resistant nephrotic syndrome, however, limited clinical studies on plasmapheresis have shown inconclusive results. Although plasmapheresis has been described as leading to decreased proteinuria and stabilized renal function in some patients, reports have varied in terms of the characteristics of patients studied, the presence or absence of concomitant use of immunosuppressive agents, and conditions of plasmapheresis; reported plasmapheresis efficacy rates have been 57, 25, and 72 %, respectively, with significant variation and without known long-term benefits [149–151]. One report has suggested that plasmapheresis would be more useful when applied early in the course of the disease and prior to any histopathological changes [149]. Combination therapy of plasmapheresis with immunosuppressive therapy is therefore recommended.

Reports from clinical studies have been limited with regards to side effects of plasmapheresis for refractory steroid-resistant nephrotic syndrome [149]. Typical side effects of plasmapheresis that require caution include those associated with extracorporeal circulation, allergic reactions to the replacement fluid, and infection, including sepsis [149].

Plasmapheresis can be performed in physically smaller children because a smaller amount of blood is required compared with LDL apheresis. While the advantages of plasmapheresis include removal of pathological humoral factors and correction of dyslipidemia, its disadvantages include removal of beneficial substances from blood as well as the use of a blood product as the replacement fluid, which should be well understood before application.

LDL apheresis and plasmapheresis up to 12 sessions in 3 months are covered by health insurance, in dyslipidemic patients with refractory nephrotic syndrome with FSGS (diagnosis in the list of health insurance coverage, focal glomerulosclerosis).

2. Rituximab

Given that data is currently insufficient to clarify the efficacy and safety of rituximab in the treatment of refractory steroid-resistant nephrotic syndrome, it appears too early to recommend the use of this drug. However, rituximab therapy may be considered in the treatment of refractory steroid-resistant nephrotic syndrome because its use seems justified due to the poor prognosis of patients with refractory steroid-resistant nephrotic syndrome who are resistant to various treatments and continue to have severe proteinuria. The recommendation grade has thus been classified as C1. Considering the off-label status of its usage at this point (at preparation of this guideline), as well as the serious side effects reported with rituximab, risks and benefits should be carefully weighed before use and careful administration is advised.

Limited clinical studies for rituximab use in for refractory steroid-resistant nephrotic syndrome have been published. One study reported that 83 % of patients with steroid-dependent nephrotic syndrome sustained remission at 12 months and 48 % of patients with refractory steroid-resistant nephrotic syndrome showed remission (complete or partial) at 6 months [81]. Another study of rituximab reported a good initial response in 82 % of patients with steroid-dependent nephrotic syndrome and 44 % of patients with steroid-resistant nephrotic syndrome [79]. These data support an increasing view that rituximab is also efficacious for steroid-resistant nephrotic syndrome, though less so than it is for steroid-dependent nephrotic syndrome. The KDIGO guideline does not recommend rituximab for steroid-resistant nephrotic syndrome due to lack of randomized controlled trials and the risk of serious side effects. A recent report from an open-label, randomized, controlled trial states that rituximab was not efficacious for refractory steroid-resistant nephrotic syndrome [152]. However, this conclusion is doubtful given that the follow-up duration in the randomized controlled trial was as short as 3 months and treatment given concomitantly with rituximab could be insufficient.

For the use of rituximab in the treatment of refractory steroid-resistant nephrotic syndrome, the dosage, number of doses, dosing intervals, therapy duration, or effective concomitant treatments have not yet been fully established; many reports, however, have used 375 mg/m^2 once every week for a total of 4 doses [81].

Side effects of rituximab are mostly acute and insignificant, but rare cases of serious side effects have been reported. Late-onset side effects, occurring long after rituximab therapy, are unclear (for details on side effects of rituximab, see Chapter 4.

3. Tacrolimus

Tacrolimus has been documented to be efficacious in five observational studies and one randomized cyclosporine-controlled trial [119, 153–157], but no large-scale randomized controlled trials exist. Thus, the recommendation grade has been classified as C1. The only available randomized, controlled trial conducted in a small number of children at a single center in India reported no difference between tacrolimus and cyclosporine in the complete remission rates of 85.7 % (18/21) and 80.0 % (16/20), respectively, after 6 months of treatment. The proportion of patients who experienced relapse, however, was significantly smaller in those receiving tacrolimus compared with cyclosporine (11 vs. 50 %; $p = 0.01$) [119]. Patients in both groups experienced nephrotoxicity (38.0 vs. 60.0 %), hypertrichosis (0.0 vs. 95.0 %), gingival hypertrophy (4.7 vs. 60.0 %), and diarrhea (28.6 vs. 5 %). With

the exception of diarrhea, the frequency of side effects, especially cosmetic side effects, was lower in tacrolimus-treated patients compared with cyclosporine-treated patients.

The dosage of tacrolimus recommended in the guidelines by the KDIGO and the Children's Nephrotic Syndrome Consensus Conference (CNSCC) (US) is 0.05–0.1 mg/kg/day in two divided doses, with a target trough level of 5–10 ng/mL. This dosage is based on clinical studies in kidney transplant patients, and the efficacy and safety of its long-term use in the treatment of steroid-resistant nephrotic syndrome are unclear.

Side effects reported with tacrolimus include impaired glucose tolerance and hemolytic uremic syndrome requiring discontinuation of the treatment, as well as chronic nephrotoxicity at follow-up kidney biopsy similar to that associated with cyclosporine [155, 156, 158].

4. Other (mycophenolate mofetil)

Mycophenolate mofetil use in the treatment of steroid-resistant nephrotic syndrome has been described in very few reports [159–161] and the remission rates have been low. A high remission rate was shown only by one Chinese uncontrolled study, but this could be due to the small proportion of initial non-responders, who typically have poor responses to treatments, as well as patients with FSGS that were part of the study [160]. Although mycophenolate mofetil may be effective in the treatment of steroid-resistant nephrotic syndrome if combined with steroid pulse therapy or other treatments, current evidence is insufficient. The KDIGO guideline recommends mycophenolate mofetil in children who fail to achieve remission with calcineurin inhibitors and steroids. This recommendation is based on a National Institute of Health-funded randomized controlled trial that compared a combination of mycophenolate mofetil and dexamethasone to cyclosporine in patients with steroid-resistant FSGS. The report demonstrated no inter-group differences in the remission rate (46 % in the cyclosporine group vs. 33 % in the mycophenolate mofetil/dexamethasone group; $p = 0.11$) [162]. However, interpretation of the results requires caution; this randomized controlled trial enrolled patients aged 2–40 years who had early morning urine protein creatinine ratio of >1 g/gCr and the eligibility criteria did not include hypoproteinemia. Therefore, the study included many adult patients and non-nephrotic syndrome patients.

Bibliography

1. Szczepiorkowski ZM, Winters JL, Bandarenko N, Kim HC, Linenberger ML, Marques MB, Sarode R, Schwartz J, Weinstein R, Shaz BH; Apheresis Applications Committee of the American Society for Apheresis. Guidelines on the use of therapeutic apheresis in clinical practice—evidence-based approach from the Apheresis Applications Committee of the American Society for Apheresis. J Clin Apher. 2010;25:83–177.

Chapter 7. Long-term pharmacotherapy for pediatric idiopathic nephrotic syndrome

Recommendation statements:

1. In steroid therapy for the induction of remission in patients around transition age, we suggest that a switch from the ISKDC regimen to a regimen close to that used for adults be considered as necessary. [Recommendation grade C1]
2. Cyclosporine may be repeatedly used for 2 to 3 years when unavoidable, but attention should be given to the appropriateness of the therapy duration, blood drug concentration, and cumulative dose, and we suggest the consideration of kidney biopsy to monitor for nephrotoxicity, as necessary. [Recommendation grade C1]
3. We recommend cyclophosphamide therapy be limited to one course during a patient's lifetime, with cumulative doses taken into account. [Recommendation grade A]
4. When combination therapy of steroids and multiple immunosuppressive agents is required, we suggest that prior to use, a thorough understanding of all characteristics and side effects for each of the steroids and immunosuppressive agents be known. [Recommendation grade C1]

Explanation

A considerable population of patients, with frequently-relapsing idiopathic nephrotic syndrome that originates in childhood, can relapse in adulthood, and some patients require prolonged medicinal therapy [163]. In children with long-standing disease, it is important to minimize the physical, mental, and social disabilities from treatments as they grow into adults. Caution should be used to avoid life-long side effects that can occur with excessive treatments in exchange for a shortsighted, unnecessary fear of relapse. What matters most is not relapse but prolonged disabilities. For example, long-term steroid therapy can be beneficial to a patient if it is selected after anticipated relapse-preventing effect and foreseeable side effects are considered along with the patient's relapse history. Having a

sense of how safely the long-standing disease can be managed is a key strategy. The attending physician as well as the patient's family should all understand the impact of extended treatments. Literature articles that directly relate to the recommendation statements provided in this chapter are scarce, but search results are provided as references. Also, respective chapters should be looked at for the use of individual drugs in long-term management.

High-level evidence, such as randomized controlled trials, on long-term management of nephrotic syndrome has not yet been published. Reported clinical studies typically aim to evaluate the short-term effects of drugs. Some studies follow patients over a long period of time, but only obtained long-term outcomes under very limited conditions; this data often cannot be generalized to the real clinical setting. For this reason, the recommendation levels in this chapter of the guideline have been determined by committee consensus and using previous reports as references.

When providing long-term care, the attending physician should well understand the characteristics of the drugs, to use them as a single agent or in combination as appropriate at his/her discretion, and according to the clinical course and circumstances of individual patients [163].

Patients with steroid-resistant nephrotic syndrome and failing to achieve remission over an extended period of time are ultimately likely to suffer renal failure and require strong immunosuppressive therapy. However, the decision to decrease or discontinue immunosuppressive therapy will also be essential to avoid a fatal outcome as a result of jeopardizing the patient's life in an attempt to improve renal outcome.

Off-label drug use may be acceptable in patients when the use is desirable, based on available evidence accumulated from Japan and other countries [92, 100]; inconsiderate use, however, can lead to unforeseeable adverse events and other problems that may preclude clinical trials aiming to expand the indications. The use of unapproved drugs after adequate procedures can provide useful basic data for later clinical trials or expansion of indications, and therefore can be helpful.

1. Steroids

In steroid therapy for induction of remission in patients around the childhood-adult transition age, it may be considered necessary to switch from the ISKDC regimen to a regimen close to that used for adults [164]. This was a controversial issue in the questionnaire among the councilor board members of the Japanese Society for Pediatric Nephrology (conducted in May 2010): 15 members (29 %) indicated that "after puberty, the ISKDC regimen should be changed to a regimen close to that for adults"; 23 members (44 %) indicated that "after puberty, the dose for daily dosing should be 40 mg or lower, followed immediately by alternate-day dosing; and 14 members (27 %) indicated that "even after puberty, the regimen should remain in line with the ISKDC regimen." No evidence exists on any superiority or inferiority of these approaches. Taken together, it appears that, as long as steroid therapy induces remission and has no effects on subsequent relapse, the maximum steroid dose in the induction therapy may be changed as necessary. Often in the context of long-term care, treatment of a relapse can be difficult in certain patients, such as those who already have avascular necrosis of the femoral head, because steroid therapy is the only available option for induction of remission. In such patients, the steroid use for remission induction should be minimized in both dose and duration and strong immunosuppressive therapy should be given to prevent relapse, with the risks taken into account. In summary, steroid use during the long course of the disease often entails difficult decisions in individual cases, and decisions should be made after careful assessment concerning the incidence of side effects and other pertinent information. An association between steroid use and height has been described [165–168].

2. Cyclosporine

Although many reports describe that cyclosporine can be used over a long period, attention should be paid to the appropriateness of therapy duration, blood drug concentration, and cumulative doses, and a kidney biopsy should be considered as appropriate to monitor for nephrotoxicity [13, 14, 36, 41, 122, 169–177]. Some specialists point to the tendency of nephrotic syndrome to be protracted after use of cyclosporine therapy, but whether this is true or not should be fully examined in future studies. Whichever is the case, it is important that clinicians recognize cyclosporine as a drug better avoided. Inconsiderate long-term use of cyclosporine for prevention of relapse should be avoided. When long-term use is unavoidable, maintaining the blood drug concentration below the target concentration recommended for initial treatment, and within the range that is efficacious, should be considered.

3. Cyclophosphamide

Cyclophosphamide has been associated with gonadal dysfunction [178, 179], and may be given only one course during a lifetime, with cumulative doses taken into account (see Chapter 3 of Part 1, page 10).

For mizoribine, there has been little evidence provided for long-term use, and further investigation is warranted. Mycophenolate mofetil, tacrolimus, and rituximab are currently used off-label for nephrotic syndrome in Japan, and evidence for their long-term use has been scarce.

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References

1. Schlesinger ER, Sultz HA, Mosher WE, Feldman JG. The nephrotic syndrome. Its incidence and implications for the community. Am J Dis Child. 1968;116:623–32.
2. Koskimies O, Vilska J, Rapola J, Hallman N. Long-term outcome of primary nephrotic syndrome. Arch Dis Child. 1982;57:544–8.
3. Tarshish P, Tobin JN, Bernstein J, Edelmann CM Jr. Prognostic significance of the early course of minimal change nephrotic syndrome: report of the International Study of Kidney Disease in Children. J Am Soc Nephrol. 1997;8:769–76.
4. Arbeitsgemeinschaft für Pädiatrische Nephrologie. Effect of cytotoxic drugs in frequently relapsing nephrotic syndrome with and without steroid dependence. N Engl J Med. 1982;306:451–4
5. Fukui T, Yoshida M, Yamaguchi N. Minds Handbook for Guideline Development 2007. Tokyo: IGAKU-SHOIN Ltd.; 2007 (article in Japanese).
6. Lohr KN. Clinical practice guidelines: directions for a new program. Washington, DC: National Academy Press. Field MJ; 1990.
7. The primary nephrotic syndrome in children. Identification of patients with minimal change nephrotic syndrome from initial response to prednisone. A report of the International Study of Kidney Disease in Children. J Pediatr. 1981;98:561–4.
8. International Study of Kidney Disease in Children. Nephrotic syndrome in children: prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. A report of the International Study of Kidney Disease in Children. Kidney Int. 1978;13:159–65
9. Gulati S, Sharma AP, Sharma RK, Gupta A, Gupta RK. Do current recommendations for kidney biopsy in nephrotic syndrome need modifications? Pediatr Nephrol. 2002;17:404–8.
10. Cattran DC, Rao P. Long-term outcome in children and adults with classic focal segmental glomerulosclerosis. Am J Kidney Dis. 1998;32:72–9.
11. Kim JH, Park SJ, Yoon SJ, Lim BJ, Jeong HJ, Lee JS, Kim PK, Shin JI. Predictive factors for ciclosporin-associated nephrotoxicity in children with minimal change nephrotic syndrome. J Clin Pathol. 2011;64:516–9.
12. Kengne-Wafo S, Massella L, Diomedi-Camassei F, Gianviti A, Vivarelli M, Greco M, Stringini GR, Emma F. Risk factors for cyclosporin A nephrotoxicity in children with steroid-dependant nephrotic syndrome. Clin J Am Soc Nephrol. 2009;4:1409–16.
13. Iijima K, Hamahira K, Tanaka R, Kobayashi A, Nozu K, Nakamura H, Yoshikawa N. Risk factors for cyclosporine-induced tubulointerstitial lesions in children with minimal change nephrotic syndrome. Kidney Int. 2002;61:1801–5.
14. Fujinaga S, Kaneko K, Muto T, Ohtomo Y, Murakami H, Yamashiro Y. Independent risk factors for chronic cyclosporine induced nephropathy in children with nephrotic syndrome. Arch Dis Child. 2006;91:666–70.
15. Ishikura K, Ikeda M, Hattori S, Yoshikawa N, Sasaki S, Iijima K, Nakanishi K, Yata N, Honda M. Effective and safe treatment with cyclosporine in nephrotic children: a prospective, randomized multicenter trial. Kidney Int. 2008;73:1167–73.
16. Ishikura K, Yoshikawa N, Hattori S, Sasaki S, Iijima K, Nakanishi K, Matsuyama T, Yata N, Ando T, Honda M, for Japanese Study Group of Renal Disease in Children. Treatment with microemulsified cyclosporine in children with frequently relapsing nephrotic syndrome. Nephrol Dial Transplant. 2010; 25:3956–62.
17. Morgan C, Sis B, Pinsk M, Yiu V. Renal interstitial fibrosis in children treated with FK506 for nephrotic syndrome. Nephrol Dial Transplant. 2011;26:2860–5.
18. Alternate-day versus intermittent prednisone in frequently relapsing nephrotic syndrome. A report of "Arbeitsgemeinschaft für Pädiatrische Nephrologie". Lancet. 1979;1:401–3.
19. Ueda N, Chihara M, Kawaguchi S, Niinomi Y, Nonoda T, Matsumoto J, Ohnishi M, Yasaki T. Intermittent versus long-term tapering prednisolone for initial therapy in children with idiopathic nephrotic syndrome. J Pediatr. 1988;112:122–6.
20. Ehrich JH, Brodehl J. Long versus standard prednisone therapy for initial treatment of idiopathic nephrotic syndrome in children. Arbeitsgemeinschaft for Pediatrische Nephrologie. Eur J Pediatr. 1993;152:357–61.
21. Ksiazek J, Wyszyńska T. Short versus long initial prednisone treatment in steroid-sensitive nephrotic syndrome in children. Acta Paediatr. 1995;84:889–93.
22. Bagga A, Hari P, Srivastava RN. Prolonged versus standard prednisolone therapy for initial episode of nephrotic syndrome. Pediatr Nephrol. 1999;13:824–7.
23. Hiraoka M, Tsukahara H, Matsubara K, Tsurusawa M, Takeda N, Haruki S, Hayashi S, Ohta K, Momoi T, Ohshima Y, Suganuma N, Mayumi M. West Japan Cooperative Study Group of Kidney Disease in Children. A randomized study of two long-course prednisolone regimens for nephrotic syndrome in children. Am J Kidney Dis. 2003;41:1155–62.
24. Norero C, Delucchi A, Lagos E, Rosati P. Initial therapy of primary nephrotic syndrome in children: evaluation in a period of 18 months of two prednisone treatment schedules. Chilean Co-operative Group of Study of Nephrotic Syndrome in Children. Rev Med Chil. 1996;124:567–72 (article in Spanish).
25. Yoshikawa N, Ito H, Takekoshi Y, Honda M, Awazu M, Iijima K, Nakamura H, Seino Y, Takeda N, Hattori S, Matsuda I. Standard versus long-term prednisolone with Sairei-to for initial therapy in childhood steroid-responsive nephrotic syndrome: a prospective controlled study. Jpn J Nephrol. 1998;40:587–90 (article in Japanese).
26. Lande MB, Gullion C, Hogg RJ, Gauthier B, Shah B, Leonard MB, Bonilla-Felix M, Nash M, Roy S 3rd, Strife CF, Arbus G. Long versus standard initial steroid therapy for children with the nephrotic syndromeA report from the Southwest Pediatric Nephrology Study Group. Pediatr Nephrol. 2003;18:342–6.
27. Hirano D, Nishizaki N, Kanai H, Hara S, Ohtomo Y, Umino D, Fujinaga S. Long-term outcome of children treated with the

ISKDC regimen for the first episode of INS. Jpn J Nephrol. 2010;52:1029–36 (article in Japanese).
28. Hodson EM, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. Cochrane Database Syst Rev. 2007;(4):CD001533.
29. Ekka BK, Bagga A, Srivastava RN. Single- versus divided-dose prednisolone therapy for relapses of nephrotic syndrome. Pediatr Nephrol. 1997;11(5):597–9.
30. Hoyer PF, Brodeh J. Initial treatment of idiopathic nephrotic syndrome in children: prednisone versus prednisone plus cyclosporine A: a prospective, randomized trial. J Am Soc Nephrol. 2006;17:1151–7.
31. Hayashi M, Kimura N, Fukatsu A. Combined effect of cyclosporin and prednisolone for minimal change nephrotic syndrome: comparison with prednisolone therapy. Jpn J Nephrol. 2008;50:581–7 (article in Japanese).
32. Yoshikawa N, Ito H. Kampo medicine for pediatric renal disease: nephrotic syndrome. J Tradit Sino-Jpn Med. 1991;12:24–7 (article in Japanese).
33. Hodson EM, Willis NS, Craig JC. Non-corticosteroid treatment for nephrotic syndrome in children. Cochrane Database Syst Rev. 2008;(1):CD002290.
34. Ponticelli C, Edefonti A, Ghio L, Rizzoni G, Rinaldi S, Gusmano R, Lama G, Zacchello G, Confalonieri R, Altieri P. Cyclosporin versus cyclophosphamide for patients with steroid-dependent and frequently relapsing idiopathic nephrotic syndrome: a multicentre randomized controlled trial. Nephrol Dial Transplant. 1993;8:1326–32.
35. Niaudet P, Broyer M, Habib R. Treatment of idiopathic nephrotic syndrome with cyclosporin A in children. Clin Nephrol. 1991;35 Suppl1:S31–6.
36. El-Husseini A, El-Basuony F, Mahmoud I, Sheashaa H, Sabry A, Hassan R, Taha N, Hassan N, Sayed-Ahmad N, Sobh M. Long-term effects of cyclosporine in children with idiopathic nephrotic syndrome: a single-centre experience. Nephrol Dial Transplant. 2005;20:2433–8.
37. Kitano Y, Yoshikawa N, Tanaka R, Nakamura H, Ninomiya M, Ito H. Ciclosporin treatment in children with steroid-dependent nephrotic syndrome. Pediatr Nephrol. 1990;4(5):474–7.
38. Tanaka R, Yoshikawa N, Kitano Y, Ito H, Nakamura H. Long-term ciclosporin treatment in children with steroid-dependent nephrotic syndrome. Pediatr Nephrol. 1993;7:249–52.
39. Inoue Y, Iijima K, Nakamura H, Yoshikawa N. Two-year cyclosporin treatment in children with steroid-dependent nephrotic syndrome. Pediatr Nephrol. 1999;13(1):33–8.
40. Ishikura K, Yoshikawa N, Nakazato H, Sasaki S, Iijima K, Nakanishi K, Matsuyama T, Ito S, Yata N, Ando T, Honda M. Japanese Study Group of Renal Disease in Children. Two-year follow-up of a prospective clinical trial of cyclosporine for frequently relapsing nephrotic syndrome in children. Clin J Am Soc Nephrol. 2012;7:1576–83.
41. Kemper MJ, Kuwertz-Broeking E, Bulla M, Mueller-Wiefel DE, Neuhaus TJ. Recurrence of severe steroid dependency in cyclosporin A-treated childhood idiopathic nephrotic syndrome. Nephrol Dial Transplant. 2004;19:1136–41.
42. Niaudet P, Reigneau O, Humbert H. A pharmacokinetic study of Neoral in childhood steroid-dependent nephrotic syndrome. Pediatr Nephrol. 2001;16:154–5.
43. David-Neto E, Araujo LM, Brito ZM, Alves CF, Lemos FC, Yagyu EM, Nahas WC, Ianhez LE. Sampling strategy to calculate the cyclosporin-A area under the time-concentration curve. Am J Transplant. 2002;2:546–50.
44. Filler G. How should microemulsified cyclosporine A (Neoral) therapy in patients with nephrotic syndrome be monitored. Nephrol Dial Transplant. 2005;20:1032–4.
45. Suzuki K, Oki E, Tsuruga K, Aizawa-Yashiro T, Ito E, Tanaka H. Benefits of once-daily administration of cyclosporine a for children with steroid-dependent, relapsing nephrotic syndrome. Tohoku J Exp Med. 2010;220:183–6.
46. Fujinaga S, Hirano D, Murakami H, Ohtomo Y, Shimizu T, Kaneko K. Nephrotoxicity of once-daily cyclosporine A in minimal change nephrotic syndrome. Pediatr Nephrol. 2012;27:671–4.
47. Barratt TM, Soothill JF. Controlled trial of cyclophosphamide in steroid-sensitive relapsing nephrotic syndrome of childhood. Lancet. 1970;2:479–82.
48. International Study of Kidney Disease in Children (ISKDC). Prospective, controlled trial of cyclophosphamide therapy in children with nephrotic syndrome. Report of the International study of Kidney Disease in Children. Lancet. 1974;2:423–7.
49. Barratt TM, Cameron JS, Chantler C, Ogg CS, Soothill JF. Comparative trial of 2 weeks and 8 weeks cyclophosphamide in steroid-sensitive relapsing nephrotic syndrome of childhood. Arch Dis Child. 1973;48:286–90.
50. Cyclophosphamide treatment of steroid dependent nephrotic syndrome: comparison of eight week with 12 week course. Report of Arbeitsgemeinschaft für Pädiatrische Nephrologie. Arch Dis Child 1987;62:1102–6.
51. Ueda N, Kuno K, Ito S. Eight and 12 week courses of cyclophosphamide in nephrotic syndrome. Arch Dis Child. 1990;65:1147–50.
52. Kyrieleis HA, Levtchenko EN, Wetzels JF. Long-term outcome after cyclophosphamide treatment in children with steroid-dependent and frequently relapsing minimal change nephrotic syndrome. Am J Kidney Dis. 2007;49:592–7.
53. Cammas B, Harambat J, Bertholet-Thomas A, Bouissou F, Morin D, Guigonis V, Bendeddouche S, Afroukh-Hacini N, Cochat P, Llanas B, Decramer S, Ranchin B. Long-term effects of cyclophosphamide therapy in steroid-dependent or frequently relapsing idiopathic nephrotic syndrome. Nephrol Dial Transplant. 2011;26:178–84.
54. Vester U, Kranz B, Zimmermann S, Hoyer PF. Cyclophosphamide in steroid-sensitive nephrotic syndrome: outcome and outlook. Pediatr Nephrol. 2003;18:661–4.
55. Azib S, Macher MA, Kwon T, Dechartres A, Alberti C, Loirat C, Deschênes G, Baudouin V. Cyclophosphamide in steroid-dependent nephrotic syndrome. Pediatr Nephrol. 2011;26:927–32.
56. Srivastava RN, Agarwal RK, Choudhry VP, Moudgil A, Bhuyan UN, Sunderam KR. Cyclophosphamide therapy in frequently relapsing nephrotic syndrome with and without steroid dependence. Int J Pediatr Nephrol. 1985;6:245–50.
57. Zagury A, de Oliveira AL, de Moraes CA, de Araujo Montalvão JA, Novaes RH, de Sá VM, Monteiro de Carvalho Dde B, Matuck T. Long-term follow-up after cyclophosphamide therapy in steroid-dependent nephrotic syndrome. Pediatr Nephrol. 2011;26:915–20.
58. Garin EH, Pryor ND, Fennell RS 3rd, Richard GA. Pattern of response to prednisone in idiopathic, minimal lesion nephrotic syndrome as a criterion in selecting patients for cyclophosphamide therapy. J Pediatr. 1978;92:304–8.
59. Kemper MJ, Altrogge H, Ludwig K, Timmermann K, Müller-Wiefel DE. Unfavorable response to cyclophosphamide in steroid-dependent nephrotic syndrome. Pediatr Nephrol. 2000;14:772–5.
60. Latta K, von Schnakenburg C, Ehrich JH. A meta-analysis of cytotoxic treatment for frequently relapsing nephrotic syndrome in children. Pediatr Nephrol. 2001;16:271–82.
61. Siegel NJ, Gaudio KM, Krassner LS, McDonald BM, Anderson FP, Kashgarian M. Steroid-dependent nephrotic syndrome in children: histopathology and relapses after cyclophosphamide treatment. Kidney Int. 1981;19:454–9.

62. Tejani A, Phadke K, Nicastri A, Adamson O, Chen CK, Trachtman H, Tejani C. Efficacy of cyclophosphamide in steroid-sensitive childhood nephrotic syndrome with different morphological lesions. Nephron. 1985;41:170–3.
63. Gulati S, Pokhariyal S, Sharma RK, Elhence R, Kher V, Pandey CM, Gupta A. Pulse cyclophosphamide therapy in frequently relapsing nephrotic syndrome. Nephrol Dial Transplant. 2001; 16:2013–7.
64. Bircan Z, Kara B. Intravenous cyclophosphamide is the drug of choice for steroid dependent nephrotic syndrome. Pediatr Int. 2003;45:65–7.
65. Prasad N, Gulati S, Sharma RK, Singh U, Ahmed M. Pulse cyclophosphamide therapy in steroid-dependent nephrotic syndrome. Pediatr Nephrol. 2004;19:494–8.
66. Donia AF, Gazareen SH, Ahmed HA, Moustafa FE, Shoeib AA, Ismail AM, Khamis S, Sobh MA. Pulse cyclophosphamide inadequately suppresses reoccurrence of minimal change nephrotic syndrome in corticoid-dependent children. Nephrol Dial Transplant. 2003;18:2054–8.
67. Wetzels JF. Cyclophosphamide-induced gonadal toxicity: a treatment dilemma in patients with lupus nephritis. Neth J Med. 2004;62:347–52.
68. Hodson EM, Craig JC, Willis NS. Evidence-based management of steroid-sensitive nephrotic syndrome. Pediatr Nephrol. 2005;20:1523–30.
69. Rivkees SA, Crawford JD. The relationship of gonadal activity and chemotherapy-induced gonadal damage. JAMA. 1988;259: 2123–5.
70. Yoshioka K, Ohashi Y, Sakai T, Ito H, Yoshikawa N, Nakamura H, Tanizawa T, Wada H, Maki S. A multicenter trial of mizoribine compared with placebo in children with frequently relapsing nephrotic syndrome. Kidney Int. 2000;58:317–24.
71. Kawasaki Y, Hosoya M, Kobayashi S, Ohara S, Onishi N, Takahashi A, Isome M, Suzuki H. Oral mizoribine pulse therapy for patients with steroid-resistant and frequently relapsing steroid-dependent nephrotic syndrome. Nephrol Dial Transplant. 2005;20(10):2243–7.
72. Kawasaki Y, Takano K, Isome M, Suzuki J, Suyama K, Kanno H, Fujiki T, Suzuki H, Hosoya M. Efficacy of single dose of oral mizoribine pulse therapy two times per week for frequently relapsing nephrotic syndrome. J Nephrol. 2007;20:52–6.
73. Fujieda M, Ishihara M, Morita T, Hayashi A, Utsunomiya Y, Ohta T, Sakano T, Wakiguchi H. Effect of oral mizoribine pulse therapy for frequently relapsing steroid-dependent nephrotic syndrome. Clin Nephrol. 2008;69:179–84.
74. Ohtomo Y, Fujinaga S, Takada M, Murakami H, Akashi S, Shimizu T, Kaneko K, Yamashiro Y. High-dose mizoribine therapy for childhood-onset frequently relapsing steroid-dependent nephrotic syndrome with cyclosporin nephrotoxicity. Pediatr Nephrol. 2005;20:1744–9.
75. Fujinaga S, Hirano D, Nishizaki N, Someya T, Ohtomo Y, Ohtsuka Y, Shimizu T, Kaneko K. Single daily high-dose mizoribine therapy for children with steroid-dependent nephrotic syndrome prior to cyclosporine administration. Pediatr Nephrol. 2011;26:479–83.
76. Goto M, Ikeda M, Hataya H, Ishikura K, Hamasaki Y, Honda M. Beneficial and adverse effects of high-dosage MZR therapy in the management of children with frequently relapsing nephrotic syndrome. Jpn J Nephrol. 2006;48:365–70 (article in Japanese).
77. Guigonis V, Dallocchio A, Baudouin V, Dehennault M, Hachon-Le Camus C, Afanetti M, Groothoff J, Llanas B, Niaudet P, Nivet H, Raynaud N, Taque S, Ronco P, Bouissou F. Rituximab treatment for severe steroid- or cyclosporine-dependent nephrotic syndrome: a multicentric series of 22 cases. Pediatr Nephrol. 2008;23:1269–79.
78. Kamei K, Ito S, Nozu K, Fujinaga S, Nakayama M, Sako M, Saito M, Yoneko M, Iijima K. Single dose of rituximab for refractory steroid-dependent nephrotic syndrome in children. Pediatr Nephrol. 2009;24:1321–8.
79. Prytuła A, Iijima K, Kamei K, Geary D, Gottlich E, Majeed A, Taylor M, Marks SD, Tuchman S, Camilla R, Ognjanovic M, Filler G, Smith G, Tullus K. Rituximab in refractory nephrotic syndrome. Pediatr Nephrol. 2010;25:461–8.
80. Sellier-Leclerc AL, Macher MA, Loirat C, Guérin V, Watier H, Peuchmaur M, Baudouin V, Deschênes G. Rituximab efficiency in children with steroid-dependent nephrotic syndrome. Pediatr Nephrol. 2010;25:1109–15.
81. Gulati A, Sinha A, Jordan SC, Hari P, Dinda AK, Sharma S, Srivastava RN, Moudgil A, Bagga A. Efficacy and safety of treatment with rituximab for difficult steroid-resistant and -dependent nephrotic syndrome: multicentric report. Clin J Am Soc Nephrol. 2010;5:2207–12.
82. Fujinaga S, Hirano D, Nishizaki N, Kamei K, Ito S, Ohtomo Y, Shimizu T. Kaneko K.ingle infusion of rituximab for persistent steroid-dependent minimal-change nephrotic syndrome after long-term cyclosporine. Pediatr Nephrol. 2010;25:539–44.
83. Sinha A, Bagga A, Gulati A, Hari P. Short-term efficacy of rituximab versus tacrolimus in steroid-dependent nephrotic syndrome. Pediatr Nephrol. 2012;27:235–41.
84. Ravani P, Magnasco A, Edefonti A, Murer L, Rossi R, Ghio L, Benetti E, Scozzola F, Pasini A, Dallera N, Sica F, Belingheri M, Scolari F, Ghiggeri GM. Short-term effects of rituximab in children with steroid- and calcineurin-dependent nephrotic syndrome: a randomized controlled trial. Clin J Am Soc Nephrol. 2011;6:1308–15.
85. Kemper MJ, Gellermann J, Habbig S, Krmar RT, Dittrich K, Jungraithmayr T, Pape L, Patzer L, Billing H, Weber L, Pohl M, Rosenthal K, Rosahl A, Mueller-Wiefel DE, Dötsch J. Long-term follow-up after rituximab for steroid-dependent idiopathic nephrotic syndrome. Nephrol Dial Transplant. 2012;27:1910–5.
86. Sellier-Leclerc AL, Baudouin V, Kwon T, Macher MA, Guérin V, Lapillonne H, Deschênes G, Ulinski T. Rituximab in steroid-dependent idiopathic nephrotic syndrome in childhood–follow-up after CD19 recovery. Nephrol Dial Transplant. 2012;27:1083–9.
87. Hiramoto R, Matsumoto S, Eguchi H, Miyoshi Y, Komori I, Akikusa B, Shibata S, Kamei K. Iijima K A case of a 7-year-old boy with steroid-dependent nephrotic syndrome who developed severe neutropenia three months after the administration of rituximab. Japanese Journal of Pediatric Nephrology. 2009;22: 97–101 (article in Japanese).
88. Sato M, Ito S, Ogura M, Kamei K, Miyairi I, Miyata I, Higuchi M, Matsuoka K. Atypical Pneumocystis jiroveci pneumonia with multiple nodular granulomas after rituximab for refractory nephrotic syndrome. Pediatr Nephrol. 2013;28:145–9
89. Gea-Banacloche JC. Rituximab-associated infections. Semin Hematol. 2010;47:187–98.
90. Chaumais MC, Garnier A, Chalard F, Peuchmaur M, Dauger S, Jacqz-Agrain E, Deschênes G. Fatal pulmonary fibrosis after rituximab administration. Pediatr Nephrol. 2009;24:1753–5.
91. Ardelean DS, Gonska T, Wires S, Cutz E, Griffiths A, Harvey E, Tse SM, Benseler SM. Severe ulcerative colitis after rituximab therapy. Pediatrics. 2010;126:e243–6.
92. Bagga A, Hari P, Moudgil A, Jordan SC. Mycophenolate mofetil and prednisolone therapy in children with steroid-dependent nephrotic syndrome. Am J Kidney Dis. 2003;42:1114–20.
93. Hogg RJ, Fitzgibbons L, Bruick J, Bunke M, Ault B, Baqi N, Trachtman H, Swinford R. Mycophenolate mofetil in children with frequently relapsing nephrotic syndrome: a report from the Southwest Pediatric Nephrology Study Group. Clin J Am Soc Nephrol. 2006;1:1173–8.

94. Afzal K, Bagga A, Menon S, Hari P, Jordan SC. Treatment with mycophenolate mofetil and prednisolone for steroid-dependent nephrotic syndrome. Pediatr Nephrol. 2007;22:2059–65.
95. Barletta GM, Smoyer WE, Bunchman TE, Flynn JT, Kershaw DB. Use of mycophenolate mofetil in steroid-dependent and -resistant nephrotic syndrome. Pediatr Nephrol. 2003;18:833–7.
96. Ulinski T, Dubourg L, Saïd MH, Parchoux B, Ranchin B, Cochat P. Switch from cyclosporine A to mycophenolate mofetil in nephrotic children. Pediatr Nephrol. 2005;20:482–5.
97. Mendizábal S, Zamora I, Berbel O, Sanahuja MJ, Fuentes J, Simon J. Mycophenolate mofetil in steroid/cyclosporine-dependent/resistant nephrotic syndrome. Pediatr Nephrol. 2005;20:914–9.
98. Okada M, Sugimoto K, Yagi K, Yanagida H, Tabata N, Takemura T. Mycophenolate mofetil therapy for children with intractable nephrotic syndrome. Pediatr Int. 2007;49:933–7.
99. Fujinaga S, Ohtomo Y, Umino D, Takemoto M, Shimizu T, Yamashiro Y, Kaneko K. A prospective study on the use of mycophenolate mofetil in children with cyclosporine-dependent nephrotic syndrome. Pediatr Nephrol. 2007;22:71–6.
100. Fujinaga S, Ohtomo Y, Hirano D, Nishizaki N, Someya T, Ohtsuka Y, Kaneko K, Shimizu T. Mycophenolate mofetil therapy for childhood-onset steroid dependent nephrotic syndrome after long-term cyclosporine: extended experience in a single center. Clin Nephrol. 2009;72:268–73.
101. Gellermann J, Querfeld U. Frequently relapsing nephrotic syndrome: treatment with mycophenolate mofetil. Pediatr Nephrol. 2004;19:101–4.
102. Dorresteijn EM. Kist-van Holthe JE, Levtchenko EN, Nauta J, Hop WC, van der Heijden AJ. Mycophenolate mofetil versus cyclosporine for remission maintenance in nephrotic syndrome. Pediatr Nephrol. 2008;23:2013–20.
103. Novak I, Frank R, Vento S, Vergara M, Gauthier B, Trachtman H. Efficacy of mycophenolate mofetil in pediatric patients with steroid-dependent nephrotic syndrome. Pediatr Nephrol. 2005;20:1265–8.
104. Al-Akash S, Al-Makdama A. Mycophenolate mofetil in children with steroid-dependent and/or frequently relapsing nephrotic syndrome. Ann Saudi Med. 2005;25:380–4.
105. Baudouin V, Alberti C, Lapeyraque AL, Bensman A, André JL, Broux F, Cailliez M, Decramer S, Niaudet P, Deschênes G, Jacqz-Aigrain E, Loirat C. Mycophenolate mofetil for steroid-dependent nephrotic syndrome: a phase II Bayesian trial. Pediatr Nephrol. 2012;27:389–96.
106. Dittrich K, Knerr I, Rascher W, Dötsch J. Transient insulin-dependent diabetes mellitus in children with steroid-dependent idiopathic nephrotic syndrome during tacrolimus treatment. Pediatr Nephrol. 2006;21:958–61.
107. Sinha MD, MacLeod R, Rigby E, Clark AG. Treatment of severe steroid-dependent nephrotic syndrome (SDNS) in children with tacrolimus. Nephrol Dial Transplant. 2006;21:1848–54.
108. Dötsch J, Dittrich K, Plank C, Rascher W. Is tacrolimus for childhood steroid-dependent nephrotic syndrome better than ciclosporin A. Nephrol Dial Transplant. 2006;21:1761–3.
109. Ehrich JH, Geerlings C, Zivicnjak M, Franke D, Geerlings H, Gellermann J. Steroid-resistant idiopathic childhood nephrosis: overdiagnosed and undertreated. Nephrol Dial Transplant. 2007;22:2183–93.
110. Mori K, Honda M, Ikeda M. Efficacy of methylprednisolone pulse therapy in steroid-resistant nephrotic syndrome. Pediatr Nephrol. 2004;19:1232–6.
111. Hamasaki Y, Yoshikawa N, Hattori S, Sasaki S, Iijima K, Nakanishi K, Matsuyama T, Ishikura K, Yata N, Kaneko T, Honda M. Japanese Study Group of Renal Disease. Cyclosporine and steroid therapy in children with steroid-resistant nephrotic syndrome. Pediatr Nephrol. 2009;24:2177–85.
112. Bagga A, Mudigoudar BD, Hari P, Vasudev V. Enalapril dosage in steroid-resistant nephrotic syndrome. Pediatr Nephrol. 2004;19:45–50.
113. Karle SM, Uetz B, Ronner V, Glaeser L, Hildebrandt F, Fuchshuber A. Novel mutations in NPHS2 detected in both familial and sporadic steroid-resistant nephrotic syndrome. J Am Soc Nephrol. 2002;13:388–93.
114. Weber S, Gribouval O, Esquivel EL, Morinière V, Tête MJ, Legendre C, Niaudet P, Antignac C. NPHS2 mutation analysis shows genetic heterogeneity of steroid-resistant nephrotic syndrome and low post-transplant recurrence. Kidney Int. 2004;66:571–9.
115. Chernin G, Heeringa SF, Gbadegesin R, Liu J, Hinkes BG, Vlangos CN, Vega-Warner V, Hildebrandt F. Low prevalence of NPHS2 mutations in African American children with steroid-resistant nephrotic syndrome. Pediatr Nephrol. 2008;23:1455–60.
116. Santín S, Bullich G, Tazón-Vega B, García-Maset R, Giménez I, Silva I, Ruíz P, Ballarín J, Torra R, Ars E. Clinical utility of genetic testing in children and adults with steroid-resistant nephrotic syndrome. Clin J Am Soc Nephrol. 2011;6:1139–48.
117. Ponticelli C, Rizzoni G, Edefonti A, Altieri P, Rivolta E, Rinaldi S, Ghio L, Lusvarghi E, Gusmano R, Locatelli F, Pasquali S, Castellani A, Della Casa Alberighi O. A randomized trial of cyclosporine in steroid-resistant idiopathic nephrotic syndrome. Kidney Int. 1993;43:1377–84.
118. Lieberman KV, Tejani A. A randomized double-blind placebo-controlled trial of cyclosporine in steroid-resistant idiopathic focal segmental glomerulosclerosis in children. J Am Soc Nephrol. 1996;7:56–63.
119. Choudhry S, Bagga A, Hari P, Sharma S, Kalaivani M, Dinda A. Efficacy and safety of tacrolimus versus cyclosporine in children with steroid-resistant nephrotic syndrome: a randomized controlled trial. Am J Kidney Dis. 2009;53:760–9.
120. Mahmoud I, Basuni F, Sabry A, El-Husseini A, Hassan N, Ahmad NS, Elbaz M, Moustafa F, Sobh M. Single-centre experience with cyclosporin in 106 children with idiopathic focal segmental glomerulosclerosis. Nephrol Dial Transplant. 2005;20:735–42.
121. Hamasaki Y, Yoshikawa N, Nakazato H, Sasaki S, Iijima K, Nakanishi K, Matsuyama T, Ishikura K, Ito S, Kaneko T, Honda M, for Japanese Study Group of Renal Disease in Children. Prospective 5-year follow-up of cyclosporine treatment in children with steroid-resistant nephrosis. Pediatr Nephrol. 2013;28:765–71.
122. Ingulli E, Singh A, Baqi N, Ahmad H, Moazami S, Tejani A. Aggressive, long-term cyclosporine therapy for steroid-resistant focal segmental glomerulosclerosis. J Am Soc Nephrol. 1995;5:1820–5.
123. Cattran DC, Appel GB, Hebert LA, Hunsicker LG, Pohl MA, Hoy WE, Maxwell DR, Kunis CL. A randomized trial of cyclosporine in patients with steroid-resistant focal segmental glomerulosclerosis. North America Nephrotic Syndrome Study Group. Kidney Int. 1999;56:2220–6.
124. Heering P, Braun N, Müllejans R, Ivens K, Zäuner I, Fünfstück R, Keller F, Krämer BK, Schollmeyer P, Risler T, Grabensee B. German Collaborative Glomerulonephritis Study Group Cyclosporine A and chlorambucil in the treatment of idiopathic focal segmental glomerulosclerosis. Am J Kidney Dis. 2004;43:10–8.
125. Niaudet P. Treatment of childhood steroid-resistant idiopathic nephrosis with a combination of cyclosporine and prednisone. French Society of Pediatric Nephrology. J Pediatr. 1994;125:981–6.
126. Sako M, Iijima K, Saito M, Ohashi Y, Yoshikawa N. Cyclosporine C2 monitaring for frequently relapsing nephrotic

syndrome in children: a randomized controlled trial. Jpn J Nephrol. 2012;54:253 (article in Japanese).
127. Naito M, Takei T, Eguchi A, Uchida K, Tsuchiya K, Nitta K. Monitoring of blood cyclosporine concentration in steroid-resistant nephrotic syndrome. Intern Med. 2008;47:1567–72.
128. Ishikura K, Ikeda M, Hamasaki Y, Hataya H, Nishimura G, Hiramoto R, Honda M. Nephrotic state as a risk factor for developing posterior reversible encephalopathy syndrome in paediatric patients with nephrotic syndrome. Nephrol Dial Transplant. 2008;23:2531–2536.
129. Segarra A, Vila J, Pou L, Majó J, Arbós A, Quiles T, Piera LL. Combined therapy of tacrolimus and corticosteroids in cyclosporin-resistant or -dependent idiopathic focal glomerulosclerosis: a preliminary uncontrolled study with prospective follow-up. Nephrol Dial Transplant. 2002;17:655–62.
130. Waldo FB, Benfield MR, Kohaut EC. Therapy of focal and segmental glomerulosclerosis with methylprednisolone, cyclosporine A, and prednisone. Pediatr Nephrol. 1998;12:397–400.
131. Yorgin PD, Krasher J, Al-Uzri AY. Pulse methylprednisolone treatment of idiopathic steroid-resistant nephrotic syndrome. Pediatr Nephrol. 2001;16:245–50.
132. Shenoy M, Plant ND, Lewis MA, Bradbury MG, Lennon R, Webb NJ. Intravenous methylprednisolone in idiopathic childhood nephrotic syndrome. Pediatr Nephrol. 2010;25:899–903.
133. Tarshish P, Tobin JN, Bernstein J, Edelmann CM Jr. Cyclophosphamide does not benefit patients with focal segmental glomerulosclerosis. A report of the International Study of Kidney Disease in Children. Pediatr Nephrol. 1996;10:590–3.
134. Plank C, Kalb V, Hinkes B, Hildebrandt F, Gefeller O, Rascher W. Arbeits-gemeinschaft für Pädiatrische Nephrologie. Cyclosporin A is superior to cyclophosphamide in children with steroid-resistant nephrotic syndrome-a randomized controlled multicentre trial by the Arbeitsgemeinschaft für Pädiatrische Nephrologie. Pediatr Nephrol. 2008;23:1483–93.
135. Yi Z, Li Z, Wu XC, He QN, Dang XQ, He XJ. Effect of fosinopril in children with steroid-resistant idiopathic nephrotic syndrome. Pediatr Nephrol. 2006;21:967–72.
136. Paik KH, Lee BH, Cho HY, Kang HG, Ha IS, Cheong HI, Jin DK, Moon KC, Choi Y. Primary focal segmental glomerular sclerosis in children: clinical course and prognosis. Pediatr Nephrol. 2007;22:389–95.
137. Troyanov S. Wall CA, Miller JA, Scholey JW, Cattran DC; Toronto Glomerulonephritis Registry Group. Focal and segmental glomerulosclerosis: definition and relevance of a partial remission. J Am Soc Nephrol. 2005;16:1061–8.
138. Martinelli R, Okumura AS, Pereira LJ, Rocha H. Primary focal segmental glomerulosclerosis in children: prognostic factors. Pediatr Nephrol. 2001;16:658–61.
139. Abeyagunawardena AS, Sebire NJ, Risdon RA, Dillon MJ, Rees L, Van't Hoff W, Kumarasiri PV, Trompeter RS. Predictors of long-term outcome of children with idiopathic focal segmental glomerulosclerosis. Pediatr Nephrol. 2007;22:215–21.
140. Crenshaw G, Bigler S, Salem M, Crook ED. Focal segmental glomerulosclerosis in African Americans: effects of steroids and angiotensin converting enzyme inhibitors. Am J Med Sci. 2000;319:320–5.
141. Stiles KP, Abbott KC, Welch PG, Yuan CM. Effects of angiotensin-converting enzyme inhibitor and steroid therapy on proteinuria in FSGS: a retrospective study in a single clinic. Clin Nephrol. 2001;56:89–95.
142. Muso E, Mune M, Yorioka N, Nishizawa Y, Hirano T, Hattori M, Sugiyama S, Watanabe T, Kimura K, Yokoyama H, Sato H, Saito T. Beneficial effect of low-density lipoprotein apheresis (LDL-A) on refractory nephrotic syndrome (NS) due to focal glomerulosclerosis (FGS). Clin Nephrol. 2007;67:341–4.
143. Muso E, Mune M, Fujii Y, Imai E, Ueda N, Hatta K, Imada A, Takemura T, Miki S, Kuwahara T, Takamitsu Y, Tsubakihara Y; Kansai FGS, LDL Apheresis Treatment (K-FLAT) Study Group. Significantly rapid relief from steroid-resistant nephrotic syndrome by LDL apheresis compared with steroid monotherapy. Nephron. 2001;89:408–15.
144. Muso E, Mune M, Fujii Y, Imai E, Ueda N, Hatta K, Imada A, Miki S, Kuwahara T, Takamitsu Y, Takemura T, Tsubakihara Y, Kansai-FGS-Apheresis Treatment (K-FLAT) Study Group. Low density lipoprotein apheresis therapy for steroid-resistant nephrotic syndrome. Kidney Int Suppl. 1999;71:122–5.
145. Tojo K, Sakai S, Miyahara T. Possible therapeutic application of low density lipoprotein apheresis (LDL-A) in conjunction with double filtration plasmapheresis (DFPP) in drug-resistant nephrotic syndrome due to focal glomerular sclerosis (FGS). Nihon Jinzo Gakkai Shi. 1988;30:1153–60.
146. Hattori M, Chikamoto H, Akioka Y, Nakakura H, Ogino D, Matsunaga A, Fukazawa A, Miyakawa S, Khono M, Kawaguchi H, Ito K. A combined low-density lipoprotein apheresis and prednisone therapy for steroid-resistant primary focal segmental glomerulosclerosis in children. Am J Kidney Dis. 2003;42:1121–30.
147. Yokoyama K, Sakai S, Sigematsu T, Takemoto F, Hara S, Yamada A, Kawaguchi Y, Hosoya T. LDL adsorption improves the response of focal glomerulosclerosis to corticosteroid therapy. Clin Nephrol. 1998;50:1–7.
148. Okada T, Takahashi H, Ogura M, Nakao T, Shimizu T. Complete remission of steroid-resistant minimal-change nephrotic syndrome by cyclosporin after additional low-density lipoprotein apheresis treatment. Jpn J Nephrol. 1996;38:46–51 (article IN Japanese).
149. Franke D, Zimmering M, Wolfish N, Ehrich JH, Filler G. Treatment of FSGS with plasma exchange and immunadsorption. Pediatr Nephrol. 2000;14:965–9.
150. Feld SM, Figueroa P, Savin V, Nast CC, Sharma R, Sharma M, Hirschberg R, Adler SG. Plasmapheresis in the treatment of steroid-resistant focal segmental glomerulosclerosis in native kidneys. Am J Kidney Dis. 1998;32:230–7.
151. Mitwalli AH. Adding plasmapheresis to corticosteroids and alkylating agents: does it benefit patients with focal segmental glomerulosclerosis. Nephrol Dial Transplant. 1998;13:1524–8.
152. Magnasco A, Ravani P, Edefonti A, Murer L, Ghio L, Belingheri M, Benetti E, Murtas C, Messina G, Massella L, Porcellini MG, Montagna M, Regazzi M, Scolari F, Ghiggeri GM. Rituximab in children with resistant idiopathic nephrotic syndrome. J Am Soc Nephrol. 2012;23:1117–24.
153. Loeffler K, Gowrishankar M, Yiu V. Tacrolimus therapy in pediatric patients with treatment-resistant nephrotic syndrome. Pediatr Nephrol. 2004;19:281–7.
154. Bhimma R, Adhikari M, Asharam K, Connolly C. Management of steroid-resistant focal segmental glomerulosclerosis in children using tacrolimus. Am J Nephrol. 2006;26:544–51.
155. Gulati S, Prasad N, Sharma RK, Kumar A, Gupta A, Baburaj VP. Tacrolimus: a new therapy for steroid-resistant nephrotic syndrome in children. Nephrol Dial Transplant. 2008;23:910–3.
156. Butani L, Ramsamooj R. Experience with tacrolimus in children with steroid-resistant nephrotic syndrome. Pediatr Nephrol. 2009;24:1517–23.
157. Roberti I, Vyas S. Long-term outcome of children with steroid-resistant nephrotic syndrome treated with tacrolimus. Pediatr Nephrol. 2010;25:1117–24.
158. Pandirikkal VB, Jain M, Gulati S. Tacrolimus-induced HUS: an unusual cause of acute renal failure in nephrotic syndrome. Pediatr Nephrol. 2007;22:298–300.
159. de Mello VR, Rodrigues MT, Mastrocinque TH, Martins SP, de Andrade OV, Guidoni EB, Scheffer DK, Martini Filho D,

Toporovski J, Benini V. Mycophenolate mofetil in children with steroid/cyclophosphamide-resistant nephrotic syndrome. Pediatr Nephrol. 2010;25:453–60.
160. Li Z, Duan C, He J, Wu T, Xun M, Zhang Y, Yin Y. Mycophenolate mofetil therapy for children with steroid-resistant nephrotic syndrome. Pediatr Nephrol. 2010;25:883–8.
161. Gargah TT, Lakhoua MR. Mycophenolate mofetil in treatment of childhood steroid-resistant nephrotic syndrome. J Nephrol. 2011;24:203–7.
162. Gipson DS, Trachtman H, Kaskel FJ, Greene TH, Radeva MK, Gassman JJ, Moxey-Mims MM, Hogg RJ, Watkins SL, Fine RN, Hogan SL, Middleton JP, Vehaskari VM, Flynn PA, Powell LM, Vento SM, McMahan JL, Siegel N, D'Agati VD, Friedman AL. Clinical trial of focal segmental glomerulosclerosis in children and young adults. Kidney Int. 2011;80:868–78.
163. Kyrieleis HA, Löwik MM, Pronk I, Cruysberg HR, Kremer JA, Oyen WJ, van den Heuvel BL, Wetzels JF, Levtchenko EN. Long-term outcome of biopsy-proven, frequently relapsing minimal-change nephrotic syndrome in children. Clin J Am Soc Nephrol. 2009;4:1593–600.
164. Requião-Moura LR, Veras de S Freitas T, Franco MF, Pereira AB, Mastroianni-Kirsztajn G. Should adolescents with glomerulopathies be treated as children or adults? Nephron Clin Pract. 2008;109:c161–7.
165. Simmonds J, Grundy N, Trompeter R, Tullus K. Long-term steroid treatment and growth: a study in steroid-dependent nephrotic syndrome. Arch Dis Child. 2010;95:146–9.
166. Emma F, Sesto A, Rizzoni G. Long-term linear growth of children with severe steroid-responsive nephrotic syndrome. Pediatr Nephrol. 2003;18:783–8.
167. Takahashi T, Inaba S, Oshima T, Ishihara S, Toyoda Y, Kurose K, Takai R, Yoshida A, Okada T, Takada T, Yanagihara T. Growth of children with idiopathic nephrotic syndrome. The effect of steroid therapy. J Jpn Pediatr Soc. 1991;95:1850–5 (article in Japanese).
168. Kaku Y, Ohtsuka Y, Komatsu Y, Ohta T, Nagai T, Kaito H, Kondo S, Ikezumi Y, Tanaka S, Matsumoto S, Sako M, Tsuruga K, Nakanishi K, Kamei K, Saito H, Fujinaga S, Hamasaki Y, Chikamoto H, Ishikura K, Iijima K. Clinical practice guideline for pediatric idiopathic nephrotic syndrome 2013: general therapy, clinical and experimental nephrology. Clin Exp Nephrol. doi:10.1007/s10157-014-1031-9.
169. Kranz B, Vester U, Büscher R, Wingen AM, Hoyer PF. Cyclosporine-A-induced nephrotoxicity in children with minimal-change nephrotic syndrome: long-term treatment up to 10 years. Pediatr Nephrol. 2008;23:581–6.
170. Drube J, Geerlings C, Taylor R, Mengel M, Ehrich JH. Fifteen-year remission of a steroid-resistant nephrotic syndrome sustained by cyclosporine A. Pediatr Nephrol. 2007;22:600–2.
171. Ghiggeri GM, Catarsi P, Scolari F, Caridi G, Bertelli R, Carrea A, Sanna-Cherchi S, Emma F, Allegri L, Cancarini G, Rizzoni GF, Perfumo F. Cyclosporine in patients with steroid-resistant nephrotic syndrome: an open-label, nonrandomized, retrospective study. Clin Ther. 2004;26:1411–8.
172. Chishti AS, Sorof JM, Brewer ED, Kale AS. Long-term treatment of focal segmental glomerulosclerosis in children with cyclosporine given as a single daily dose. Am J Kidney Dis. 2001;38:754–60.
173. Hino S, Takemura T, Okada M, Murakami K, Yagi K, Fukushima K, Yoshioka K. Follow-up study of children with nephrotic syndrome treated with a long-term moderate dose of cyclosporine. Am J Kidney Dis. 1998;31:932–9.
174. Gregory MJ, Smoyer WE, Sedman A, Kershaw DB, Valentini RP, Johnson K, Bunchman TE. Long-term cyclosporine therapy for pediatric nephrotic syndrome: a clinical and histologic analysis. J Am Soc Nephrol. 1996;7:543–9.
175. Neuhaus TJ, Burger HR, Klingler M, Fanconi A, Leumann EP. Long-term low-dose cyclosporin A in steroid dependent nephrotic syndrome of childhood. Eur J Pediatr. 1992;151:775–8.
176. Melocoton TL, Kamil ES, Cohen AH, Fine RN. Long-term cyclosporine A treatment of steroid-resistant and steroid-dependent nephrotic syndrome. Am J Kidney Dis. 1991;18:583–8.
177. Fujinaga S, Ohtomo Y, Akashi S, Kaneko K. Chronic cyclosporine-induced nephropathy in children with nephrotic syndrome. Japanese Journal of Pediatric Nephrology. 2004;17:66–71 (article in Japanese).
178. Bogdanović R, Banićević M, Cvorić A. Testicular function following cyclophosphamide treatment for childhood nephrotic syndrome: long-term follow-up study. Pediatr Nephrol. 1990;4:451–4.
179. Jones DP, Stapleton FB, Roy S 3rd, Wyatt RJ. Beneficial effect of second courses of cytotoxic therapy in children with minimal change nephrotic syndrome. Pediatr Nephrol. 1988;2:291–5.

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GUIDELINE

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

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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.

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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.

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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%203001 12%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.

(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 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

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].