

minimal change nephrotic syndrome. In the evaluation of efficacy, a high response rate of  $\geq 90\%$  was found. Steroid pulse therapy may be considered when absorption of oral steroids seems difficult because of intestinal edema, diarrhea, and other conditions.

**CQ2. Is cyclosporine recommended for reducing urinary protein level and preventing the decline of renal function in minimal change nephrotic syndrome?**

**Recommendation grade: C1**

In minimal change nephrotic syndrome, we recommend prescribing cyclosporine with steroid for reducing urinary protein level in steroid-resistant and relapsing cases.

**Recommendation grade: not graded**

However, it is not clear whether cyclosporine is effective for preventing the decline of renal function.

**[Summary]**

Compared to steroid alone treatment, the combination treatment of cyclosporine and steroid is effective for reducing urinary protein level and shortening the duration of achieving remission in relapsing cases of minimal change nephrotic syndrome. However, it is not clear whether cyclosporine is effective for preventing the decline of renal function.

**CQ3. Is steroid therapy recommended for reducing urinary protein level and preventing the decline of renal function in focal segmental glomerulosclerosis?**

**Recommendation grade: C1**

In focal segmental glomerulosclerosis, we recommend steroid therapy be prescribed for reducing urinary protein level and preventing the decline of renal function at the initial treatment.

**Recommendation grade: not graded**

Steroid pulse therapy may be considered when absorption of oral steroids seems difficult.

**[Summary]**

Oral steroid therapy as an initial treatment is effective for focal segmental glomerulosclerosis, showing a remission induction rate of 20–50%. However, the efficacy of steroids varies depending on histological variants. The

concomitant use of immunosuppressants is necessary for steroid-resistant cases.

**CQ4. Is cyclosporine recommended for reducing urinary protein level and preventing the decline of renal function in focal segmental glomerulosclerosis?**

**Recommendation grade: C1**

In focal segmental glomerulosclerosis, we recommend the combination treatment of cyclosporine and steroid be prescribed for reducing urinary protein level.

**Recommendation grade: not graded**

The combination treatment of cyclosporine and steroid seems to be effective for preventing the decline of renal function in focal segmental glomerulosclerosis.

**[Summary]**

The combination treatment of cyclosporine and steroid is effective for inducing remission in focal segmental glomerulosclerosis. Evidence showing that the combination treatment of cyclosporine and steroid is effective for preventing the decline renal function is limited; however, some extent of efficacy is expected. The possibilities of cyclosporine nephrotoxicity with the long-term use of the drug are unclear.

**CQ5. Is the addition of immunosuppressive agents to steroid recommended for reducing urinary protein level or preventing the decline of renal function in frequently relapsing nephrotic syndrome**

**Recommendation grade: C1**

In frequently relapsing nephrotic syndrome in adults, we recommend cyclosporine or cyclophosphamide be additionally prescribed with steroid for reducing urinary protein level.

**Recommendation grade: C1**

The addition of mizoribine to steroid decreases the relapse rate of frequently relapsing nephrotic syndrome in children; however, it is not known whether the same is true in adults. Mizoribine may be considered depending on the cases.

**Recommendation grade: not graded**

It is not clear whether the addition of cyclosporine, cyclophosphamide, or mizoribine to steroid can inhibit the decline in renal function.

**[Summary]**

The addition of oral cyclosporine or cyclophosphamide to steroid is effective for the reduction of urinary protein level in frequently relapsing nephrotic syndrome in adults. However, the efficacy of mizoribine is unknown. Although renal function might be preserved by maintaining complete remission, there is no clear evidence indicating that these additional immunosuppressive agents are effective for preventing the decline of renal function.

**CQ6. Are additional immunosuppressive agents to steroid recommended for reducing the urinary protein level and preventing the decline of renal function in steroid-resistant focal segmental glomerulosclerosis?**

**Recommendation grade: C1**

In steroid-resistant focal segmental glomerulosclerosis in adults, we recommend additional cyclosporine ( $3.5 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ ) treatment with low-dose steroids for reducing urinary protein.

**Recommendation grade: not graded**

However, it is not known whether the addition of other immunosuppressive agents is effective for reducing the urinary protein level and preventing the decline of renal function in steroid-resistant focal segmental glomerulosclerosis in adults.

**[Summary]**

The addition of cyclosporine is effective for reducing the urinary protein level in steroid-resistant focal segmental glomerulosclerosis in adults. Maintaining the remission of nephrotic syndrome is associated with preventing the decline of renal function. However, the addition of chlorambucil and mycophenolate mofetil is not superior to that of cyclosporine for reducing urinary protein level. There are no sufficient data indicating that these immunosuppressive agents have direct renoprotective effects in adult cases of steroid-resistant focal segmental glomerulosclerosis.

**[Membranous nephropathy]**

**CQ7. Is no treatment or supportive treatment alone without immunosuppressive agents recommended for reducing the urinary protein level and preventing the decline of renal function in membranous nephropathy with nephrotic syndrome?**

**Recommendation grade: C1**

In some patients with membranous nephropathy with nephrotic syndrome, we suggest that no treatment or supportive treatment alone without immunosuppressive agents may reduce the urinary protein level.

**Recommendation grade: not graded**

We do not recommend no treatment or supportive treatment alone without immunosuppressive agents in the long term because it cannot prevent declining renal function in patients with membranous nephropathy showing nephrotic syndrome.

**[Summary]**

No treatment or supportive therapy alone without immunosuppressive agents is effective for reducing the urinary protein level in some patients with membranous nephropathy showing nephrotic syndrome; however, these are not expected to prevent the decline of renal function. In particular, this type treatment may worsen the renal prognosis of patients with severe urinary protein excretion.

**CQ8. Is steroid-alone treatment recommended for reducing the urinary protein level and preventing the decline of renal function in membranous nephropathy?**

**Recommendation grade: C1**

In membranous nephropathy, we recommend steroid-alone treatment for preventing the decline of renal function.

**Recommendation grade: not graded**

It is not clear whether treatment with steroid alone is effective for reducing the urinary protein level.

**[Summary]**

Compared with no treatment, steroid-alone treatment is not effective for reducing the urinary protein level in membranous nephropathy. In a retrospective study in Japanese patients with membranous nephropathy, the remission rates did not show any significant differences between three

treatment groups (steroid alone, steroid and cyclophosphamide, and supportive treatment); however, treatment with steroid alone and the combination of steroid and cyclophosphamide showed significant effectiveness in preventing the decline of renal function compared with supportive treatment.

**CQ9. Is cyclosporine recommended for reducing the urinary protein level and preventing the decline of renal function in membranous nephropathy?**

**Recommendation grade: C1**

In steroid-resistant membranous nephropathy, we recommend the combination of steroid and cyclosporine be given for reducing the urinary protein level and preventing the decline of renal function.

**[Summary]**

The combination treatment with steroid and cyclosporine is effective for reducing the urinary protein level and preventing the decline of renal function compared with treatment with steroid alone. Between steroid with cyclosporine and steroid with alkylating agents, the superiority of treatment with steroid and cyclosporine has not been recognized.

**CQ10. Is mizoribine recommended for reducing the urinary protein level and preventing the decline in renal function in membranous nephropathy?**

**Recommendation grade: C1**

In steroid-resistant or refractory membranous nephropathy, we suggest that the addition of mizoribine is effective for reducing the urinary protein level.

**Recommendation grade: not graded**

It is not clear whether the addition of mizoribine is effective for preventing the decline in renal function.

**[Summary]**

It has been reported that the addition of mizoribine to steroid reduces the urinary protein level in patients with membranous nephropathy. However, this effect of mizoribine has not been confirmed in appropriately sized randomized control trials. The dose of mizoribine should be carefully reduced in patients with chronic renal failure.

**CQ11. Are alkylating agents recommended for reducing the urinary protein level and preventing the decline of renal function in membranous nephropathy?**

**Recommendation grade: C1**

In membranous nephropathy, we recommend the addition of cyclophosphamide to steroid for reducing the urinary protein level and preventing the decline of renal function. Because of the frequent adverse effects and the very few evidences showing the efficacy of alkylating agents in Japanese patients, we suggest that the use of alkylating agents be considered carefully.

**[Summary]**

In overseas countries, it is generally accepted that the combination treatment with steroid and alkylating agents is superior to steroid-alone treatment for inducing the remission of nephrotic syndrome in membranous nephropathy. Although the study is retrospective, the results suggest that the efficacy of steroid-alone treatment is similar to that of the combination treatment with steroid and alkylating agents in Japanese patients. Attention should be given to the high frequency of adverse effects of alkylating agents. Cyclophosphamide has fewer adverse effects than chlorambucil.

**CQ12. Are conservative treatments recommended for reducing the urinary protein level and preventing the decline of renal function in non-nephrotic membranous nephropathy?**

**Recommendation grade: C1**

In some patients with non-nephrotic membranous nephropathy, we suggest that conservative treatment with RAS inhibitors, lipid-lowering agents, or antiplatelet agents may be effective for reducing the urinary protein level in some cases.

**Recommendation grade: not graded**

However, it is not clear whether those conservative treatments are effective for preventing the decline of renal function.

**[Summary]**

Conservative therapies with RAS inhibitors, lipid-lowering agents, or antiplatelet agents are effective for reducing the urinary protein level in some patients with membranous nephropathy accompanied by a non-nephrotic

rage of proteinuria. However, these conservative treatments are not expected to prevent the decline of renal function.

**[Membranoproliferative glomerulonephritis]**

**CQ13. Is steroid recommended for reducing the urinary protein level and preventing the decline of renal function in idiopathic nephrotic membranoproliferative glomerulonephritis?**

**Recommendation grade: C1**

In children with idiopathic nephrotic membranoproliferative glomerulonephritis, we suggest that steroid be prescribed for reducing the urinary protein level and preventing the decline of renal function.

Although the benefit of steroid in adults with nephrotic membranoproliferative glomerulonephritis is not known, we suggest that steroids may be effective for reducing the urinary protein level and preventing the decline of renal function in some adult patients.

**[Summary]**

Observational studies suggest that steroid is beneficial for reducing the urinary protein level and preventing the decline of renal function in children with idiopathic membranoproliferative glomerulonephritis. Although evidences concerning the treatment of adult patients with idiopathic membranoproliferative glomerulonephritis are inconsistent, we suggest that steroid is the acceptable treatment agent in some adult patients with idiopathic membranoproliferative glomerulonephritis.

**2. How to use steroids**

**CQ14. Is oral steroid treatment recommended during intervals between steroid pulse treatment (i.e., at days when steroid pulse treatment is not given)?**

**Recommendation grade: not graded**

Oral steroid treatment should be considered at least on days when steroid pulse therapy is not given.

**[Summary]**

The half-life of methylprednisolone is short, i.e., 1–3 h, whereas that of oral steroids is long, i.e., 12–36 h. Therefore, oral steroid treatment is considered necessary on days when steroid pulse therapy is not given.

**CQ15. Is the increase of oral steroid doses or the change in administration routes recommended for patients with systemic edema?**

**Recommendation grade: C1**

In patients with severe intestinal edema associated with systemic edema, we suggest that increasing the dose of oral steroid or changing the prescription routes be considered.

**[Summary]**

The efficacy of oral steroid seems to be diminished in patients with systemic edema. Therefore, it may be necessary to consider intravenous steroid therapy or steroid pulse therapy in patients with systemic edema.

**CQ16. Is alternate-day steroid administration as a means of steroid dose reduction effective for inhibiting the incidence of adverse effects?**

**Recommendation grade: Not graded**

The efficacy of alternate-day steroid administration is not clear because there are few relevant reports in adult nephrotic syndrome.

**[Summary]**

Limited evidence exists on whether alternate-day steroid treatment for nephritis as a means of dose reduction is effective for inhibiting adverse reactions. Further studies are warranted.

**CQ17. In the treatment of recurrent nephrotic syndrome, is reducing the dose of steroid compared with that of the first treatment recommended?**

**Recommendation grade: C1**

We recommend that the steroid dose be decided appropriately depending on the relapse condition of individual patients.

**Recommendation grade: not graded**

Concerning steroid treatment of recurrent nephrotic syndrome, opinions differ about whether the dose should be the same or reduced compared with that in the first treatment.

**[Summary]**

In steroid treatment of recurrent nephrotic syndrome, opinions differ about whether the treatment should be different from the initial treatment. There are two conflicting opinions: (i) recurrent nephrotic syndrome should be treated in the same way as the initial treatment, and (ii) recurrent nephrotic

syndrome should be treated with prednisolone at a dose of 20–30 mg/day. No consensus has been reached.

**CQ18. Is there a standard period for steroid maintenance therapy after nephrotic syndrome has remitted?**

**Recommendation grade: C1**

We recommend that a period for steroid maintenance treatment be set after nephrotic syndrome has remitted.

**Recommendation grade: not graded**

The duration of this period should be decided according to the disease types and pathologies of individual patients.

**[Summary]**

There is no clear evidence suggesting a standard period for steroid maintenance therapy after nephrotic syndrome has remitted.

### 3. Immunosuppressive agents not allowed by medical insurance (at the time of description of this guideline in 2013)

**CQ19. Is rituximab recommended for reducing the urinary protein level and preventing the decline of renal function in nephrotic syndrome?**

**Recommendation grade: C1**

It is not clear whether rituximab is effective for reducing the urinary protein level and preventing the decline of renal function. In cases of frequently relapsing or steroid-resistant nephrotic syndrome, we suggest that rituximab may be effective for reducing the urinary protein level and preventing the decline of renal function. (The use of rituximab for nephrotic syndrome is not allowed by medical insurance.)

**[Summary]**

Rituximab may be effective for reducing the urinary protein level in nephrotic syndrome; however, clinical studies are rare in adult cases. Rituximab could be an option for the treatment of nephrotic syndrome, but we cannot conclude that it is an effective agent.

**CQ20. Is mycophenolate mofetil recommended for reducing the urinary protein level and preventing the decline of renal function in nephrotic syndrome?**

**Recommendation grade: C1**

It is not clear whether mycophenolate mofetil is effective for reducing the urinary protein level and preventing the decline of renal function. In cases of frequently relapsing or steroid-resistant nephrotic syndrome, we suggest that mycophenolate mofetil may be effective for reducing the urinary protein level and preventing the decline of renal function. (The use of mycophenolate mofetil for nephrotic syndrome is not allowed by medical insurance.)

**[Summary]**

Mycophenolate mofetil may be effective for reducing the urinary protein level in nephrotic syndrome; however, clinical studies are rare in adult patients with nephrotic syndrome. Mycophenolate mofetil could be an option for the treatment of nephrotic syndrome, but we cannot conclude that it is an effective agent.

**CQ21. Is azathioprine recommended for reducing the urinary protein level and preventing the decline of renal function in nephrotic syndrome?**

**Recommendation grade: C2**

In nephrotic syndrome, we do not recommend azathioprine as an initial treatment because it is not clear whether this agent is effective for reducing the urinary protein level and preventing the decline of renal function.

**Recommendation grade: C1**

We suggest that azathioprine may be prescribed as a second treatment agent for the purpose of steroid dose reduction or in patients with steroid-resistant nephrotic syndrome.

**[Summary]**

Azathioprine may be effective for reducing the urinary protein level in nephrotic syndrome; however, clinical studies of adult cases of nephrotic syndrome are rare. Azathioprine could be an option for the treatment of primary nephrotic syndrome, but we cannot conclude that it is an effective agent. We do not recommend this agent for initial treatment.

#### 4. Nephrotic syndrome in the elderly

**CQ22. Are immunosuppressive agents recommended for elderly patients with nephrotic syndrome?**

**Recommendation grade: C1**

In elderly patients with nephrotic syndrome, we recommend the careful use of immunosuppressive agents, with adequate attention to adverse effects. The efficacy and safety of immunosuppressive agents is unclear in elderly patients with nephrotic syndrome.

**[Summary]**

Few clinical studies have evaluated the efficacy of immunosuppressive agents in elderly patients with nephrotic syndrome; however, the efficacy for reducing the urine protein level was reported to be similar to that in younger patients. In contrast, the incidence rate of adverse effects in elderly patients is higher than that in younger patients. The incidence rate of adverse effects of chlorambucil is higher than that of cyclophosphamide.

#### 5. Adjunctive and supportive treatments

**CQ23. Are renin-angiotensin system (RAS) inhibitors recommended for reducing the urinary protein level in nephrotic syndrome?**

**Recommendation grade: B**

In patients with hypertension and nephrotic syndrome, we recommend RAS inhibitors for reducing the urinary protein level. It is not clear whether RAS inhibitors are effective for patients with nephrotic syndrome without hypertension.

**[Summary]**

A number of studies have shown that RAS inhibitors reduce the urinary protein level in patients with membranous nephropathy, membranoproliferative glomerulonephritis, and focal segmental glomerulosclerosis with nephrotic syndrome; however, complete remission by RAS inhibitors alone has been seldom reported. Furthermore, very little is known about the effect of RAS inhibitors in patients with nephrotic syndrome without hypertension.

**CQ24. Are diuretics recommended for the reduction of edema in nephrotic syndrome?**

**Recommendation grade: B**

In edematous patients with nephrotic syndrome, we recommend oral diuretics, particularly loop diuretics, for reducing edema.

**Recommendation grade: B**

The use of intravenous diuretics should be considered if the effect of oral diuretics is insufficient, as they effectively reduce the volume of body fluids.

**[Summary]**

Oral loop diuretic monotherapy or oral loop diuretics combined with thiazide diuretics are effective for edema reduction in patients with nephrotic syndrome. Intravenous loop diuretics are considered appropriate for patients with severe edema. No study has compared the effects of single injection, multiple injection, and continuous injection.

**CQ25. Is albumin administration recommended for improving hypoalbuminemia in nephrotic syndrome?**

**Recommendation grade: D**

Albumin administration does not improve hypoalbuminemia or edema in patients with nephrotic syndrome and may exacerbate hypertension; therefore, its use is not recommended in patients with nephrotic syndrome.

**Recommendation grade: C1**

However, in cases of severe shock or pulmonary edema, albumin administration may have a temporary but useful effect.

**[Summary]**

It is not clear whether albumin administration improves edema or has a diuretic effect in patients with nephrotic syndrome. Rather, it may exacerbate hypertension.

**CQ26. Are antiplatelet and anticoagulant agents recommended for reducing the urinary protein level and preventing thrombosis in nephrotic syndrome?**

**Recommendation grade: C2**

In nephrotic syndrome, we do not recommend antiplatelets and anticoagulants because it is not clear whether these agents are effective for reducing the urinary protein level when used as monotherapies.

**Recommendation grade: C1**

In nephrotic syndrome, we suggest that anticoagulants may be prescribed for preventing thrombosis (preventative administration is not covered by insurance). The efficacy of antiplatelet agents for preventing thrombosis is not clear.

**[Summary]**

There is very little evidence to suggest that urinary protein levels are reduced in patients with nephrotic syndrome by antiplatelet and anticoagulant monotherapies; thus, their effectiveness is unclear. However, warfarin has been reported to reduce the incidence of fatal pulmonary embolism.

**CQ27. Are statins recommended to improve lipid metabolism abnormalities and life prognosis in nephrotic syndrome?****Recommendation grade: C1**

In nephrotic syndrome, we recommend that statins be prescribed for lipid metabolism abnormalities because they have been proven effective for improving such conditions.

However, it is not clear whether statins inhibit the incidence of cardiovascular disease and improve life prognosis.

**[Summary]**

Statins can lower triglyceride, total cholesterol, and LDL cholesterol levels and increase HDL cholesterol levels in patients with nephrotic syndrome, similar to its effect in healthy persons. However, there are no prospective studies with primary endpoints such as the prevention of cardiovascular disease or the improvement of life prognosis, and its effectiveness on prognosis is unclear.

**CQ28. Is ezetimibe recommended for improving lipid metabolism abnormalities and life prognosis in nephrotic syndrome?****Recommendation grade: C2**

In nephrotic syndrome, we do not recommend ezetimibe monotherapy because it is not clear whether ezetimibe alone improves the lipid metabolism abnormalities or life prognosis of patients.

**[Summary]**

Studies verifying the clinical effect of ezetimibe monotherapy in patients with

nephrotic syndrome have not been conducted, and the effect of this treatment on improving dyslipidemia or life prognosis is unclear.

**CQ29. Is LDL apheresis recommended for reducing the urinary protein levels in patients with refractory nephrotic syndrome?****Recommendation grade: C1**

In patients with refractory nephrotic syndrome and high LDL cholesterol levels, we recommend LDL apheresis for reducing the urinary protein level.

**[Summary]**

LDL apheresis is reported to be effective in reducing the urinary protein levels in approximately 50% of cases of refractory nephrotic syndrome.

**CQ30. Is the extracorporeal ultrafiltration method (ECUM) recommended for refractory edema and ascites in patients with nephrotic syndrome?****Recommendation grade: C1**

In nephrotic syndrome, we recommend the extracorporeal ultrafiltration method (ECUM) for removing body fluids in refractory edema and ascites that are difficult to control using drug-based treatment.

**[Summary]**

ECUM has been reported to be effective in improving edema and ascites in patients with nephrotic syndrome.

**CQ31. Is the trimethoprim-sulfamethoxazole combination recommended for preventing infectious diseases during immunosuppressive therapy of the nephrotic syndrome?****Recommendation grade: C1**

In nephrotic syndrome, we recommend treatment with the trimethoprim-sulfamethoxazole combination for preventing pneumocystis pneumonia during immunosuppressive therapy.

**[Summary]**

Although there are no direct evidences in nephrotic syndrome, guidelines for other similar immunosuppressive conditions recommend the prophylactic administration of the trimethoprim-sulfamethoxazole combination for pneumocystis pneumonia. Therefore, this drug combination is recommended

for preventing pneumocystis pneumonia during immunosuppressive therapy of nephrotic syndrome.

**CQ32. Is immunoglobulin supply recommended for preventing infectious diseases in nephrotic syndrome?**

**Recommendation grade: C1**

In nephrotic syndrome, we suggest supplying immunoglobulin to patients with hypogammaglobulinemia for preventing infectious diseases. (Prevention treatment with immunoglobulins is not covered by medical insurance.)

**[Summary]**

Although there is limited evidence, immunoglobulin supply could prevent infectious diseases in patients with nephrotic syndrome presenting with hypogammaglobulinemia. However, the risks and economic disadvantages of this treatment should be carefully considered.

**CQ33. Is treatment with antituberculous drugs recommended for preventing tuberculous infection in nephrotic syndrome?**

**Recommendation grade: C1**

In nephrotic syndrome, we recommend antitubercular agents for patients who are suspected to have latent tuberculosis. (Prevention treatment with antitubercular agents is not covered by medical insurance.)

**[Summary]**

Immunosuppressive therapy for nephrotic syndrome increases the risk of progression of latent tuberculosis to active tuberculosis. There are few reports about the treatment of latent tuberculosis in patients with nephrotic syndrome; however, this treatment is necessary in patients with nephrotic syndrome undergoing immunosuppressive therapy.

**CQ34. Should immunosuppressive therapy be administered to patients with hepatitis B-positive nephrotic syndrome?**

**Recommendation grade: C1**

In nephrotic syndrome, we recommend that immunosuppressive therapy be administered after the initiation of hepatitis B treatment.

**[Summary]**

Before administering immunosuppressive therapy for nephrotic syndrome, hepatitis B infection should be evaluated first. In case infection is present, immunosuppressive therapy should be administered after the treatment of hepatitis B infection.

#### 6. Lifestyle and dietary instruction

**CQ35. Is the incidence of cancer in patients with membranous nephropathy higher than that in the general population?**

**Recommendation grade: not graded**

The incidence of cancer among patients with membranous nephropathy is not higher in Japan than in Europe and the United States. However, it is unclear whether the incidence of cancer in patients with membranous nephropathy is higher than that in the general population in Japan.

**[Summary]**

The incidence of cancer in patients with membranous nephropathy is lower in Japanese patients than in Europeans and Americans. However, it is unclear whether the incidence of cancer in patients with membranous nephropathy is higher than that in the general population in Japan.

**CQ36. Is bed rest and/or exercise restriction recommended in nephrotic syndrome?**

**Recommendation grade: C2**

In nephrotic syndrome, we do not recommend bed rest and/or exercise restriction because it is not clear whether these measures have beneficial effects.

**[Summary]**

There have been no studies directly proving the beneficial effects of bed rest or exercise restriction in patients with nephrotic syndrome. Excessive bed rest is undesirable from the viewpoint of preventing pulmonary thrombosis and embolism, as well as deep vein thrombosis due to the hypercoagulable condition of nephrotic syndrome and the congestive condition associated with long-term bed rest. Moderate exercise is considered acceptable.

**CQ37. Is vaccination recommended in patients with nephrotic syndrome during treatment with corticosteroids and immunosuppressive drugs?**

**Recommendation grade: B**

During the treatment of patients with nephrotic syndrome with corticosteroids and immunosuppressive agents, we recommend administering inactivated vaccines against influenza virus and *Streptococcus pneumoniae* according to the risk of infection.

**[Summary]**

Few studies have proved the direct blocking effect of vaccination against influenza virus and *Pneumococcus* in patients with nephrotic syndrome undergoing treatment with steroid or immunosuppressive agents. Nephrotic patients have a high infection risk, and vaccination can provide safety benefits for these patients. Therefore, we recommend vaccination in patients with nephrotic syndrome, except in cases where vaccination is inappropriate. However, the efficacy and safety of live vaccine in nephrotic syndrome are controversial.

**CQ38. Are there any preventive measures against steroid-induced femoral head necrosis in nephrotic syndrome?**

**Recommendation grade: not graded**

There are no studies on the preventive measures against femoral head necrosis (FHN) in patients with nephrotic syndrome. The use of only the essential dose of steroid may prevent steroid-induced FHN.

**[Summary]**

No study has directly evaluated the preventive measures for steroid-induced FHN. In nephrotic syndrome, avoiding the excess use of steroid may prevent steroid-induced FHN.

**CQ39. Is the avoidance of mental stress recommended to prevent the onset and relapse of nephrotic syndrome?**

**Recommendation grade: C1**

In steroid-dependent or frequently relapsing nephrotic syndrome in children, the avoidance of mental stress is effective for preventing relapse; thus, we recommend the avoidance of mental stress in these patients. However, it is

not clear whether the avoidance of mental stress is effective for preventing relapse of nephrotic syndrome in adult patients.

**[Summary]**

There have been no reports that evaluated the relation between the new onset of nephrotic syndrome and mental stress. In children with nephrotic syndrome, the strong relation between the relapse of nephrotic syndrome and mental stress has already been suggested. However, the relation between the onset or relapse of nephrotic syndrome and mental stress in adulthood has not been investigated thus far. Further studies are required in the future.

**CQ40. Is a fat-restricted diet recommended for improving dyslipidemia and life prognosis in patients with nephrotic syndrome?**

**Recommendation grade: C1**

We recommend that patients with nephrotic syndrome be given a fat-restricted diet for the treatment of dyslipidemia. It is not clear whether a fat-restricted diet improves the prognosis of nephrotic patients.

**[Summary]**

In patients with nephrotic syndrome, a fat-restricted diet consisting of low cholesterol-containing food and vegetables/beans ameliorates dyslipidemia. No study has proved that a fat-restricted diet improves the life prognosis of these patients.

## **2. [Dietary Instruction]**

Salt restriction is essential for the alleviation of edema in nephrotic syndrome. Some patients with nephrotic syndrome show inhibited plasma renin activity (PRA) and elevated atrial natriuretic peptide (ANP) level that are comparable to the condition of salt accumulation described in the overflowing hypothesis. The efficacy of strict protein restriction is controversial; therefore, extreme protein restriction is not recommended in patients with nephrotic syndrome. The published guideline from the Japanese Society of Nephrology, "Guidelines of lifestyle and diet therapy for patients with chronic kidney disease," recommends a protein intake of 1.0–1.1 g/kg body weight (BW)/day in minimal change nephrotic syndrome and 0.8 g/kg BW/day in other nephrotic syndromes. To keep the nitrogen balance, a calorie intake of 35 kcal/kg BW/day is recommended.

### 3. [Treatment Interpretation and Treatment Algorithm]

We summarized the treatments by histological types. The treatment strategies and the statements or answers of related clinical questions are comprehensively described for each strategy. Concerning adjunctive and supportive treatments or lifestyle and dietary instructions, some of the statements or answers of related clinical questions are listed.

The treatments mentioned here referred to the previous Japanese guideline “Clinical guideline for refractory nephrotic syndrome 2002” and the second revised version, “Clinical guideline for nephrotic syndrome 2011,” published by the Research Group on Progressive Renal Disease of the Ministry of Health, Labor and Welfare. Additionally a novel idea is introduced in the treatment strategies based on published papers.

Unfortunately, we could not endorse all of mentioned treatment strategies and treatment algorithms through our clinical questions. We provided the clinical questions to a maximum extent for decision making.

Patients with nephrotic syndrome are aging; thus, they have many medical complications. Treatment for these patients must be decided on a case-by-case basis rather than strictly adhering to the guidelines. For the selection of agents, we provide the opinions of members of the guideline committee, with reference to the previous two guidelines in Japan. We consider that we cannot use the same types or doses of agents as those recommended by articles published overseas.

Use of treatment agents not allowed by medical insurance depends on the decision established in 2013, when the present guideline is published. In the future, this decision may change.

#### 1) Minimal change nephrotic syndrome (MCNS)

##### 1. Initial treatment

Oral prednisolone is administered at a single daily dose starting at 0.8–1 mg·kg<sup>-1</sup>·day<sup>-1</sup> (maximum 60 mg/day), and continued for 1–2 weeks after remission. Thus, the initial dose is maintained for 2–4 weeks. Tapering of prednisolone is performed through the following program: a 5–10 mg dose reduction every 2–4 weeks. After the prednisolone dose is reduced to 5–10 mg/day, the minimum dose must be continued for preventing relapse for approximately 2 years, and then gradually tapered and discontinued.

Steroid pulse therapy should not be performed readily; however, it may be

considered for cases in which absorption of steroid from the gastrointestinal tract is doubted (Fig. 1)

- In the evaluation of efficacy, MCNS shows a high response rate to initial oral steroid treatment (CQ1).
- We recommend that oral steroid alone be prescribed for preventing the acute decline of renal function at the initial treatment (CQ1).
- Steroid pulse therapy may be considered when absorption of oral steroids seems difficult (CQ1).
- Oral steroid administration should be considered on days when patients are not receiving steroid pulse treatment (CQ14).
- In patients with severe intestinal edema associated with systemic edema, we suggest that increasing the dose of oral steroid or changing the administration routes be considered (CQ15).
- The efficacy of alternate-day steroid administration is not clear because there are few relevant reports in adult nephrotic syndrome (CQ16).
- There is no clear goal about the duration of continued steroid therapy after remission; however, at least 24 weeks may be necessary in MCNS (CQ18).

##### 2. Relapse cases

Steroids are administered at equal or lower doses than the initial dose at the relapse of nephrotic syndrome.

- As for steroid therapy for recurrent nephrotic syndrome, the opinions differ as to whether the dose of treatment should be the same as that of the first treatment or lower than that of the first treatment (CQ17).

##### 3. Frequently relapsing, steroid-dependent, and steroid-resistant cases

Immunosuppressive agents such as cyclosporine (1.5–3.0 mg·kg<sup>-1</sup>·day<sup>-1</sup>), cyclophosphamide (50–100 mg/day), or mizoribine (150 mg/day) are administered in addition to steroid.

The efficacy of mizoribine has been confirmed in children but not in adults. Therefore, the choice of mizoribine for adult patients is suggested here. During treatment with immunosuppressive agents, the patient’s age and

complications should be considered. Elderly patients easily develop complications.

- In MCNS, we recommend that cyclosporine with steroid be prescribed for reducing the urinary protein level in steroid-resistant and relapse cases (CQ2, CQ5).
- In frequently relapsing nephrotic syndrome derived from MCNS and FSGS in adult patients, we recommend cyclosporine or cyclophosphamide be additionally prescribed to steroid for reducing the urinary protein level (CQ5).
- The addition of mizoribine to steroid decreases the relapse rate in children with frequently relapsing nephrotic syndrome, whereas it is not known whether the same is true in adults. Mizoribine may be considered depending on the cases (CQ5).
- In steroid-dependent or steroid-resistant nephrotic syndrome derived from MCNS and FSGS, we recommend cyclosporine or cyclophosphamide be additionally administered with steroid for reducing the urinary protein level (CQ5).
- Recently, MCNS is found even in elderly patients. Few clinical studies have evaluated the efficacy of immunosuppressive agents in elderly patients with nephrotic syndrome; however, the efficacy of these agents for reducing the urine protein level was reported to be similar to that in younger patients. The incidence rate of adverse effects in elderly patients is higher than that in younger patients. Careful observation is necessary in the treatment of elderly patients with nephrotic syndrome (CQ22).

#### **4. Immunosuppressive agents not covered by medical insurance (at the time of description of this guideline in 2013)**

The use of agents not covered by medical insurance in Japan, such as rituximab, mycophenolate mofetil, and azathioprine, may be considered for patients resistant to agents allowed by medical insurance. However, it is not clear whether these agents are effective for reducing the urinary protein level and preventing the decline of renal function in nephrotic syndrome. For patients with frequently relapsing or steroid-resistant nephrotic syndrome, we suggest that these agents may be effective for reducing the urinary protein level and preventing the decline of renal function (CQ19, CQ20, CQ21).

## **2) Focal segmental glomerulosclerosis (FSGS)**

### **1. Initial treatment**

Oral prednisolone is administered at a single daily dose starting at 0.8–1 mg·kg<sup>-1</sup>·day<sup>-1</sup> (maximum 60 mg/day) for 2–4 weeks as the initial treatment. Steroid pulse therapy is considered for cases with massive urine protein excretion or severe systemic edema. After remission, tapering of steroid dose is performed following the program of MCNS (Fig.2).

- Oral steroid therapy as an initial treatment is effective for FSGS, showing a remission induction rate from 20% to 50%. We recommend steroid therapy as the initial treatment (CQ3).
- Steroid pulse therapy may be considered for patients with severe intestinal edema (CQ3).
- Oral steroid should be administered on days when patients are not receiving steroid pulse treatment (CQ14).
- In patients with severe intestinal edema associated with systemic edema, we suggest increasing the oral steroid or changing the prescription routes (CQ15).
- The efficacy of alternate-day steroid administration is not clear in preventing the adverse effects of steroid (CQ16).
- There is no clear goal about the duration of continued steroid use after remission; however, steroid was continually used for at least 6 months in observational studies in patients with FSGS (CQ18).
- The efficacy of immunosuppressive agents for reducing the urine protein level in elderly patients was reported to be similar to that in younger patients. The incidence rate of adverse effects in elderly patients is higher than that in younger patients. Careful observation is necessary in the treatment of elderly patients with nephrotic syndrome. The selection of steroid treatment or combination treatment with steroid and immunosuppressive agents should be determined on the basis of the age or complications of patients (CQ22).

### **2. Relapsing and frequently relapsing cases**

The combination of oral steroid and cyclosporine, 2.0–3.0 mg·kg<sup>-1</sup>·day<sup>-1</sup>, is selected for relapsing and frequently relapsing cases.

- The combination of oral steroid and cyclosporine is selected for patients with relapsing and frequently relapsing FSGS instead of steroid-alone treatment (CQ5, CQ17, CQ22).

### 3. Steroid-dependent and steroid-resistant cases

If steroid-alone treatment for >4 weeks fails to attain complete or incomplete remission, cyclosporine, 2.0–3.0 mg·kg<sup>-1</sup>·day<sup>-1</sup>, is added to steroid therapy.

- Compared with steroid-alone treatment, the combination treatment of cyclosporine and steroid may be more effective for reducing the urinary protein level in steroid-resistant FSGS. The nephrotoxicity of cyclosporine due to long-term use is unclear (CQ4).
- It is not clear whether cyclosporine is more effective than mizoribine or cyclophosphamide for reducing the urinary protein level (CQ6).
- The efficacy of immunosuppressive agents for reducing the urine protein level in elderly patients was reported to be similar to that in younger patients. The incidence rate of adverse effects in elderly patients is higher than that in younger patients. Careful observation is necessary in the treatment of elderly patients with nephrotic syndrome. The selection of steroid treatment or combination treatment with steroid and immunosuppressive agents should be determined on the basis of the age or complications of patients (CQ22).

### 4. Immunosuppressive agents not covered by medical insurance (at the time of description of this guideline in 2013)

The use of agents not covered by medical insurance in Japan, such as rituximab, mycophenolate mofetil, and azathioprine, may be considered for patients resistant to agents covered by medical insurance. However, it is not clear whether these agents are effective for reducing the urinary protein level and preventing the decline of renal function in nephrotic syndrome. In cases of frequently relapsing or steroid-resistant nephrotic syndrome, we suggest that these agents may be effective for reducing the urinary protein level and preventing the decline of renal function (CQ19, CQ20, CQ21).

### 3) Membranous nephropathy (MN)

#### 1. Initial treatment

Oral prednisolone is administered at a single daily dose starting at 0.6–0.8 mg·kg<sup>-1</sup>·day<sup>-1</sup> and continued for 4 weeks. Instead of oral steroid alone, prednisolone and cyclophosphamide are administered as a starting dose of 50–100 mg/day. Lower-dose oral steroid and cyclosporine as the initial treatment is considered for patients who are concerned about the adverse effects of steroids, such as diabetic patients (Fig.3).

- In some patients with MN with nephrotic syndrome, we suggest that no treatment or supportive treatment alone without immunosuppressive agents may reduce the urinary protein level. However, we cannot expect that no treatment or supportive treatment alone is effective for preventing the decline of renal function (CQ7).
- Steroid-alone treatment is not more effective than no treatment for reducing the urinary protein level. We recommend steroid-alone treatment for preventing the decline of renal function (CQ8).
- In a retrospective study on Japanese patients with MN, the remission rates did not show any significant differences between three treatment groups (steroid alone, steroid and cyclophosphamide, and supportive treatment); however, treatment with steroid alone and the combination of steroid and cyclophosphamide showed significant effectiveness in preventing the decline of renal function when compared with supportive treatment (CQ8).
- In steroid-resistant MN, we recommend the combination of steroid and cyclosporine for reducing the urinary protein level and preventing the decline of renal function (CQ9).
- Between steroid with cyclosporine and steroid with alkylating agents, the superiority of the treatment with steroid with cyclosporine has not been recognized (CQ9).
- In patients with severe intestinal edema associated with systemic edema, we suggest increasing the dose of oral steroid or changing the prescription (CQ15).
- The efficacy of alternate-day administration is not clear in preventing the adverse effects of steroid (CQ16).

- There is no clear goal about the period of continued steroid administration after remission; however, steroid was continued for at least 6 months in observational studies on patients with MN (CQ18).
- The efficacy of immunosuppressive agents for reducing the urine protein level in elderly patients was reported to be similar to that in younger patients. The incidence rate of adverse effects in elderly patients is higher than that in younger patients. Careful observation is necessary in the treatment of elderly patients with nephrotic syndrome. The selection of steroid treatment or combination treatment with steroid and immunosuppressive agents should be determined on the basis of the age or complications of patients (CQ22).

## 2. Steroid-resistant cases

If steroid-alone treatment for >4 weeks fails to attain complete or incomplete remission, cyclosporine (2.0 - 3.0 mg/kg/day), mizoribine (150 mg/day), or cyclophosphamide (50-100 mg/day) is added to steroid therapy.

- In steroid-resistant MN, we recommend the combination of steroid and cyclosporine for reducing the urinary protein level and preventing the decline of renal function (CQ9).
- In steroid-resistant or refractory MN, we suggest that the addition of mizoribine to steroid is effective for reducing the urinary protein level (CQ10).
- In MN, we recommend the addition of cyclophosphamide to steroid for reducing the urinary protein level and preventing the decline of renal function (CQ11). Because of the frequent adverse effects of alkylating agents and the limited evidence of the efficacy of these agents in Japanese patients, we suggest that the use of alkylating agents be considered carefully.

## 3. Non-nephrotic cases

- In patients with MN showing non-nephrotic proteinuria, we suggest that conservative treatment with RAS inhibitors, lipid-lowering agents, or antiplatelet agents is effective for reducing the urinary protein level in some cases. (CQ12).

- However, it is not clear whether those conservative treatments are effective for preventing the decline of renal function (CQ12).

## 4) Membranoproliferative glomerulonephritis (MPGN)

- In children with MPGN, steroid is recommended for reducing the urinary protein level and preventing the decline of renal function. In adult cases, the efficacy of steroid is unclear, although steroid may be considered in some patients with MPGN (CQ13).

## 5) Adjunctive and supportive treatments

### 1. Renin-angiotensin system (RAS) inhibitors

- In patients with hypertension and nephrotic syndrome, we recommend RAS inhibitors be prescribed for reducing the urinary protein level. It is not known whether RAS inhibitors are effective for patients with nephrotic syndrome without hypertension (CQ23).

### 2. Diuretics

- In edematous patients with nephrotic syndrome, we recommend oral diuretics, particularly loop diuretics, be prescribed for reducing edema. The use of intravenous diuretics should be considered if the effect of oral diuretics is insufficient, because they effectively reduce body fluid volumes (CQ24).

### 3. Albumin agents

- Albumin administration does not improve hypoalbuminemia or edema in patients with nephrotic syndrome and may exacerbate hypertension; therefore, it is not recommended for this condition. However, in cases of severe shock or pulmonary edema, albumin administration may have a temporary but useful effect (CQ25).

### 4. Antiplatelet and anticoagulant agents

- For patients with nephrotic syndrome, we do not recommend prescribing antiplatelets and anticoagulants as monotherapies because their effectiveness in reducing the urinary protein level is not clear. We suggest that administration of anticoagulants may be prescribed for preventing thrombosis (preventative administration is not covered by insurance). The efficacy of antiplatelet agents for preventing thrombosis is not clear (CQ26).

#### 5. Statins

- In nephrotic syndrome, we recommend statins be prescribed for lipid metabolism abnormalities because they have been proven effective for improving such conditions. However, it is not clear whether statins reduce the incidence of cardiovascular disease and improve prognosis (CQ27).

#### 6. Ezetimibe

- In nephrotic syndrome, it is not clear whether this treatment improves the lipid metabolism abnormalities or prognosis of patients (CQ28).

#### 7. Low-density lipoprotein (LDL) apheresis

- In patients with refractory nephrotic syndrome and high LDL cholesterol levels, we recommend LDL apheresis for reducing the urinary protein level (CQ29).

#### 8. Extracorporeal ultrafiltration method (ECUM)

- In patients with nephrotic syndrome, we recommend the ECUM for the removal of body fluids in refractory edema and ascites that are difficult to control using drug-based therapy (CQ30).

#### 9. Trimethoprim-sulfamethoxazole combination

- In patients with nephrotic syndrome, we recommend treatment with the trimethoprim-sulfamethoxazole combination for preventing pneumocystis pneumonia during immunosuppressive therapy (CQ31).

#### 10. Immunoglobulin supply

- In nephrotic syndrome, we suggest supplying immunoglobulin to patients with hypogammaglobulinemia for the prevention of infectious diseases. (Prevention treatment with immunoglobulin supply is not covered by medical insurance.) (CQ32).

#### 11. Antituberculous drugs

- We recommend antitubercular agents be given for patients with nephrotic syndrome who are suspected to have latent tuberculosis. (Prevention treatment with antitubercular agents is not covered by medical insurance.) (CQ33)

#### 12. Hepatitis B virus treatment

- In patients with nephrotic syndrome, we recommend that immunosuppressive therapy be started after the initiation of hepatitis B treatment (CQ34).

#### 6) Lifestyle and dietary instruction

##### 1. Screening for cancer

- The incidence of cancer in patients with membranous nephropathy is not higher in Japan than in Europe and the United States. However, it is unclear whether the incidence of cancer in patients with membranous nephropathy is higher than that in the general population in Japan (CQ35).

##### 2. Bed rest and/or exercise restriction

- We do not recommend bed rest and/or exercise restriction for patients with nephrotic syndrome because it is not clear whether these measures have beneficial effects (CQ36).

### 3. Vaccination

- During the treatment with corticosteroids and immunosuppressive agents, we recommend administering inactivated vaccines against influenza virus and *Streptococcus pneumoniae* according to the risk of infection to patients with nephrotic syndrome (CQ37).

### 4. Steroid-induced femoral head necrosis (FHN)

- No study has investigated the preventive measures against FHN in patients with nephrotic syndrome. The use of only the essential dose of steroid may prevent the development of steroid-induced FHN (CQ38).

### 5. Avoidance of mental stress

- In steroid-dependent and/or frequently relapsing nephrotic syndrome in children, avoidance of mental stress is effective to prevent relapse; thus, we recommend the avoidance of mental stress in these patients. However, it is not clear whether avoidance of mental stress is effective for preventing the relapse of nephrotic syndrome in adults (CQ39).

### 6. Fat-restricted diet

- We recommend providing fat-restricted diet for the treatment of dyslipidemia in patients with nephrotic syndrome. It is not clear whether a fat-restricted diet improves the prognosis of nephrotic patients (CQ40).

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### II. Diagnosis

#### 1. Symptomatology • Clinical manifestation

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### III. Epidemiology • Prognosis

#### 1. Incidence • Prevalence • Recurrence rate

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- #### 2. Remission rate • Nonresponsive rate • Renal prognosis
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#### IV. Treatment

##### 1. Clinical questions for treatment

##### 1) Minimal change nephrotic syndrome · Focal segmental glomerulosclerosis

##### **CQ 1. Is oral steroid recommended for reducing urinary protein level and preventing the decline of renal function in minimal change nephrotic syndrome?**

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##### **CQ 2 . Is cyclosporine recommended for reducing urinary protein level and preventing the decline of renal function in minimal change nephrotic syndrome?**

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11. Chang JW, et al. *Pediatr Int* 2007 ; 49 : 349-54. (Level 4)
12. Pena A, et al. *Pediatr Nephrol* 2007 ; 22 : 1875-80. (Level 4)
13. Tune BM, et al. *J Am Soc Nephrol* 1997 ; 8 : 824-32. (Level 4)

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2. Durkan AM, et al. *Kidney Int* 2001 ; 59 : 1919-27. (Level 1)
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5. Ishikura K, et al. *Kidney Int* 2008 ; 73 : 1167-73. (Level 2)
6. Ponticelli C, et al. *Kidney Int* 1993 ; 43 : 1377-84. (Level 2)
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10. Heering P, et al. *Am J Kidney Dis* 2004 ; 43 : 10-8. (Level 2)

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**frequently relapsing nephrotic syndrome?**

1. Ponticelli C, et al. Nephrol Dial Transplant 1993 ; 8 : 1326-32. (Level 2)
2. Mak SK, et al. Nephrol Dial Transplant 1996 ; 11 : 2192-201. (Level 4)
3. Nolasco F, et al. Kidney Int 1986 ; 29 : 1215-23. (Level 4)
4. Yoshioka K, et al. Kidney Int 2000 ; 58 : 317-24. (Level 2)
5. Fujieda M, et al. Clin Nephrol 2008 ; 69 : 179-84. (Level 5)
6. Doi T, et al. Clin Nephrol 2008 ; 69 : 433-5. (Level 5)

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2. Cattran DC, et al. Kidney Int 1999 ; 56 : 2220-6. (Level 2)
3. Heering P, et al. Am J Kidney Dis 2004 ; 43 : 10-8. (Level 2)
4. Gipson DS, et al. Kidney Int 2011 ; 80 : 868-78. (Level 2)

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1. Polanco N, et al. J Am Soc Nephrol 2010 ; 21 : 697-704. (Level 4)
2. Gansevoort RT, et al. Nephrol Dial Transplant 1992 ; 7 (Suppl 1) : 91-6. (Level 3)
3. Praga M, et al. Am J Kidney Dis 1992 ; 20 : 240-8. (Level 5)
4. Shiiki H, et al. Kidney Int 2004 ; 65 : 1400-7. (Level 4)

**CQ 8. Is steroid-alone treatment recommended for reducing urinary protein level and preventing the decline of renal function in membranous nephropathy?**

1. Coggins CH, et al. N Engl J Med 1979 ; 301 : 1301-6. (Level 2)
2. Cattran DC, et al. N Engl J Med 1989 ; 320 : 210-5. (Level 2)
3. Cameron JS, et al. QJM 1990 ; 74 : 133-56. (Level 2)
4. Shiiki H, et al. Kidney Int 2004 ; 65 : 1400-7. (Level 4)

5. Ponticelli C, et al. N Engl J Med 1992 ; 327 : 599-603. (Level 2)
6. Pahari DK, et al. J Assoc Physicians India 1993 ; 41 : 350-1. (Level 3)
7. Cattran DC, et al. Kidney Int 2001 ; 59 : 1484-90. (Level 2)

**CQ 9. Is cyclosporine recommended for reducing urinary protein level and preventing the decline of renal function in membranous nephropathy?**

1. Schieppati A, et al. Cochrane Database Syst Rev 2004 (4) : CD004293 (Level 2)
2. Perna A, et al. Am J Kidney Dis 2004 ; 44 : 385-401. (Level 1)
3. Cattran DC, et al. Kidney Int 2001 ; 59 : 1484-90. (Level 2)
4. Alexopoulos E, et al. Nephrol Dial Transplant 2006 ; 21 : 3127-32. (Level 4)
5. Naumovic R, et al. Biomed Pharmacother 2011 ; 65 : 105-10. (Level 2)
6. Satio T, et al. Clin Exp Nephrol, in press (Level 2)

**CQ 10. Is mizoribine recommended for reducing urinary protein level and preventing the decline of renal function in membranous nephropathy?**

1. Shibasaki T, et al. Clin Exp Nephrol 2004 ; 8 : 117-26. (Level 3)

**CQ 11. Are alkylating agents recommended for reducing urinary protein level and preventing the decline of renal function in membranous nephropathy?**

1. Schieppati A, et al. Cochrane Database Syst Rev 2004 (4) : CD004293 (Level 2)
2. Perna A, et al. Am J Kidney Dis 2004 ; 44 : 385-401. (Level 1)
3. Ponticelli C, et al. N Engl J Med 1992 ; 327 : 599-603. (Level 2)
4. Falk RJ, et al. Ann Intern Med 1992 ; 116 : 438-45. (Level 2)
5. Shiiki H, et al. Kidney Int 2004 ; 65 : 1400-7. (Level 4)
6. Hofstra JM, et al. Nephrol Dial Transplant 2008 ; 23 : 3534-8. (Level 4)
7. Naumovic R, et al. Biomed Pharmacother 2010 ; 64 : 633-8. (Level 4)
8. Eriguchi M, et al. Nephrol Dial Transplant 2009 ; 24 : 3082-8. (Level 1)
9. Bizzarri D, et al. Contrib Nephrol 1993 ; 105 : 65-70. (Level 4)
10. Branten AJ, et al. Am J Kidney Dis 2007 ; 50 : 248-56. (Level 3)
11. Ponticelli C, et al. J Am Soc Nephrol 1998 ; 9 : 444-50. (Level 2)

**CQ 12. Are conservative treatments recommended for reducing urinary**