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11. Herzenberg AM, et al. Kidney Int 2011 ; 80 : 310–7.
12. Shi SF, et al. Clin J Am Soc Nephrol 2011 ; 6 : 2175–84.
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14. Kang S, et al. Nephrol Dial Transplant 2012 ; 27 : 252–8.
15. Alamartine E, et al. Clin J Am Soc Nephrol 2011 ; 6 : 2384–88.
16. Tsuboi N, et al. Clin J Am Soc Nephrol 2010 ; 5 : 39–44.
17. Haas M. Am J Kidney Dis 1997 ; 29 : 829–42.
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18. Working Group of the International IgA Nephropathy Network and the Renal Pathology Society. Kidney Int 2010 ; 77 : 921–7.

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20. Yau T, et al. Am J Nephrol 2011 ; 34 : 435–44.
21. Shi SF, et al. Clin J Am Soc Nephrol 2011 ; 6 : 2175–84.
22. Alamartine E, et al. Clin J Am Soc Nephrol 2011 ; 6 : 2384–8.
23. Katafuchi R, et al. Clin J Am Soc Nephrol 2011 ; 6 : 2806–13.
24. Kang SH, et al. Nephrol Dial Transplant 2012 ; 27 : 252–8.
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26. Shima Y, et al. Pediatr Nephrol 2012 ; 27 : 783–92.
27. Kawamura. T, et al. J Nephrol 2013 ; 26 : 350–7.

10. Atypical forms of IgA nephropathy

1) Minimal change nephrotic disease (MCD) with mesangial IgA deposits

1. Mustonen J, et al. Clin Nephrol 1983 ; 20 : 172.6.
2. Lai KN, et al. Am J Clin Pathol 1986 ; 86 : 716.23.
3. Lai KN, et al. Clin Nephrol 1986 ; 26 : 174.80.
4. Fukushi K, et al. Jpn J Nephrol 1988 ; 30 : 253.8.
5. Kim SM, et al. J Korean Med Sci 2009 ; 24 Suppl : S44.9.

2) Acute kidney injury (AKI) associated with macroscopic hematuria

1. Bennett WM, et al. Kidney Int 1983 ; 23 : 393–400.
2. Praga M, et al. Kidney Int 1985 ; 28 : 69–74.
3. Delclaux C, et al. 1993 ; 8 : 195–9.
4. Kveder R, et al. Ther Apher Dial 2009 ; 13 : 273–7.
5. Gutiérrez E, et al. Clin J Am Soc Nephrol 2007 ; 2 : 51–7.

3) Crescentic IgA nephropathy

1. Abuelo JG, et al. Medicine (Baltimore) 1984 ; 63 : 396–406.
2. Roccatello D, et al. Nephrol Dial Transplant 1995 ; 10 : 2054–9.
3. Chambers ME, et al. J Clin Apher 1999 ; 14 : 185–7.
4. Tumlin JA, et al. Nephrol Dial Transplant 2003 ; 18 : 1321–9.
5. Bazzi C, et al. Clin J Am Soc Nephrol 2009 ; 4 : 929–35.
6. Lai KN, et al. Am J Kidney Dis 1987 ; 10 : 66–70.
7. Welch TR, et al. Am J Dis Child 1988 ; 142 : 789–93.
8. Harper L, et al. J Nephrol 2000 ; 13 : 360–6.
9. Nicholls K, et al. Am J Kidney Dis 1985 ; 5 : 42–6.
10. Coppo R, et al. Int J Artif Organs 1985 ; Suppl 2 : 55–8.
11. McIntyre CW, et al. Clin Nephrol 2001 ; 56 : 193–8.
12. Tang Z, et al. Am J Nephrol 2002 ; 22 : 480–6.

III. Epidemiology, prognosis, and follow-up

8. Incidence and prevalence

1. Donadio JV, et al. N Engl J Med 2002 ; 347 : 738–48.
2. Utsunomiya Y, et al. Pediatr Nephrol 2003 ; 18 : 511–5.
3. McGrogan A, et al. Nephrol Dial Transplant 2011 ; 26 : 414–30.

9. Natural course

1. Shen P, et al. Nephron Clin Pract 2007 ; 106 : c157–61.
2. Chauveau D, et al. Contrib Nephrol 1993 ; 104 : 1–5.
3. Koyama A, et al. Am J Kidney Dis 1997 ; 29 : 526–32.
4. D' Amico G. Semin Nephrol 2004 ; 24 : 179–96.
5. Kusumoto Y, et al. Clin Nephrol 1987 ; 28 : 118–24.

10. Changes in prognosis with changes in treatment guidelines

1. Komatsu H, et al. Am J Nephrol 2009 ; 30 : 19–25.
2. Yata N, et al. Pediatr Nephrol 2008 ; 23 : 905–12.
3. Asaba K, et al. Intern Med 2009 ; 48 : 883–90.

11. Clinical predictors of progression at the time of initial examination or renal biopsy

1. Wakai K, et al. Nephrol Dial Transplant 2006 ; 21 : 2800–8.
2. Manno C, et al. Am J Kidney Dis 2007 ; 49 : 763–75.
3. Goto M, et al. Nephrol Dial Transplant 2009 ; 24 : 3068–74.
4. Berthoux F, et al. J Am Soc Nephrol 2011 ; 22 : 752–61.
5. D' Amico G. Semin Nephrol 2004 ; 24 : 179–96.
6. Eiro M, et al. Nephron 2002 ; 90 : 432–41.
7. Ieiri N, et al. Clin Exp Nephrol 2012 ; 16 : 122–9.

12. Clinical predictors of progression during follow-up

1. Kobayashi Y, et al. Nephrology 1997 ; 3 : 35–40.
2. Bartosik LP, et al. Am J Kidney Dis 2001 ; 38 : 728–35.
3. Donadio JV, et al. Nephrol Dial Transplant 2002 ; 17 : 1197–203.
4. Reich HN, et al. J Am Soc Nephrol 2007 ; 18 : 3177–83.
5. Berthoux F, et al. J Am Soc Nephrol 2011 ; 22 : 752–61.
6. Le WB, et al. Nephrol Dial Transplant 2012 ; 27 : 1479–85.
7. Pozzi C, et al. J Am Soc Nephrol 2004 ; 15 : 157–63.
8. Cheng J, et al. Int J Clin Pract 2009 ; 63 : 880–8.
9. Lv J, et al. Am J Kidney Dis 2009 ; 53 : 26–32.
10. Manno C, et al. Nephrol Dial Transplant 2009 ; 24 : 3694–701.
11. Hwang HS, et al. Nephrology 2010 ; 15 : 236–41.

12. Payton CD, et al. Nephrol Dial Transplant 1988 ; 3 : 138–42.

13. Remission of urinary findings and its significance

1. Hotta O, et al. Am J Kidney Dis 2001 ; 38 : 736–43.
2. Komatsu H, et al. Clin J Am Soc Nephrol 2008 ; 3 : 1301–7.
3. Miura N, et al. Clin Exp Nephrol 2009 ; 13 : 460–6.
4. Kawaguchi T, et al. Nephrology 2010 ; 15 : 116–23.
5. Tatematsu M, et al. Clin Exp Nephrol 2012 : 1–9.
6. Hwang HS, et al. Nephrology 2010 ; 15 : 236–41.
7. Pozzi C, et al. Lancet 1999 ; 353 : 883–7.
8. Hotta O, et al. Am J Kidney Dis 2002 ; 39 : 493–502.
9. Matsuzaki K, et al. Clin Exp Nephrol 2013 ; 17 : 827–33.

14. Follow-up

1. Hotta O, et al. Am J Kidney Dis 2001 ; 38 : 736–43.
2. Szeto C, et al. Am J Med 2001 ; 110 : 434–37.
3. Shen P, et al. Nephron Clin Pract 2007 ; 106 : c157–61.
4. Goto M, et al. Nephrol Dial Transplant 2009 ; 24 : 3068–74.
5. Goto M, et al. Nephrol Dial Transplant 2009 ; 24 : 1242–7.
6. Shen P, et al. Neth J Med 2008 ; 66 : 242–7.

IV. Treatment

7. A summary of management of IgAN in adults, with a focus on prevention of renal dysfunction

8. Clinical questions (CQs) about immunosuppressive therapy (adults)

CQ 1. Are corticosteroids recommended in IgA nephropathy?

1. Lv J, et al. J Am Soc Nephrol 2012 ; 23 : 1108–16 (Level 1)
2. Zhou YH, et al. PLoS One 2011 ; 6 : e18788 (Level 4)
3. Cheng J. Am J Nephrol 2009 ; 30 : 315–22 (Level 1)
4. Samuels JA, et al. Cochrane Database Syst Rev 2003 ; 4 : CD003965. (Level 3)
5. Lv J, et al. Am J Kidney Dis 2009 ; 53 : 26–32 (Level 2)
6. Manno C, et al. Nephrol Dial Transplant 2009 ; 24 : 3694–701. (Level 2)
7. Pozzi C, et al. Lancet 1999 ; 353 : 883–7 (Level 2)
8. Pozzi C, et al. J Am Soc Nephrol 2004 ; 15 : 157–63 (Level 2)
9. Lai KN, et al. Clin Nephrol 1986 ; 26 : 174–80 (Level 2)
10. Julian BA, et al. Contrib Nephrol 1993 ; 104 : 198–206 (Level 2)
11. Katafuchi R, et al. Am J Kidney Dis 2003 ; 41 : 972–83 (Level 2)
12. Hogg RJ. Clin J Am Soc Nephrol 2006 ; 1 : 467–74 (Level 2)
13. Koike M, et al. Clin Exp Nephrol 2008 ; 12 : 250–5 (Level 2)
14. Shoji T, et al. Am J Kidney Dis 2000 ; 35 : 194–201 (Level 2)

CQ 2. Is tonsillectomy combined with steroid pulse therapy recommended?

1. Hotta O, et al. Am J Kidney Dis 2001 ; 38 : 736–43 (Level 4)
2. Kawaguchi T, et al. Nephrology (Carlton) 2010 ; 15 : 116–23 (Level 4)
3. Sato M, et al. Nephron Clin Pract 2003 ; 93 : c137–45 (Level 4)
4. Komatsu H, et al. Clin J Am Soc Nephrol 2008 ; 3 : 1301–7 (Level 3)
5. Miura N, et al. Clin Exp Nephrol 2009 ; 13 : 460–6 (Level 4)
6. Hotta O, et al. Jpn J Nephrol 1993 ; 35 : 967–73 (Level 4)
7. Hotta O, et al. Acta Otolaryngol Suppl 1996 ; 523 : 165–8 (Level 4)
8. Kawamura T, et al. Nephrol Dial Transplant 2014 ; 29 : 1546—53.

CQ 3. Is tonsillectomy (alone) recommended?

1. Iino Y, et al. Acta Otolaryngol Suppl 1993 ; 508 : 29–35 (Level 4)
2. Kosaka M. Nihon Jibiinkoka Gakkai Kaiho 1998 ; 101 : 916–23 (Level 4)
3. Rasche FM, et al. Clin Nephrol 1999 ; 51 : 147–52 (Level 4)
4. Chen, Y, et al. Am J Nephrol 2007 ; 27 : 170–5 (Level 4)
5. Xie, Y, et al. Kidney Int 2003 ; 63 : 1861–7 (Level 4)
6. Akagi H, et al. Acta Otolaryngol Suppl 2004 ; 555 : 38–42 (Level 4)
7. Wang, Y, et al. Nephrol Dial Transplant 2011 ; 26 : 1923–31 (Level 4)
8. Komatsu H, et al. Ren Fail 2012 ; 34 : 448–53 (Level 4)
9. Maeda I, et al. Nephrol Dial Transplant 2012 ; 27 : 2806–13 (Level 4)

CQ 4. Are non-steroidal immunosuppressive agents recommended?

1. Walker RG, et al. Clin Nephrol 1990 ; 34 : 103–7 (Level 2)
2. Ballardie FW, et al. J Am Soc Nephrol 2002 ; 13 : 142–8 (Level 2)
3. Pozzi C, et al. J Am Soc Nephrol 2010 ; 21 : 1783–90 (Level 2)
4. Harmankaya O, et al. Int Urol Nephrol 2002 ; 33 : 167–71 (Level 2)
5. Lai KN, et al. BMJ 1987 ; 295 : 1165–8 (Level 2)
6. Frisch G, et al. Nephrol Dial Transplant 2005 ; 20 : 2139–45 (Level 2)
7. Tang S, et al. Kidney Int 2005 ; 68 : 802–12 (Level 2)
8. Maes BD, et al. Kidney Int 2004 ; 65 : 1842–9 (Level 2)
9. Xu G, et al. Am J Nephrol 2009 ; 29 : 362–7 (Level 1)
10. Xie Y, et al. Am J Med Sci 2011 ; 341 : 367–72 (Level 2)

9. CQs about immunosuppressive therapy (children)

CQ 5. Is immunosuppressive therapy recommended in childhood IgA nephropathy?

1. Yoshikawa N, et al. Pediatr Nephrol 2001 ; 16 : 446–57.
2. Yoshikawa N, et al. Nihon Jinzo Gakkai Shi. 1997 Jul ; 39(5) : 503–6.
3. Yoshikawa N, et al. J Am Soc Nephrol 1999 ; 10 : 101–9 (Level 2)
4. Yata N, et al. Pediatr Nephrol 2008 ; 23 : 905–12 (Level 4)
5. Kamei K, et al. Clin J Am Soc Nephrol 2011 ; 6 : 1301–7 (Level 2)

CQ 6. Is combination "cocktail" therapy recommended in childhood IgA nephropathy?

1. Yoshikawa N, et al. J Am Soc Nephrol 1999 ; 10 : 101–9 (Level 2)
2. Yoshikawa N, et al. Clin J Am Soc Nephrol 2006 ; 1 : 511–7 (Level 2)
3. Kamei K, et al. Clin J Am Soc Nephrol 2011 ; 6 : 1301–7 (Level 2)
4. Yoshikawa N, et al. Pediatr Nephrol 2008 ; 23 : 757–63 (Level 4)
5. Pozzi C, et al. J Am Soc Nephrol 2010 ; 21 : 1783–90.

10. CQs about supportive therapy (adults)

CQ 7. Are RAS blockers recommended in IgA nephropathy?

1. Cheng J, et al. Int J Clin Pract 2009 ; 63 : 880–8 (Level 1)
2. Reid S, et al. Cochrane Database Syst Rev 2011 ; 3 : CD003962 (Level 1)
3. Praga M, et al. J Am Soc Nephrol 2003 ; 14 : 1578–83 (Level 2)
4. Woo KT, et al. Cell Mol Immunol 2007 ; 4 : 227–32 (Level 2)
5. Ruggenenti P, et al. Am J Kidney Dis 2000 ; 35 : 1155–65 (Level 2)
6. Woo KT, et al. Kidney Int 2000 ; 58 : 2485–91 (Level 2)
7. Park HC, et al. Nephrol Dial Transplant 2003 ; 18 : 1115–21 (Level 2)
8. Li PK, et al. Am J Kidney Dis 2006 ; 47 : 751–60 (Level 2)
9. Nakamura T, et al. Am J Nephrol 2000 ; 20 : 373–9 (Level 2)
10. Coppo R, et al. J Am Soc Nephrol 2007 ; 18 : 1880–8 (Level 2)
11. Horita Y, et al. Hypertens Res 2004 ; 27 : 963–70 (Level 2)
12. Nakamura T, et al. Am J Hypertens 2007 ; 20 : 1195–201 (Level 2)

CQ 8. Are antiplatelet agents recommended in IgA nephropathy?

1. Taji Y, et al. Clin Exp Nephrol 2006 ; 10 : 268–73 (Level 4)
2. Liu XJ, et al. Intern Med 2011 ; 50 : 2503–10 (Level 1)
3. Chan MK, et al. Am J Kidney Dis 1987 ; 9 : 417–21 (Level 2)
4. Lee GSL, et al. Nephrology 1997 ; 3 : 117–21 (Level 2)
5. Camara S, et al. Nephron 1991 ; 58 : 13–6 (Level 2)
6. Cheng I, et al. Nephrology 1998 ; 4 : 19–26 (Level 2)

CQ 9. Are n-3 fatty acids (fish oil) recommended in IgA nephropathy?

1. Miller ER Ⅲ, et al. Am J Clin Nutr 2009 ; 89 : 1937–45 (Level 4)
2. Bennett WM, et al. Clin Nephrol 1989 ; 31 : 128–31 (Level 2)
3. Pettersson EE, et al. Clin Nephrol 1994 ; 41 : 183–90 (Level 2)
4. Donadio JV, Jr., et al. J Am Soc Nephrol 1999 ; 10 : 1772–7 (Level 2)
5. Alexopoulos E, et al. Ren Fail 2004 ; 26 : 453–9 (Level 2)
6. Ferraro PM, et al. Nephrol Dial Transplant 2009 ; 24 : 156–60 (Level 2)
7. Liu LL, et al. Clin Nephrol 2012 ; 77 : 119–25 (Level 1)
8. Hogg RJ, et al. Clin J Am Soc Nephrol 2006 ; 1 : 467–74 (Level 2)
9. Reid S, et al. Cochrane Database Syst Rev 2011 ; 3 : CD003962 (Level 1)
10. Donadio JV, Jr., et al. N Engl J Med 1994 ; 331 : 1194–9 (Level 2)
11. Donadio JV Jr., et al. J Am Soc Nephrol 2001 ; 12 : 791–9 (Level 2)

11. CQs about lifestyle and dietary guidance in IgA nephropathy

CQ 10. Should limitation of salt intake be recommended?

1. Vogt L, et al. J Am Soc Nephrol 2008 ; 19 : 999–1007 (Level 2)
2. Slagman MC, et al. BMJ 2011 ; 343 : d4366 (Level 2)
3. Lin J, et al. Clin J Am Soc Nephrol 2010 ; 5 : 836–43 (Level 4)
4. Vegter S, et al. J Am Soc Nephrol 2012 ; 23 : 165–73 (Level 4)
5. Stolarz-Skrzypek K, et al. JAMA 2011 ; 305 : 1777–85 (Level 4)
6. O' Donnell MJ, et al. JAMA 2011 ; 306 : 2229–38 (Level 4)
7. Cook NR, et al. BMJ 2007 ; 334 : 885–8 (Level 4)

CQ 11. Should restricted protein intake be recommended?

1. Pedrini MT, et al. Ann Intern Med 1996 ; 124 : 627–32 (Level 3)
2. Fouque D, et al. Cochrane Database Syst Rev 2009 ; 3 : CD001892 (Level 1)
3. Kasiske BL, et al. Am J Kidney Dis 1998 ; 31 : 954–61 (Level 1)
4. Koya D, et al. Diabetologia 2009 ; 52 : 2037–45 (Level 2)
5. Cianciaruso B, et al. Am J Kidney Dis 2009 ; 54 : 1052–61 (Level 2)
6. Menon V, et al. Am J Kidney Dis 2009 ; 53 : 208–17 (Level 2)

CQ 12. Should weight loss be recommended?

1. Tanaka M, et al. Nephron Clin Pract 2009 ; 112 : c71–8 (Level 4)
2. Bonnet F, et al. Am J Kidney Dis 2001 ; 37 : 720–7 (Level 4)

CQ 13. Should exercise restriction be recommended?

1. Fuiano G, et al. Am J Kidney Dis 2004 ; 44 : 257–63 (Level 4)
2. Eidemak I, et al. Nephron 1997 ; 75 : 36–40 (Level 4)
3. Boyce ML, et al. Am J Kidney Dis 1997 ; 30 : 180–92 (Level 4)
4. Painter PL, et al. Transplantation 2002 ; 74 : 42–8 (Level 4)
5. Toyama K, et al. J Cardiol 2010 ; 56 : 142–6 (Level 4)
6. Pechter U, et al. Int J Rehabil Res 2003 ; 26 : 153–6 (Level 4)

CQ 14. Should smoking cessation be recommended?

1. Yamamoto R, et al. Am J Kidney Dis 2010 ; 56 : 313–24 (Level 4)
2. Orth SR, et al. Kidney Int 1998 ; 54 : 926–31 (Level 4)
3. Hallan SI, et al. Kidney Int 2011 ; 80 : 516–23 (Level 4)
4. Yamagata K, et al. Kidney Int 2007 ; 71 : 159–66 (Level 4)
5. Ishizaka N, et al. Hypertens Res 2008 ; 31 : 485–92 (Level 4)

12. Adverse events associated with steroid therapy and immunosuppressive agents

1. Cheng J, et al. Am J Nephrol 2009 ; 30 : 315–22 (Level 1)
2. Lv J, et al. J Am Soc Nephrol 2012 ; 23 : 1108–16. (Level 1)
3. Zhou YH, et al. PLoS One 2011 ; 6 : e18788. (Level 1)
4. Weinstein RS. Endocrine 2012 ; 41 : 183–90.
5. Drescher W, et al. Nephrol Dial Transplant 2011 ; 26 : 2728–31.
6. Fujimoto S, et al. Am J Nephrol 1990 ; 10 : 231–6. (Level 4)
7. Ballardie FW, et al. J Am Soc Nephrol 2002 ; 13 : 142–8. (Level 2)
8. Pozzi C, et al. J Am Soc Nephrol 2010 ; 21 : 1783–90. (Level 2)
9. Stangou M, et al. Clin Exp Nephrol 2011 ; 15 : 373–80. (Level 2)
10. Maes BD, et al. Kidney Int 2004 ; 65 : 1842–9. (Level 2)
11. Tang S, et al. Kidney Int 2005 ; 68 : 802–12. (Level 2)
12. Frisch G, et al. Nephrol Dial Transplant 2005 ; 20 : 2139–45. (Level 2)
13. Yoshikawa N, et al. Clin J Am Soc Nephrol 2006 ; 1 : 511–7. (Level 2)
14. Yoshikawa N, et al. J Am Soc Nephrol 1999 ; 10 : 101–9. (Level 2)
15. Yoshikawa N, et al. Pediatr Nephrol 2008 ; 23 : 757–63. (Level 4)
17. Salonen A, et al. Laryngoscope 2002 ; 112 : 94–8.
18. Heiser C, et al. Laryngoscope 2010 ; 120 : 2119–24.
19. Heiser C, et al. Laryngoscope 2012 ; 122 : 1265–6.
20. Windfuhr JP, et al. Eur Arch Otorhinolaryngol 2010 ; 267 : 289—93.
21. Windfuhr JP, et al. Ann Otol Rhinol Laryngol 2003 ; 112 : 63—70.
22. Lowe D, et al. Lancet 2004 ; 364 : 697–702.
23. Walker P, et al. Otolaryngol Head Neck Surg 2007 ; 136 (4 Suppl) : S27–31.
24. Arnoldner C, et al. Wien Klin Wochenschr 2008 ; 120 : 336–42.
25. Hessén Söderman AC, et al. Laryngoscope 2011 ; 121 : 2322–6.
26. Tomkinson A, et al. Laryngoscope 2011 ; 121 : 279–88.
27. Kennoki T, et al. Transplantation 2009 ; 88 : 935–41.
28. Kurata N, et al. Nihon Jibiinkoka Gakkai Kaiho.2012 Jan ; 115(1) : 29–36.
31. Pratt LW. Trans Am Acad Ophthalmol Otolaryngol 1970 ; 74 : 1146–54.

Table 1. Histologic classification presented by a multicenter case-control study on patients with IgAN in Japan

A. Histological grade

Histological grade	% glomeruli with pathological variables* predicting progression to ESRD	Acute lesion only	Acute and chronic lesion	Chronic lesion only
H-Grade I	0-24.9%	A	A/C	C
H-Grade II	25-49.9%	A	A/C	C
H-Grade III	50-74.9%	A	A/C	C
H-Grade IV	>75%	A	A/C	C

*Acute lesion (A): cellular crescent, tuft necrosis, fibrocellular crescent
Chronic lesion (C): global sclerosis, segmental sclerosis, fibrous crescent

B. Clinical grade

Clinical grade	Proteinuria (g/day)	eGFR (ml/min/1.73m^2)
C-Grade I	<0.5	—
C-Grade II	0.5≦	60≦
C-Grade III		<60

C. Grading system for predicting progression to ESRD

Histological grade / Clinical grade	H-Grade I	H-Grade II	H-Grade III + IV
C-Grade I	Low	Moderate	High
C-Grade II	Moderate	Moderate	High
C-Grade III	High	High	Super high

Low risk group: *1 of 72 (1.4%) of IgAN patients developed to ESRD in 18.6 yr after RBx.
Moderate risk group: *13 of 115 (11.3%) of IgAN patients developed to ESRD in 11.5 (3.7-19.3) yr. after RBx.
High risk group: *12 of 49 (24.5%) of IgAN patients developed to ESRD in 8.9 (2.8-19.6) yr. after RBx.
Super high risk group: *22 of 34 (64.7%) of IgAN patients developed to ESRD in 5.1 (0.7-13.1) yr. after RBx.
*The data from retrospective multicenter case-control study on IgAN (n=287)

Table 2. Definitions of pathological variables used in the Oxford classification

Variable	Definition		Score
Mesangial hypercellularity	<4	Mesangial cells/mesangial area = 0	M0≦0.5
	4-5	Mesangial cells/mesangial area = 1	M1＞0.5[a]
	6-7	Mesangial cells/mesangial area = 2	
	≧8	Mesangial cells/mesangial area = 3	
		The mesangial hypercellularity score is the mean score for all glomeruli	
Segmental glomerulosclerosis	Any amount of the tuft involved in sclerosis, but not involving the whole tuft or the presence of an adhesion		S0 - absent
			S1 - present
Endocapillary hypercellularity	Hypercellularity due to increased number of cells within glomerular capillary lumina causing narrowing of the lumina		E0 - absent
			E1 - present
Tubular atrophy/interstitial fibrosis	Percentage of cortical area involved by the tubular atrophy or interstitial fibrosis, whichever is greater		T0 - 0-25%
			T1 - 26-50%
			T2 - >50%

[a]Mesangial score should be assessed in periodic acid-Schiff-stained sections. If more than half the glomeruli have more than three cells in a mesangial area, this is categorized as M1. Therefore, a formal mesangial cell count is not always necessary to derive the mesangial score.

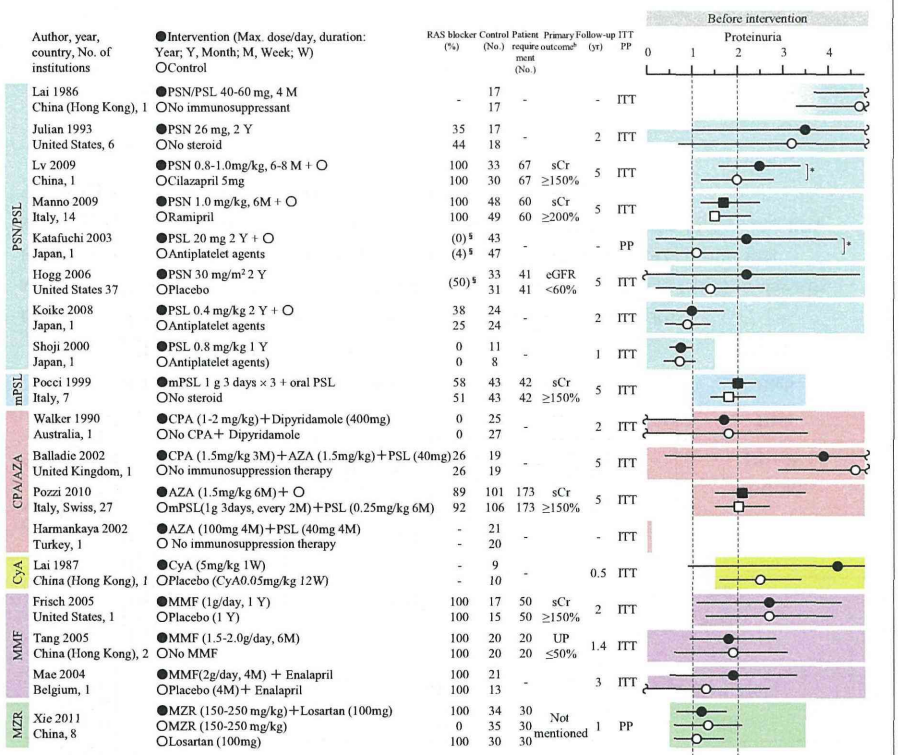
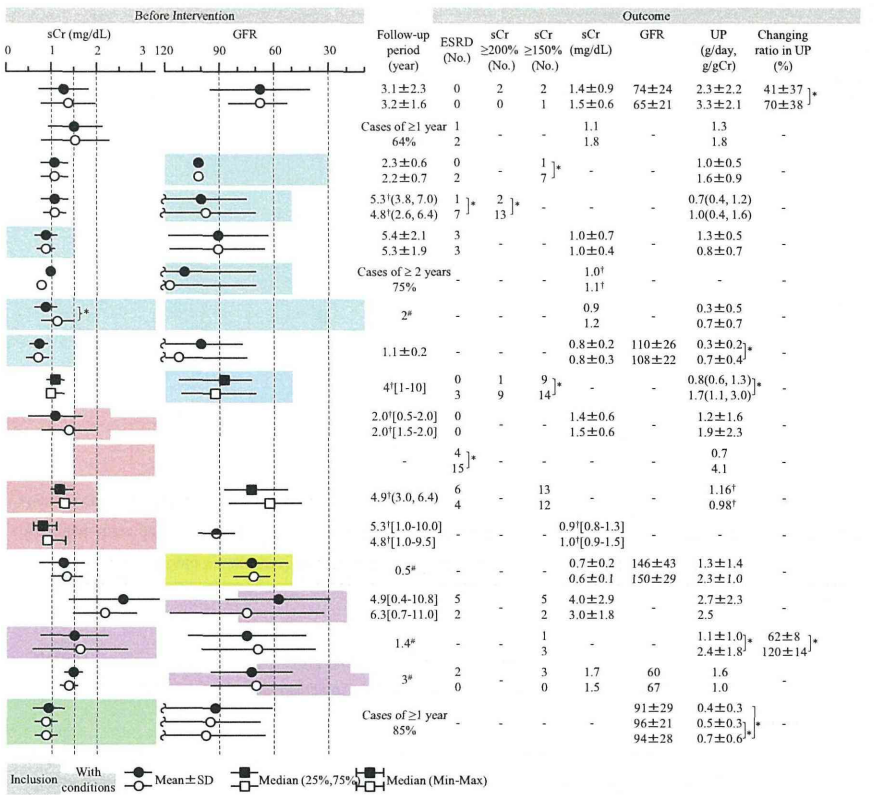


Figure 1 (Left)



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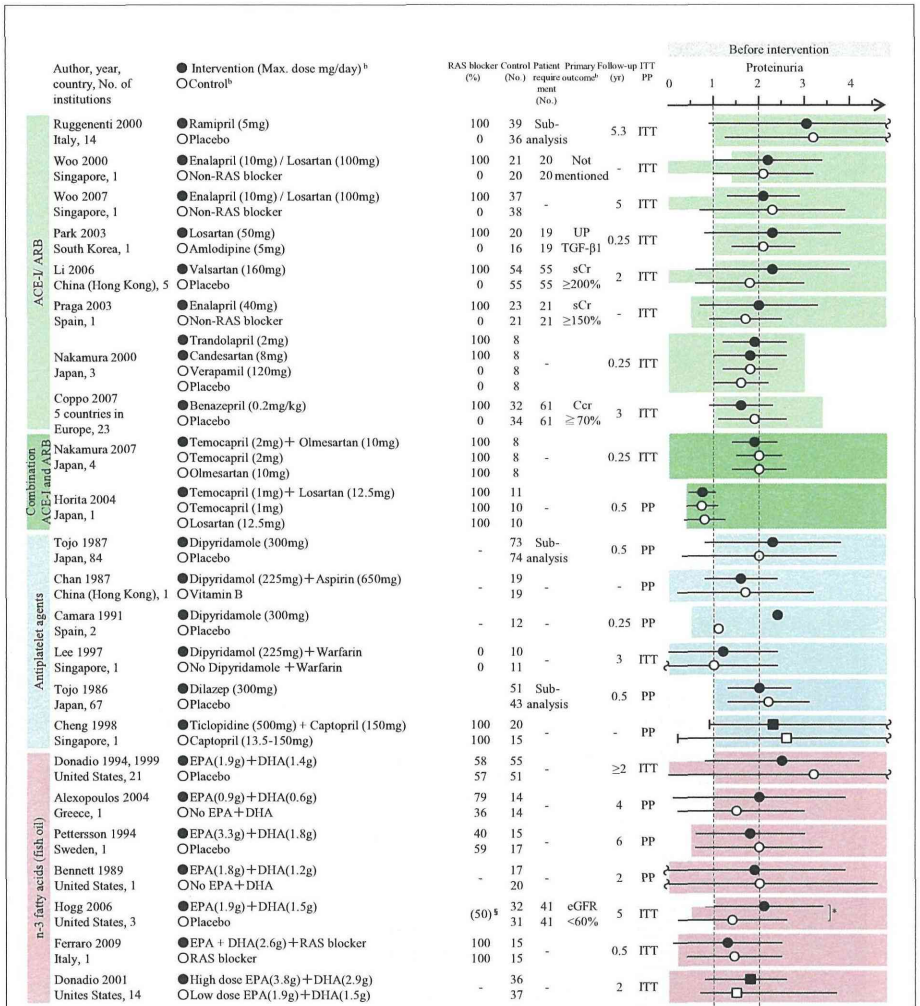

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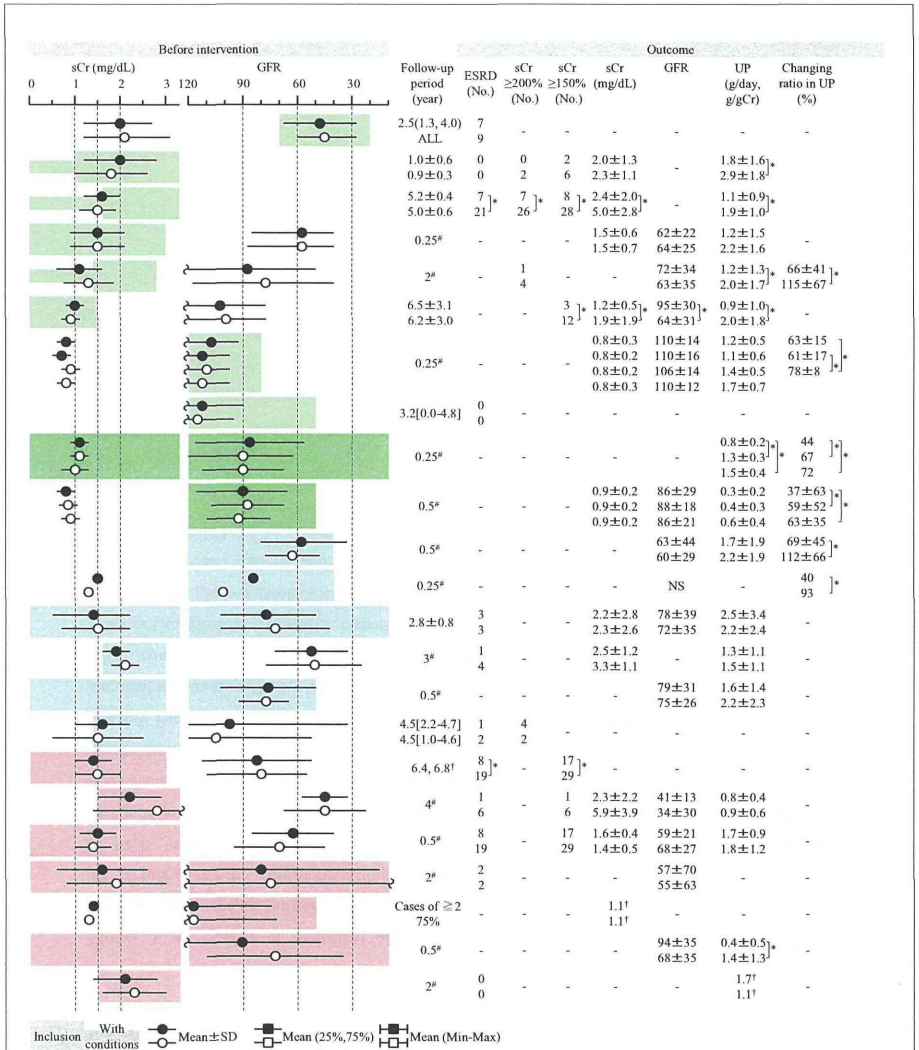

Figure 2 (Right)

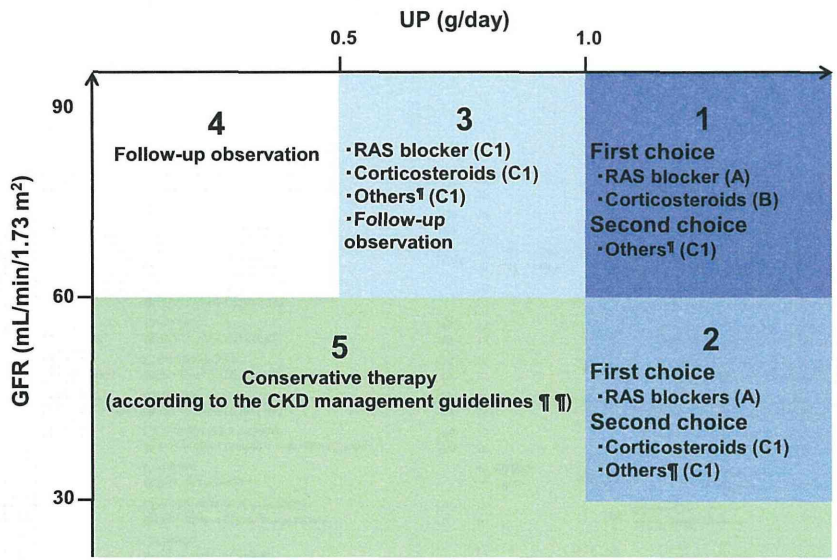

Figure 3

Figure 1. The summary of randomized controlled trials of corticosteroids and immunosuppressive agents in adult patients with IgAN

Figure 2. The summary of randomized controlled trials of RAS blockers, antiplatelet agents, and fish oils in adult patients with IgAN

Figure 3. An outline of treatment of IgAN in adults with a focus on prevention of renal dysfunction (based on randomized controlled trials for IgAN)

This figure shows the indications for treatment intervention, based mainly on the results (Figs. 1, 2) of RCTs, often focusing on renal function and amount of urinary protein excreted as patient inclusion/exclusion criteria. In actual clinical practice, besides renal function and urinary protein level, other factors such as renal histopathological findings and age should also be considered to carefully decide the indications for these treatment interventions.

Others¶: Tonsillectomy (combined with high-dose pulse corticosteroid therapy) and therapy with non-steroidal immunosuppressive agents, antiplatelet agents, and n-3 fatty acids (fish oil).

CKD management guidelines ¶¶: The Japanese Society of Nephrology Evidence based Clinical Practice Guideline for CKD 2013: Hypertension (Chapter 4), salt intake (Chapters 3, 4), lipid disorders (Chapter 14), glucose intolerance (Chapter 9), obesity (Chapter 15), smoking (Chapter 2), anemia (Chapter 7), CKD mineral and bone disorders (CKD-MBD, Chapter 8), and metabolic acidosis (Chapter 3) should also be managed as necessary.

Evidence-Based Clinical Practice Guidelines for Rapidly Progressive Glomerulonephritis 2014

Authors

Clinical Guidelines for Rapidly Progressive Glomerulonephritis 2014
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Preface

1. Background of this guideline

Rapidly progressive glomerulonephritis (RPGN) is defined in Japan as "a syndrome that progresses rapidly within a few weeks or months to renal failure and is accompanied by urinary findings of nephritis." The clinical concept of RPGN includes various renal diseases that cause renal function to deteriorate over a subacute course. Necrotizing crescentic glomerulonephritis is often observed in histopathological findings.

In 2002, a joint committee formed by JSN and a research group on progressive renal disorders from the specific disease program of the Ministry of Health, Labour, and Welfare released Japan's first "Clinical Guidelines for Rapidly Progressive Glomerulonephritis." These landmark guidelines were based on the results of research conducted overseas and a national survey on RPGN and took the particular characteristics of Japan into consideration. The RPGN guidelines were divided into diagnostic guidelines for early discovery and guidelines for making definitive diagnoses. RPGN was categorized into either a myeloperoxidase (MPO-ANCA) or proteinase-3 antineutrophil cytoplasmic (PR3-ANCA) type based on ANCA-related vasculitis. Furthermore, a practical therapeutic algorithm was created for MPO-ANCA types that took into consideration factors such as clinical severity, age, and presence of dialysis. Treatment guidelines for anti-GBM antibody RPGN were also presented. These guidelines were widely used in Japan and contributed greatly to improving RPGN prognosis.

These guidelines were revised 9 years later, in 2011, and published as "Clinical Guidelines for Rapidly Progressive Glomerulonephritis—2nd edition." This edition took into account medical advances that had occurred since 2002, and eGFR, not serum creatinine level, was adopted for diagnosing RPGN. Moreover, MPO-ANCA RPGN and PR3-ANCA RPGN were combined under ANCA-positive RPGN. The new edition also included concise statements for treatments and dealing with complications.

Since then, marked progress has been made in RPGN research both in Japan and overseas. Globally, KDIGO (Kidney Disease Improving Global Outcomes) released clinical guidelines for glomerulonephritis ("pauci-immune focal and segmental necrotizing glomerulonephritis," "anti-GBM antibody glomerulonephritis," and "lupus nephritis" were addressed as diseases that present with RPGN, and treatment guidelines with recommendation levels were given). In 2012, the American College of Rheumatology and EULAR/ERA-EDTA (European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association) published guidelines for lupus nephritis. There was also the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides, which changed the names of vasculitis diseases and performed other tasks. In Japan, the biological drug rituximab for ANCA-related vasculitis (microscopic polyangiitis, granulomatosis with polyangiitis) became eligible for health insurance coverage in 2013. Against this background, JNS and a research group on progressive renal disorders from the Ministry of Health, Labour, and Welfare decided to create the "2014 RPGN Clinical Guidelines Based on Evidence." A working group was formed to draft the guidelines.

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

The objective of these guidelines is to present evidence-based clinical guidelines that reflect the conditions in Japan. The text was created in the format of answers to CQ that nephrologists have when treating RPGN in everyday practice. Each answer comes in the form of a statement, and statements related to treatment are given recommendation grades based on the level of evidence. The first part is in a text format and describes areas that include the definition, concept, classification, epidemiology, diagnosis, and pathology of RPGN. Data from Japan is presented in figures and tables. These guidelines are not intended to serve as a comprehensive textbook but rather to answer nephrologists' questions and provide information on standard medical care to aid clinical judgments. For this reason, the RPGN clinical guidelines working group independently evaluated the related evidence and presented applicability criteria for therapeutic interventions, with the goals of suppressing the advance of renal dysfunction and improving survival prognosis.

Evidence from the literature can provide information but is no substitute for the specialized skills and experiences of individual physicians. Whether a particular statement applies and how it applies to a particular patient

depends on the specialist abilities of each physician. The times demand that medical care shift from a one-size-fits-all approach to a tailor-made approach. Clinical guidelines are not supposed to impose a uniform style of care on physicians. Each physician needs to determine what kind of care each patient needs, based on an understanding of the content of clinical guidelines. As such, these guidelines are not intended to limit physicians to certain forms of medical behavior but were created to assist them in exercising their discretion to decide the type of care to be provided. In addition, it should be stated clearly that these guidelines are not criteria for deciding physician-patient conflicts or medical malpractice lawsuits.

3. Patients within the scope of the guidelines

In clinical practice, RPGN encompasses a wide range of renal diseases such as ANCA-positive RPGN, anti-GBM antibody RPGN, proliferative lupus nephritis, IgA nephropathy, and forms of immune complex RPGN such as purpura nephritis, as well as infection-associated RPGN, acute interstitial nephritis, and thrombotic microangiopathy. As each of these has different prognoses and treatment strategies, it is not possible to encompass all the diseases. These guidelines focus on ANCA-positive RPGN, which appears frequently and for which there is relatively strong evidence, and on addressing the severe primary diseases, namely lupus nephritis and anti-GBM antibody RPGN. Treatment strategies with recommendation grades are presented for each of these diseases. There is little evidence for other forms of RPGN, so these are merely mentioned in the text. These guidelines apply to RPGN patients of all ages. Finally, pregnancy-related items were, as a rule, not included.

4. Preparation procedure

Creating evidence-based guidelines first requires the enormous task of gathering and evaluating evidence. We would like to sincerely thank the members of the RPGN Clinical Guidelines Working Group for their dedication and effort. (show list of contributors)

The first meeting of the clinical guidelines working group was held on September 23, 2011. The group was led by Dr. Kenjiro Kimura of the St. Marianna University School of Medicine, who explained the significance of creating the guidelines and the procedures for the task.

The working group then met three more times, submitting on August 24, 2012, a table of contents and a draft of the CQ. The RPGN clinical guidelines committee met on August 25 for the first time as the working group for drafting the guidelines. This was essentially considered the startup meeting. From then on, the working group began drafting the guidelines based on a shared understanding. The MINDS handbook for creating clinical guidelines was followed, and the Delphi method was used in composing CQ, which is the core of the guidelines. Recommendation grades were determined by an informal consensus. As a rule, PubMed records up to July 2012 were used to search the literature. If necessary, important studies from after this date were included, with reasons given.

Several meetings of the RPGN clinical guidelines committee were held (including review discussions among committee members through e-mail). Through this process, the initial CQ and text items were appropriately revised, and a few deletions and additions were made. The algorithm was also repeatedly revised to make the guidelines easier to use. From September 13 to October 13, 2013, each part was reviewed by two designated referees and two designated academic societies. Simultaneously, public comments were solicited from members of the Japanese Society of Nephrology (JSN). The manuscript was then revised based on the referees' opinions and public comments. The RPGN clinical guidelines committee met on January 26, 2014, to examine the revised manuscript. Afterward, additional revisions were made as needed until a final draft was obtained. The guidelines, as well as responses to the referees' opinions and public comments, were posted on the JSN Web site.

5. Contents of the guideline

The guidelines comprise the following chapters: I. Disease Concepts and Definitions, II. Diagnosis, III. Epidemiology and Prognosis, IV. Algorithms, and V. Diagnostic and Treatment CQ. Chapters I to III and the section on the side effects of immunosuppressant therapy and the methods of treating these effects are in text format. Chapter V contains 20 CQ on particularly problematic areas of everyday care. The answers to these come in the form of

statements and are accompanied by recommendation grades. The evidence and background for the recommended treatments are explained in the commentary, which should be referenced as needed. The algorithms of chapter IV are presented in flowcharts for diagnosis and treatment, which were created so the location of the CQ can be easily determined. Note that these guidelines were created in tandem with the "2013 CKD Clinical Guideline Based on Evidence," and so were written by the same authors.

6. Evidence levels and recommendation grades

Evidence levels were evaluated in a manner similar to that described in the "2013 CKD Clinical Guideline Based on Evidence."

[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.

Evidence levels for meta-analyses and systematic reviews were determined from the designs of the studies on which they were based. If the underlying studies had mixed designs, consensus was reached to adhere to the lowest level (e.g., a meta-analysis of cohort studies would be level 4, as would a meta-analysis that included both RCT and cohort studies).

Consensus was also reached to assign evidence level 4 to all RCT subanalyses and post hoc analyses. Therefore, an RCT with a clear primary outcome would be considered level 2, while a subanalysis or post hoc analysis of this RCT would be considered level 4.

The following recommendation grades were assigned to statements about treatments, which were based on the level of evidence for each statement.

[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.

As a rule, standard treatments in Japan were recommended, but eligibility for health insurance coverage was not necessarily required. Drugs ineligible for insurance coverage were denoted as such. Recommendation grades were assigned to statements about treatment-related CQ. In addition, questions such as "To which subgroup would this be recommended?" and "To which subgroup would this not be recommended?" were addressed whenever possible. Recommendation grades were decided through consultations among the working group members by considering the tradeoffs between and balance of benefits, damage, side effects, and risk. If differing views existed among the referees or in the public comments, the group reexamined the area through an exchange of opinions. The reasons for choosing a recommendation grade and the decision-making process involved were described in the commentary, as a rule.

7. Issues on the preparation of this guideline

Although evidence regarding renal diseases that present with RPGN is gradually increasing in Japan, it is still insufficient, which means that these guidelines were heavily influenced by evidence from Europe and the United States. Whether the results of clinical research from the West can be applied as is to Japan is a question that deserves careful consideration. Even in the West, only a few large clinical studies on RPGN have been conducted, so the quality of evidence is limited. In creating the guidelines, we strove to ensure they would not deviate greatly from clinical practice in Japan.

The guidelines were made to be used by nephrologists. Furthermore, although there have been calls recently for clinical guidelines to address the viewpoint of patients and provide information on medical economics, these areas were not taken into consideration.

8. Financial sources and conflict of interest

The funds used in creating the guidelines were provided by a research group on progressive kidney disorders funded by the Ministry of Health, Labour,

and Welfare's research project for overcoming intractable diseases. These funds were used to pay for transportation to and from meetings, to rent space for meetings, and for box lunches and snacks. The committee members received no compensation. Everyone involved in creating the guidelines (including referees) submitted conflict-of-interest statements based on academic society rules, which are managed by JSN. Opinions were sought from multiple referees and related academic societies to prevent the guidelines from being influenced by any conflicts of interest. Drafts were shown to the society members, and revisions were made based on their opinions (public comments).

9. Publication and Future Revisions

The guidelines are to be published in Japanese-language journal of JNS and concurrently released in book form by Tokyo Igakusha. They will also be posted on the JSN Web site and on the MINDS Web site of the Japan Council for Quality Health Care.

It will also be necessary to verify the extent to which these guidelines are being implemented and complied with, particularly for treatments of recommendation grade B. We hope to form a new working group on RPGN to follow up on compliance under a Ministry of Health, Labour, and Welfare research group. In addition, we want to extract and organize the various research questions that came up while creating these guidelines so that new clinical research (particularly prospective interventional studies) and basic research can be conducted. We intend to participate in structuring further evidence that is accumulated on RPGN for rituximab and other new therapies. At the same time, by continuing to collect evidence regarding RPGN overall, we hope to work toward a revision of these guidelines several years from now. We will also study how to address in the next guidelines the viewpoint of patients and medical economics, which were not mentioned this time. In the future, guidelines for patients also need to be considered.

Content

function and survival in patients with RPGN who are receiving dialysis at the time of diagnosis?
CQ 13. Is rituximab recommended for improving renal function and survival in patients with RPGN?
CQ 14. Is initial therapy with plasmapheresis recommended for improving renal function and survival in patients with RPGN?
CQ 15. Do anticoagulant or antiplatelet therapy improve mortality and morbidity in patients with RPGN?
CQ 16. Do intravenous immunoglobulins (IVIg) improve renal and patient survival in RPGN?
CQ 17. Is maintenance therapy with corticosteroids alone recommended for improving renal function and survival in patients with RPGN?
CQ 18. What should be the reduction rate of oral corticosteroids?
CQ 19. Is maintenance therapy with immunosuppressive agents recommended for improving renal function and survival in patients with RPGN?
CQ 20. Does trimethoprim/sulfamethoxazole improve renal prognosis and life prognosis?

I. Disease entity・definition (pathogenesis・pathophysiology)

The World Health Organization defines rapidly progressive glomerulonephritis (RPGN)/rapidly progressive nephritic syndrome as an abrupt or insidious onset of macroscopic hematuria, proteinuria, anemia, and rapidly progressing renal failure. The Research Committee of Progressive Glomerular Disease of the Ministry of Health, Labor and Welfare of Japan and the Japanese Society of Nephrology defined RPGN as rapidly progressing renal failure within several weeks to several months that is associated with urinary findings such as proteinuria, hematuria, red blood cell casts, and granular casts indicating glomerulonephritis. Without treatment, most patients will develop end-stage renal disease. RPGN is one of the clinical syndromes resulting from glomerulonephritis. In most cases of RPGN, the histopathological diagnosis is necrotizing crescentic glomerulonephritis (NCGN). NCGN is classified into three types—linear, granular, and paucity-immune pattern—based on immunofluorescence microscopic findings. A linear pattern indicates anti-glomerular basement disease, including in situ immune complex formation disease based on the Chapel Hill consensus criteria (2012). Granular staining is seen in circulating immune complex diseases such as systemic lupus erythematosus and IgA vasculitis. Most cases with the paucity-immune pattern are glomerulonephritis induced by anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis. Myeloperoxidase (MPO)-specific ANCA-associated vasculitis is more widely known than proteinase 3 ANCA-associated vasculitis in Japan.

II. Diagnosis (symptoms and signs)

General fatigue, slight fever, appetite loss, flu-like symptoms, and abnormal body weight loss are also frequently observed. Microscopic, or occasionally macroscopic, hematuria is observed accompanied by dysmorphism of red blood cells and cellular cast formation. Proteinuria is frequently present; however, nephrotic syndrome accompanying systemic edema is rare. Recently, asymptomatic cases found through urinary screening during sporadic health checks are increasing. When the causative disease of RPGN is systemic (vasculitis, systemic lupus erythematosus, etc.), a variety

of extrarenal symptoms are observed, such as disorders of the upper respiratory tract, lung (pulmonary bleeding, interstitial pneumonitis), skin (purpura, erythema), digestive organ (melena, abdominal pain), or neurons.
In blood chemistry tests, elevation of serum creatinine, decrease of estimated glomerular filtration rate, and elevation of C-reactive protein and erythrocyte sedimentation rate, often refractory to treatment by antibiotics, are observed. Rapidly progressive anemia, gradual elevation of neutrophil-dominant white blood cells, and thrombocytes are frequently observed. Complement levels tend to be elevated in RPGN because of systemic vasculitis; in contrast, systemic lupus erythematosus (SLE) decreases complement levels. As autoantibodies for detecting the causative disease of RPGN, anti- glomerular basement membrane (GBM) antibody, ANCA, and anti-dsDNA antibody are highly specific. Concerning signs in renal imaging, renal atrophy on echography is relatively rare. Renal pathology frequently reveals crescentic glomerulonephritis.
The "Clinical criteria of RPGN for early discovery of the disease," which promotes early presentation of patients to specialists, and the "Guideline for the definite diagnosis of RPGN," are proposed as diagnostic criteria for RPGN.

Diagnostic differential criteria for diseases that manifest RPGN
Important differential diagnoses include primary vasculitis syndrome, Goodpasture syndrome, SLE, IgA vasculitis, malignancies, cryoglobulinemia, infectious diseases such as post-streptococcal acute glomerulonephritis, infectious endocarditis, and type C hepatitis infection. It is important to first exclude infectious diseases and malignancies.

III. Epidemiology and prognosis (incidence, prevalence, and outcome)

1) Epidemiology
RPGN is a rare renal disease; however, the number of Japanese patients with RPGN has increased in recent years. Although the precise incidence of RPGN in Japan or worldwide is not known, a recent questionnaire survey estimated the number of new cases of RPGN in Japan at 1,600 to 1,800 per year. Based on a questionnaire survey of 1,772 Japanese cases collected from 1989 to 2007, the most common clinical form of RPGN in this country is pauci-immune-type necrotizing glomerulonephritis without systemic vasculitis, and the second most common form is microscopic polyangiitis. In recent years, the age at onset has increased.

2) Prognosis
The survival and renal prognosis of Japanese patients with RPGN or ANCA-associated RPGN has improved in recent years. In contrast, patients with anti-GBM antibody-associated RPGN show an extremely poor prognosis. Infection has been, and continues to be, the leading cause of death in patients with RPGN.

IV. Treatment

1. Treatment Algorithm

Figure 1.
Table 1, 2, 3, 4

2. Clinical Questions for Treatment

CQ 1. Do the different ANCA assays influence the diagnostic assessment and disease activity evaluation in ANCA-associated vasculitis?
Recommendation grade: not graded Different measurement procedures for ANCA potentially influence the diagnostic assessments and disease activity evaluation. The absolute values obtained through different assay procedures cannot be directly compared, and the values may be influenced by the assay methods used. In clinical practice, assessment of disease activity should not rely on the ANCA binding level alone but should include relevant clinical manifestations, especially if the assay method has changed, or for comparison of data with other study sites.

[Summary]
Indirect immunofluorescence (IIF) and enzyme immunoassay (EIA) have been used for ANCA testing. The labeling characteristics (cytoplasmic or perinuclear) are obtained by IIF, and identification of the specific target antigen with quantitative measurements is achieved by EIAs: enzyme-linked immunosorbent assay (ELISA), fluorescence enzyme immunoassay (FEIA), and chemiluminescent enzyme immunoassay (CLEIA). The different

procedures for the measurement of ANCA affect the diagnostic assessments and disease activity evaluation. The absolute values obtained through different assays cannot be directly compared, and multicenter clinical/epidemiological studies need to consider the differences in assay methods when comparing data. It should also be noted that assessment of disease activity should not rely on the ANCA binding level alone, but should be evaluated together with clinical manifestations, especially when using data obtained at different times with different methods. The absence of a positive test does not rule out a diagnosis. Duplicated serial measurements or measurements with both IIF and EIA are recommended for making decisions concerning positivity and negativity.

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

Recommendation grade: not graded

ANCA measurements are useful markers of the treatment response in ANCA-associated vasculitis manifesting with rapidly progressive glomerulonephritis (RPGN). The persistence of ANCA after induction therapy and an increase in ANCA during the remission period increases the relapse risk of ANCA-associated vasculitis with RPGN.

Serial ANCA measurements monthly in the acute phase and once every 1 to 3 months during the remission maintenance phase are recommended. An increase in ANCA may indicate future relapse of vasculitis or deterioration of RPGN, and the clinical manifestations should be monitored carefully.

[Summary]

Remission is defined as the absence of disease activity after a course of induction treatment for ANCA-associated vasculitis. The remission maintenance phase is defined as the period of sustained absence of disease activity. Relapse is a new or recurrent disease activity that occurs after remission has been initially induced. There are no definitions for "remission" and "relapse" in RPGN.

The ANCA binding level usually decreases in response to the treatment; thus, it is a useful marker that reflects disease activity. Persistent ANCA may occur in some cases. Treatment should not be tapered solely based on the ANCA level, and a comprehensive evaluation with careful observation of clinical symptoms and other physical/laboratory manifestations is required.

Persistence of ANCA positivity after induction therapy or an increase in ANCA during the remission phase increases the risk of relapse in ANCA-associated vasculitis. It is recommended to check the ANCA level once every 1 to 3 months during the remission maintenance phase. There is a lack of evidence to support changing of treatment to prevent disease relapse based on the reappearance of ANCA or an increase in ANCA binding level during the remission maintenance phase. An increase in ANCA indicates an increase in relapse risk, and clinical manifestations should be monitored carefully. Treatment should not be escalated solely because of an increase in ANCA.

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?

Recommendation grade: not graded

Anti-GBM antibodies are a useful clinical tool for the treatment of anti-GBM nephritis and Goodpasture syndrome because there is a significant correlation between anti-GBM antibody titer and the activity of those diseases. The levels of anti-GBM antibodies seem to be a useful tool in monitoring the recurrence of anti-GBM nephritis and Goodpasture syndrome.

[Summary]

Anti-GBM disease, also known as Goodpasture disease, is an autoimmune disorder characterized by rapidly progressive glomerulonephritis (RPGN) and a high risk for alveolar hemorrhage. Anti-GBM antibodies have been proven to be pathogenic in disease initiation. The target GBM antigen for circulating antibodies was subsequently identified as the noncollagenous-1 (NC1) domain of the α3 chain of collagen IV, whereas further studies revealed that collagen IV is a family of six α-chains (α1 through α6). Two major immunodominant regions, EA and EB, have been mapped to residues 17–31 and 127–141 of α3(IV)NC1. Antibodies against linear epitopes on the Goodpasture autoantigen could be detected in human anti-GBM disease and were associated with kidney injury. Another study defines them as conformational epitopes that are sequestrated in the quaternary structure of GBM dependent on a critical sulfilimine bond.

No high-level evidence exists from published clinical trials on the association

between anti-GBM antibody levels and disease activity, although many experiment-based studies are well established. According to a retrospective study, high antibody titers at diagnosis seemed to be associated with poor renal and patient survival. Therefore, treatment with plasmapheresis in combination with immunosuppression is recommended to remove the antibodies. In patients with a recurrence of anti-GBM disease, the anti-GBM level is useful in the diagnosis and in deciding the therapy.

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

Recommendation grade: C1

Renal biopsy is useful in determining the treatment strategy for RPGN. It is important to evaluate and examine the histological parameters that determine the response to therapy and affect the renal prognosis.

[Summary]

Evidence for the necessity to perform treatment, along with the presence of adverse effects, can be obtained through renal biopsy when the findings show reversible lesions. Excess immunosuppression can be prevented if the findings show irreversible changes. Thus, renal biopsy is useful in determining the treatment strategy for RPGN. On the other hand, treatment should be prioritized in patients who are positive for ANCA or anti-GBM antibody and are at high risk of complications with renal biopsy. In most papers, the renal prognosticator of ANCA-associated nephritis has been reported to be the percentage of normal glomeruli. A scoring system for glomerular, tubulointerstitial, and vascular lesions of ANCA associated-vasculitis was proposed in Japan in 2008. EUVAS (European Vasculitis Society) proposed the new classification stratified only based on glomerular lesions. In anti-GBM glomerulonephritis, most papers report the percentage of crescents to be the renal prognosticator .

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?

Recommendation grade: C1

For ANCA-negative pauci-immune RPGN, we recommend that the treatment be similar to that of ANCA-positive disease.

[Summary]

Reports from Japan and other countries showed that some patients with pauci-immune RPGN lacked ANCA. Some showed that there were no differences between patients with ANCA and those without ANCA; however, other studies reported the opposite. Because treatment of ANCA-negative pauci-immune RPGN has not been discussed in detail, we recommend that the treatment be similar to that of ANCA-positive disease.

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

Recommendation grade: B

For ANCA-associated RPGN, we recommend that the treatment be based on the severity and extent of disease, not on the ANCA subtype.

[Summary]

PR3-ANCA-positive RPGN is more common in Europe and the United States, whereas MPO-ANCA-positive RPGN is more common in Japan. Therefore, the treatment in Europe and the United States, which focuses on PR3-ANCA-positive RPGN, should not be directly adopted in Japan. However, the recent treatments introduced in Europe and the United States as well as in Japan are based on the severity and extent of disease, and not on the ANCA subtype. In fact, in Europe and the United States as well as in Japan, no differences in renal outcome and survival were observed between ANCA subtypes. However, special care should be taken to prevent relapse of PR3-ANCA-positive RPGN.

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

Recommendation grade: B

Because older patients with ANCA-associated RPGN have a higher risk of infection compared with younger patients, we recommend decreasing the dose of immunosuppressants (especially cyclophosphamide) in older patients.

[Summary]

Patients with RPGN in Japan are older compared with those in Europe and

the United States. Recently, Japanese patients with RPGN have shown better survival. Therefore, we recommend preventing infection due to over-immunosuppression in patients older than 70 years old, although they may have a higher risk of relapse. Infection is the most common and severe complication of ANCA-associated vasculitis in Europe and the United States, as well as in Japan. It is recommended that older patients, especially those with poor renal function, should be given reduced cyclophosphamide dose according to their age. Furthermore, steroids could cause serious adverse events such as diabetes mellitus, bone fractures, and cerebrovascular accidents, as well as infection. Careful attention should be given to the dose given to older patients to prevent the high incidence of serious adverse events with the use of several drugs.

CQ 8. Is initial therapy with corticosteroids alone recommended for improving renal function and survival in patients with RPGN ?
Recommendation grade: C1 In patients with ANCA-positive RPGN, high or moderate doses of corticosteroids have been shown to improve renal function and survival. However, combination with immunosuppressive agents is more effective; therefore, initial therapy with corticosteroids alone is recommended only in cases in which the use of immunosuppressive agents is not desirable.
Recommendation grade: C1 ・In patients with lupus nephritis presenting with RPGN (class IV and some class III cases), high or moderate doses of corticosteroids have been shown to improve renal function and survival. However, combination with immunosuppressive agents is more effective, and therefore initial therapy with corticosteroids alone is recommended only in cases in which the use of immunosuppressive agents is not desirable.
Recommendation grade: C1 ・In patients with anti-GBM antibody glomerulonephritis presenting with RPGN, high doses of corticosteroids may improve renal function and survival. However, the combined use of immunosuppressive agents is more effective; therefore, initial therapy with corticosteroids alone is recommended, in combination with plasmapheresis, in cases in which the use of immunosuppressive agents is not desirable.

[Summary]
In patients with ANCA-positive RPGN, the combined use of corticosteroids and immunosuppressive agents is currently recommended as the standard therapy, and there are no randomized controlled trials (RCTs) that compared treatment with and without corticosteroids. Therefore, initial therapy with corticosteroids alone is indicated only in cases in which aggressive treatment is required but the use of immunosuppressive agents is not desirable, such as in patients in whom systemic infection is present or cannot be ruled out, thus conferring increased risk by addition of immunosuppressive agents; dialysis-dependent patients; elderly patients (particularly those older than 70 years); and those in whom immunosuppressive agents are contraindicated because of leukopenia and liver dysfunction.
In patients with lupus nephritis presenting with RPGN (class IV and some class III cases), the combined use of corticosteroids and immunosuppressive agents is the current standard therapy. Therefore, initial therapy with corticosteroids alone is indicated only in cases in which aggressive treatment is required to prevent the progression of renal disease or to improve severe systemic complications in other vital organs, including the lung and the central nervous system, but in which the use of immunosuppressive agents is not desirable.
The prognosis of anti-GBM antibody disease is poor without treatment, with the worst patient survival in the presence of pulmonary hemorrhage. In patients with anti-GBM antibody glomerulonephritis presenting with RPGN, the combined use of corticosteroids and immunosuppressive agents, in addition to plasmapheresis, is suggested as the standard treatment. Therefore, initial therapy with corticosteroids alone is recommended, usually combined with plasmapheresis, in cases in which the use of immunosuppressive agents is not desirable because of adverse effects.

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?
Recommendation grade: C1 In patients with ANCA-positive RPGN, adding intravenous pulse corticosteroid therapy to oral corticosteroids may be considered when the decline of renal function is very rapid, or when severe systemic complications such as pulmonary hemorrhage are present.

Recommendation grade: C1

In patients with lupus nephritis presenting with RPGN (class IV and some class III cases), adding intravenous pulse corticosteroid therapy to oral corticosteroids is recommended when the decline of renal function is very rapid, or when severe systemic complications such as pulmonary hemorrhage or central nervous system (CNS) lupus are present.

Recommendation grade: C1

In patients with anti-GBM antibody disease presenting with RPGN, adding intravenous pulse corticosteroid therapy to oral corticosteroids is recommended to improve survival when pulmonary hemorrhage is present (i.e., Goodpasture syndrome). In patients with anti-GBM antibody glomerulonephritis without pulmonary hemorrhage, adding intravenous pulse corticosteroid therapy to oral corticosteroids is recommended to improve renal function, except for those whose renal function is not likely to recover even with aggressive immunosuppressive therapy.

[Summary]

In ANCA-positive glomerulonephritis, lupus nephritis (class IV and some class III cases), or anti-GBM antibody glomerulonephritis presenting as RPGN, there are no RCTs that have compared the effect on renal survival or patient survival between oral corticosteroids and intravenous pulse corticosteroid therapy. However, this is considered to confer rapid, strong anti-inflammatory and immunosuppressive effects in patients with high disease activities such as

・ANCA-positive glomerulonephritis, in which the decline of renal function is very rapid or is associated with severe systemic complications, including pulmonary hemorrhage

・Lupus nephritis presenting with RPGN (class IV and some class III cases), in which the decline of renal function is very rapid or is associated with severe systemic complications, including pulmonary hemorrhage and CNS lupus

・Anti-GBM antibody glomerulonephritis presenting with RPGN but without pulmonary hemorrhage, except for those whose renal function is not likely to recover despite aggressive therapy, or almost all cases of Goodpasture syndrome that is complicated by pulmonary hemorrhage

The standard protocol in pulse corticosteroid therapy is intravenous administration of 500 mg to 1 g of methylprednisolone for 3 consecutive days, followed by 0.6 to 0.8 mg/kg body weight of oral prednisolone.

CQ 10. Is initial 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 initial therapy has been shown to improve renal function and survival. We recommend immunosuppressive agents with corticosteroids as the initial 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 initial therapy has been shown to improve renal function and survival. We recommend immunosuppressive agents with corticosteroids as the initial therapy for these patients.

Recommendation grade: C1

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

[Summary]

1) ANCA-positive RPGN

Treatment with corticosteroids and cyclophosphamide has improved the outcome of patients with ANCA-positive RPGN. We recommend daily oral cyclophosphamide (25–100 mg/day) or intravenous pulses of cyclophosphamide (250–750 mg m^{-2} $month^{-1}$) with corticosteroids as the initial therapy, considering the clinical grade, patient age, and dialysis requirement.

2) Lupus nephritis presenting with RPGN

We recommend immunosuppressive agents (cyclophosphamide or mycophenolate mofetil) with corticosteroids as the initial therapy for patients with diffuse proliferative lupus nephritis.

3) Anti-GBM antibody-positive RPGN

Patient survival and kidney survival in anti-GBM antibody-positive RPGN are poor. The clinical guideline in Japan recommends immunosuppressive