Farmaci rispamiatori di cortisone….

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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

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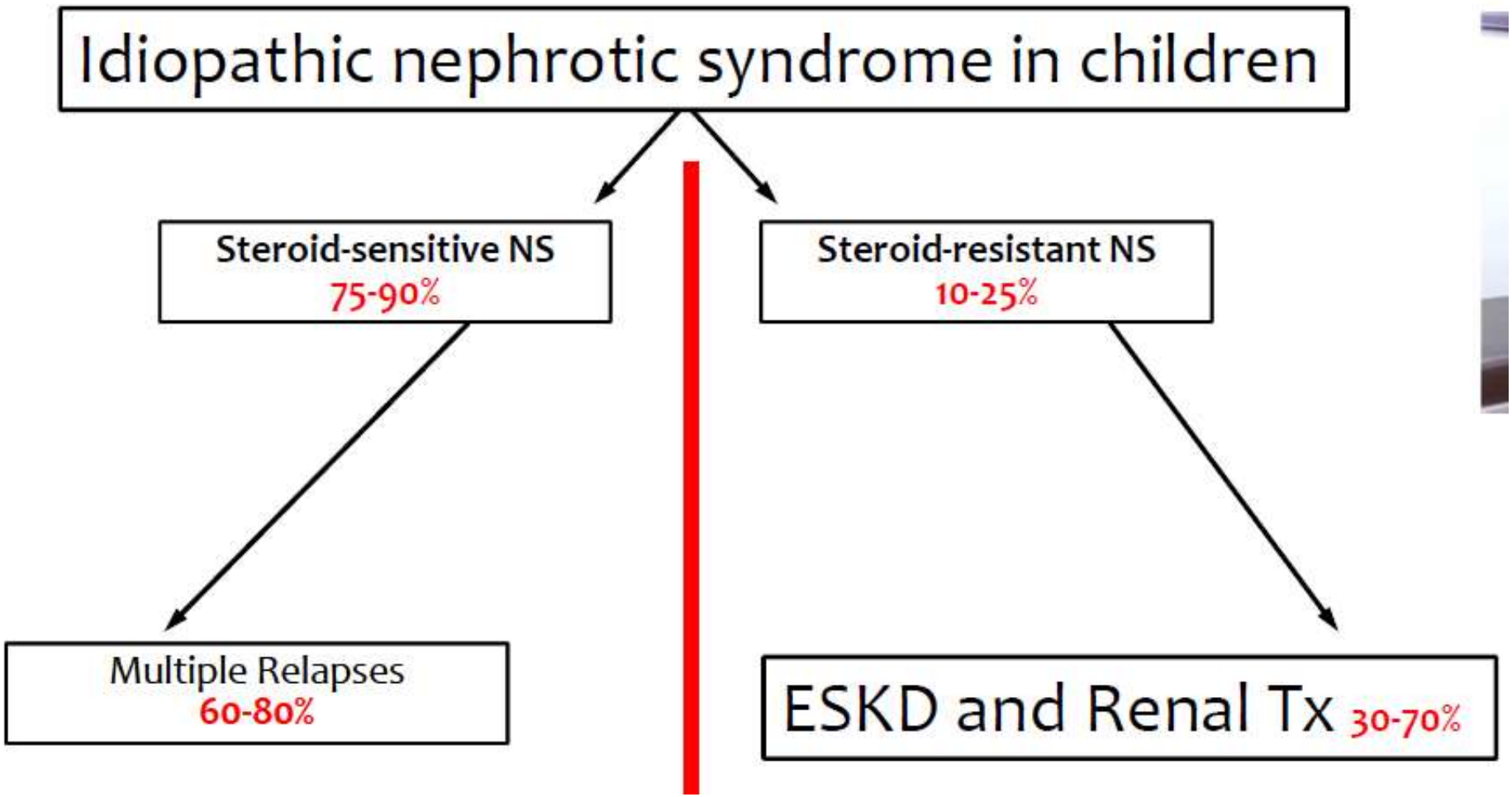
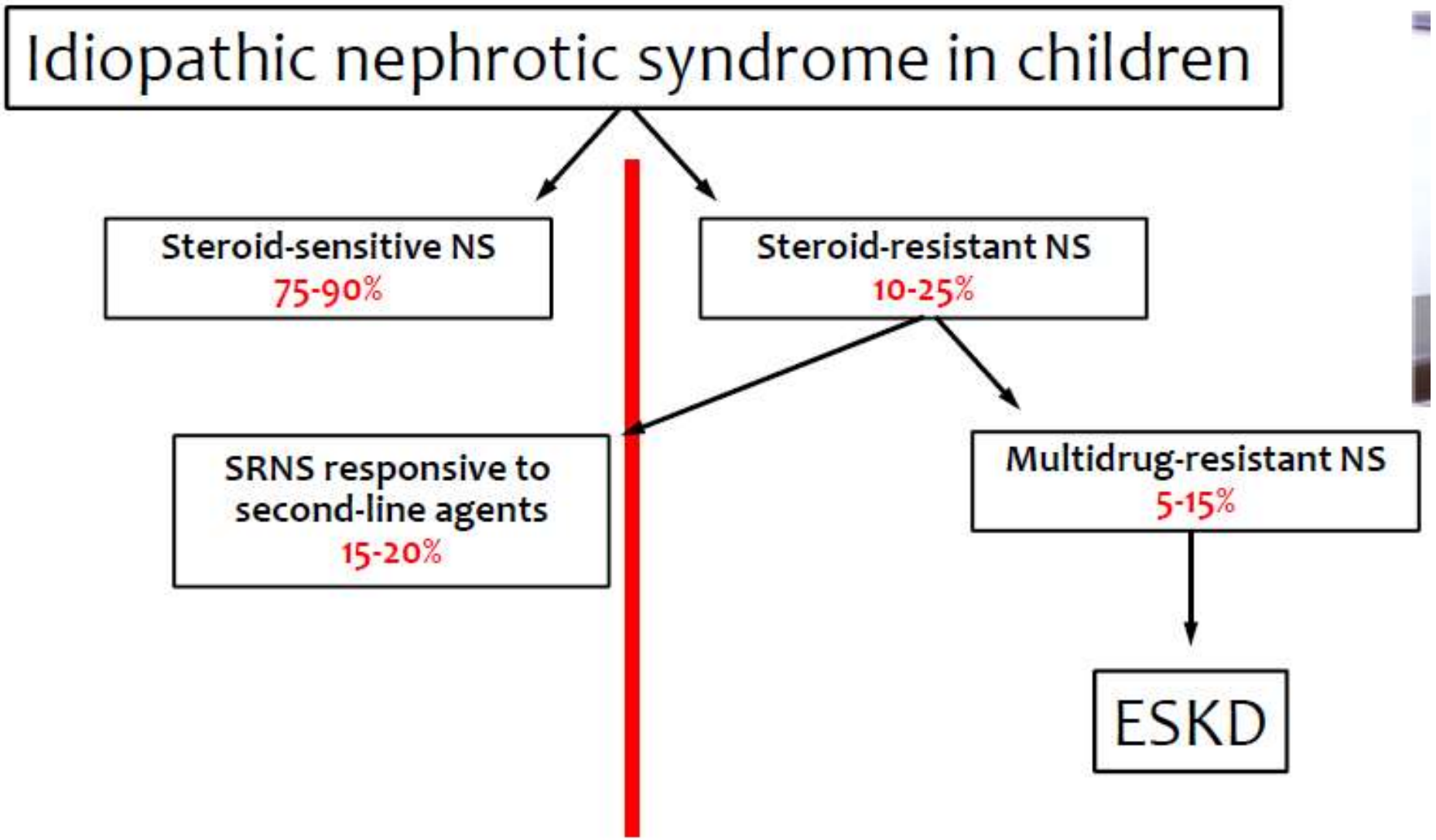
Table 5 Steroid protocol

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


Idiopathic nephrotic syndrome in children
Steroid-sensitive NS
75-90%
Steroid-resistant NS
10-25%
Multiple Relapses
60-80%
ESKD and Renal Tx 30-70%


Idiopathic nephrotic syndrome in children
Steroid-sensitive NS
75-90%
Steroid-resistant NS
10-25%
SRNS responsive to second-line agents
15-20%
Multidrug-resistant NS
5-15%
ESKD

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SUPPLEMENT TO

kidney INTERNATIONAL

KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases

VOLUME 100 | ISSUE 4S | OCTOBER 2021

KDIGO 2021 Guideline for the Management of Glomerular Diseases

- Summary of recommendation statements and practice points
- Chapter 1. General principles for the management of glomerular disease
- Chapter 2. Immunoglobulin A nephropathy/Immunoglobulin A vasculitis
- Chapter 3. Membranous nephropathy
- Chapter 4. Nephrotic syndrome in children
- Chapter 5. Minimal change disease in adults
- Chapter 6. Focal segmental glomerulosclerosis in adults
- Chapter 7. Infection-related glomerulonephritis
- Chapter 8. Immunoglobulin and complement-mediated glomerular diseases with an membranoproliferative glomerulonephritis (MPGN) pattern of injury.
- Chapter 9. ANCA-associated vasculitis
- Chapter 10. Lupus nephritis
- Chapter 11. Anti-GBM antibody glomerulonephritis

Nephrotic syndrome in children

Recommendation 4.3.1.1: **We recommend that oral glucocorticoids be given for 8 weeks** (4 weeks of daily glucocorticoids followed by 4 weeks of alternate-day glucocorticoids) **or 12 weeks** (6 weeks of daily glucocorticoids followed by 6 weeks of alternate-day glucocorticoids) **(1B).**

Recommendation 4.3.2.1: **For children with frequently relapsing and steroid-dependent nephrotic syndrome who are currently taking alternate-day glucocorticoids or are off glucocorticoids, we recommend that daily glucocorticoids 0.5 mg/kg be given during episodes of upper respiratory tract and other infections for 5–7 days to reduce the risk of relapse (1C).**

Recommendation 4.3.2.2: **For children with frequently relapsing nephrotic syndrome who develop serious glucocorticoid-related adverse effects and for all children with steroid-dependent nephrotic syndrome, we recommend that glucocorticoid-sparing agents* be prescribed, rather than no treatment or continuation with glucocorticoid treatment alone (1B).**

* oral cyclophosphamide, levamisole, mycophenolate mofetil (MMF), rituximab, or calcineurin inhibitors (CNIs)

STEROID-RESISTANT NEPHROTIC SYNDROME IN CHILDREN

Recommendation 4.4.1: We recommend using cyclosporine or tacrolimus as initial second-line therapy for children with steroid-resistant nephrotic syndrome (1C).

Indication for kidney biopsy*	• Children presenting with nephrotic syndrome ≥ 12 years of age • Steroid-resistant nephrotic syndrome or subsequent failure to respond to glucocorticoids in steroid-sensitive nephrotic syndrome (secondary steroid-sensitive nephrotic syndrome) • A high index of suspicion for a different underlying pathology (macroscopic hematuria, systemic symptoms of vasculitis, hypocomplementemia, etc.) • At onset, kidney failure not related to hypovolemia. Subsequently, decreasing kidney function in children receiving calcineurin inhibitors or prolonged exposure to calcineurin inhibitors (2 to 3 years)
Genetic testing	• Steroid-resistant nephrotic syndrome • Congenital and infantile forms of nephrotic syndrome (<1 year of age) • Nephrotic syndrome associated with syndromic features • Family history of steroid-resistant nephrotic syndrome or focal segmental glomerulosclerosis
Vitamin D/calcium	In patients with steroid-sensitive nephrotic syndrome and normal vitamin D levels, supplementation is not required. However, in frequent relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome children or in the presence of a known vitamin D deficiency, a reduction in bone mineral content can be prevented by oral supplementation with oral calcium and vitamin D.[1,2]
Gastroprotection	There is insufficient evidence of benefit to recommend prophylactic use of proton-pump inhibitors in children with nephrotic syndrome in the absence of risk factors for gastrotoxicity

Recommendation 4.3.2.2: For children with frequently relapsing nephrotic syndrome who develop serious glucocorticoid-related adverse effects and for all children with steroid-dependent nephrotic syndrome, we recommend that glucocorticoid-sparing agents be prescribed, rather than no treatment or continuation with glucocorticoid treatment alone *(1B)*.

Practice Point 4.3.2.5: Patients should ideally be in remission with glucocorticoids prior to the initiation of glucocorticoid-sparing agents such as oral cyclophosphamide, levamisole, mycophenolate mofetil (MMF), rituximab, or calcineurin inhibitors (CNIs). Coadministration of glucocorticoids is recommended for ≥2 weeks following initiation of glucocorticoid-sparing treatment.

Practice Point 4.3.2.6: Choosing the most appropriate glucocorticoid-sparing agent from among oral cyclophosphamide, levamisole, MMF, rituximab, and CNI is a decision that requires careful consideration of specific patient-related issues such as resources, adherence, adverse effects, and patient preferences. Oral cyclophosphamide and levamisole may be preferable glucocorticoid-sparing therapies in frequently relapsing nephrotic syndrome. MMF, rituximab, CNIs, and to a lesser extent, oral cyclophosphamide may be preferable to glucocorticoid-sparing therapies in children with steroid-dependent nephrotic syndrome (Figure 41[178]).

Treatment	Dose and duration	Clinical tips
First line:		
• **Oral cyclophosphamide**	2 mg/kg/d for 12 weeks (maximum cumulative dose 168 mg/kg)	Cyclophosphamide should not be started until the child has achieved remission with glucocorticoids. Moreover, second courses of alkylating agents should not be given. Weekly Cl are recommended during the treatment course to assess for severe leukopenia or overall bone marrow suppression prompting dose reduction or treatment cessation
• **Mycophenolate mofetil**	Starting dose of 1200 mg/m^2/d (given in two divided doses)	Target area under the curve >50 µg•h/ml.* Mycophenolate mofetil should be continued for at least 12 months, as most children will relapse when it is stopped. In children experienci significant abdominal pain on mycophenolate mofetil, other mycophenolic acid analogs (MPAAs), such as sodium mycophenolate, may be employed at equivalent doses (360 m of sodium mycophenolate corresponds to 500 mg of mycophenolate mofetil)

• Calcineurin inhibitors†		CNI should be continued for at least 12 months as most children will relapse upon discontinuation. Monitor CNI levels during therapy to limit toxicity
– Cyclosporine	4 to 5 mg/kg/d (starting dose) in two divided doses	Cyclosporine may be preferable in patients at risk for diabetic complications. Target 12 hour trough level of 60–150 ng/ml [50–125 nmol/l] aiming for lowest levels to maintain remission and avoid toxicity
– Tacrolimus	0.1 mg/kg/d (starting dose) given in two divided doses	Tacrolimus may be preferred over cyclosporine in patients for whom the cosmetic side effects of cyclosporine are unacceptable. Target 12 hour trough level of 5–10 ng/ml [6–12 nmol/l] aiming for lowest levels to maintain remission and avoid toxicity

Steroid-resistant nephrotic syndrome in children

4.4 Treatment

Recommendation 4.4.1: We recommend using cyclosporine or tacrolimus as initial second-line therapy for children with steroid-resistant nephrotic syndrome *(1C)*.

Pediatric Nephrology (2023) 38:877–919
https://doi.org/10.1007/s00467-022-05739-3

GUIDELINES

IPNA clinical practice recommendations for the diagnosis and management of children with steroid-sensitive nephrotic syndrome

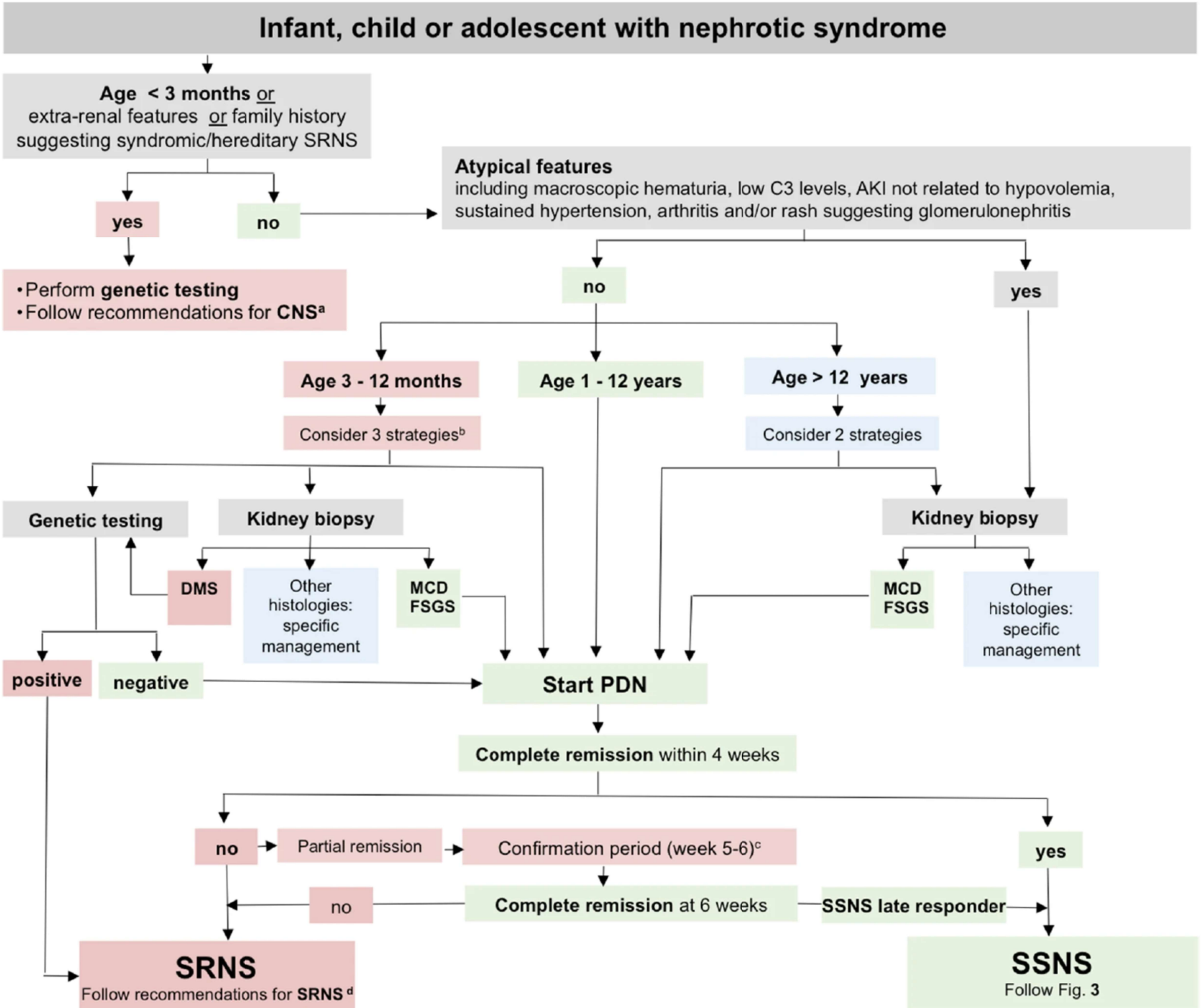
Agnes Trautmann[1] · Olivia Boyer[2] · Elisabeth Hodson[3] · Arvind Bagga[4] · Debbie S. Gipson[5] · Susan Samuel[6] · Jack Wetzels[7] · Khalid Alhasan[8] · Sushmita Banerjee[9] · Rajendra Bhimma[10] · Melvin Bonilla-Felix[11] · Francisco Cano[12] · Martin Christian[13] · Deirdre Hahn[14] · Hee Gyung Kang[15] · Koichi Nakanishi[16] · Hesham Safouh[17] · Howard Trachtman[18] · Hong Xu[19] · Wendy Cook[20] · Marina Vivarelli[21] · Dieter Haffner[22] · on behalf of the International Pediatric Nephrology Association

OBIETTIVO: MANTENERE LA REMISSIONE

.....E RIDURRE AL MINIMO USO DI LO STEROIDE

FARMACO	Efficacia	Indicazione	Commenti
Ciclosporina e Tacrolimus	+++++	SDNS	Tossicità renale / ipertensione
Micofenolato mofetile	++++	FRNS/SDNS	Spesso necessarie alte dosi (> 600 mg/m^2)
Levamisolo	+++	FRNS	Difficile da reperire
Ciclofosfamide	+++	?	Tossicità; talora nn protettivo
Rituximab	Buona	?	Può compromettere la memoria immunologica

Altri farmaci innovativi


Infant, child or adolescent with nephrotic syndrome
Age < 3 months or extra-renal features or family history suggesting syndromic/hereditary SRNS
yes
no
•Perform genetic testing
•Follow recommendations for CNS[a]
Atypical features
including macroscopic hematuria, low C3 levels, AKI not related to hypovolemia, sustained hypertension, arthritis and/or rash suggesting glomerulonephritis
no
yes
Age 3 - 12 months
Age 1 - 12 years
Age > 12 years
Consider 3 strategies[b]
Consider 2 strategies
Genetic testing
Kidney biopsy
Kidney biopsy
DMS
Other histologies: specific management
MCD FSGS
MCD FSGS
Other histologies: specific management
positive
negative
Start PDN
Complete remission within 4 weeks
no
Partial remission
Confirmation period (week 5-6)[c]
yes
no
Complete remission at 6 weeks
SSNS late responder
SRNS
Follow recommendations for SRNS[d]
SSNS
Follow Fig. 3

Trattamento di seconda linea nelle frequenti ricadute (FRNS) e corticodipendenti (SDNS)

- Si consiglia l'utilizzo del trattamento di mantenimento in tutti i pazienti con FRNS o SDNS
- Nei pazienti con FRNS, raccomandiamo l'introduzione di un agente risparmiatore di steroidi o PDN di mantenimento a basso dosaggio somministrato a giorni alterni o una dose giornaliera
- Raccomandiamo l'introduzione di un agente risparmiatore di steroidi nei bambini:

– che non sono controllati durante la terapia, o

– che soffrono di una ricaduta complicata, o

– con SDNS

- Raccomandiamo che la scelta del farmaco sia fatto in collaborazione con pazienti o tutori al fine di scegliere il farmaco più appropriato per ogni paziente secondo i suoi valori e le sue preferenze.

Ciò richiede non solo informazioni sull'efficacia di questi farmaci ma anche su possibili effetti collaterali

- Uno dei seguenti agenti risparmiatori di steroidi: inibitori della calcineurina, ciclofosfamide, levamisolo e micofenolato mofetile / sodio micofenolico
- Utilizzare RTX come agente risparmiatore di steroidi nei bambini con FRNS o SDNS che non sono controllati dalla terapia dopo trattamento con almeno un altro agente risparmiatore di steroidi a dose adeguata, in particolare in caso di non aderenza
- Si consiglia di passare a un diverso farmaco risparmiatore di steroidi quando un paziente non è controllato in terapia con il farmaco iniziale
- Si consiglia di prendere in considerazione la riduzione graduale e l'interruzione del trattamento di mantenimento con PDN, LEV, MMF/MPS, o un CNI in tutti i bambini in remissione prolungata per almeno 12 mesi

- Non ci sono prove sufficienti per stabilire la migliore opzione iniziale e la sequenza ottimale di agenti dal meno al più efficace o dal meno al più tossico

- La scelta dovrebbe essere basata sulle preferenze della famiglia e del medico e il profilo di rischio associato alle complicazioni del farmaco

- I fattori da considerare includono il tipo di malattia/gravità, età (compreso l'inizio della pubertà), potenziale aderenza terapeutica, profilo degli effetti collaterali, comorbidità, costo e disponibilità

Inibitori della calcineurina (ciclosporina e tacrolimus)

- consigliato il monitoraggio terapeutico dei farmaci per garantire un dosaggio ottimale
- Ciclosporina A (CsA) iniziare alla dose di 3-5 mg/kg/die (dose massima 250 mg) suddivisa in 2 dosi (ogni 12 h) per raggiungere il livelli di 60–100 ng/mL o livelli post-dose 2 h di 300–550 ng/mL
- Tacrolimus (TAC), si consiglia di iniziare alla dose di 0,1-0,2 mg/kg/giorno (dose massima 10 mg) in 2 dosi (ogni 12 ore) per raggiungere i livelli ematici minimi di 3-7 ng/mL
- Si consiglia di utilizzare la dose minima efficace di CNI
- Si consiglia di evitare l'uso prolungato di CNI oltre i 2-3 anni
- Se le CNI devono essere continuate, raccomandiamo che la biopsia renale sia presa in considerazione dopo 2-3 anni per escludere una nefrotossicità

CSA

Very efficient…

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
No of relapses before CsA	rel/years	2.3 [1.6 - 5.2]	53
No 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

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

Ciclosporina

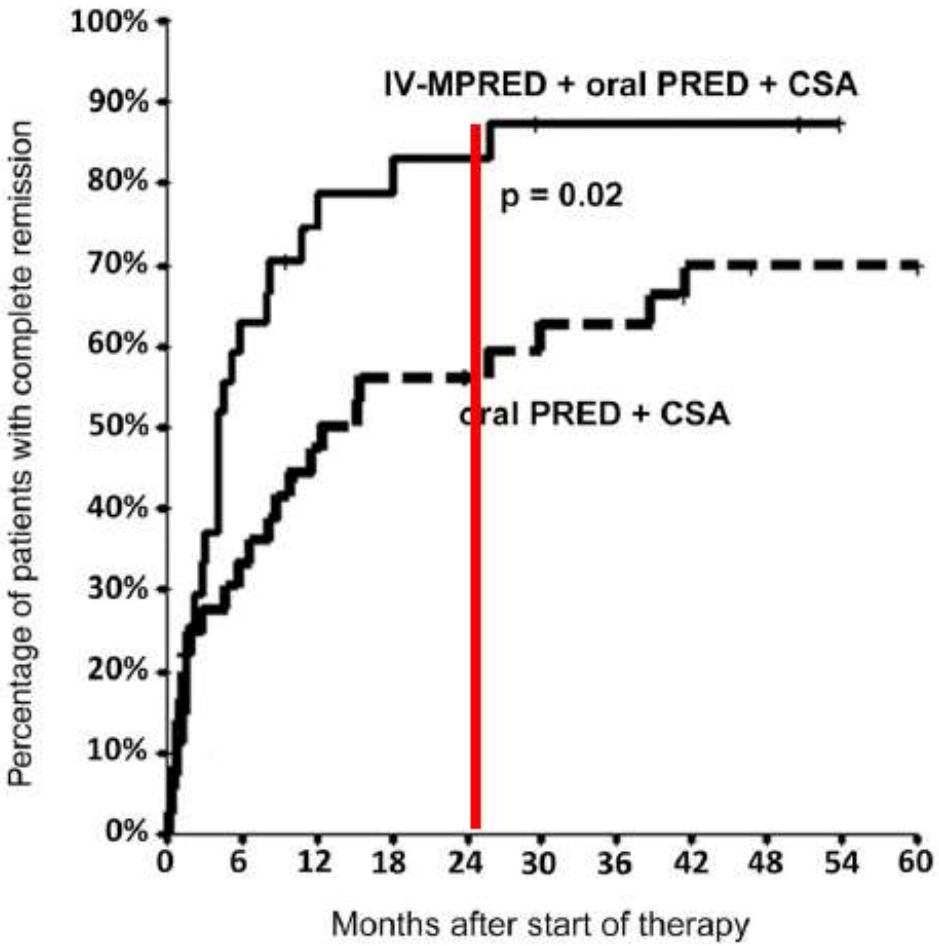
efficace ma …

- ipertensione arteriosa
- richiede il controllo dei livelli nel sangue
- potente Immunosoppressivo
- potenziale tossicità renale

TACROLIMUS (FK506)

- Probabilmente più efficace della ciclosporina
- Minor grado di ipertensione
- altri effetti collaterali (diabete)
- probabilmente ugualmente nefrotossico

How long before you give up on a CNI in a child



Ehrich et al, Nephrol Dial Transpl 2007

It can take a lo

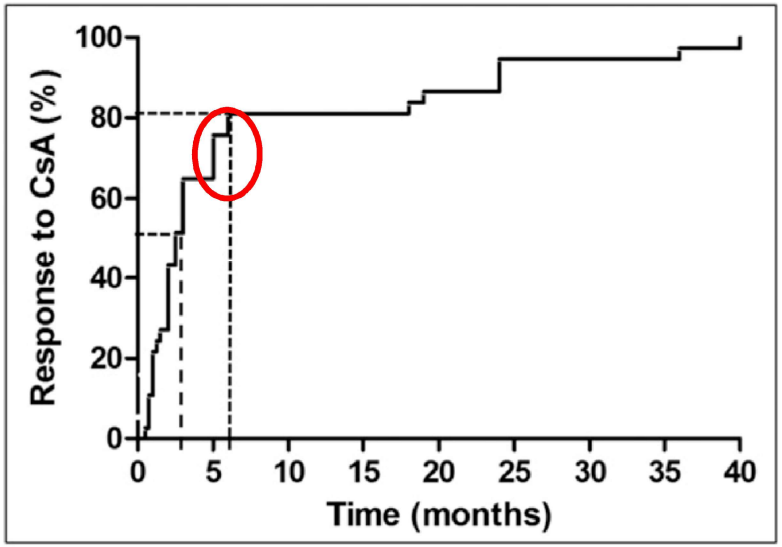
However:

- Need to avo unnecessar non-respon
- Opportunit therapeutic

Nongenetic SRNS in children

Rapid Response to Cyclosporin A and Favorable Renal Outcome in Nongenetic Versus Genetic Steroid–Resistant Nephrotic Syndrome

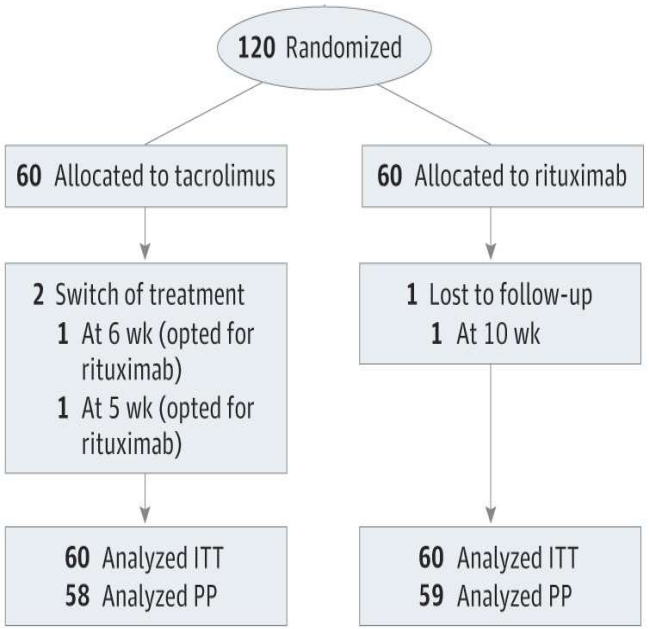
Anja K. Büscher, Bodo B. Beck,† Anette Melk,‡ Julia Hoefele,§ Birgitta Kranz,‖ Daniel Bamborschke,† Sabrina Baig,‡ Bärbel Lange-Sperandio,¶ Theresa Jungraithmayr,** Lutz T. Weber,†† Markus J. Kemper,‡‡ Burkhard Tönshoff,§§ Peter F. Hoyer,* Martin Konrad,‖ and Stefanie Weber* for the German Pediatric Nephrology Association (GPN)*

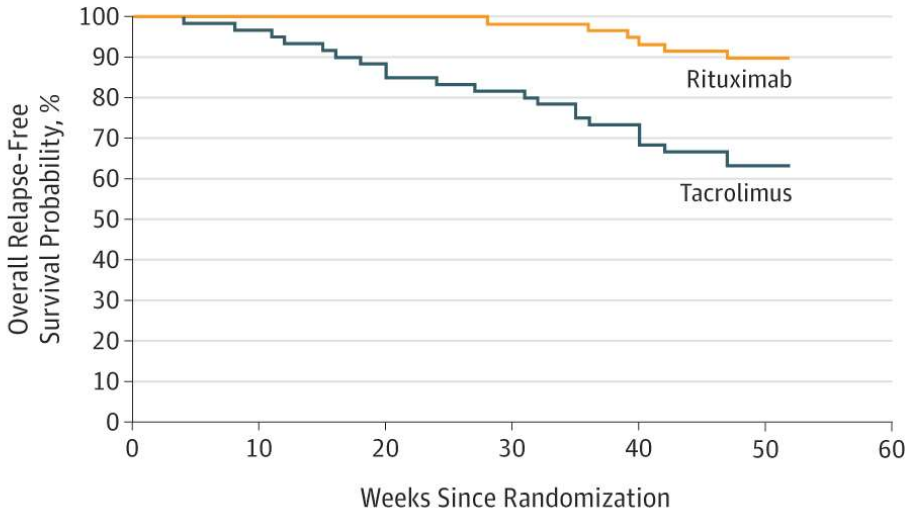


- Remission in nongenetic SRNS: 78%
- 82% responded within 6 months of therapy

RTX vs Tacrolimus for SDNS: RCT

SDNS – no previous steroid sparing agent





No. at risk

Rituximab	60	60	59	58	56	53
Tacrolimus	60	58	53	49	44	38

MICOFENOLATO

- **non presenta tossicità renale**
- causa immunosoppressione
- tossicità gastrointestinale e ematologica
- teratogenico (?)
- Probabilmente meno efficace degli inbitori di calcineurine
- **Farmacocinetica molto individuale**

Micofenolato mofetile/micofenolico sodico

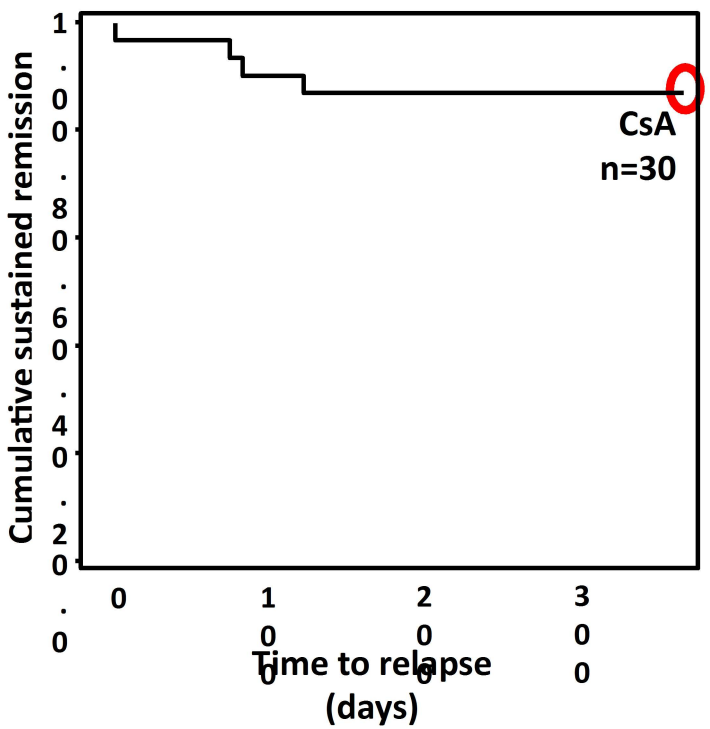
- si consiglia una dose iniziale di 1200 mg/m2 BSA (massima dose 3000 mg) suddivisa in due dosi orali ogni 12 h

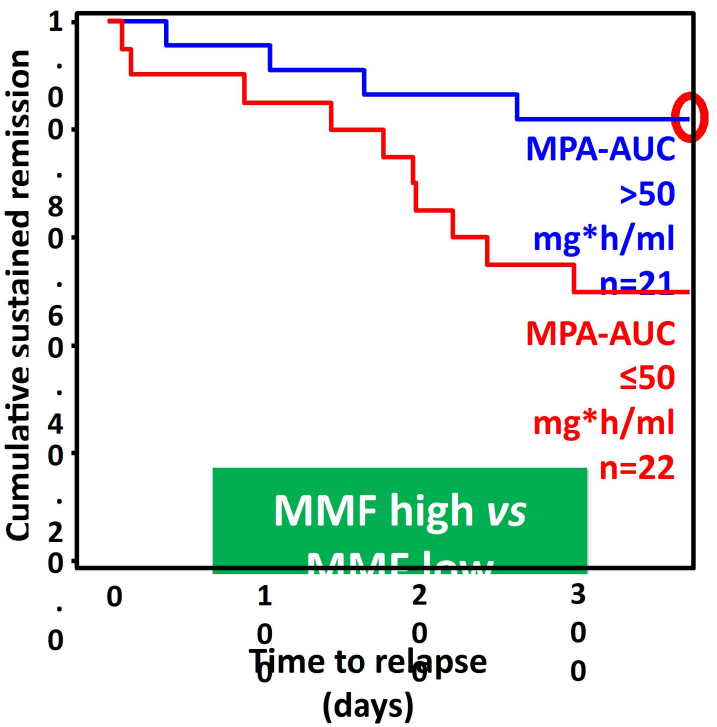
- In alternativa, si consiglia di utilizzare il corrispondente dosaggio di sodio micofenolico (MPS), cioè 360 mg che corrisponde a 500 mg di MMF
- Iniziare la terapia con MMF/MPS mentre il bambino sta ancora ricevendo una terapia steroidea a giorni alterni perchè l'effetto immunosoppressivo di MMF/MPS è ritardato. Nella maggior parte dei bambini, gli steroidi a giorni alterni possono quindi essere ridotti gradualmente e sospesi entro 6-12 settimane.
- Nei pazienti in cui nonostante il dosaggio corretto non ci dimostri efficacia terautica si consiglia di monitorizzare il livello farmaci con target dell’area sotto la curva a 12 ore superiore a 50 mg h/L
- Raccomandiamo che le adolescenti sessualmente attive ricevono MMF/MPS solo se usano una contraccezione adeguata

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)





Should we still use alkylating agents?

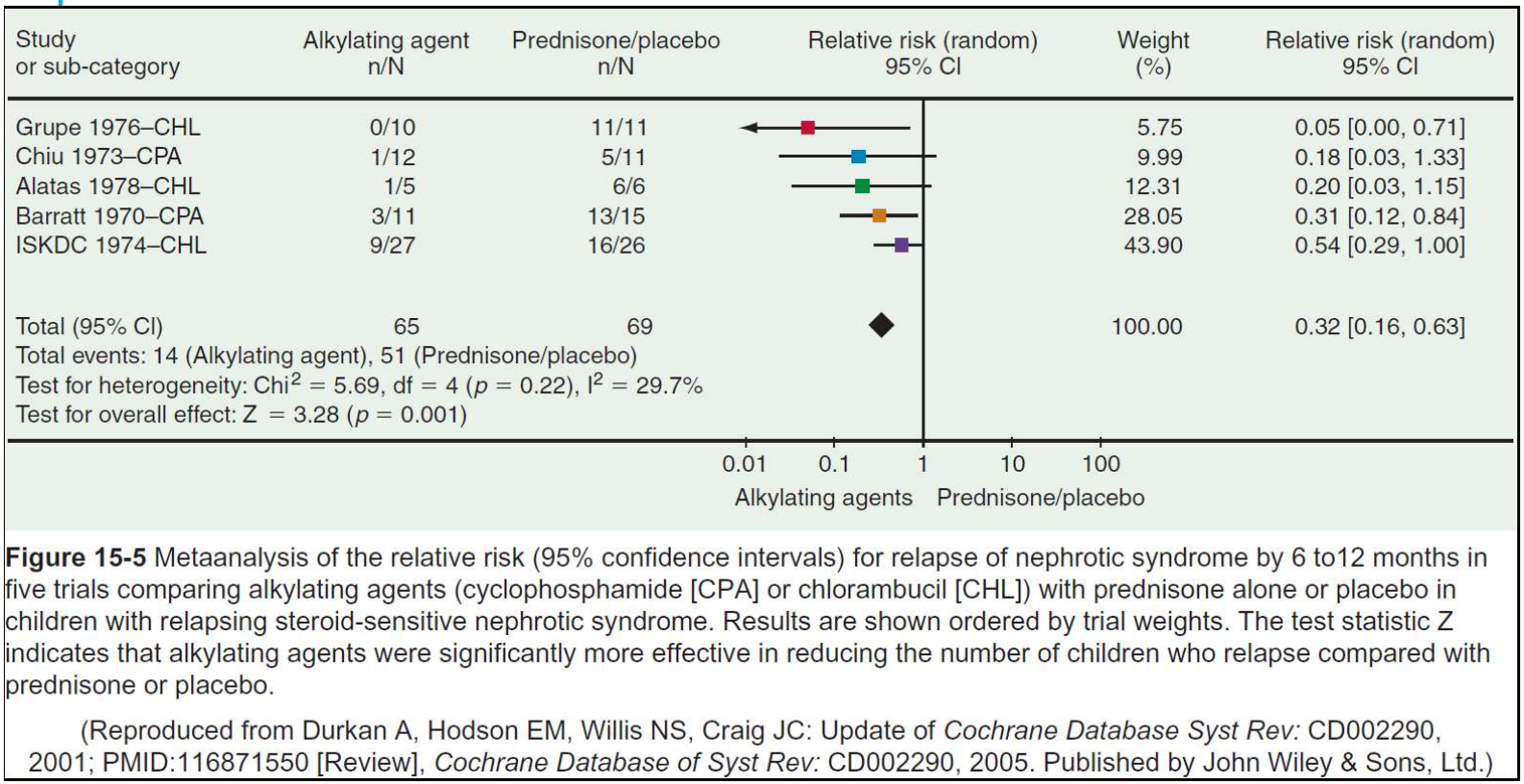


Figure 15-5 Metaanalysis of the relative risk (95% confidence intervals) for relapse of nephrotic syndrome by 6 to12 months in five trials comparing alkylating agents (cyclophosphamide [CPA] or chlorambucil [CHL]) with prednisone alone or placebo in children with relapsing steroid-sensitive nephrotic 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.)

Cell-mediated Antibody-mediated

But, only work well in patients that don't need them…

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

Ciclofosfamide

Utilizzata nella SN pediatrica da oltre 5 decenni.

E’ relativamente economico e i requisiti di monitoraggio comportano test standard facilmente disponibili. Rispetto ad agenti come LEV, MMF e CNI, ciclofosfamide viene somministrato per un periodo breve con un effetto prolungato dopo l'interruzione.

Il rischio di tossicità gonadica è ridotto con un'appropriata restrizione della dose cumulativa totale. Deve essere usato con cautela nei maschi peri-puberali. Il rischio di cistite emorragica è molto basso

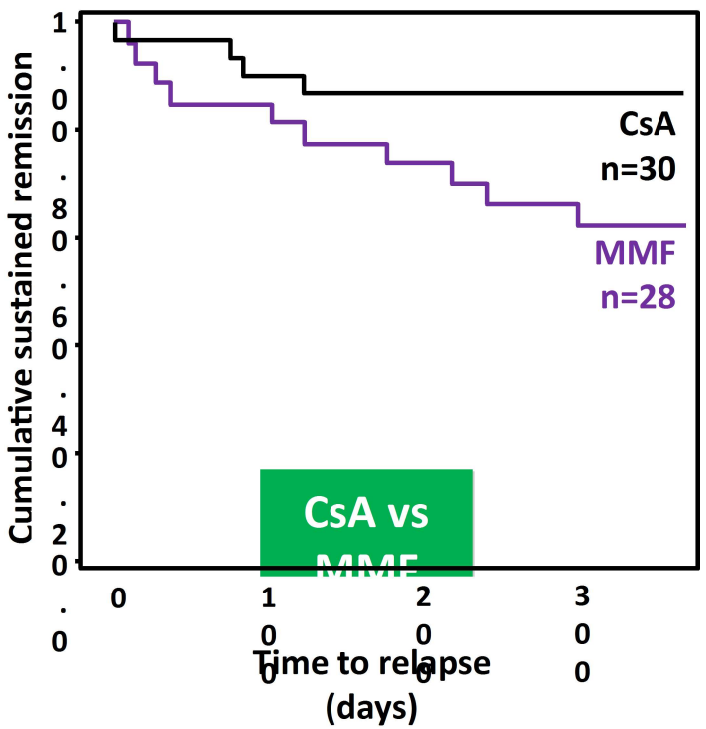
La leucopenia/neutropenia è l'evento avverso più comune ma usualmente si gestisce bene con adattamento della dose.

A conti fatti, i potenziali rischi di ciclofosfamide possono favorire l'uso di altri agenti risparmiatori di steroidi, se disponibili.

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)



Riassumendo, l'uso dei farmaci non steroidei nella SN cortico-sensibile…

- Levamisolo: nelle forme meno severe
- Ciclofosfamide: bambini 5-10 anni - un solo ciclo
- Inibitori di calcineurina: molto efficaci, ma effetti secondari
- Micofenolato efficace ma somministrazione prolungata e necessita di dosaggio corretto
- Rituximab: efficacia dipende dalla severità della SN / rischio di ipogammaglobulinemia

Gli studi proseguono sempre….

clinical investigation www.kidney-international.org

A multicenter retrospective study of calcineurin inhibitors in nephrotic syndrome secondary to podocyte gene variants

see commentary on page 839

Lay Summary

Calcineurin inhibitors (CNI) are immunosuppressive medications very efficacious in childhood steroid-resistant nephrotic syndrome (SRNS). However, there is a subgroup of children with genetic mutations responsible for the disease in whom CNI are considered non-efficacious and are contraindicated. Yet, to date, there are no studies that have specifically addressed the efficacy of CNI in genetic SRNS and how they could affect long-term kidney prognosis. We retrospectively assessed the records of 141 children with genetically confirmed SRNS from 37 international pediatric nephrology centers who had received CNI treatment. Approximately 1 in 4 children showed response to therapy, but more importantly, children responding to this treatment had a 75% lower risk for kidney failure compared with those who did not respond. Our study is the first to show that CNI can actually work in children with genetic SRNS and increase kidney survival, reducing the need for kidney replacement therapy.

Grazie per l’attenzione !

a disposizione per le domande !