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The Polish Society for Pediatric Nephrology (PTNFD) recommendations on the management of children with nephrotic syndrome

ABSTRACT

On behalf of the Polish Society for Pediatric Nephrology, a group of experts has upgraded the previously announced recommendations* on the management of children with nephrotic syndrome. Recommendations are based on the published European and American guidelines, the results of reliable trials and meta-analyses, as well as local experience. They should be regarded as advisory for pediatricians in their personal experience-driven choice of the optimal available strategy for the diagnostics and treatment of individual pediatric nephrotic syndrome (NS) patients. The recommendations will be re-updated by the Society in the forthcoming years to account for the continued rapid progress of clinical research and knowledge in the field of glomerulonephritis.

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Key words: children, immunosuppressive therapy, nephrotic syndrome, nephrotic syndrome complications, steroid-resistant nephrotic syndrome, steroid-dependent nephrotic syndrome, symptomatic therapy, vaccinations

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PREFACE

The following are the recommendations regarding the management of nephrotic syndrome (NS) in children aged 1 year or older, i.e. excluding the cases of congenital nephrotic syndrome.

This update of the first edition of recommendations as published in "Forum Nefrologiczne" in 2015 takes into account the American guidelines developed by the *Kidney Disease: Improving Global Outcomes* (KDIGO) team [1, 2] published in 2012 and updated in 2020, the comments to these recommendations, as voiced by both American [3, 4] and European pediatric nephrologists, and the available literature published by the end of the third quarter of 2020 [5, 6]. The guidelines were developed on the basis of meta-analyses and highly reliable clinical studies. Individual recommendations were updated by the authors; all recommendations were discussed and consulted in detail by the expert group until the content of the recommendation has been accepted by all members.

Recommendations are provided with indications on the quality of evidence (grades A, B, C, and D — Table 1) and recommendation strength (levels 1, 2, or uncategorized — Table 2).

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INTRODUCTION

The nephrotic system develops as a result of proteins, particularly albumin. Nephrotic syndrome develops as a result of loss of protein, particularly albumin, in the urine, in quantities exceeding the systemic compensation capabilities. Increased proteinuria is due to the increased permeability of the glomerular filter membrane secondary to various pathological factors or microstructural defects.

The diagnostic criteria of NS are as follows:

- Urinary protein loss (determined in the first-morning urine or 24-hour urine collection): urine protein to creatinine ratio (uPCR) of ≥ 2 mg protein/1 mg creatinine (≥ 200 mg protein/1 mmol creatinine) or dipstick protein test result of > 3+; alternatively, proteinuria of > 50 mg/kg/d in 24-hour urine collection;
- serum albumin reduced to < 3.0 g/dL or edema when serum albumin cannot be determined.

The listed disorders may be accompanied by hyperlipidemia.

Urinary protein loss as described above without concurrent reduction in the serum albumin level is referred to as nephrotic proteinuria.

NEPHROTIC SYNDROME CLASSIFICATION

Primary NS — isolated NS symptoms, no symptoms from other organ systems. This includes idiopathic nephrotic syndrome (INS) and other primary glomerulonephritis involving large protein losses (as described above).

Secondary NS — accounts for 5% of NS cases in children (0–12 years).

In this case, NS may be caused by:

- systemic vasculitis/autoimmune diseases;
- congenital microstructural glomerular malformations not related to structural podocyte abnormalities (e.g. Alport's syndrome);
- infections;
- specific medicines;
- diabetes;
- hemopoietic system neoplasms (leukemia, lymphoma).

Congenital and infantile NS occurs in children aged 0–3 months and 4–12 months, respectively.

In pediatric patients, INS is the most common etiology of nephrotic syndrome. Histopathological background of INS may include minimal change disease (MCD, submicroscopic nephropathy), mesangial proliferative glomerulonephritis (MPGN), or focal segmental glomerulosclerosis (FSGS). In most children, INS develops from MCD.

EPIDEMIOLOGY OF NEPHROTIC SYNDROME

Idiopathic nephrotic syndrome accounts for 90% of NS cases in children aged 1–10 years and 50% of NS cases in children above 10 years of age. The incidence is estimated at 2–7 new cases per 100000 children under 15 years of age, and the prevalence (including recurrence) amounts to 16 cases per 100000 children [7, 8].

TREATMENT RESPONSE

In 80% of children with NS, disease remission can be achieved following corticosteroid therapy (steroid-dependent NS). About 20% of children are suffering from steroid-resistant NS.

Table 3 presents the classification of NS according to the corticosteroid treatment response.

Table 1. The basis for recommendation grading

Grade	Quality of evidence
A	Randomized clinical trials
B	Non-randomized clinical trials
C	Case series
D	Expert's opinion

Table 2. Key for interpretation of recommendation levels for different audiences (acc. to [1])

Recommendation level	Implications	
	for physicians	for managers
Level 1 "is recommended"	The recommended procedure should be implemented in most patients.	The recommendation may be considered for the development of a reference standard or quality indicator.
Level 2 "is suggested"	Different options may be appropriate for different patients.	The development of a management standard based on such a suggestion would require numerous opinions being taken into account.
Uncategorized	Recommendations based on informal observation rather than scientific data. These are formulated as simple statements; their strength should not be considered higher than that of level 1 and 2 recommendations.	

Table 3. Classification and definitions of NS depending on the corticosteroid treatment response.

Definition	Description
Steroid-sensitive nephrotic syndrome	Proteinuria resolving within 4 weeks after initiation of treatment with corticosteroids at standard doses.
Steroid-dependent nephrotic syndrome	Proteinuria recurring during prednisone therapy (regardless of dose) or within less than 15 days after discontinuation.
Infrequently relapsing nephrotic syndrome	One relapse within 6 months of completion of preliminary treatment or 1–3 relapses within every 12 months.
Frequently relapsing nephrotic syndrome	Two or more relapses within 6 months of completion of preliminary treatment, or 4 or more relapses within every 12 months.
Primary steroid resistance	Absence of complete remission after 4 weeks of first-line corticosteroid treatment of NS.
Late response	Complete remission achieved after 6 weeks of first-line corticosteroid treatment of NS.
Secondary steroid resistance	No response to corticosteroid treatment in previously steroid-sensitive or steroid-dependent NS.
Complete remission of nephrotic syndrome	uPCR of < 0.2 mg protein/1 mg creatinine (< 20 mg protein/1 mmol creatinine) in the first morning urine or 24-hour urine collection or the result of < 1+ in the dipstick test on 3 consecutive days.
Partial remission of nephrotic syndrome	uPCR of > 0.2 mg protein/1 mg creatinine (< 20 mg protein/1 mmol creatinine) but < 2 mg protein/1 mg creatinine (< 200 mg protein/1 mmol creatinine) in the first morning urine or 24-hour urine collection and serum albumin level of > 3 g/dL
Nephrotic syndrome relapse	Nephrotic proteinuria persisting for > 3 days; protein dipstick test results of > 3+ for 3 days and > 1+ for 7 days.
Calcineurin inhibitor-sensitive nephrotic syndrome	Partial remission after 6 months or complete remission after 12 months of treatment with calcineurin inhibitors.
Calcineurin inhibitor-resistant nephrotic syndrome	No partial remission after 6 months of treatment with calcineurin inhibitors at adequate doses and drug level monitoring.
Multi-drug pharmacotherapy--resistant nephrotic syndrome	No complete remission after 12 months of treatment with two medications with different treatment targets.

Proteinuria results as determined by the dipstick test:

Negative:	0–15 mg/dL
Trace:	15–30 mg/dL
1+:	30–100 mg/dL
2+:	100–300 mg/dL
3+:	300–1000 mg/dL
4+:	> 1000 mg/dL

The prognosis for children with the first episode of NS depends on the initial response to empirical steroid therapy and the incidence of relapses within the first year of the disease. Therefore, there is no need to perform a renal biopsy during the first episode of NS; biopsy should be performed only in cases of atypical clinical manifestations, as well as in all cases of confirmed steroid-resistant disease.

INDICATIONS FOR RENAL BIOPSY IN A CHILD WITH THE FIRST NS EPISODE:

- first NS episode above the age of 12 years;
- NS concomitant to nephritic syndrome (hematuria and/or hypertension and/or hypocomplementemia);
- NS with persistent glomerular filtration impairment;
- suspected systemic disease;
- primary steroid resistance.

DURING THE TREATMENT OF NS OR FOLLOWING NS RELAPSE, A RENAL BIOPSY CAN BE PERFORMED TO:

- assess the activity of lesions and/or progression of glomerular sclerosis and stromal fibrosis before stepping up or discontinuing immunosuppressive treatment;
- determine the cause of secondary steroid resistance;
- assess the nephrotoxicity of the calcineurin inhibitors used.

In recent years, it was found that steroid-resistant NS may be caused by mutations of genes coding for correct development, structure, and function of podocytes. NS of genetic origin is observed not only in children in the first months of life (congenital NS) but also in older children and adults. To date, more than 40 mutations responsible for the development of steroid-resistant NS have been identified. In children, immediate genetic testing is required

Table 4. Genes associated with steroid-dependent nephrotic syndrome (modified after [10])

Gene	Inheritance pattern	OMIM No	Protein subject to mutational damage
Actin cytoskeleton			
ACTN4	AD	*604638	α-Actinin-4
INF2	AD	*610982	Inverted formin-2
MYO1E	AR	*601479	Non-muscular myosin 1e
ANLN	AD	*616027	Actin-binding protein — anillin
ARHGAP24	AD	*610586	ρGTPase activating protein 24
ARHGDIA	AR	*601925	ρGDP dissociation inhibitor α
PTPRO	AR	*600579	Protein tyrosine phosphatase receptor type O
EMP2	AR	*602334	Epithelial membrane protein 2
KANK1	AR	*607704	Kidney motif ankyrin repeat-containing protein 1
KANK2	AR	*614610	Kidney motif ankyrin repeat-containing protein 2
KANK4	AR	*614612	Kidney motif ankyrin repeat-containing protein 4
Transcription factors and nuclear proteins			
WT1	AD	*607102	Wilms tumor protein 1
LMX1B	AD	*602575	LIM homeobox transcription factor 1β
SMARCAL1	AR	*606622	SMARCA-like protein
XPO5	AR	*607845	Exportin 5
NUP93	AR	*614351	Nucleoporin 93
NUP107	AR	*607617	Nucleoporin 107
NUP205	AR	*616893	Nucleoporin 205
Cleft membrane-related proteins			
CD2AP	AD	*604241	CD2-associated protein
NPHS1	AR	*602716	Nephrin
NPHS2	AR	*604766	Podocin
TRPC6	AD	*603652	Transient receptor potential cation channel, subfamily C, member 6
CRB2	AR	*609720	Crumbs homolog 2
FAT1	AR	*600976	FAT tumor suppressor homolog 1
Glomerular basal membrane and adhesion proteins			
COL4A3	AD/AR	*120070	Collagen α3(IV) chain.
COL4A4	AD/AR	*120131	Collagen α4(IV) chain.
ITGA3	AR	*605025	Integrin α3
ITGB4	AD	*147557	Integrin β4
LAMB2	AR	*150325	Laminin β2
Mitochondrial proteins			
COQ2	AR	*609825	Coenzyme Q2
COQ6	AR	*614647	Coenzyme Q6
ADCK4	AR	*615567	aarF Domain-containing kinase 4
PDSS2	AR	*610564	Decaprenyl diphosphate synthase subunit 2
Metabolism and cytosolic proteins			
TTC21B	AR	*612014	Tetratricopeptide repeat protein 21B
DGKE	AR	*601440	Diacylglycerol kinase ε
ALG1	AR	*605907	Asparagine-linked glycosylation protein 1
CFH	AR	*134370	Complement factor H
Other			
MEFV	AD/AR	*608107	Pyrin
NEIL1	AR	*608844	Endonuclease VIII-like 1
PLCE1	AR	*608414	Phospholipase C ε
WDR73	AR	*616144	WD repeat domain 73

AD — autosomal dominant; AR — autosomal recessive

in cases of confirmed steroid-resistant disease. In Europe, the most common mutations include the mutations of podocin (*NPHS2* gene mutation), WT1 transcription factor, and nephrin (*NPHS1* gene mutation).

In the case of the absence of the most common mutations, the search should be extended to include further genes. The next-generation sequencing (NGS) method, available in Poland for many years, facilitates simultaneous examination of many of the over 40 genetic mutations currently known to be associated with steroid-resistant NS, as shown in Table 4 [9, 10].

In the PodoNet registry study carried out in Poland and in Europe in children with steroid-resistant SN, the genetic background of NS was confirmed in 23% of patients. This percentage was the highest at the age of 1 year (66%), and it further decreased with age until reaching a steady level of around 15–16% in school-age children and adolescents [11].

References

1. Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for Glomerulonephritis. Kidney Int. ; 2(Suppl. 2012): 139–274.
2. Rovin BH, Caster DJ, Cattran DC, et al. Conference Participants. Management and treatment of glomerular diseases (part 2): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2019; 95(2): 281–295, doi: 10.1016/j.kint.2018.11.008, indexed in Pubmed: 30665569.
3. Beck L, Bomback AS, Choi MJ, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for glomerulonephritis. Am J Kidney Dis. 2013; 62(3): 403–441, doi: 10.1053/j.ajkd.2013.06.002, indexed in Pubmed: 23871408.
4. Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for Glomerulonephritis. Kidney Int. 2020; 2: 153–176.
5. Lombel RM, Gipson DS, Hodson EM, et al. Kidney Disease: Improving Global Outcomes. Treatment of steroid-sensitive nephrotic syndrome: new guidelines from KDIGO. Pediatr Nephrol. 2013; 28(3): 415–426, doi: 10.1007/s00467-012-2310-x, indexed in Pubmed: 23052651.
6. Lombel RM, Gipson DS, Hodson EM, et al. Kidney Disease: Improving Global Outcomes, Kidney Disease: Improving Global Outcomes. Treatment of steroid-resistant nephrotic syndrome in children: new guidelines from KDIGO. Pediatr Nephrol. 2013; 28(3): 409–414, doi: 10.1007/s00467-012-2304-8, indexed in Pubmed: 23052648.
7. Nephrotic syndrome in children: prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. A report of the International Study of Kidney Disease in Children. Kidney Int. 1978; 13(2): 159–165, doi: 10.1038/ki.1978.23, indexed in Pubmed: 713276.
8. Eddy AA, Symons JM. Nephrotic syndrome in childhood. Lancet. 2003; 362(9384): 629–639, doi: 10.1016/S0140-6736(03)14184-0, indexed in Pubmed: 12944064.
9. Bierzynska A, Soderquest K, Koziell A. Genes and podocytes - new insights into mechanisms of podocytopathy. Front Endocrinol (Lausanne). 2014; 5: 226, doi: 10.3389/fendo.2014.00226, indexed in Pubmed: 25667580.
10. Varner JD, Chryst-Stangl M, Esezobor CI, et al. Genetic testing for steroid-resistant-nephrotic syndrome in an outbred population. Front Pediatr. 2018; 6: 307, doi: 10.3389/fped.2018.00307, indexed in Pubmed: 30406062.
11. Trautmann A, Bodria M, Ozaltin F, et al. PodoNet Consortium. Spectrum of steroid-resistant and congenital nephrotic syndrome in children: the PodoNet registry cohort. Clin J Am Soc Nephrol. 2015; 10(4): 592–600, doi: 10.2215/CJN.06260614, indexed in Pubmed: 25635037.

FIRST-LINE TREATMENT OF NEPHROTIC SYNDROME

RECOMMENDATION 1:
Prednisone at 60 mg/m^2/d or 2 mg/kg/d (max. 60 mg/d) for 4 weeks is recommended as the first-line treatment of nephrotic syndrome [1A].
1.1. If no remission of nephrotic syndrome is achieved within 14 days from treatment initiation, it is suggested that the treatment at 60 mg/m^2/d or 2 mg/kg/d (max. 60 mg/d) be extended to 6 weeks [2D].
1.2. The following regimen is recommended for dose reduction of prednisone [1B]:
— prednisone 40 mg/m^2/48 h or 1.5 mg/kg/48 h for 4 weeks;
— further gradual reduction of the prednisone dose over the next 4 weeks until complete withdrawal:
• week 1 — 30 mg/m^2/48 h,
• week 2 — 20 mg/m^2/48 h,
• week 3 — 10 mg/m^2/48 h,
• week 4 — 5 mg/m^2/48 h [2D].
(total treatment duration: 12 weeks) [1A].
1.3. Extension of initial corticosteroid treatment to 16–24 weeks may be considered in younger children (under 4–6 years of age), especially in those who achieve late remissions (after 7–10 days) [1B].
1.4. A single dose of prednisone administered in the morning is the recommended dosage regimen [1A].
1.5. It is recommended that the prednisone dose be determined as per the body area [2B]

COMMENTARY

In the 1970s, the members of the International Study of Kidney Disease in Children (ISKDC) group declared prednisone at the dose of 60 mg/m^2/d, followed by 40 mg/m^2/48 h to be the standard regimen for the treatment of the first episode of idiopathic NS in children [1]. No studies evaluating the efficacy of other, lower doses of prednisone, are available. Prednisone is commonly dosed based on body area or body weight, i.e. 60 mg/m^2/d and 40 mg/m^2/48 h or 2 mg/kg/d and 1.5 mg/kg/48 h, respectively. As demonstrated by Feber et al.,

doses calculated with respect to body weight are lower than those calculated with respect to body area in children weighing below 30 kg [2]. Saadeh et al. observed a higher rate of relapses within the follow-up period of 6 months in a group treated with prednisone at the dose calculated with respect to body weight [3]. On this basis, we suggest that the dose of prednisone to be used in the first-line treatment of NS be calculated with respect to body area.

As shown by Ekka et al., a single daily dose of prednisolone as compared to a split dosing regimen is equally effective in the treatment of relapsing NS while improving compliance and potentially reducing adrenal cortex suppression [4]. As recommended by ISKDC, the treatment of the first NS episode should last a total of 8 weeks, including 60 mg/m^2/d for 4 weeks and 40 mg/m^2 3 days a week for the following 4 weeks. This regimen has been modified in different ways including longer treatment times and higher total corticosteroid doses. As shown by a meta-analysis published in the Cochrane Database in 2007, extending the treatment time from 2 to at least 3 months reduced the risk of disease recurrence within a period of up to 2 years after the completion of the initial treatment by about 30% without increasing the risk of serious adverse effects. An inverse linear relationship was observed between the duration of treatment and the risk of recurrence. The analysis showed that the treatment of the first episode of NS should last at least 3 months (12 weeks), with the possibility of further reducing the risk of recurrence by extending the treatment duration to 7 months (6 months of Q2D dosing) [5–10]. These findings served as the basis for the 2012 KDIGO recommendations [11], as well as for the previous edition of the Polish Society for Pediatric Nephrology recommendations [12]. Subsequent randomized studies [13–15] failed to confirm any benefits of steroid therapy being extended beyond 2–3 months. After these studies were included in the next analysis published by the Cochrane Database in 2015, it was concluded that steroid therapy extended to 6 months does not reduce the risk of recurrence as compared to treatment lasting for 2 to 3 months in children aged 1 to 17 years at the time of disease diagnosis [16, 17]. The French recommendations limited the duration of initial treatment to 4.5 months [18]. In the 2017 recommendations of the Italian Society for Pediatric Nephrology, the recommended treatment period for the first episode of ZN is 3 months (prednisone at 60 mg/m^2/d for 6 weeks followed by 40 mg/m^2/48 h for 6 weeks) [19]. The results of the PREDNOS study and the latest 2020 KDIGO guidelines also suggest the need to shorten the duration of initial treatment of NS to 8–12 weeks [20, 21]. No effect of initial treatment extension for NS was confirmed in the Cochrane Systematic Review published in 2020 [22]. Regarding the most recent publications, the recommendation regarding the duration of treatment of the first episode of NS in our guidelines has been modified, with the recommended necessary duration being reduced to 3 months (12 weeks).

Regardless of the immunosuppressive treatment status, attempts should always be made to eliminate infective outbreaks in children with NS. Children should undergo dental and laryngological checkups, and any detected infections should be treated.

References

1. Abramowicz M, Barnett HL, Edelmann CM, et al. Controlled trial of azathioprine in children with nephrotic syndrome. A report for the international study of kidney disease in children. The Lancet. 1970; 295(7654): 959–961, doi: 10.1016/s0140-6736(70)91093-7.
2. Feber J, Al-Matrafi J, Farhadi E, et al. Prednisone dosing per body weight or body surface area in children with nephrotic syndrome: is it equivalent? Pediatr Nephrol. 2009; 24(5): 1027–1031, doi: 10.1007/s00467-008-1089-2, indexed in Pubmed: 19165504.
3. Saadeh SA, Baracco R, Jain A, et al. Weight or body surface area dosing of steroids in nephrotic syndrome: is there an outcome difference? Pediatr Nephrol. 2011; 26(12): 2167–2171, doi: 10.1007/s00467-011-1961-3, indexed in Pubmed: 21769641.
4. Ekka BK, Bagga A, Srivastava RN. Single- versus divided-dose prednisolone therapy for relapses of nephrotic syndrome. Pediatr Nephrol. 1997; 11(5): 597–599, doi: 10.1007/s004670050344, indexed in Pubmed: 9323286.
5. Hodson EM, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. Cochrane Database Syst Rev. 2007(4): CD001533, doi: 10.1002/14651858.CD001533.pub4, indexed in Pubmed: 17943754.
6. Ueda N, Chihara M, Kawaguchi S, et al. Intermittent versus long-term tapering prednisolone for initial therapy in children with idiopathic nephrotic syndrome. J Pediatr. 1988; 112(1): 122–126, doi: 10.1016/s0022-3476(88)80136-7, indexed in Pubmed: 3335948.
7. Ehrich JH, Brodehl J, Brodehl J, et al. The treatment of minimal change nephrotic syndrome (lipoid nephrosis): cooperative studies of the Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN). Klin Padiatr. 1982; 194(3): 162–165, doi: 10.1055/s-2008-1033800, indexed in Pubmed: 6752557.
8. Ksiazek J, Wyszyńska T. Short versus long initial prednisone treatment in steroid-sensitive nephrotic syndrome in children. Acta Paediatr. 1995; 84(8): 889–893, doi: 10.1111/j.1651-2227.1995.tb13787.x, indexed in Pubmed: 7488812.

9. Bagga A, Hari P, Srivastava RN. Prolonged versus standard prednisolone therapy for initial episode of nephrotic syndrome. Pediatr Nephrol. 1999; 13(9): 824–827, doi: 10.1007/s004670050708, indexed in Pubmed: 10603129.
10. Hiraoka M, Tsukahara H, Matsubara K, et al. A randomized study of two long-course prednisolone regimens for nephrotic syndrome in children. American Journal of Kidney Diseases. 2003; 41(6): 1155–1162, doi: 10.1016/s0272-6386(03)00346-9.
11. Lombel RM, Gipson DS, Hodson EM, et al. Kidney Disease: Improving Global Outcomes. Treatment of steroid-sensitive nephrotic syndrome: new guidelines from KDIGO. Pediatr Nephrol. 2013; 28(3): 415–426, doi: 10.1007/s00467-012-2310-x, indexed in Pubmed: 23052651.
12. Ziółkowska H, Bałasz-Chmielewska I, Grenda R, et al. Zalecenia Polskiego Towarzystwa Nefrologii Dziecięcej (PTNFD) dotyczące postępowania z dzieckiem z zespołem nerczycowym. Forum Nefrol. 2015; 8: 238–256.
13. Teeninga N, Kist-van Holthe JE, van Rijswijk N, et al. Extending prednisolone treatment does not reduce relapses in childhood nephrotic syndrome. J Am Soc Nephrol. 2013; 24(1): 149–159, doi: 10.1681/ASN.2012070646, indexed in Pubmed: 23274956.
14. Sinha A, Saha A, Kumar M, et al. 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. Kidney Int. 2015; 87(1): 217–224, doi: 10.1038/ki.2014.240, indexed in Pubmed: 25029428.
15. Yoshikawa N, Nakanishi K, Sako M, et al. Japanese Study Group of Kidney Disease in Children. A multicenter randomized trial indicates initial prednisolone treatment for childhood nephrotic syndrome for two months is not inferior to six-month treatment. Kidney Int. 2015; 87(1): 225–232, doi: 10.1038/ki.2014.260, indexed in Pubmed: 25054775.
16. Hahn D, Hodson EM, Willis NS, et al. Corticosteroid therapy for nephrotic syndrome in children. Cochrane Database Syst Rev. 2015(3): CD001533, doi: 10.1002/14651858.CD001533.pub5, indexed in Pubmed: 25785660.
17. Hodson EM, Hahn D, Craig JC. Corticosteroids for the initial episode of steroid-sensitive nephrotic syndrome. Pediatr Nephrol. 2015; 30(7): 1043–1046, doi: 10.1007/s00467-015-3106-6, indexed in Pubmed: 25912994.
18. Couderc A, Bérard E, Guigonis V, et al. [Treatments of steroid-dependent nephrotic syndrome in children]. Arch Pediatr. 2017; 24(12): 1312–1320, doi: 10.1016/j.arcped.2017.09.002, indexed in Pubmed: 29146214.
19. Pasini A, Benetti E, Conti G, et al. 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. Ital J Pediatr. 2017; 43(1): 41, doi: 10.1186/s13052-017-0356-x, indexed in Pubmed: 28427453.
20. Ramachandran R, Jha V. Integration with Kidney Disease Improving Global Outcomes (KDIGO). Glomerulonephritis. 2019: 87–95, doi: 10.1007/978-3-319-49379-4_6.
21. Webb NJa, Woolley RL, Lambe T, et al. Sixteen-week versus standard eight-week prednisolone therapy for childhood nephrotic syndrome: the PREDNOS RCT. Health Technol Assess. 2019; 23(26): 1–108, doi: 10.3310/hta23260, indexed in Pubmed: 31156083.
22. Hahn D, Hodson EM, Willis NS, et al. Corticosteroid therapy for nephrotic syndrome in children. Cochrane Database Syst Rev. 2015; 30(3): CD001533–1046, doi: 10.1002/14651858.CD001533.pub5, indexed in Pubmed: 25785660.

TREATMENT OF INFREQUENT RELAPSES OF STEROID-SENSITIVE NEPHROTIC SYNDROME

RECOMMENDATION 2:
Prednisone at the dose of 60 mg/m^2/d or 2 mg/kg/d (maximum of 60 mg/d) is recommended for a period not shorter than required to achieve remission lasting for 3 days (3 consecutive negative urine protein test results) [1B].
2.1. The following regimen is recommended for dose reduction of prednisone:
— prednisone 40 mg/m^2/48 h or 1.5 mg/kg/48 h for 4 weeks [1B];
— further gradual reduction of the prednisone dose over the next 4 weeks until complete withdrawal:
• week 1 – 30 mg/m^2/48 h,
• week 2 – 20 mg/m^2/48 h,
• week 3 – 10 mg/m^2/48 h,
• week 4 – 5 mg/m^2/48 h [2D].
2.2. In the case of infection developing in the child receiving prednisone administered every second day to reduce the risk of disease relapse, it is recommended that the current prednisone dose be administered daily or a dose of 0.5 mg/kg be administered throughout the infection period [1B].

COMMENTARY

The proposed treatment of the first and infrequent rare relapses of nephrotic syndrome is based on the ISKDC recommendations and the 2020 KDIGO recommendations. Only a few studies comparing different steroid therapy regimens in the treatment of NS relapses are available in the literature. One of them showed that the efficacy of the ISKDC-recommended regimen (prednisone at 60 mg/m^2/d until 3 consecutive negative urine protein test results followed by prednisone at 40 mg/m^2/48 h for 4 weeks) was comparable to that of daily full-dose prednisone treatment extended to 4 weeks [1, 2]. In another study, better treatment efficacy was demonstrated for prednisone administered every other day as compared to interrupted therapy (daily doses of prednisone for 3 consecutive days a week) [3].

Respiratory tract infections often precede the relapses of nephrotic syndrome [4]. As demonstrated in several studies, increasing the Q2D prednisone dosing to QD dosing for a period of 5–7 days reduces the risk of NS relapse [5–7]. In 2014, a randomized PREDNOS 2 study was launched to confirm this observation [8].

References

1. Nephrotic syndrome in children: A randomized trial comparing two prednisone regimens in steroid-responsive patients who relapse early. The Journal of Pediatrics. 1979; 95(2): 228–233, doi: 10.1016/s0022-3476(79)80658-7.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for Glomerulonephritis. Kidney Int. Suppl. 2020; 2: 153–176.
3. Alternate-day prednisone is more effective than intermittent prednisone in frequently relapsing nephrotic syndrome. A report of "Arbeitsgemeinschaft für Pädiatrische Nephrologie. Eur J Pediatr. 1981; 135(3): 229–237, doi: 10.1007/BF00442096, indexed in Pubmed: 7227377.
4. MacDonald NE, Wolfish N, McLaine P, et al. Role of respiratory viruses in exacerbations of primary nephrotic syndrome. J Pediatr. 1986; 108(3): 378–382, doi: 10.1016/s0022-3476(86)80876-9, indexed in Pubmed: 3005537.
5. Mattoo TK, Mahmoud MA. Increased maintenance corticosteroids during upper respiratory infection decrease the risk of relapse in nephrotic syndrome. Nephron. 2000; 85(4): 343–345, doi: 10.1159/000045684, indexed in Pubmed: 10940745.
6. Abeyagunawardena AS, Thalgahagoda RS, Dissanayake PV, et al. Short courses of daily prednisolone during upper respiratory tract infections reduce relapse frequency in childhood nephrotic syndrome. Pediatr Nephrol. 2017; 32(8): 1377–1382, doi: 10.1007/s00467-017-3640-5, indexed in Pubmed: 28341877.
7. Gulati A, Sinha A, Sreenivas V, et al. Daily corticosteroids reduce infection-associated relapses in frequently relapsing nephrotic syndrome: a randomized controlled trial. Clin J Am Soc Nephrol. 2011; 6(1): 63–69, doi: 10.2215/CJN.01850310, indexed in Pubmed: 20847092.
8. Webb N, Frew E, Brettell E, et al. Short course daily prednisolone therapy during an upper respiratory tract infection in children with relapsing steroid-sensitive nephrotic syndrome (PREDNOS 2): protocol for a randomised controlled trial. Trials. 2014; 15(1), doi: 10.1186/1745-6215-15-147.

TREATMENT OF STEROID-DEPENDENT AND FREQUENTLY RELAPSING NEPHROTIC SYNDROME

RECOMMENDATION 3:
In the treatment of steroid-dependent and frequently relapsing nephrotic syndrome, prednisone at the dose of 60 mg/m^2/d or 2 mg/kg/d (maximum of 60 mg/d) is recommended for a period not shorter than required to achieve remission lasting for 3 days [1B].
The following regimen is recommended for dose reduction of prednisone:
— prednisone 40 mg/m^2/48 h or 1.5 mg/kg/48 h for at least 4 weeks [2B];
— further gradual reduction of prednisone dose over 4 weeks:
• week 1 — 30 mg/m^2/48 h,
• week 2 — 20 mg/m^2/48 h,
• week 3 — 10 mg/m^2/48 h,
• week 4 — 5 mg/m^2/48 h [2D].
Steroid monotherapy is suggested unless adverse effects of the treatment are observed [2D].
In cases of relapses with severe clinical presentation, treatment may be initiated with 3–6 intravenous pulses of methylprednisolone at a dose of 10–15 mg/kg per 24 or 48 hours (≤ 1.0 g/1.73 m^2 body area and ≤ 1.0 g/dose) [2D].
In the event of infection developing in the child receiving prednisone administered every second day to reduce the risk of disease relapse or a child not receiving steroid therapy, it is recommended that the current prednisone dose be administered daily, or a dose of 0.5 mg/kg be administered throughout the infection period [1B].

COMMENTARY

Recommendations on the dose levels and durations of corticosteroid treatment in relapsing and steroid-dependent NS are aimed at achieving the desired effect with a minimum effective dose.

Failure to achieve the desired effect as manifested by persisting or increased frequency of relapses is an indication for the treatment being expanded to include other drugs (see further recommendations).

Several studies are available confirming the suggestion that increasing the dose of corticosteroids during respiratory infection to daily dosing or including corticosteroids for the period of infection in children with recurrent NS in remission and off therapy reduces the risk of disease recurrence [1–6].

References

1. Lombel RM, Gipson DS, Hodson EM, et al. Kidney Disease: Improving Global Outcomes. Treatment of steroid-sensitive nephrotic syndrome: new guidelines from KDIGO. Pediatr Nephrol. 2013; 28(3): 415–426, doi: 10.1007/s00467-012-2310-x, indexed in Pubmed: 23052651.
2. Nakanishi K, Iijima K, Ishikura K, et al. Japanese Study Group of Renal Disease in Children. Two-year outcome of the ISKDC regimen and frequent-relapsing risk in children with idiopathic nephrotic syndrome. Clin J Am Soc Nephrol. 2013; 8(5): 756–762, doi: 10.2215/CJN.09010912, indexed in Pubmed: 23371961.
3. Hodson EM, Knight JF, Willis NS, et al. Corticosteroid therapy for nephrotic syndrome in children. Cochrane Database Syst Rev. 2000(4): CD001533, doi: 10.1002/14651858.CD001533, indexed in Pubmed: 11034723.
4. Gulati A, Sinha A, Sreenivas V, et al. Daily corticosteroids reduce infection-associated relapses in frequently relapsing nephrotic syndrome: a randomized controlled trial. Clin J Am Soc Nephrol. 2011; 6(1): 63–69, doi: 10.2215/CJN.01850310, indexed in Pubmed: 20847092.
5. Webb NJ, Frew E, Brettell EA, et al. for PREDNOS 2 study group. Trials. 2014; 15: 147.
6. Hahn D, Hodson EM, Willis NS, et al. Corticosteroid therapy for nephrotic syndrome in children. Cochrane Database Syst Rev. 2015; 30(3): CD001533–1046, doi: 10.1002/14651858.CD001533.pub5, indexed in Pubmed: 25785660.

TREATMENT OF STEROID-DEPENDENT AND FREQUENTLY RELAPSING NEPHROTIC SYNDROME USING MEDICATIONS OTHER THAN CORTICOSTEROIDS

RECOMMENDATION 4:
The use of corticosteroid-sparing medication is recommended in all children in all pediatric patients with steroid-dependent nephrotic syndrome, as well as in pediatric patients with frequent relapses of nephrotic syndrome who had experienced adverse effects of their previous treatment.
4.1. It is recommended to start corticosteroid-sparing medication after achieving remission of the nephrotic syndrome with corticosteroids.
4.2. Inclusion of cyclophosphamide* is recommended in children with steroid-dependent and frequently relapsing nephrotic syndrome [1B].
Recommended dose: 2 mg/kg/d for 8–12 weeks (maximum cumulative dose: 168 mg/kg).
4.3. Levamizole* may be used in frequent relapses of nephrotic syndrome and steroid-dependent nephrotic syndrome.
Recommended dose: 2.5 mg/kg every 48 h for 12 months [2B].
4.4. Mycophenolate mofetil (MMF)* is recommended in children with frequently relapsing and steroid-dependent nephrotic syndrome [1C].
— Recommended dose: MMF 1200 mg/m^2/d in 2 divided doses.
— Serum levels of mycophenolic acid (MPA) — the active metabolite of MMF — and/or the area under the curve (AUC) of MPA concentration# should be monitored in individual cases of MMF treatment failure or adverse reactions [2C].
4.5. Calcineurin inhibitors may be used to treat frequent relapses of steroid-dependent nephrotic syndrome.
Recommended dose:
— cyclosporin A (CsA) — 4 to 6 mg/kg/d in two divided doses under blood level control [1A];
— tacrolimus (TAC) — 0.1 mg/kg/d in two divided doses [2D] under blood level control [2C].
4.6. Rituximab (RTX)* is reserved for cases of previous treatment failure and/or extensive adverse effects as well as for clinical trials [2C]. Trimethoprim-sulfamethoxazole should be administered prophylactically to prevent lung infection with *Pneumocystis jiroveci*.

#Area under the drug concentration curve as determined by several measurements at different time points — a pharmacokinetic parameter calculated from the appropriate formula

COMMENTARY

In children receiving chronic corticosteroid treatment for steroid-dependent NS or frequently relapsing NS, other treatments are being sought to reduce the dose of corticosteroids or to ensure an alternative way to maintain remission. The most common adverse effects of corticosteroids justifying the initiation of alternative therapy include growth disorders, steroid-induced cataracts, changes in bone calcification, obesity and steroid-induced diabetes, hypertension, behavioral changes, exacerbated acne, or extensive stretch marks [1].

The alternative medication should be chosen on a case-by-case basis, the decision depending on [1–3]:

— the patient's age (the importance of gonadal toxicity of cyclophosphamide [CYC]);
— concomitant diseases (epilepsy and its chronic pharmacotherapy are relative contraindications for CsA and TAC treatment);
— the ability to monitor drug levels (CSA and TAC levels should be monitored in all patients while MPA levels should be monitored on a case-by-case basis; CYC metabolites are not routinely monitored).

In rare (genetically conditioned) cases of rapid metabolism of calcineurin inhibitors occurring along the cytochrome P450 pathway, three daily doses may be required.

Intolerance and/or adverse effects of a particular drug are an indication for a treatment switch. Remission achieved using corticosteroids may be maintained by switching CsA to MMF and vice versa. In rare cases of the inefficacy of CsA or MMF in maintaining the remission, a combination of both medicines can be attempted, but experience in this field has, so far, been limited.

Levamisole (not available in Poland, off-label use), facilitates reduction in concomitant corticosteroids and, in some children, complete withdrawal of corticosteroids (over the administration period of 6 to 12 months) [1].

With regard to the alkylating drugs, CYC has a wider therapeutic window (range between efficacy and toxicity) than chlorambucil and is, therefore, used more frequently. It can be given orally or in monthly IV pulses in children in whom concerns regarding compliance have been raised. The total dose of CYC per treatment should not exceed 168 mg/kg, and, therefore, the treatment should be used only once due to the risk of infertility after the cumulative dose threshold is exceeded. Alkylating drugs are the only drugs that not only maintain NS remission but may also contribute to reducing rates of future relapses after being discontinued following 3 months of treatment [4–6].

MMF is an alternative medication to maintain remission in children with steroid-de-

pendent NS or frequently relapsing NS. It is used to avoid the adverse effects of both steroids and calcineurin inhibitors [7–9]. Since hypoalbuminemia and hypertriglyceridemia significantly alter MPA levels in the blood, it is recommended that in selected difficult cases (of treatment inefficacy or specific toxicity), a pharmacokinetic profile assessment is performed in addition to the assessment of point MPA concentration before the dose (C_0). The purpose is to assess the AUC and to adjust the dosage so that the AUC of MPA exceeds 45 mg/h/L, were formulated [10, 11].

One should keep in mind that although drugs such as CSA, MMF, and levamisole effectively maintain the remission of NS while the treatment is being continued, the disease recurs in about one-half of patients following treatment discontinuation. In some children, combination treatment with calcineurin inhibitors and MMF is required to successfully maintain remission.

Calcineurin inhibitors replace corticosteroids in the maintenance of NS remission, relieving the patient from the troublesome adverse effects of the latter, as complete discontinuation or significant reduction in corticosteroid dose is possible at least in some cases. However, calcineurin inhibitors cause a number of specific side effects, and should, therefore, be used at the lowest effective dose level. Safe use of CsA requires regular monitoring of its blood levels [1, 2].

Prolonged administration of CsA may result in chronic nephrotoxicity, its initial symptoms (observed in consecutive studies) consisting of increased serum levels of uric acid and progressive reduction in glomerular filtration rate. In selected cases and when planning for further use, a kidney biopsy is indicated. In cases of lesions within small intrarenal vessels and interstitial fibrosis and tubular atrophy (IF/TA), continued therapy is contraindicated.

Cosmetic (gingival hyperplasia, excessive hair growth) and metabolic (hyperuricemia) changes, concomitant with CsA administration, are observed less frequently for chronic TAC use.

RTX is increasingly used in children with steroid-dependent NS or frequently relapsing NS. As in the case of several other aforementioned corticosteroid-saving medications, RTX is used off-label for this indication*. Studies conducted to date lead to the conclusion that the treatment is very effective and well-tolerated, rarely causing any adverse effects (opportunistic infections in the course of lymphopenia, hypogammaglobulinemia) and giving hope for a much better quality of life for patients with steroid-dependent NS/frequently relapsing NS. The position of RTX in the treatment regimens in this group of patients has still not been established, and its optimum dosage is the subject of numerous ongoing clinical trials. Therefore, the use of RTX is usually reserved for complicated cases of children experiencing excessive adverse effects of corticosteroids or other immunosuppressive drugs, as well as for clinical trials [12–18].

Note: *Despite many years of experience in off-label use in children, NS treatment is not listed among the licensed indications for CYC, MMF, TAC, levamisole, or RTX in the respective Summaries of Product Characteristics (SmPCs). Therefore, the administration of these medications should be preceded by obtaining informed consent from the patient's legal guardians. In Poland, no reimbursements are available for CYC, levamisole, or RTX treatments.

Immunosuppressive agents, other than those listed (azathioprine, mizoribine), are not recommended in children with frequently relapsing or steroid-dependent NS. No efficacy could be demonstrated for azathioprine while mizoribine is used only in Japan.

References

1. Hodson EM, Willis NS, Craig JC. Non-corticosteroid treatment for nephrotic syndrome in children. Cochrane Database Syst Rev. 2008(1): CD002290, doi: 10.1002/14651858.CD002290.pub3, indexed in Pubmed: 18254005.
2. Ishikura K, Ikeda M, Hattori S, et al. Effective and safe treatment with cyclosporine in nephrotic children: a prospective, randomized multicenter trial. Kidney Int. 2008; 73(10): 1167–1173, doi: 10.1038/ki.2008.24, indexed in Pubmed: 18305467.
3. Niaudet P. Comparison of cyclosporin and chlorambucil in the treatment of steroid-dependent idiopathic nephrotic syndrome: a multicentre randomized controlled trial. The French Society of Paediatric Nephrology. Pediatr Nephrol. 1992; 6(1): 1–3, doi: 10.1007/BF00856817, indexed in Pubmed: 1536727.
4. Ponticelli C, Edefonti A, Ghio L, et al. Cyclosporin versus cyclophosphamide for patients with steroid-dependent and frequently relapsing idiopathic nephrotic syndrome: a multicentre randomized controlled trial. Nephrol Dial Transplant. 1993; 8(12): 1326–1332, indexed in Pubmed: 8159300.
5. Cammas B, Harambat J, Bertholet-Thomas A, et al. Long-effects of cyclophosphamide therapy in steroid-dependent and frequently relapsing idiopathic nephrotic syndrome. Nephrol Dial Transplant. 2011; 26: 178–184.

TREATMENT OF STEROID-RESISTANT RENAL SYNDROME

RECOMMENDATION 5:
5.1. In the case of steroid-resistant nephrotic syndrome, initiation of proteinuria-lowering treatment angiotensin convertase inhibitors (ACEi) and/or angiotensin receptor blockers (ARB)] is recommended [1B].
5.2. Renal biopsy [1A] is recommended in every case of pediatric steroid-resistant nephrotic syndrome.
5.3. Available genetic studies are recommended in all children with steroid resistant nephrotic syndrome [1A]. Genetic studies are strongly indicated in children aged 1–3 years and in cases of primary steroid resistance [1B].
5.4. CsA is recommended as the drug of first choice in children with steroid resistant idiopathic nephrotic syndrome diagnosed of minimal change disease, mesangial glomerulonephritis, or focal/segmental glomerulonephritis [1A].
During CsA treatment, corticosteroids may be continued in small doses (0.5 mg/kg/48 h) or discontinued completely in children with probable immunological etiology of nephrotic syndrome [2C]. Failure to obtain partial remission after 6 months of CsA treatment classifies the disease as CsA-resistant [2B].
5.5. After remission is achieved as a result of CsA treatment, the treatment should be continued for at least 12 months [2B]. If sustained remission is obtained as a result of CsA treatment, calcineurin inhibitor may be replaced over time with MMF as another remission-maintaining agent [2C].
5.6. In specific cases, combined treatment with calcineurin inhibitors and MMF may be used to obtain and maintain remission [2C].
5.7. Rituximab may be attempted in cases of secondary steroid resistance and minimal change disease observed in renal biopsy [2C].

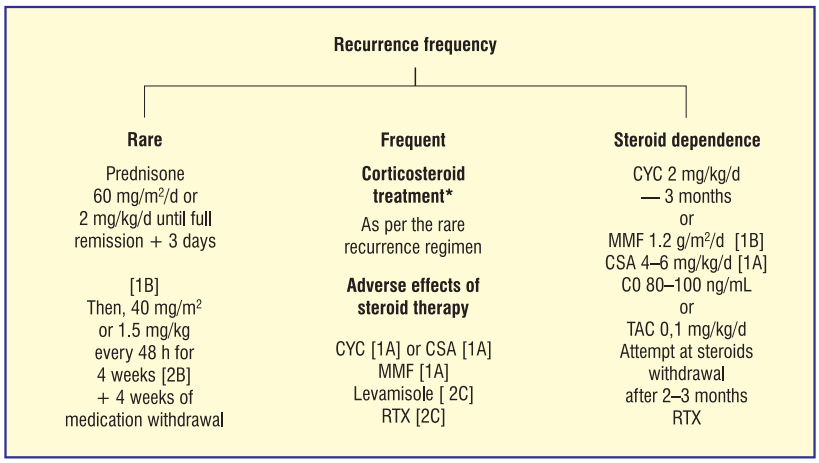

Figure 1. Management of steroid-dependent and recurrent nephrotic syndrome (strategy of treatment)

*Steroid therapy can be used for subsequent relapses unless adverse effects occur

6. Latta K, von Schnakenburg C, Ehrich JH. A meta-analysis of cytotoxic treatment for frequently relapsing nephrotic syndrome in children. Pediatr Nephrol. 2001; 16(3): 271–282, doi: 10.1007/s004670000523, indexed in Pubmed: 11322378.
7. Dorresteijn EM, Kist-van Holthe JE, Levtchenko EN, et al. Mycophenolate mofetil versus cyclosporine for remission maintenance in nephrotic syndrome. Pediatr Nephrol. 2008; 23(11): 2013–2020, doi: 10.1007/s00467-008-0899-6, indexed in Pubmed: 18622632.
8. Gellerman J, Querfeld U. Frequently relapsing steroid-sensitive nephrotic syndrome (SSNS) in children and adolescents: treatment with mycophenolate mofetil (MMF) vs cyclosporine (CsA). Pediatr Nephrol. 2011; 26: 1579–1582.
9. Fujinaga S, Ohtomo Y, Umino D, et al. A prospective study on the use of mycophenolate mofetil in children with cyclosporine-dependent nephrotic syndrome. Pediatr Nephrol. 2007; 22(1): 71–76, doi: 10.1007/s00467-006-0294-0, indexed in Pubmed: 17086405.
10. Kirpalani A, Rothfels L, Sharma AP, et al. Nephrotic state substantially enhances apparent mycophenolic acid clearance . Clin Nephrol. 2019; 91(3): 162–171, doi: 10.5414/CN109583, indexed in Pubmed: 30574862.
11. Hackl Á, Cseprekál O, Gessner M, et al. Mycophenolate mofetil therapy in children with idiopathic nephrotic syndrome: does therapeutic drug monitoring make a difference? Ther Drug Monit. 2016; 38(2): 274–279, doi: 10.1097/FTD.0000000000000258, indexed in Pubmed: 26488204.
12. Guigonis V, Dallocchio A, Baudouin V, et al. Rituximab treatment for severe steroid- or cyclosporine-dependent nephrotic syndrome: a multicentric series of 22 cases. Pediatr Nephrol. 2008; 23(8): 1269–1279, doi: 10.1007/s00467-008-0814-1, indexed in Pubmed: 18465150.
13. Ravani P, Rossi R, Bonanni A, et al. Rituximab in children with steroid-dependent nephrotic syndrome: a multicenter, open-label, noninferiority, randomized controlled trial. J Am Soc Nephrol. 2015; 26(9): 2259–2266, doi: 10.1681/ASN.2014080799, indexed in Pubmed: 25592855.
14. Sellier-Leclerc AL, Baudouin V, Kwon T, et al. Rituximab in steroid-dependent idiopathic nephrotic syndrome in childhood--follow-up after CD19 recovery. Nephrol Dial Transplant. 2012; 27(3): 1083–1089, doi: 10.1093/ndt/gfr405, indexed in Pubmed: 21810762.
15. Lombel RM, Gipson DS, Hodson EM, et al. Kidney Disease: Improving Global Outcomes. Treatment of steroid-sensitive nephrotic syndrome: new guidelines from KDIGO. Pediatr Nephrol. 2013; 28(3): 415–426, doi: 10.1007/s00467-012-2310-x, indexed in Pubmed: 23052651.
16. Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for Glomerulonephritis. Kidney Int. Suppl. 2020; 2: 153–176.
17. Chan EYH, Tullus K. Rituximab in children with steroid sensitive nephrotic syndrome: in quest of the optimal regimen. Pediatr Nephrol. 2021; 36(6): 1397–1405, doi: 10.1007/s00467-020-04609-0, indexed in Pubmed: 32577808.
18. Larkins NG, Liu ID, Willis NS, et al. Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. Cochrane Database Syst Rev. 2020; 4: CD002290, doi: 10.1002/14651858.CD002290.pub5, indexed in Pubmed: 32297308.

COMMENTARY

Before initiation of new treatment for steroid-resistant SN, a renal biopsy should be performed and analyzed as therapeutic management may vary depending on the morphological diagnosis (Fig. 1, 2).

Genetic screening for mutations encoding podocyte-related proteins should be an additional element of diagnostic procedures aimed at the determination of causes of primary steroid resistance. The younger the child (particularly at the age of less than 1 year), the more likely it is that the steroid resistance is due to genetic defects [1, 2]. The most common mutations diagnosed at the age of more than 3 months include those in the podocin-encoding gene (NPHS2) and the *WT1* gene. In Poland, mutational screening of these genes is available and reimbursed from the National Health Fund (Department of Biology and Genetics, Medical University of Gdańsk) and should be performed after steroid-resistant NS is diagnosed in the patient. If nephrin and *WT1* gene mutations are ruled out, the scope of genetic screening should be extended to include NGS in search for less frequent mutations. Confirmation of the genetic origin of the disease is a contraindication for intensified and extended treatment with corticosteroids and immunosuppressants other than CsA. Attempts may be made on case-by-case basis regarding empirical use of CsA at doses of 2 to 3 mg/kg, along with an ACEi and/or ARB in the hope of achieving their proteinuria-lowering effect [3, 4].

One should remember that irrespective of the attempts to take advantage of the non-specific effects of CsA action on the glomeruli and the possibility of partial remission (reduction of protein losses) being achieved therefrom, the prognosis regarding renal function in patients with genetically determined NS is significantly worse than that in children with sporadic steroid-resistant disease. If a renal biopsy is performed, the presence of diffuse mesangial glomerulosclerosis is the histological marker with the greatest negative impact on prognosis [5].

When suspecting immunological origin of steroid-dependent idiopathic NS, treatment may be initiated with 6–12 intravenous pulses of methylprednisolone at a dose of 10–15 mg/kg per 24 or 48 hours (≤ 1.0 g/1.73 m^2 body area and ≤ 1.0 g/dose) [6].

Cyclosporin should be used in the treatment of steroid-resistant NS for at least

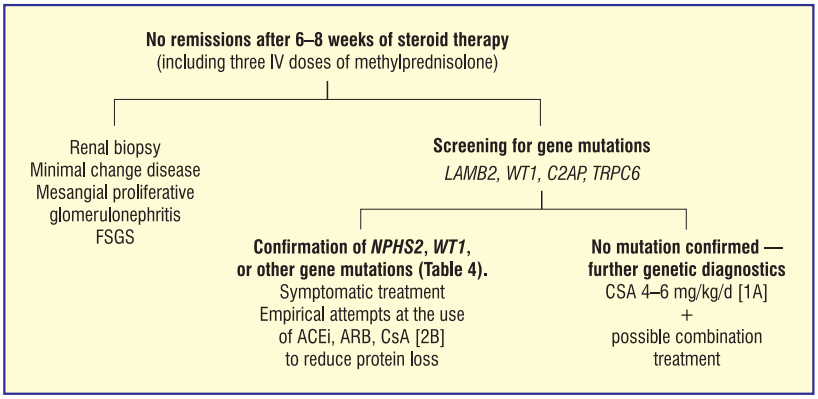

Figure 2. Management of steroid-resistant nephrotic syndrome (strategy of treatment)

6 months. If partial remission is achieved in this period, the treatment should be extended to ≥ 12 months. No difference in efficacy was demonstrated between CsA and TAC in the treatment of steroid-resistant NS. If sustained remission is obtained as a result of CsA treatment, calcineurin inhibitor may over time be replaced with MMF as another remission-maintaining agent. Such conversion may improve the glomerular filtration as previously reduced in the course of CsA therapy [3, 7–10].

When CsA is administered in cases without documented genetic background, the lowest effective dose of corticosteroids (0,5 mg/kg/48 h) may be used as additional treatment or corticosteroids may be completely discontinued [5].

In cases of specific cosmetic complications related to CsA use (gingival hyperplasia or excessive hair growth), the drug can be switched to TAC [6].

No reliable clinical data are available to support the efficacy of repeated plasmapheresis in steroid-resistant idiopathic NS in children despite the availability of data on the efficacy of such treatment (when combined with immunosuppressants, including RTX) in episodes of NS relapse following a kidney transplant.

The efficacy of RTX (as the primary treatment) in steroid-resistant NS has not been explicitly confirmed (Tab. 5) [11].

References

1. Sadowski CE, Lovric S, Ashraf S, et al. SRNS Study Group. A single-gene cause in 29.5% of cases of steroid-resistant nephrotic syndrome. J Am Soc Nephrol. 2015; 26(6): 1279–1289, doi: 10.1681/ASN.2014050489, indexed in Pubmed: 25349199.
2. Santín S, Bullich G, Tazón-Vega B, et al. Clinical utility of genetic testing in children and adults with steroid-resistant

Table 5. Rules for the use of individual medications [12–19]

Medication	Rules for use
Methylprednisolone (MP)**	Intravenous pulses at 10 to 15 mg/kg per 24 or 48 hours (≤ 1 g/1.73 m^2 body area and ≤ 1 g/dose); 4-hour infusion Corticosteroid dose equivalents: • prednisone — 1.0 mg • prednisolone — 1.0 mg. • methylprednisolone — 0.8 mg • deflazacort — 1.15 mg. • dexamethasone — 0.15 mg.
Cyclosporin A (CSA)*	Initial dose of 4 to 6 mg/kg/24 h in two divided doses (in younger children, three doses are sometimes used due to rapid metabolism); chronic treatment with the lowest effective dose under to blood level control — C_0 prior to the next dose usually in the range of 60 to 100 ng/mL; in the event of no efficacy, the dose may be increased and the C_0 maintained at 120–150 ng/mL, with a simultaneous gradual reduction in prednisolone dose to 0.5 mg/kg/48 h; if remission is achieved, the treatment is to be continued for at least 12 months; if no remission is achieved after 6 months, consider treatment change.
Cyclophosphamide (CYC)**	Initial dose of 2 mg/kg/24 h so as not to exceed the cumulative dose of 168 mg/kg per 3-month treatment; simultaneous prednisone at 0.5 mg/kg/48 h; monthly monitoring of blood counts including platelets and transaminase levels; adequate supply of fluids. Tablets are indivisible and should not be crushed. Do not repeat the full treatment course (after the accumulated dose is exhausted) [2C]. Intravenous CYC therapy (6 × 0.5–0.75 g/m^2 every month) can be used if oral drug is not tolerated or non-compliance is suspected.
Mycophenolate mofetil (MMF)**	Initial dose of 2 × 0.6 g/m^2 of body area with blood levels monitoring — C_0 of MPA prior to the next dose maintained at 2–3 μg/mL; in cases of inefficacy or toxicity, AUC should be calculated (based on the measurements of MPA levels at several time points after administration), with the target value of > 45 mg/h/l)
Levamisole**	2.5 mg/kg/24 h for 4 weeks and then 2 times a week for 12 to 24 months; monthly monitoring of blood counts including platelets
Rituximab (RTX)**	375 mg/m^2 body area administered intravenously at weekly intervals to obtain CD19 depletion (typically 1–2 doses, maximum of 4 doses) with CD19 count monitoring.
Tacrolimus (TAC)**	Initially 0.1 mg/d in two doses; C_0 (prior to next dose) < 5 ng/mL.
Chlorambucil (CL)**	Dosed at 0.1–0.2 mg/kg/d; maximum cumulative dose of 11.2 mg/kg/treatment; treatment duration of 8 weeks; blood counts control; epilepsy must be ruled out before drug initiation. Do not repeat the full treatment course (after the accumulated dose is exhausted) [2C].

*Medication registered for use in pediatric patients with NS

**Medication not registered for use in pediatric patients with NS

nephrotic syndrome. Clin J Am Soc Nephrol. 2011; 6(5): 1139–1148, doi: 10.2215/CJN.05260610, indexed in Pubmed: 21415313.

3. Ponticelli C, Rizzoni G, Edefonti A, et al. A randomized trial of cyclosporine in steroid-resistant idiopathic nephrotic syndrome. Kidney Int. 1993; 43(6): 1377–1384, doi: 10.1038/ki.1993.194, indexed in Pubmed: 8315953.
4. Bagga A, Mudigoudar BD, Hari P, et al. Enalapril dosage in steroid-resistant nephrotic syndrome. Pediatr Nephrol. 2004; 19(1): 45–50, doi: 10.1007/s00467-003-1314-y, indexed in Pubmed: 14648339.
5. Trautmann A, Bodria M, Ozaltin F, et al. PodoNet Consortium. Spectrum of steroid-resistant and congenital nephrotic syndrome in children: the PodoNet registry cohort. Clin J Am Soc Nephrol. 2015; 10(4): 592–600, doi: 10.2215/CJN.06260614, indexed in Pubmed: 25635037.
6. Shenoy M, Plant ND, Lewis MA, et al. Intravenous methylprednisolone in idiopathic childhood nephrotic syndrome. Pediatr Nephrol. 2010; 25(5): 899–903, doi: 10.1007/s00467-009-1417-1, indexed in Pubmed: 20108003.
7. Lieberman KV, Tejani A. A randomized double-blind placebo-controlled trial of cyclosporine in steroid-resistant idiopathic focal segmental glomerulosclerosis in children. J Am Soc Nephrol. 1996; 7(1): 56–63, doi: 10.1681/ASN.V7156, indexed in Pubmed: 8808110.
8. Choudhry S, Bagga A, Hari P, et al. Efficacy and safety of tacrolimus versus cyclosporine in children with steroid-resistant nephrotic syndrome: a randomized controlled trial. Am J Kidney Dis. 2009; 53(5): 760–769, doi: 10.1053/j.ajkd.2008.11.033, indexed in Pubmed: 19268410.
9. de Mello VR, Rodrigues MT, Mastrocinque TH, et al. Mycophenolate mofetil in children with steroid/cyclophosphamide-resistant nephrotic syndrome. Pediatr Nephrol. 2010; 25(3): 453–460, doi: 10.1007/s00467-009-1356-x, indexed in Pubmed: 19937060.
10. Gellermann J, Ehrich JHH, Querfeld U. Sequential maintenance therapy with cyclosporin A and mycophenolate mofetil for sustained remission of childhood steroid-resistant nephrotic syndrome. Nephrol Dial Transplant. 2012; 27(5): 1970–1978, doi: 10.1093/ndt/gfr572, indexed in Pubmed: 21976740.

11. Prytuła A, Iijima K, Kamei K, et al. Rituximab in refractory nephrotic syndrome. Pediatr Nephrol. 2010; 25(3): 461–468, doi: 10.1007/s00467-009-1376-6, indexed in Pubmed: 20033225.
12. Tarshish P, Tobin JN, Bernstein J, et al. Cyclophosphamide does not benefit patients with focal segmental glomerulosclerosis. A report of the International Study of Kidney Disease in Children. Pediatr Nephrol. 1996; 10(5): 590–593, doi: 10.1007/s004670050167, indexed in Pubmed: 8897562.
13. Elhence R, Gulati S, Kher V, et al. Intravenous pulse cyclophosphamide--a new regime for steroid-resistant minimal change nephrotic syndrome. Pediatr Nephrol. 1994; 8(1): 1–3, doi: 10.1007/BF00868243, indexed in Pubmed: 8142205.
14. Lombel RM, Gipson DS, Hodson EM, et al. Kidney Disease: Improving Global Outcomes, Kidney Disease: Improving Global Outcomes. Treatment of steroid-resistant nephrotic syndrome in children: new guidelines from KDIGO. Pediatr Nephrol. 2013; 28(3): 409–414, doi: 10.1007/s00467-012-2304-8, indexed in Pubmed: 23052648.
15. Tarshish P, Tobin JN, Bernstein J, et al. Cyclophosphamide does not benefit patients with focal segmental glomerulosclerosis. A report of the International Study of Kidney Disease in Children. Pediatr Nephrol. 1996; 10(5): 590–593, doi: 10.1007/s004670050167, indexed in Pubmed: 8897562.
16. Jellouli M, Charfi R, Maalej B, et al. Rituximab in the management of pediatric steroid-resistant nephrotic syndrome: A systematic review. J Pediatr. 2018; 197: 191–197.e1, doi: 10.1016/j.jpeds.2018.01.008, indexed in Pubmed: 29680473.
17. Hackl Á, Cseprekál O, Gessner M, et al. Mycophenolate mofetil therapy in children with idiopathic nephrotic syndrome: Does therapeutic drug monitoring make a difference? Ther Drug Monit. 2016; 38(2): 274–279, doi: 10.1097/FTD.0000000000000258, indexed in Pubmed: 26488204.
18. Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for Glomerulonephritis, Kidney Int. Suppl. ; 2: 153–176.
19. Trautmann A, Vivarelli M, Samuel S, et al. International Pediatric Nephrology Association. IPNA clinical practice recommendations for the diagnosis and management of children with steroid-resistant nephrotic syndrome. Pediatr Nephrol. 2020; 35(8): 1529–1561, doi: 10.1007/s00467-020-04519-1, indexed in Pubmed: 32382828.

TREATMENT OF NEPHROTIC EDEMA

RECOMMENDATION 6:
6.1. Low sodium diet (< 35 mg/kg/d) is recommended to reduce nephrotic edema [1B].
6.2. Before the initiation of diuretic treatment, it is suggested that the patient be qualified for the hypo- or normo-/hypervolemic group.
In patients with normo/hypervolemia, oral diuretics are recommended, such as furosemide, hydrochlorothiazide, or spironolactone [1B].
In patients with hypovolemia, administration of 20% albumin is recommended at a dose of 0.5–2 g/kg/d by slow intravenous infusion followed by intravenous furosemide administration [1B].

COMMENTARY

Treatment of edema in NS depends on its severity and the pathomechanism leading to its onset. Nutritional recommendations apply to all children in the acute phase of NS. In cases of mild to moderate edema, reducing the intake of salt to 35 mg/kg/d is sufficient [1, 2]. If edema is accompanied by hyponatremia, the supply of fluids should also be reduced [3, 4]. More severe edema requires pharmacological treatment [3–6]. Diuretics and intravenous volemia-increasing agents require that the pediatric patient be subjected to previous clinical evaluation and qualification for the hypovolemia or normo-/hypervolemia group [1, 5]. The results of laboratory tests may be useful in this assessment in addition to the results of physical examination (tab. 6).

Patients with normo-/hypervolemia, moderate edema, and normal glomerular filtration rate may require oral diuretic drugs [1, 4, 5]:
— furosemide at 1–3 mg/kg/d in 3 to 4 doses;
— hydrochlorothiazide at 1–2 mg/kg/d in 2 to 4 doses;
— spironolactone at 1–4 mg/kg/d in 2–4 doses.

Doses of furosemide in patients with NS must be higher than the standard doses due to hypoalbuminemia which, by secondarily increasing the extra-vascular distribution volume, reduces the level of the drug in the blood and thus furosemide's secretion to the proximal tubular lumen where the sodium reabsorption blocking activity is exerted. In case of outcomes following oral loop diuretic being unsatisfactory, it is advisable to administer furosemide as intravenous infusion [1,4,5].

An alternative to the above therapy may be combining furosemide with a diuretic that inhibits Na absorption in the collecting tubule, may consist in combining furosemide with a diuretic that inhibits sodium absorption within the collecting tubule, e.g. amiloride, which is an inhibitor of the ENaC sodium channel [5, 6]. Caution is required when using combination regimens including diuretic drugs due to the risk of hypokalemia and alkalosis. Limitations in patients with impaired glomerular filtration should also be taken into account. Thiazides are effective only in patients with glomerular filtration rate of > 30 mL/min, whereas furosemide, which is used independently of the GFR value, remains the drug of choice in patients with glomerular filtration rate of < 30 mL/min [1, 2, 5].

Hypovolemic patients require slow intravenous infusion of volemia-increasing

Table 6. Clinical and biochemical parameters in the assessment of the hydration level in a pediatric NS patient

Clinical and biochemical parameters	Hypovolemia, underfill hypothesis	Normo-/hypervolemia, overfill hypothesis
Primary cause of edema	Hypoalbuminemia → ↓ oncotic pressure	Increase in activity of the ENaC sodium channel in the renal collecting tubule → Na retention
Cold extremities	+	–
Capillary refill time	> 2 s	< 2 s
Tachycardia	+	–
Arterial blood pressure	Paradoxical hypertension at the onset, hypotension as a late symptom	Normal blood pressure or hypertension
Orthostatic hypotension	+	–
Abdominal pain (bowel ischemia)	+	–
Glomerular filtration	Correct	Correct/reduced
Serum albumin	< 20 g/L	> 20 g/L
Urine sodium	< 10 mmol/L	> 10 mmol/L
Fractional excretion of sodium in urine	< 0.2%	> 0.2%
uK/[uK + uNa] (%)	> 60%	< 60%
Plasma renin activity	Elevated	Reduced

agents followed by intravenous furosemide at a dose of 5–10 mg/kg/d. The available preparations include:

— 20% solution of albumins at a dose of 0.5 to 2 g/kg/d (usually 1 g, i.e. 5 mL/kg/d), for patients with symptomatic hypovolemia and serum albumin levels of < 15 g/L [1, 4, 5];
— dextran-40 at a dose of 5 to 10 mL/kg/d (may be used as part of individual site experience) [1].

The use of the above preparations requires particular care due to the risk of serious complications, such as pulmonary edema upon administration of albumins or anaphylactic shock upon administration of dextran.

If no effect is observed, an attempt can be made at one-time simultaneous administration of albumins and furosemide as their combined intravenous administration significantly improves the diuretic and natriuretic effect for the first 8 hours of such treatment [7, 8].

The urinary potassium to total urinary potassium and sodium level ratio (uK/[uK+uNa]) facilitates the detection of hypovolemia (> 60%) in NS and, thus, identification of children who would benefit from the infusion of albumins [9].

References

1. Wyszyńska T, Litwin M, Książek J, Borowski A, Jarmoliński T. Zespół nerczycowy [Nephrotic syndrome]. [In:] Sieniawska M., (Eds). Nefrologia dziecięca, t. I. Ośrodek Informacji Naukowej „Polfa" Sp. z o.o. In: Wyszyńska T, Litwin M, Książek J, Borowski A, Jarmoliński T. ed. Nefrologia dziecięca, t. I. Ośrodek Informacji Naukowej „Polfa" Sp. z o.o., Warszawa 2003.
2. Grenda R, Pańczyk-Tomaszewska M, Ziółkowska H. Choroby kłębuszków nerkowych [Renal glomerular diseases]. In: Kawalec W, Grenda R, Kulus M. ed. Pediatria, t. I. PZWL, Warszawa 2008.
3. Cadnapaphornchai MA, Tkachenko O, Shchekochikhin D, et al. The nephrotic syndrome: pathogenesis and treatment of edema formation and secondary complications. Pediatr Nephrol. 2014; 29(7): 1159–1167, doi: 10.1007/s00467-013-2567-8, indexed in Pubmed: 23989393.
4. Bockenhauer D. Over- or underfill: not all nephrotic states are created equal. Pediatr Nephrol. 2013; 28(8): 1153–1156, doi: 10.1007/s00467-013-2435-6, indexed in Pubmed: 23529637.
5. Ellis D. Pathophysiology, evaluation, and management of edema in childhood nephrotic syndrome. Front Pediatr. 2015; 3: 111, doi: 10.3389/fped.2015.00111, indexed in Pubmed: 26793696.
6. Kallash M, Mahan JD. Mechanisms and management of edema in pediatric nephrotic syndrome. Pediatr Nephrol. 2021; 36(7): 1719–1730, doi: 10.1007/s00467-020-04779-x, indexed in Pubmed: 33216218.
7. Kitsios GD, Mascari P, Ettunsi R, et al. Co-administration of furosemide with albumin for overcoming diuretic resistance in patients with hypoalbuminemia: a meta-analysis. J Crit Care. 2014; 29(2): 253–259, doi: 10.1016/j.jcrc.2013.10.004, indexed in Pubmed: 24268626.
8. Pasini A, Benetti E, Conti G, et al. 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. Ital J Pediatr. 2017; 43(1): 41, doi: 10.1186/s13052-017-0356-x, indexed in Pubmed: 28427453.
9. Keenswijk W, Ilias MI, Raes A, et al. Urinary potassium to urinary potassium plus sodium ratio can accurately identify hypovolemia in nephrotic syndrome: a provisional study. Eur J Pediatr. 2018; 177(1): 79–84, doi: 10.1007/s00431-017-3029-2, indexed in Pubmed: 29022080.

PROPHYLAXIS OF THROMBOEMBOLIC COMPLICATIONS OF NEPHROTIC SYNDROME IN CHILDREN

RECOMMENDATION 7:
7.1. In children with nephrotic syndrome and history of thromboembolic disease, low-molecular heparin at a prophylactic dose of 50 IU/kg/d* (subcutaneous) or acetylsalicylic acid at a dose of 2–3 mg/kg/d is recommended during nephrotic syndrome episodes.
The use of heparin may be time-limited and conversion to acetylsalicylic acid may follow at a later stage of management [2C].
7.2. The generally accepted principles should be followed in the treatment of thromboembolic complications [1D].

*Enoxaparin sodium — dosage in mg (1 mg contains about 100 IU anti-XA), nadroparin — dosage in anti-XA IUs

COMMENTARY

Anticoagulation prophylaxis is not required in most children with NS despite the increased risk of thrombosis in uncontrolled NS.

A history of thromboembolic disease in a patient with a clinically overt NS episode is an absolute indication for such prophylaxis management [1–3].

Anticoagulation treatment is initiated in clinical situations where the risk of thrombosis is further increased [4]. Some physicians use low doses of acetylsalicylic acid in prolonged episodes of severe steroid-resistant NS [5].

The risk of thrombosis increases as serum albumin is reduced to < 2.5 g/dL (25 g/L), and, therefore, as proteinuria is increased. In addition, the risk of thrombosis is increased in the following clinical situations [6–9]:

— increased blood viscosity, thrombocytopenia;
— immobilization (massive edema);
— use of diuretics, hypovolemia;
— fibrinogen concentration > 6 g/L, antithrombin III concentration < 70%;
— hyperlipidemia;
— obesity;
— history of surgery;
— cancer;
— membranous nephropathy, antiphospholipid syndrome nephropathy.

RELATIVE INDICATIONS FOR THROMBOEMBOLIC PROPHYLAXIS INCLUDE [2, 3, 7, 9–12]:

— albumin levels of < 20 g/L;
— proteinuria of > 10.0 g/L;
— BMI of > 35 kg/m$^{2;}$
— family history of thromboembolic disease with documented genetic background (thrombophilia);
— NYHA (New York Heart Association) class III/IV heart failure;
— recent history of abdominal or orthopedic surgery;
— prolonged immobilization;
— concomitant septic condition and/or a deep venous access catheter installed.

One should keep in mind that the prevention of thrombotic disease is associated with an increased risk of bleeding.

CONTRAINDICATIONS FOR PROPHYLACTIC USE OF ANTICOAGULANTS INCLUDE [7, 12]:

— patient/parent non-compliance;
— signs of hemorrhagic diathesis;
— previous gastrointestinal bleeding;
— central nervous system disorders with bleeding potential (brain tumor, aneurysm).

It is not recommended to perform screening for thrombophilia in children with INS during the first episode unless their family history includes thrombotic events occurring at a young age (< 50 years).

No separate standards for the treatment of thromboembolic complications in children with NS have been established; however, they are included in the guidelines for the treatment of such complications in other diseases [8, 13].

Albeit rare, thromboembolic complications occurring in children with NS can be life-threatening. The most frequently described complications include cerebral thrombosis, pulmonary thrombosis, and deep vein thrombosis. Complications require timely diagnosis and early, aggressive treatment [12, 14, 15].

References

1. Kerlin BA, Blatt NB, Fuh B, et al. Epidemiology and risk factors for thromboembolic complications of childhood nephrotic syndrome: a Midwest Pediatric Nephrology Consortium (MWPNC) study. J Pediatr. 2009; 155(1): 105–10, 110.e1, doi: 10.1016/j.jpeds.2009.01.070, indexed in Pubmed: 19394032.
2. Bauman M, Massicotte MP, Yiu V. Disordered hemostasis and renal disorders. In: Geary DF, Schaefe F. ed. Comprehensive pediatric nephrology. Mosby 2008: 385–394.
3. KDIGO General principles in the management of glomerular disease. Kidney Int. Suppl. 2012; 2: 156–162.
4. Zaffanello M, Franchini M. Thromboembolism in childhood nephrotic syndrome: a rare but serious complication. Hematology. 2007; 12(1): 69–73, doi: 10.1080/10245330600940048, indexed in Pubmed: 17364996.

5. Ziółkowska H. Zespół nerczycowy. Pediatr Dypl. 2013; 17: 17–28.
6. Lilova MI, Velkovski IG, Topalov IB. Thromboembolic complications in children with nephrotic syndrome in Bulgaria (1974-1996). Pediatr Nephrol. 2000; 15(1-2): 74–78, doi: 10.1007/s004679900253, indexed in Pubmed: 11095017.
7. Glassock RJ. Prophylactic anticoagulation in nephrotic syndrome: a clinical conundrum. J Am Soc Nephrol. 2007; 18(8): 2221–2225, doi: 10.1681/ASN.2006111300, indexed in Pubmed: 17599972.
8. Grenda R, Ziółkowska H. Choroby układu moczowego. In: Kawalec W, Grenda R, Ziółkowska H. ed. Pediatria. PZWL, Warszawa 2013: 657–740.
9. Park SeJ, Shin JIl. Complications of nephrotic syndrome. Korean J Pediatr. 2011; 54(8): 322–328, doi: 10.3345/kjp.2011.54.8.322, indexed in Pubmed: 22087198.
10. Yang GF, Schoepf UJ, Zhu H, et al. Thromboembolic complications in nephrotic syndrome: imaging spectrum. Acta Radiol. 2012; 53(10): 1186–1194, doi: 10.1258/ar.2012.120259, indexed in Pubmed: 23081957.
11. Kerlin BA, Haworth K, Smoyer WE. Venous thromboembolism in pediatric nephrotic syndrome. Pediatr Nephrol. 2014; 29(6): 989–997, doi: 10.1007/s00467-013-2525-5, indexed in Pubmed: 23812352.
12. Suri D, Ahluwalia J, Saxena AK, et al. Thromboembolic complications in childhood nephrotic syndrome: a clinical profile. Clin Exp Nephrol. 2014; 18(5): 803–813, doi: 10.1007/s10157-013-0917-2, indexed in Pubmed: 24346593.
13. Monagle P, Chan AKC, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141(2 Suppl): e737S–e801S, doi: 10.1378/chest.11-2308, indexed in Pubmed: 22315277.
14. Wright JM, Watts RG. Venous thromboembolism in pediatric patients: epidemiologic data from a pediatric tertiary care center in Alabama. J Pediatr Hematol Oncol. 2011; 33(4): 261–264, doi: 10.1097/MPH.0b013e3182134111, indexed in Pubmed: 21516021.
15. Pasini A, Benetti E, Conti G, et al. 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. Ital J Pediatr. 2017; 43(1): 41, doi: 10.1186/s13052-017-0356-x, indexed in Pubmed: 28427453.
16. Carpenter SL, Goldman J, Sherman AK, et al. Association of infections and venous thromboembolism in hospitalized children with nephrotic syndrome. Pediatr Nephrol. 2019; 34(2): 261–267, doi: 10.1007/s00467-018-4072-6, indexed in Pubmed: 30194664.

TREATMENT OF LIPID DISORDERS IN CHILDREN WITH IDIOPATHIC NEPHROTIC SYNDROME

RECOMMENDATION 8:
A low-fat diet alone is recommended for the treatment of lipid disorders in the course of nephrotic syndrome.
8.1. Statin-based pharmacotherapy should be reserved for exceptional cases (prolonged and intense lipid disorders) [2B].

COMMENTARY

Most cases of NS are accompanied by hyperlipidemia. According to some data, the occurrence and severity of hyperlipidemia depend on the severity of proteinuria and hypoalbuminemia rather than the underlying cause of NS [1–3]. Additional factors with potential impacts on these disorders include age, nutritional status, and the use of corticosteroids, diuretics, and β-blockers. Some children with NS present with elevated cholesterol, triglycerides, low-density lipoprotein, and very-low-density lipoprotein levels even after remission of nephrotic syndrome [2, 3].

Diet therapy. In most clinical situations, diet therapy is considered to be the physiological modality causing (if any) only minor side effects. However, diet therapy may not be sufficient in cases of increased hypercholesterolemia. According to the few available literature recommendations, dietary management should include reducing the amount of consumed fat to approximately 30% of the total energy demand, reducing saturated fatty acids to 10%, and cholesterol intake to less than 300 mg/day. This does not necessarily translate to an improved clinical course of NS.

Pharmacological treatment. HMG-COA reductase inhibitors can be used in the monotherapy of lipid disorders. In recent years, much interest was paid to this group of drugs due to their high efficacy in reducing serum cholesterol levels with a small number of reported side effects. Notably, HMG-COA reductase inhibitors may also exert direct action on mesangial proliferative glomerulonephritis and epithelial cells [4–7]. Currently, drugs from this group are most commonly used to treat hyperlipidemia in NS. In some patients, mainly adults with prolonged proteinuria, this treatment appears to be an integral part of the treatment process. There are few reports on the use of statins in children with dyslipidemia and normal kidney function. According to these data, statins may lower the low-density lipoprotein-associated cholesterol levels by 17–50% [8–10]. Optimum management of hyperlipidemia in pediatric patients with NS has not been unambiguously established. In children with chronic kidney disease, statins are allowed in severe lipid metabolism disorders. One should keep in mind that statins metabolized by CYP3A4 may interact with cyclosporin. In such cases, the activity of statins (not CsA) is elevated, potentially leading to adverse

Table 7. Statins used in pediatric patients

Name	Age (years)	Dose [mg/d]	Metabolic pathway	Lipophilicity
Simvastatin	10–17	10–40	CYP3A3/4 substrate	+++
Lovastatin	10–17	10–40	CYP3A3/4 substrate	++
Atorvastatin	10–17	10–20	CYP3A3/4 substrate CYP3A4 inhibitor	+
Pravastatin	8–13 14–18	20 40	CYP3A3/4 substrate CYP3A4, CYP2C8/9, CYP2D6 inhibitor	– –

reactions, including, but not limited to, muscle damage. During this combination treatment, blood creatine phosphokinase activity should be periodically monitored.

The recommended doses of statins in children are shown in Table 7 [11–13].

References

1. Prescott WA, Streetman DaD, Streetman DS. The potential role of HMG-CoA reductase inhibitors in pediatric nephrotic syndrome. Ann Pharmacother. 2004; 38(12): 2105–2114, doi: 10.1345/aph.1D587, indexed in Pubmed: 15507504.
2. Eddy AA, Symons JM. Nephrotic syndrome in childhood. Lancet. 2003; 362(9384): 629–639, doi: 10.1016/S0140-6736(03)14184-0, indexed in Pubmed: 12944064.
3. Saland JM, Ginsberg H, Fisher EA. Dyslipidemia in pediatric renal disease: epidemiology, pathophysiology, and management. Curr Opin Pediatr. 2002; 14(2): 197–204, doi: 10.1097/00008480-200204000-00009, indexed in Pubmed: 11981290.
4. Gipson DS, Massengill SF, Yao L, et al. Management of childhood onset nephrotic syndrome. Pediatrics. 2009; 124(2): 747–757, doi: 10.1542/peds.2008-1559, indexed in Pubmed: 19651590.
5. Avis HJ, Hutten BA, Gagné C, et al. Efficacy and safety of rosuvastatin therapy for children with familial hypercholesterolemia. J Am Coll Cardiol. 2010; 55(11): 1121–1126, doi: 10.1016/j.jacc.2009.10.042, indexed in Pubmed: 20223367.
6. de Jongh S, Ose L, Szamosi T, et al. Simvastatin in Children Study Group. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized, double-blind, placebo-controlled trial with simvastatin. Circulation. 2002; 106(17): 2231–2237, doi: 10.1161/01.cir.0000035247.42888.82, indexed in Pubmed: 12390953.
7. Knipscheer HC, Boelen CC, Kastelein JJ, et al. Short-term efficacy and safety of pravastatin in 72 children with familial hypercholesterolemia. Pediatr Res. 1996; 39(5): 867–871, doi: 10.1203/00006450-199605000-00021, indexed in Pubmed: 8726243.
8. McCrindle BW, Helden E, Cullen-Dean G, et al. A randomized crossover trial of combination pharmacologic therapy in children with familial hyperlipidemia. Pediatr Res. 2002; 51(6): 715–721, doi: 10.1203/00006450-200206000-00009, indexed in Pubmed: 12032266.
9. McCrindle BW, Ose L, Marais AD. Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebo-controlled trial. J Pediatr. 2003; 143(1): 74–80, doi: 10.1016/S0022-3476(03)00186-0, indexed in Pubmed: 12915827.
10. Stein EA, Illingworth DR, Kwiterovich PO, et al. Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia: a randomized controlled trial. JAMA. 1999; 281(2): 137–144, doi: 10.1001/jama.281.2.137, indexed in Pubmed: 9917116.
11. Chapter 4: Pharmacological cholesterol-lowering treatment in children. Kidney Int Suppl (2011). 2013; 3(3): 282–283, doi: 10.1038/kisup.2013.36, indexed in Pubmed: 25019002.
12. Dogra GK, Watts GF, Herrmann S, et al. Statin therapy improves brachial artery endothelial function in nephrotic syndrome. Kidney Int. 2002; 62(2): 550–557, doi: 10.1046/j.1523-1755.2002.00483.x, indexed in Pubmed: 12110017.
13. Belay B, Belamarich PF, Tom-Revzon C. The use of statins in pediatrics: knowledge base, limitations, and future directions. Pediatrics. 2007; 119(2): 370–380, doi: 10.1542/peds.2006-0787, indexed in Pubmed: 17272627.
14. Noone D, Iijima K, Parekh R. Idiopathic nephrotic syndrome in children. The Lancet. 2018; 392(10141): 61–74, doi: 10.1016/s0140-6736(18)30536-1.

PREVENTION OF SKELETAL COMPLICATIONS OF NEPHROTIC SYNDROME

RECOMMENDATION 9:
9.1. 25(OH)D_3 level monitoring is recommended in pediatric patients with nephrotic syndrome.
9.2. Vitamin D supplementation is recommended at the dose of 2000 IU per day during the treatment with daily doses of prednisone and at the dose of 1000 IU per day in NS patients during the period of steroid therapy being administered every 48 hours and for 3 months thereafter if discontinuation takes place between October and March [1A].
The supplement should be delivered under control of blood 25(OH)D_3 levels. The recommended value is 30–50 ng/mL.
9.3. Diet with normal calcium content is recommended as follows:
children between 1 and 3 years of age — 500 mg/d;
children between 4 and 8 years of age — 800 mg/d;
children between 9 and 18 years of age — 1300 mg/d;
If elimination diets (e.g. hypoallergenic, milk-free) diets are used, the diet should be supplemented with calcium so as to achieve the recommended daily intake [2B].
9.4. In children receiving chronic steroid therapy due to frequently recurrent, steroid dependent or steroid resistant, nephrotic syndrome, bone density scans are recommended every 12 months.

COMMENTARY

The loss of proteins and minerals in the course of NS and the treatment with corticosteroids may lead to changes in patients' bone tissue. Lower concentrations of $25(OH)D_3$ levels are observed during NS episodes as a result of the loss of vitamin D transport proteins. Reduced $25(OH)D_3$ levels may also persist in disease remissions [1, 2]. In addition to the negative effects of proteinuria on their skeletal system, children with ZN are also at risk of adverse effects of corticosteroid therapy which, by inhibiting osteoblastogenesis and stimulating apoptosis of osteoblasts, contribute to reduced bone turnover and osteoporosis. In patients with NS receiving corticosteroids, mineralization disorders (osteomalacia) are observed in biopsy specimens both in adults [3] and in children [4], as is the reduction of bone mineral density in densitometric tests [5].

A few available randomized studies demonstrate the protective role of vitamin D and calcium supplementation during corticosteroid treatment of children with NS [6–9].

Children with frequently recurring and steroid-dependent NS are also at risk of growth retardation as a result of being exposed to high cumulative doses of corticosteroids [10, 11]. Alternate-day dosing of corticosteroids has no significant effect on the inhibition of growth retardation and facilitates achieving the correct final growth [12, 13].

References

1. Banerjee S, Basu S, Sengupta J. Vitamin D in nephrotic syndrome remission: a case-control study. Pediatr Nephrol. 2013; 28(10): 1983–1989, doi: 10.1007/s00467-013-2511-y, indexed in Pubmed: 23708762.
2. Weng FL, Shults J, Herskovitz RM, et al. Vitamin D insufficiency in steroid-sensitive nephrotic syndrome in remission. Pediatr Nephrol. 2005; 20(1): 56–63, doi: 10.1007/s00467-004-1694-7, indexed in Pubmed: 15602667.
3. Mittal SK, Dash SC, Tiwari SC, et al. Bone histology in patients with nephrotic syndrome and normal renal function. Kidney Int. 1999; 55(5): 1912–1919, doi: 10.1046/j.1523-1755.1999.00413.x, indexed in Pubmed: 10231454.
4. Freundlich M, Jofe M, Goodman WG, et al. Bone histology in steroid-treated children with non-azotemic nephrotic syndrome. Pediatr Nephrol. 2004; 19(4): 400–407, doi: 10.1007/s00467-003-1378-8, indexed in Pubmed: 14991389.
5. Gulati S, Godbole M, Singh U, et al. Are children with idiopathic nephrotic syndrome at risk for metabolic bone disease? American Journal of Kidney Diseases. 2003; 41(6): 1163–1169, doi: 10.1016/s0272-6386(03)00348-2.
6. Choudhary S, Agarwal I, Seshadri MS. Calcium and vitamin D for osteoprotection in children with new-onset nephrotic syndrome treated with steroids: a prospective, randomized, controlled, interventional study. Pediatr Nephrol. 2014; 29(6): 1025–1032, doi: 10.1007/s00467-013-2720-4, indexed in Pubmed: 24414607.
7. Banerjee S, Basu S, Sen A, et al. The effect of vitamin D and calcium supplementation in pediatric steroid-sensitive nephrotic syndrome. Pediatr Nephrol. 2017; 32(11): 2063–2070, doi: 10.1007/s00467-017-3716-2, indexed in Pubmed: 28725977.
8. Yadav VK, Sharma S, Debata PK, et al. Change in bone mineral density and role of vitamin D and calcium supplementation during treatment of first episode nephrotic syndrome. J Clin Diagn Res. 2017; 11(9): SC18–SC21, doi: 10.7860/JCDR/2017/27030.10657, indexed in Pubmed: 29207799.
9. Selewski DT, Chen A, Shatat IF, et al. Vitamin D in incident nephrotic syndrome: a Midwest Pediatric Nephrology Consortium study. Pediatr Nephrol. 2016; 31(3): 465–472, doi: 10.1007/s00467-015-3236-x, indexed in Pubmed: 26498119.
10. Emma F, Sesto A, Rizzoni G. Long-term linear growth of children with severe steroid-responsive nephrotic syndrome. Pediatr Nephrol. 2003; 18(8): 783–788, doi: 10.1007/s00467-003-1176-3, indexed in Pubmed: 12811653.
11. Donatti TL, Koch VH, Fujimura MD, et al. Growth in steroid-responsive nephrotic syndrome: a study of 85 pediatric patients. Pediatr Nephrol. 2003; 18(8): 789–795, doi: 10.1007/s00467-003-1142-0, indexed in Pubmed: 12750984.
12. Elzouki AY, Jaiswal OP. Long-term, small dose prednisone therapy in frequently relapsing nephrotic syndrome of childhood. Effect on remission, statural growth, obesity, and infection rate. Clin Pediatr (Phila). 1988; 27(8): 387–392, doi: 10.1177/000992288802700807, indexed in Pubmed: 3135974.
13. Jabs K, Sullivan EK, Avner ED, et al. Alternate-day steroid dosing improves growth without adversely affecting graft survival or long-term graft function. A report of the North American Pediatric Renal Transplant Cooperative Study. Transplantation. 1996; 61(1): 31–36, doi: 10.1097/00007890-199601150-00008, indexed in Pubmed: 8560569.

VACCINATIONS IN NEPHROTIC SYNDROME

RECOMMENDATION 10:
10.1. In children with nephrotic syndrome, vaccination against invasive pneumococcal disease and annual vaccination against influenza is recommended to reduce the risk of severe infectious diseases in children and family members living together [1A].
10.2. In the case of live vaccines, recommendations include:
• deferral of vaccination until prednisone dose is reduced to less than 1 mg/kg/d (< 20 mg/d) or 2 mg/kg/48 h (< 40 mg/48 h);
• a minimum 1-month interval prior to the administration of a live vaccine in children with nephrotic syndrome treated with immunosuppressive agents such as calcineurin inhibitors, levamizole, mycophenolate mofetil;
• a minimum 3-month interval prior to the administration of a live vaccine in children with nephrotic syndrome treated with cytotoxic agents such as cyclophosphamide, chlorambucil;

• a minimum 6-month interval prior to the administration of a live vaccine in children with nephrotic syndrome treated with anti-lymphocyte B antibodies (rituximab);
• avoiding vaccination in patients treated with corticosteroids in combination with immunosuppressive agents;
• maintaining special precautions for 3 to 6 weeks after any live vaccines have been administered to family members living together with the child receiving immunosuppressive therapy to minimize the risk of disease transmission [1A].
10.3. It is recommended that varicella-zoster vaccine children with nephrotic syndrome receiving immunosuppressive treatment be given immunoglobulins against the varicella-zoster virus within 72 hours after a contact with a smallpox patient [1A].
10.4. It is recommended that children receiving immunosuppressive treatment receive acyclovir or valacyclovir from the very onset of varicella symptoms [2A].

COMMENTARY

The risk of infection in children with NS is greater than the populational risk due to their immunity being compromised in the course of the disease and their susceptibility to streptococcal, particularly, pneumococcal, infections, invasive diseases, and immunosuppressive treatment. A more severe course of some infectious diseases, particularly varicella, is also observed in children with NS; in immunosuppressed patients, the disease can be life-threatening [1].

According to the recommendations of the American Advisory Committee on Immunization Practice (ACIP) and the American Academy of Pediatrics Committee on Infectious Diseases (AAP CID), anaphylactic reaction to an earlier dose of vaccine or any component thereof is the only permanent contraindication for preventive vaccination.

Temporary contraindications include:

— acute moderate to severe disease;
— exacerbation of chronic disease [2].

Children with NS should be included in the Polish preventive vaccination schedule as modified according to restrictions resulting from immunosuppressive treatment or high-dose corticosteroids as described below. Compliance with the vaccination schedules with only actual periodic contraindications (same as in the healthy population) being taken into account is very important.

Avoiding vaccination in fear of disease recurrence may result in a complete lack of resistance to many infectious diseases [3].

In addition, under the current vaccination schedule in force in Poland (*Communication from the Chief Sanitary Inspector of 31 October 2017 on the preventive vaccination program for 2018. Official Journal of the Minister of Health, item 108 of 31 October 2017*):

— Vaccination against *Streptococcus pneumoniae* is compulsory for all children born after 31 December 2016; three primary vaccination doses are required in NS patients unless the manufacturer advises otherwise;
— Immunocompromised children below 12 years of age, children at high risk of severe disease progression, or children before initiation of immunosuppressive therapy are subject to mandatory varicella vaccination (additionally, vaccination is required in siblings of NS children, if they had not been sick with varicella in the past). A two-dose vaccination schedule is recommended. Varicella-zoster vaccination is safe in patients receiving low doses of prednisone;
— Recommended vaccinations for pediatric NS patients include vaccination against influenza according to the generally applicable rules [4].

The safety of individual vaccines in children with NS receiving corticosteroid and/or immunosuppressive treatment is presented in Table 8 [5].

VACCINATION AGAINST INVASIVE PNEUMOCOCCAL DISEASE

According to the 2013 ACIP recommendations, children and adolescents from selected groups at high risk of invasive pneumococcal disease should receive the 13-valent pneumococcal conjugate vaccine (PCV13). Immunocompromised patients aged 6 to 18 who require immunosuppressive treatment or present with chronic renal insufficiency and NS are also included in this recommendation. In addition, a 23-valent pneumococcal polysaccharide vaccine (PPV23) is recommended as part of anti-pneumococcal vaccinations in children from groups with the increased risk of invasive pneumococcal infections above the age of 2 years [5–9].

In the Committee's view, vaccination with PCV13 should be carried out even if the patient had already been given a 7-valent vaccine and/or PPV23. In addition, it is recommended that one dose of the vaccine be administered to patients between 6 and 18 years of age who had not previously received PPV23.

Detailed US recommendations for vaccination of children with NS or other chronic

Table 8. Use of individual vaccines in children with nephrotic syndrome (acc. to [5])

Vaccine	High corticosteroid dose*	Low corticosteroid dose	Immunosuppression
Diphtheria, pertussis, tetanus, polio, *Haemophilus influenzae* type B	Yes	Yes	Yes
Meningococci of groups B, C	Yes	Yes	Yes
Viral hepatitis B	Yes	Yes	Yes
Pneumococcal conjugate/ /pneumococcal polysaccharide	Yes	Yes	Yes
Human papilloma virus	Yes	Yes	Yes
Influenza	Yes	Yes	Yes
Varicella-zoster	No	Yes	No

*High corticosteroid dose: 2 mg/kg/24 h or ≥ 20 mg/24 h for children with a body weight of more than 10 kg administered for 14 or more days

Table 9. Principles for vaccination against pneumococcal diseases in children with nephrotic syndrome or other chronic kidney diseases (adapted from [7, 8])

Age at first dose	Previously received doses of PCV7/PCV13	Previously received doses of PPV23	Recommended PCV13 vaccination regimen	Recommended PPV23 vaccination regimen
2–23 months	0–4 doses	Not applicable	As in healthy children	Month 24 (at least 8 weeks after the last dose of PCV13) repeat after 5 years
24–71 months	Non-vaccinated	Not applicable	2 doses at an interval of at least 8 weeks	1 dose at least 8 weeks after PCV13, repeat after 5 years
24–71 months	< 3 doses	Not applicable	1 dose at the earliest 8 weeks after the last dose	1 dose at least 8 weeks after PCV13, repeat after 5 years
24–71 months	4 doses of PCV7	No	1 dose at the earliest 8 weeks after the last dose	1 Dose at least 8 weeks after PCV13, repeat after 5 years
24–71 months	4 doses of PCV7	1 or 2 doses	1 dose at the earliest 8 weeks after the last dose	Repeat PPV23 after 5 years (if only one dose administered previously)
6–18 years	Each PCV7 vaccination	No	1 dose	1 Dose more than 8 weeks after PCV13, repeat after 5 years
6–18 years	Each PCV7 vaccination	1 or 2 doses	1 dose	Repeat PPV23 after 5 years (if only one dose administered previously)

PCV7 — 7-valent pneumococcal conjugate vaccine; PCV13 — 13-valent pneumococcal conjugate vaccine; PPV23 — 23-valent pneumococcal polysaccharide vaccine

kidney diseases against pneumococcal diseases using PCV13 and PPV23 vaccines, depending on the patient's age and previous vaccines, are set out in Table 9 [7, 8].

Other vaccination schedules do not differ from those used in the population of healthy children.

A few studies on the response to vaccination, particularly against pneumococcal diseases and influenza in patients with NS treated with corticosteroids and/or immunosuppressants, indicate achieving satisfactory post-vaccination responses in these patients [10–14]. Kamei et al. presented the results of their studies on the efficacy and safety of immunization with live attenuated vaccines (against measles, rubella, varicella-zoster, and mumps) in children with NS receiving immunosuppressive treatment with one or two of the following drugs: CsA, TAC, MMF, MZR without steroid therapy or additionally treated with prednisolone at the dose of < 1 mg/kg/d or < 2 mg/kg/48 h. In prospective studies involving 60 stable-course patients to whom immunosuppressive treatment could not be administered, vaccination with live attenuated vaccines was demonstrated to be safe and effective over at least one year of follow-up [15]. These patients had been in remission for at least 6 months and presented with no confirmed deficits of cell-mediated and humoral response (correct CD4 counts, normal IgG levels, normal blast transformation test results) while maintaining plasma concentrations within the desired therapeutic limits.

References

1. Chapter 3: Steroid-sensitive nephrotic syndrome in children. Kidney Int Suppl (2011). 2012; 2(2): 163–171, doi: 10.1038/kisup.2012.16, indexed in Pubmed: 25028636.
2. Czajka H, Wysocki J. Szczepienia w profilaktyce chorób zakaźnych. Vademecum. Helpmed, Kraków 2010.
3. Rubik J. Szczepienia u pacjentów nefrologicznych — kiedy i jakie szczepionki są konieczne? Klinika Pediatryczna. 2008; 16: 350–353.
4. Komunikat Głównego Inspektora Sanitarnego z dnia 31 października 2017 r. w sprawie Programu Szczepień Ochronnych na rok 2018. Dziennik Urzędowy Ministra Zdrowia, poz. 108 z 31 października 2017 r.
5. Immunisation guideline for children with chronic kidney disease. Renal Unit Royal Hospital for Sick Children Yorkhill Division, Nov. 2011;. https://www.clinicalguidelines.scot.nhs.uk/nhsggc-paediatric-clinical-guidelines/nhsggc-guidelines/kidney-diseases/immunisation-guideline-for-children-with-chronic-kidney-disease/.
6. Nuorti JP, Whitney CG. Centers for Disease Control and Prevention (CDC). Prevention of pneumococcal disease among infants and children - use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine - recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2010; 59(RR-11): 1–18, indexed in Pubmed: 21150868.
7. https://publications.aap.org/redbook.
8. http://www.cdc.gov/vaccines/schedules/hcp/index.html.
9. Alpay H, Yildiz N, Onar A, et al. Varicella vaccination in children with steroid-sensitive nephrotic syndrome. Pediatr Nephrol. 2002; 17(3): 181–183, doi: 10.1007/s00467-001-0789-7, indexed in Pubmed: 11956856.
10. Poyrazoğlu HM, Düşünsel R, Gündüz Z, et al. Antibody response to influenza A vaccination in children with nephrotic syndrome. Pediatr Nephrol. 2004; 19(1): 57–60, doi: 10.1007/s00467-003-1301-3, indexed in Pubmed: 14648340.
11. Ulinski T, Leroy S, Dubrel M, et al. High serological response to pneumococcal vaccine in nephrotic children at disease onset on high-dose prednisone. Pediatr Nephrol. 2008; 23(7): 1107–1113, doi: 10.1007/s00467-008-0782-5, indexed in Pubmed: 18324419.
12. Immunisation of the immunocompromised child. Best Practice Statement. February 2002. Royal College of Paediatrics and Child Healt. http://rcpch.adlibhosting.com/files/Immunisation%20of%20the%20Immunocompromised%20Child%C2%A02002-02.pdf..
13. Janus N, Vacher LV, Karie S, et al. Vaccination and chronic kidney disease. Nephrol Dial Transplant. 2008; 23(3): 800–807, doi: 10.1093/ndt/gfm851, indexed in Pubmed: 18065804.
14. Kamei K, Miyairi I, Ishikura K, et al. Prospective study of live attenuated vaccines for patients with nephrotic syndrome receiving immunosuppressive agents. J Pediatr. 2018; 196: 217–222.e1, doi: 10.1016/j.jpeds.2017.12.061, indexed in Pubmed: 29499990.