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GUIDELINE

Clinical practice guideline for pediatric idiopathic nephrotic syndrome 2013: general therapy

Yoshitsugu Kaku · Yasufumi Ohtsuka · Yasuhiro Komatsu · Toshiyuki Ohta · Takuhito Nagai · Hiroshi Kaito · Shuji Kondo · Yohei Ikezumi · Seiji Tanaka · Shinsuke Matsumoto · Mayumi Sako · Kazushi Tsuruga · Koichi Nakanishi · Koichi Kamei · Hiroshi Saito · Shuichiro Fujinaga · Yuko Hamasaki · Hiroko Chikamoto · Kenji Ishikura · Kazumoto Iijima

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Introduction

Pediatric idiopathic nephrotic syndrome is a very important disease in the field of pediatric nephrology. The Japanese Society for Pediatric Nephrology published the "Clinical Practice Guideline for Medical Treatment of Pediatric Idiopathic Nephrotic Syndrome (version 1.0) (in Japanese)" in 2005. The guideline, aiming to support appropriate decision and treatment for pediatric idiopathic nephrotic syndrome, illustrated standard regimens of medical treatment of pediatric idiopathic nephrotic syndrome at that time and has been credited with standardization and optimization of the treatment. In 2011, 6 years after the publication, the need to revise the guideline became recognized against the background of changes in care setting including introduction of rituximab. Additionally, development of guideline covering general therapies was required.

The Scientific Committee of the Japanese Society for Pediatric Nephrology established a new operation to revise the guideline and published the "Clinical Practice Guideline for Pediatric Idiopathic Nephrotic Syndrome 2013 (in

The Scientific Committee in the Japanese Society for Pediatric Nephrology published the "Clinical Practice Guideline for Pediatric Idiopathic Nephrotic Syndrome 2013" in 2013. This is the English translation from the "General Therapy" portion of the guideline.

Y. Kaku
Department of Nephrology, Fukuoka Children's Hospital, 5-1-1 Kashii-Teriha, Higashi-ku, Fukuoka, Japan

Y. Ohtsuka
Department of Pediatrics, Faculty of Medicine, Saga University, Saga, Japan

Y. Komatsu
Division of Nephrology, Department of Medicine, St. Luke's International Hospital, Tokyo, Japan

T. Ohta
Department of Pediatric Nephrology, Hiroshima Prefectural Hospital, Hiroshima, Japan

T. Nagai
Department of Nephrology, Aichi Children's Health and Medical Center, Aichi, Japan

H. Kaito · K. Iijima
Department of Pediatrics, Kobe University Graduate School of Medicine, Kobe, Japan

S. Kondo
Department of Pediatrics, Institute of Health Bioscience, Tokushima University, Tokushima, Japan

Y. Ikezumi
Department of Pediatrics, Niigata University Medical and Dental Hospital, Niigata, Japan

S. Tanaka
Department of Pediatrics and Child Health, Kurume University Medical Center, Fukuoka, Japan

S. Matsumoto
Department of Pediatrics, Matsudo City Hospital Children's Medical Center, Chiba, Japan

Japanese)" (Shindan To Chiryo Sha, Inc., Tokyo, Japan) on September 25, 2013. The committee herein published the guideline in English, with an aim to introduce it to pediatricians around the world.

The portion of the guideline includes recommendations and suggestions by the Committee for general therapies such as management of edema, diet therapy, exercise limitations, side effect management of steroids, and vaccination. Recommendation statements are provided at the beginning of each chapter. In light of busy schedules of clinical practitioners, brief evidence-based clinical guides based on evidence are provided. The strength of each recommendation was ranked from Grade A to Grade D (Table 2).

For details of development and position of the guideline and levels of evidence, refer to the other portion of the guideline, "Clinical Practice Guideline for Pediatric Idiopathic Nephrotic Syndrome 2013: Medical Therapy" [1].

Off-label drug use requires adequate understanding of the drug's characteristics and side effects. Inconsiderate off-label use should be avoided. It should be noted that the adverse drug reaction relief service does not cover side effects or other problems resulting from off-label use of drugs and this should be informed to the patients and their guardians. Adverse reactions to immunosuppressive agents are not covered by the adverse drug reaction relief service.

This guideline uses the "standard body weight for the height of the patient" and not a measured body weight or a standard body weight for age. More specifically, the child growth curve prepared is based on the "2000 Report on Infants and Young Children Physical Development Research Report", issued by the Ministry of Health, Labour and Welfare and the "Annual Report of School Health Statistics Research 2000", issued by the Ministry of Education, Culture, Sports, Science and Technology. These reports were used to determine a calendar age where the standard height is equal to the patient's actual height, and the standard body weight for that age is used as the patient's standard body weight.

M. Sako
Division for Clinical Trials, Department of Development Strategy, Center for Social and Clinical Research, National Research Institute for Child Health and Development, Tokyo, Japan

K. Tsuruga
Department of Pediatrics, Hirosaki University Graduate School of Medicine, Hirosaki, Japan

K. Nakanishi
Department of Pediatrics, Wakayama Medical University, Wakayama, Japan

K. Kamei
Department of Nephrology and Rheumatology, National Center for Child Health and Development, Tokyo, Japan

H. Saito
Department of Pediatrics, Nihon University School of Medicine, Tokyo, Japan

S. Fujinaga
Division of Nephrology, Saitama Children's Medical Center, Saitama, Japan

Y. Hamasaki
Department of Pediatric Nephrology, Toho University Faculty of Medicine, Tokyo, Japan

H. Chikamoto
Department of Pediatric Nephrology, Tokyo Women's Medical University, School of Medicine, Tokyo, Japan

K. Ishikura (✉)
Department of Nephrology, Tokyo Metropolitan Children's Medical Center, 2-8-29 Musashidai, Fuchu, Tokyo 183-8561, Japan
e-mail: kenzo@ii.e-mansion.com

Chapter 1. Management of edema

Recommendation statements:

1. We suggest evaluation of effective circulating volume and body fluid volume as treatment for generalized edema, using various examinations including physical examination, blood tests, urinalysis, diagnostic imaging and/or physiological tests. [Recommendation grade C1]

1) Circulatory failure commonly occurs in children as abdominal symptoms or shock, with decreased effective circulating volume. Caution should be exercised with symptoms that occur due to overload of body fluid.

2) In cases with decreased effective circulating volume, the following signs should be confirmed: increased levels of fractional excretion of sodium (FENa), increased Na/K exchange index in the distal renal tubule, presence of hyponatremia, and/or an elevation in hematocrit.

3) In cases with increased effective circulating volume, evaluation of body weight and imaging tests (chest radiography or sonoradiography) are required.

2. Mild edema generally requires no treatment and we suggest not using diuretic agents or human albumin. [Recommendation grade C2]

For symptomatic refractory edema, we recommend sodium restrictions, use of diuretic agents, or human albumin, based on evaluation of the body fluid distribution. [Recommendation grade B]

1) In cases of normal or increased effective circulating volume, diuretic agents, including loop diuretics, should be used. Combination therapy of human albumin and loop diuretics provides higher diuretic effect; however, caution should be exercised for complications with fluid overload such as lung edema.

2) In cases where circulatory failure is observed with decreased effective circulating volume, intravenous extracellular fluids or human albumin should be administered.

3) In cases of edema refractory to medical therapy, or when associated with severe complications, consultation with a pediatric nephrologist is required.

3. We suggest that sodium restriction be required for the treatment of edema, but not fluid restriction (See Chapter 2, Part 2.). [Recommendation grade C1]

Explanation

1. Evaluation of edema and effective circulating volume

Edema is a typical symptom observed in patients with pediatric nephrotic syndrome. Mild edema is resolved by treatment for the primary disease and thus treatment with steroid therapy is preferred. In cases with severe edema or refractory edema accompanied with difficulty of fluid control, specific treatment is required [2–5].

Edema is characterized by an increase of fluid accumulation in the interstitium, and patients with pediatric nephrotic syndrome present generalized edema. The mechanism of edema includes: (1) reduced intravascular oncotic pressure due to hypoproteinemia; (2) increased resorption of sodium in the epithelial sodium channel (ENaC) in distal renal tubule and collecting tubule and in the sodium–potassium pump (Na^+–K^+ ATPase); and (3) fluid imbalance due to altered capillary permeability. The pathophysiology has led to the establishment of two hypotheses known as the "underfilling" and "overfilling" theories. The "underfilling" theory explains that edema causes a decrease in effective circulating volume. Hypoalbuminemia due to proteinuria reduces the intravascular oncotic pressure, disturbing the balance in the starling force in the capillaries, resulting in the transfer of fluid from intravascular to interstitium, thus forming edema and decreasing effective circulating volume. In this case, the renin-angiotensin system (RAS), catecholamine sympathetic nerve system, and antidiuretic hormone are activated; this activation causes secondary resorption of fluid and sodium in the kidney and induces an exacerbation of edema. The "overfilling" theory explains that the primary accumulation of sodium and fluid in the kidney leads to an increase in body fluid volume, thereby causing edema. Hypoalbuminemia produces mild or no changes in the oncotic pressure; however, the primary resorption of fluid and sodium in the distal renal tubule and collecting tubule increases the effective circulating volume, producing elevated hydrostatic pressure and transferring the fluid to the interstitium to form edema. There are no changes in RAS or the catecholamine sympathetic nerve system according to this theory [6, 7].

In the "underfilling" theory, the decrease in effective circulating volume is the primary focus. Specifically, a precipitous decline in the serum protein level requires caution since this is associated with circulatory failure. On the other hand, overfilling is observed in many patients. Time-dependent body fluid changes that occur require constant monitoring. This includes symptom evaluation, vital signs, body weight, urine volume, blood and urine biochemical tests, imaging tests (radiography or ultrasonography), and physiological tests.

(1) Change of effective circulating volume and symptoms

Generalized edema, complicated by pediatric nephrotic syndrome, is commonly associated with a body-weight gain of more than 5 %, and symptoms depend on the distribution of

body fluids. [3, 8] The "underfilling" symptoms are often observed at initial onset or early stage of relapse and may progress to shock. These symptoms include: tachycardia, lethargy, cold sweat, decreased peripheral circulation, hypouresis, and anuria. Among these, abdominal symptoms such as nausea and vomiting, abdominal pain, and diarrhea are major complications in children, occurring in 20–62 % of the patients [9–12]. The "overfilling" symptoms include refractory edema, lethargy, hypertension, meteorism, and dyspnea. Cases with heart failure or pulmonary edema dictate special caution [13, 14]. Treatment diuretic agents or human albumin should be monitored since such treatment is accompanied with changes in the distribution of body fluids. In addition, infections (peritonitis, sepsis, pneumonia, cellulitis and fungal infections), venous thrombosis, and acute renal failure are considered as complications. Fever, abdominal pain, vomiting, decreased blood pressure, and lethargy accompany peritonitis and sepsis. Thrombosis of the renal or pulmonary vein is associated with macrohematuria, tachypnea, and breathing disorders. Acute renal failure is rarely observed but requires careful attention since it develops from various causes, including prerenal factors and tubulointerstitial edema due to decreased effective circulating volume, infections, and drug-induced renal impairment.

(2) Decrease of effective circulating volume and testing

Oncotic pressure decreases in the interstitium as well as in plasma, suggesting that hypoalbuminemia does not necessarily contribute to the progress of edema [7]. However, in "underfilling" cases, hypoalbuminemia that progresses in a short period decreases the oncotic pressure, inducing circulatory failure symptoms at serum albumin levels of 1.5–2 g/dL [9]. In this course, hyponatremia (<135 mEq/L), elevated hemoglobin (>16 g/dL), temporal elevated hematocrit, and decreased glomerular filtration rates may be observed [10–12, 19, 22, 34]. Both the "underfilling" and "overfilling" cases with hypoalbuminemia show decreased levels of fractional excretion of sodium (FENa)* [1] of less than 1 % due to enhanced sodium resorption in the kidney. In "underfilling" cases that have progressed, FENa is further decreased to less than 0.5 %. Excessive "underfilling" correlates to increased plasma aldosterone levels of more than 60 % in the distal nephron Na/K exchange index (normal range 20–30 %)* [2] Cases that developed circulatory failure symptoms showed a FENa of 0.2–0.3 %, and the distal nephron Na/K exchange index of 71–86 % [11, 12, 21].

(3) Increase of effective circulating volume and testing

Chest radiography is a useful modality that can detect pleural effusion, pulmonary edema, and cardiothoracic ratio (CTR) for evaluation of body fluid volume. In addition, ultrasonography is considered useful for the evaluation of intravascular volume [18–20, 34]. The inferior vena cava diameter (IVCD), inferior vena cava index (IVCI) and inferior vena cava collapsibility index (IVCCI) are measured as echographic parameters. IVCD is a hemodynamic parameter and IVCI increases in "overfilling" cases. IVCCI is an index of right atrial pressure; IVCCI of less than 50 % corresponds to right atrial pressure of less than 10 m Hg. Thus, "overfilling" cases show decreased IVCCI. Recently, body-fluid volume measurement using bioelectrical impedance analysis has been employed in pediatric nephrotic syndrome management as well as in chronic renal failure, heart failure, and obesity cases. [18, 23] A study reported that edema without changes in effective circulating volume could be evaluated by total body water measured by the bioelectrical impedance analysis. Although the number of the cases using the analysis is limited, the bioelectrical impedance analysis is expected to be an accurate method.

Most cases that require the control of edema are severe, requiring refractory and steroid therapies, thus careful management of the edema and body fluids should be performed. It is also important to monitor the general condition of the patients during such management.

2. Medical therapy for edema

Since proteinuria is decreased 1–2 weeks after the start of steroid therapy for pediatric nephrotic syndrome, diuretic agents are not required for mild edema. For edema accompanied with a body weight gain of 7–10 %, or persistent edema suspected as the "overfilling" type, diuretic agents can be effective (Table 1). The purpose of diuretic agents is to stimulate the elimination of sodium and fluids from the body [4]. Monotherapy with loop diuretics, or combination therapy with loop diuretics and thiazide diuretics or aldosterone antagonists, has been found to be useful. Combination therapy with furosemide and thiazide diuretics (hydrochlorothiazide and Metolazone [not available in Japan]) is expected to increase urine volume by 50 %, compared with furosemide monotherapy. In cases without drastic "underfilling", the use of diuretic agents only, such as a combination therapy with furosemide and spironolactone, has a similar effect as human albumin infusion. Combination therapy of human albumin with diuretic agents can enhance the elimination of sodium and fluids. In previous studies, the combination of furosemide with human albumin was associated with a two-fold increase in urine volume, compared with furosemide monotherapy [28–30]. Understanding the side effects of the therapy is also required. Use of diuretics without thorough consideration may induce "underfilling" and lead to a drop in blood pressure and prerenal renal failure. Inappropriate use of human albumin in "overfilling" cases has the risk of heart failure or pulmonary edema [14].

Table 1 Diuretic agents available for infants/children

Diuretic agent	Dosage	Interval (h)	Route	Dosage in adults
Loop diuretics				
Furosemide	Neonates: 1 mg/kg/dose	12–24	IV/oral	40–80 mg QD everyday or every other day
	Infants/children: 1–4 mg/kg/day	6–12	Oral	
	1–2 mg/kg/dose	6–12	IV	
	After IV administration at 1–2 mg/kg, cont'd at 0.1–0.4 mg/kg/h	Cont'd	IV	
Thiazide diuretics				
Trichlormethiazide	Infants: 0.04 mg/kg/dose	12–24	Oral	2–8 mg/day at 1–2 doses
Hydrochlorothiazide	Infants: 1–2 mg/kg/day	12–24	Oral	25–100 mg QD or BID
Mefruside	Infants: 15 mg/day for 3 years old	12–24	Oral	25–50 mg once (morning) or twice (morning and daytime)
	25 mg/day for 7.5 years old			
	25–50 mg/day for 12 years old			
Aldosterone antagonists				
Spironolactone	Preterm infant (<32 weeks): 1 mg/kg/day	24	Oral	50–100 mg/day dividedly administered
	Mature infants: 1–2 mg/kg/day	12	Oral	
	Infants/children: 1–3 mg/kg/day	6–12	Oral	
Potassium canrenoate	Infants: 1–4 mg/kg/day	12–24	IV	100–200 mg IV once or twice daily. Not to exceed 600 mg/day. Treatment period within 2 weeks
Triamterene	Infants: 1–2 mg/kg/day	8–12	Oral	90–200 mg/day, 2–3 doses

IV intravenous, *QD* quaque die, *BID* bis in die

(1) Diuretic agents

Loop diuretics are agents with the highest efficacy, inhibiting 20–30 % of sodium resorption in the renal tubule. Agents pass from the bloodstream into the lumen via the proximal tubule, where they then inhibit Na–K–2Cl transport in the ascending limb of loop of Henle, increasing the elimination of sodium, potassium, and chlorine. Furosemide is most commonly used among loop diuretics and administered orally or intravenously. The duration of action, when orally administered, is 4–6 h; when intravenously administered, the duration of action is 2–3 h. Urine volume output is dose-dependent, increasing with higher doses. In children, there is a risk for excessive diuretic effect due to too much elimination of furosemide into the tubules. In children with nephrotic syndrome, this effect may be made insufficient by edema in the intestinal tract or by renal impairment [24–26]. Intravenous administration should be limited to cases where oral administration fails to elicit an adequate response. When the diuretic effect is insufficient, dosing can be increased up to two times. The maximum dose in adults with normal renal function is 80–120 mg per dose [27]. An overdose of loop diuretics may result in hearing loss so judicious use should be considered. For the treatment of heart failure and for intensive care purposes in children, continuous intravenous infusion has been a useful method, preventing a reduced therapeutic response of furosemide through repeated dosing and maintenance of elevated blood levels. After intravenous administration of 1–2 mg/kg, furosemide is continued at a dose of 0.1–0.4 mg/kg/h [24–26]. There is no evidence regarding this therapy, however, for use in pediatric nephrotic syndrome and further studies are warranted. Side effects of the therapy include electrolyte abnormality, metabolic alkalosis, renal calcification, and hearing loss. Other loop diuretics, such as torasemide, azosemide, and piretanide, have been used as treatments for heart failure but lack evidence in cases of pediatric nephrotic syndrome.

Thiazide diuretics inhibit the thiazide-sensitive Na–Cl co-transporter (NCTT) in the distal renal tubule, thereby stimulating the elimination of sodium and chlorine. Resorption of sodium in the distal renal tubule is increased in nephrotic syndrome, and thus thiazide diuretics, which act at the very site, are thought to be promising. Thiazide diuretics are used when loop diuretics cannot control edema, with caution to hypokalemia.

Aldosterone antagonists inhibit the binding of aldosterone to mineralocorticoid receptors at the collecting tubule and suppress reabsorption through sodium channels. Aldosterone antagonists have a less diuretic effect, but have a potassium-conserving effect as well. Therefore, they are used in combination with loop or thiazide diuretics to prevent hypokalemia and reinforcement of the diuretic effect. Caution should be paid to side effects such as hyperkalemia and gynecomastia.

Other diuretic agents include osmotic diuretics and atrial natriuretic peptide (ANP). A case study reported that the combination therapy of 20 % D-mannitol and furosemide in a patient without renal impairment could control edema refractory to human albumin and diuretic agents. However, further research is still needed [31]. Atrial natriuretic peptide has showed diuretic effects in adult patients; however, efficacy and safety in children with nephrotic syndrome are not clear [32].

(2) Albumin

Infusion of human albumin promotes the transfer of sodium and fluids from interstitium to intravascular by increasing the blood osmolarity. The indications of human albumin infusion are: (1) symptoms or signs of shock due to a decrease in effective circulating volume, and (2) refractory edema to which diuretic agents do not respond [3, 4]. The decrease in effective circulating volume commonly occurs during the period the patient has massive proteinuria and by triggers such as infections, diarrhea, or overuse of diuretic agents. Human albumin infusion should be used properly after examining "underfilling" based on the evaluation of symptoms, body fluid volume and distribution of the fluids. For circulatory failure, extracellular fluid such as physiological saline is intravenously administered at 10–20 ml/kg over a time period of 30–60 min. When symptoms of circulatory failure are not improved, high-concentration human albumin (20, 25 %) is administered with the infusion solution at 0.5–1.0 g/kg/dose over a course of 2–4 h.

Refractory edema that does not respond to diuretic agents is often "overfilling", as well as accompanied with hypoalbuminemia. Combination therapy with human albumin infusion and diuretic agents can increase the elimination of sodium and body fluids. After the administration of high-concentration human albumin (20, 25 %) at 0.5–1.0 g/kg/dose over a time course of 2–4 h, furosemide at 1–2 mg/kg/dose is intravenously injected. In adults, the most common dose is 25 % human albumin at 50–100 ml. When severe proteinuria persists, human albumin is likely to be repeatedly administered since the activity of human albumin is temporal [33]. Caution should be taken to prevent heat failure or pulmonary edema by overdose and rapid infusion.

Haws and Baum [14] reported that a mean number of 5.4 treatment courses of human albumin infusion and furosemide, 1–3 doses daily, in 21 children with nephrotic syndrome, resulted in hypertensive complications in 70 % of the patients; 3 children developed respiratory failure or congestive heart failure. The authors suggested that human albumin infusion should take more than 2–4 h. Heart rate and blood pressure should be closely monitored, and dose intervals should be more than 24 h. Use of human albumin may be accompanied with severe complications and risk of allergy and infections. In addition, direct nephrotoxicity has been reported in animals treated with human albumin infusion. Therefore, treatment with albumin requires careful consideration of the indication.

(3) Other therapies

Severe edema that cannot be controlled by diuretic agents or human albumin infusion may progress to pulmonary edema or heart failure due to "overfilling." Additionally, clinical conditions of severe edema also often involve complicated acute renal failure, shock, infection, renal vein thrombosis, and drug-induced renal impairment. Intensive management is required under consultation with a pediatric nephrologist and dialysis therapy (peritoneal dialysis or extracorporeal circulation) may be considered. Since rapid fluid removal increases the risk of prerenal renal failure, slow and continuous ultrafiltration is preferred, keeping the removal rate appropriate. In adults, extracorporeal ultrafiltration methods have been reported as effective only for the control of edema, but evidence for using such methods in children does not exist [15–17, 34].

Bibliography

1. Igarashi T, Watanabe H, Kizu J. Revised dosage of pediatric drugs [in Japanese], 6th edn. Tokyo: Shindan to Chiryo Sha; 2012.
2. Gejo F, Uchiyama M, Tomino Y, Imai H. Nephrology for specialist physicians. Tokyo: Igaku Shoin; 2012.

Chapter 2. Diet therapy

Recommendation statements:
1. We suggest sodium restrictions for remission of edema associated with nephrotic syndrome. [Recommendation grade C1]
2. We suggest that the degree of sodium restrictions be determined based on the status of edema and the amount of food intake. [Recommendation grade C1]
3. For patients with nephrotic syndrome and normal renal function, we suggest that protein consumption be based on the nutrient requirement for healthy children of the same age. [Recommendation grade C1]
4. For patients with nephrotic syndrome, we suggest that the intake of caloric energy be based on the age of the patient. [Recommendation grade C1]

Explanation

1. Sodium restriction

Sodium restriction is a major leading therapy for edema associated with nephrotic syndrome. While randomized, controlled studies and meta-analysis do not provide much supportive evidence for the effectiveness of sodium

restrictions for the remission of edema, empirical evidence in the form of inferences taken from pathophysiology, experiences in clinical practice, and results from observational studies, support its use. There is no evidence that shows sodium restrictions shorten the time to remission of proteinuria or improves the response to medical therapies such as steroid treatments.

Generalized edema is a major sign of nephrotic syndrome. Although it rarely progresses to advanced edema, accompanied with heart failure and pulmonary edema, even moderate generalized edema is considered to carry a psychological burden on the patient.

The mechanism of generalized edema is thought to be due to sodium retention by impaired renal excretion of sodium and an transudation of plasma fluid into extravascular spaces due to the decrease in intravascular oncotic pressure by hypoalbuminemia. The two mechanisms for sodium retention by the kidney are: secondary stimulus to the renin-angiotensin system by a decrease in intravascular oncotic pressure, and a primary enhanced sodium reabsorption in the kidney. Sodium restrictions have therefore been recommended for edema in nephrotic syndrome. There is no standard for the level of sodium restrictions based on published evidence, but on an empirical basis, sodium intake is likely to be limited to 2–3 g/day (corresponding to 5–7.5 g/day as salt).

Fluid restriction for edema is not necessary unless accompanied with oliguric renal failure or hyponatremia.

2. Adjustment of sodium restriction

Sodium restrictions are to be adjusted based on the status of edema and dietary consumption by the patient.

In most cases with nephrotic syndrome, urine protein decreases within 2 weeks after the start of steroid therapy, followed by the diuretic phase, and thus there is no need for any sodium restrictions. However, in Japan, diets with a high salt content, including snacks, fast food, and frozen foods, are being increasingly consumed. Consumption of such high-sodium foods and seasonings (dietary salt, soy sauce, or Worcestershire sauce) should be avoided in patients with edema prior to the diuretic phase. Table 2 indicates dietary salt intake for the Japanese population by age group.

In cases where refractory nephrotic syndrome is accompanied by persistent proteinuria and severe edema, sodium restrictions are recommended to improve the efficacy of diuretic agents. Note that excessive sodium restrictions can decrease the appetite and can therefore hinder appropriate nutritional consumption.

3. Protein intake

Nephrotic syndrome results in the loss of massive protein levels, which leads to hypoalbuminemia. In the past, high-protein diets were recommended to replace the protein lost in urine. On the contrary, in adult patients with decreased renal function, studies have reported that protein restrictions might improve renoprotection and decrease urine protein and therefore was recommended [35, 36].

In patients with pediatric nephrotic syndrome, urine protein decreases within 2 weeks after the start of steroid therapy and serum albumin levels return to normal. We suggest that the amount of protein intake be based on the nutrient requirement for healthy children of the same age, considering both the unlikelihood of progression to renal failure and their growth. Table 1 shows the dietary reference intake for the Japanese population in terms of protein and grouped according to age.

Table 2 Dietary reference intake for Japanese population

Dietary reference intake: sodium chloride equivalent, g/day		
Age (years)	Target intake for males	Target intake for females
1–2	<4.0	<4.0
3–5	<5.0	<5.0
6–7	<6.0	<6.0
8–9	<7.0	<7.0
10–11	<8.0	<7.5
12–14	<9.0	<7.5
15–17	<9.0	<7.5

Dietary reference intake: protein, g/day				
Age (years)	Target intake for males		Target intake for females	
	EAR	RDA		EAR
1–2	15	20	1–2	15
3–5	20	25	3–5	20
6–7	25	30	6–7	25
8–9	30	40	8–9	30
10–11	40	45	10–11	40
12–14	45	60	12–14	45
15–17	50	60	15–17	50

Dietary reference intake: estimated energy requirement (EER), g/day						
Age (years)	Target for males			Target for females		
Physical activity level	I	II	III	I	II	III
1–2		1000			900	
3–5		1300			1250	
6–7	1350	1550	1700	1250	1450	1650
8–9	1600	1800	2050	1500	1700	1900
10–11	1950	2250	2500	1750	2000	2250
12–14	2200	2500	2750	2000	2250	2550
15–17	2450	2750	3100	2000	2250	2500

Physical activity level: I, low; II, middle, III, high

EAR estimated average requirements, *RDA* recommended dietary allowance

4. Energy (caloric) intake

In adult patients with nephrotic syndrome, higher energy (caloric) intake is recommended in parallel with the dietary protein restriction aforementioned. The intent of this recommendation is to maintain an adequate nitrogen balance. However, in children with nephrotic syndrome, in whom dietary protein is not restricted, there is no need to instruct them to consume a higher number of calories. Excessive restrictions on caloric intake may do more harm from a physical and psychological perspective. It is thereby appropriate to instruct the children to consume the number of calories consistent with their age. Some patients on steroid therapy may gain weight and become obese due to an increased appetite. Therefore, it is important to instruct the families of patients to arrange their diet in such a way to prevent obesity.

Bibliography

1. Mehta M, Bagga A, Pande P, Bajaj G, Srivastava RN. Behavior problems in nephrotic syndrome. Indian Pediatr. 1995;32:1281–6.
2. Guha P, De A, Ghosal M. Behavior profile of children with nephrotic syndrome. Indian J Psychiatry. 2009;51:122–6.
3. Ichikawa I, Rennke HG, Hoyer JR, et al. Role for intrarenal mechanisms in the impaired salt excretion of experimental nephrotic syndrome. J Clin Invest. 1983;71:91–103.
4. Doucet A, Favre G, Deschenes G. Molecular mechanism of edema formation in nephrotic syndrome: therapeutic implications. Pediatr Nephrol. 2007;22:1983–90.
5. Vasudevan A, Mantan M, Bagga A. Management of edema in nephrotic syndrome. Indian Pediatr. 2004;41(8):787–95.
6. Matsuo S, Imai E, Saito T, Taguchi T, Yokoyama H, Narita I, Yuzawa I, Imada T, Tsuruya K, Sato H, Kiyomoto H, Maruyama S. Guidelines for the treatment of nephrotic syndrome [in Japanese]. J Jpn Soc Nephrol. 2011;53(2):78–122.
7. Scottish Paediatric Renal and Urology Network (SPRUN). Guideline for the Management of Idiopathic Nephrotic Syndrome of Childhood. March 2012. http://www.clinicalguidelines.scot.nhs.uk/Renal%20Unit%20Guidelines/Nephrotic%20syndrome%20Guideline/Guideline%20for%20the%20Management%20of%20Nephrotic%20Syndrome%20-%20SPRUN%20300112%20v10%20Final%20%20-%20amd%2009.03.12.pdf. Accessed 31 Aug 2014.
8. Kodner C. Nephrotic Syndrome in Adults: Diagnosis and Management. Am Fam Physician. 2009;80(10):1129–34.
9. Ministry of Health, labour, and Welfare, Japan. Dietary reference intake for Japanese-recommended dietary allowance (2010). http://www.mhlw.go.jp/shingi/2009/05/s0529-4.html. Accessed 31 Aug 2014.
10. Blainey JD. High protein diets in the treatment of the nephrotic syndrome. Clin Sci (Lond). 1954;13:567–81.
11. Watson AR, Coleman JE. Dietary management in nephrotic syndrome. Arch Dis Child. 1993;69(2):179–180.
12. Kaysen GA, Gambertoglio J, Jimenez I, Jones H, Hutchison FN. Effect of dietary protein intake on albumin homeostasis in nephrotic patients. Kidney Int. 1986;29:572–7.
13. Rosenberg ME, Swanson JE, Thomas BL, Hostetter TH. Glomerular and hormonal responses to dietary protein intake in human renal disease. Am J Physiol. 1987;253(6 Pt 2):F1083–F1090.

Chapter 3. Exercise limitations

Recommendation statements:
1. We suggest that limiting exercise is not useful to induce remission or prevent relapse. [Recommendation grade C2]
2. We suggest exercise limitations for severe cases in the acute phase with abnormal blood pressure and/or lung edema. [Recommendation grade C1]
3. We suggest avoiding excessive limitations on exercise in order to help prevent thrombosis in the acute phase, drug-induced osteoporosis associated with steroid therapy, and for the prevention of obesity. [Recommendation grade C1]

Explanation

Exercise limitations in patients with nephrotic syndrome should be considered on the basis of impact on: (1) the nephrotic syndrome, (2) complicating thrombosis in the acute phase, and (3) side effects due to long-term and high-dose steroid therapy. In general, radical limitations on exercise may lower the quality of life for many children. Multiple western medical textbooks mention that immobility should be avoided in terms of a psychological and emotional perspective. This section discusses limitations on exercise and is based on "Health Care Guidance" literature published by the Japanese Society of School Health.

1. Exercise limitation for induction of remission and prevention for relapse

Previous reports indicate that the impact of exercise can cause stress on renal functions and uric protein. Exercise decreases renal plasma flow and glomerular filtration rates, and raises the filtration fraction, which leads to an increase in uric protein [37]. However, specifically, the impact of exercise on the duration of remission or frequency of relapse in patients with pediatric nephrotic syndrome has not yet been studied. However, one published document, with limited findings, reports that school-time swimming did not decrease short-term renal function before or after the exercise and showed no significant difference in the frequency of relapse or total dose of steroid consumption. [38, 39] In an authorized guideline for patient education in Japan called the "Guidelines for Lifestyle and Dietary Therapy for Kidney Diseases", recommendations for exercise limitations by age are provided. The guidelines recommend immobility during the induction therapy phase for nephrotic syndrome and prohibition of active exercise in patients treated with steroids even after achieving remission and disease stability, as shown in Table 3

(prepared by the Japanese Society of School Health). The recommendation is based on risk considerations from the exercise in terms of side-effects for proteinuria and renal function. However, our guidelines recommend that exercise limitations should not be issued unless special concerns arise, since it is unclear how the transient changes induced by exercise are associated with long-term outcomes. Side effects from limitations imposed on activities in daily life on nephrotic syndrome have not yet been identified. The recommendation grade of the guideline development committee has been classified as C2.

2. Exercise limitations in acute and unstable phases

A case report was presented that showed a patient who was unaware of his primary nephrotic syndrome, detected by urinalysis in a mass school screening, had developed acute renal failure after intense exercise stress, [40] suggesting the risk of excessive exercise in the acute phase. As mentioned in the previous section, limitations on exercise are not considered useful to induce remission or prevent relapse; however, in cases with unstable circulation dynamics due to decreased oncotic pressure or with hypertension and/or pulmonary edema due to overflow of fluids, exercise limitations are required in accordance with the condition of the patient. Based on a consensus by the committee members, regardless of the absence of evidence, the guideline development committee has classified the recommendation grade as C1.

3. Avoiding excessive limitation of exercise

(1) Thrombosis and exercise limitation

In cases with nephrotic syndrome who experience continuous elimination of large amount of protein in the urine, the risk of arterial and deep-venous thrombosis is increased [41]. The increase of risk of thrombosis is known to be caused by hemoconcentration due to decreased effective circulating volume associated with hypercholesteremia and hypoalbuminemia and by loss of protein with fibrolytic activity in urine. Previous studies reported that 2–5 % of children with nephrotic syndrome were complicated by deep venous thrombosis and suggested higher risk in steroid-resistant nephrotic syndrome [42, 43]. Other risk factors include: hemoconcentration, severe proteinuria, prolonged immobility, and placement of central venous catheter [44, 45]. Adequate water replacement and infusion of albumin are required to reduce the risk and excessive limitation of exercise should be avoided. In the guidelines for adult patients, routine prophylaxis using anticoagulant agents for nephrotic syndrome is not recommended with the exception of cases with thromboembolism or accidental deep venous thrombosis. In children, there is no evidence of efficacy.

Table 3 Health classification by the status of nephrotic syndrome

Classification	Status of nephrotic syndrome
A (at home)	Requiring at-home or hospital treatment
B (classroom activity only)	Able to attend school but not achieving stable disease
C (mild exercise)	Achieving stable disease and receiving steroid therapy
D (mild to moderate exercise)	Maintenance of remission by alternate-day administration of steroids
E (normal activities)	Maintenance of remission without administration of steroids

Cited with modifications from In: Urinalysis in school (revised)—from planning to subsequent measures. The Japanese Society of School Health; 2003. Chapter III, Management and treatment, p. 55–85

(2) Impact on side effect of steroids

Long-term steroid therapy for children with steroid-resistant and -dependent or frequent-relapsing nephrotic syndrome is known to be associated with risk of loss of bone mineral [45] and obesity [46, 47]. Therefore, adequate exercise is recommended in the remission phase, instead of excessive limitation of exercise. In adult patients, according to index shown in the "Evidence-based practice guideline for the treatment of chronic kidney disease 2009" published by the Japanese Society of Nephrology, patients with stable nephrotic syndrome are recommended to regularly perform mild exercise (5.0–6.0 METs). For lifestyle guidance in children, see the next section.

Obesity is not only the problem as side effect of steroids, but also as one of clinical conditions of metabolic syndrome associated with increased patients with hypertension [48]. Obesity in children migrates to adult obesity at a high rate, and thus it is important to decrease obesity regardless of presence of hypertension. Exercise decreases the obesity, and thereby improves and maintains insulin resistance and hyperlipidemia [49]. In children with obesity and normal renal functions, adequate exercise is recommended.

(3) Exercise guidance in practice

Conventional guidance tended to excessively limit exercise. The Japanese Society of School Health published the "Health classification by the status of nephrotic syndrome" as a guide based on "Health-care Guidance" for renal diseases and the guidance has been used in the clinical settings. However, thinking out of the conventional idea that the children with nephrotic syndrome are different

Table 4 Health classification by the status of nephrotic syndrome

	Every day administration of steroids, proteinuria	Alternate-day administration of steroids, proteinuria	Proteinuria, no edema or hypertension	Chronic disease, hypoalbuminemia and mild edema	Frequent relapse, remission under immunosuppression
A	1	0	0	0	0
B	3	0	5 (B/C 4)	10 (B/C 5)	
C	13 (C/D 1)	4 (C/D 2)	14 (C/D 7)	25 (C/D 7)	2 (C/D 2)
D	4 (D/E 1)	14 (D/E 3)	16 (D/E 2)	9 (D/E 3)	5 (D/E 1)
D/E comment*	14	9	6	5	7
E	15	21	12	4	38
Others	4	5	1	1	2
Total	54	54	54	54	54

"/" indicates that either of the classification may be chosen based on the situation

A at home, *B* classroom activity only, *C* mild exercise, *D* mild to moderate exercise, *E* normal activity

from healthy children, their development should also be considered.

Goto et al. [50] conducted a survey using a questionnaire about exercise limitation for patients with renal diseases targeting the panels of the Japanese Society for Pediatric Nephrology. The five items for nephrotic syndrome are shown in Table 4. In the survey, patients presenting proteinuria had some limitation of exercise ranging B (activities only in classroom) to D (mild to moderate exercise). Patients with maintained remission had the limitation of D at highest, and the selection of limitation was based on the bone mineral density and exercise applying load, an index that the "Health-care Guidance" did not include, was limited. The limitation was much less strict than that of "Guidelines for Life Style and Dietary Therapy for Kidney Diseases" published by the Japanese Society of Nephrology. These results are based on questionnaire survey among 54 panel members of the Japanese Society for Pediatric Nephrology and may be used as an expert opinion.

The "Health-care Guidance" was revised in 2011, in accordance with the survey, as shown in Table 5.

Although not mentioned in the survey, a short-term exercise limitation is commonly performed at the discharge (start of school attendance) in consideration of decrease in muscle strength and cardiopulmonary functions due to stay at the hospital.

Table 5 Revised health classification by the status of nephrotic syndrome

Classification	Status of nephrotic syndrome
A (at home)	Requiring at-home or hospital treatment
B (classroom activity only)	Not achieving stable disease
C (mild exercise)	
D (mild to moderate exercise)	Having proteinuria of (++) or more severe
E (normal activities)	No consideration of fracture with administration of steroids or symptoms

Cited with modifications from In: Urinalysis in school (revised in 2011). The Japanese Society of School Health; 2012. Chapter III, Management and treatment, p. 55–84

Bibliography

1. The Japanese Society of Nephrology. Guideline for life style and dietary therapy for patients with kidney disease [in Japanese]. Jpn J Nephrol. 1997;39:1–37.
2. Gipson DS, Massengill SF, Yao L, Nagaraj S, Smoyer WE, Mahan JD, Wigfall D, Miles P, Powell L, Lin JJ, Trachtman H, Greenbaum LA. Management of childhood onset nephrotic syndrome. Pediatrics. 2009;124:747–57.
3. Niaudet P. Complications of idiopathic nephrotic syndrome in children. In: Basow DS editor. UpToDate. 2013. http://www.uptodate.com/contents/complications-of-idiopathic-nephrotic-syndrome-in-children?source=search_result&search=C+omplicalionso+fid+iopathic+nephrotics+yndrome+inc+hildre&selectedTitle=10~150. Accessed 31 Aug 2014.
4. Editorial Committee on Japanese Guideline for Prevention of Venous Thromboembolism. Japanese guideline for prevention of venous thromboembolism [in Japanese]. Tokyo: Medical Front International; 2004.
5. The Japanese Society of Nephrology. Evidence-based clinical practice guideline for CKD 2009 [in Japanese]. Jpn J Nephrol. 2009;51:934–9.
6. Committee on Revision of "School urinalysis screening." Management and treatment. In: School urinalysis screening: revised in 2011 [in Japanese]. Tokyo: Japanese Society of School Health; 2012. pp. 55–84.

Chapter 4. Side effect of steroids: osteoporosis

Recommendation statements:
1. We suggest that nephrotic syndrome is a risk factor for decreases in bone mineral density and compression fractures. [Recommendation grade C1]
2. We suggest measurement of bone mineral density using dual-energy x-ray absorptiometry (DXA) in patients with nephrotic syndrome. [Recommendation grade C1]
3. There is insufficient evidence on available medical therapies for treatment of pediatric steroid-induced osteoporosis. [No recommendation grade]
4. We suggest the reduction or discontinuation of steroids for the prevention and treatment of pediatric steroid-induced osteoporosis. [Recommendation grade C1]

Explanation

1. Bone complications associated with steroid use

Steroids are commonly used for treatment of pediatric nephrotic syndrome and are known to be associated with a decrease in bone mass by breaking down the equilibrium state between bone resorption and osteogenesis due to following effects: (1) direct effects to both osteoblast and osteoclastic cells, (2) inhibition of calcium absorption via the small intestine, (3) stimulation of calcium elimination from the kidney, and (4) inhibition of the secretion of androgen and estrogen. The decrease in bone mass shows a two-phase clinical course: rapid progression at 6 months following the start of steroid therapy, with a gradual slowing thereafter. A survey of 22846 children with fractures, and on glucocorticoid therapy, reported that the risk of fractures in children receiving 4 or more courses of oral steroids (mean days of course, 6.4 days) was higher (odds ratio 1.32) than that of similarly-aged children with no steroid therapy [51]. This infers that caution to the decrease in bone mineral density and compression fractures is necessary in patients with steroid-sensitive pediatric nephrotic syndrome. These results suggest that shorter treatment time with steroids may be required. Another study, in patients over the age of 4 and with steroid-sensitive pediatric nephrotic syndrome, reported no significant difference in bone density of the lumbar spine region when results were adjusted to the bone area, age, sex, maturity, and race of control subjects [52]. The insight provided by this study is that the decrease in bone mineral density and compression fractures due to steroid therapy, is attributable to the primary disease, and the risk in nephrotic syndrome may be less than other diseases. The study, however, may be biased by the treatment regimen of the steroid therapy (i.e., alternate-day administration). In addition, Freundlich et al. [53] reported that onset of osteoporosis depended on the disease progression of nephrotic syndrome and that steroid therapy caused the osteogenesis and metabolic abnormality. Comprehensively examining these findings, our guideline committee built a consensus and concluded that nephrotic syndrome may be a risk factor for a decrease in bone mineral density and compression fractures. In particular, refractory nephrotic syndrome, which requires treatment with a large volume of steroids, should be closely monitored for osteoporosis.

2. Measurement of bone mineral density

Reyes et al. [54] reported the risk of a compression fracture of the spine in children receiving steroids significantly increased in cases with z-score of less than −1.8, and in such cases, treatment intervention should be considered. However, diagnosis criteria for pediatric osteoporosis have not been established and thus the therapeutic strategy has not yet been determined. This is due, in particular, to bone metabolism in children: the unstable balance between bone resorption and osteogenesis precludes diagnosis of osteoporosis based on bone mineral density. In addition, the cutoff level for lumbar spine bone density fractures was 10 % higher in adults with steroid-induced osteoporosis, compared to those with primary osteoporosis. Patients with steroid-induced osteoporosis can develop more fractures than those patients with primary osteoporosis, regardless of higher bone mineral density, suggesting that steroid therapy may adversely affect bone substance as well as bone mineral density.

Current medical testing incorporates bone mineral density into the diagnosis of young patients. Although dual-energy X-ray absorptiometry (DXA) has become a common measurement method of bone mineral density, it is still difficult to diagnose pediatric steroid-induced osteoporosis and/or to evaluate the risk of fracture for reasons mentioned above. However, DXA enables the observation of decreases in bone mineral density over time in a patient. Since there is no testing method that is superior to DXA for the evaluation of osteoporosis and the risk of fracture, it is preferred to perform routine bone mineral density measurements using DXA. Details such as administration intervals are to be determined and at present should be individually decided based on the status of nephrotic syndrome and change of bone mineral density.

3. Medical therapy

Bisphosphonates have been proven to be effective for the treatment and prevention of steroid-induced osteoporosis in adults. In children, a published report presented significant increases in bone mineral density when treated with bisphosphonates during steroid therapy; however, it did not provide sufficient evidence since the sample size of the study was small [55].

In addition, other side effects have been reported and are as follows: excessive inhibition of bone metabolic turnover, resulting in the suppression of the longitudinal growth of bone, and decreased bone strength due to inhibition of bone remodeling [51]. Use of bisphosphonates requires careful attention and the indication should be applied only to patients with nephrotic syndrome after the period of adolescence, as those patients do not have concern for their growth. Comprehensive consideration for efficacy and safety should also be dictated in these patients. Administration of bisphosphonates to patients with renal impairment is not recommended. For therapeutic strategies for nephrotic syndrome in children after the growth phase, guides from the "The Japanese Guidelines for the Prevention and Treatment of Osteoporosis, 2011" and "Guidelines on the Management and Treatment of Glucocorticoid-Induced Osteoporosis, 2004" should be followed. The package inserts of bisphosphonates describe: "bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of weeks to years" and "should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus." Bisphosphonates should be administered carefully to women in the transitional phase.

Activated vitamin D3 has been reported to have efficacy on the prevention for vertebral body fractures in adults. In children, a randomized, controlled study in patients with pediatric nephrotic syndrome, including relapsing cases, indicated that administration of vitamin D and calcium preparations at the initiation of steroid therapy suppressed the decrease of bone mineral density [56]. However, the study also demonstrated a significant increase in serum and urine calcium levels, suggesting a higher risk for hypercalciuria and urolithiasis. This evidence is insufficient due to the small sample size, and efficacy and safety of vitamin D3 in children have not yet been established. Also not yet established is the efficacy and safety for the use of vitamin K, selective estrogen receptor modulator, and parathyroid hormone.

4. Reduction and discontinuation of steroids

There is no sufficient evidence on medical treatments for steroid-induced osteoporosis in patients with pediatric nephrotic syndrome. Presently, the reduction or discontinuation of steroids is recommended for the treatment of steroid-induced osteoporosis. Immunosuppressants other than steroids should be used as applicable in patients with frequently relapsing or steroid-dependent nephrotic syndrome. Reduction or discontinuation of steroids is also recommended for the prevention of steroid-induced osteoporosis.

Bibliography

1. Manolagas SC, Weinstein RS. New developments in the pathogenesis and treatment of steroid-induced osteoporosis. J Bone Miner Res. 1999;14:1061–6.
2. Leonard MB. Glucocorticoid-induced osteoporosis in children: impact of the underlying disease. Pediatrics. 2007;119 (Suppl 2): S166–74.
3. Nawata H, Soen S, Takayanagi R, Tanaka I, Takaoka K, Fukunaga M, Matsumoto T, Suzuki Y, Tanaka H, Fujiwara S, Miki T, Sagawa A, Nishizawa Y, Seino Y, Subcommittee to Study Diagnostic Criteria for Glucocorticoid-Induced Osteoporosis. Guidelines on the management and treatment of glucocorticoid-induced osteoporosis of the Japanese Society for Bone and Mineral Research (2004). J Bone Miner Metab. 2005;23:105–9.
4. Bachrach LK, Ward LM. Clinical review 1: Bisphosphonate use in childhood osteoporosis. J Clin Endocrinol Metab. 2009;94:400–9.
5. Committee for Developing Guidelines for Prevention and Treatment of Osteoporosis. Japanese 2011 guidelines for prevention and treatment of osteoporosis [in Japanese]. Tokyo: Life Science Publishing; 2011.
6. The Japanese Society for Bone and Mineral Reserch. Japanese 2004 guidelines for prevention and treatment of osteoporosis [in Japanese]. Tokyo: Life Science Publishing; 2004.

Chapter 5. Side effect of steroids: growth deficiency

Recommendation statements:
1. Alternate-day administration of steroids reduces the risk of growth deficiency (short stature) and thus we recommend it as applicable. [Recommendation grade B]

Explanation

Growth deficiency in patients with pediatric nephrotic syndrome is one of the most important side effects of long-term use of steroids. Height growth is affected by endochondral bone growth in the direction of the long axis. Steroids directly suppress chondrocyte maturation on the epiphyseal growth plate, which inhibits the endochondral bone growth, leading to growth deficiency. Steroids also inhibit the secretion of growth hormone and activity of insulin-like growth factor 1 (IGF-1) at the epiphyseal growth plate, causing growth deficiency.

Daily administration of steroids has been involved in inducing growth deficiency. It has been reported in patients who received daily administration of steroids for renal disease or kidney transplantation, an improvement in growth deficiency by switching to alternate-day administration [57, 58]. Although focusing primarily on steroid therapy following kidney transplantation, these studies have demonstrated the efficacy of alternate-day administration of steroids for relief of growth deficiency [58–61]. Since the 1970s,

alternate-day administration of steroids has been carefully studied as a useful method for alleviating several complications of steroid use, including growth deficiency in pediatric renal diseases [62]. However, except for growth deficiency, any other usefulness has not yet been clearly established. Although an improvement of growth deficiency has not been observed in all children treated with alternate-day administration of steroids, a significant improvement in growth deficiency in children treated with alternate-day administration of steroids after kidney transplantation has been reported, as compared to those treated with a daily administration of steroids [58]. Another published report suggests that alternate-day administration of steroids prevents patients with diseases other than renal disease (i.e. juvenile idiopathic arthritis) from any onset of growth deficiency [63]. Therefore, it is considered that alternate-day administration of steroids is beneficial for the improvement of growth deficiency.

With respect to dosage amount that may lead to growth deficiency in patients with pediatric nephrotic syndrome, one report concluded that a 6-month administration course of prednisolone at, or more than 0.75 mg/kg/day (converted dosage per day), was associated with the development of growth deficiency [64]. Another study estimated the yearly growth rates of patients with growth deficiencies following the administration of prednisolone over 3 years for asthma or pediatric nephrotic syndrome; this study showed that, in patients who continued treatment with prednisolone at or more than 0.35 mg/kg/day, growth hormone treatment did not improve the growth rate [65]. Steroid therapy, even at low doses, induces growth deficiency in a dose-dependent manner based on the duration of treatment. Thus, in patients with pediatric nephrotic syndrome who require long-term steroid therapy, steroid dosage should be reduced or discontinued as soon as possible by using immunosuppressants such as cyclosporine to avoid growth deficiency [59].

Alternate-day administration of steroids is effective in alleviating growth deficiencies complications from steroid therapy in patients with pediatric nephrotic syndrome. Most major guidelines, including KDIGO guidelines and Cochrane reviews, have espoused the alternate-day administration of steroids as the basic therapeutic strategy, and, in patients with renal diseases, the dosage of steroids after induction of remission should be reduced to alternate-day administration.

Bibliography

1. Avioli LV. Glucocorticoid effects on statural growth. Br J Rheumatol. 1993;32(Suppl 2):27–30.

Chapter 6. Side effect of steroids: ophthalmologic complications

Recommendation statements:
1. We suggest an ophthalmologic examination early on after the commencement of steroid therapy to lower the risk of steroid-induced glaucoma. [Recommendation grade C1]
2. We suggest regular ophthalmologic examinations during steroid therapy to detect steroid-induced cataract formation in the early phases and to lower the risk of any cataract progression. [Recommendation grade C1]

Explanation

Major ophthalmologic complications with steroid therapy include glaucoma and cataract formation. It has not been demonstrated that early ophthalmologic examinations can significantly lower the risk of glaucoma and cataracts. Previous studies reported that 10–56 % of children with renal disease, and treated with steroids, developed cataracts [66–73]. With respect to glaucoma, some studies found no increase in intraocular pressure; [72, 73] however, other studies reported an increase of intraocular pressure in 20 % of the patients [71, 74]. This variation in results is attributable to different timing of examination.

1. Glaucoma

Steroid-induced glaucoma develops as a result of raised intraocular pressure due to steroid therapy and, when left untreated, leads to impairment of optic nerves and visual (field) disturbances. At the beginning of high-dose steroid therapy, intraocular pressure may be elevated in the early phase, and in most cases, then decreases as the steroid therapy is reduced or discontinued [71]. However, one study reported a case with ocular hypertension that had elevated intraocular pressure after cessation of steroid therapy, and the patient had to undergo a trabeculectomy. This result therefore suggests the need to be cautious during and following steroid treatment [71]. Ocular hypertension can be improved by ophthalmic solutions with early detection and avoidance of continuous ocular hypertension can halt any progression of optic nerve disorders. Early ophthalmologic examinations are preferred.

There is no consensus on adequate timing for ophthalmologic examinations following steroid therapy. In general, it is preferable to visit an ophthalmologist during the time when a stable general condition has been achieved and

with an improvement in edema by the steroid therapy. In patients with relapsed nephrotic syndrome and a history of steroid-induced ocular hypertension specifically, where patients require high-dose administration such as steroid pulse therapy, then early examinations, including intraocular pressure measurements, are necessary. Patients developing symptoms of glaucoma, such as ocular pain, headaches, and decreased vision, should be referred to an ophthalmologist as soon as possible.

2. Cataracts

Steroid-induced cataracts often present as posterior subcapsular cataracts. The onset rate of posterior subcapsular cataracts does not appear to have a significant association with dose volume or steroid therapy, [66–69] suggesting that steroid sensitivity may be responsible. [69] Kobayashi et al. and Hayasaka et al. [70, 71] reported that dose volume and steroid therapy duration are both associated with the rate of formation of cataracts. In general, use of prednisolone at or more than 10 mg/day or long-term treatment (more than 1 year) is accompanied by an increased onset of cataracts. Multiple ophthalmic solutions for cataracts are available, but the number of randomized, controlled studies are limited; accumulation of further evidence is warranted. Patients receiving long-term, high-dose therapy may require surgery for reduced visual acuity due to opacity of the lens. Although there is no obvious rationale for recommending early ophthalmologic examinations after steroid therapy, regular ophthalmologic examinations enable physicians to assess any complications as well as any potential progression of cataracts at the early stage, where the usage of steroids and immunosuppressants would be considered.

Bibliography

1. Committee for Developing Guidelines for Glaucoma of the Japan Glaucoma Society. The Japan Glaucoma Society Guidelines for Glaucoma (3rd Edition) [in Japanese]. In: Japanese Ophthalmological Society. 2011. http://www.nichigan.or.jp/member/guideline/glaucoma3.jsp. Accessed 31 Aug 2014.
2. Saaga KG. Major side effects of systemic glucocorticoids. In: Basow DS editor. UpToDate. 2014. http://www.uptodate.com/contents/major-side-effects-of-systemic-glucocorticoids Accessed 31 Aug 2014.

Chapter 7. Immunization and infection control

Recommendation statements:

1. Patients with nephrotic syndrome are considered immunocompromised. Since acquired infection may lead to severe disease in such patients, we therefore suggest immunizations be performed, when applicable. [Recommendation grade C1]
2. We suggest that vaccination with inactivated vaccines be considered even during steroid and immunosuppressant treatment. [Recommendation grade C1]
3. In general, we suggest live attenuated vaccines not be used in patients during steroid or immunosuppressant treatment. [Recommendation grade C2] However, the decision to use attenuated vaccines may be determined on a case-by-case basis and according to the condition of the patient and epidemic. [Recommendation grade C1]
4. When any family member of the patient does not have a history or has not been vaccinated against the prevalent infection, we suggest proactive vaccination to the family member. [Recommendation grade C1]
5. In cases where the household has been in close contact with varicella, we recommend prophylaxis with antiviral drugs (acyclovir or valaciclovir). [Recommendation grade B]
6. In cases of long-term, high-dose therapy with steroids or immunosuppressants, we suggest use of prophylactic antibiotics be carefully considered by a specialist. [Recommendation grade C1]

Explanation

1. Vaccination of patients with nephrotic syndrome

Patients with nephrotic syndrome are immunosuppressed due to severe hypoproteinemia, including immunoglobulin, and thus are susceptible to infections, which can easily become severe [75–79]. Annual mortality rates for patients with pediatric nephrotic syndrome were as high as 20 % before steroids became indicated for the disease. Most of the cases died from bacterial infections, which appeared to

develop at the time of recurrence and were further complicated with severe hypoalbuminemia or edema. The dominant type of nephrotic syndrome is steroid-sensitive, minimal change nephrotic syndrome. Since steroids came into use for the treatment of the disease, hypoalbuminemia and edema can be immediately controlled and the mortality rate from infection has dramatically decreased. However, in cases with steroid-dependent or -resistant disease, long-term treatment with steroids cannot be avoided, and immunosuppressants are then used to circumvent any side effects of steroid treatment. Such patients are still considered immunocompromised and at high risk of developing severe infections. Therefore, infection control in patients with nephrotic syndrome is an important management target and performing vaccinations is recommended, when applicable [75–79].

In Japan, vaccinations administered to immunodeficient individuals, including patients with nephrotic syndrome, were conventionally withheld for the following possible reasons: lower antibody acquisition rate and acquired antibody value when compared against healthy children, shorter duration of acquired antibody, and risk of infection by the activation of any given attenuated virus.

Accumulating knowledge based on domestic and international studies suggests that, in patients with nephrotic syndrome not using steroids or immunosuppressants, routine vaccinations that are legally required (DPT, Hib, pneumococcal, measles, rubella, and Japanese encephalitis vaccines) and commonly performed (varicella, mumps, influenza, and hepatitis B vaccines) are effective and can be safely provided [79–85].

Note that for recently approved vaccines of human papillomavirus, inactivated poliovirus, and rotavirus, the efficacy and safety in immunodeficient patients, including those with nephrotic syndrome, have not been fully established, even worldwide.

Information, such as the necessity of vaccinations, their timing, and their availability according to the treatment and type of vaccine, is unlikely to be conveyed to the patients and their families. For example, the partial amendment to the Preventive Vaccination Act in January 2013 made pediatric nephrotic syndrome and focal glomerular sclerosis applicable to these preferential measures, which permits vaccination within 2 years, after the dissolution of excluding factors for vaccination to certify as legally required routine vaccinations. Providing the families of patients with full access to this information about such vaccinations is required.

2. Inactivated vaccinations to patients with nephrotic syndrome

Accumulating domestic and international evidence, from small studies and foreign guidelines that incorporate such data, suggests that, in patients with nephrotic syndrome not using steroids or immunosuppressants, inactivated vaccinations are effective and can be safely provided.

Pneumococcus is the most common cause of bacterial infections observed in patients with nephrotic syndrome. The predominance has not been changed even after the start of steroid usage. Pneumococcus causes peritonitis and sepsis, which are the major causes of death in patients with the disease [76–78]. Immunocompromised patients are susceptible to pandemic influenza, which can easily become severe. In guidelines published by the Centers for Disease Control and Prevention and KDIGO, the 7- or 23-valent pneumococcal vaccines and yearly influenza vaccine are recommended. [79–84] The efficacy of 7- and 23-valent pneumococcal vaccines has been previously reported in patients with nephrotic syndrome. Vaccination using the 23-valent pneumococcal vaccine in patients treated with high-dose prednisolone (60 mg/m^2/day) has been reported to have comparable efficacy to that in patients treated with low-dose, alternate-day steroid administration [80, 81]. In Japan, vaccination of both 7- and 23-valent pneumococcal vaccines is approved. The 7-valent pneumococcal vaccine with an adjuvant effect is indicated in children between the ages of 2 months and 9 years, and commonly, three additional vaccinations have been completed by the time they are 15 months old. The indication of the 23-valent vaccine, a polysaccharide vaccine, is in children greater than 2 years-old. The duration of effect is shorter than that of the 7-valent vaccine, which requires a booster vaccination after 5 years in immunocompromised patients, including the elderly. These vaccines thus require differential use in accordance to the age of the patients. Note that the indication of the 23-valent vaccine is for immunocompromised patients, including those with nephrotic syndrome and chronic kidney disease; however, only splenectomized patients are covered by health insurance in Japan.

Our guidelines do not include vaccination with pneumococcal vaccines, based on the current situation in Japan. However, in patients with nephrotic syndrome who are at high risk for severe pneumococcal infections, including peritonitis and sepsis, vaccination with pneumococcal vaccines is recommended as early as possible, as stated in foreign guidelines [79–82].

3. Vaccination using live attenuated vaccines to patients with nephrotic syndrome

The safety and efficacy of vaccination using live attenuated vaccines (BCG, measles, varicella, rubella, mumps, and rotavirus) in immunocompromised patients has not been established. Immunocompromised patients using steroids or immunosuppressants have been known to be susceptible to varicella and are at risk for increased severity [76]. Guidelines published in the United States and Europe recommend vaccination based on reports regarding the safety and efficacy of the vaccination of varicella in patients treated with low-dose steroids [85]. Patients during

treatment with high-dose steroids (converted dose in prednisolone, >2 mg/kg/day; or in children weighing ≥10 kg, ≥20 mg/day) should not be vaccinated.

For the safety and efficacy of vaccination using live attenuated vaccines in patients during treatment with immunosuppressants, definitive evidence has not been established. Immunosuppressants available in Japan are contraindicated to the use of live attenuated vaccines, as stated in the package inserts. The vaccination should be avoided until 3 months following the discontinuation of immunosuppressants. In cases where the benefit of the vaccination is considered to outweigh the disadvantages, in terms of the condition of the patient and pandemic (for example, patients with progressive renal dysfunction due to steroid-resistant nephrotic syndrome that may undergo transplantation or dialysis), vaccination using live attenuated vaccines may then be considered.

4. Prevention of intra-familial infection

Close contact with family members, specifically contact with infected siblings, is associated with the highest risk for transmission of infection in children. In cases where there is a family member without any history of vaccination and living together with a patient treated with steroids or immunosuppressants, we recommend that the family member be vaccinated, when applicable. Specifically, for varicella [76, 85] and influenza [83], vaccinations should be proactively administered.

5. Prophylaxis in cases of close contact to varicella

In cases where patients with lowered immunity come into close contact with varicella, or where varicella is within the household, guidelines in the United States recommend vaccination with varicella-zoster immunoglobulin. This vaccination, however, is not implemented in Japan. Prophylactic use of acyclovir has been reported to be effective [86]. In cases where children at high risk for severe infection have been in close contact with varicella patients, prophylaxis using acyclovir of 80 mg/kg/day, divided into four doses, or valacyclovir of 60 mg/kg/day, divided into three dose for 7 days and 7–10 days after the contact, is recommended, according to a report by the American Academy of Pediatrics [86].

6. Other infection control strategies

Immunosuppressants such as cyclophosphamide and cyclosporine have been increasingly used in patients with refractory (steroid-dependent and -resistant) nephrotic syndrome. There are no published studies directly targeting patients with nephrotic syndrome under treatment with immunosuppressants and thus the prevalence of infection due to use of immunosuppressants in patients with nephrotic syndrome has not yet been determined. There is also not enough sufficient evidence concerning the efficacy of immunoglobulin or antibiotics as prophylaxis in patients with severe hypoimmunoglobulinemia or immunosuppression. However, in studies that have been performed on collagen diseases and organ transplantations, treatment with immunosuppressants or high-dose steroids is associated with the frequent occurrence of severe complications, including Pneumocystis pneumonia. In cases of prolonged nephrotic syndrome and an immunosuppressed state, prophylactic use of immunoglobulin or antibiotics (i.e., sulfamethoxazole/trimethoprim) may be considered under the consultation of a specialist. Use of immunosuppressants requires considerable caution as excessive immunosuppression by overdose can occur, and proper administration by a specialist is preferred.

Bibliography

1. Kidney Disease Improving Global Outcomes: Steroid-sensitive nephrotic syndrome in children. Kidney Int Suppl 2012;2:163–71.
2. Committee on Infectious Diseases. Immunization in special clinical circumstance. In: Red Book. Pickering LK, Meissner HC, Long SS, Kimberlin DW, Bernstein HH, Baker CJ, editors. Red book. Elk Grove Village: American Academy of Pediatrics; 2012. pp. 69–109.
3. National Center for Immunization and Respiratory Diseases. General recommendations on immunization—recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2011;60(2):1–64.
4. 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;59:1–18.
5. Committee on Infectious Diseases. Va ricela-Zoster lnfections, In: Red Book. Pickering LK, Meissner HC, Long SS, Kimberlin DW, Bernstein HH, Baker CJ, editors. Red book. Elk Grove Village: American Academy of Pediatrics; 2012. pp. 774–89.
6. Thomas CF Jr, Limper AH. Pneumocystis pneumonia. N Engl J Med. 2004;350:2487–98.
7. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant. 2009;9 Suppl 3:S1–155.

Chapter 8. Transition

Recommendation statements:
1. We suggest that supportive programs be implemented in cooperation with other departments from the early phases of nephrotic syndrome, in consideration of the childhood to adult transition. [Recommendation grade C1]

Explanation

1. Implementation of supportive programs of transition

(1) Rate of transition

Nephrotic syndrome appears to increase during the transition from childhood to adult. When alkylating agents, such as cyclophosphamide, were commonly used as immunosuppressants in patients with frequently-relapsing and steroid-dependent nephrotic syndrome, the rate of transition of idiopathic nephrotic syndrome developed in childhood into adulthood (at or more than the age of 18) was 5–10 % [87, 88]. Recently, with increasing use of calcineurin inhibitors such as cyclosporine, the transition rate has increased to 33–42.2 % [89, 90]. As mentioned in section 7 in part 1 of this guideline, consideration for the childhood-adult transition is needed at the onset of nephrotic syndrome.

(2) Support to transition

Transition is defined as "a process that involves purposeful, planned efforts to prepare the pediatric patient to move from caregiver-directed care to disease self-management in the adult unit." Supportive programs have recently been established to achieve this transition. The programs can be divided into six sections as follows: self-support, independent health care, sexual management, psychological support, educational/occupational plan, and health and lifestyle. Systematic support in these sections enable a patient to fit into the responsibilities of adulthood regardless of the disease and to transition without any problems. Implementation of the supportive programs cannot be performed only by physicians and requires cooperation from the paramedical staff. However, improvements to the current environment are still needed to facilitate such cooperation. The number of institutions that have implemented supportive programs is limited and thus educational activity to healthcare providers should be promoted. A consensus statement by the International Society of Nephrology (ISN) and the International Pediatric Nephrology Association (IPNA) was published in 2011, proposing the TRxANSITION Scale which consists of 10 checkpoints. The statement put forward the importance of an individualized process that also allows for the conditions of the patients, family, and local custom.

Japan is behind other western countries in both research and practice of the childhood-adult transition. Programs implemented in the United States and Europe may be referred to; however, the establishment of programs adapted to the medical context and characteristics in Japan is considered important. The creation of an individualized support system is currently in progress.

(3) Economic burden after transition

An economic challenge with the childhood-adult transition is that the clinical course may worsen due to refraining from the use of expensive drugs, since the medical aid program for chronic pediatric diseases of specified categories in Japan is terminated at the age of 20 [91].

Bibliography

1. Blum RW, Garell D, Hodgman CH, Jorissen TW, Okinow NA, Orr DP, Slap GB. Transition from child-centered to adult health-care systems for adolescents with chronic conditions. A position paper of the Society for Adolescent Medicine. J Adolesc Health. 1993;14:570–6.
2. Adolescent transitional care guidance for nursing staff. In: Royal College of Nursing. 2004. http://www.rcn.org.uk/__data/assets/pdf_file/0011/78617/004510.pdf. Accessed 31 Aug 2014.
3. Watson AR, Harden P, Ferris M, Kerr PG, Mahan J, Ramzy MF. Transition from pediatric to adult renal services: a consensus statement by the International Society of Nephrology (ISN) and the International Pediatric Nephrology Association (IPNA). Pediatr Nephrol. 2011;26:1753–7.
4. Watson AR, Harden PN, Ferris ME, Kerr PG, Mahan JD, Ramzy MF, International Society of Nephrology; International Pediatric Nephrology Association. Transition from pediatric to adult renal services: a consensus statement by the International Society of Nephrology (ISN) and the International Pediatric Nephrology Association (IPNA). Kidney Int. 2011;80:704–7.
5. Adolescent transitional care manual for nurses and health care workers [in Japanese]. Tokyo: International Nursing Development, Graduate School of Health Care Sciences, Tokyo Medical and Dental University. 2012.

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References

1. Ishikura K, Matsumoto S, Sako M, Tsuruga K, Nakanishi K, Kamei K, Saito H, Fujinaga S, Hamasaki Y, Chikamoto H, Ohtsuka Y, Komatsu Y, Ohta T, Nagai T, Kaito H, Kondo S, Ikezumi Y, Tanaka S, Kaku Y, Iijima K. Clinical practice guideline for pediatric idiopathic nephrotic syndrome 2013: medical therapy, clinical and experimental nephrology. doi:10.1007/s10157-014-1030-x.
2. Gipson DS, Massengill SF, Yao L, Nagaraj S, Smoyer WE, Mahan JD, Wigfall D, Miles P, Powell L, Lin JJ, Trachtman H, Greenbaum LA. Management of childhood onset nephrotic syndrome. Pediatrics. 2009;124(2):747–57.
3. Indian Pediatric Nephrology Group, Indian Academy of Pediatrics, Bagga A, Ali U, Banerjee S, Kanitkar M, Phadke KD, Senguttuvan P, Sethi S, Shah M. Management of steroid sensitive nephrotic syndrome: revised guidelines. Indian Pediatr. 2008;45(3):203–14.
4. Vasudevan A, Mantan M, Bagga A. Management of edema in nephrotic syndrome. Indian Pediatr. 2004;41(8):787–95.
5. Park SJ, Shin JI. Complications of nephrotic syndrome. Korean J Pediatr. 2011;54(8):322–8.
6. Doucet A, Favre G, Deschênes G. Molecular mechanism of edema formation in nephrotic syndrome: therapeutic implications. Pediatr Nephrol. 2007;22(12):1983–90.
7. Siddall EC, Radhakrishnan J. The pathophysiology of edema formation in the nephrotic syndrome. Kidney Int. 2012;82(6):635–42.
8. Avner ED, Harmon WE, Niaudet P, Yoshikawa N, editors. Pediatric nephrology. 6th ed. Baltimore: Lippincott Williams and Wilkins; 2009.
9. Vande Walle JG, Donckerwolcke RA, van Isselt JW, Derkx FH, Joles JA, Koomans HA. Volume regulation in children with early relapse of minimal-change nephrosis with or without hypovolaemic symptoms. Lancet. 1995;15:148–52.
10. Wang SJ, Tsau YK, Lu FL, Chen CH. Hypovolemia and hypovolemic shock in children with nephrotic syndrome. Acta Paediatr Taiwan. 2000;41:179–83.
11. Vande Walle JG, Donckerwolcke RA, Koomans HA. Pathophysiology of edema formation in children with nephrotic syndrome not due to minimal change disease. J Am Soc Nephrol. 1999;10:323–31.
12. Van de Walle JG, Donckerwolcke RA, Greidanus TB, Joles JA, Koomans HA. Renal sodium handling in children with nephrotic relapse: relation to hypovolaemic symptoms. Nephrol Dial Transplant. 1996;11:2202–8.
13. Reid CJ, Marsh MJ, Murdoch IM, Clark G. Nephrotic syndrome in childhood complicated by life threatening pulmonary oedema. BMJ. 1996;312:36–8.
14. Haws RM, Baum M. Efficacy of albumin and diuretic therapy in children with nephrotic syndrome. Pediatrics. 1993;91:1142–6.
15. Agarwal N, Phadke KD, Garg I, Alexander P. Acute renal failure in children with idiopathic nephrotic syndrome. Pediatr Nephrol. 2003;18:1289–92.
16. Loghman-Adham M, Siegler RL, Pysher TJ. Acute renal failure in idiopathic nephrotic syndrome. Clin Nephrol. 1997;47:76–80.
17. Sakarcan A, Timmons C, Seikaly MG. Reversible idiopathic acute renal failure in children with primary nephrotic syndrome. J Pediatr. 1994;125(5 Pt 1):723–7.
18. Gurgoze MK, Gunduz Z, Poyrazoglu MH, Dursun I, Uzum K, Dusunsel R. Role of sodium during formation of edema in children with nephrotic syndrome. Pediatr Int. 2011;53:50–6.
19. Dönmez O, Mir S, Ozyürek R, Cura A, Kabasakal C. Inferior vena cava indices determine volume load in minimal lesion nephrotic syndrome. Pediatr Nephrol. 2001;16:251–5.
20. Tabel Y, Mungan I, Karakurt C, Kocak G, Gungor S. Is edema in minimal change disease of childhood really hypovolemic? Int Urol Nephrol. 2008;40:757–61.
21. Donckerwolcke RA, France A, Raes A, Vande Walle J. Distal nephron sodium–potassium exchange in children with nephrotic syndrome. Clin Nephrol. 2003;59:259–66.
22. Kapur G, Valentini RP, Imam AA, Jain A, Mattoo TK. Serum osmolal gap in patients with idiopathic nephrotic syndrome and severe edema. Pediatrics. 2007;119(6):e1404–7.
23. Bozzetto S, Piccoli A, Montini G. Bioelectrical impedance vector analysis to evaluate relative hydration status. Pediatr Nephrol. 2010;25:329–34.
24. van der Vorst MM, Kist JE, van der Heijden AJ, Burggraaf J. Diuretics in pediatrics: current knowledge and future prospects. Paediatr Drugs. 2006;8(4):245–64.
25. Eades SK, Christensen ML. The clinical pharmacology of loop diuretics in the pediatric patient. Pediatr Nephrol. 1998;12(7):603–16.
26. Prandota J. Pharmacokinetics of furosemide urinary elimination by nephrotic children. Pediatr Res. 1983;17(2):141–7.
27. Brater DC. Diuretic therapy. N Engl J Med. 1998;339(6):387–95.
28. Garin EH. A comparison of combinations of diuretics in nephrotic edema. Am J Dis Child. 1987;141:769–71.
29. Kapur G, Valentini RP, Imam AA, Mattoo TK. Treatment of severe edema in children with nephrotic syndrome with diuretics alone—a prospective study. Clin J Am Soc Nephrol. 2009;4:907–13.
30. Dharmaraj R, Hari P, Bagga A. Randomized cross-over trial comparing albumin and frusemide infusions in nephrotic syndrome. Pediatr Nephrol. 2009;24:775–82.
31. Lewis MA, Awan A. Mannitol and frusemide in the treatment of diuretic resistant oedema in nephrotic syndrome. Arch Dis Child. 1999;80:184–5.
32. Kanzaki M, Wada J, Kikumoto Y, Akagi S, Nakao K, Sugiyama H, Makino H. The therapeutic potential of synthetic human atrial natriuretic peptide in nephrotic syndrome: a randomized controlled trial. Int J Nephrol Renovasc Dis. 2012;5:91–6.
33. Bircan Z, Kervancioğlu M, Katar S, Vitrinel A. Does albumin and furosemide therapy affect plasma volume in nephrotic children? Pediatr Nephrol. 2001;16:497–9.
34. Fauchald P, Noddeland H, Norseth J. An evaluation of ultrafiltration as treatment of diuretic-resistant oedema in nephrotic syndrome. Acta Med Scand. 1985;217:127–31.
35. Kaysen GA, Gambertoglio J, Jimenez I, Jones H, Hutchison FN. Effect of dietary protein intake on albumin homeostasis in nephrotic patients. Kidney Int. 1986;29:572–7.
36. Rosenberg ME, Swanson JE, Thomas BL, Hostetter TH. Glomerular and hormonal responses to dietary protein intake in human renal disease. Am J Physiol 1987;253 F1083–F1090.
37. Poortmans JR, Vanderstraeten J. Kidney function during exercise in healthy and diseased humans. An update. Sports Med. 1994;18:419–37.
38. Nagasaka Y, Yogi S, Taguchi H, Yoshida Y, Fujiwara Y. Participation to swimming lessons and relapse of nephrotic syndrome [in Japanese]. J Jpn Pediatr Soc. 1986;90:2737–41.
39. Nagasaka Y. The effect of swimming on renal function in children with renal disease [in Japanese]. Jpn J Nephrol. 1986;28:1465–70.
40. Miura H, Fukui H, Hayano K, Otsuka Y, Hattori S. A case of minimal change nephrotic syndrome associated with acute renal failure after excessive exercise. Nihon Jinzo Gakkai Shi. 1993;35:387–91.
41. Kayali F, Najjar R, Aswad F, Matta F, Stein PD. Venous thromboembolism in patients hospitalized with nephrotic syndrome. Am J Med. 2008;121(3):226–30.

42. Hoyer PF, Gonda S, Barthels M, Krohn HP, Brodehl J. Thromboembolic complications in children with nephrotic syndrome. Risk and incidence. Acta Paediatr Scand. 1986;75:804–10.
43. Kerlin BA, Blatt NB, Fuh B, Zhao S, Lehman A, Blanchong C, Mahan JD, Smoyer WE. Epidemiology and risk factors for thromboembolic complications of childhood nephrotic syndrome: a Midwest Pediatric Nephrology Consortium (MWPNC) Study. J Pediatr. 2009;155:105–10.
44. Lilova MI, Velkovski IG, Topalov IB. Thromboembolic complications in children with nephrotic syndrome in Bulgaria (1974–1996). Pediatr Nephrol. 2000;15:74–8.
45. Hegarty J, Mughal MZ, Adams J, Webb NJ. Reduced bone mineral density in adults treated with high-dose corticosteroids for childhood nephrotic syndrome. Kidney Int. 2005;68:2304–9.
46. Foster BJ, Shults J, Zemel BS, Leonard MB. Risk factors for glucocorticoid-induced obesity in children with steroid-sensitive nephrotic syndrome. Pediatr Nephrol. 2006;21:973–80.
47. Merritt RJ, Hack SL, Kalsch M, Olson D. Corticosteroid therapy-induced obesity in children. Clin Pediatr (Phila). 1986;25:149–52.
48. Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, Allen K, Lopes M, Savoye M, Morrison J, Sherwin RS, Caprio S. Obesity and the metabolic syndrome in children and adolescents. N Engl J Med. 2004;350:2362–74.
49. Savoye M, Shaw M, Dziura J, Tamborlane WV, Rose P, Guandalini C, Goldberg-Gell R, Burgert TS, Cali AM, Weiss R, Caprio S. Effects of a weight management program on body composition and metabolic parameters in overweight children: a randomized controlled trial. JAMA. 2007;297:2697–704.
50. Goto M, Ninomiya M, Uemura O, Matsuyama K, Ito Y, Hataya H, Ito S, Yamakawa S, Ishikawa T, Honda M. A questionnaire survey on exercise limitation in children with kidney disease [in Japanese]. Jpn J Pediatr Nephrol. 2012;25(6):17.
51. van Staa TP, Cooper C, Leufkens HG, Bishop N. Children and the risk of fractures caused by oral corticosteroids. J Bone Miner Res. 2003;18(5):913–8.
52. Leonard MB, Feldman HI, Shults J, Zemel BS, Foster BJ, Stallings VA. Long-term, high-dose glucocorticoids and bone mineral content in childhood glucocorticoid-sensitive nephrotic syndrome. N Engl J Med. 2004;351:868–75.
53. Freundlich M, Jofe M, Goodman WG, Salusky IB. Bone histology in steroid-treated children with non-azotemic nephrotic syndrome. Pediatr Nephrol. 2004;19:400–7.
54. Reyes ML, Hernández MI, King A, Vinet AM, Vogel A, Lagomarsino E, Mericq MV, Méndez C, Gederlini A, Talesnik E. Corticosteroid-induced osteoporosis in children: outcome after two-year follow-up, risk factors, densitometric predictive cut-off values for vertebral fractures. Clin Exp Rheumatol. 2007;25:329–35.
55. Rudge S, Hailwood S, Horne A, Lucas J, Wu F, Cundy T. Effects of once-weekly oral alendronate on bone in children on glucocorticoid treatment. Rheumatology (Oxford). 2005;44(6):813–8.
56. Bak M, Serdaroglu E, Guclu R. Prophylactic calcium and vitamin D treatments in steroid-treated children with nephrotic syndrome. Pediatr Nephrol. 2006;21:350–4.
57. Kaiser BA, Polinsky MS, Palmer JA, Dunn S, Mochon M, Flynn JT, Baluarte HJ. Growth after conversion to alternate-day corticosteroids in children with renal transplants: a single-center study. Pediatr Nephrol. 1994;8:320–5.
58. Broyer M, Guest G, Gagnadoux MF. Growth rate in children receiving alternate-day corticosteroid treatment after kidney transplantation. J Pediatr. 1992;120:721–5.
59. Guest G, Broyer M. Growth after renal transplantation: correlation with immunosuppressive therapy. Pediatr Nephrol. 1991;5:143–6.
60. Hokken-Koelega AC, Van Zaal MA, de Ridder MA, Wolff ED, De Jong MC, Donckerwolcke RA, De Muinck Keizer-Schrama SM, Drop SL. Growth after renal transplantation in prepubertal children: impact of various treatment modalities. Pediatr Res. 1994;35:367–71.
61. Jabs K, Sullivan EK, Avner ED, Harmon WE. 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;61:31.
62. Yamashita F, Funatsu T, Nagayama K, Arihiro H, Anan S. Evaluation of alternate-day steroid therapy for nephrotic syndrome in childhood by cross-over study. Kurume Med J. 1971;18:153–60.
63. Kimura Y, Fieldston E, Devries-Vandervlugt B, Li S, Imundo L. High dose, alternate day corticosteroids for systemic onset juvenile rheumatoid arthritis. J Rheumatol. 2000;27:2018–24.
64. Simmonds J, Trompeter R, Tullus K. Long-term steroid treatment and growth: a study in steroid-dependent nephrotic syndrome. Arch Dis Child. 2010;95:146–9.
65. Rivkees SA, Danon M, Herrin J. Prednisone dose limitation of growth hormone treatment of steroid-induced growth failure. J Pediatr. 1994;125:322–5.
66. Bachmann HJ, Schildberg P, Olbing H, Krämer D, Waubke T. Cortisone cataract in children with nephrotic syndrome. Eur J Pediatr. 1977;124:277–83.
67. Brocklebank JT, Harcourt RB, Meadow SR. Corticosteroid-induced cataracts in idiopathic nephrotic syndrome. Arch Dis Child. 1982;57:30–4.
68. Forman AR, Loreto JA, Tina LU. Reversibility of corticosteroid-associated cataracts in children with the nephrotic syndrome. Am J Ophthalmol. 1977;84:75–8.
69. Limaye SR, Pillai S, Tina LU. Relationship of steroid dose to degree of posterior subcapsular cataracts in nephrotic syndrome. Ann Ophthalmol. 1988;20:225–7.
70. Kobayashi Y, Akaishi K, Nishio T, Kobayashi Y, Kimura Y. Posterior subcapsular cataract in nephrotic children receiving steroid therapy. Am J Dis Child. 1974;128:671–3.
71. Hayasaka Y, Hayasaka S, Matsukura H. Ocular findings in Japanese children with nephrotic syndrome receiving prolonged corticosteroid therapy. Ophthalmologica. 2006;220:181–5.
72. Kaye LD, Kalenak JW, Price RL, Cunningham R. Ocular implications of long-term prednisone therapy in children. J Pediatr Ophthalmol Strabismus. 1993;30:142–4.
73. Ng JS, Wong W, Law RW, Hui J, Wong EN, Lam DS. Ocular complications of paediatric patients with nephrotic syndrome. Clin Exp Ophthalmol. 2001;29:239–43.
74. Chen CH, Chen CM. Lee PP. The effect of betamethasone on intraocular pressure in nephrotic children. Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi. 1994;35:197–201.
75. Alwadhi RK, Mathew JL, Rath B. Clinical profile of children with nephrotic syndrome not on glucorticoid therapy, but presenting with infection. J Paediatr Child Health. 2004;40:28–32.
76. Dowell SF, Bresee JS. Severe varicella associated with steroid use. Pediatrics. 1993;92:223–8.
77. Uncu N, Bülbül M, Yildiz N, Noyan A, Koşan C, Kavukçu S, Calişkan S, Gündüz Z, Beşbaş N. Gür Güven A. Primary peritonitis in children with nephrotic syndrome: results of a 5-year multicenter study. Eur J Pediatr. 2010;169:73–6.
78. Tain YL, Lin G, Cher TW. Microbiological spectrum of septicemia and peritonitis in nephrotic children. Pediatr Nephrol. 1999;13:835–7.
79. Hsu K, Pelton S, Karumuri S, Heisey-Grove D, Klein J. Massachusetts Department of Public Health Epidemiologists. Population-based surveillance for childhood invasive pneumococcal

disease in the era of conjugate vaccine. Pediatr Infect Dis J. 2005;24:17–23.
80. Ulinski T, Leroy S, Dubrel M, Danon S, Bensman A. High serological response to pneumococcal vaccine in nephrotic children at disease onset on high-dose prednisone. Pediatr Nephrol. 2008;23:1107–13.
81. Aoun B, Wannous H, Azéma C, Ulinski T. Polysaccharide pneumococcal vaccination of nephrotic children at disease onset-long-term data. Pediatr Nephrol. 2010;25:1773–4.
82. Liakou CD, Askiti V, Mitsioni A, Stefanidis CJ, Theodoridou MC, Spoulou VI. Safety, immunogenicity and kinetics of immune response to 7-valent pneumococcal conjugate vaccine in children with idiopathic nephrotic syndrome. Vaccine. 2011;16(29):6834–7.
83. Poyrazoğlu HM, Düşünsel R, Gündüz Z, Patiroğlu T, Köklü S. Antibody response to influenza A vaccination in children with nephrotic syndrome. Pediatr Nephrol. 2004;19:57–60.
84. Laube GF, Berger C, Goetschel P, Leumann E, Neuhaus TJ. Immunization in children with chronic renal failure. Pediatr Nephrol. 2002;17:638–42.
85. Furth SL, Arbus GS, Hogg R, Tarver J, Chan C, Fivush BA, Southwest Pediatric Nephrology Study Group. Varicella vaccination in children with nephrotic syndrome: a report of the Southwest Pediatric Nephrology Study Group. J Pediatr. 2003;142:145–8.
86. Goldstein SL, Somers MJ, Lande MB, Brewer ED, Jabs KL. Acyclovir prophylaxis of varicella in children with renal disease receiving steroids. Pediatr Nephrol. 2000;14:305–8.
87. Trompeter RS, Lloyd BW, Hicks J, White RH, Cameron JS. Long-term outcome for children with minimal-change nephrotic syndrome. Lancet. 1985;1:368–70.
88. Wynn SR, Stickler GB, Burke EC. Long-term prognosis for children with nephrotic syndrome. Clin Pediatr (Phila). 1988;27:63–8.
89. Fakhouri F, Bocquet N, Taupin P, Presne C, Gagnadoux MF, Landais P, Lesavre P, Chauveau D, Knebelmann B, Broyer M, Grünfeld JP, Niaudet P. Steroid-sensitive nephrotic syndrome: from childhood to adulthood. Am J Kidney Dis. 2003;41:550–7.
90. Rüth EM, Kemper MJ, Leumann EP, Laube GF, Neuhaus TJ. Children with steroid-sensitive nephrotic syndrome come of age: long-term outcome. J Pediatr. 2005;147:202–7.
91. Ishimori S, Kaito H, Ohtsubo H, Hashimoto F, Ninchoji T, Hashimura Y, Morisada N, Iijima K. Current status and complications of adult patients with childhood-onset steroid-sensitive nephrotic syndrome [in Japanese]. J Jpn Pediatr Soc. 2013;117:90–6.