</sup>	1327 (1265–1510)	1293 (1160–1642)	0.65
Time to remission, d	6 (5–8)	5 (4–7)	0.20
Relapse during treatment, n	7/40 (18)	0/38 (0)	0.01
Relapse at 6 months, n	23/40 (58)	16/38 (42)	0.26



Patients at risk	0	3	6	9	12
Short arm:	38	28	23	16	13
Long arm:	40	30	18	10	10

# Linee guida SiNePe

Pasini et al. *Italian Journal of Pediatrics* (2017) 43:41  
DOI 10.1186/s13052-017-0356-x

Italian Journal of Pediatrics

REVIEW

Open Access

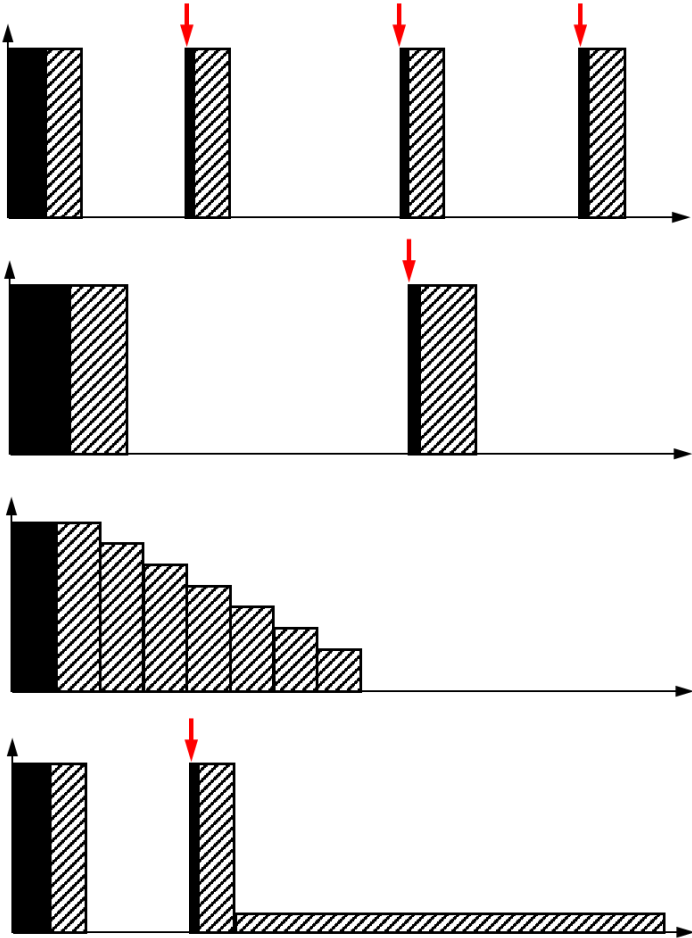
## The Italian Society for Pediatric Nephrology (SiNePe) consensus document on the management of nephrotic syndrome in children: Part I - Diagnosis and treatment of the first episode and the first relapse



Andrea Pasini<sup>1\*</sup>, Elisa Benetti<sup>2</sup>, Giovanni Conti<sup>3</sup>, Luciana Ghio<sup>4</sup>, Marta Lepore<sup>4</sup>, Laura Massella<sup>5</sup>, Daniela Molino<sup>6</sup>, Licia Peruzzi<sup>7</sup>, Francesco Emma<sup>5</sup>, Carmelo Fedè<sup>3</sup>, Antonella Trivelli<sup>8</sup>, Silvio Maringhini<sup>9</sup>, Marco Materassi<sup>10</sup>, Giovanni Messina<sup>11</sup>, Giovanni Montini<sup>4</sup>, Luisa Murer<sup>2</sup>, Carmine Pecoraro<sup>6</sup> and Marco Pennesi<sup>12</sup>

Prednisone (PDN)	Dosage	Duration
Treatment of the first episode		
60 mg/m <sup>2</sup> (maximum 60 mg)	in single or 2 divided doses	6 weeks
40 mg/m <sup>2</sup> (maximum 40 mg)	on alternate days	6 weeks
Treatment of the first relapse		
60 mg/m <sup>2</sup> (maximum 60 mg)	in a single or 2 divided doses	Until urine protein is negative for 5 days
40 mg/m <sup>2</sup> (maximum 40 mg)	on alternate days	4 weeks

# Principi della terapia steroidea



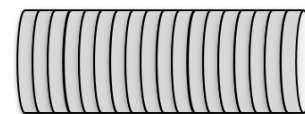
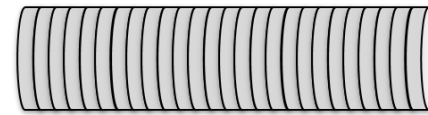
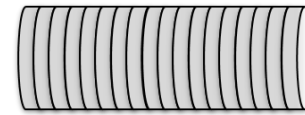
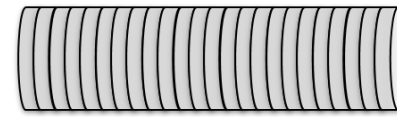
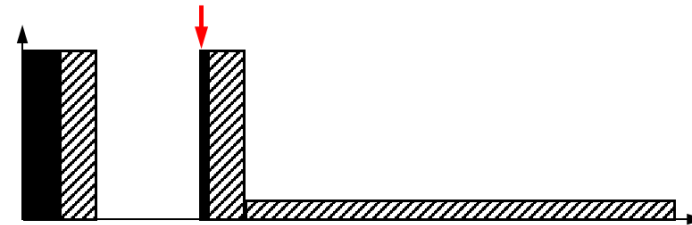
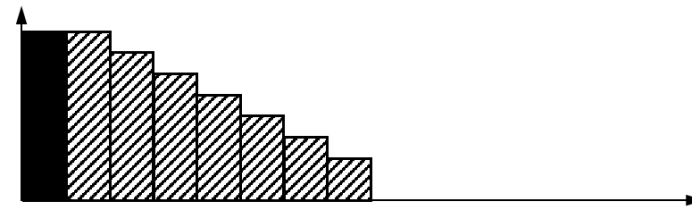
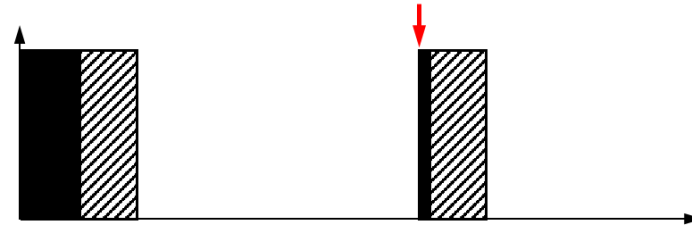
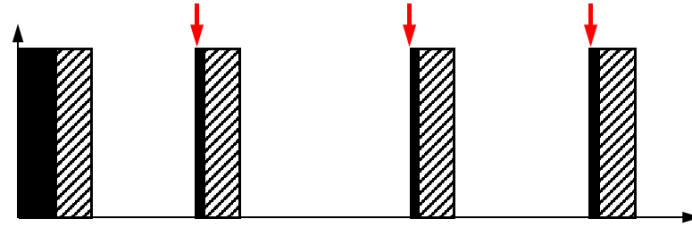
# Principi della terapia steroidea

Cumulative dose of PDN



**THE BEST**

**THE BEST**



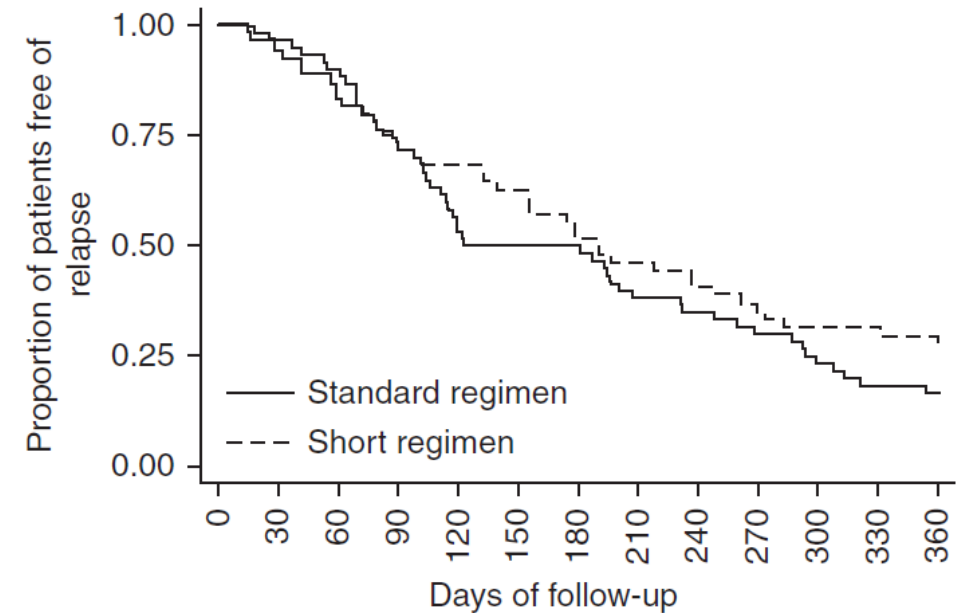
# PDN per le ricadute in pazienti con forme leggere

## Short-Duration Prednisolone in Children with Nephrotic Syndrome Relapse

### A Noninferiority Randomized Controlled Trial

Deepika Kainth,<sup>1</sup> Pankaj Hari,<sup>1</sup> Aditi Sinha,<sup>1</sup> Shivam Pandey,<sup>2</sup> and Arvind Bagga<sup>1</sup>

- Infrequently relapsing nephrotic syndrome
- 40 mg/m<sup>2</sup>: 2 weeks vs. 4 weeks



	0	30	60	90	120	150	180	210	240	270	300	330	360
Standard regimen	60	58	54	44	32	30	30	23	21	18	14	11	10
Short regimen	54	51	45	40	37	34	28	25	22	19	17	17	16

# PDN a piccole dosi giornaliere nei pazienti con forme più severe

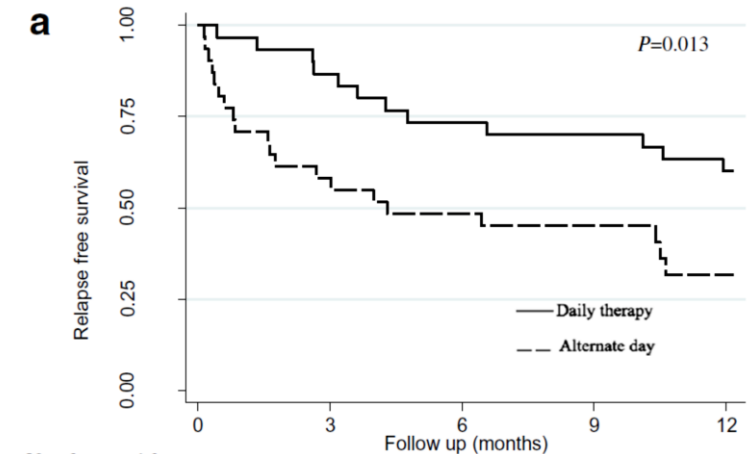
## Efficacy of low-dose daily versus alternate-day prednisolone in frequently relapsing nephrotic syndrome: an open-label randomized controlled trial

Menka Yadav<sup>1</sup> · Aditi Sinha<sup>1</sup> · Priyanka Khandelwal<sup>1</sup> · Pankaj Hari<sup>1</sup> · Arvind Bagga<sup>1</sup>

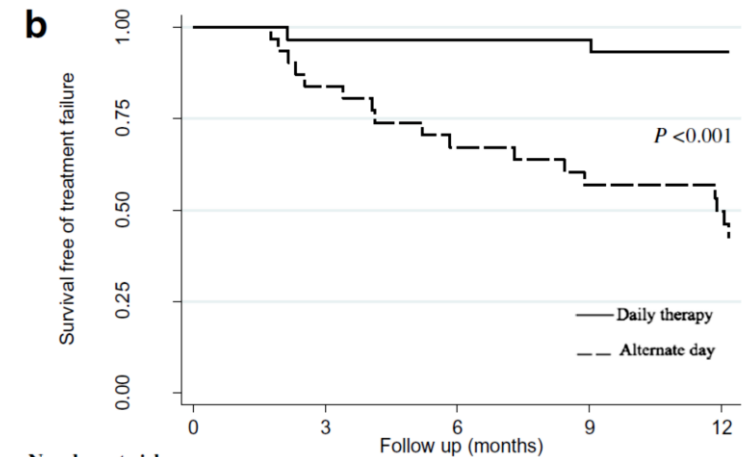
- Prednisolone for 12 months
- 0.2–0.3 mg/kg/d vs. 0.5–0.7 mg/kg/alt.day

### Results:

- Fewer relapses
- More sustained remission
- Less treatment failure
- Lower prednisolone use  
( $0.27 \pm 0.07$  versus  $0.39 \pm 0.19$  mg/kg/day;  $p = 0.003$ )



Number at risk						
Alternate day	31	18	15	11	7	
Daily therapy	30	26	22	21	18	



Number at risk						
Alternate day	31	26	20	16	14	
Daily therapy	30	29	29	29	28	



# PDN (~15 mg/m<sup>2</sup>) durante le infezioni delle alte vie respiratorie

## Patients treated with or without low dose alternate day PDN

### **Increased Maintenance Corticosteroids during Upper Respiratory Infection Decrease the Risk of Relapse in Nephrotic Syndrome**

Tej K. Mattoo Mustapha A. Mahmoud

Maternity and Children's Hospital, and King Fahad National Guard Hospital, Riyadh, Kingdom of Saudi Arabia;  
Division of Nephrology, Children's Hospital of Michigan, Detroit, Mich., USA

Nephron 2000

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

Asiri S. Abeyagunawardena<sup>1</sup> · R. S. Thalgahagoda<sup>1</sup> · Pathum V. Dissanayake<sup>1</sup> ·  
Shamali Abeyagunawardena<sup>2</sup> · Y. A. Illangasekera<sup>3</sup> · Umeshi I. Karunadasa<sup>1</sup> ·  
Richard S. Trompeter<sup>4</sup>

Pediatric Nephrol 2017

### **Increasing the dose of prednisolone during viral infections reduces the risk of relapse in nephrotic syndrome: a randomised controlled trial**

A S Abeyagunawardena,<sup>1</sup> R S Trompeter<sup>2</sup>

Arch Dis Child 2008

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

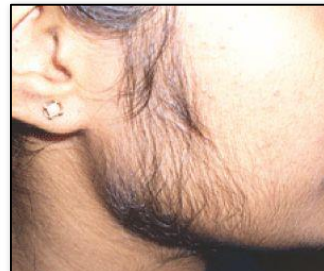
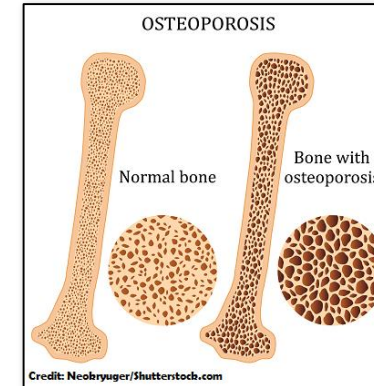
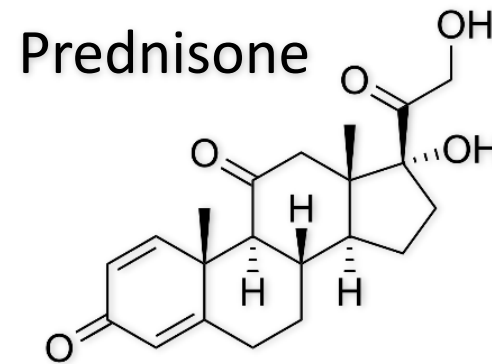
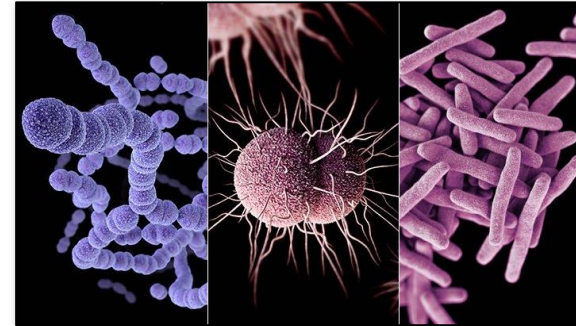
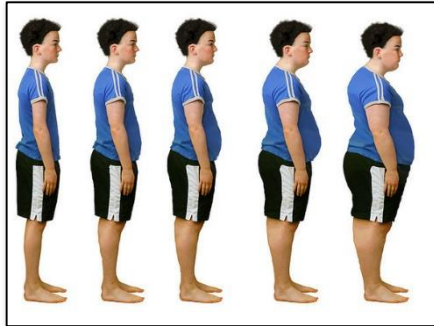
Ashima Gulati,\* Aditi Sinha,\* Vishnubhatla Sreenivas,<sup>†</sup> Aparna Math,\* Pankaj Hari,\* and Arvind Bagga\*

CJASN 2011

# Riassumendo, l'uso degli steroidi nella SN cortico-sensibile...

- All'inizio: stesso protocollo per tutti
- Frequenti recidive: mantenimento a gg alterni
- Forme più severe: bassa dose giornaliera?
- Forme più leggere: trattamento breve delle recidive?
- Infezioni delle alte vie respiratorie: terapia giornaliera per una settimana

# Tossicità steroidea

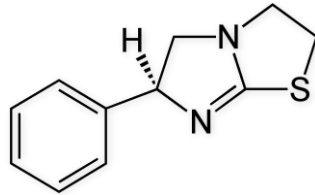


# Alternative terapeutiche

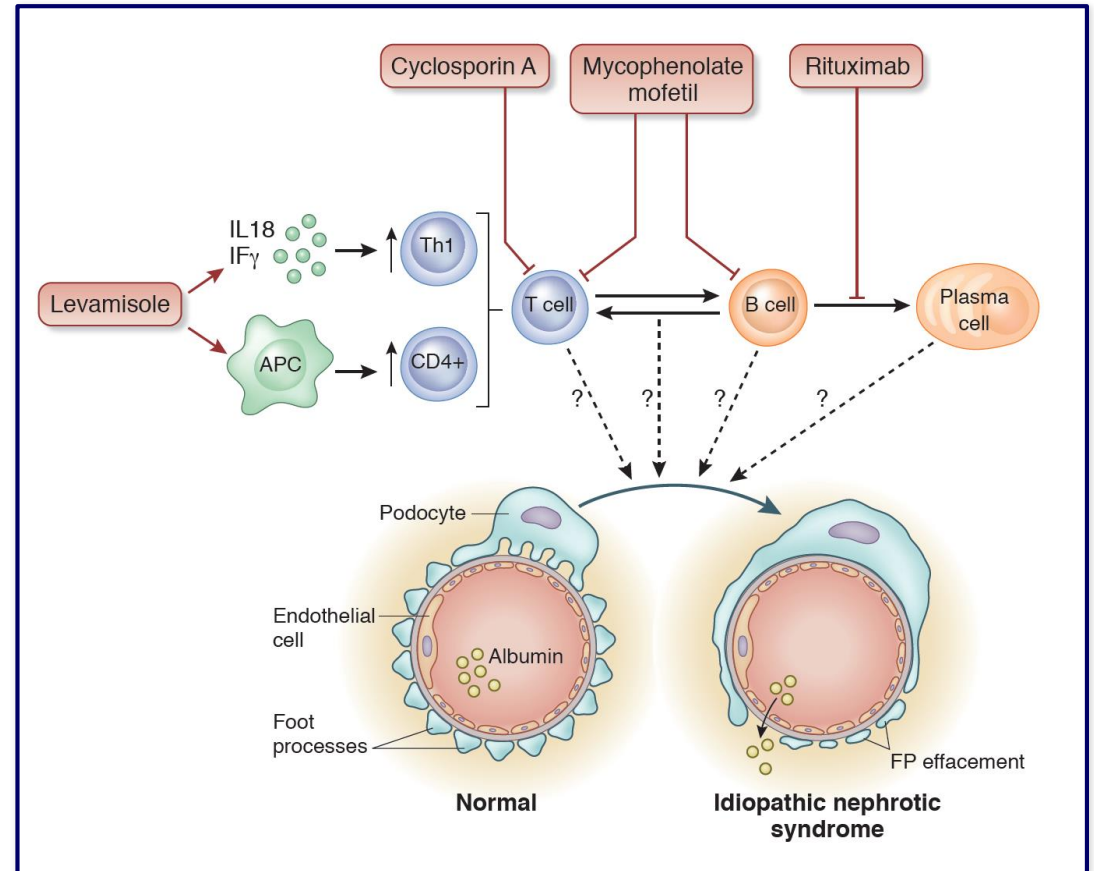
<b>Drug</b>	<b>Efficacy</b>	<b>Indication</b>
<b>Calcineurin inhibitors</b>	<b>+++++</b>	<b>SDNS</b>
<b>Mofetil mycofenolate</b>	<b>++++</b>	<b>FRNS/SDNS</b>
<b>Rituximab</b>	<b>++++</b>	<b>FRNS/SDNS</b>
<b>Levamisole</b>	<b>+++</b>	<b>FRNS</b>
<b>Cyclophosphamide</b>	<b>+++</b>	<b>FRNS</b>

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# Levamisolo



- Agente anti elmintico
- Proprietà immunomodulatorie
- In passato usato per terapie anti-tumorali ed «immunitarie» (aftosi orale, sindrome di Behcet, sindrome nefrosica)
- Molto usato nei paesi in via di sviluppo (basso costo!)



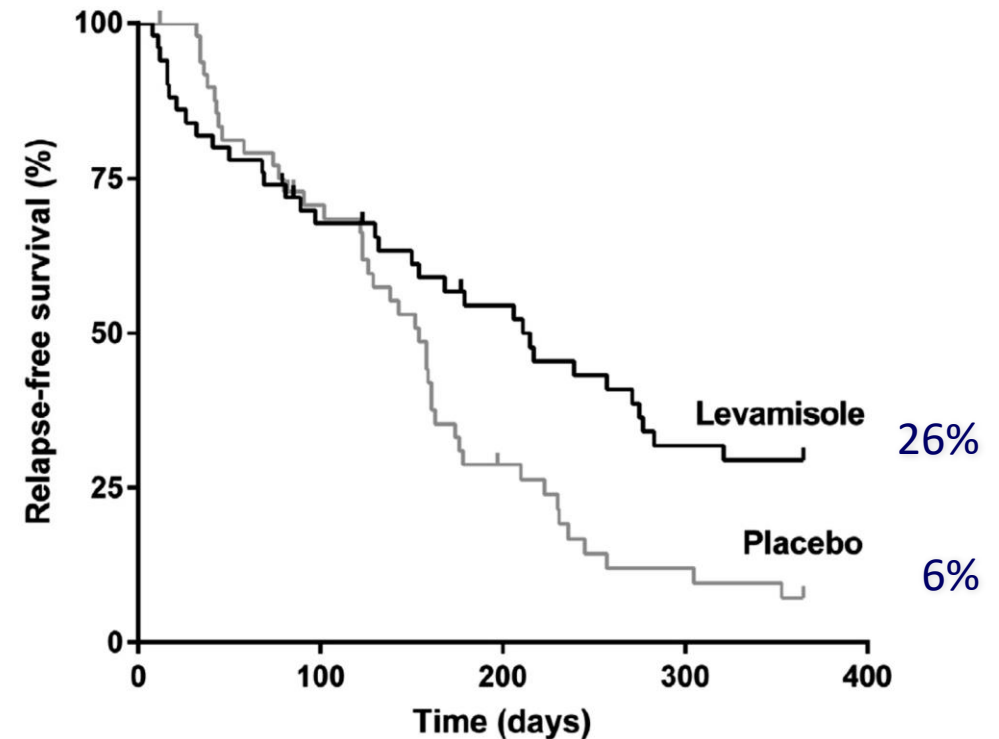
# Levamisole

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



see commentary on page 310  
OPEN

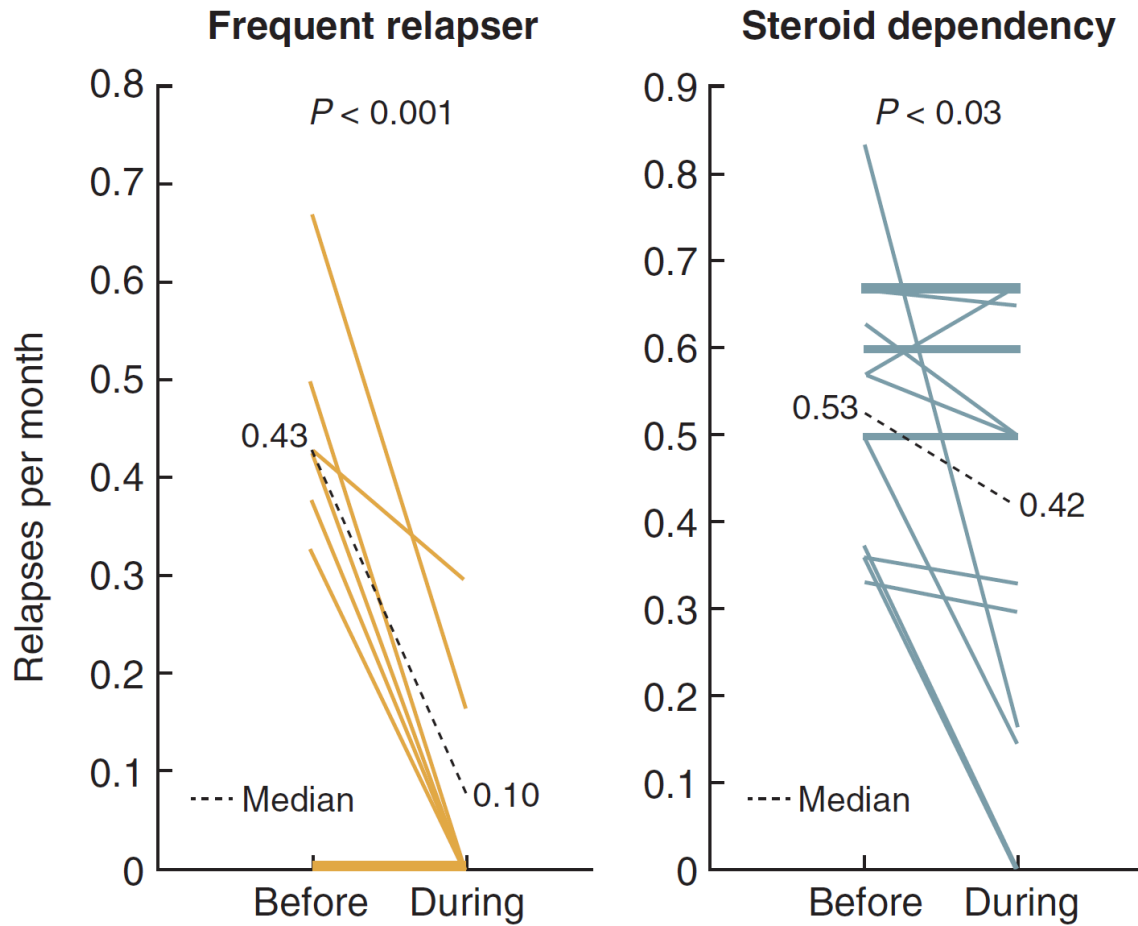
- Multicentric, placebo controlled RCT
- 99 children with FRNS/SDNS treated for 12 months
- Good safety profile
  - 4 cases of non-symptomatic neutropenia
    - ✓ 2 resolved spontaneously
    - ✓ 2 resolved after discontinuation
  - 1 case of ANCA-associated arthritis
- Subgroup analysis: higher effectiveness in Indian children
  - India: 58% FRNS
  - Europe centers: 11% FRNS



#### Numbers at risk

L	50	32	24	14	13
P	49	32	12	5	3

# Candidati per la terapia con levamisolo



Attenzione!

- Circa 20% positività per ANCA  
possibili artriti e vasculiti cutanee
- Leucopenia

# ANCA-associated disease under levamisole therapy



Rongioletti et al, Br J Dermatol 1999

- Some children develop arthritis and/or cutaneous vasculitis
- On average of 2 years after starting levamisole
- ANCA positivity
- Reversible upon treatment discontinuation + steroids
- ANCA may persist for several months/years

## Our recent experience:

- Monitoring of ANCA every 6 months
- 25 children treated for 2-4 years
- 5 (20%) developed ANCA, usually after >2 years
- Levamisole was always stopped: none developed symptoms



Grazie



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