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GUIDELINE

A digest of the Evidence-Based Clinical Practice Guideline for Nephrotic Syndrome 2020

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Levels of evidence:

A—High: We are confident that the true effect lies close to the estimate of the effect.

B—Moderate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

C—Low: The true effect may be substantially different from the estimate of the effect.

D—Very low: The estimate of effect is very uncertain and often will be far from the truth.

Grades of recommendations:

1—"We recommend"

2—"We suggest"

None

In 2020, the Research for Intractable Renal Diseases of the Ministry of Health, Labour and Welfare of Japan established the Committee of Guideline for Nephrotic Syndrome, which published (A Digest from Evidence-Based Clinical Practice Guideline for Nephrotic Syndrome 2020) on the website (jin-shogai.jp/policy/index.html). This is the English version of that digest.

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Definitions, underlying diseases, pathophysiology

Definitions/diagnosis

Nephrotic syndrome is a clinical syndrome characterized by severe proteinuria and hypoproteinemia (or hypoalbuminemia). Massive proteinuria is caused by abnormal permeability of the glomerular filtration barrier, which is based on the glomerular insult. Nephrotic syndrome is classified as primary in the absence of an underlying cause, and secondary in the presence of a causal factor. The diagnostic criteria for nephrotic syndrome are shown in Table 1.

Pathophysiology of underlying diseases

Each underlying disease that causes primary nephrotic syndrome has distinct epidemiological and clinical features; however, the final diagnosis is made using histopathology with renal biopsy. Each disease includes both primary and secondary diseases. The classification has been evolving gradually with advances in pathophysiological understanding.

Minimal change disease

Approximately 40% of patients with primary nephrotic syndrome in Japan are diagnosed with minimal change disease (MCD). MCD accounts for approximately 70–80% of pediatric primary nephrotic syndrome cases, and the

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Table 1 Clinical definition of adult nephrotic syndrome

1. Persistent proteinuria: ≧3.5 g/day (comparable to ≧3.5 g/gCr at spot urine)
2. Hypoalbuminemia: Serum albumin ≦3.0 g/dL
Serum total protein ≦ 6.0 g/dL is supportive
3. Edema
4. Dyslipidemia (High level of serum LDL-cholesterol)
Proteinuria and hypoalbuminemia listed above are prerequisites for the clinical diagnosis of nephrotic syndrome
Edema is not a prerequisite but an important finding for nephrotic syndrome
Dyslipidemia is not a prerequisite for nephrotic syndrome
Oval fat body may be a supportive finding for diagnosis of nephrotic syndrome

proportion decreases in the older population; wherein, in the age group of > 60 years, MCD accounts for more than 20% of cases.

This disease is clinically characterized as acute-onset nephrotic syndrome with severe proteinuria and hypoalbuminemia. It is often associated with dyslipidemia. It is important to note that MCD occasionally results in acute kidney injury. The only consistent pathological finding is diffuse effacement of foot processes observed by electron microscopy.

Glucocorticoid therapy is the standard treatment for MCD and shows a high response rate; however, it should be noted that MCD often relapses. In particular, a substantial number of cases show frequently relapsing nephrotic syndrome, which results in relapses occurring more than twice in six months, or steroid-dependent nephrotic syndrome (SDNS), in which glucocorticoids cannot be withdrawn due to two consecutive relapses during tapering or after cessation of treatment.

Focal segmental glomerulosclerosis

Focal segmental glomerulosclerosis (FSGS) refers to a histopathological pattern of glomerular scarring that affects a subset of glomeruli (i.e., focal) and involves only a portion of the glomerular tuft (i.e., segmental). Historically, the disease concept of FSGS originated from pediatric cases of steroid-resistant nephrotic syndrome. Since then, morphologic variants of FSGS have been recognized, and numerous secondary causes of FSGS, including genetic and acquired forms, have been identified.

While primary FSGS typically develops in a pattern similar to that of minimal change nephrotic syndrome (MCNS), it often results in refractory nephrotic syndrome and end-stage kidney disease. FSGS accounts for approximately 10% of all primary nephrotic syndromes in Japan. Although the hallmark of the pathogenesis of this disease is believed to be podocyte injury, the precise mechanism remains to be unknown.

Membranous nephropathy

Membranous nephropathy (MN) is the most common underlying primary nephrotic syndrome in middle-aged and older patients. The development of this disease is based on subepithelial immune deposits. MN is classified as a primary or secondary form of disease according to the presence or absence of underlying factors, respectively.

The recent discovery of pathological antigens, such as phospholipase A2 receptor (PLA2R) and thrombospondin type 1 domain-containing 7A (THSD7A), has accelerated the elucidation of disease mechanisms. The secondary etiologies of MN include malignancy, autoimmune diseases, therapeutic agents, and infections.

Membranoproliferative glomerulonephritis

Membranoproliferative glomerulonephritis (MPGN) refers to a morphological pattern that includes thickening of the glomerular capillary wall with duplication of the basement membrane and an increase in the number of cells in the glomerular tuft. MPGN can be classified into two forms, i.e., primary (with no specific causal factors) or secondary (with specific causal factors). Primary MPGN occurs almost exclusively during childhood or adolescence.

The secondary form of MPGN may be secondary to a wide variety of disease states, such as thrombotic microangiopathy (TMA), antiphospholipid antibody syndrome (APS), cryoglobulinemia, malignant lymphoma, and post-bone marrow transplantation.

The clinical characteristics vary, and patients may present with nephrotic syndrome, acute kidney injury, or chronic deterioration of kidney function with mild abnormal urinalysis.

Based on recent advances in the understanding of the pathophysiology of MPGN, new classifications according to its etiology have been proposed C3 glomerulopathy, which shows C3-dominant staining with little or no immunoglobulins and complements in the classical pathway (i.e., C1q, C4), has been well recognized. Genetic abnormalities of complement regulatory factors and autoantibodies against complement regulatory factors have been implicated in its pathogenesis.

Diagnosis

Symptomatology/clinical symptoms

The main symptoms of nephrotic syndrome are edema, pleural effusion, and ascites due to fluid volume overload. In severe proteinuria, foamy urine is prominent, and severe hypoalbuminemia reduces urine volume. Depending on the primary disease, some nephrotic syndromes have a more acute onset, while some have a more chronic onset. Nephrotic syndrome may also be triggered by infection or allergic symptoms.

Laboratory findings

In addition to the diagnostic criteria of hypoalbuminemia (hypoproteinemia), severe proteinuria, and associated dyslipidemia, a variety of abnormal laboratory findings are observed in patients with nephrotic syndrome. Nephritis type with hematuria and nephrotic type without hematuria are particularly important to differentiate the primary diseases. Blood tests reveal renal dysfunction, electrolyte abnormality, coagulation/fibrinolysis abnormalities, anemia, and hormonal disorders. Immuno-serological abnormalities are also important in differentiating primary diseases.

Biomarkers

Among the biomarkers for nephrotic syndrome, MN has been the most developed. Autoantibodies against PLA2R (NCBI Gene ID: 22925) and THSD7A (NCBI Gene ID: 2281), which are antigens responsible for primary MN, have been shown to be useful for not only differentiating the primary disease but also as therapeutic indicators.

Genetic testing

The pathogenesis of steroid-resistant nephrotic syndrome can be attributed to (1) immunological mechanisms and (2) abnormalities in the podocyte structure associated with abnormalities in genes encoding podocyte-related proteins. Identification of the causative genes by genetic testing may be useful to determine the treatment strategy, including renal transplantation, and predict patient prognosis. Full consideration should be given to patients and their families, and genetic consultation should be provided before and after genetic testing, as required.

CQ on diagnosis (CQ1)

CQ1 Is the measurement of anti-PLA2R antibody recommended for the diagnosis of primary MN in adult patients with nephrotic syndrome?

> Recommendation Grade 2D
> Serum anti-PLA2R antibody for the diagnosis of primary MN in adult patients with nephrotic syndrome may be measured when a renal biopsy is difficult to perform. (Strength of recommendation: "Conditional recommendation" / Certainty in evidence: "Very low")
> Ancillary note: Presently, the serum anti-PLA2R antibody assay for the diagnosis of primary MN is not approved by the public health insurance

Summary

The measurement of serum anti-PLA2R antibody may be useful for the diagnosis of primary MN in adult patients with nephrotic syndrome. However, this test is not recommended in all cases because it is not approved by the public health insurance. It can be measured when a renal biopsy is contraindicated or difficult to perform.

Treatment

Minimal Change Nephrotic Syndrome (Fig. 1)

Initial treatment

Oral prednisolone is administered once daily, starting at 0.8–1.0 mg/kg/day (maximum 60 mg/day) and continued for 1 to 2 weeks after remission. Prednisolone is tapered through the following steps: a 5–10 mg dose reduction every 2 to 4 weeks. When the prednisolone dose reaches 5–10 mg/day, it is continued for at least 6 months. Thereafter, the minimum dose is gradually tapered and discontinued in approximately 1 year, although it should be determined according

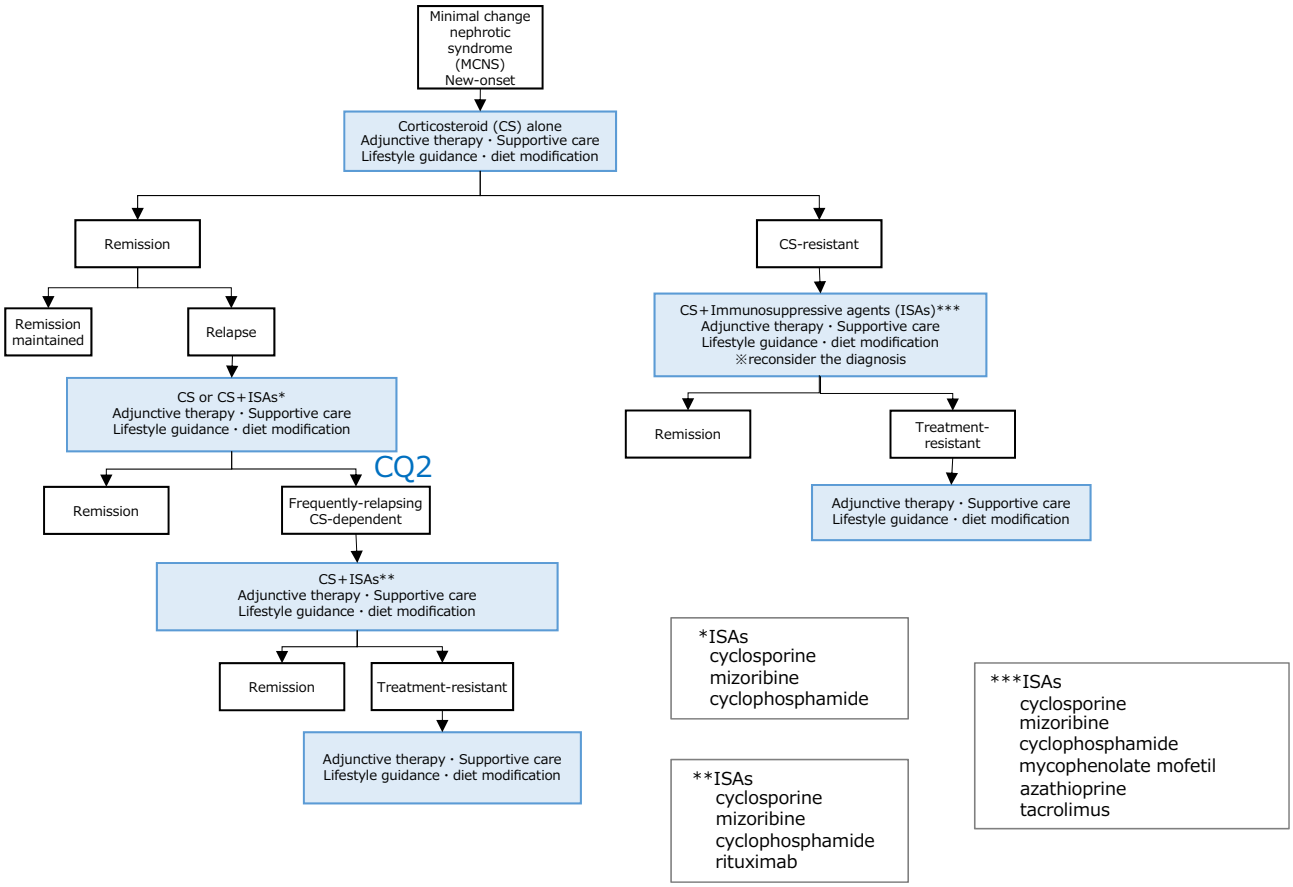

Fig. 1 Treatment algorithm for minimal change nephrotic syndrome

to the case in which the minimum dose will be maintained and tapered off. MCNS shows a high response rate to initial oral steroid treatment. Intravenous administration or pulse therapy with corticosteroids may be considered for patients with impaired absorption of corticosteroids associated with severe intestinal edema.

Relapsing cases

Corticosteroids are administered at doses equal to or lower than the initial dose at relapse of nephrotic syndrome. In recurrent MCNS, we suggest that cyclosporine should be added to corticosteroids to achieve proteinuria remission, prevent relapse of nephrotic syndrome, and preserve renal function. Cyclosporine is initiated at 1.5–3.0 mg/kg/day, and the dose is adjusted in accordance with blood levels. In some cases, additional administration of another immunosuppressive agent (cyclophosphamide 50–100 mg/day or mizoribine 150 mg/day) may be considered.

Frequently relapsing, steroid-dependent, or steroid-resistant cases

For patients with frequently relapsing or SDNS due to MCNS, an immunosuppressive agent, such as cyclosporine (1.5–3.0 mg/kg/day), cyclophosphamide (50–100 mg/day), or mizoribine (150 mg/day), may be added to treatment with corticosteroids. For steroid-resistant nephrotic syndrome, administration of cyclosporine or cyclophosphamide is also considered in addition to corticosteroids. We suggest rituximab for frequently recurrent and steroid-dependent patients with MCNS who do not respond to corticosteroids alone or in combination with the above immunosuppressive agents. The use of agents not covered by public health insurance in Japan (i.e., mycophenolate mofetil, azathioprine, or tacrolimus) may be considered for patients resistant to approved immunosuppressants. However, these immunosuppressants are not first-line drugs.

CQ2 What is the recommended treatment for adult MCNS?

Recommendation grade 2D
We suggest that cyclosporine should be added to corticosteroids in adult patients with recurrent MCNS. (Strength of recommendation: "weak" / Certainty in evidence: "Very low")

Supplementary items:
1) There is no evidence for immunosuppressive or non-immunosuppressive agents other than cyclosporine.
2) This proposal mainly targets at non-elderly patients, and there may be uncertainty of evidence in the proposal for elderly patients.

Summary

In adult patients with recurrent MCNS, the combined use of cyclosporine and corticosteroids is effective for achieving proteinuria remission, preventing recurrence of nephrotic syndrome, and preserving renal function.

Focal segmental glomerulosclerosis (Fig. 2)

Initial treatment

Oral prednisolone is administered once daily, starting at 0.8–1 mg/kg/day (maximum 60 mg/day), for 2–4 weeks as the initial treatment for primary FSGS with nephrotic syndrome. Corticosteroid pulse therapy is considered in severe cases. After remission, prednisolone is tapered according to the initial treatment of MCNS. The optimal duration of corticosteroid therapy after achieving remission has not yet been established. Corticosteroid therapy is continued for approximately 6 months on average in observational studies for FSGS.

Relapsing cases

Owing to little evidence, we suggest that relapsing cases of steroid-sensitive primary FSGS should be treated using the same approach as relapsing cases of MCNS. Combined with predonisolone, cyclosporine should be administered at 1.5–3.0 mg/kg/day as the initial dose. The serum levels of cyclosporine should be monitored. The use of cyclophosphamide (50–100 mg/day) or mizoribine (150 mg/day) may be considered as an alternative immunosuppressive agent.

Frequently relapsing or steroid-dependent cases

Owing to little evidence, we suggest that frequently relapsing or steroid-dependent cases of primary FSGS in adults should be treated using the same approach as frequently relapsing or steroid-dependent cases of MCNS. Rituximab may be considered in cases of frequently relapsing or steroid-dependent primary FSGS who are treated with a combination of corticosteroids and other immunosuppressive agents, such as cyclosporine, cyclophosphamide, or mizoribine.

Steroid-resistant cases

In cases of steroid-resistant primary FSGS, immunosuppressive agents such as cyclosporine, mizoribine, cyclophosphamide, or mycophenolate mofetil are prescribed. Compared with corticosteroids alone, the combination treatment of corticosteroids and cyclosporine may be more effective in achieving remission and preventing the decline in renal function in steroid-resistant primary FSGS (CQ3). Potential nephrotoxicity with prolonged cyclosporine treatment should be carefully monitored (CQ3). Although the combination treatment with mycophenolate mofetil and high-dose dexamethasone may be effective for achieving remission, mycophenolate mofetil is not covered by the public health insurance in Japan. The non-inferiority of mizoribine, cyclophosphamide, azathioprine, and chlorambucil to cyclosporine for reducing proteinuria in steroid-resistant primary FSGS has not been demonstrated. Several observational studies have shown the efficacy of low-density lipoprotein (LDL) apheresis for inducing remission in steroid-resistant FSGS. In patients with refractory nephrotic syndrome, conservative therapy should be continued. In some selected cases of steroid-resistant FSGS, genetic testing to identify mutations in podocyte-related genes may be considered.

CQ3 What is the recommended treatment for adults with steroid-resistant primary FSGS?

Recommendation Grade: 2C
In adults with steroid-resistant primary FSGS, we suggest a combination treatment with steroids and cyclosporine. (Strength of recommendation: “Weak” / Certainty in evidence: “Low”)

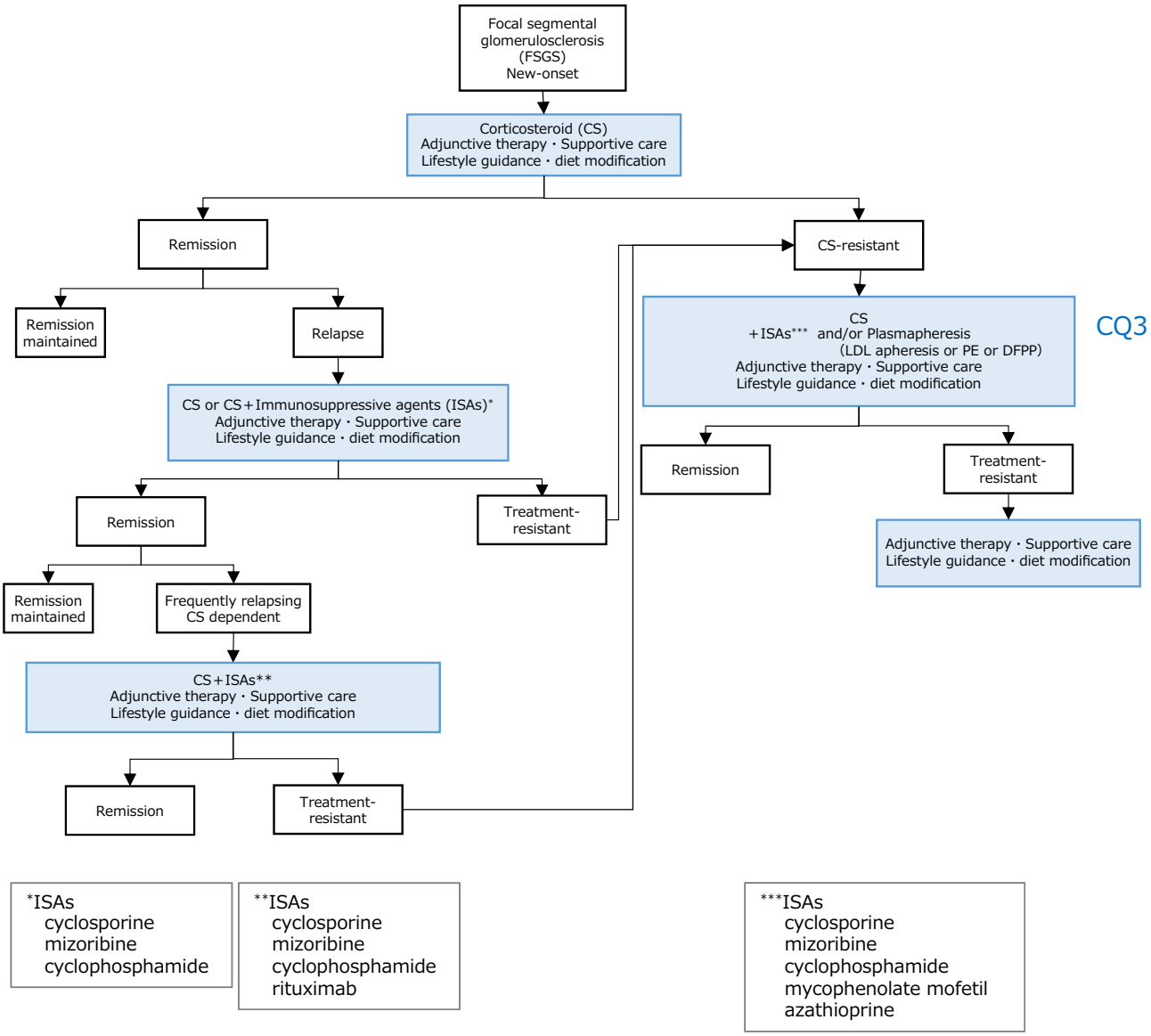

Fig. 2 Treatment algorithm for primary FSGS. This algorithm is for primary FSGS in adults with nephrotic syndrome and not for FSGS in adults without nephrotic syndrome

Recommendation Grade: 2D
In adult patients with steroid-resistant primary FSGS, we suggest a combination treatment with mycophenolate mofetil and high-dose dexamethasone. (Strength of recommendation: "Weak" / Certainty in evidence: "Very low")

Supplementary items:
1) There is little evidence that supports the administration of immunosuppressive agents other than cyclosporine and mycophenolate mofetil.
2) Mycophenolate mofetil for primary FSGS is not covered by the public health insurance in Japan.

Summary

Several studies have reported that combination treatment with corticosteroids and cyclosporine is effective for achieving remission and preventing a decline in renal function in adults with steroid-resistant primary FSGS. In addition, one study reported that combination therapy with mycophenolate mofetil and high-dose dexamethasone is effective for inducing remission.

Membranous nephropathy (Fig. 3)

Initial treatment

Initial treatment for patients with nephrotic MN could be any of the following: (1) conservative therapy (adjuvant therapy, supportive care, lifestyle guidance, diet modification) alone, or, in addition to (1), (2) corticosteroid monotherapy (predonisolone 0.6–0.8 mg/kg/day for 4 weeks) or (3) combination treatment with corticosteroids and immunosuppressive agents. If the patient does not achieve complete remission or incomplete remission type I after 6 months of conservative therapy, consider switching to corticosteroid monotherapy or combination treatment with corticosteroids and immunosuppressive agents.

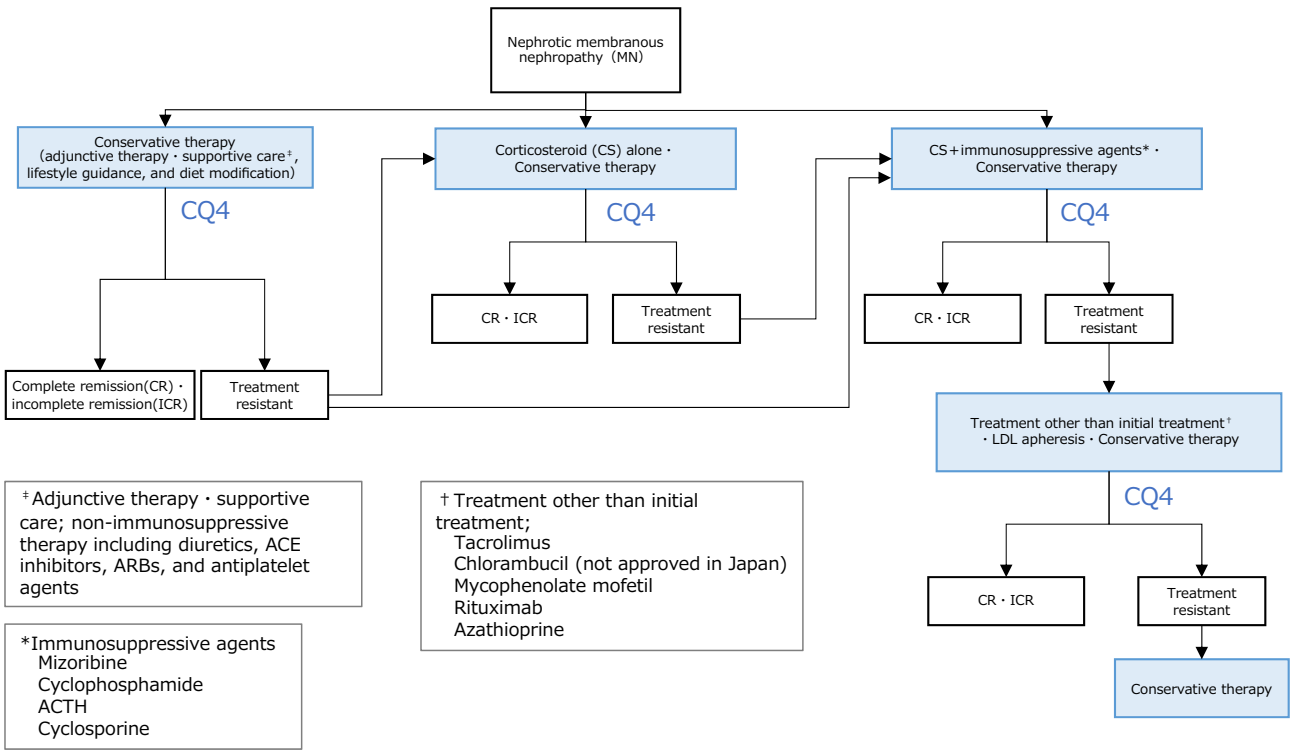

Fig. 3 Treatment algorithm for primary MN. This algorithm is used for primary MN in adults with nephrotic syndrome. For MN patients without nephrotic syndrome, conservative therapy should be the first choice, and immunosuppressive agents may be administered if necessary

According to previous studies, corticosteroid monotherapy for nephrotic MN is not superior to supportive care in terms of remission (CQ4). However, some retrospective observational studies in Japanese patients have shown that corticosteroid monotherapy is more effective than supportive care.

Regarding combination treatment with corticosteroids and immunosuppressive agents, some studies have shown that cyclophosphamide, mizoribine, or adrenocorticotropic hormone (ACTH) is superior to conservative care in terms of remission. However, in Japan, cyclosporine is often used as the first-line treatment. Although several lines of evidence have demonstrated that combination treatment with corticosteroids and cyclosporine is more effective than corticosteroid monotherapy for nephrotic MN; a systematic review performed for this clinical practice guideline showed that combination treatment with corticosteroids and cyclosporine for nephrotic MN is not superior to conservative care in terms of remission (CQ4).

Treatment-resistant MN

If the patient does not achieve complete remission or incomplete remission type I after 4 weeks of corticosteroid monotherapy, additional treatment should be considered. As of 2020, rituximab treatment for adult-onset MN is not approved in Japan. However, there are some reports showing the efficacy of rituximab in treating nephrotic MN. It should be noted that based on the current systematic analysis, rituximab therapy for adult-onset nephrotic MN is not superior to conservative care in terms of remission at 12 months, and there are limited reports as of 2020 (CQ4).

CQ4 What is the recommended treatment for primary MN presenting as nephrotic syndrome in adults?

Recommendation Grade: None

(1) In adults with primary MN presenting with nephrotic syndrome, combination treatment with cyclophosphamide and corticosteroid is recommended over conservative care alone. (Strength of recommendation: "Weak" / Certainty in evidence: "Very low")

(2) In adults with primary MN presenting as nephrotic syndrome, combination treatment with mizoribine and corticosteroid is recommended over conservative care alone. (Strength of recommendation: "Weak" / Certainty in evidence: "Very low")

(3) In adults with primary MN presenting as nephrotic syndrome, combination treatment with tacrolimus and corticosteroid is recommended over conservative care alone. (Strength of recommendation: "Weak" / Certainty in evidence: "Very low")

(4) In adults with primary MN presenting as nephrotic syndrome, combination treatment with chlorambucil and corticosteroid is recommended over conservative care alone. (Strength of recommendation: "Weak" / Certainty in evidence: "Very low")

(5) In adults with primary MN presenting as nephrotic syndrome, treatment with ACTH is recommended over conservative care alone. (Strength of recommendation: "Weak" / Certainty in evidence: "Very low")

Additional information
1) Currently, the use of tacrolimus for MN is not covered by the public health insurance in Japan.
2) The use of chlorambucil is not approved in Japan.

Summary:

In adult patients with primary MN presenting as nephrotic syndrome, we suggest combination treatment with corticosteroids, cyclophosphamide, mizoribine, tacrolimus, or chlorambucil, or treatment with ACTH, rather than conservative care alone.

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