therapy (corticosteroids and cyclophosphamide) plus plasmapheresis. We recommend cyclophosphamide (1–2 mg/kg/day) for patients with refractory GN. However, it is necessary to reduce the dose of cyclophosphamide in patients with advanced renal dysfunction.

CQ 11. Which is recommended for improving renal and patient survival in RPGN, oral cyclophosphamide or intravenous pulses of cyclophosphamide?

Recommendation grade: B

There are no differences in renal and patient survival between oral cyclophosphamide and intravenous pulses of cyclophosphamide. Both therapies have been shown to improve renal function and survival in patients with RPGN.

[Summary]

The clinical guideline in Japan recommends immunosuppressive agents with corticosteroids as the initial therapy, considering the clinical grade, patient age, and dialysis requirement. The guideline recommends daily oral cyclophosphamide (25–100 mg/day) or intravenous pulses of cyclophosphamide (250–750 mg/m-2/day/month) in patients with clinical grade I and II in whom the effects of corticosteroids are not enough, and in patients with clinical grade III and IV who are younger than 70 years. There are no differences in renal and patient survival between oral cyclophosphamide and intravenous pulses of cyclophosphamide, although treatment with intravenous pulses of cyclophosphamide has reduced the rate of relapse and adverse events.

CQ 12. Is immunosuppressive therapy recommended for improving renal function and survival in patients with RPGN who are receiving dialysis at the time of diagnosis?

Recommendation grade: C1

In patients with ANCA-positive RPGN who are receiving dialysis at the time of diagnosis, immunosuppressive therapy is shown to improve renal function and survival.

Recommendation grade: C1

In patients with lupus nephritis presenting with RPGN (class IV and some class III cases) who are receiving dialysis at the time of diagnosis, immunosuppressive therapy is shown to improve renal function and survival.

Recommendation grade: not graded

In patients with anti-GBM antibody glomerulonephritis presenting with RPGN who are receiving dialysis at the time of diagnosis, immunosuppressive therapy may not improve renal survival. However, in patients with pulmonary hemorrhage, immunosuppressive agents are recommended to improve survival.

[Summary]

In patients with granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) who have severe active renal disease, the addition of plasma exchange to cyclophosphamide and glucocorticoid therapy is currently recommended by EULAR (the European League Against Rheumatism) guideline. Even in patients with dialysis-dependent ANCA-associated vasculitis, the chance of renal recovery is high when they have a high percentage of normal glomeruli. However, as therapy-related deaths usually occur in older patients and in those with poor general condition, carefully decisions for safer treatment regimens are warranted.

In patients with lupus nephritis presenting with RPGN (class IV and some class III cases), the combined use of corticosteroids and immunosuppressive agents such as intravenous cyclophosphamide or mycophenolate mofetil is the current standard therapy by ACR (American College of Rheumatology) guideline. Liang reported that 59.3% patients with lupus nephritis with recent-onset renal failure recovered their renal function after 6 months of follow-up, whereas 11.1% had died. As the chronic component of renal function loss is often irreversible with immunosuppressive therapy, renal echogram and renal biopsy should be performed to determine whether the renal failure is reversible.

In patients with anti-GBM antibody glomerulonephritis presenting with RPGN who are receiving dialysis at the time of diagnosis, immunosuppressive therapy may not improve renal survival. However, in patients with pulmonary hemorrhage, immunosuppressive agents are recommended to improve survival.

CQ 13. Is rituximab recommended for improving renal function and survival in patients with RPGN?

Recommendation grade: B

As the initial therapy for ANCA-positive RPGN, addition of rituximab to corticosteroids may improve renal and patient survival. Therefore, rituximab is recommended in cases in which standard therapy cannot be given because of adverse effects, or in those who are refractory to or relapsed after standard therapy (insurance is applicable only for patients with MPA and GPA in Japan).

Recommendation grade: C1

In patients with lupus nephritis presenting with RPGN (class IV and some class III cases), there is no evidence to support that treatment with rituximab improves renal function and survival; however, it could be considered if there is no other treatment available (not covered by insurance in Japan).

Recommendation grade: not graded

In patients with anti-GBM antibody disease presenting with RPGN, there is no evidence to support that treatment with rituximab improves renal function and survival.

[Summary]

B-cell-targeted therapy has recently been introduced for patients with ANCA-associated vasculitis, considering that production of ANCA may be involved in the pathogenesis of this disease. Based on the promising results of two recent RCTs, rituximab has just become available in Japan, as well as in the United States and Europe, but only for cases in which standard therapy cannot be given because of adverse effects or in patients who are refractory to or relapsed after standard therapy. However, the patient profiles of renal-limited ANCA-positive or MPO-ANCA-associated RPGN, which is more common in Japan, were not described in those trials. Moreover, there is a substantial risk of infection, as well as concerns about long-term safety concerning the incident risk of malignancy and leukoencephalopathy. Thus, it is necessary to perform screening tests to detect infection and to take preventive measures before starting rituximab. Furthermore, careful follow-up to detect the occurrence of infection and other adverse events is mandatory after the administration of rituximab.

B-cell-targeted therapy has been used for patients with SLE to suppress antibody production and immune complex formation. However, in lupus nephritis presenting with RPGN (class IV and some class III cases), there have been no RCTs that demonstrate the superiority of B-cell-targeted therapy over standard immunosuppressive therapy. Therefore, the use of rituximab may be considered only if standard therapy cannot be given because of adverse effects, or in patients who are refractory to or relapsed after standard therapy.

In patients with anti-GBM antibody disease with or without pulmonary hemorrhage, a treatment regimen including rituximab has been attempted for suppressing the production of anti-GBM antibody, and evidence is accumulating that suggests its effectiveness. However, rituximab is usually given concomitant with other drugs such as corticosteroids, cyclophosphamide, and plasmapheresis; thus, at present, there is no sufficient evidence that rituximab itself is actually effective.

CQ 14. Is initial therapy with plasmapheresis recommended for improving renal function and survival in patients with RPGN?

Recommendation grade: C1

In patients with ANCA-positive RPGN complicated with advanced renal dysfunction or pulmonary hemorrhage, the addition of plasmapheresis to immunosuppressive therapy as the initial therapy may improve renal function and survival. We recommend the addition of plasmapheresis in such patients.

Recommendation grade: C1

In patients with lupus nephritis presenting with RPGN (class IV and some class III cases) in whom the standard therapy is insufficient, the addition of plasmapheresis to immunosuppressive therapy as the initial therapy may improve renal function and survival. We recommend the addition of plasmapheresis in such patients.

Recommendation grade: B

In patients with anti-GBM antibody-positive RPGN, the addition of plasmapheresis to immunosuppressive therapy as the initial therapy has improved renal function and survival. We recommend plasmapheresis for these patients.

[Summary]

1) ANCA-positive RPGN

ANCA is thought to be involved in the clinical conditions of ANCA-associated vasculitis and RPGN. The removal of ANCA may therefore result in

controlling disease activity and preventing organ damage. The addition of plasmapheresis to the initial therapy with corticosteroids and cyclophosphamide is indicated for patients presenting with advanced kidney failure (serum creatinine, >5.8 mg/dL) or those with diffuse alveolar hemorrhage.

2) Lupus nephritis presenting with RPGN

The addition of plasmapheresis to the initial therapy is indicated for patients in whom the standard therapy (corticosteroids and immunosuppressive agents) is insufficient.

3) Anti-GBM antibody-positive RPGN

We recommend the addition of plasmapheresis for improving renal function and survival in patients with anti-GBM antibody-positive RPGN. On the other hand, in patients with advanced kidney failure or a requirement for dialysis, there is rare evidence that the addition of plasmapheresis improves renal function and survival.

4) Medical care insurance

Patients with SLE presenting with RPGN have insurance coverage for plasmapheresis. However, plasmapheresis for patients with ANCA-positive RPGN and anti-GBM antibody-positive RPGN is not covered by the medical care insurance in Japan.

CQ 15. Do anticoagulant or antiplatelet therapy improve mortality and morbidity in patients with RPGN?
Statement: Anticoagulants or antiplatelet therapies may improve mortality and morbidity in patients with RPGN in the condition that they have no hemorrhagic lesions.
Recommendation grade: C1 Anticoagulants or antiplatelet therapies are recommended if the patient has no hemorrhagic lesions.
Recommendation grade: D Anticoagulants or antiplatelet therapies are not recommended if the patient has any hemorrhagic lesions.

[Summary]

The efficacy of anticoagulant or antiplatelet therapy in improving mortality and morbidity in the treatment of rapidly progressive glomerulonephritis has not been established by solid evidences. However, anticoagulants such as heparin and warfarin or antiplatelet therapies with aspirin and eicosapentaenoic acid were reported to be helpful in the treatment of ANCA-associated vasculitis in some cases. In fact, these agents are sometimes used to prevent thrombosis-associated cardiovascular events, especially in patients treated with steroids. On the other hand, as pulmonary hemorrhage and/or gastrointestinal bleeding can occur as complications in ANCA-associated vasculitis, careful attention should be given to treatment with anticoagulants and antiplatelet drugs.

CQ 16. Do intravenous immunoglobulins (IVIg) improve renal and patient survival in RPGN?
Recommendation grade: C1 Although there is limited evidence showing that IVIg improves renal and patient survival in RPGN, IVIg can be used as an alternative option for patients with refractory ANCA-associated vasculitis or those with concurrent complications such as severe infections when it is advisable to avoid the standard therapy with high-dose steroids and immunosuppressant (off-label use).

[Summary]

IVIg can be used as alternative option for patients with refractory ANCA-associated vasculitis or those with concurrent complications such as severe infections when the optimal standard therapy with high-dose steroids and immunosuppressant is not recommended (off-label use). Sulfonated immunoglobulin has been used according to label directions for refractory peripheral neuropathy caused by eosinophilic granulomatosis with polyangiitis/Churg-Strauss syndrome since 2010 in Japan, and it has been reported to improve polyneuropathy and cardiac function, as well as to have a steroid sparing effect. In addition, a clinical trial to evaluate the efficacy for MPA with peripheral neuropathy has been initiated. Thus, IVIg might improve renal and patient survival in RPGN, although evidence is lacking thus far and there is a need for further evaluation in clinical trials.

CQ 17. Is maintenance therapy with corticosteroids alone recommended for improving renal function and survival in patients with RPGN?
Recommendation grade: A In patients with ANCA-positive RPGN, low-dose corticosteroids have been

shown to improve renal function and survival. We recommend corticosteroids as maintenance therapy for these patients.

Recommendation grade: A
In patients with lupus nephritis presenting with RPGN (class IV and some class III cases), low-dose corticosteroids have been shown to improve renal function and survival. We recommend corticosteroids as maintenance therapy for these patients.

Recommendation grade: B
In patients with anti-GBM antibody glomerulonephritis presenting with RPGN, low-dose corticosteroids have been shown to improve renal function and survival. We recommend corticosteroids as maintenance therapy for these patients.

[Summary]
Maintenance immunosuppressive therapy for RPGN may prevent relapse, although it may also increase the risk of opportunistic infection. Therefore, it is necessary to consider the total duration of treatment and the dose of corticosteroids in maintenance therapy to prevent relapse and opportunistic infection.

1) ANCA-positive RPGN
We recommend a corticosteroid dose of <10 mg/day orally as maintenance therapy, and suggest continuing administration for 12–18 months in patients who remain in complete remission. A study reported that a reduction rate >0.8 mg/month was associated with a higher relapse rate. Shortening the treatment period should be considered in aged or dialysis-dependent patients.

2) Lupus nephritis presenting with RPGN
We recommend continuing low-dose corticosteroids (5–7.5 mg/day) orally as maintenance therapy in patients with lupus nephritis presenting with RPGN.

3) Anti-GBM antibody-positive RPGN
There is rare evidence suggesting the efficacy of low-dose corticosteroids in patients with anti-GBM antibody-positive RPGN. We suggest continuing corticosteroids for 6–12 months as maintenance therapy.

CQ 18. What should be the reduction rate of oral corticosteroids?

Recommendation grade: B
We recommend a reduction of oral prednisolone dose to 20 mg within 8 weeks at the initial therapy and a reduction rate of <0.8 mg/month during maintenance therapy.

[Summary]
We recommend a reduction of the oral prednisolone dose to 20 mg within 8 weeks at the initial therapy to prevent opportunistic infection. However, a too early decrease in the amount of steroid was reported to be a risk factor for relapse, and the recommended reduction rate of the oral prednisolone dose during maintenance therapy is <0.8 mg/month.

CQ 19. Is maintenance therapy with immunosuppressive agents recommended for improving renal function and survival in patients with RPGN?

Recommendation grade: B
In patients with ANCA-positive RPGN, the addition of immunosuppressive agents to corticosteroids in the maintenance therapy has been shown to improve renal function and survival. We recommend immunosuppressive agents with corticosteroids as maintenance therapy for these patients.

Recommendation grade: A
In patients with lupus nephritis presenting with RPGN (class IV and some class III cases), the addition of immunosuppressive agents to corticosteroids in the maintenance therapy has been shown to improve renal function and survival. We recommend immunosuppressive agents with corticosteroids as maintenance therapy for these patients.

Recommendation grade: C1
In patients with anti-GBM antibody-positive RPGN, the addition of immunosuppressive agents to corticosteroids in the maintenance therapy may improve renal function and survival. We recommend the use of immunosuppressive agents with corticosteroids as maintenance therapy for these patients.

[Summary]
Maintenance immunosuppressive therapy for patients with RPGN may

prevent relapse; however, it may also increase the risk of opportunistic infection. Therefore, it is necessary to consider immunosuppressive agents as maintenance therapy to prevent relapse and opportunistic infection. We recommend treatment with azathioprine or mizoribine in patients with ANCA-positive RPGN, and mycophenolate mofetil or azathioprine in patients with lupus nephritis presenting with RPGN as maintenance therapy to prevent relapse.

1) ANCA-positive RPGN

The effectiveness of cyclophosphamide along with azathioprine, mizoribine, mycophenolate mofetil, and methotrexate as immunosuppressive agents in patients with ANCA-associated vasculitis has been reported. We recommend either azathioprine or mizoribine in combination with corticosteroids as maintenance therapy in patients with ANCA-positive RPGN, to prevent relapse.

2) Lupus nephritis presenting with RPGN

The effectiveness of azathioprine and mycophenolate mofetil as immunosuppressive agents in patients with lupus nephritis has been reported. We recommend either azathioprine or mycophenolate mofetil in combination with corticosteroids as maintenance therapy in patients with lupus nephritis presenting with RPGN, to prevent relapse.

3) Anti-GBM antibody-positive RPGN

There is rare evidence in patients with anti-GBM antibody-positive RPGN. We suggest continuing corticosteroids and immunosuppressive agents (azathioprine, etc.) for 6–12 months as maintenance therapy.

CQ 20. Does trimethoprim/sulfamethoxazole improve renal prognosis and life prognosis?
Recommendation grade: A The use of trimethoprim/sulfamethoxazole (TMP/SMX) improves life prognosis in RPGN. Therefore, prophylactic use of TMP/SMX is recommended in patients with RPGN treated with immunosuppressive therapy.
Recommendation grade: not graded

The effects of TMP/SMX on renal prognosis have not been clarified.

[Summary]

The rate of pneumocystis pneumonia (PCP) without the prophylactic use of TMP/SMX has been reported to be 4.0% or 17.6% in Japan. In other countries, the rate of PCP has been reported to be 1%, 6%, or 20%. The doses of corticosteroids and cyclophosphamide used may be related with the incidence. The mortality rate after the onset of PCP has been reported to be 9–60%. When TMP/SMX was administered, a 91% reduction of PCP incidence rate was observed and PCP-related mortality was significantly reduced according to a systematic review and meta-analysis of randomized controlled trials of PCP prophylaxis for immunocompromised non-HIV-infected patients.

I. Disease entity · definition (pathogenesis · pathophysiology)

1. Jennette JC, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013 ; 65 : 1–11.
2. Pedchenko V, et al. Molecular architecture of the Goodpasture autoantigen in anti-GBM nephritis. N Engl J Med 2010 ; 363 : 343–54.
3. Levy JB, et al. Clinical features and outcome of patients with both ANCA and anti–GBM antibodies. Kidney Int 2004 ; 66 : 1535–40.
4. Rutgers A, et al. Coexistence of anti—glomerular basement membrane antibodies and myeloperoxidase—ANCAs in crescentic glomerulonephritis. Am J Kidney Dis 2005 ; 46 :
253—62.
5. Yang R, et al. Antigen and epitope specificity of anti—glomerular basement membrane antibodies in patients with Goodpasture disease with or without anti—neutrophil cytoplasmic antibodies. J Am Soc Nephrol 2007 ; 18 : 1338–43.
6. Olson SW, et al. Asymptomatic autoantibodies associate with future anti—glomerular basement membrane disease. J Am Soc Nephrol 2011 ; 22 : 1946–52.
7. Belmont HM, et al. Pathology and pathogenesis of vascular injury in systemic lupus erythematosus. Interactions of inflammatory cells and activated endothelium. Arthritis
Rheum 1996 ; 39 : 9–22.

II. Diagnosis (symptoms and signs)

1. Matsuo S, et al. Guidelines for the treatment of rapidly progressive glomerulonephritis, second version. Nihon Jinzo Gakkai Shi. 2011; 53: 509-55
2. Guidelines for the management of rapidly progressive glomerulonephritis. Nihon Jinzo Gakkai Shi 2002 ; 44 : 55–82.
3. Shigematsu H, et al. Glomerulointerstitial events in rapidly progressive nephritic syndrome, with special reference to histologic grade and stage on the renal lesions : Clin Exp Nephrol 1998 ; 2 : 330–8.
4. Joh K, et al. Renal pathology of ANCA–related vasculitis : Proposal for standardization of pathological diagnosis in Japan. Clin Exp Nephrol 2008 ; 12 : 277–91.
5. Berden AE, et al. Histopathologic classification of ANCA-associated glomerulonephritis. J Am Soc Nephrol 2010 ; 21 : 1628–36.
6. Chang DY, et al. Re-evaluation of the histopathologic classification of ANCA–associated glomerulonephritis : a study of 121 patients in a single center. Nephrol Dial Transplant 2012 ; 27 : 2343–9.
7. Muso E, et al. Evaluation of the newly proposed simplified histological classification in Japanese cohorts of MPO-ANCA—associated glomerulonephritis in comparison with
other Asian and European cohorts. Clin Exp Nephrol 2013 ; 17 : 659–62.
8. Kussmaul A, et al. Ubereinenichtbisherbeschriebeneeigenthumliche Arterienerkrankung (Periarteritisnodosa) , diemitMorbusBrightii und rapid fortschreitenderallgemeiner-Muskelahmungeinhergeht. Deutsche Archiv KlinischeMedizin 1866 ; 1 : 484–518.
9. Leavitt RY, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum 1990 ; 33 : 11017.
10. Jennette JC, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum 1994 ; 37 : 187–92.
11. Yoshida M, et al. Report of Clinical Research subcommittee of small and medium-sized vessel vasculitis. Annual Report of the subgroup for intractable vasculitis in the fiscal year of 1998, from Research committee on specified immunological diseases, the Ministry of Health and Welfare of Japan. 1999, 239-46. (Japanese)
12. Koyama A, et al. A nationwide survey of rapidly progressive glomerulonephritis in Japan : etiology, prognosis and treatment diversity. Clin Exp Nephrol 2009 ; 13 : 633–50.
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14. Watts R, et al. Development and validation of a consensus methodology for the classification of the ANCA—associated vasculitides and polyarteritis nodosa for epidemiological studies. Ann Rheum Dis 2007 ; 66 : 222–7.
15. Sada KE, Yamamura M, et al.; Research Committee on Intractable Vasculitides, the Ministry of Health, Labour, Welfare of Japan. Issues associated with the Ministry of Health, Labour and Welfare diagnostic criteria for antineutrophil cytoplasmic antibody-associated vasculitides: Reclassification of patients in the associated vasculitides according to the MHLW criteria. Mod Rheumatol 2015; 25: 657-9.
16. Pankhurst T, et al. Malignancy is increased in ANCA—associated vasculitis. Rheumatology (Oxford) 2004 ; 43 : 1532–5.
17. Karube M, et al. ANCA related vasculitis and malignant tumor. Annual Review Jinzo 2007. Chugai-Igaku-Sha, Tokyo, Japan. 2007 ; 69–75. (Japanese)
18. Naicker S, et al. Infection and glomerulonephritis. Semin Immunopathol 2007 ; 29 : 397–414.
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III. Epidemiology and prognosis (incidence, prevalence, and outcome)

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2. Watanabe T, et al. National epidemiological survey and Application to the Research on Target Number of the Patient from DPC Database. Report of Progressive Renal Disease Research 2011, Research on Intractable Disease,

the Ministry of Health, Labour and Welfare of Japan. 2012, 53-62. (Japanese)
3. Sugiyama H, et al. Japan Renal Biopsy Registry : the first nationwide, web—based, and prospective registry system of renal biopsies in Japan. Clin Exp Nephrol 2011 ; 15 : 493–503.
4. Yokoyama H, et al. Construction of Japan Kidney Disease Registry and Its Analysis Report of Progressive Renal Disease Research 2008-2010, Research on Intractable Disease, the Ministry of Health, Labour and Welfare of Japan. 2011, 17-22. (Japanese)
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8. Hedger N, et al. Incidence and outcome of pauci—immune rapidly progressive glomerulonephritis in Wessex, UK : a 10-year retrospective study. Nephrol Dial Transplant 2000 ; 15 : 1593–9.
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10. Koyama A, et al. A nationwide survey of rapidly progressive glomerulonephritis in Japan : etiology, prognosis and treatment diversity. Clin Exp Nephrol 2009 ; 13 : 633–50.
11. Day CJ, et al. Prediction of ESRD in pauci—immune necrotizing glomerulonephritis : quantitative histomorphometric assessment and serum creatine. Am J Kidney Dis 2010 ; 55 : 250–8. 23

IV. Treatment

3. Treatment Algorithm

4. Clinical Questions for Treatment

CQ 1. Do the different ANCA assays influence the diagnostic assessment and disease activity evaluation in ANCA-associated vasculitis?

1. Hagen EC, et al. Kidney Int 1998 ; 53 : 743–53. (Level 4)
2. Csernok E, et al. Rheumatology (Oxford) 2004 ; 43 : 174–80. (Level 4)
3. Holle JU, et al. Ann Rheum Dis 2005 ; 64 : 1773–9. (Level 4)
4. Trevisin M, et al. Am J Clin Pathol 2008 ; 129 : 42–53. (Level 4)
5. Ito–Ihara T, et al. Clin Exp Rheumatol 2008 ; 26 : 1027–33. (Level 4)

CQ 2. Do changes in ANCA levels in response to therapy predict disease relapse during the remission period of ANCA-associated vasculitis?

1. Han WK, et al. Kidney Int 2003 ; 63 : 1079–85. (Level 4)
2. Tomasson G, et al. Rheumatology (Oxford) 2012 ; 51 : 100–9. (Level 1)

CQ 3. Is monitoring of anti-GBM antibody levels a useful tool to assess the disease activity and relapse in patients with anti-GBM nephritis and Goodpasture syndrome accompanied by RPGN?

1. Lockwood CM, et al. Lancet 1976 ; (1 7962) : 711–5. (Level 5)
2. Johnson JP, et al. Am J Med 1978 ; 64 : 354–9. (Level 5)
3. Johnson JP, et al. Medicin (e Baltimore) 1985 ; 64 : 219–27. (Level 2)
4. Yang R, et al. Nephrol Dial Transplant 2009 ; 24 : 1838–44. (Level 4)
5. Pedchenko V, et al. N Engl J Med 2010 ; 363 : 343–54. (Level 4)
6. Jia XY, et al. Clin J Am Soc Nephrol 2012 ; 7 : 926–33. (Level 4)
7. Herody M, et al. Clin Nephrol 1993 ; 40 : 249–55. (Level 4)
8. Levy JB, et al. Ann Intern Med 2001 ; 134 : 1033–42. (Level 4)
9. Cui Z, et al. Medicine (Baltimore) 2011 ; 90 : 303–11. (Level 4)
10. Levy JB, et al. Am J Kidney Dis 1996 ; 27 : 573–8. (Level 5)
11. Kalluri R, et al. Transplantation 2000 ; 69 : 679–83.

CQ 4. Is renal biopsy useful in determining the treatment strategy for RPGN?

1. Bajema IM, et al. Kidney Int 1999 ; 56 : 1751–8. (Level 4)
2. Vergunst CE, et al. Am J Kidney Dis 2003 ; 41 : 532–8. (Level 4)
3. de Lind van Wijngaarden RA, et al. J Am Soc Nephrol 2006 ; 17 : 2264–74.

(Level 2)
4. Day CJ, et al. Am J Kidney Dis 2010 ; 55 : 250–8. (Level 4)
5. Hauer HA, et al. Kidney Int 2002 ; 62 : 1732–42. (Level 4)
6. de Lind van Wijngaarden RA, et al. J Am Soc Nephrol 2007 ; 18 : 2189–97. (Level 2)
7. Berden AE, et al. J Am Soc Nephrol 2010 ; 21 : 1628–36. (Level 4)
8. Muso E, et al. Clin Exp Nephrol 2013 ; 17 : 659–62. (Level 4)
9. Pagnoux C, et al. Arthritis Rheum 2010 ; 62 : 616–26. (Level 4)
10. Inoue M, et al. Hum Pathol 1998 ; 29 : 223–7. (Level 5)
11. Bajema IM, et al. Nephrol Dial Transplant 1996 ; 11 : 1989–95. (Level 4)
12. Joh K, et al. Clin Exp Nephrol 2008 ; 12 : 277–91. (Level 4)
13. Johnson JP, et al. Medicin (e Baltimore) 1985 ; 64 : 219–27. (Level 2)
14. Merkel F, et al. Nephrol Dial Transplant 1994 ; 9 : 372–6. (Level 4)
15. Levy JB, et al. Ann Intern Med 2001 ; 134 : 1033–42. (Level 4)
16. Walker RG, et al. Q J Med 1985 ; 54 : 75–89. (Level 4)

CQ 5. Is it recommended that the immunosuppressive treatment of anti-neutrophil cytoplasmic antibody (ANCA)-negative pauci-immune rapidly progressive glomerulonephritis (RPGN) be the same as that of ANCA-positive disease?

1. Hedger N, et al. Nephrol Dial Transplant 2000 ; 15 : 1593–9. (Level 4)
2. Chen M, et al. J Am Soc Nephrol 2007 ; 18 : 599–605. (Level 4)
3. Hauer HA, et al. Kidney Int 2002 ; 61 : 80–9. (Level 5)

CQ 6. Is it recommended that the treatment of PR3-ANCA-positive RPGN be the same as that of MPO-ANCA-positive disease?

1. Yamagata K, et al. Clin Exp Nephrol 2012 ; 16 : 580–8. (Level 4)
2. Harper L, et al. Rheumatology (Oxford) 2005 ; 44 : 495–501. (Level 4)
3. Pagnoux C, et al. Arthritis Rheum 2008 ; 58 : 2908–18. (Level 4)

CQ 7. Should special care be given in the treatment of older patients with ANCA-associated RPGN compared with younger patients?

1. Harper L, et al. Rheumatology (Oxford) 2005 ; 44 : 495–501.
2. Yamagata K, et al. Clin Exp Nephrol 2012 ; 16 : 580–8. (Level 4)

CQ 8. Is initial therapy with corticosteroids alone recommended for improving renal function and survival in patients with RPGN ?

1. Frohnert PP, et al. Am J Med 1967 ; 43 : 8–14. (Level 5)
2. Bolton WK, et al. Am J Med 1979 ; 66 : 495–502. (Level 5)
3. Couser WG. Am J Nephrol 1982 ; 2 : 57–69. (Level 5)
4. Nachman PH, et al. J Am Soc Nephrol 1996 ; 7 : 33–9. (Level 3)
5. Hogan SL, et al. Ann Intern Med 2005 ; 143 : 621–31. (Level 4)
6. Adu D, et al. QJM 1997 ; 90 : 401–9. (Level 2)
7. Lionaki S, et al. Kidney Int 2009 ; 76 : 644–51. (Level 4)
8. Bolton WK, et al. Am J Nephrol 1989 ; 9 : 368–75. (Level 4)
9. Hogan SL, et al. J Am Soc Nephrol 1996 ; 7 : 23–32. (Level 4)
10. de Lind van Wijngaarden RA, et al. J Am Soc Nephrol 2006 ; 17 : 2264–74. (Level 4)
11. Austin HA Ⅲ, et al. N Engl J Med 1986 ; 314 : 614–9. (Level 2)
12. Gourley MF, et al. Ann Intern Med 1996 ; 125 : 549–57. (Level 2)
13. Cui Z, et al. Medicine (Baltimore) 2011 ; 90 : 303–11. (Level 4)
14. Levy JB, et al. Ann Intern Med 2001 ; 134 : 1033–42. (Level 4)
15. Johnson JP, et al. Medicin (e Baltimore) 1985 ; 64 : 219–27. (Level 2)

CQ 9. Which of oral corticosteroid or intravenous pulse corticosteroid is recommended as an initial corticosteroid therapy for improving renal function and survival in patients with RPGN?

1. Adu D, et al. QJM 1997 ; 90 : 401–9. (Level 2)
2. Bolton WK, et al. Am J Nephrol 1989 ; 9 : 368–75. (Level 4)
3. Jayne DR, et al. J Am Soc Nephrol 2007 ; 18 : 2180–8. (Level 2)
4. Austin HA Ⅲ, et al. N Engl J Med 1986 ; 314 : 614–9. (Level 2)
5. Gourley MF, et al. Ann Intern Med 1996 ; 125 : 549–57. (Level 2)
6. Houssiau FA, et al. Arthritis Rheum 2002 ; 46 : 2121–31. (Level 2)
7. Mok CC, et al. Am J Kidney Dis 2001 ; 38 : 256–64. (Level 3)
8. Appel GB, et al. J Am Soc Nephrol 2009 ; 20 : 1103–12. (Level 2)
9. Levy JB, et al. Ann Intern Med 2001 ; 134 : 1033–42. (Level 4)
10. Johnson JP, et al. Medicine (e Baltimore) 1985 ; 64 : 219–27. (Level 2)
11. Cui Z, et al. Medicine (Baltimore) 2011 ; 90 : 303–11. (Level 4)

CQ 10. Is initial therapy with immunosuppressive agents recommended for improving renal function and survival in patients with RPGN?

1. Nachman PH, et al. J Am Soc Nephrol 1996 ; 7 : 33–9. (Level 3)

2. Hogan SL, et al. J Am Soc Nephrol 1996 ; 7 : 23–32. (Level 3)
3. De Groot K, et al. Arthritis Rheum 2005 ; 52 : 2461–9. (Level 2)
4. Steinberg AD, et al. Arthritis Rheum 1991 ; 34 : 945–50. (Level 2)
5. Houssiau FA, et al. Arthritis Rheum 2002 ; 46 : 2121–31. (Level 2)
6. Houssiau FA, et al. Ann Rheum Dis 2010 ; 69 : 61–4. (Level 2)
7. Chan TM, et al. N Engl J Med 2000 ; 343 : 1156–62. (Level 2)
8. Ginzler EM, et al. N Engl J Med 2005 ; 353 : 2219–28. (Level 2)
9. Kamanamool N, et al. Medicine (Baltimore) 2010 ; 89 : 227–35. (Level 1)
10. Levy JB, et al. Ann Intern Med 2001 ; 134 : 1033–42. (Level 4)
11. Cui Z, et al. Medicine (Baltimore) 2011 ; 90 : 303–11. (Level 4)

CQ 11. Which is recommended for improving renal and patient survival in RPGN, oral cyclophosphamide or intravenous pulses of cyclophosphamide?

1. de Groot K, et al. Ann Intern Med 2009 ; 150 : 670–80. (Level 2)
2. Adu D, et al. QJM 1997 ; 90 : 401–9. (Level 2)
3. Guillevin L, et al. Arthritis Rheum 1997 ; 40 : 2187–98. (Level 2)
4. Haubitz M, et al. Arthritis Rheum 1998 ; 41 : 1835–44. (Level 2)
5. Walters GD, et al. BMC Nephrol 2010 ; 11 : 12. (Level 1)

CQ 12. Is immunosuppressive therapy recommended for improving renal function and survival in patients with RPGN who are receiving dialysis at the time of diagnosis?

1. Jayne DR, et al. J Am Soc Nephrol 2007 ; 18 : 2180–8. (Level 2)
2. Pepper RJ, et al. Clin J Am Soc Nephrol 2013 ; 8 : 219–24. (Level 4)
3. de Lind van Wijngaarden RA, et al. J Am Soc Nephrol 2006 ; 17 : 2264–74. (Level 2)
4. de Lind van Wijngaarden RA, et al. J Am Soc Nephrol 2007 ; 18 : 2189–97. (Level 2)
5. Kamanamool N, et al. Medicine (Baltimore) 2010 ; 89 : 227–35. (Level 1)
6. Liang L, et al. J Rheumatol 2004 ; 31 : 701–6. (Level 4)
7. Hind C, et al. Lancet 1983 ; (1 8319) : 263–5. (Level 4)
8. Levy JB, et al. Ann Intern Med 2001 ; 134 : 1033–42. (Level 4)
9. Flores JC, et al. Lancet 1986 ; (1 8471) : 5–8. (Level 5)

CQ 13. Is rituximab recommended for improving renal function and survival in patients with RPGN?

1. Specks U, et al. Arthritis Rheum 2001 ; 44 : 2836–40. (Level 5)
2. Keogh KA, et al. Am J Respir Crit Care Med 2006 ; 173 : 180–7. (Level 4)
3. Jones RB, et al. N Engl J Med 2010 ; 363 : 211–20. (Level 2)
4. Stone JH, et al. N Engl J Med 2010 ; 363 : 221–32. (Level 2)
5. Jones RB, et al. Arthritis Rheum 2009 ; 60 : 2156–68. (Level 4)
6. Berden AE, et al. J Am Soc Nephrol 2012 ; 23 : 313–21. (Level 4)
7. Specks U, et al. N Engl J Med 2013 ; 369 : 417–27. (Level 2)
8. Gregersen JW, et al. Scand J Rheumatol 2013 ; 42 : 207–10. (Level 4)
9. Mansfield N, et al. Nephrol Dial Transplant 2011 ; 26 : 3280–6. (Level 4)
10. Cartin-Ceba R, et al. Arthritis Rheum 2012 ; 64 : 3770–8. (Level 4)
11. Rhee EP, et al. Clin J Am Soc Nephrol 2010 ; 5 : 1394–400. (Level 4)
12. Díaz-Lagares C, et al. Autoimmun Rev 2012 ; 11 : 357–64. (Level 4)
13. Jónsdóttir T, et al. Rheumatology (Oxford) 2013 ; 52 : 847–55. (Level 4)
14. Melander C, et al. Clin J Am Soc Nephrol 2009 ; 4 : 579–87. (Level 4)
15. Rovin BH, et al. Arthritis Rheum 2012 ; 64 : 1215–26. (Level 2)
16. Pepper R, et al. Nephrol Dial Transplant 2009 ; 24 : 3717–23. (Level 4)
17. Condon MB, et al. Ann Rheum Dis 2013 ; 72 : 1280–6. (Level 4)
18. Li EK, et al. Rheumatology (Oxford) 2009 ; 48 : 892–8. (Level 2)
19. Syeda UA, et al. Semin Arthritis Rheum 2013 ; 42 : 567–72. (Level 5)

CQ 14. Is initial therapy with plasmapheresis recommended for improving renal function and survival in patients with RPGN?

1. Jayne DR, et al. J Am Soc Nephrol 2007 ; 18 : 2180–8. (Level 2)
2. Szpirt WM, et al. Nephrol Dial Transplant 2011 ; 26 : 206–13. (Level 2)
3. Walters GD, et al. BMC Nephrol 2010 ; 11 : 12. (Level 1)
4. Walsh M, et al. Am J Kidney Dis 2011 ; 57 : 566–74. (Level 1)
5. Yamagata K, et al. J Clin Apher 2005 ; 20 : 244–51. (Level 4)
6. Wei N, et al. Lancet 1983 ; 1 (8314–5) : 17–22. (Level 2)
7. Lewis EJ, et al. N Engl J Med 1992 ; 326 : 1373–9. (Level 2)
8. Euler HH, et al. Arthritis Rheum 1994 ; 37 : 1784–94. (Level 5)
9. Yamaji K, et al. Ther Apher Dial 2008 ; 12 : 298–305. (Level 5)
10. Loo CY, et al. Transfus Apher Sci 2010 ; 43 : 335–40. (Level 2)
11. Cui Z, et al. Medicine (Baltimore) 2011 ; 90 : 303–11. (Level 4)
12. Flores JC, et al. Lancet 1986 ; 1 (8471) : 5–8. (Level 5)

CQ 15. Do anticoagulant or antiplatelet therapy improve mortality and

morbidity in patients with RPGN?

1. BP Silfverskiöld. Scand Arch Physiol 1940 ; 175–82.
2. Kleinerman J. Lab Invest 1954 ; 3 : 495–508.
3. Vassalli P, et al. Am J Pathol 1964 ; 45 : 653–77.
4. Halpern B, et al. Nature 1965 ; 205 : 257–9.
5. Kincaid–Smith P, et al. Lancet 1968 ; 2 (7583) : 1360–3. (Level 5)
6. Arieff AI, et al. Arch Intern Med 1972 ; 129 : 77–84. (Level 5)
7. Brown CB, et al. Lancet 1974 ; 2 (7890) : 1166–72. (Level 5))
8. Fye KH, et al. Arch Intern Med 1976 ; 136 : 995–9. (Level 5)
9. Cunningham RJ Ⅲ, et al. Pediatr Res 1980 ; 14 : 128–32. (Level 5)
10. Hirahashi J, et al. Ann Intern Med 2012 ; 156 : 755–6. (Level 5)
11. Taji Y, et al. Clin Exp Nephrol 2006 ; 10 : 268–73.
12. Liu XJ, et al. Intern Med 2011 ; 50 : 2503–10.
13. Kessenbrock K, et al. Nat Med 2009 ; 15 : 623–5.
14. Hakkim A, et al. Proc Natl Acad Sci U S A 2010 ; 107 : 9813–8.
15. Clark SR, et al. Nat Med 2007 ; 13 : 463–9.
16. Fuchs TA, et al. Proc Natl Acad Sci U S A 2010 ; 107 : 15880-5.

CQ 16. Do intravenous immunoglobulins (IVIg) improve renal and patient survival in RPGN?

1. Martinez V, et al ; French Vasculitis Study Group. Arthritis Rheum 2008 ; 58 : 308–17. (Level 3)
2. Jayne DR, et al. QJM 2000 ; 93 : 433–9. (Level 2)
3. Muso E, et al. Jpn J Infect Dis 2004 ; 57 : S17–8. (Level 3)
4. Ito–Ihara T, et al. Nephron Clin Pract 2006 ; 102 : c35–42. (Level 3)

CQ 17. Is maintenance therapy with corticosteroids alone recommended for improving renal function and survival in patients with RPGN?

1. Frohnert PP, et al. Am J Med 1967 ; 43 : 8–14. (Level 4)
2. Bolton WK, et al. Am J Med 1979 ; 66 : 495–502. (Level 4)
3. Couser WG. Am J Nephrol 1982 ; 2 : 57–69. (Level 5)
4. Bolton WK, et al. Am J Nephrol 1989 ; 9 : 368–75. (Level 4)
5. Nachman PH, et al. J Am Soc Nephrol 1996 ; 7 : 33–9. (Level 3)
6. Adu D, et al. QJM 1997 ; 90 : 401–9. (Level 2)
7. Walsh M, et al. Arthritis Care Res 2010 ; 62 : 1166–73. (Level 1)
8. Ozaki S, et al. Mod Rheumatol 2012 ; 22 : 394–404. (Level 4)
9. Austin HA Ⅲ, et al. N Engl J Med 1986 ; 314 : 614–9. (Level 2)
10. Gourley MF, et al. Ann Intern Med 1996 ; 125 : 549–57. (Level 2)
11. Houssiau FA, et al. Arthritis Rheum 2002 ; 46 : 2121–31. (Level 2)
12. Levy JB, et al. Ann Intern Med 2001 ; 134 : 1033–42. (Level 4)

CQ 18. What should be the reduction rate of oral corticosteroids?

1. Walsh M, et al. Arthritis Care Res 2010 ; 62 : 1166–73. (Level 1)
2. Jayne D, et al. N Engl J Med 2003 ; 349 : 36–44. (Level 2)
3. Wada T, et al. J Rheumatol 2012 ; 39 : 545–51. (Level 4)
4. Ozaki S, et al. Mod Rheumatol 2012 ; 22 : 394–404. (Level 4)

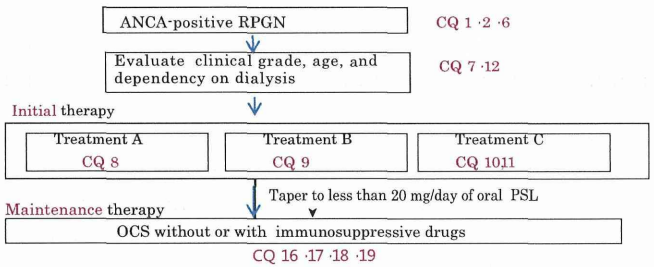
CQ 19. Is maintenance therapy with immunosuppressive agents recommended for improving renal function and survival in patients with RPGN?

1. Jayne D, et al. N Engl J Med 2003 ; 349 : 36–44. (Level 2)
2. Hirayama K, et al. Am J Kidney Dis 2004 ; 44 : 57–63. (Level 5)
3. Langford CA, et al. Arthritis Rheum 1999 ; 42 : 2666–73. (Level 4)
4. Langford CA, et al. Am J Med 2003 ; 114 : 463–9. (Level 4)
5. Hiemstra TF, et al. JAMA 2010 ; 304 : 2381–8. (Level 2)
6. Houssiau FA, et al. Ann Rheum Dis 2010 ; 69 : 2083–9. (Level 2)
7. Dooley MA, et al. N Engl J Med 2011 ; 365 : 1886–95. (Level 2)
8. Levy JB, et al. Ann Intern Med 2001 ; 134 : 1033–42. (Level 4)

CQ 20. Does trimethoprim/sulfamethoxazole improve renal prognosis and life prognosis?

1. Itabashi M, et al. Nephron Clin Pract 2010 ; 115 : c21–c27. (Level 4)
2. Ozaki S, et al. Mod Rheumatol 2012 ; 22 : 394–404. (Level 3)
3. Reinhold–Keller E, et al. Arthritis Rheum 2000 ; 43 : 1021–32. (Level 4)
4. Ognibene FP, et al. Am J Respir Crit Care Med 1995 ; 151 : 795–9. (Level 4)
5. Guillevin L, et al. Arthritis Rheum 1997 ; 40 : 2187–98. (Level 2)
6. Green H, et al. Mayo Clin Proc 2007 ; 82 : 1052–9. (Level 1)
7. Stegeman CA, et al. N Engl J Med 1996 ; 4 ; 335 : 16–20. (Level 2)
8. Delanaye P, et al. Nephron Clin Pract 2011 ; 119 : c187–93. (Level 5)

Figure 1. Treatment algorithm for ANCA-positive RPGN and CQs
(changed from reference: the RPGN clinical practice guide 2011 by the Progressive Renal Disease Research, from the Ministry of Health, Labour and Welfare of Japan)



* For older patients over 70 years, lower-grade treatment may be considered including the regimen without pulse methylprednisolone

* At the specialized hospital, higher-grade treatment may be considered under careful management irrespective of age and clinical grades.

Please see other treatments (CQ 13 for Rituximab therapy, CQ 14 for Plasma exchange therapy, CQ15 for anti-coagulation and anti-platelet therapy, and CQ20 for co-trimoxazole therapy).

RPGN : rapidly progressive glomerulonephritis PSL : prednisolone OCS: oral corticosteroid

CQ on diagnosis and treatment

Table 1. Treatment choices by clinical grades, age, and dependency on dialysis

Clinical grade	Age ≧ 70 years or on dialysis	Age < 70 years and not on dialysis
I or II	A	B
III or IV	B	C

Table 2. The clinical grading system for predicting RPGN patient prognosis

Clinical Score	Serum creatinine (mg / dL)*	Age (years)	Lung involvement	Serum CRP (mg / dL)*
0	[Cr] < 3	< 60	No	< 2.6
1	3 ≦ [Cr] < 6	60-69		2.6-10
2	6 ≦ [Cr]	≧ 70	Yes	> 10
3	Dialysis			

*values at the time of treatment initiation

Clinical grade	Total scores
I	0 ~ 2
II	3 ~ 5
III	6 ~ 7
IV	8 ~ 9

Table 3. Treatment regimen

Grade	Treatment regimen
A	Oral corticosteroid alone (Prednisolone 0.6-1.0 mg / kg / day)
B	Pulse Methylprednisolone, followed by oral corticosteroid (Pulse methylprednisolone 500-1,000 mg i.v. daily × 3 days, followed by oral prednisolone 0.6-0.8 mg/kg/day)
C	Pulse Methylprednisolone, followed by oral corticosteroid + oral CY (Pulse methylprednisolone 500-1,000 mg i.v. daily × 3 days, followed by oral prednisolone 0.6-0.8 mg/kg/day + oral CY 25-100 mg/day)

Table 4. Pulsed CYC reductions for renal function and age

Age (years)	Creatinine, 1.7-3.4 mg / dL	Creatinine, 3.4-5.7 mg / dL
<60	15 mg / kg / pulse	12.5 mg / kg / pulse
60-70	12.5 mg / kg / pulse	10 mg / kg / pulse
≧70	10 mg / kg / pulse	7.5 mg / kg / pulse

(adapted from BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis, 2014)

CQ on diagnosis and treatment

The algorithm for diagnosis and treatment with corresponding CQs are shown in Figure 2.

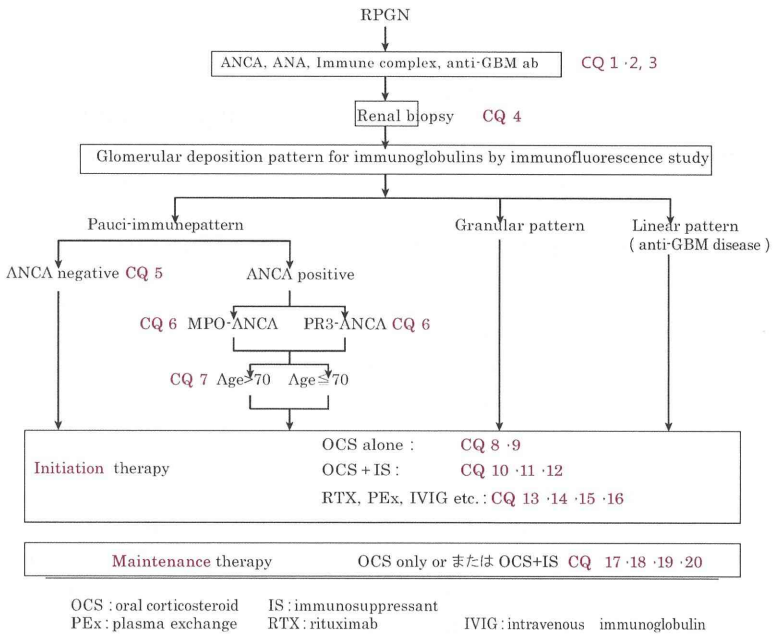


Figure 2. Differential diagnosis of RPGN and treatment options.

Evidence-Based Clinical Practice Guidelines for Nephrotic Syndrome 2014

July 27th, 2015

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The Japanese Society for Pediatric Nephrology
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Preface

1. Background of this guideline

In Japan, original researches on nephrotic syndrome (NS) were initially performed by the Ministry of Health, Labour and Welfare (MHLW) NS research group. The first definition of NS was reported by the MHLW NS research group in 1973. Subsequently, the criteria for treatment effects were documented in 1974. Based on the continued clinical researches and social actions by the HLWM NS research group, the definition of refractory NS was determined in 1999. NS already treated with various agents, including steroids, that does not reach complete or incomplete remission within 6 months after the initiation of treatment is known as refractory NS.

In 2002, the HLWM NS research group published the "Guideline for Refractory Nephrotic Syndrome (Adult Cases)." This was the first NS guideline in Japan. Consequently, this group and the Japanese Society of Nephrology (JSN) published the second guideline, "Guideline for Nephrotic Syndrome," in 2011. Currently, the collaborative working group of the MHLW and JSN aimed to publish and establish the third NS guideline in 2014. The new guideline aims to provide recommendations in clinical settings according to evidence-based medicine and it uses a description of clinical questions (CQs) according to the policy of publication for the clinical practice guidelines of the Medical Information Network Distribution Service (MINDS).

In 2012, an international guideline for glomerulonephritis, including NS, the "Guideline for Glomerulonephritis," was published by the Kidney Disease Improving Global Outcome (KDIGO). Thus, the working group of the third NS guideline examined the contents of the KDIGO guideline as an important reference and re-evaluated Japanese treatment strategy in the past and the contents of previous guidelines already published in our country. We attempted that the third clinical guideline was considered to be appropriate for recent clinical practices for NS in Japan.

2. The Intended Purpose, Anticipated Users, and Predicted Social Significance of the Guidelines

The third NS guideline is intended as a reference for physicians engaging in the treatment of patients with NS. Practical clinical information on NS was included in this guideline for both specialists and nonspecialists of nephrology.

We described essential knowledge concerning NS in the first part and proposed many CQs associated with treatment in the later part. The response to each question was written as a statement with a recommendation grade. In the last part, we proposed a summary of a treatment strategy. In this summarized strategy, we proposed new treatment ideas based on previous ideas. The new strategy with algorithm figures may be helpful for the decision for treatment by physicians seeing nephrotic patients.

We found only limited articles on the treatments of adults with NS. The number of subjective patients was small in these articles. Therefore, the strategy addressed in this guideline did not absolutely force physicians to follow the stereotyped protocol, but rather we expected that our strategy would be helpful in decision making for the treatment of an individual patient with NS. Because aging patients with NS having various complications are increasing, the individual decision for the treatment of each patient is also necessary. We want to strongly insist that this guideline is not a decision basis for medical malpractice lawsuits or trials.

2. Patients within the scope of the guidelines

This guideline is intended as a reference for the treatment of patients with primary NS. In the preparation process of the guideline, we used evidence articles of pediatric patients if we could not find evidence articles of adult patients. In a part of the guideline, we referred to non-nephrotic cases. Recurrent NS occurring after kidney transplantation and NS associated with pregnancy were excluded from this guideline. For pregnant cases with NS, we hope that you refer to the "Clinical Guideline for Pregnancy of Kidney Disease Patients" that was edited by the JSN.

3. Preparation procedure

At first, we collected evidence articles available for guideline preparation. The working group of the NS guideline was set up. Nephrologists with sufficient knowledge and experience voluntarily participated in this working group.

On September 9, 2011, a progressive kidney disease research group supported by the MHLW research foundation, which acts to control refractory disease, opened the first collaborative meeting concerning 4 major nephrology diseases, including IgAN, NS, rapidly progressive glomerulonephritis, and polycystic kidney disease. Dr. Tsuguya Fukui, the president of St. Luke's

International Hospital, was invited as an adviser of this meeting. The members of the 4 working groups of the guideline learned the significant meaning of the guideline and the procedures for guideline preparation from his lecture. Thereafter, we began to write our guideline using common concepts.

Consequently, our working group of the NS guideline determined CQs with the Delphi method and free cross-talk communication. The survey of reference articles was performed using the PubMed database. For a basic survey, evidence articles were collected from already published papers until July 2012, and important articles were selected on demand from papers published after July 2012. Through several working group meetings and E-mail discussions, our working group summarized the contents of the NS guideline. In addition, several collaborative meetings concerning the 4 major kidney diseases, IgAN, NS, rapidly progressive glomerulonephritis, and polycystic kidney disease, were opened. In these meetings, the first CQs were properly revised. From August 2013 to October 2013, our working group asked for a review of the guideline by designated reviewers belonging to related academic societies. At the same time, we announced that we welcomed public comments from the members of the JSN. According to the suggestions from reviewers and public comments, we revised our guideline, established the final version, and publically answered the comments on the home page of the JSN.

4. Contents of the guideline

The contents of this guideline are related to those in Chapter 11 of the "2013 CKD Clinical Guideline Based on Evidence" and the guidelines for the 4 major kidney diseases, IgA nephropathy, NS, rapid progressive glomerulonephritis, and polycystic kidney, which were created based on research on progressive kidney diseases that was funded by scientific research aid from the MHLW.

5. Evidence levels and recommendation grades

Evidence was classified into 6 levels based on study design, and it was arranged roughly from the most reliable study type (Level 1) to the least reliable (Level 6). These levels do not necessarily represent rigorous scientific standards; they are intended for use as a convenient reference for quickly assessing the significance of various clinical data during the physician's decision-making process.

[Evidence Levels]

Level 1: Systematic review/meta-analysis.
Level 2: At least 1 randomized controlled trial (RCT).
Level 3: A non-RCT.
Level 4: An analytical epidemiologic study (cohort study or case-control study) or a single-arm intervention study (no controls).
Level 5: A descriptive study (case report or case series).
Level 6: Opinion of an expert committee or an individual expert, which is not based on patient data.

However, for systematic review/meta-analysis, the evidence level was decided based on the designs of underlying studies. If underlying study designs were mixed, the lowest level underlying the study was used to determine the overall evidence level. For example, meta-analysis of cohort studies would be Level 4, but the same Level 4 would also be assigned to meta-analysis including both RCTs and cohort studies.

In addition, a decision based on committee consensus was that all subanalyses and post hoc analyses of RCTs should be categorized at evidence Level 4. Accordingly, it was decided that the evidence level of findings representing the primary endpoints of a RCT would be Level 2, but that the evidence level of findings that were determined through subanalysis or post hoc analysis of that RCT would be Level 4.

When a statement related to a certain treatment was presented, consideration was given to the level of evidence serving as the basis of that statement, and a recommendation grade was assigned as follows:

[Recommendation Grades]

Grade A: Strongly recommended because the scientific basis is strong.
Grade B: Recommended because there is some scientific basis.
Grade C1: Recommended despite having only a weak scientific basis.
Grade C2: Not recommended because there is only a weak scientific basis.
Grade D: Not recommended because scientific evidence shows treatment to be ineffective or harmful.

If we found only a weak scientific basis for a certain statement concerning treatment, the members of the committee discussed the matter and decided on C1 or C2 for the recommendation grade. Thus, discrimination between C1 and C2 statements was based on expert consensus.

7. Issues on the preparation of this guideline

(1) Little evidence on Japanese patients

Compared with evidence articles regarding NS in foreign adult patients and Japanese children, evidence articles concerning Japanese adults with NS are less. Therefore, our statements were strongly affected by evidence from overseas countries and children with NS. It is doubtful whether the evidence from overseas country is suitable for Japanese nephrotic patients. Therefore, we paid careful attention to differences in the clinical status of NS between overseas countries and Japan. In Japan, observational and intervention studies of adults with NS have gradually progressed, and further active studies are expected in this field.

(2) Compatibility with the CKD clinical guideline and past NS guidelines

We paid careful attention to compatibility with the contents of Chapter 11 of the "2013 CKD Clinical Guideline." There were no major conflict points between the current guideline and the past 2 guidelines, the "Guideline for Refractory Nephrotic Syndrome (Adult Cases)" and the "Guideline for Nephrotic Syndrome." The current guideline was prepared according to the policy of the MINDS. The previous Japanese NS guidelines were not compliant with that policy. Therefore, some statements of the current guideline were distinct from the statements of previous guidelines. The statements and algorithm of this guideline were determined by mutual understanding of members belonging to the working group.

(3) Issues on medical resources

In general, the clinical guideline must consider medical resources associated with recommended statements. However, the current guideline did not discuss issues on medical cost; thus medical financial problems did not affect the contents of our guideline. In the next guideline, this point may be included.

(4) Guideline reflecting the opinions of patients

During the preparation processes of the clinical guideline, we needed to introduce the opinions of patients. However, this time, we unfortunately could not include the opinions of patients. We should refer to the opinions of patients in the next guideline, particularly in the case that the guideline is used for patients.

8. Financial sources and conflict of interest

All financial sources for this guideline were paid by the JSN and used for traffic fees, conference fees, etc. No payments were made to the members of the working group of this guideline.

All members of the working group of the guideline submitted documents for their conflicts of interest to the JSN. The submitted documents were kept with the JSN. We were asked to revise the guideline according to the suggestions from many reviewers from associated societies to avoid conflicts of interest. We asked for public comments from the members of the JSN. Finally, we revised this guideline referring to the suggestions from reviewers.

9. Publication and Future Revisions

(1) Public information on the guideline

This guideline was published in the Japanese version of the journal of the JSN and was concurrently released as a book in Japanese (by Tokyo Igakusha, Tokyo). This guideline was also uploaded to the homepage of the JSN. An English-translated condensed version was published in Clinical and Experimental Nephrology, which is the English version of the journal of the JSN. We hope this guideline will also be published on the MINDS website. Finally, we are planning to inform general physicians and medical staff regarding the contents of this guideline for the purpose of education them on the clinical strategy for NS.

(2) Practice and adherence to this guideline

We are planning to evaluate the states of practice and adherence to this guideline through a survey on the practical acts in the issue with grade B recommendation.

(3) Setting of necessary research themes in the future

From the statements with a C1 recommendation, we will choose new research questions and determine the necessary research themes in the CKD field. This point will be discussed in the Committee of CKD Action of the JSN. Active clinical research on the treatment strategy that focuses on Japanese adult patients with NS using approved immunosuppressive agents in our country are absolutely necessary because our country has approved only

limited immunosuppressive agent use in the insurance system compared with overseas countries.

(4) Plan for revision

Revision of this guideline should be done 3 or 5 years later because new evidence is gradually increasing and new immunosuppressive agents are expected to be approved in the insurance system. At that time, we must document information from the perspective of patients and medical economy.

Content

2) Membranous nephropathy

CQ 7. Is no treatment or supportive treatment alone without immunosuppressive agents recommended for reducing urinary protein level and preventing the decline of renal function in membranous nephropathy with nephrotic syndrome?

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

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

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

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

CQ 12. Are conservative treatments recommended for reducing urinary protein level and preventing the decline of renal function in membranous nephropathy showing a non-nephrotic range of proteinuria?

3) Membranoproliferative glomerulonephritis

CQ 13. Is steroid treatment recommended for reducing urinary protein level and preventing the decline of renal function in idiopathic membranoproliferative glomerulonephritis showing nephrotic syndrome?

4) Steroid treatment

CQ 14. Is oral steroid treatment recommended during intervals between steroid pulse treatments (i.e., at days when no steroid pulse treatment is given)?

CQ 15. Is the increase of oral steroid doses or the change of administration routes recommended for patients with systemic edema?

CQ 16. Is alternate-day administration as a means of steroid dose reduction effective for inhibiting the incidence of adverse effects?

CQ 17. Is reducing the steroid dose compared with that of the first treatment recommended for the treatment of recurrent nephrotic syndrome?

CQ 18. Is there a standard period for steroid maintenance therapy after nephrotic syndrome has remitted?

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

CQ 19. Is rituximab recommended for reducing urinary protein level and preventing the decline of renal function in nephrotic syndrome?

CQ 20. Is mycophenolate mofetil recommended for reducing urinary protein level and preventing the decline of renal function in nephrotic syndrome?

CQ 21. Is azathioprine recommended for reducing urinary protein level and preventing the decline of renal function in nephrotic syndrome?

6) Nephrotic syndrome in the elderly

CQ 22. Are immunosuppressive agents recommended for elderly patients with nephrotic syndrome?

7) Adjunctive and supportive treatments

CQ 23. Are renin-angiotensin system (RAS) inhibitors recommended for reducing urinary protein level in nephrotic syndrome?

CQ 24. Are diuretics recommended for reducing edema in nephrotic syndrome?

CQ 25. Is albumin administration recommended to improve hypoalbuminemia in nephrotic syndrome?

CQ 26. Are antiplatelet and anticoagulant agents recommended for reducing urinary protein level and preventing thrombosis in nephrotic syndrome?

CQ 27. Are statins recommended to improve dyslipidemia and life prognosis in nephrotic syndrome?

CQ 28. Is ezetimibe recommended to improve lipid metabolism abnormalities and life prognosis in nephrotic syndrome?

CQ 29. Is low-density lipoprotein (LDL) apheresis recommended for reducing urinary protein levels in refractory nephrotic syndrome?

CQ 30. Is the extracorporeal ultrafiltration method (ECUM) recommended for refractory edema and ascites in nephrotic syndrome?

CQ 31. Is the trimethoprim-sulfamethoxazole combination recommended for preventing infectious disease during immunosuppressive therapy in nephrotic syndrome?

CQ 32. Is immunoglobulin supply recommended for preventing infectious disease in nephrotic syndrome?
CQ 33. Is treatment with antitubercular agents recommended for preventing tuberculous infection in nephrotic syndrome?
CQ 34. Is immunosuppressive therapy recommended for patients with hepatitis B-positive nephrotic syndrome?

8) Lifestyle and dietary instruction

CQ 35. Is the prevalence rate of cancer in patients with membranous nephropathy higher than that in the general population?
CQ 36. Is bed rest/exercise restriction recommended in nephrotic syndrome?
CQ 37. Is vaccination recommended in patients with nephrotic syndrome during treatment with corticosteroids and immunosuppressive drugs?
CQ 38. Are there any preventive measures against steroid-induced femoral head necrosis in nephrotic syndrome?
CQ 39. Is the avoidance of mental stress recommended to prevent the onset and relapse of nephrotic syndrome?
CQ 40. Is a fat-restricted diet recommended to improve dyslipidemia and life prognosis in nephrotic syndrome?

I. [Disease entity・Definition (Pathogenesis)]

Nephrotic syndrome is a clinical syndrome showing specific features of heavy proteinuria and hypoalbuminemia or hypoproteinemia as its consequence. It is caused by increased permeability of serum protein through the damaged basement membrane in the renal glomerulus. The definition of nephrotic syndrome includes both massive proteinuria (≥3.5 g/day) and hypoalbuminemia (serum albumin ≤3.0 g/dL) (Table 1,4). Primary nephrotic syndrome has no background diseases, whereas secondary nephrotic syndrome has any background diseases. As a result of massive proteinuria and hypoalbuminemia, this syndrome is frequently accompanied by edema, dyslipidemia, abnormalities in coagulation/fibrinolysis, reduced renal function, and immunological disorders. The effect of treatment is determined by the urinary protein level after treatment (Table 2,3).

II. [Diagnosis]

1. Symptomatology ・Clinical condition

The predominant symptom of nephrotic syndrome is edema. In the early phase, edema appears in local parts such as the eyelids; in the advanced phase, generalized edema occurs with pleural effusion and ascites. Nephrotic syndrome is sometimes induced by upper respiratory infection or allergic reaction provoked by insect bites. It is important to evaluate the possibilities of secondary glomerular diseases in elderly patients with nephrotic syndrome.

2. Laboratory findings

Patients with nephrotic syndrome show various urinary abnormalities and renal dysfunction (Table 5,6). The degrees of proteinuria and hematuria differ with each histological type of nephrotic syndrome. High urinary specific gravity and various kinds of cast formation, including hyaline, granular, waxy, and fatty, are frequently noticed in nephrotic syndrome. Hematological abnormalities such as hypoalbuminemia, hypercholesterolemia, renal and liver dysfunction, electrolyte disorders, coagulation/fibrinolysis disorders, hormonal disorders, and anemia are usually found in patients with nephrotic syndrome.

III. [Epidemiology・Prognosis]

1. Incidence・Prevalence・Recurrence rate

The researchers of the Committee for the Standardization of Renal Pathological Diagnosis and the Working Group for the Renal Biopsy Database of the Japanese Society of Nephrology had set up the J-RBR/J-KDR (Japan Renal Biopsy and Kidney Disease Registry) since 2007, and the epidemiology of nephrotic syndrome in Japan was gradually revealed. In the analysis of cases registered to the J-RBR until the end of 2010, primary glomerular disease was the most frequently occurring glomerular disease and diabetic nephropathy was the most frequent among the secondary glomerular diseases. The total cases of membranous nephropathy (MN) and minimal change nephrotic syndrome (MCNS) were close to 80% among the primary glomerular diseases. In the analysis of nephrotic syndrome patients aged ≥65 years, the ratios of diabetic nephropathy and amyloid nephropathy were highest, next to primary glomerular disease .

MCNS, focal segmental glomerulosclerosis (FSGS), MN, and membranoproliferative glomerulonephritis are known to relapse frequently. However, a wide range of relapse rates was reported in previous articles; thus, prospective follow-up surveys such as the Japanese Nephrotic Syndrome Cohort Study (JNSCS) are expected to provide precise rates.

2. Remission rate・Nonresponsive rate・Renal prognosis

Remission rates, nonresponsive rates, and prognosis vary across the histological types of nephrotic syndrome. MCNS shows a higher remission rate of ≥90%, whereas the recurrence rate is also higher at 30–70%. Compared with MCNS, FSGS shows a lower remission rate and poorer renal prognosis resulting in end-stage renal disease. About half of the cases of FSGS are nonresponders to steroid treatment. The responsive rates and renal prognosis vary across the variant types of FSGS. In the data in Japan, the renal survival rate was 33.5% at the 20-year follow-up examination. MN showed a high remission rate in Japanese patients. Complete or incomplete remission by single steroid treatment was achieved in 73.1%. Approximately 30% of cases showed spontaneous remission. However, the renal survival rate was 59% at the 20-year follow-up examination.

3. Incidence of complications

Various complications develop in patients with nephrotic syndrome. Although cohort studies performed abroad revealed a high incidence of cardiovascular events, the actual state in Japan seems to be different. Treatment with glucocorticoids and/or immunosuppressants, and nephrotic syndrome itself, often make patients susceptible to infection, the true rate of which remains to be determined. Reports from abroad also highlighted a high incidence of thromboembolic events. Furthermore, the westernized lifestyle makes the Japanese population more susceptible to thrombosis and therefore should receive research attention. Malignant tumors have been considered a common complication in patients with nephrotic syndrome. However, according to recent surveys, the co-occurrence rate of malignant tumors with nephrotic syndrome seems relatively low in Asian countries such as Japan and China compared with that in Western countries. Acute renal failure is another representative complication in patients with nephrotic syndrome, especially in the elderly.

V. [Clinical Questions for Treatment]

1. Treatment of glomerular diseases

[Minimal change nephrotic syndrome and focal segmental glomerulosclerosis]

CQ1. Is oral steroid recommended for reducing urinary protein level and preventing the decline of renal function in minimal change nephrotic syndrome?

Recommendation grade: B

In minimal change nephrotic syndrome, we recommend oral steroids be prescribed for reducing urinary protein level at the initial treatment.

Recommendation grade: C1

In minimal change nephrotic syndrome, we recommend oral steroid alone be prescribed for preventing the acute 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 is usually administered as the initial treatment for