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KDOQI Commentary

KDOQI US Commentary on the 2012 KDIGO Clinical Practice Guideline for Glomerulonephritis

Laurence Beck, MD, PhD,[1] Andrew S. Bomback, MD,[2] Michael J. Choi, MD,[3] Larry B. Holzman, MD,[4] Carol Langford, MD, MHS,[5] Laura H. Mariani, MD,[6] Michael J. Somers, MD,[7] Howard Trachtman, MD,[8] and Meryl Waldman, MD[9]

Glomerulonephritis (GN) is an important cause of morbidity and mortality in patients of all ages throughout the world. Because these disorders are relatively rare, it is difficult to perform randomized clinical trials to define optimal treatment for many of the specific glomerulopathies. In the absence of high-grade evidence to guide the care of glomerular diseases, in June 2012, KDIGO (Kidney Disease: Improving Global Outcomes) published an international clinical guideline for GN. The Work Group report represents an important review of the literature in this area and offers valid and useful guidelines for the most common situations that arise in the management of patients with glomerular disease. This commentary, developed by a panel of clinical experts convened by the National Kidney Foundation, attempts to put the GN guideline into the context of the US health care system. Overall, we support the vast majority of the recommendations and highlight select areas in which epidemiological factors and medical practice patterns in this country justify modifications and adjustments in order to achieve favorable outcomes. There remain large gaps in our knowledge of the best approaches to treat glomerular disease and we strongly endorse an expanded clinical research effort to improve the health and long-term outcomes of children and adults with GN.
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KDIGO (Kidney Disease: Improving Global Outcomes) is an organization with the mission to develop and implement clinical practice guidelines for worldwide use. In June 2012, KDIGO published a guideline for glomerulonephritis (GN).[1] This is the first guideline on GN ever published and is comprehensive in scope (143 pages in length). It addresses a major aspect of the clinical care provided by nephrologists to patients of all ages around the globe. KDIGO guidelines are developed for international application; however, implementation of the guideline needs to be put in the context of regional health care systems. To accomplish this, the NKF-KDOQI (National Kidney Foundation–Kidney Disease Outcomes Quality Initiative) program organized a work group of experts to review the GN guideline and comment on the applicability of the recommendations to the practice of nephrology in the United States.

As the first document of its kind that focuses exclusively on GN, the KDIGO report is in the enviable position of defining the terms of the conversation in this area for the immediate future. Nonetheless, as we are sure the authors of the KDIGO GN guideline will readily acknowledge, it is unlikely to be the final word on the topic. As it says in the rabbinical teachings compiled in *Ethics of the Fathers* (chapter 2, paragraph 16), "It is not incumbent upon you to finish the task, but neither are you free to absolve yourself from it." We congratulate the KDIGO GN Work Group on its preparation of a wide-ranging up-to-date review and for initiating a careful analysis of the evidence regarding the diagnosis and management of GN. We offer this KDOQI Commentary to help identify areas of consensus in the management of GNs, highlight areas in which more work is needed to define optimal clinical practice guidelines, and define research needs for specific types of GN (summarized in the closing section) in GNs. Most importantly, we hope that our review promotes ongoing dialogue in this heretofore neglected area of nephrology.

GUIDELINE AND COMMENTARY PROCESS

KDIGO Guideline Process

This KDIGO guideline focuses on the evaluation and treatment of GN in both adults and children beginning at the point when the diagnosis has been established by biopsy. It was written primarily for

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From the [1]Boston University School of Medicine, Boston, MA; [2]Columbia University Medical Center, New York, NY; [3]Johns Hopkins University School of Medicine, Baltimore, MD; [4]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [5]Cleveland Clinic, Cleveland, OH; [6]University of Michigan School of Medicine, Ann Arbor, MI; [7]Boston Children's Hospital, Boston, MA; [8]New York University Langone Medical Center, New York, NY; and [9]National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD.

Address correspondence to Michael J. Choi, MD, Department of Medicine, Division of Nephrology, Johns Hopkins University, 1830 E Monument St, Ste 416, Baltimore, MD 21287. E-mail: mchoi3@jhmi.edu

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Table 1. Nomenclature and Description for Ratings of Recommendation Statement Strength and Quality of Evidence

Rating Strength of Recommendation

Grade[a]	Implications for Patients	Implications for Clinicians	Implications for Policy
Level 1 "We recommend"	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

Rating Quality of Evidence

Grade	Quality of Evidence	Meaning
A	High	We are confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very Low	The estimate of effect is very uncertain, and often will be far from the truth.

Note: Within each recommendation, the strength of recommendation is indicated as Level 1, Level 2, or Not Graded, and the quality of the supporting evidence is shown as A, B, C, or D.

[a]The additional category "Not Graded" was used, typically to provide guidance based on common sense or when the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

nephrologists, but other health care professionals involved in the care of patients with GN will find it useful. The guideline addresses the following forms of GN:

- Steroid-sensitive nephrotic syndrome (SSNS) and steroid-resistant nephrotic syndrome (SRNS) in children
- Minimal-change disease (MCD) and idiopathic focal segmental glomerulosclerosis (FSGS) in children and adults
- Idiopathic membranous nephropathy (IMN)
- Idiopathic membranoproliferative glomerulonephritis (MPGN)
- GN associated with infections
- Immunoglobulin A (IgA) nephropathy (IgAN) and Henoch-Schönlein purpura (hsp) nephritis
- Lupus nephritis (LN)
- Renal vasculitis
- Anti–glomerular basement membrane (anti-GBM) GN

The guideline was developed by an 18-member international work group with the support of a professional evidence review team, who conducted literature searches, managed the abstract and article screening process, coordinated the methodological and analytic processes of the report, defined standardized methods for performing these searches and data extraction, and prepared summaries of the evidence. The work group evaluated the evidence and developed the recommendation statements and supporting rationale. The recommendations were then classified by the strength of the recommendation and the quality of the supporting evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) evidence grading scale (see Table 1). Reflecting the general lack of evidence in this area, and as stated in the foreward to the guideline, there were just 4 (2%) recommendations for which the overall quality of evidence was graded A, while 34 (20%) were graded B, 66 (40%) were graded C, and 63 (38%) were graded D. Even though there can be reasons besides quality of evidence to assign a grade 1 or 2 recommendation, overall, there is a correlation between the quality of overall evidence and the strength of the recommendation. Thus, there were 46 (28%) recommendations graded 1 and 121 (72%) graded 2. There were 4 (2%) recommendations graded 1A, 24 (14%) were 1B, 15 (9%) were 1C, and 3 (2%) were 1D. There were 0 (0%) graded 2A, 10 (6%) were 2B, 51 (31%) were 2C, and 60 (36%)

were 2D. There were 28 (14%) statements that were not graded.

KDOQI Process for Interpretation of the KDIGO Guideline for the US Audience

KDOQI convened a work group to review this international guideline and interpret the relevance and applicability of the recommendations to the US health care system and patients. Consideration was given to differences in epidemiology of the diseases (prevalence, etc) compared to the worldwide population, unique demographic considerations or comorbid condition differences, issues unique to US health care (eg, therapies or tests not available in the United States), and issues related to implementation of treatment recommendations, such as familiarity and current practices, relative costs, regulatory issues, and logistic hurdles to a treatment guideline.

Through a series of teleconferences, the work group reached a general consensus on the following commentary. For ease of navigation, the headings of this commentary specify the chapter and section of the KDIGO guideline being discussed. Numbered text within horizontal rules in the body of the article is quoted directly from the KDIGO document, using the same numbering scheme as in the original. All material is reproduced with permission of KDIGO. A list of key abbreviations used in the guideline excerpts included in this commentary is provided in Box 1.

Box 1. Abbreviations Used in Guideline Recommendations

ACE-I: angiotensin-converting enzyme inhibitor
AKI: acute kidney injury
ANCA: antineutrophil cytoplasmic antibody
ARB: angiotensin receptor blocker
CKD: chronic kidney disease
CNI: calcineurin inhibitor
ESRD: end-stage renal disease
FR: frequently relapsing
FSGS: focal segmental glomerulosclerosis
GBM: glomerular basement membrane
GFR: glomerular filtration rate
GN: glomerulonephritis
HBV: hepatitis B virus
HCV: hepatitis C virus
HIV: human immunodeficiency virus
HSP: Henoch-Schönlein purpura
IgAN: immunoglobulin A nephropathy
IMN: idiopathic membranous nephropathy
i.v.: intravenous
LN: lupus nephritis
MCD: minimal-change disease
MMF: mycophenolate mofetil
MN: membranous nephropathy
MPGN: membranoproliferative glomerulonephritis
NS: nephrotic syndrome
NSAIDs: nonsteroidal anti-inflammatory drugs
RAS: renin-angiotensin system
RCT: randomized controlled trial
SCr: serum creatinine
SD: steroid-dependent
SRNS: steroid-resistant nephrotic syndrome
SSNS: steroid-sensitive nephrotic syndrome

CHAPTER 3: KDIGO RECOMMENDATIONS FOR SSNS IN CHILDREN

3.1: Treatment of the Initial Episode of SSNS

3.1.1: We recommend that corticosteroid therapy (prednisone or prednisolone)* be given for at least 12 weeks. (*1B*)

3.1.1.1: We recommend that oral prednisone be administered as a single daily dose (*1B*) starting at 60 mg/m^2/d or 2 mg/kg/d to a maximum 60 mg/d. (*1D*)

3.1.1.2: We recommend that daily oral prednisone be given for 4-6 weeks (*1C*) followed by alternate-day medication as a single daily dose starting at 40 mg/m^2 or 1.5 mg/kg (maximum 40 mg on alternate days) (*1D*) and continued for 2-5 months with tapering of the dose. (*1B*)

*Prednisone and prednisolone are equivalent, used in the same dosage, and have both been used in RCTs depending on the country of origin. All later references to prednisone in this chapter refer to prednisone or prednisolone. All later references to oral corticosteroids refer to prednisone or prednisolone.

Commentary

We agree with the general recommendations in Section 3.1. However, the impact of patient adherence when treating the initial episode of nephrotic syndrome (NS) for more than 8 weeks needs to be addressed. Patients and parents should be counseled regarding treatment adherence and that steroid therapy extended beyond the child's initial response may decrease the long-term risk of frequent relapses. Because more than 80% of children with new-onset NS relapse, altering the timing and frequency of future relapses is of broad import.

As stated in the guideline, many of the steroid dosing recommendations are empirical in nature and draw on the International Study of Kidney Disease in Children (ISKDC) protocols designed more than 4 decades ago. Dose regimens can be tailored for an individual patient, for example, slow tapering versus abrupt cessation of alternate-day regimens, based on both experience gained over time with regard to the child's prior response to steroids during relapses and insight gained from the ongoing dialogue between the nephrologist and parent/guardian on the effect of varying steroid doses on key neurobehavioral sequelae. For example, slower tapering of the steroid dose may help some children maintain a remission and prevent the need for higher steroid doses that may affect behavior or activity deleteriously, whereas the shortest

possible exposure to steroids may be the better approach with other children. A recent study suggests that if steroid therapy is extended beyond the standard course, the actual cumulative dosage prescribed is more important than simply prolonging therapy in maintaining remission.[2]

Dosing steroids in children who are significantly overweight should probably be based on ideal body weight, which may spare unnecessary steroid exposure. There may be consideration of a maximum dose of prednisone of 80 mg daily. In children who have gained significant weight related to steroid therapy, a best estimate of premorbid weight may be useful.

3.2: Treatment of Relapsing SSNS With Corticosteroids

3.2.1: Corticosteroid therapy for children with infrequent relapses of SSNS:
3.2.1.1: We suggest that infrequent relapses of SSNS in children be treated with a single-daily dose of prednisone 60 mg/m^2 or 2 mg/kg (maximum of 60 mg/d) until the child has been in complete remission for at least 3 days. (*2D*)
3.2.1.2: We suggest that, after achieving complete remission, children be given prednisone as a single dose on alternate days (40 mg/m^2 per dose or 1.5 mg/kg per dose: maximum 40 mg on alternate days) for at least 4 weeks. (*2C*)
3.2.2: Corticosteroid therapy for frequently relapsing (FR) and steroid-dependent (SD) SSNS:
3.2.2.1: We suggest that relapses in children with FR or SD SSNS be treated with daily prednisone until the child has been in remission for at least 3 days, followed by alternate-day prednisone for at least 3 months. (*2C*)
3.2.2.2: We suggest that prednisone be given on alternate days in the lowest dose to maintain remission without major adverse effects in children with FR and SD SSNS. (*2D*)
3.2.2.3: We suggest that daily prednisone at the lowest dose be given to maintain remission without major adverse effects in children with SD SSNS where alternate-day prednisone therapy is not effective. (*2D*)
3.2.2.4: We suggest that daily prednisone be given during episodes of upper respiratory tract and other infections to reduce the risk for relapse in children with FR and SD SSNS already on alternate-day prednisone. (*2C*)

Commentary

We agree with the overall recommendations in Section 3.2. While daily administration of corticosteroids during upper respiratory tract illnesses in children with frequently relapsing (FR) or steroid-dependent (SD) NS can prevent relapses, it does not lower cumulative steroid exposure.[3] Therefore, the efficacy of this strategy should be assessed periodically to make sure there are no significant side effects from the ongoing use of and cumulative exposure to corticosteroids.

3.3: Treatment of FR and SD SSNS With Corticosteroid-Sparing Agents

3.3.1: We recommend that corticosteroid-sparing agents be prescribed for children with FR SSNS and SD SSNS, who develop steroid-related adverse effects. (*1B*)
3.3.2: We recommend that alkylating agents, cyclophosphamide or chlorambucil, be given as corticosteroid-sparing agents for FR SSNS. (*1B*) We suggest that alkylating agents, cyclophosphamide or chlorambucil, be given as corticosteroid-sparing agents for SD SSNS. (*2C*)
3.3.2.1: We suggest that cyclophosphamide (2 mg/kg/d) be given for 8-12 weeks (maximum cumulative dose 168 mg/kg). (*2C*)
3.3.2.2: We suggest that cyclophosphamide not be started until the child has achieved remission with corticosteroids. (*2D*)
3.3.2.3: We suggest that chlorambucil (0.1-0.2 mg/kg/d) may be given for 8 weeks (maximum cumulative dose 11.2 mg/kg) as an alternative to cyclophosphamide. (*2C*)
3.3.2.4: We suggest that second courses of alkylating agents not be given. (*2D*)
3.3.3: We recommend that levamisole be given as a corticosteroid-sparing agent. (*1B*)
3.3.3.1: We suggest that levamisole be given at a dose of 2.5 mg/kg on alternate days (*2B*) for at least 12 months (*2C*) as most children will relapse when levamisole is stopped.
3.3.4: We recommend that the calcineurin inhibitors cyclosporine or tacrolimus be given as corticosteroid-sparing agents. (*1C*)
3.3.4.1: We suggest that cyclosporine be administered at a dose of 4-5 mg/kg/d (starting dose) in two divided doses. (*2C*)
3.3.4.2: We suggest that tacrolimus 0.1 mg/kg/d (starting dose) given in two divided doses be used instead of cyclosporine when the cosmetic side-effects of cyclosporine are unacceptable. (*2D*)
3.3.4.3: Monitor CNI levels during therapy to limit toxicity. (*Not Graded*)
3.3.4.4: We suggest that CNIs be given for at least 12 months, as most children will relapse when CNIs are stopped. (*2C*)
3.3.5: We suggest that MMF be given as a corticosteroid-sparing agent. (*2C*)
3.3.5.1: We suggest that MMF (starting dose 1200 mg/m^2/d) be given in two divided doses for at least 12 months, as most children will relapse when MMF is stopped. (*2C*)
3.3.6: We suggest that rituximab be considered only in children with SD SSNS who have continuing frequent relapses despite optimal combinations of prednisone and corticosteroid-sparing agents, and/or who have serious adverse effects of therapy. (*2C*)
3.3.7: We suggest that mizoribine not be used as a corticosteroid-sparing agent in FR and SD SSNS. (*2C*)
3.3.8: We recommend that azathioprine not be used as a corticosteroid-sparing agent in FR and SD SSNS. (*1B*)

Commentary

We agree with the overall recommendations in Section 3.3. However, it is important to emphasize that the number of relapses by itself should not drive a decision to use a second-line agent. It is as important to assess how the child is tolerating steroids and whether there is a need to reduce steroid burden due to actual sequelae, including neurobehavioral effects.[4]

Since reduction in long-term therapy-related sequelae may be as important as reduction in the actual relapse rate, this should be considered in the decision to begin steroid-sparing drugs. A second-line agent that is more likely to result in long-lived steroid-free remission, but at the expense of significant short-term or long-term sequelae, may be less preferable than an alternative agent that may not reduce relapse rate as dramatically but has a lower risk of new clinical complications.

The ordering of the agents enumerated in this section should not be interpreted as a strict hierarchy of preference for these steroid-sparing drugs. In view of the permanent toxicity associated with alkylating agents (gonadal and bladder), it is questionable whether they should be considered as the best initial option even though there are more historical experience and randomized controlled trials (RCTs) for this class of drugs compared with other agents. Only a single course of an alkylating agent should be given to most children with FR NS or SD NS.

Although there is little head-to-head comparison of cyclosporine and tacrolimus, the favorable side-effect profile and comparable cost probably make tacrolimus an agent that is being used more widely in practice.

Although levamisole is not commercially available, it is effective and can be utilized for children whose parents have access to supplies of the drug from abroad. However, levamisole should always be administered under the care and supervision of a pediatric nephrologist experienced with its use.

We would suggest that mycophenolate mofetil (MMF) be considered as a valid option as second-line therapy because of its widespread availability, ease of administration, and favorable side-effect profile compared with alkylating agents or calcineurin inhibitors (CNIs). While there are few randomized studies comparing MMF with other drugs, it has been given to more than 125 children with FR NS or SD NS in open-label studies with reasonable efficacy and suitable patient tolerance.

We agree that there may be a role for rituximab in certain cases of SSNS, most notably with cases of FR NS or SD NS with suboptimal response to second-line agents. The best use and most optimal dosing of rituximab (amount per dose and frequency of administration) for children with SSNS requires further clarification in controlled clinical trials.

Novel immunomodulatory therapies or new formulations of current agents are frequently offered as potential treatment options in patients with FR NS and SD NS. It is difficult to endorse their use in the absence of controlled clinical trials or widespread experience demonstrating added efficacy or other specific benefit over standard therapy. We do not recommend use of ACTH (adrenocorticotropic hormone; corticotropin) as a steroid-like option as it is very expensive and has not been studied in children with SSNS or SRNS.

3.4: Indication for Kidney Biopsy

3.4.1: Indications for kidney biopsy in children with SSNS are (*Not Graded*):

- late failure to respond following initial response to corticosteroids;
- a high index of suspicion for a different underlying pathology;
- decreasing kidney function in children receiving CNIs.

Commentary

We agree with these recommendations about indications for kidney biopsy, but would add that there may also be a role for biopsy in selected cases of new-onset NS, based on epidemiological associations of SRNS and histologic FSGS with demographic factors such as age and African American background.

In view of the technical and diagnostic limitations of the kidney biopsy in defining the cause and prognosis of childhood NS, particularly in SRNS, greater attention should be given to the role of genetic testing to supplement histologic examination of the renal tissue, especially as there comes to be better understanding of the relationship between certain mutations and therapeutic response or prognosis.

3.5: Immunizations in Children With SSNS

3.5.1: To reduce the risk of serious infections in children with SSNS (*Not Graded*):

- Give pneumococcal vaccination to the children.
- Give influenza vaccination annually to the children and their household contacts.
- Defer vaccination with live vaccines until prednisone dose is below either 1 mg/kg daily (<20 mg/d) or 2 mg/kg on alternate days (<40 mg on alternate days).
- Live vaccines are contraindicated in children receiving corticosteroid-sparing immunosuppressive agents.
- Immunize healthy household contacts with live vaccines to minimize the risk of transfer of infection to the immunosuppressed child but avoid direct exposure of the child to gastrointestinal,

urinary, or respiratory secretions of vaccinated contacts for 3-6 weeks after vaccination.
- Following close contact with Varicella infection, give nonimmune children on immunosuppressive agents varicella zoster immune globulin, if available.

Commentary

We agree with the recommendations in Section 3.5. Clinicians should be knowledgeable of current guidelines for the use of newly introduced vaccines (eg, meningococcal vaccine and rotavirus vaccine) in children with FR NS and SD NS who are on treatment with steroids or other immunosuppressive drugs.

CHAPTER 4: KDIGO RECOMMENDATIONS FOR SRNS IN CHILDREN

4.1: Evaluation of Children With SRNS

4.1.1: We suggest a minimum of 8 weeks treatment with corticosteroids to define steroid resistance. (*2D*)
4.1.2: The following are required to evaluate the child with SRNS (*Not Graded*):
- a diagnostic kidney biopsy;
- evaluation of kidney function by GFR or eGFR;
- quantitation of urine protein excretion.

Commentary

We agree with the recommendation for a kidney biopsy to define the cause of SRNS. However, limitations of both the procedure (eg, inadequate or unrepresentative sample) and the existing histopathological categories should be recognized. Given that genetic causes are seen more frequently in SRNS, predominately due to mutations of podocyte-related genes, genetic testing when available may be used to supplement histologic information.

4.2: Treatment Recommendations for SRNS

4.2.1: We recommend using a calcineurin inhibitor (CNI) as initial therapy for children with SRNS. (*1B*)
4.2.1.1: We suggest that CNI therapy be continued for a minimum of 6 months and then stopped if a partial or complete remission of proteinuria is not achieved. (*2C*)
4.2.1.2: We suggest CNIs be continued for a minimum of 12 months when at least a partial remission is achieved by 6 months. (*2C*)
4.2.1.3: We suggest that low-dose corticosteroid therapy be combined with CNI therapy. (*2D*)
4.2.2: We recommend treatment with ACE-I or ARBs for children with SRNS. (*1B*)
4.2.3: In children who fail to achieve remission with CNI therapy:
4.2.3.1: We suggest that mycophenolate mofetil (*2D*), high-dose corticosteroids (*2D*), or a combination of these agents (*2D*) be considered in children who fail to achieve complete or partial remission with CNIs and corticosteroids.
4.2.3.2: We suggest that cyclophosphamide not be given to children with SRNS. (*2B*)
4.2.4: In patients with a relapse of nephrotic syndrome after complete remission, we suggest that therapy be restarted using any one of the following options: (*2C*)
- oral corticosteroids (*2D*);
- return to previous successful immunosuppressive agent (*2D*);
- an alternative immunosuppressive agent to minimize potential cumulative toxicity (*2D*).

Commentary

We agree with the recommendations in Section 4.2. The discussion defining SR in children and the importance of graded reductions in proteinuria on long-term maintenance of kidney function is excellent. Dipstick testing of first morning urine may be the optimal method available to define SR in locations where resources to quantitate urine protein-creatinine ratios are limited.

The spectrum of clinical outcomes for patients with SRNS may be broader than outlined in the KDIGO summary. There are reports in which children with histologically confirmed FSGS fared better than expected. In addition, there may be selected patients with SRNS or specific clinical circumstances (the obese patient in whom the proteinuria is likely secondary) for whom blockade of the renin-angiotensin axis may be the preferred initial therapy rather than immunosuppressive agents.[5]

Similar to comments in Section 3.3, the order of presentation of treatments in this section should also not imply a hierarchy of preferred therapies. The preference for cyclosporine over tacrolimus may represent its earlier introduction into clinical practice more than better efficacy. There may also be data regarding certain patient populations that need to be considered when choosing a therapy. For example, the use of pulse intravenous corticosteroids in SRNS may be ineffective in African American children.[6]

Given the limited number of adequately sized studies, the cautionary notes in the KDIGO guidelines about alkylating agents and MMF for the treatment of SRNS are well stated. Similarly, the statement on rituximab is strong and appropriate. Because this agent is costly and the long-term adverse consequences are unknown, it is recommended that for SRNS and presumed FSGS, rituximab should only be administered in the context of a clinical trial. This is true even in light of preliminary evidence suggesting that the antibody may alter sphingomyelinase in podocytes.

With increased recognition of the persistence of NS into adulthood, the importance of transition of care from pediatric to internal medicine nephrologists is emphasized. Similarly, there is a need to assess the

risks and benefits of exposure to certain steroid-sparing therapy early in childhood if indeed there is likely to be a need for therapy later in life as well. There is also persistent uncertainty about the prognosis of patients with SRNS who continue into adulthood without end-stage renal disease (ESRD) and the best way to approach their management.

It is important to determine the percentage of cases of SSNS and SRNS caused by genetic mutations and the impact of these findings on response to therapy, long-term course, and outcome after kidney transplantation. There is also a need to identify serum and urinary biomarkers that may be useful in assessing prognosis and therapeutic response and that could complement the current limited histopathologic categorization of SRNS.

CHAPTER 5: KDIGO RECOMMENDATIONS FOR MCD IN ADULTS

5.1: Treatment of Initial Episode of Adult MCD

5.1.1: We recommend that corticosteroids be given for initial treatment of nephrotic syndrome. (*1C*)

5.1.2: We suggest prednisone or prednisolone* be given at a daily single dose of 1 mg/kg (maximum 80 mg) or alternate-day single dose of 2 mg/kg (maximum 120 mg). (*2C*)

5.1.3: We suggest the initial high dose of corticosteroids, if tolerated, be maintained for a minimum period of 4 weeks if complete remission is achieved, and for a maximum period of 16 weeks if complete remission is not achieved. (*2C*)

5.1.4: In patients who remit, we suggest that corticosteroids be tapered slowly over a total period of up to 6 months after achieving remission. (*2D*)

5.1.5: For patients with relative contraindications or intolerance to high-dose corticosteroids (e.g., uncontrolled diabetes, psychiatric conditions, severe osteoporosis), we suggest oral cyclophosphamide or CNIs as discussed in frequently relapsing MCD. (*2D*)

5.1.6: We suggest using the same initial dose and duration of corticosteroids for infrequent relapses as in Recommendations 5.1.2, 5.1.3, and 5.1.4. (*2D*)

*Prednisone and prednisolone are equivalent, used in the same dosage, and have both been used in RCTs depending on the country of origin. All later references to prednisone in this chapter refer to prednisone or prednisolone. All later references to oral corticosteroids refer to prednisone or prednisolone.

Commentary

In evaluating adults with newly diagnosed MCD, we agree that consideration of rare secondary causes (Box 2) is important, although evaluation should only be pursued for those causes suggested by history or physical examination.

In contrast to children with NS, MCD accounts for only 10%-15% of NS cases in adults.[7,8] The low prevalence of this disease has been a barrier to adequately powered studies and data guiding treatment decisions in adult patients are limited and often extrapolated from pediatric studies. Two early small randomized trials in adults, published in 1970 and 1986, compared steroid therapy to placebo but lack detailed baseline and outcome data. In both trials, while patients treated with steroids had shorter times to remission, there was no difference seen in rates of remission by the end of the study periods.[9,10] More recent observational studies have been consistent with these findings and suggest that a greater proportion of those treated with steroids achieve remission.[11-14]

Based on the limited data available, we agree that a trial of corticosteroids is recommended for treatment of an initial episode of MCD in adults. The majority of adult patients (>80%) respond within 8 weeks and often more quickly.[9,10,14] While there are reports of patients responding after nearly 16 weeks of therapy,[11,13] the toxicity of prolonged high-dose corticosteroids is significant and may limit therapy.[15] No randomized trials have been done to identify optimal dose or duration of steroid therapy for MCD in adults.[16] The high-dose steroid regimens recommended here have been extrapolated from trials done in children. Of note, the early trial in adults by Black et al[9] successfully used an initial mean dose of 26 mg/d of prednisone. A randomized trial that compared high-dose intravenous and oral steroid versus oral steroid alone found no difference in complete remission between the groups.[17] We believe that therapy should be individualized based on the therapeutic response of the patient and the need to minimize corticosteroid toxicity. An earlier transition to steroid-sparing agents, rather than prolonged corticosteroid tapers, might be necessary in patients at high risk for significant

Box 2. Secondary Causes of Minimal Change Disease

Malignancy
- Hodgkin and non-Hodgkin lymphoma
- Leukemia

Infection
- Syphilis
- HIV
- Tuberculosis
- Ehrlichiosis
- Mycoplasma

Drugs
- NSAIDs
- Lithium
- 5-Aminosalicylic acid (5-ASA)
- Bisphosphonates
- Ampicillin
- Penicillamine
- Immunizations

Allergy
- Food and environmental allergens

steroid side effects. We agree that for those who have an initial response, repeating a similar course of therapy for an infrequent relapse is appropriate.

5.2: FR/SD MCD

5.2.1: We suggest oral cyclophosphamide 2-2.5 mg/kg/d for 8 weeks. (*2C*)
5.2.2: We suggest CNI (cyclosporine 3-5 mg/kg/d or tacrolimus 0.05-0.1 mg/kg/d in divided doses) for 1-2 years for FR/SD MCD patients who have relapsed despite cyclophosphamide, or for people who wish to preserve their fertility. (*2C*)
5.2.3: We suggest MMF 500-1000 mg twice daily for 1-2 years for patients who are intolerant of corticosteroids, cyclophosphamide, and CNIs. (*2D*)

Commentary

The data for therapy of adults with FR and SD MCD are also limited and extrapolated from observational data and pediatric trials. Despite these limitations, both cyclophosphamide and CNIs have been shown to lead to remission in a significant proportion of patients. One randomized trial, which included a small number of adults, demonstrated that those treated with cyclophosphamide had fewer relapses compared with those treated with cyclosporine, possibly arguing for the use of this agent.[18] The value of using CNIs in the setting of FR/SD MCD is uncertain since CNIs might alter proteinuria by reversible vasoconstrictor effects rather than by fundamentally altering the underlying biology of disease. This concern is supported by the observation that CNIs used in this setting often result in partial remission of proteinuria and frequent relapse following discontinuation of therapy. The therapeutic value of using MMF in this setting is supported only by limited case reports.[19-21]

5.3: Corticosteroid-Resistant MCD

5.3.1: Re-evaluate patients who are corticosteroid-resistant for other causes of nephrotic syndrome. (*Not Graded*)

Commentary

We agree that patients with corticosteroid-resistant MCD should be assessed for other causes of NS. One observational study reported that this group is less likely to respond to alternative immunosuppressive agents compared with SD patients.[13] Optimal treatment in this group of patients remains to be determined.

5.4: Supportive Therapy

5.4.1: We suggest that MCD patients who have AKI be treated with renal replacement therapy as indicated, but together with corticosteroids, as for a first episode of MCD. (*2D*)
5.4.2: We suggest that, for the initial episode of nephrotic syndrome associated with MCD, statins not be used to treat hyperlipidemia, and ACE-I or ARBs not be used in normotensive patients to lower proteinuria. (*2D*)

Commentary

Acute kidney injury (AKI) in the setting of newly diagnosed MCD has been reported to be as high as 25% in case series from major referral centers, but may be lower in nonreferral centers.[12,13] When biopsy was available, it most often demonstrated tubular epithelial cell injury, suspected to be associated with the use of diuretics and renin-angiotensin blockade. We agree that decreased GFR (glomerular filtration rate) is often reversible with steroid treatment.

Treatment of hyperlipidemia in the setting of new-onset MCD is not necessary if there is rapid resolution of the syndrome with therapy. The cardiovascular risk in this patient population is largely unknown, especially in patients with frequent relapses or steroid dependence, and there is no evidence that statin therapy is protective. There is evidence that resolution of hyperlipidemia can lag behind resolution of proteinuria[22]; for this reason, the caregiver might delay institution of lipid-lowering therapy.

Treatment with renin-angiotensin system blockade may also be unnecessary in those patients who have a rapid response to corticosteroid therapy. However, if response is delayed, these agents remain an important part of management of the NS.

CHAPTER 6: KDIGO RECOMMENDATIONS FOR IDIOPATHIC FSGS IN ADULTS

6.1: Initial Evaluation of FSGS

6.1.1: Undertake thorough evaluation to exclude secondary forms of FSGS. (*Not Graded*)
6.1.2: Do not routinely perform genetic testing. (*Not Graded*)

Commentary

FSGS is the leading cause of acquired kidney disease leading to ESRD in children and there is evidence that its incidence is increasing in adults.[23] The need for recommendations on how best to treat patients with FSGS is imperative, but in making them, we are limited by a paucity of clinical trial data. While an understanding of the genetics and biology underlying FSGS is improving rapidly, this emerging information has not yet reached clinical utility. As such, therapy decisions for an individual patient must be individualized, weighing the considerable risks of immunosuppression with the potential benefits.

Box 3. Causes of FSGS

Primary
- Idiopathic
  - Genetic disorders
    - Slit diaphragm proteins: NPHS1, NPHS2, CD2AP
    - Cell membrane–associated proteins: TRPC6, PTPRO, LAMB2, ITGB4, CD151, ITGA3
    - Cytosolic or cytoskeletal proteins: ACTN4, PLCE1, MYH9, INF2, MYO1E, ARHGAP24
    - Nuclear proteins: WT1, SMARCAL1
    - Mitochondrial components: mtDNA-A3242G, COQ2, COQ6
    - Lysosomal protein: SCARB2
  - Circulating pathogenic factor(s)

Secondary
- Virus-associated: HIV, parvovirus B19
- Medication-associated: interferon α, β, or γ, lithium, bisphosphonates, anabolic steroids
- Adaptation to reduced kidney mass: oligomeganephronia, unilateral kidney agenesis, kidney dysplasia, cortical necrosis, reflux nephropathy, surgical kidney ablation, chronic allograft nephropathy, advanced chronic kidney disease with reduced functioning nephrons, sickle cell anemia
- Initially normal kidney mass: diabetes, hypertension, obesity, cyanotic congenital heart disease
- Nonspecific pattern of FSGS caused by kidney scarring in glomerular disease

FSGS is a histological phenotype; it is not a disease. That FSGS histopathology is representative of multiple distinct biological disorders probably explains clinical variability in presentation, natural history, and response to therapy observed in these patients. Segmental sclerosis is secondary to podocyte loss that occurs for a variety of reasons: these include, for example, genetic mutation–induced abnormality in podocyte function, inability to adapt to hypertrophy-inducing stress or hemodynamic stress, abnormalities in cell energetics, or inflammatory damage.[24]

We suggest modifying the KDIGO classification to recognize that genetic diseases are primary in nature (Box 3).[25,26] We take the term "idiopathic" to represent the group of primary diseases for which underlying biology has not yet been discerned and that cannot be distinguished clinically.

We agree that routine genetic testing is not currently indicated in adults, as $<$10% of patients with SR FSGS have a known mutation[27,28] and no prospective studies show that routine genetic testing is useful to inform therapeutic decision making. However, this recommendation may change in the future as our knowledge of the genetic underpinnings of glomerular disease evolves. Retrospective analyses have suggested that some monogenetic mutations result in glomerular disease that is not responsive to immunosuppressive therapy.[29-31] However, these retrospective studies must be complemented by prospective natural history studies and clinical trials before a strong recommendation to withhold therapy can be issued. The therapeutic implication of identifying high-risk alleles, such as *APOL1*, in a patient is presently unknown and recommendations regarding treatment, transplantation, and kidney donation remain premature.

Distinguishing primary from secondary FSGS can be difficult. Nevertheless, making this distinction can have important therapeutic implications since immunosuppressive therapy is not always indicated in secondary FSGS for which other treatments (eg, antiretroviral therapy for HIV [human immunodeficiency virus] infection and weight loss for obesity) or discontinuing offending medications might be appropriate in a particular setting. It is important to note that segmental scarring is often encountered in the setting of other primary glomerular diseases; treatment in this setting should be aimed at the primary disease.

6.2: Initial Treatment of FSGS

6.2.1: We recommend that corticosteroid and immunosuppressive therapy be considered only in idiopathic FSGS associated with clinical features of the nephrotic syndrome. (*1C*)

6.2.2: We suggest prednisone* be given at a daily single dose of 1 mg/kg (maximum 80 mg) or alternate-day dose of 2 mg/kg (maximum 120 mg). (*2C*)

6.2.3: We suggest the initial high dose of corticosteroids be given for a minimum of 4 weeks; continue high-dose corticosteroids up to a maximum of 16 weeks, as tolerated, or until complete remission has been achieved, whichever is earlier. (*2D*)

6.2.4: We suggest corticosteroids be tapered slowly over a period of 6 months after achieving complete remission. (*2D*)

6.2.5: We suggest CNIs be considered as first-line therapy for patients with relative contraindications or intolerance to high-dose corticosteroids (e.g., uncontrolled diabetes, psychiatric conditions, severe osteoporosis). (*2D*)

*Prednisone and prednisolone are equivalent, used in the same dosage, and have both been used in RCTs depending on the country of origin. All later references to prednisone in this chapter refer to prednisone or prednisolone. All later references to oral corticosteroids refer to prednisone or prednisolone.

Commentary

Therapeutic decisions should be individualized and based on all aspects of the patient's specific presentation, trajectory, comorbid conditions, and wishes. The goals, reasonable expectations, and risks of therapy should frame a discussion with patients prior to initiation of treatment. Expectations of therapy might include: (1) "disease cure," defined as eliminating proteinuria and progressive loss of GFR; (2) "disease

control," defined as decreased rate of protein excretion and slowing progressive loss of GFR or progression to ESRD; and (3) decreasing the probability of or time to extrarenal morbidity or mortality (eg, cardiovascular disease, infection, malignancy, and poor quality of life). The risks of immunosuppressive therapy are significant. Patients should understand the probability of treatment success and should be informed that we are presently unable to predict whether a response can be expected. Patients should also be informed of the probability of disease relapse.

Patients with non–nephrotic-range proteinuria do not necessarily require immunosuppression. However, it is important to recognize that the KDIGO recommendation that corticosteroid therapy be withheld in patients without NS is based on a subjective and arbitrary cutoff of a continuous variable. Other considerations, such as the degree of interstitial fibrosis present on renal biopsy and the patient's response to initial conservative therapy, might alter the clinician's decision to initiate immunosuppressive therapy.

Aggressive blood pressure control and renin-angiotensin-aldosterone-system (RAS) blockade is an important component of the initial management of patients with FSGS. Because there might be significant symptomatic benefit from lowering blood pressure and reducing proteinuria, we recommend initiating these medications immediately. An optimal blood pressure target is not known and the reported risk of AKI in this setting is extrapolated from MCD.[32,33] A measurement of baseline proteinuria (ie, at least 2 if not 3 determinations of the rate of protein excretion) should be obtained as a reference point prior to starting immunosuppressive therapy that will later become useful to the clinician in judging response to therapy.

Although corticosteroid therapy is widely employed in treating primary FSGS, the data supporting this type of initial treatment have limitations. There are no placebo-controlled trials and no randomized trials to support the specific magnitude or duration of the recommended steroid regimens. Rather, data used to make the KDIGO recommendation are retrospective and observational. The largest retrospective study of 281 patients with FSGS found that there was an association between using high-dose corticosteroids with achieving either partial or complete remission.[34] This study, other retrospective studies, and empirical experience suggest that there are patients who appear to respond to steroids with a complete or partial remission. These data support a correlation between decreased proteinuria (either partial or complete remission) and improved renal survival, but prospective protocols are needed to confirm that reduced proteinuria, by any therapy, fully captures the net effect of an intervention on renal survival.

Data for steroid dosage, duration, and tapering schedule are similarly limited and based on retrospective observational data. The average time to complete remission following treatment with high-dose corticosteroids is approximately 3-4 months.[35] For this reason, it is recommended that patients who are treated with corticosteroids require prolonged therapy before being considered unresponsive, recognizing the associated risk of significant steroid-related toxicities.

There is no evidence for or against initial or early use of steroid "sparing" agents. Nevertheless, we concur with the recommendation to consider CNIs for patients with a relative contraindication to steroids. The data available to support this recommendation are based on small observational studies.[36,37] Relapses are common following withdrawal of CNIs. For this reason, the observed partial decrease in proteinuria toward normal may reflect CNI-induced hemodynamic changes rather than amelioration of the underlying disease process. There are insufficient data to support the use of MMF in these patients.

6.3: Treatment for Relapse

6.3.1: We suggest that a relapse of nephrotic syndrome is treated as per the recommendations for relapsing MCD in adults (see Chapters 5.1 and 5.2). (*2D*)

Commentary

We agree that repeated or additional therapy is indicated for patients who relapse with NS after a clear response to initial therapy. However, as there are no data to guide therapy choices in this situation, the recommendations made here are extrapolated from limited observational data in adults with a relapse of MCD. Consequently, reintroducing the successful initial therapy or switching to a trial of cyclophosphamide or CNIs is rational.

The natural history of many patients does not fit the necessarily strict definition of relapse used in clinical study design because these patients either do not reach a true complete remission following initial therapy or because relapse occurs with proteinuria <3.5 g/d. Persistent or worsening proteinuria in some patients is due to the natural history of the disease process underlying the generation of FSGS, with accumulated loss of podocytes and secondary sclerosis resulting in persistent proteinuria that is unresponsive to therapy. Clinically it is presently not possible to identify patients who would respond to additional immunosuppressive therapy in this situation. For this reason, additional therapy is empirical and must be individualized, taking into consideration the ability of the patient to tolerate drug toxicity. Certainly, some pa-

tients may be more appropriately treated only with conservative therapy.

6.4: Treatment for SR FSGS

6.4.1: For steroid-resistant FSGS, we suggest that cyclosporine at 3-5 mg/kg/d in divided doses be given for at least 4-6 months. (*2B*)
6.4.2: If there is a partial or complete remission, we suggest continuing cyclosporine treatment for at least 12 months, followed by a slow taper. (*2D*)
6.4.3: We suggest that patients with steroid-resistant FSGS, who do not tolerate cyclosporine, be treated with a combination of mycophenolate mofetil and high-dose dexamethasone. (*2C*)

Commentary

SR FSGS is defined as persistent proteinuria despite treatment with prednisone at 1 mg/kg/d or 2 mg/kg every other day for at least 4 months. There is evidence from randomized trials to support the use of cyclosporine in SR FSGS.[38-41] In one trial, cyclosporine appeared to decrease the rate of doubling of serum creatinine level. In 2 additional trials and in observational studies, cyclosporine was associated with increased rates of remission (defined by decreased proteinuria), but relapses were common (up to 80%) when therapy was discontinued. As noted earlier, CNIs might decrease proteinuria in this setting by virtue of their vasoconstrictor effects without altering true underlying disease mechanisms. Given the known nephrotoxicity associated with CNIs, caution is appropriate in employing long-term use of CNIs in SR or FR FSGS.[42] An underpowered prospective randomized trial of MMF and dexamethasone versus cyclosporine in children and adults showed no difference in rates of remission.[43]

CHAPTER 7: KDIGO RECOMMENDATIONS FOR MN

The KDIGO guideline on MN arises at a time of transition for this disease due to recent advances in biological markers, namely circulating antibodies to the phospholipase A_2 receptor (anti-PLA_2R), that appear to specifically detect immunologically active primary MN. The finding of the PLA_2R antigen within immune deposits in MN also appears to be indicative of the importance of anti-PLA_2R antibodies in the immunopathogenesis of primary MN.[44] A genome-wide association study has reported very strong associations with single-nucleotide polymorphisms in the genes encoding HLA-DQA1 and PLA_2R1, confirming the importance of PLA_2R in this disease.[45]

Approximately 80% of nephrotic patients with primary MN have been found to be anti-PLA_2R positive. The etiology in the other 20% is not known, although other autoantibodies have been found in adult patients with primary MN.[46]

Currently, tests for anti-PLA_2R antibodies are not available outside the research setting, although several renal pathology laboratories are starting to stain for the PLA_2R antigen in biopsy specimens. In anticipation that these tests will become more widely accessible in the United States prior to the next publication of the KDIGO GN guideline, we tentatively propose that these tests be used as follows.

In nephrotic patients who are found to have the histological pattern of MN on biopsy, a positive anti-PLA_2R antibody test result indicates immunologically active MN. Thus, the majority of patients with MN who are labeled primary or idiopathic have a renal-limited autoimmune disorder. In a small subset of those who are anti-PLA_2R seronegative in the setting of a recent spontaneous remission, localization of the PLA_2R antigen within immune deposits on biopsy also indicates primary MN. Patients with neither circulating anti-PLA_2R antibodies nor PLA_2R within immune deposits may represent the 20% of patients with truly "idiopathic" primary MN, or instead may have a secondary form of the disease and may warrant further investigation for less common secondary causes of MN or for malignancy. A few patients with anti-PLA_2R antibodies may also have features of another disorder such as lupus, HBV (hepatitis B virus) infection, or HCV (hepatitis C virus) infection. Future research will need to identify the best manner in which to determine whether the 2 disease processes are coincidentally or causally related.

In seropositive patients, it appears that anti-PLA_2R levels indicate the degree of immunologic activity. Increases or decreases in the antibody titer may precede parallel changes in proteinuria and clinical activity. Thus, directional changes in anti-PLA_2R might indicate the need to start, stop, or change immunosuppressive therapy. We therefore suggest that future definitions of complete and partial remissions, as currently detailed in Guideline Table 14, be modified to reflect both the clinical (proteinuria) *and* immunological (anti-PLA_2R antibody) status of disease. The combination of these parameters may be a more accurate reflection of the disease process than measurement of proteinuria alone. Also, use of these broader definitions of remission may help compare the efficacy of different therapeutic agents in clinical trials.

7.1: Evaluation of MN

7.1.1: Perform appropriate investigations to exclude secondary causes in all cases of biopsy-proven MN. (*Not Graded*)

Commentary

In general, we agree with recommendation 7.1.1 to exclude secondary causes of MN. The main secondary causes in the United States are lupus, HBV, therapeutic agents (especially NSAIDs [nonsteroidal anti-inflammatory drugs]), and malignancy. The conditions listed in Guideline Table 13 have all been observed in conjunction with a pathological diagnosis of MN; however, it is not clear that they are true secondary causes and might have occurred coincidentally with primary MN. It is impractical to rule out all these processes.

The occurrence of malignancy in patients with MN may be causative in some cases and coincidental in others. There is a greater-than-expected frequency of cancer in patients with MN, most evident in older patients. As the tumor may not be clinically apparent at the time of renal diagnosis, the clinical presentation may be difficult to distinguish from that of IMN.[47] At this time, we suggest limiting a malignancy workup in patients with MN to age-appropriate cancer screening unless specific risk factors or symptoms suggest the need for additional testing.

7.2: Selection of Adult Patients With IMN to Be Considered for Treatment With Immunosuppressive Agents

7.2.1: We recommend that initial therapy be started only in patients with nephrotic syndrome *AND* when at least one of the following conditions is met:
- urinary protein excretion persistently exceeds 4 g/d AND remains at >50% of the baseline value, AND does not show progressive decline, during antihypertensive and antiproteinuric therapy during an observation period of at least 6 mo; (*1B*)
- the presence of severe, disabling, or life-threatening symptoms related to the nephrotic syndrome; (*1C*)
- SCr has risen by 30% or more within 6-12 mo from the time of diagnosis but the eGFR is not less than 25-30 ml/min per 1.73 m^2 AND this change is not explained by superimposed complications (*2C*)

7.2.2: Do not use immunosuppressive therapy in patients with a SCr persistently > 3.5 mg/dl (or an eGFR < 30 ml/min per 1.73 m^2) AND reduction of kidney size on ultrasound (e.g., <8 cm in length) OR those with concomitant severe or potentially life-threatening infections. (*Not Graded*)

Commentary

The proper selection of patients for treatment of MN (Section 7.2) is of utmost importance given the toxicities and expense of current immunosuppressive therapies. Complicating this treatment decision are the following particular issues with MN: (1) the tendency for the disease to undergo spontaneous remission, (2) a lag between immunological and clinical remission, (3) and the possibility of residual proteinuria from structural defects despite immunologic remission. The recent large GLOSEN (Spanish Group for the Study of Glomerular Diseases) multicenter study from Spain of 328 nephrotic patients with IMN suggests that careful observation prior to initiating immunosuppressive treatment may be appropriate for some high-risk patients if they are not experiencing complications of the NS or declining renal function, particularly if there is a gradual decline in proteinuria. A decline in proteinuria >50% of baseline during the first year of follow-up, even if still nephrotic, significantly predicted spontaneous remission.[48]

We agree with close monitoring of clinical status in the first 6 months after diagnosis, with consideration of immunosuppressive therapy for severe proteinuria that does not decrease and/or for progressive loss of GFR. During this observation period, conservative management with diuretics, sodium restriction, and ACE inhibitors/ARBs (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers) are advocated, although the efficacy of ACE inhibitors/ARBs in MN is unproved.

We agree that the risk of immunosuppressive treatment outweighs benefit in those with serum creatinine levels >3.5 mg/dL and/or estimated GFR (eGFR) <30 mL/min/1.73 m^2 and small echogenic kidneys and thus should be avoided.

7.3: Initial Therapy of IMN

7.3.1: We recommend that initial therapy consist of a 6-mo course of alternating monthly cycles of oral and i.v. corticosteroids, and oral alkylating agents (See Guideline Table 15). (*1B*)

7.3.2: We suggest using cyclophosphamide rather than chlorambucil for initial therapy. (*2B*)

7.3.3: We recommend patients be managed conservatively for at least 6 mo following the completion of the regimen before being considered a treatment failure if there is no remission, unless kidney function is deteriorating or severe, disabling, or potentially life-threatening symptoms related to the nephrotic syndrome are present. (*1C*)

7.3.4: Perform a repeat kidney biopsy only if the patient has rapidly deteriorating kidney function (doubling of SCr over 1-2 month of observation), in the absence of massive proteinuria (>15 g/d). (*Not Graded*)

7.3.5: Adjust the dose of cyclophosphamide or chlorambucil according to the age of the patient and eGFR. (*Not Graded*)

7.3.6: We suggest that continuous daily (noncyclical) use of oral alkylating agents may also be effective, but can be associated with greater risk of toxicity, particularly when administered for >6 mo. (*2C*)

Commentary

We agree with guideline 7.3 that oral cyclophosphamide in conjunction with corticosteroids should be

used for initial therapy for MN. The current recommendations provide guidance for minimizing the risk of toxicity of cyclophosphamide. The guideline provides a reasonable description of the "modified Ponticelli" regimen (Guideline Table 15) that includes alternating months of corticosteroids and cyclophosphamide, as well as a listing of situations in which alkylating agents are contraindicated (Guideline Table 17). Recommendation 7.3.6 mentions the noncyclical use of alkylating agents. A 12-month regimen popularized by the Dutch has been efficacious, but leads to a large cumulative dose of cyclophosphamide. This regimen uses oral cyclophosphamide (1.5-2 mg/kg/d) for 1 year plus corticosteroids (intravenous methylprednisolone, 1 g, daily for 3 days in months 1, 3, and 5 and oral prednisone, 0.5 mg/kg, every other day for 6 months, with subsequent tapering).

7.4: Alternative Regimens for the Initial Therapy of IMN: CNI Therapy

7.4.1: We recommend that cyclosporine or tacrolimus be used for a period of at least 6 mo in patients who meet the criteria for initial therapy (7.2.1), but who choose not to receive the cyclical corticosteroid/alkylating-agent regimen or who have contraindications to this regimen (Guideline Table 18). (*1C*)

7.4.2: We suggest that CNIs be discontinued in patients who do not achieve complete or partial remission after 6 mo of treatment. (*2C*)

7.4.3: We suggest that the dosage of CNIs be reduced at intervals of 4-8 wk to a level of about 50% of the starting dosage, provided that remission is maintained and no treatment-limiting CNI-related nephrotoxicity occurs, and continued for at least 12 mo. (*2C*)

7.4.4: We suggest that CNI blood levels be monitored regularly during the initial treatment period, and whenever there is an unexplained rise in SCr (>20%) during therapy (Guideline Table 18). (*Not Graded*)

Commentary

We agree with the use of CNIs as evidence-based alternative agents in the treatment of MN. CNI-containing regimens appear to have similar efficacy to alkylating agents with respect to remission rates, but are associated with higher relapse rates. The decision to use a particular CNI (cyclosporine vs tacrolimus) versus cyclophosphamide depends a great deal on clinician experience and patient preference, especially in terms of trying to balance potential benefits and risks. CNIs are also associated with adverse effects, including the potential for nephrotoxicity with prolonged use, hypertension and sodium retention, neurotoxicity, hyperglycemia, gingival hyperplasia, hirsuitism (cyclosporine), or hair loss (tacrolimus).

As noted elsewhere, CNIs have a clear hemodynamic effect, as well as a possible podocyte cytoprotective effect, that can result in a rapid decrease in proteinuria, which may be enough to achieve a partial remission, but should not necessarily be assumed to represent the immunologic effect of drug, which more likely takes months to achieve.

The necessity of low-dose steroids in combination with CNIs in the treatment of MN is not clear. Some use low-dose prednisone every other day or daily while others choose to avoid steroids. As is indicated in Guideline Table 18, studies with tacrolimus did not treat with low-dose steroids, whereas the earlier studies with cyclosporine did. We suggest targeting tacrolimus levels ≤8-10 ng/mL. For both CNIs, patients should be closely monitored for an acute increase in serum creatinine level that could indicate nephrotoxicity.

Because the optimal duration of therapy with CNIs has not been established and it might take several weeks to achieve the target dose of the agent, we do not agree with recommendation 7.4.2 and would not automatically discontinue CNIs at 6 months if the patient has not achieved complete or partial remission, particularly for those with high-grade baseline proteinuria. It is more appropriate to look at overall trends. We recommend considering CNI therapy ineffective only if there is not a substantial reduction in proteinuria (ie, 30%-50%) after 4-6 months of therapy with CNI trough levels ***within target range***. We would also like to clarify recommendation 7.4.3 to note that the taper should commence only after a remission has been obtained. Therapy for at least 1 year is recommended for patients with an initial response to these agents as the number of remissions (and proportion of complete remissions) increases with duration of treatment.[49] Most complete remissions with CNIs occur after at least 6 months of therapy and the number increases as treatment continues for more than 12 months. Thus, if a patient has not yet achieved a remission but shows some response, we recommend continuing the initial therapy, targeting goal trough levels for at least 1 year, and only starting to reduce the dosage of CNI at 4- to 8-week intervals once partial or complete remission has been obtained.[49-52]

7.5: Regimens Not Recommended or Suggested for Initial Therapy of IMN

7.5.1: We recommend that corticosteroid monotherapy not be used for initial therapy of IMN. (*1B*)

7.5.2: We suggest that monotherapy with MMF not be used for initial therapy of IMN. (*2C*)

Commentary

We agree that corticosteroids and MMF monotherapy not be used as initial therapy for IMN.

Use of rituximab and ACTH is also discussed in the text of this KDIGO guideline; we comment on the use of these agents in the next section.

7.6: Treatment of IMN Resistant to Recommended Initial Therapy

7.6.1: We suggest that patients with IMN resistant to alkylating agent/steroid-based initial therapy be treated with a CNI. (*2C*)
7.6.2: We suggest that patients with IMN resistant to CNI-based initial therapy be treated with an alkylating agent/steroid-based therapy. (*2C*)

Commentary

We agree with recommendations 7.6.1 and 7.6.2 with respect to substituting one first-line agent with the alternative first-line agent for initial treatment failure. We also emphasize that failure to respond to one agent does not preclude response to another.

Use of the anti–B-cell agent rituximab for MN is not specifically recommended by the KDIGO guideline as there are no RCTs comparing this agent to others for the treatment of MN. However, there are a number of short-term observational studies suggesting the effectiveness of rituximab in MN.[53-55] For patients who fail to respond to either cyclophosphamide or CNIs and have contraindication to the alternative agent as recommended in Section 7.6, a trial of rituximab would be reasonable. The 2 Mayo Clinic/Toronto single-arm studies included approximately 50% who had failed previous immunosuppressive therapy.[54,55] The likelihood of remission was not related to previous treatment. The Italian experience with rituximab has recently been reported by Ruggenenti et al[56]; 65 of 100 patients exhibited a clinical response.[56] The 32 patients who received rituximab as second-line therapy had overall outcomes similar to those for whom rituximab was used as first-line therapy.

The optimal dosing for rituximab has yet to be determined. Two commonly used approaches, 2 biweekly doses of 1 g/m^2 or 4 weekly doses of 375 mg/m^2, appear to be clinically equivalent. Controlled prospective trials are needed to compare the efficacy and toxicity of rituximab with CNIs and cytotoxic drugs. Also lacking are sufficient data to clarify the role of rituximab in patients with decreased or declining kidney function and the impact of rituximab on hard end points such as dialysis and death.

Although the evidence of the efficacy of MMF in IMN is mixed,[57-60] it may be a therapeutic option for some patients with MN who are unable to tolerate other therapies. There are low-quality data for its use in those who have either relapsed after treatment with standard agents or who show resistance to standard agents. The optimal dosing of MMF is not known, although extended duration of treatment (ie, >12 months) is likely necessary. It is also unclear whether corticosteroids are needed in combination with MMF. Other concerns include an apparently high rate of relapse after stopping MMF, the lack of studies examining renal survival outcomes with MMF, and a black box warning for MMF (as with rituximab) regarding progressive multifocal leukoencephalopathy.

The use of ACTH in MN also requires further study. The purified porcine ACTH agent approved for use in the United States is different in formulation and dosing than the synthetic version that has been more adequately tested in Europe. Only small studies have been conducted with the US formulation; these appear to show a therapeutic effect in MN, but the data are very preliminary and do not yet support using this treatment outside clinical research studies. We do not recommend ACTH for initial treatment of IMN at this time. Adverse effects of ACTH (myopathy, cataracts, and hyperglycemia) are not insignificant. Issues that need to be resolved for this agent include: (1) optimal dosing regimens, (2) rate of relapse (which may be high, based on the European experience), and (3) mechanisms of action as both immune-mediated and immune-independent mechanisms with systemic as well as local podocytes effects have been proposed.[61]

7.7: Treatment for Relapses of NS in Adults With IMN

7.7.1: We suggest that relapses of nephrotic syndrome in IMN be treated by reinstitution of the same therapy that resulted in the initial remission. (*2D*)
7.7.2: We suggest that, if a 6-mo cyclical corticosteroid/alkylating agent regimen was used for initial therapy, the regimen be repeated only once for treatment of a relapse. (*2B*)

Commentary

We agree with recommendation 7.7.1 in that a repeated course of an agent that initially induced remission is likely to work for relapse, and that a cumulative dose of cyclophosphamide should be taken into consideration (recommendation 7.7.2). As stated in the discussion of this section, it is reasonable to treat "mild relapses" conservatively at the start; however, these patients need to be closely monitored for increasing proteinuria and consideration of immunosuppressive treatment if proteinuria is clearly worsening.

7.8: Treatment of IMN in Children

7.8.1: We suggest that treatment of IMN in children follows the recommendations for treatment of IMN in adults. (*2C*)
7.8.2: We suggest that no more than one course of the cyclical corticosteroid/alkylating agent regimen be given in children. (*2D*)

Commentary

Pediatric MN is not necessarily the same disease as in adults, and we urge caution in automatically applying the aforementioned therapeutic strategies to children with MN. MN is a very uncommon histological lesion in children, although it is more common in adolescents.[62]

Anti-PLA_2R–associated primary MN can occur in adolescents as young as 12 years.[63]

Nevertheless, searching for a secondary cause is particularly important in children. Lupus should be strongly considered in young women who demonstrate features on biopsy that are suggestive of a secondary cause of MN, even in the absence of antinuclear antibody.

Recently, an exogenous antigen, cationic bovine serum albumin (BSA), has been implicated in rare cases of early-childhood MN (aged <5 years).[64] Further work in this field is needed to confirm the relevance of this environmental trigger in pediatric MN, but a diagnosis of BSA-related MN should be considered in very young children with MN. This should trigger analysis of immune deposits for BSA and, if detected, eliminating this protein from the diet (mainly cow's milk and possibly other beef products) might be beneficial.

There are no controlled treatment trials and only limited uncontrolled observations to guide the treatment of MN in children. Due to the low prevalence of MN in children, an individualized approach needs to be adopted. It is reasonable to provide conservative management and to avoid immunosuppression in children with non-nephrotic proteinuria as they are at low risk of progressive renal disease. Children with NS may be treated with dose-adjusted immunosuppression including alkylating agents or CNIs. One option that provides less exposure to cyclophosphamide (<200 mg/kg total dose) involves a 12-week regimen using noncyclical cyclophosphamide (2 mg/kg/d) and alternate-day steroids.[65] Some may also choose a trial of corticosteroid monotherapy to see if there is any response, although it has been shown to be ineffective as monotherapy in adults.

7.9: Prophylactic Anticoagulation in IMN

7.9.1: We suggest that patients with IMN and nephrotic syndrome, with marked reduction in serum albumin (<2.5 g/dl) and additional risks for thrombosis, be considered for prophylactic anticoagulant therapy, using oral warfarin. (*2C*)

Commentary

We agree with this recommendation, with the observation that anticoagulation is not as commonly used in the United States as it is in Europe for NS. NS, due to an altered balance of pro- and antithrombotic factors, is a thrombophilic milieu. MN (compared to FSGS and IgAN) appears to be an independent risk for venous thromboembolism even after adjustment for gender, degree of proteinuria, serum albumin level, and history of malignancy.[66] The mechanisms underlying this disease-specific risk of venous thromboembolism in MN are not clear. Although risk increased with declining serum albumin level, in one study, the threshold albumin level identified for overall risk was 2.8 g/dL.[66] Anticoagulation is warranted in patients who initially present with a thrombotic event such as renal vein thrombosis or pulmonary embolism. There is no clear consensus as to when to stop anticoagulation, although most thromboembolic events occur in the first 6 months after the diagnosis of NS. The thrombophilia should gradually resolve if the NS resolves.

CHAPTER 8: KDIGO RECOMMENDATIONS FOR IDIOPATHIC MPGN

8.1: Evaluation of MPGN

8.1.1: Evaluate patients with the histological (light-microscopic) pattern of MPGN for underlying diseases before considering a specific treatment regimen (see Guideline Table 20). (*Not Graded*)

Commentary

The KDIGO recommendations for MPGN, as was the case for MN, appear at a time of major transition. There have been significant developments in our understanding of the molecular bases of this group of diseases.[67,68] While the guideline is reflective of our current state of knowledge, we recommend that clinicians be aware that clinical practices in this area may continue to evolve rapidly.

There are limitations to the current histologic classification of MPGN into types I, II, and III using only light and electron microscopy. This has been the subject of several excellent reviews[69,70] and is beyond the scope of this guideline. In light of these limitations, there is a proposal for a new classification system for MPGN that places greater emphasis on the pattern of immunofluorescence in combination with electron microscopy findings on renal biopsy[71,72] and reflects recent advances in our understanding of the different pathophysiologic mechanisms that lead to the development of MPGN. True "idiopathic" MPGN is probably very uncommon and will likely become even more so as additional underlying disease mechanisms are identified.

The classification system identifies MPGN as immunoglobulin positive (immune complex mediated) or immunoglobulin negative (primarily complement me-

Box 4. Secondary Causes of Immune Complex–Mediated MPGN

Infectious
- Hepatitis B and C
- Chronic microbial infections (fungal, parasitic, protozoal, mycoplasma, mycobacterial)

Autoimmune disorders
- Mixed cryoglobulinemia
- SLE
- Sjögren syndrome
- Rheumatoid arthritis

Neoplasms
- Leukemia (ie, chronic lymphocytic leukemia [CLL])
- Lymphoma
- Carcinoma
- Plasma cell dyscrasia or monoclonal gammopathy of undetermined significance (MGUS)

Miscellaneous
- Castleman disease (angiofollicular lymph node hyperplasia)
- Cystic fibrosis
- Celiac disease
- Sickle cell disease
- Sarcoidosis
- α_1-Antitrypsin deficiency

diated).[69] An immunofluorescence microscopy pattern that is immunoglobulin positive and thus suggestive of immune complex–mediated MPGN suggests activation of the classical pathway of the complement system. Such findings should prompt a thorough evaluation for an underlying cause of antigenemia that can trigger the classical pathway, some of which are outlined in Box 4. These include infections, autoimmune diseases, and monoclonal gammapathies (in adults), among others. Diagnostic testing should be guided by clinical circumstances. Immunoglobulin-negative but C3-positive MPGN has been labeled "C3 glomerulopathy." This umbrella term encompasses dense deposit disease and C3 GN and suggests dysregulation of the alternative complement pathway (Table 2).[73]

The workup for this group of disorders should include a search for hereditary or acquired defects in the alternative complement cascade. When this pattern occurs in children, it suggests a genetic etiology, whereas in adults, autoantibodies to complement factors are more likely to be responsible. Investigations that might be considered are listed in Box 5, but this list is not exhaustive.[70,71] Consultation with institutions with greater experience with these diseases may be warranted. Most of the tests listed in Box 5 are not readily accessible but may be available through selected research or clinical laboratories (eg, at University of Iowa [www.healthcare.uiowa.edu/labs/morl] and National Jewish Health [www.nationaljewish.org/professionals/clinical-services/diagnostics]).

Box 5. Possible Investigations to Consider for C3 Glomerulopathy

Genetic: screening for mutations, including allele variants
- C3
- Complement factors H, I, B
- CD46 (membrane cofactor protein)
- Complement factor H–related proteins (CFHR) 1-5

Acquired
- Antibody to C3 convertase (C3 nephritic factor [C3Nef])
- Anti-factor H antibody

Finally, an MPGN pattern with neither immunoglobulin nor C3 (and without electron-dense deposits in the mesangium or along the glomerular capillary wall) should raise the suspicion of chronic thromobotic microangiopathy, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, scleroderma, transplant glomerulopathy, antiphospholipid syndrome, or malignant hypertension.

Due to the rarity of the diagnosis of MPGN and importance of proper classification of the MPGN variants, it is recommended that renal biopsy specimens with a diagnosis of MPGN be evaluated by nephropathologists experienced at interpretation of such biopsies.

Table 2. Distinguishing Types of MPGN

MPGN Categories	Immunofluorescence Staining		Location of Electron-Dense Deposits[a]	Complement Pathway Involved
	IgG and/or IgM	Complement C3		
Immunoglobulin mediated				
MPGN I	+	+	M, SEN	Classical
MPGN III	+	+	M, SEN, SEP	
C3 glomerulopathy				
DDD	−	+	M, IM	Alternative
C3GN	−	+	M, SEN, SEP and/or IM	

[a]IM, intramembranous; M, mesangial; SEN, subendothelial; SEP, subepithelial.

8.2: Treatment of Idiopathic MPGN

8.2.1: We suggest that adults or children with presumed idiopathic MPGN accompanied by nephrotic syndrome *AND* progressive decline of kidney function receive oral cyclophosphamide or MMF plus low-dose alternate-day or daily corticosteroids with initial therapy limited to less than 6 months. (*2D*)

Commentary

Data regarding the treatment of MPGN are exceptionally weak and consist of uncontrolled observational, retrospective, or underpowered studies. Most of the existing trials were performed prior to our understanding of the pathogenic processes that lead to MPGN and therefore lumped disease subtypes together (ie, unrecognized secondary MPGN, pediatric and adult cases, immune complex and complement mediated). This limits interpretation of the current evidence base and makes it difficult to give strong recommendations about optimal choices for initial therapy or relapse. The approach to these patients must be highly individualized.

Indications for immunosuppressive therapy may be broadened beyond what is recommended in 8.2.1 to include the NS with *or without* progressive decline in kidney function, active nephritic syndrome, or rapidly progressive disease, with or without crescents. Patients with normal eGFR and non–nephrotic-range proteinuria may be treated conservatively with measures described previously as their long-term outcome is good. However, close follow-up is needed to assess progression of disease based on renal function, proteinuria, and urine microscopy. Patients with advanced chronic kidney disease (CKD), severe tubulointerstitial fibrosis, small kidney size, or other findings consistent with chronic inactive disease should not be treated with immunosuppression.

A trial of steroids in children with MPGN and NS and/or impaired renal function may be warranted as first-line treatment even though the data are not entirely convincing. The potential benefit of long-term alternate-day corticosteroid therapy in children was suggested by several uncontrolled studies and one randomized controlled trial in which 80 children with all types of MPGN and heavy proteinuria were randomized to receive either 40 mg/m^2 of prednisone on alternate days or placebo for a mean duration of 41 months.[74] Renal survival at 130 months was 61% among patients receiving prednisone and 12% among placebo-treated patients ($P = 0.07$). Although this study used extremely long courses of corticosteroids, a reasonable approach is a trial of alternate-day steroids (ie, 40 mg/m^2) for a period of 6 to 12 months (and possibly longer if there is a clear clinical response). If no significant reduction of proteinuria is observed, steroids should be tapered and discontinued.

The data from pediatric MPGN studies regarding steroids cannot necessarily be extrapolated to adults with MPGN as the mechanisms of disease may be quite different. Data on the treatment of adults with steroids are very limited and there is no persuasive evidence of the efficacy of steroids modifying disease activity or progression in adults. Steroids have also not shown benefit in dense deposit disease and there is a suggestion that type III MPGN is less responsive to steroids than type I.[75]

Limited uncontrolled data suggest that CNIs and MMF may reduce proteinuria in some patients with MPGN and may be an option with high-grade proteinuria resistant to steroids.[76-80] There is insufficient evidence to support the use of cyclophosphamide and rituximab.

At present, there is no proven effective therapy for the C3 glomerulopathies. Targeted inhibition of complement using the anti-C5 monoclonal antibody eculizumab may be a rational approach, but its role in this disease is still undefined.[81-84] Plasma exchange and infusion may have potential efficacy where deficiencies are found (ie, factor H deficiency), but there are no RCTs to support this.[81]

CHAPTER 9: KDIGO RECOMMENDATIONS FOR INFECTION-RELATED GN

9.1: Infection-Related GN

9.1: For the following infection-related GN, we suggest appropriate treatment of the infectious disease and standard approaches to the management of the kidney manifestations: (*2D*)

- post-streptococcal GN;
- infective endocarditis-related GN;
- shunt nephritis.

Commentary

Poststreptococcal GN is the prototypical infection-related acute GN. Although classic poststreptococcal GN occurs 1-3 weeks after the initial clinical manifestations of pharyngitis or impetigo, affected individuals should be treated with penicillin (or erythromycin, if penicillin-allergic) even in the absence of persistent infection in order to decrease the antigenic load. The nephritic syndrome should be treated with diuretics, antihypertensives, supportive care, and dialysis if necessary. Corticosteroids are suggested for severe crescentic GN based on anecdotal evidence only.

As noted in the KDIGO guideline, the etiologic agents associated with endocarditis and subsequent

GN are changing, with increasing occurrence due to staphylococcal species and health care–associated endocarditis. Antibiotic treatment needs to be continued for 4-6 weeks, although the hematuria, proteinuria, and azotemia may not resolve for months.

An IgA-dominant postinfectious GN is an increasingly recognized variant that typically occurs in association with infection with staphylococcus,[85] including methicillin-resistant *Staphylococcus aureus* (MRSA).[86] It is most common in the elderly and in diabetics, which perhaps explains its association with poor renal outcomes. Hypocomplementemia is present in the majority of cases. It needs to be distinguished from idiopathic IgAN and HSP so that it is not treated with corticosteroids.

9.2: HCV Infection–Related GN

9.2.1: For HCV-infected patients with CKD Stages 1 or 2 CKD and GN, we suggest combined antiviral treatment using pegylated interferon and ribavirin as in the general population. (*2C*)

9.2.1.1: Titrate ribavirin dose according to patient tolerance and level of renal function. (*Not Graded*)

9.2.2: For HCV-infected patients with CKD Stages 3, 4, or 5 and GN not yet on dialysis, we suggest monotherapy with pegylated interferon, with doses adjusted to the level of kidney function. (*2D*)

9.2.3: For patients with HCV and mixed cryoglobulinemia (IgG/IgM) with nephrotic proteinuria or evidence of progressive kidney disease or an acute flare of cryoglobulinemia, we suggest either plasmapheresis, rituximab, or cyclophosphamide, in conjunction with i.v. methylprednisolone, and concomitant antiviral therapy. (*2D*)

Commentary

In general, we agree with these recommendations and additionally refer the reader to the 2008 KDIGO recommendations and KDOQI US commentary on HCV infection.[87] Treatment of HCV in patients with GN and/or CKD is problematic because many practitioners limit treatment due to fear of adverse effects, such as hemolytic anemia, associated with decreased GFR. No dose adjustments for treatment with interferon alfa and ribavirin are needed for GFR >60 mL/min/1.73 m^2, but dose reductions and/or avoidance altogether of ribavirin are indicated for stage 3-5 CKD. Even with a lower dose ribavirin regimen, there is risk of significant toxicity, and weekly hemoglobin levels are advised. The 2008 KDOQI commentary on the KDIGO guideline for HCV provides a useful table summarizing the dose adjustments and adverse effects of HCV treatment in CKD.[87] Dose-reduced combination therapy may be feasible for early stage 3 CKD, but interferon monotherapy is recommended for eGFR <50 mL/min/1.73 m^2. These recommendations are based on very limited evidence, and the safest and most efficacious treatment in stage 3-5 CKD is not clear. Treatment decisions must be individualized and the nephrologist must have a close working relationship with the hepatologist.

Two new protease inhibitors, telaprevir and boceprevir, have recently emerged that appear to be useful as adjunctive therapy to polyethylene glycol–conjugated interferon and ribavirin for genotype 1 HCV infections. Although neither agent requires dose adjustment in CKD, they have not been studied in HCV-infected patients with stage 3-5 CKD. They also may increase the risk of anemia when used in conjunction with interferon and ribavirin.

Treatment of severe disease, such as cryoglobulinemic vasculitis, rapidly progressive renal disease, or uncontrolled NS, can be attempted with plasmapheresis, rituximab, or cyclophosphamide in conjunction with corticosteroids, although their use is not evidence based. It is important to treat the underlying infection as noted above. As use of interferon may exacerbate cryoglobulinemic vasculitis, antiviral therapy may be withheld until after the acute flare has been controlled.[88,89] The timing of antiviral therapy has not been well established, but it may be reasonable to wait until severe symptoms and renal dysfunction have been controlled with immunosuppressive therapy before initiating antiviral agents.

Recent trials suggest that rituximab may be a good option for treatment of severe cryoglobulinemic disease in patients who cannot receive antiviral therapy or who are failing treatment with conventional immunosuppressive therapy.[90,91] The role of rituximab in other types of HCV-associated glomerular disease has not been studied.

9.3: HBV Infection–Related GN

9.3.1: We recommend that patients with HBV infection and GN receive treatment with interferon-α or with nucleoside analogues as recommended for the general population by standard clinical practice guidelines for HBV infection (see Guideline Table 23). (*1C*)

9.3.2: We recommend that the dosing of these antiviral agents be adjusted to the degree of kidney function. (*1C*)

Commentary

We agree that treatment of patients with HBV infection and GN should be conducted using standard clinical practice guidelines for HBV infection; this is often done in conjunction with a hepatologist. The majority of the data regarding use of antiviral agents comes from HBV-infected patients without renal involvement; therefore, efficacy in the setting of GN is inferred from these more generalized trials. RCTs comparing various treatment strategies for HBV-

related renal disease are unavailable, although nonrandomized studies and uncontrolled observations suggest that antiviral therapy may be beneficial in patients with HBV GN or vasculitis. The optimal choice of agent and duration of therapy are unclear, and a long duration of therapy (several years) may be required. Although recommendation 9.3.1 suggests use of standard interferon alfa, polyethylene glycol–conjugated interferon is most commonly used in the treatment of chronic HBV infection. However, its efficacy has not been specifically studied for HBV GN.[92,93]

HBV-associated MN in children has a good prognosis and high spontaneous remission rate. In adults in developed countries, HBV-associated MN occurs most often in intravenous drug abusers; in this setting, the disease is often progressive and only rarely resolves without antiviral treatment. Guideline Table 23 provides a useful table of the US Food and Drug Administration (FDA)-approved nucleotide and nucleoside analogs available for the treatment of HBV infection. Dose adjustment for decreased GFR is required for all these agents. It may be advisable to avoid tenofovir and adefovir due to their known additional nephrotoxicity.

Available evidence does not support the use of immunosuppression for HBV GN (with the exception of rapidly progressive GN or vasculitis, see below) due to concerns of the induction of viral replication, deterioration of renal function, and exacerbation of chronic hepatitis, particularly when immunosuppression is withdrawn.

HBV may also be associated with polyarteritis nodosa, as well as cryoglobulinemia, leading to renal impairment. In patients with severe vasculitis or rapidly progressive GN, a short course of corticosteroids may be considered but should always be used in combination with antiviral therapy.

Pertinent to the present discussion, we recommend that HBV status be investigated in any patient being considered for rituximab treatment for any indication since its use in some HBV-infected patients has resulted in HBV viral reactivation and fatal acute hepatitis.[94] Virological screening (to detect HBV surface antigen and antibodies to core and surface antigens) is recommended to identify patients with chronic, occult, or resolved infection and consultation with a hepatologist should be sought regarding treatment or prophylactic use of antivirals prior to the initiation of rituximab.

9.4: HIV Infection–Related Glomerular Disorders

9.4.1: We recommend that antiretroviral therapy be initiated in all patients with biopsy-proven HIV-associated nephropathy, regardless of CD4 count. (*1B*)

Commentary

It is now clear that the rapidly progressive, collapsing glomerulopathy initially termed HIV-associated nephropathy (HIVAN) is only one of the myriad GNs and causes of renal dysfunction in patients infected with HIV. Up to 50% of HIV-infected patients with glomerular disease may have a lesion other than classic HIVAN. Renal biopsy is recommended unless there is strong suspicion of a nonglomerular etiology of renal dysfunction, such as nephrotoxic combination antiretroviral therapy (cART) medications, acute tubular necrosis (ATN), or other comorbid conditions.

cART is recommended as definitive treatment for all forms of HIV-associated GN, although cART therapy has not been shown to be of benefit in other non-HIVAN GNs. However, the rapidly progressive nature of classic HIVAN may warrant temporizing measures, such as the use of inhibitors of the renin-angiotensin system and perhaps corticosteroids. Observational studies suggest that a limited course of corticosteroid therapy in selected patients ***with*** rapid progression of azotemia due to HIVAN (and absence of other active infections) may help limit proteinuria and reduce the rate of progression to ESRD.[95] However, the optimal dose and duration of treatment are not clear.

Renal transplantation is feasible in selected HIV-infected patients.[96] Criteria that have been used for selection of patients include absence of AIDS-defining diseases, CD4 count $>$200 cells/μL, and undetectable viral load. Patient survival and renal allograft survival are similar to non–HIV-infected patients,[97] though there appear to be higher rejection rates. Optimal immunosuppresion regimens have not yet been established.

As these forms of disease are not endemic to the United States (although can occasionally be seen in our immigrant population or visitors returning from these areas), we do not comment further and refer the reader to the text provided in the KDIGO Guideline.

CHAPTER 10: KDIGO RECOMMENDATIONS FOR IgAN

10.1: Initial Evaluation Including Assessment of Risk of Progressive Kidney Disease

10.1.1: Assess all patients with biopsy-proven IgAN for secondary causes of IgAN. (*Not Graded*)

10.1.2: Assess the risk of progression in all cases by evaluation of proteinuria, blood pressure, and eGFR at the time of diagnosis and during follow-up. (*Not Graded*)

10.1.3: Pathological features may be used to assess prognosis. (*Not Graded*)

Commentary

There have been exciting advances in understanding the pathogenesis of IgAN that are likely to impact on the diagnosis and treatment of IgAN in the coming years. These include improved understanding of post-translational modification of the IgA1 molecule and the role of immune complexes in triggering renal inflammation and injury.[98-100]

There is controversy regarding the exact level of proteinuria (<1 vs <0.5 g/d) that is associated with the most favorable outcome in IgAN. In addition, it is uncertain whether graded intensity of blood pressure control, in other words, <130/80 mm Hg for proteinuria >0.3 g/d and <125/75 mm Hg for proteinuria >1 g/d reduces CKD progression in IgAN. Finally, the Oxford pathology classification is just entering widespread use.[101-103]

Regarding children, different practices limit comparison with adults, but the same risk factors for CKD are validated in both adults and children. Current expert opinion in children advocates a target level of proteinuria <0.5-1 g/d/1.73 m^2 as well as control of blood pressure, ideally to a level below the 90th percentile for age and gender.

10.2: Antiproteinuric and Antihypertensive Therapy

10.2.1: We recommend long-term ACE-I or ARB treatment when proteinuria is >1 g/d, with up-titration of the drug depending on blood pressure. (*1B*)

10.2.2: We suggest ACE-I or ARB treatment if proteinuria is between 0.5 to 1 g/d (in children, between 0.5 to 1 g/d per 1.73 m^2). (*2D*)

10.2.3: We suggest the ACE-I or ARB be titrated upwards as far as tolerated to achieve proteinuria <1 g/d. (*2C*)

10.2.4: In IgAN, use blood pressure treatment goals of <130/80mmHg in patients with proteinuria <1 g/d, and <125/75mmHg when initial proteinuria is >1 g/d (see Chapter 2). (*Not Graded*)

Commentary

Registry data suggest that proteinuria <1 g/d, either at the time of biopsy or after therapy, leads to a better prognosis in IgAN.[104,105] However, some trials started an ACE inhibitor if protein excretion was >0.5 g/d.[106] While ACE inhibitors/ARBs can reduce proteinuria and slow the decline in GFR,[106-108] there are no trials showing that these agents decrease the risk for ESRD from IgAN. Of note, many of these trials had what would be presently considered a suboptimal goal blood pressure of <140/90 mm Hg.[106-108] Given the lack of objective evidence that decreasing proteinuria in children with IgAN to <0.5 g/d/1.73 m^2 is superior to <1 g/d/1.73 m^2, there should be consideration of the potential risks of therapies employed to reach a goal that has been set by opinion rather than data. In view of the expected normal growth during childhood, it is important to normalize protein excretion to current body surface area to accurately assess the efficacy of therapy or progression of disease.

Blood pressure goals in children with proteinuric IgAN should be based on gender and age norms outlined by the National Institutes of Health's (NIH) Task Force on Blood Pressure Control in Children, aiming to decrease blood pressure below the 95th percentile.[109]

10.3: Corticosteroids

10.3.1: We suggest that patients with persistent proteinuria ≥1 g/d, despite 3-6 months of optimized supportive care (including ACE-I or ARBs and blood pressure control), and GFR >50 ml/min per 1.73 m^2, receive a 6-month course of corticosteroid therapy. (*2C*)

Commentary

Given the side effects associated with corticosteroids, we agree with initially treating patients with proteinuria ≥1 g/d with an eGFR >50 mL/min/1.73 m^2 with an ACE inhibitor/ARB alone for 3 to 6 months.

Although there is low-quality evidence that corticosteroids provide additional benefit over supportive treatment, we also agree with the recommendation to treat with corticosteroids to patients who have not improved after several months of optimized supportive care. An Italian trial showed long-term benefit in IgAN patients treated with a 6-month course of intravenous and oral steroids versus no immunosuppression with 10-year renal survival of 97% versus 53%.[110] These patients had suboptimal blood pressure control during treatment (<140/90 mm Hg) and only 15% of patients were receiving an ACE inhibitor at randomization.

The trials by Manno et al[112] and Lv et al[111] used ACE inhibitors and an oral prednisone regimen (Table 3) versus ACE inhibitors alone for 6 months and showed a renal survival benefit in the group treated with both medications. Lv et al[111] showed long-term benefit in the combination group for decreasing the rate of doubling serum creatinine or ESRD versus prednisone alone (4.2% vs 26.5%). It should be stressed that 2 trials showing a benefit of corticosteroids only included patients with GFR >50 mL/min/1.73 m^2 or serum creatinine <1.5 mg/dL.[110,112] The other trial included a majority of patients (89%) with serum creatinine <1.5 mg/dL.[111] This suggests that a trial of corticosteroids should only be considered in patients with preserved renal function.

Although there are no studies that compare corticosteroid dose regimens, one recent meta-analysis of corticosteroid treatment in IgAN appeared to show increased efficacy with shorter term high-dose therapy (prednisone >30 mg/d or high-dose pulse intravenous methylprednisolone with duration <1 year) compared

Table 3. Corticosteroid Regimens in Patients With IgAN

	Pozzi et al[113]	Manno et al[112]; Lv et al[111]
Regimen	IV bolus injections of 1 g methylprednisolone for 3 days each at months 1, 3, and 5, followed by oral steroid 0.5 mg/kg prednisone on alternate days for 6 mo	6-mo regime of oral prednisone[a] starting with 0.8-1 mg/kg/d for 2 mo and then reduced by 0.2 mg/kg/d per month for the next 4 mo

Reproduced with permission of KDIGO from the *KDIGO Clinical Practice Guideline for Glomerulonephritis*.[1]
Abbreviations: IgAN, immunoglobulin A nephropathy; IV, intravenous.
[a]Prednisone and prednisolone are equivalent and can be used interchangeably with the same dosing regimen.

to no improvement using longer term low-dose therapy with regard to doubling of serum creatinine, halving of the GFR, or ESRD.[114]

10.4: Immunosuppressive Agents (Cyclophosphamide, Azathioprine, MMF, Cyclosporine)

10.4.1: We suggest not treating with corticosteroids combined with cyclophosphamide or azathioprine in IgAN patients (unless there is crescentic IgAN with rapidly deteriorating kidney function; see Recommendation 10.6.3). (*2D*)
10.4.2: We suggest not using immunosuppressive therapy in patients with GFR <30 ml/min per 1.73 m^2 unless there is crescentic IgAN with rapidly deteriorating kidney function (see Section 10.6). (*2C*)
10.4.3: We suggest not using MMF in IgAN. (*2C*)

Commentary

We agree with 10.4.1 and 10.4.2. A single-center trial compared a tapering dose of corticosteroids plus cyclophosphamide for 3 months followed by azathioprine for a total of 2 years versus control in high-risk IgAN patients.[115] These patients had a serum creatinine exceeding 1.47 mg/dL with at least a 15% increase within the preceding year, and heavy proteinuria. Although the active treatment group showed superior kidney survival (72% vs 6%) at 5 years, there was no corticosteroid group comparison, ACE inhibitor/ARB use was not specified, and the blood pressure goal was high (<160/90 mm Hg). Two RCTs comparing cyclophosphamide, dipyridamole, and warfarin versus control showed no benefit.[116,117] Azathioprine combined with intravenous and oral corticosteroids for 6 months showed no benefit versus corticosteroids alone in adults.[118]

We generally agree with the recommendation to not use MMF in patients with IgAN, although there may be some benefit of azathioprine in children of Asian ancestry with diffuse mesangial proliferation when used in combination with prednisolone, warfarin, and dipyridamole for 24 months. However, medication burden is high and adherence would be difficult with this combination regimen.[119] There have been 3 prospective trials published in the English-language literature using MMF monotherapy in IgAN, with both Belgian and American trials showing no benefit with MMF treatment.[120,121] A trial conducted in Asian patients with treatment for 6 months showed benefit in reducing ESRD risk (10%) versus control (45%) after 6 years of follow-up.[122,123] Thus, it may be reasonable to use MMF as an alternative agent if corticosteroids fail or are poorly tolerated in patients of Asian ancestry.

The best treatment approach for SR and relapsing IgAN is unknown.

10.5: Other Treatments

10.5.1: We suggest using fish oil in the treatment of IgAN with persistent proteinuria ≥1 g/d, despite 3-6 months of optimized supportive care (including ACE-I or ARBs and blood pressure control). (*2D*)
10.5.2: We suggest not using antiplatelet agents to treat IgAN. (*2C*)
10.5.3: We suggest that tonsillectomy not be performed for IgAN. (*2C*)

Commentary

We agree with recommendation 10.5.1. Evidence on the efficacy of fish oil supplements from RCTs is conflicting,[124-127] but there is little risk. Cardiovascular benefits from fish oil supplements are unproven. It is unclear when fish oil supplements should be started in relation to starting corticosteroids.

We agree there is low-quality evidence as to the beneficial effect of antiplatelet therapy (recommendation 10.5.2**)** as it is often combined with other immunosuppressive medications and adherence with the 3-times-a-day regimen with dipyridamole is likely to be difficult.

We agree that tonsillectomy should not be performed routinely in IgAN (recommendation 10.5.3**),** although there is low-grade evidence of some benefit when combined with corticosteroids in patients with recurrent bouts of tonsillitis and macroscopic hematuria. A meta-analysis of 7 retrospective series showed no benefit of corticosteroids alone or tonsillectomy alone, but there was benefit when tonsillectomy was combined with corticosteroids.[128]

10.6: Atypical Forms of IgAN

10.6.1.1: We recommend treatment as for MCD (see Chapter 5) in nephrotic patients showing pathological findings of MCD with mesangial IgA deposits on kidney biopsy. (*2B*)

10.6.2.1: Perform a repeat kidney biopsy in IgAN patients with AKI associated with macroscopic hematuria if, after 5 days from the onset of kidney function worsening, there is no improvement. (*Not Graded*)

10.6.2.2: We suggest general supportive care for AKI in IgAN, with a kidney biopsy performed during an episode of macroscopic hematuria showing only ATN and intratubular erythrocyte casts. (*2C*)

10.6.3.1: Define crescentic IgAN as IgAN with crescents in more than 50% of glomeruli in the renal biopsy with rapidly progressive renal deterioration. (*Not Graded*)

10.6.3.2: We suggest the use of steroids and cyclophosphamide in patients with IgAN and rapidly progressive crescentic IgAN, analogous to the treatment of ANCA vasculitis (see Chapter 13). (*2D*)

Commentary

We agree with recommendation 10.6.1 that IgAN patients, who have biopsy features showing minimal light microscopic changes and diffuse foot-process effacement, should be treated similarly to patients with MCD.[129-131]

Prolonged macroscopic hematuria in IgAN with AKI is uncommon; it is usually from tubular obstruction from erythrocyte casts. Hemoglobin, heme pigment, and free iron with oxidative stress may contribute to the AKI.[132] Some patients who develop AKI do not recover back to baseline.[133,134] Kidney biopsy in AKI will differentiate ATN from crescentic IgAN. However, we disagree with recommendation 10.6.2 that all patients who are not improving should have a biopsy after 5 days. Two series of AKI with macroscopic hematuria did not reveal an association with crescentic GN.[133,135] Thus, additional studies are needed to clarify the relationship between AKI and exacerbations of glomerular disease in patients with IgAN. In the absence of definitive data, we suggest that the performance and timing of the procedure should be individualized for each patient. For instance, if AKI with gross hematuria previously resolved, a repeat biopsy may not be required with a subsequent episodes.[135]

It is reasonable to define crescentic IgAN by the presence of crescents in >50% of glomeruli (recommendation 10.6.3)[136,137] with rapidly progressive renal deterioration, although as noted in the guideline, some studies have used a smaller percentage of glomeruli.[138] We agree with recommendation 10.6.3.2 as observational studies support the use of intravenous and oral steroids plus cyclophosphamide for this group of patients.[136,138] Patients with rapid deterioration in GFR without ATN and with crescents approaching 50% of glomeruli on renal biopsy should probably also be treated for crescentic IgAN as there may be sampling error affecting renal biopsy interpretation.

CHAPTER 11: KDIGO RECOMMENDATIONS FOR HSP NEPHRITIS

11.1: Treatment of HSP Nephritis in Children

11.1.1: We suggest that children with HSP nephritis and persistent proteinuria, >0.5-1 g/d per 1.73 m^2, are treated with ACE-I or ARBs. (*2D*)

11.1.2: We suggest that children with persistent proteinuria, >1 g/d per 1.73 m^2, after a trial of ACE-I or ARBs, and GFR >50 ml/min per 1.73 m^2, be treated the same as for IgAN with a 6-month course of corticosteroid therapy (see Chapter 10). (*2D*)

Commentary

Since the vast majority of children with renal involvement from HSP have self-limited disease and do well long term, until there are data to the contrary, therapeutic interventions need to be confined to those children with NS or nephritic syndrome rather than isolated proteinuria exceeding 1 g/d, or those with persistent heavy proteinuria during follow-up. Renal biopsy should be performed in children with decreased renal function at presentation or with severe NS/nephritic syndrome.

Although there is no evidence for long-term benefit of ACE inhibitors or ARBs in children with HSP and its consideration is based on extrapolation of results with IgAN, we agree with angiotensin blockade children with HSP and persistent significant proteinuria. As with IgAN, there is insufficient evidence to indicate that attempting to decrease proteinuria in children with HSP to <0.5 g/d/1.73 m^2 is superior to targeting protein excretion <1 g/d/1.73 m^2 and is likely to increase medication side effects. Normalizing proteinuria to body surface area addresses interval growth of children with proteinuria over time.

We disagree that the threshold for corticosteroid treatment in children with HSP should be proteinuria >1 g/d/1.73 m^2. There are limited data that support steroid therapy in children with HSP and proteinuria.[139,140] Thus, we would consider initiating corticosteroid therapy only if nephrotic-range proteinuria has not improved after a trial of angiotensin blockade as outlined for IgAN. Additional studies are needed before a recommendation can be made to administer corticosteroids to patients with HSP nephritis who have lower levels of proteinuria.

11.2: Treatment of Crescentic HSP Nephritis in Children

11.2.1: We suggest that children with crescentic HSP with nephrotic syndrome and/or deteriorating kidney function are treated the same as for crescentic IgAN (see Recommendation 10.6.3). (*2D*)

Commentary

We agree with recommendation 11.2.1. In crescentic HSP nephritis, high-dose intravenous corticosteroid therapy may be beneficial in children.[141] The only other immunosuppressive agent with any evidence that it is beneficial in children with HSP and crescentic nephritis is cyclophosphamide, and that is based on a single RCT.[142]

Cyclosporine may also be effective in children with heavy proteinuria and crescentic HSP,[143,144] though there is no evidence to suggest that long-term outcomes are significantly better with this approach than with high-dose intravenous corticosteroids.[145] The nephrotoxicity of cyclosporine limits its use in children with relapse after an initial course of therapy.

11.3: Prevention of HSP Nephritis in Children

11.3.1: We recommend not using corticosteroids to prevent HSP nephritis. (*1B*)

Commentary

We agree there is moderate quality evidence that corticosteroids are not beneficial at the onset of HSP to prevent nephritis or decrease the risk of severe persistent nephritis or relapsing disease.

11.4: HSP Nephritis in Adults

11.4.1: We suggest that HSP nephritis in adults be treated the same as in children. (*2D*)

Commentary

We agree with recommendation 11.4.1 that limited data, mostly from retrospective case series, suggest that prognosis in adult HSP is worse with protein excretion >1 g/d. Outcome data in adults with HSP are from retrospective series and many suggest that adults are more likely to have severe initial renal involvement with risk of progression, though other clinical factors that make renal disease in general more common in adults than children may be confounding these data. There is no evidence to suggest that the approach to treatment in adults should differ from that in children, although long-term benefit of steroid therapy for nephrotic-range or persistent proteinuria or intravenous corticosteroids and other immunosuppressive agents for crescentic HSP in adults has not been proved.

CHAPTER 12: KDIGO RECOMMENDATIONS FOR LN

Among the GNs, LN stands out as having a substantial amount of evidence from RCTs to guide treatment.[146] The KDIGO guideline handles the existing evidence well, particularly for class III and IV LN. It is interesting to compare the KDIGO guideline with the simultaneously published American College of Rheumatology (ACR) guidelines for LN.[147] The major discrepancies lie in the ACR guideline recommending: (1) no role for oral cyclophosphamide and (2) use of MMF as first-line therapy for pure class V GN, both of which are more consistent with modern treatment practices despite the lack of robust supportive evidence.

12.1 and 12.2: Class I LN (Minimal-Mesangial LN) and Class II (Mesangial Proliferative GN)

12.1.1: We suggest that patients with class I LN be treated as dictated by the extrarenal clinical manifestations of lupus. (*2D*)

12.2.1: Treat patients with class II LN and proteinuria <1 g/d as dictated by the extrarenal clinical manifestations of lupus. (*2D*)

12.2.2: We suggest that class II LN with proteinuria >3 g/d be treated with corticosteroids or CNIs as described for MCD (see Chapter 5). (*2D*)

Commentary

This guideline makes no specific mention for the use of blockade of the renin-angiotensin axis in LN, although chapter 2 suggests that all patients with proteinuria >500 mg/d should be treated, which presumably includes patients with systemic lupus erythematosus (SLE). ACE inhibitor use has been reported in a group of 378 patients who had no evidence of kidney disease at the time of enrollment to delay the development of renal involvement in SLE and is associated with an approximately 45% decreased risk of disease activity.[148] Thus, as with the recommendation 12.6 that all patients with LN be treated with hydroxychloroquine unless there is a specific contraindication, we suggest a similar recommendation be made for RAS blockade. As the majority of patients with LN are women of childbearing potential, appropriate use of contraception while on RAS blockade should be advised.

Patients with SLE and MCD, or what has been termed a lupus podocytopathy,[149] usually have a light microscopy pattern of class II LN. As these patients respond to a short course of high-dose corticosteroids similar to patients with idiopathic MCD, the recommendation to treat with steroids is appropriate.

12.3: Class III LN (Focal LN) and Class IV LN (Diffuse LN)—Initial Therapy

12.3.1: We recommend initial therapy with corticosteroids (*1A*), combined with either cyclophosphamide (*1B*) or MMF (*1B*).

12.3.2: We suggest that, if patients have worsening LN (rising SCr, worsening proteinuria) during the first 3 months of treatment, a change be made to an alternative recommended initial therapy, or a repeat kidney biopsy be performed to guide further treatment. (*2D*)

Commentary

We agree with recommendation 12.3.1 that initial treatment of class III and IV LN should include corticosteroids with either cyclophosphamide or MMF. Intravenous methylprednisolone ("pulse steroids") is often given initially in a dose of 500-1,000 mg/d for 3 days or 7 mg/kg/d for 3 days (though the dosing is not evidence based), followed by a tapering course of oral steroids.[146,150] There are insufficient data on which to base a recommendation for a particular steroid taper as renal and extrarenal manifestations are variable.

The guideline gives relatively equal weight to the NIH intravenous cyclophosphamide regimen, the Euro-Lupus intravenous cyclophosphamide regimen, and oral cyclophosphamide regimens. The majority of cyclophosphamide use in LN, though, is with intravenous cyclophosphamide, as reflected in the ACR guideline.[147] This is due to lower cumulative dosages and consequently a lower adverse event rate than with oral cyclophosphamide. In addition, monitoring for neutropenia is needed less frequently with intravenous cyclophosphamide (monthly) as compared with oral cyclophosphamide (weekly). There are also more options for bladder protection with intravenous cyclophosphamide (coadministration with mesna) than with oral cyclophosphamide (vaguely stated as "drink extra fluid," although oral mesna is available). We therefore suggest that when cyclophosphamide is prescribed, intravenous dosing using the NIH or Euro-Lupus regimen is preferable over oral dosing unless there is a compelling indication for the latter. The guideline appropriately points out that the data supporting the Euro-Lupus regimen are based on patients who were white and generally without clinically severe disease; its benefit in other ethnic or racial groups and in those with more severe disease is unproved. However, it is important to note that the cohort comprised 23% class III, 69% class IV, and 8% class V.[151] The guideline does not explicitly state that the long-term data on Euro-Lupus, with good 10-year outcomes, were in patients where the majority (~75%) remained on steroids out to 10 years.[152]

Use of leuprolide to preserve fertility in women who desire future childbearing is recommended in those treated with intravenous cyclophosphamide. Since it needs to be dosed in relation to cyclophosphamide exposure, its use with oral cyclophosphamide is limited. Ovarian tissue cryopreservation is mentioned as an alternative to leuprolide, but the expense and risks of this procedure, including high-dose hormonal exposure and delay in starting cyclophosphamide, limit its use. In men, sperm banking is a safer alternative to the recommended use of high-dose testosterone, although this may also delay the start of cyclophosphamide treatment.

MMF is now the preferred induction regimen for patients wishing to preserve fertility and has clearly emerged as a noninferior regimen to intravenous cyclophosphamide.[153] The guideline appropriately points out uncertainty regarding the efficacy of MMF in LN with an rapidly progressive GN presentation[154,155] and long-term (ie, >5 years) renal preservation. Despite a lack of clinical evidence supporting use of mycophenolic acid rather than MMF, it is reasonable to consider mycophenolic acid in patients intolerant of MMF. Mycophenolic acid in a dose of 1,440-2,160 mg/d is roughly equivalent to MMF doses of 2,000-3,000 mg/d.

The combination of steroids, MMF, and a CNI is discussed as an option for mixed class IV/V lesions, based on one promising study from China.[156] Adding a CNI to MMF after 3 months if proteinuria remains in the nephrotic range instead of administering the CNI from the outset, as was done in this study, may also be a reasonable alternative strategy (albeit without evidence base) for class IV/V lesions. As noted in this guideline, data derived from treatment of Asian populations, which typically have shown the highest response rates to LN therapy, are not necessarily generalizable to African American and Hispanic patients, who have historically demonstrated lower response rates.

12.4: Class III LN (Focal LN) and Class IV LN (Diffuse LN)—Maintenance Therapy

12.4.1: We recommend that, after initial therapy is complete, patients with class III and IV LN receive maintenance therapy with azathioprine (1.5-2.5 mg/kg/d) or MMF (1-2 g/d in divided doses), and low-dose oral corticosteroids (≤10 mg/d prednisone equivalent). (*1B*)

12.4.2: We suggest that CNIs with low-dose corticosteroids be used for maintenance therapy in patients who are intolerant of MMF and azathioprine. (*2C*)

12.4.3: We suggest that, after complete remission is achieved, maintenance therapy be continued for at least 1 year before consideration is given to tapering the immunosuppression. (*2D*)

12.4.4: If complete remission has not been achieved after 12 months of maintenance therapy, consider performing

a repeat kidney biopsy before determining if a change in therapy is indicated. (*Not Graded*)

12.4.5: While maintenance therapy is being tapered, if kidney function deteriorates and/or proteinuria worsens, we suggest that treatment be increased to the previous level of immunosuppression that controlled the LN. (*2D*)

Commentary

Evidence supporting the use of azathioprine as maintenance therapy (recommendation 12.4.1) is from the MAINTAIN (Mycophenolate versus Azathioprine as Maintenance Therapy for Lupus Nephritis) trial, in which azathioprine was comparable to MMF after induction therapy with Euro-Lupus dosing of intravenous cyclophosphamide.[157] Thus, preferential use of azathioprine over MMF as maintenance therapy should be limited to whites with less severe renal disease at presentation who have been continued on prednisone, akin to the patients treated in the Euro-Lupus trials.[151,152] The ALMS (Aspreva Lupus Management Study) extension phase results, in contrast, lend strong support to using MMF rather than azathioprine for maintenance therapy,[158] particularly if steroids are to be tapered and stopped during the maintenance phase. Indeed, the ACR guideline explicitly spells out this difference by recommending as maintenance options MMF alone or azathioprine with steroids.[147] The guideline appropriately notes that there is no evidence to help determine the duration of therapy. In addition, there are no RCTs comparing steroid-free versus low-dose steroid regimens for maintenance therapy.

We agree that CNIs with low-dose corticosteroids are a reasonable alternative maintenance therapy in patients who are intolerant of MMF and azathioprine (recommendation 12.4.2), with monitoring of CNI levels as stated previously. Continuing maintenance therapy for at least 1 year after remission before tapering immunosuppression is reasonable (recommendation 12.4.3), although tapering of oral steroids can often be initiated earlier.

We agree with recommendation 12.4.4 regarding the utility of repeated kidney biopsies for patients with disease relapse or LN that does not respond to initial induction therapy. The natural history of LN includes evolving lesions, particularly among the proliferative lesions (eg, class II or class III to class IV), and repeated biopsies play an important role in guiding treatment decisions. A repeated biopsy also can delineate the degree of activity and chronicity; worsening kidney function and persistent proteinuria may be seen in the absence of inflammatory activity and should not be treated with immunosuppressive therapies.

We agree with increasing immunosuppression maintenance therapy back to the previous level that controlled LN if relapse occurs during a taper (recommendation 12.4.5), unless there are concerns for toxicity with this agent, in which case alternative regimens should be considered.

12.5: Class V LN (Membranous LN)

12.5.1: We recommend that patients with class V LN, normal kidney function, and non–nephrotic-range proteinuria be treated with antiproteinuric and antihypertensive medications, and only receive corticosteroids and immunosuppressives as dictated by the extrarenal manifestations of systemic lupus. (*2D*)

12.5.2: We suggest that patients with pure class V LN and persistent nephrotic proteinuria be treated with corticosteroids plus an additional immunosuppressive agent: cyclophosphamide (*2C*), or CNI (*2C*), or MMF (*2D*), or azathioprine (*2D*).

Commentary

Currently, no data exist to support treating class V LN and subnephrotic proteinuria with immunosuppression, and thus the recommendation (12.5.1) for conservative therapy in this population is appropriate. One caveat is how nephrotic-range proteinuria should be defined in young thin women with SLE nephritis; in such patients, it may be more appropriate to use a definition based on body surface area, such as 1 g/1.73 m^2, as is done with children with idiopathic NS, rather than a more "generic" cutoff of 3.5 g/d.

Of the treatment options considered in recommendation 12.5.2, we prefer use of corticosteroids plus MMF for treatment of class V LN with nephrotic-range proteinuria, based on the limited available evidence. Only one small RCT (3 arms, n = 15 per arm) compared prednisone alone (27% remission) versus prednisone + cyclophosphamide (60% remission) versus prednisone + cyclosporine (83% remission), which is why cyclophosphamide and CNI garner a grade of 2C. The data supporting the use of MMF for class V LN is based on post hoc analysis[159] (hence the 2D grade) combining patients from 2 MMF versus cyclophosphamide induction phase studies[160,161] with pure class V LN (n = 84; 42 randomized to MMF induction and 42 randomized to cyclophosphamide induction). Similar efficacy was demonstrated in both treatment arms. The MMF-based regimen is now commonly used as first-line therapy for pure class V lesions and, as mentioned earlier, is also the recommended initial therapy for class V LN in the recent ACR guideline.[147]

Though not addressed in recommendation 12.5.2, there may be a role for rituximab in pure class V LN, particularly in patients not responding to other initial treatment, although this is based on extrapolation of rituximab use in idiopathic MN.[54,162,163] While the LUNAR (Lupus Nephritis Assessment With Rituximab) study did not demonstrate improved clinical outcomes in patients randomized to rituximab plus MMF compared to those randomized to placebo

plus MMF, this study did not enroll pure class V subjects (only III/V or IV/V).[164]

12.6: General Treatment of LN

12.6.1: We suggest that all patients with LN of any class are treated with hydroxychloroquine (maximum daily dose of 6-6.5 mg/kg ideal body weight), unless they have a specific contraindication to this drug. (*2C*)

Commentary

While the guideline appropriately focuses on renal manifestations of SLE, it is important for all nephrologists to survey and, in many instances, manage the systemic components of lupus as extrarenal, severe organ, and life-threatening manifestations may dictate treatment decisions. As noted in recommendation 12.6.1, hydroxychloroquine is useful in reducing systemic flares of disease and may improve overall survival.[165,166] Data on improving renal outcomes with this antimalarial are weaker but we nonetheless support its use.[167] Consideration of renal transplantation and cardiovascular disease in patients with LN are important general treatment issues not addressed in the KDIGO guidelines. Some authors have recommended dialyzing patients with ESRD from LN for a 3- to 6-month period before transplantation, suggesting that this may allow further reduction in SLE symptoms and serologic activity, as well as for potential recovery of kidney function in patients with relatively rapid progression to ESRD.[168,169] Given the lack of data on this issue, individualized and patient-level decisions should be made about the appropriate time for transplantation. We also recommend attention to cardiovascular disease risk assessment and treatment in patients with LN as in other patients with CKD.

12.7: Class VI LN (Advanced Sclerosis LN)

12.7.1: We recommend that patients with class VI LN be treated with corticosteroids and immunosuppressives only as dictated by the extrarenal manifestations of systemic lupus. (*2D*)

Commentary

We agree with recommendation 12.7.1.

12.8: Relapse of LN

12.8.1: We suggest that a relapse of LN after complete or partial remission be treated with the initial therapy followed by the maintenance therapy that was effective in inducing the original remission. (*2B*)

12.8.1.1: If resuming the original therapy would put the patient at risk for excessive lifetime cyclophosphamide exposure, then we suggest a non–cyclophosphamide-based initial regimen be used (Regimen D, Guideline Table 28). (*2B*)

12.8.2: Consider a repeat kidney biopsy during relapse if there is suspicion that the histologic class of LN has changed, or there is uncertainty whether a rising SCr and/or worsening proteinuria represents disease activity or chronicity. (*Not Graded*)

Commentary

We agree with guideline 12.8.1 that one relapse of LN after complete or partial remission be treated with the initial and maintenance therapy that induced remission. The rationale for guideline 12.8.1 mentions "risk for excessive lifetime cyclophosphamide exposure" (12.8.1.1). In this regard, many clinicians think that the upper limit of lifetime exposure should be 12 g/m^2 intravenous cyclophosphamide, allowing for 2 full courses of NIH protocol induction therapy dosed at maximum of 1 g/m^2.

We agree with recommendation 12.8.2, but note that a clinically defined relapse should consider both the criteria listed in Guideline Table 29 but also increasing (ie, a doubling) proteinuria or a newly active urine sediment, with or without changes in serum creatinine. We believe, given the safety of renal biopsies, that the benefits in terms of guiding subsequent therapies often favors repeated biopsies as clinical features evolve in patients with LN.

12.9: Treatment of Resistant Disease

12.9.1: In patients with worsening SCr and/or proteinuria after completing one of the initial treatment regimens, consider performing a repeat kidney biopsy to distinguish active LN from scarring. (*Not Graded*)

12.9.2: Treat patients with worsening SCr and/or proteinuria who continue to have active LN on biopsy with one of the alternative initial treatment regimens (see Section 12.3). (*Not Graded*)

12.9.3: We suggest that nonresponders who have failed more than one of the recommended initial regimens (see Section 12.3) may be considered for treatment with rituximab, i.v. immunoglobulin, or CNIs. (*2D*)

Commentary

Given that remission may occur up to a year after initiation of therapy, the KDIGO guidelines recommend to wait at least 6 months after initiation of induction therapy before changing to another course of therapy; however, the ACR guidelines explicitly recommend to change induction regimens at 3 months if there is ≥50% worsening of proteinuria or creatinine,[147] which is more reflective of current clinical practice and is what we would suggest. If MMF is used as induction therapy, addition of a CNI rather than change to a cyclophosphamide-based regimen is a reasonable option if resistant disease is primarily proteinuria and not declining creatinine.[156,170]

We agree with recommendation 12.9.3; a number of agents have been recently studied (or are currently being studied) as induction therapies, including abatacept, rituximab, laquinimod, bortezomib, and belimumab.[146] The most likely role for these newer agents, though, is not for induction therapy but rather as therapy for resistant disease. There is a pressing need for RCTs for salvage therapies in resistant LN.

12.10: Systemic Lupus and Thrombotic Microangiopathy

12.10.1: We suggest that the antiphospholipid antibody syndrome (APS) involving the kidney in systemic lupus patients, with or without LN, be treated by anticoagulation (target international normalized ratio [INR] 2-3). (*2D*)

12.10.2: We suggest that patients with systemic lupus and thrombotic thrombocytopenic purpura (TTP) receive plasma exchange as for patients with TTP without systemic lupus. (*2D*)

Commentary

We agree with recommendations 12.10.1 and 12.10.2. In addition, we suggest that all patients with LN be screened for antiphospholipid antibodies (anticardiolipin antibody, anti-β_2 glycoprotein antibody, and lupus anticoagulant) at least once in their disease course, but that anticoagulation be reserved for those with thrombotic events (ie, not used as prophylaxis).

12.11: Systemic Lupus and Pregnancy

12.11.1: We suggest that women be counseled to delay pregnancy until a complete remission of LN has been achieved. (*2D*)

12.11.2: We recommend that cyclophosphamide, MMF, ACE-I, and ARBs not be used during pregnancy. (*1A*)

12.11.3: We suggest that hydroxychloroquine be continued during pregnancy. (*2B*)

12.11.4: We recommend that LN patients who become pregnant while being treated with MMF be switched to azathioprine. (*1B*)

12.11.5: We recommend that, if LN patients relapse during pregnancy, they receive treatment with corticosteroids and, depending on the severity of the relapse, azathioprine. (*1B*)

12.11.6: If pregnant patients are receiving corticosteroids or azathioprine, we suggest that these drugs not be tapered during pregnancy or for at least 3 months after delivery. (*2D*)

12.11.7: We suggest administration of low-dose aspirin during pregnancy to decrease the risk of fetal loss. (*2C*)

Commentary

Periodic checks of common serologic tests of SLE can be helpful monitoring tools during pregnancy, particularly in instances where worsening proteinuria raises the differential diagnosis of preeclampsia versus SLE flare. During pregnancy, we recommend goal blood pressure <130/80 mm Hg using nonteratogenic antihypertensive agents, preferring labetalol and/or nifedipine. We suggest that addition of azathioprine be reserved for women with proteinuria >3 g/d in a dose not to exceed 2 mg/kg/d. The FDA lists azathioprine as category D, which should be mentioned in patient counseling. Cyclophosphamide is also listed as a category D drug and should generally be avoided in pregnancy; however, in instances of life-threatening complications of SLE, this drug has been used late in the gestational period (ie, third trimester).[171-173]

12.12: LN in Children

12.12.1: We suggest that children with LN receive the same therapies as adults with LN, with dosing based on patient size and GFR. (*2D*)

Commentary

As with the adult population with LN, there has been a general shift in current practice toward using MMF as the preferred initial agent in children, rather than cyclophosphamide, to preserve fertility. Data from RCTs in children are entirely absent, and thus a research recommendation for trials enrolling children with LN should be stressed.

CHAPTER 13: KDIGO RECOMMENDATIONS FOR PAUCI-IMMUNE FOCAL AND SEGMENTAL NECROTIZING GN

Pauci-immune focal and segmental necrotizing and crescentic GN is the characteristic renal lesion seen in diseases frequently associated with ANCA (antineutrophil cytoplasmic antibody), which include granulomatosis with polyangiitis (Wegener), microscopic polyangiitis, and renal-isolated necrotizing and crescentic GN. The latter is also seen in eosinophilic granulomatosis with polyangiitis (Churg-Strauss). However, because patients with eosinophilic granulomatosis with polyangiitis were not included in most of the trials that formed the basis for the KDIGO clinical practice guideline, these recommendations should not be generalized to this group of patients. Granulomatosis with polyangiitis and microscopic polyangiitis are systemic diseases associated with renal and nonrenal manifestations in which extrarenal disease may dictate therapeutic decisions. It is therefore important to examine not only how these recommendations apply to necrotizing and crescentic GN but also to disease outside of the kidney.

13.1: Initial Treatment of Pauci-Immune Focal and Segmental Necrotizing GN

13.1.1: We recommend that cyclophosphamide and corticosteroids be used as initial treatment. (*1A*)
13.1.2: We recommend that rituximab and corticosteroids be used as an alternative initial treatment in patients without severe disease or in whom cyclophosphamide is contraindicated. (*1B*)

Commentary

Regarding recommendation 13.1.1, cyclophosphamide has been well established to effectively induce remission of active necrotizing and crescentic GN when given as daily oral or intermittent intravenous therapy.[174-177] Based on clinical trials[178,179] showing similar efficacy, we recommend that a decision regarding use of daily cyclophosphamide (2 mg/k/d) or intravenous cyclophosphamide (15 mg/kg every 2 weeks for 3 doses initially then every 3 weeks) be based on the individual patient and physician preference.

In Guideline Table 30, the recommended intravenous cyclophosphamide regimen of 0.75 g/m^2 every 3-4 weeks more closely resembles the regimen of 0.5-1.0 g/m^2 monthly used in LN. While there have been data from small series and meta-analyses, there have not been adequately powered comparative trials demonstrating equivalent efficacy of the monthly intravenous cyclophosphamide regimen as is used in LN to daily cyclophosphamide for the treatment of necrotizing and crescentic GN.

We agree with recommendation 13.1.2, but with comment and clarification. The results of both the RAVE (Rituximab in ANCA-Associated Vasculitis) and RITUXVAS (Rituximab Versus Cyclophosphamide in ANCA-Associated Vasculitis) trials showed that rituximab had comparable efficacy to cyclophosphamide in the rate of remission induction of newly diagnosed severe disease.[180,181] Consistent with the 2011 FDA approval of rituximab for granulomatosis with polyangiitis and microscopic polyangiitis, we recommend that rituximab be considered as equivalent to cyclophosphamide in initial treatment of severe disease and not only be considered a cyclophosphamide alternative in patients without severe disease or in whom cyclophosphamide is contraindicated. However, we note that there is greater long-term experience with cyclophosphamide compared to rituximab.

An important clarification to this recommendation about rituximab is their use of the term "severe" disease. Rituximab is not excluded for severe disease as this was the population in whom the agent was studied in both RAVE and RITUXVAS. However, patients with the most serious disease consisting of a serum creatinine >4.0 mg/dL or on mechanical ventilation from alveolar hemorrhage were excluded from the RAVE trial, such that comparability of rituximab and cyclophosphamide has not been proved in these settings.

The current literature does not allow any conclusions to be made regarding whether older patients should be preferentially treated with rituximab or cyclophosphamide. Cyclophosphamide should not be withheld from elderly patients who have an indication for treatment and who do not have an absolute contraindication. Particular attention should be made in the older population to cyclophosphamide dosing, infection prevention, and meticulous blood count monitoring.

The experience with rituximab in pediatric patients has thus far been confined to case reports and small series. While the desire to avoid cyclophosphamide side effects, particularly the potential effects on fertility, make rituximab an attractive choice, the decision to use rituximab in pediatric patients in the absence of a larger body of data must be made on an individual basis.

Severe extrarenal disease should be managed identically to that discussed for necrotizing and crescentic GN in Section 13.1. Methotrexate and corticosteroids can be used for remission induction of nonsevere extrarenal disease in patients who do not have a contraindication to this agent as a randomized trial of patients with active nonsevere disease found that methotrexate was not inferior to cyclophosphamide for remission induction.[182]

MMF may be of value in treating patients with myeloperoxidase-ANCA–associated microscopic polyangiitis and with mild to moderate renal disease,[183] but experience with this agent remains too limited to inform a recommendation or suggestion for use as induction therapy in this setting. Azathioprine has not been found to be an effective agent for remission induction of severe or nonsevere disease[174]; but has not been studied in large-scale trials.

13.2: Special Patient Populations

13.2.1: We recommend the addition of plasmapheresis for patients requiring dialysis or with rapidly increasing SCr. (*1C*)
13.2.2: We suggest the addition of plasmapheresis for patients with diffuse pulmonary hemorrhage. (*2C*)
13.2.3: We suggest the addition of plasmapheresis for patients with overlap syndrome of ANCA vasculitis and anti-GBM GN, according to proposed criteria and regimen for anti-GBM GN (see Chapter 14). (*2D*)
13.2.4: We suggest discontinuing cyclophosphamide therapy after 3 months in patients who remain dialysis dependent and who do not have any extrarenal manifestations of disease. (*2C*)

Commentary

While in general we agree with recommendation 13.2.1, it should be noted that the strongest data regarding the use of plasmapheresis in granulomatosis with polyangiitis and microscopic polyangiitis comes from the MEPEX (Methyl Prednisolone or Plasma Exchange for Severe Renal Vasculitis) trial, which studied patients with rapidly progressive GN and serum creatinine >5.8 mg/dL.[184] However, longer term analyses of these data have raised questions about the role of plasmapheresis in this setting.[185] Therefore, we recommend that clinicians make note of the less favorable, longer term plasmapheresis results from the MEPEX trial, which may put the use of plasmapheresis in rapidly progressive GN more at the level of a suggestion. Ongoing trials may provide further insight into the value of plasmapheresis in patients with severe or rapidly progressive GN.

Since plasmapheresis removes rituximab, the timing of rituximab infusion in relationship to plasmapheresis needs to be considered if this agent is used.

We also agree with recommendation 13.2.2, but note that data supporting a benefit of plasmapheresis in conjunction with corticosteroids and cyclophosphamide in pulmonary hemorrhage come from retrospective studies in which the independent role of plasmapheresis cannot be ascertained.[186] Nonetheless, because pulmonary hemorrhage requiring mechanical ventilation carries a high rate of mortality, we support its use in this setting. Plasmapheresis can be associated with hemodynamic shifts, infection, and thrombosis, risks that must be weighed when considering use of plasmapheresis and its uncertain benefits in individual patients.

We agree with recommendations 13.2.3 and 13.2.4, with the comment that patients who remain dialysis dependent and have treatment discontinued should be closely monitored for the emergence of nonrenal disease as patients who initially present with renal-limited necrotizing and crescentic GN may subsequently present with features of systemic disease.

13.3: Maintenance Therapy

13.3.1: We recommend maintenance therapy in patients who have achieved remission. (*1B*)
13.3.2: We suggest continuing maintenance therapy for at least 18 months in patients who remain in complete remission. (*2D*)
13.3.3: We recommend no maintenance therapy in patients who are dialysis-dependent and have no extrarenal manifestations of disease. (*1C*)

Commentary

Long-term data have conclusively demonstrated that the diseases associated with necrotizing and crescentic GN all have the potential to relapse after successful remission induction, and thus we agree with recommendation 13.3.1. The highest frequency of relapse appears to be with granulomatosis with polyangiitis, with relapses occurring in 50%-70% of patients. The concept of continuing some form of therapy to maintain remission after cyclophosphamide or methotrexate induction is supported by higher rates of relapse when therapy is stopped shortly after induction.[182] It is not yet clear what type of maintenance therapy should be given after rituximab as neither RAVE nor RITUXVAS included the use of maintenance in the rituximab arms after induction. It is clear though that relapses occur after rituximab treatment from as early as 5 months or years later[187-189] and thus the issue of maintenance therapy remains important after rituximab. Decisions regarding maintenance after rituximab are currently made on an individual patient basis; such treatment could consist of conventional agents (azathioprine, methotrexate, MMF) or rituximab. The optimal dose and dosing frequency for maintenance rituximab therapy when used is not clear.

The optimal duration of maintenance therapy is unknown, but nonetheless we agree with recommendation 13.3.2 that this should be for at least 18 months in the absence of toxicity.

We agree with recommendation 13.3.3 because in such patients the risk of infection is almost twice as great as the rate of relapse. However, after treatment is stopped, patients should be closely monitored for the emergence of nonrenal disease since as noted above, patients who initially present with renal-limited necrotizing and crescentic GN may later develop evidence of an underlying systemic disease.

13.4: Choice of Agent for Maintenance Therapy

13.4.1: We recommend azathioprine 1-2 mg/kg/d orally as maintenance therapy. (*1B*)
13.4.2: We suggest that MMF, up to 1 g twice daily, be used for maintenance therapy in patients who are allergic to, or intolerant of, azathioprine. (*2C*)
13.4.3: We suggest trimethoprim-sulfamethoxazole as an adjunct to maintenance therapy in patients with upper respiratory tract disease. (*2B*)
13.4.4: We suggest methotrexate (initially 0.3 mg/kg/wk, maximum 25 mg/wk) for maintenance therapy in patients intolerant of azathioprine and MMF, but not if GFR is <60 ml/min per 1.73 m^2. (*1C*)
13.4.5: We recommend not using etanercept as adjunctive therapy. (*1A*)

Commentary

The agents for which there have been the greatest published data for maintenance based on random-

ized trials are azathioprine, methotrexate, and MMF. In patients with impaired kidney function, we agree that azathioprine is the recommended choice for remission maintenance in patients who do not have contraindications, as noted in recommendation 13.4.1. Azathioprine is as effective as prolonged use of cyclophosphamide in maintaining remission.[177] Testing for thiopurine *S*-methyltransferase, an enzyme responsible for the metabolism of azathioprine, is a widely available in the United States and should be performed when possible as low or absent levels of this enzyme significantly increase the risk of myelosuppression with azathioprine. Patients with intermediate thiopurine *S*-methyltransferase levels should be treated with a lower starting dose and azathioprine should not be used at all in patients who lack functional enyzme.

MMF has been found to have a higher rate of relapse compared to azathioprine. We therefore agree with recommendation 13.4.2, with the added comment that MMF may be used for maintenance therapy in patients who are allergic to, intolerant of, or cannot take azathioprine or methotrexate. Note should also be made of the FDA recommendations to screen for pregnancy in women of child-bearing potential prior to use of MMF.

Trimethoprim-sulfamethoxazole is an important agent in these diseases, most notably for its role in prophylaxis from *Pneumocystis jiroveci* infection. We agree with recommendation 13.4.3 that trimethoprim-sulfamethoxazole may be useful in reducing the rate of relapse of upper respiratory tract disease.[190] It is also important to note that an interaction exists between methotrexate and trimethoprim-sulfamethoxazole, 160/800 mg, twice a day, although lower doses for *Pneumocystis* prevention (trimethoprim-sulfamethoxazole, 160/800 mg, 3 times a week or 80/400 mg daily) have been well tolerated.

The wording of recommendation 13.4.4 suggests that use of methotrexate be considered a third choice for maintenance after azathioprine and MMF. However, the data support that methotrexate may appropriately be considered as an equally effective alternative to these other agents even without prior intolerance to azathioprine or MMF.[191,192] While methotrexate is contraindicated with poor kidney function, we believe that it would be more correct to state that methotrexate (initially 0.3 mg/kg/wk, maximum 25 mg/wk) can be recommended for maintenance therapy, with dose reduction in patients with creatinine clearance <60 mL/min and avoidance of use with <30 mL/min.

We agree with recommendation 13.4.5; etanercept was examined as an adjunctive agent to induction/maintenance therapy in a large randomized trial and found to provide no added benefit in sustaining remission.[193]

13.5: Treatment of Relapse

13.5.1: We recommend treating patients with severe relapse of ANCA vasculitis (life- or organ-threatening) according to the same guidelines as for the initial therapy (see Section 13.1). (*1C*)

13.5.2: We suggest treating other relapses of ANCA vasculitis by reinstituting immunosuppressive therapy or increasing its intensity with agents other than cyclophosphamide, including instituting or increasing dose of corticosteroids, with or without azathioprine or MMF. (*2C*)

Commentary

We agree with recommendation 13.5.1, with a comment that this should refer to both severe renal and nonrenal disease. It should also be noted that the RAVE trial results would suggest that rituximab may be more effective than cyclophosphamide for remission induction in patients with relapsing disease.[181] Another reason to favor rituximab in patients who have previously received cyclophosphamide would be reduction in cyclophosphamide exposure and side effects.

We agree with recommendation 13.5.2 that cyclophosphamide should be avoided for nonsevere relapses. There are limited data with MMF for remission induction in selected patients with nonsevere disease. There have also been limited data with azathioprine for remission induction that did not support efficacy, such that this is generally not recommended. We recommend use of combined therapy as use of corticosteroids alone have not been effective as a treatment for active granulomatosis with polyangiitis or microscopic polyangiitis.[174,194] Methotrexate can also be used for remission induction of nonsevere relapses in patients without contraindications.[195]

13.6: Treatment of Resistant Disease

13.6.1: In ANCA GN resistant to induction therapy with cyclophosphamide and corticosteroids, we recommend the addition of rituximab (*1C*), and suggest i.v. immunoglobulin (*2C*) or plasmapheresis (*2D*) as alternatives.

Commentary

Disease that is truly resistant to cyclophosphamide is uncommon, so before concluding that resistant disease is present, noninflammatory damage, infection, medication toxicity, or other entities should be considered. In those rare instances in which resistance is determined to be present, the decision regarding treatment must be individualized as there are no evidence-based data in this setting. Rituximab would typically be given to

replace cyclophosphamide rather than added to this therapy with plasmapheresis and intravenous immunoglobulin being used in combination with cyclophosphamide.[181,184,196]

13.7: Monitoring

13.7.1: We suggest not changing immunosuppression based on changes in ANCA titer alone. (*2D*)

Commentary

We agree with recommendation 13.7.1 since changes in ANCA titer have not been found to be a reliable measure by which to assess disease activity or guide therapy.[197-199]

13.8: Transplantation

13.8.1: We recommend delaying transplantation until patients are in complete extrarenal remission for 12 months. (*1C*)

13.8.2: We recommend not delaying transplantation for patients who are in complete remission but are still ANCA-positive. (*1C*)

Commentary

Patients with necrotizing and crescentic GN can do well following transplantation such that this should not be a deterrent against considering transplantation in an otherwise eligible patient.[200,201] While we generally agree with recommendation 13.8.1 that waiting for 12 months of clinical remission before renal transplantation is reasonable, the evidence basis for this is limited and in selected patients, it may be reasonable to pursue transplantation after 6-9 months of clinical remission. We agree with recommendation 13.8.2 since there is no convincing evidence that persistent ANCA positivity should be a factor in determining the timing of renal transplantation.

CHAPTER 14: TREATMENT OF ANTI-GBM GN

14.1: Treatment of Anti-GBM GN

14.1.1: We recommend initiating immunosuppression with cyclophosphamide and corticosteroids plus plasmapheresis (see Guideline Table 31) in all patients with anti-GBM GN except those who are dialysis-dependent at presentation and have 100% crescents in an adequate biopsy sample, and do not have pulmonary hemorrhage. (*1B*)

14.1.2: Start treatment for anti-GBM GN without delay once the diagnosis is confirmed. If the diagnosis is highly suspected, it would be appropriate to begin high-dose corticosteroids and plasmapheresis (Guideline Table 31) while waiting for confirmation. (*Not Graded*)

14.1.3: We recommend no maintenance immunosuppressive therapy for anti-GBM GN. (*1D*)

14.1.4: Defer kidney transplantation after anti-GBM GN until anti-GBM antibodies have been undetectable for a minimum of 6 months. (*Not Graded*)

Commentary

Anti-GBM disease can be rapidly progressive and fatal and renal recovery has been strongly tied to early diagnosis. We agree with recommendations 14.1.1 and 14.1.2. Although the available evidence supports treatment with cyclophosphamide, corticosteroids, and plasmapheresis, it is worth noting that the only RCT of plasmapheresis involved only 17 patients randomized to receive prednisone and cyclophosphamide alone or with plasmapheresis. A higher rate of renal recovery in those who also received plasmapheresis led the authors to conclude a benefit of this additional therapy.[202] As outlined in Guideline Table 31, corticosteroids typically begin with pulse methylprednisolone followed by tapering oral prednisone for at least 6 months' duration. Daily oral cyclophosphamide is also usually given for 3 months and plasmapheresis is typically continued for 14 days or until the anti-GBM antibody is undetectable.

Regarding recommendation 14.1.1, discussion is warranted regarding patients with anti-GBM disease who are dialysis dependent, have 100% crescents on renal biopsy, and do not have pulmonary hemorrhage. While retrospective studies have indicated that such patients have a low rate of renal recovery (~8%) in clinical practice, some advocate for a limited 4- to 8-week trial of treatment with corticosteroids and plasmapheresis with or without cyclophosphamide for functionally young patients who have had very rapid loss of kidney function due to anti-GBM GN. Clearly, the risks of such an approach must be carefully considered given the limited likelihood of significant response in this setting.

We also suggest that treatment with plasmapheresis, corticosteroids, and cyclophosphamide should be considered in patients with anti-GBM disease who also have ANCA, although optimal treatment of these "double-positive patients" is unclear. For patients who are not on dialysis, treatment should be as would be used for anti-GBM disease. In patients who require dialysis, data are conflicting but limited, so no specific recommendation about treatment of such patients can be made at this time.[203,204]

Although the focus on this chapter is the renal manifestation of anti-GBM disease, there should be emphasis that all patients with pulmonary hemorrhage should be treated regardless of the presence and/or

severity of kidney involvement, as stated in the KDIGO rationale for this section.

We agree with recommendation 14.1.2. Anti-GBM disease appears to be monophasic and self-limited, with antibodies often disappearing spontaneously after 6-18 months, and we therefore agree with recommendation 14.1.3. However, relapses have rarely been reported, which makes ongoing patient and laboratory monitoring important for at least the first 2 years and lengthened out thereafter.[205,206] There is a small percentage of patients who have persistence of low levels of anti-GBM antibodies. In such patients, consideration could be made for using azathioprine after cyclophosphamide. We agree with recommendation 14.1.4.

RESEARCH RECOMMENDATIONS

Chapter 4: SSNS in Children

- Longitudinal cohort studies are needed to clarify the long-term outcome of SSNS and SRNS, both in terms of renal function and the occurrence of severe life threatening complications (eg, peritonitis, thromboembolism, malignancy).
- This data gathering could be accomplished via existing pediatric nephrology–focused registries or by expanding current cohort studies such as NEPTUNE (Nephrotic Syndrome Study Network).
- Treatment trials should be performed to define optimal management of the disorders of lipid and mineral-bone metabolism that occur in children with SSNS and SRNS.

Chapter 5: MCD in Adults

- RCTs are needed to define dose and duration of corticosteroid therapy for the first episode of adult MCD.
- We agree that RCTs are needed to evaluate the comparative efficacy of secondary agents in the setting of FR/SD MCD, including CNIs, MMF, cyclophosphamide, rituximab, and levamisole.
- We agree that long-term data on extrarenal manifestations, including cardiovascular events, infectious complications, and malignancy, are needed.

Chapter 6: Idiopathic FSGS in Children and Adults

- Studies to understand the biology of diseases that result in FSGS, including the identification of additional genetic mutants and environmental influences that result in podocyte death and loss, should be accelerated with increased investment in research. Such research will help identify new therapeutic targets that would attenuate or stop disease progression.
- Simultaneously, studies are needed to identify meaningful biomarkers that would allow for disease subclassification that would predict natural history and response to therapy. Subclassification of disease is also critical in designing clinical interventional trials to decrease study population heterogeneity, a factor that may result in inconclusive or negative findings.
- Identification of surrogate end points that reliably predict preservation of renal function, improved patient and renal survival, or improved quality of life are needed to allow for more efficient and less expensive interventional trial design.

Chapter 7: IMN

- The duration of treatment with cytotoxics, CNIs, and other agents is entirely empirical at this point and needs more systematic assessment.
- Future studies should longitudinally measure anti-PLA_2R (or other relevant autoantibodies) to correlate immunologic and clinical remissions. Validation of anti-PLA_2R as a surrogate (and more rapid) marker of remission may help determine the appropriate duration of immunosuppressive therapy and possibly reduce exposure to these agents.

Chapter 8: Idiopathic MPGN

- Given the rarity of this group of diseases, multicenter collaborative efforts are needed. A registry/biorepository should be established to allow for systematic evaluation and accurate subclassification of these patients. This would provide greater opportunity to define the natural history of the different MPGN variants and more effectively study disease mechanisms.
- There is a need to identify better biomarkers of disease activity to guide decisions about therapy and duration. There is also a need for studies to identify risk factors for recurrent disease in the renal transplantation and therapeutic strategies for management of posttransplantation recurrence.

Chapter 9: Infection-Related GN

- We agree with the research recommendations that epidemiologic studies are needed to determine the prevalence and types of glomerular lesions in HCV-infected patients.
- We highlight the need for studies to identify predisposing factors that lead to glomerular

disease in only a proportion of these infected patients.
- Future RCTs in the CKD population should focus on the relative efficacy of the standard antivirals as monotherapy versus use of the newer protease inhibitors and/or immunosuppressive agents as adjunctive therapy.
- We need more data about the safety (with respect to viral burden and long-term outcomes) of initial and/or repeated courses of rituximab in the population with cryoglobulinemic vasculitis.
- Although more information is needed as to the impact of cART on HIV-associated renal disease other than HIVAN (as the benefit in HIVAN seems to be well established), we want to clarify that future RCTs should not withhold cART to achieve this purpose.
- We agree with the research recommendation about better evaluating the role of corticosteroids in combination with cART in the treatment of HIV-associated kidney disease, but would expand this to other immunosuppressive agents as well.

Chapter 10: IgAN

- We agree that future studies with new immunosuppressive agents should be compared to corticosteroids alone with all patients receiving optimal blood pressure control and antiproteinuric therapy.
- Future investigations should compare racial differences in response to immunosuppressive agents, with inclusion of drug and metabolite levels in these RCTs when applicable.
- Therapeutic approaches in children with IgAN are based on experience in adults, underscoring the need for specific pediatric trials for IgAN.
- We agree on the need for an RCT comparing MMF and corticosteroids versus corticosteroids alone after optimal antihypertensive and antiproteinuric therapy.
- There is a need for investigations that focus on the treatment of patients with relapse after corticosteroids and corticosteroid resistance.

Chapter 11: HSP

- We agree with suggestions for a randomized controlled trial comparing 6 to 12 months of steroid therapy to shorter duration therapy for children with moderately severe HSP nephritis (acute nephritic syndrome or NS with normal kidney function and $<$50% crescents/sclerosis).
- We agree with the need for randomized controlled trials to determine whether noncorticosteroid immunosuppressive agents such as CNIs or MMF are effective in treating children with more severe HSP nephritis (acute nephritic syndrome/NS with or without decreased GFR with $>$50% crescents or sclerosis).

CONCLUSIONS

GN is an important cause of patient morbidity and mortality in children and adults around the world. However, these conditions are relatively infrequent and experience with a given condition at any individual center is often limited. The relatively uncommon nature of these diseases has also hindered the performance of adequately powered RCTs designed to guide therapy. In some diseases, such as ANCA-associated vasculitis, creation of collaborative networks has allowed for the conduct of well-designed RCTs that have produced findings that have been incorporated into clinical practice as reflected by the high quality of evidence in this section of the KDIGO guidelines. For other forms of GN, such as FSGS, efforts to form consortiums to conduct RCTs are in nascent stages and as a consequence, the evidence for particular treatments is not nearly as compelling. Thus, for the management of many types of GN, nephrologists are forced to rely upon the findings in small underpowered clinical trials that provide inconclusive guidance on how to treat an individual patient. Moreover, in many glomerular diseases, such as HSP nephritis, there is a paucity of basic science information upon which to base disease classification and approaches to therapy. For other forms of GN such as MPGN, there is rapid growth in our understanding of the disease pathophysiology that needs to be systematically incorporated into clinical practice. The KDIGO guidelines represent a groundbreaking effort to organize the approach to the diagnosis and management of GN. The recommendations are feasible and well organized and should be a useful resource to nephrologists around the world. Overall, the KDOQI work group concurred with the KDIGO guidelines. They are likely to be relevant to the vast majority of children and adults with GN being cared for in the United States. However, like any state-of-the-art report, these guidelines summarize not only the successes in the field, but also the shortcomings in the diagnosis, classification, prognostication, and treatment of GN. We strongly endorse the need to support basic science and clinical research focusing on GN so that the next set of guidelines will be able to highlight improvements in the care of our patients with glomerular disease.

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