Management and treatment of glomerular diseases (part 2): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

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In November 2017, the Kidney Disease: Improving Global Outcomes (KDIGO) initiative brought a diverse panel of experts in glomerular diseases together to discuss the 2012 KDIGO glomerulonephritis guideline in the context of new developments and insights that had occurred over the years since its publication. During this KDIGO Controversies Conference on Glomerular Diseases, the group examined data on disease pathogenesis, biomarkers, and treatments to identify areas of consensus and areas of controversy. This report summarizes the discussions on primary podocytopathies, lupus nephritis, anti-neutrophil cytoplasmic antibody–associated nephritis, complement-mediated kidney diseases, and monoclonal gammopathies of renal significance.

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The Kidney Disease: Improving Global Outcomes (KDIGO) initiative published its first ever guideline on glomerular diseases in 2012.[1] Since then our understanding of the pathogenesis of glomerular diseases has markedly advanced, new diagnostic biomarkers have entered the clinical arena, and many new therapies have been assessed in clinical trials. Therefore, a conference consisting of about 100 experts from various disciplines (nephrology, pathology, rheumatology, pediatrics) and organizations (academia, pharmaceutical industry) was convened on November 17–19, 2017. The goals were to evaluate the progress that has been made in the evaluation and management of glomerular diseases, assess continuing gaps in knowledge, and identify the existing guideline recommendations that should be revisited in the next update. The attendees were especially encouraged to outline the most controversial aspects of glomerular diseases.

This second of 2 reports covers the primary podocytopathies, complement-mediated glomerular diseases, lupus nephritis (LN), anti-neutrophil cytoplasmic antibody (ANCA)-associated nephritis, and monoclonal gammopathies of renal significance. Each disease-specific working group was asked to consider disease terminology, pathogenesis, biomarkers, treatment, and recommendations for future studies. Taken together, these 2 conference summaries will lay the basis for the guideline updating process that began in August 2018.

MCD AND FSGS

Terminology

The terms "minimal change disease" (MCD) and "focal segmental glomerulosclerosis" (FSGS) remain relevant. Although there may be pathophysiologic overlap between MCD and FSGS, the presence of focal and segmental sclerosis by light microscopy has diagnostic and prognostic importance. To discriminate between MCD and FSGS by kidney biopsy, at

least 20 glomeruli are needed, and biopsies performed soon after diagnosis may only show MCD, but the patients may later develop FSGS.[2] However, in children, kidney biopsy is not usually performed in patients that respond to prednisone treatment. Response to prednisone treatment and timing of relapses allows classification of childhood nephrotic syndrome.[3] There was consensus that the designations "steroid-sensitive" and "steroid-resistant" nephrotic syndrome are clinically useful disease descriptions in children and that most steroid-sensitive idiopathic nephrotic syndromes in children are MCD. Response to therapy is often of more prognostic value than biopsy histology.

The terms "primary/idiopathic FSGS" should be reserved for FSGS caused by as yet unknown permeability factors. Patients with genetic, adaptive (in the setting of reduced nephron mass), drug-induced, and viral-induced FSGS should not be designated as primary.[4] Primary FSGS is often characterized by acute-onset heavy proteinuria and diffuse podocyte foot process effacement histologically. Other FSGS subtypes typically show more modest proteinuria and segmental foot process effacement.[5] Further efforts are warranted to better define these FSGS subgroups in the context of their presumed pathogenesis.

Pathogenesis of MCD and primary/idiopathic FSGS

A role for dysfunctional T cells in MCD was proposed over 40 years ago.[6] More recently, a role for B cells has become evident, supported by efficacy of immunoadsorption and B-cell depletion in inducing remission.[3]

Thus far none of the reported circulating permeability factor candidates have been independently validated in primary FSGS.[7] Soluble urokinase-type plasminogen activator receptor may be a novel prognostic biomarker for chronic kidney disease, but does not appear to have a role as a diagnostic biomarker or to represent the permeability factor in FSGS.[8]

Cardiotrophin-like cytokine-1, a member of the interleukin 6 cytokine family, may be a candidate FSGS permeability factor. Cardiotrophin-like cytokine-1 has been identified in the plasma of patients with FSGS and has been found to decrease nephrin expression in podocyte culture. In patients with recurrent FSGS, its concentration may be up to 100 times that of normal subjects. Angiopoietin-like-4, a secreted glycoprotein, is highly upregulated in the serum and in podocytes in experimental models of MCD and in the human disease. This biomarker has relevant potential in patients with steroid-sensitive nephrotic syndrome.[9,10]

It has been suggested that MCD/FSGS may be mediated by podocyte CD80 (B7-1) expression induced after an innocuous event such as an infection.[11] However, CD80 overexpression on podocytes could not be confirmed.[12] A role for glomerular parietal epithelial cells in the pathogenesis of virtually all histological types of FSGS lesions has also been proposed.[13]

Biomarkers and prediction of prognosis

There are no validated biomarkers ready for clinical use in MCD or FSGS. The histological subtype of FSGS as defined by the Columbia classification[14] may support decision making and help with anticipating response to treatment and prognosis,[15] but it is not specific for underlying disease mechanisms. Immunostaining of kidney biopsy specimens for parietal epithelial cell activation markers may improve sensitivity for detecting sclerotic lesions when distinguishing primary FSGS from MCD.[16] Proteomic analysis of kidney biopsy specimens may provide additional insights.

Genetic testing

Genetic testing for pediatric nephrotic syndrome and adult FSGS is controversial, but it should be considered for patients with congenital and infantile forms of nephrotic syndrome (children <1 year of age) or less than 2 years of age with steroid-resistant nephrotic syndrome, nephrotic syndrome associated with other syndromic features, or familial forms of steroid-resistant nephrotic syndrome/FSGS.[17–19] Adding to the controversy of when to perform genetic testing, single gene mutations have been found in up to 30% of patients under age 25.[18] Testing should target relevant genes based on patient characteristics and contemporary knowledge. The role of high-risk apolipoprotein L1 genotypes in the development of glomerulosclerosis is still under investigation and the conference attendees agreed that data are still insufficient to support using this information to guide clinical decisions. Genetic testing may be considered for inclusion and stratification in clinical trials. Biospecimens should routinely be collected, and patients consented for later genetic analysis. Ethical issues should be addressed before recommending genetic analyses.

Treatment

General. While immunomodulatory therapies are the first-line treatment in primary/idiopathic FSGS caused by a permeability factor, other FSGS subtypes respond better to blood pressure control and correction of abnormal glomerular hemodynamics, such as glomerular hypertension (e.g., in adaptive FSGS), or other specific interventions. The use of immunomodulatory therapy after causative FSGS mutations are identified is controversial. Rare reports of varying degrees of remission in these patients may or may not reflect the nonimmune modulating effects of these therapies.[20] Following identification of causative mutations, treatment should include known directed therapies for specific mutations (e.g., coenzyme Q-10, vitamin B12 where applicable),[18] antiproteinuric therapy, and prompt discontinuation of immunosuppressive therapy in those with no early signal of response.[21]

Pediatric. Because ~80% of children with incident nephrotic syndrome have MCD on biopsy and of the remaining patients, some will respond to corticosteroid therapy, the conference attendees agreed that there are no data to challenge the practice of treating all pediatric nephrotic patients with corticosteroids first, except those younger than 9 to 10 months of age. Due to the increased incidence of steroid-resistant nephrotic syndrome and FSGS with age, consideration to biopsy children older than 12 years prior to treatment is

recommended. In children with steroid-sensitive nephrotic syndrome, recent data from randomized controlled trials do not support steroid exposure beyond 8 to 12 weeks.[22–24]

Controversies remain about the minimum duration of corticosteroid therapy required to define steroid resistance. The 2012 KDIGO guideline recommended at least 8 weeks of corticosteroids in children before defining steroid resistance. While consensus was not reached, the need for a globally accepted definition of "steroid resistance" to improve comparability of future clinical trials was recognized.

The efficacy of low-dose daily corticosteroids over alternate day dosing for maintaining remission in relapsing nephrotic syndrome is promising.[25] Therapy with alternative immunosuppressive agents should be considered in children with frequently relapsing nephrotic syndrome. While data support the use of cyclophosphamide (CYC), levamisole, mycophenolate mofetil (MMF), calcineurin inhibitors (CNIs), and rituximab (RTX), the precise order of therapy is not well determined.[26] Data are emerging to support an early role of RTX in the management of children with steroid-dependent nephrotic syndrome. A direct action of RTX on podocytes was not confirmed, supporting B-cell depletion as RTX's primary mechanism of action.[27] *Post hoc* analyses suggest that targeting higher area under the serum/plasma concentration-time curves for MMF could result in similar numbers of children maintaining remission with MMF as with CNIs, but this needs to be confirmed in randomized controlled trials.[28]

Nephrotic patients have a high risk of infection regardless of immunosuppression. The 2012 KDIGO guideline provides some recommendations regarding vaccinations in children but does not highlight the importance of hepatitis B screening and vaccination, especially in those receiving B-cell depleting therapies.[29] Vaccination against meningococci should also be included as based on expert opinion.

Adult. In adults, recommending a minimum duration of 16 weeks of high-dose corticosteroids as first-line therapy for FSGS or MCD was felt to be controversial, given its potential for toxicity. However, data to support alternative first-line agents or combination therapies with lower doses of corticosteroids are insufficient. The conference attendees agreed that CNIs or CYC should remain as second-line agents in adults with frequently relapsing or steroid-dependent MCD. RTX is an emerging second-line therapy in MCD in adults although evidence is observational only. The recommendation for CNIs and MMF as second- and third-line treatments, respectively, for FSGS should be maintained. Randomized controlled trials are underway to investigate the value of RTX in adult MCD (Efficacy of Rituximab in Comparison to Continued Corticosteroid Treatment in Idiopathic Nephrotic Syndrome; NCT03298698) and the CD80 inhibitor abatacept, regardless of CD80 expression on podocytes, in MCD and FSGS (Pilot Study to Evaluate the Safety and Efficacy of Abatacept in Adults and Children 6 Years and Older With Excessive Loss of Protein in the Urine Due to Either Focal Segmental Glomerulosclerosis or Minimal Change Disease; NCT02592798).

Future studies

It will be important to distinguish between primary and secondary FSGS for clinical trials and include only those patients for which an investigational therapy may be effective. Immunologic therapies should focus on primary FSGS; antifibrotic therapies could recruit all forms of FSGS. Recommendations from the 2012 guideline that should be revisited are outlined in Supplementary Table S1.

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

Terminology and diagnosis

While the term "membranoproliferative" glomerulonephritis (GN) retains value as a histologic descriptor of glomerular injury, our increasing understanding of C3 glomerulopathy (C3G) and the monoclonal gammopathies of renal significance (MGRS) (paraprotein-associated kidney diseases) illustrate the need for nomenclature based on pathogenesis and injury pattern. Additionally, the histology of these specific etiologies is not always membranoproliferative GN. Therefore, updated clinical practice guidelines should emphasize a diagnostic approach to GN that considers both pathobiology and renal histology, such as that outlined in Table 1.[30] Over time, and with greater understanding of these diseases, using such a scheme may lead to the elimination of membranoproliferative GN as a distinct category of GN in clinical practice guidelines. The following discussion highlights controversies that exist within this framework, including the issue of overlapping disease mechanisms, the conundrum of common kidney biopsy features, and the inevitable fact that some cases will remain "idiopathic" in nature.[31]

The use of nonroutine histological techniques, including pronase to unmask hidden epitopes,[32–35] C4d staining to distinguish C3G from Ig-mediated and postinfectious GN,[36] and staining for the DNA J homolog subfamily B member 9 protein in fibrillary GN[37,38] may also help in the diagnosis and possibly in understanding the pathogenesis of GN with an membranoproliferative glomerulonephritis pattern. Most of these techniques need additional verification.

C3 Glomerulopathies

Pathogenesis. C3G is caused by abnormal complement activation, deposition and/or degradation. Drivers of disease are reviewed in recent consensus[39] and KDIGO Controversies Conference reports.[40]

While it was generally agreed that human and animal data support the role of complement in well-described scenarios, as a matter of practicality it continues to be difficult to substantiate the causal role of either single nucleotide changes or C3 nephritic factors in the majority of cases.[41,42] Furthermore, the interpretation of published data is confounded by heterogeneity in the kidney biopsy criteria used for diagnosis. Addressing these controversies is especially important given that targeted anticomplement agents are available.

Biomarkers and prediction of prognosis. The role of biomarkers in the diagnosis and management of C3G has been summarized recently.[40] The utility of biomarkers such as

Table 1 | A pathogenesis-based approach to glomerulonephritis

Pathogenic type	Disease examples
Immune complex glomerulonephritis	IgA nephropathy Lupus nephritis Fibrillary glomerulonephritis (polyclonal/DNAJB9-positive subtype) Infection-associated glomerulonephritis Mixed (types II and III) cryoglobulinemic glomerulonephritis
Pauci-immune glomerulonephritis	ANCA-associated vasculitis ANCA-negative pauci-immune glomerulonephritis
Antiglomerular basement membrane glomerulonephritis	Antiglomerular basement membrane disease
Monoclonal Ig-associated glomerulonephritis	Monoclonal Ig deposition disease (LCDD, HCDD, LHCDD) Proliferative glomerulonephritis with monoclonal Ig deposits Monoclonal (type I) cryoglobulinemic glomerulonephritis Immunotactoid glomerulopathy Fibrillary glomerulonephritis (monoclonal subtype)
Complement-mediated glomerulonephritis	C3 glomerulonephritis Dense deposit disease

ANCA, anti-neutrophil cytoplasmic antibody; DNAJB9, DNA J homolog subfamily B member 9; HCDD, heavy chain deposition disease; LCDD, light chain deposition disease; LHCDD, light and heavy chain deposition disease.
Adapted from Sethi S, Haas M, Markowitz GS, et al. Mayo Clinic/Renal Pathology Society Consensus report on pathologic classification, diagnosis, and reporting of GN. *J Am Soc Nephrol.* 2016;27:1278–1287,[30] with permission. Copyright © 2016 the American Society of Nephrology.

soluble C5b-9 levels for predicting treatment response remains unclear. Controversy remains regarding the clinical utility of an extended biomarker assessment at diagnosis, and the use of serial complement testing requires further study. Testing for paraproteins in C3G has also received increased attention.[43]

Treatment. A contemporary approach to the treatment of C3G has been outlined,[40] derived mostly from case reports and retrospective case series. An important knowledge gap in the treatment of C3G is the absence of a robust understanding of its natural history. Current treatments have been empirically extrapolated from other glomerular diseases. The optimal duration of therapy remains unclear. Current treatment guidelines focus on inhibiting definable pathways (inflammation or terminal complement activity) with available targeted therapeutics (antiproliferative agents or terminal complement blockers). Treatment of active disease with MMF and corticosteroids has shown promise in 2 retrospective case series,[44,45] but was not found to be effective in a third case series in patients with more severe baseline kidney disease.[46] For patients with C3G and monoclonal gammopathy, a recent retrospective case series found superior hematologic and renal response rates, as well as renal survival, for patients treated with clone-directed chemotherapy compared with conservative or immunosuppressive treatment.[47]

Monoclonal Gammopathies of Renal Significance

Pathogenesis. Preclinical and clinical studies have elucidated the pathogenesis of some paraprotein-associated kidney diseases. For example, heavy chain deposition disease is caused by a truncated Ig heavy chain that lacks the first constant domain (CH1 deletion).[48,49] Specific physiochemical properties of the truncated heavy chain may explain its tropism for the kidney.[50] Most patients with heavy chain deposition disease have an underlying plasma cell clone that does not meet criteria for multiple myeloma (i.e., a MGRS), and evidence of the truncated heavy chain can be found in the serum and bone marrow.[50]

In MGRS, pathogenic Igs are from plasma cell or B-cell clones. Targeting these clones may improve outcomes,[47,50,51] but the clones are often undetectable. The International Kidney and Monoclonal Gammopathy Research Group recommends that all patients with paraprotein-associated kidney disease undergo hematology evaluation, including a bone marrow biopsy, but the utility of the bone marrow is not clear in patients without a detectable circulating paraprotein.[47,52–54]

Biomarkers and prediction of prognosis. In multiple myeloma and light chain amyloidosis, achieving hematologic response (improvement in levels of circulating paraprotein) is associated with improved overall and renal survival.[55–58] Moreover, stabilization or improvement in kidney function and proteinuria may be linked with long-term renal survival.[59] There are emerging data regarding the importance of hematologic response in MGRS,[50,51,60] but it is not clear how to monitor patients without a detectable circulating paraprotein beyond glomerular filtration rate (GFR) and proteinuria.

Treatment. The International Kidney and Monoclonal Gammopathy Research Group published an approach to managing MGRS based on expert opinion.[61] Risk stratification was based on kidney dysfunction and proteinuria, and treatment strategies utilized a clone-directed approach similar to that employed for multiple myeloma and lymphomas (i.e., chemotherapeutic regimens, autologous stem cell transplant). A large retrospective case series found that using bortezomib-based

therapy for monoclonal Ig deposition disease led to higher hematologic and renal response rates, and prolonged renal survival, compared with results from previously published literature.[51] As noted previously, clone-directed chemotherapy results in improved hematologic and renal outcomes for patients with paraprotein-associated C3G compared with other immunosuppression or conservative treatment.[47]

Controversy exists regarding treatment of patients without a detectable underlying clone, but recent uncontrolled data suggest benefit from empiric chemotherapy.[53] A multidisciplinary, onco-nephrologic approach to patients with MGRS is recommended.[62]

Hepatitis C-associated glomerulonephritis. The *KDIGO Clinical Practice Guideline on the Prevention, Diagnosis, Evaluation and Treatment of Hepatitis C in CKD* summarizes an approach to the treatment of these patients[63] (Table 2). This approach will require validation. The development or persistence of cryoglobulinemic vasculitis (with or without kidney involvement) after achieving sustained virologic response has been described.[64–67] Whether this presentation reflects continued B-cell production of pathogenic immune complexes requires further study.

Fibrillary GN. Immunohistochemical staining on kidney biopsy for the DNA J homolog subfamily B member 9 protein was identified as a sensitive and specific marker in fibrillary GN.[37,38] The role of DNA J homolog subfamily B member 9 in disease pathogenesis is unknown. The data on treating fibrillary GN consist of small studies using a variety of therapies, none of which have been conclusive.[68–72]

Future studies. Investigations considered critical to the development of management protocols for C3G, immune-complex GN, and monoclonal gammopathies of renal significance are outlined in Table 3. Recommendations from the 2012 guideline that should be revisited are outlined in Supplementary Table S2.

LUPUS NEPHRITIS

Terminology

LN is histologically classified by the International Society of Nephrology/Renal Pathology Society system,[73] but this classification does not consider tubulointerstitial injury, vascular lesions, or podocytopathies.[74–76] Patients with tubulointerstitial injury, thrombotic microangiopathy (TMA), and renal vasculitis have worse outcomes.[74,75,77–80] Additionally, the International Society of Nephrology/Renal Pathology Society classification lacks sufficient quantification of disease activity and chronicity, and descriptive categories lack clear prognostic value. An evidence-based approach is needed to better define clinically relevant categories within the class III/IV spectrum, including the significance of segmental necrotizing lesions,[81,82] along with the development of LN activity and chronicity indices that accurately identify patients who would benefit from immunosuppression. An international working group of leading nephropathologists recently proposed updates to the International Society of Nephrology/Renal Pathology Society classification system to address limitations within the current system.[83]

According to the Systemic Lupus International Collaborating Clinic diagnostic criteria for systemic lupus erythematosus (SLE), immune complex GN consistent with LN in the setting of a positive antinuclear antibody or anti–double-stranded DNA is sufficient for diagnosing SLE.[84] Systemic Lupus International Collaborating Clinic criteria demonstrated increased sensitivity when compared with American College of Rheumatology classification with similar specificity in the validation cohort.[84] However, when applied to a cohort of patients with immune complex GN, the Systemic Lupus International Collaborating Clinic criteria demonstrated decreased specificity compared with those of the American College of Rheumatology, with some patients incorrectly identified as having SLE.[85] Nonetheless, the Systemic Lupus International Collaborating Clinic criteria allow giving patients with lupus-like conditions a label, which may help in coping with disease and for insurance and medication coverage.

Pathogenesis

The pathogenesis of LN involves genetic, epigenetic, immunoregulatory, hormonal, and environmental phenomena.[86] Multiple gene polymorphisms have been associated with an increased risk of SLE and/or LN;[87] many of them involve immune cells and immunoregulatory pathways.[86–88] Presently, there is no clear clinical benefit from genetic testing. However, identification of these polymorphisms has given insight into pathways involved in the pathogenesis of LN.[87,89,90] LN patients of African ancestry with apolipoprotein L1 risk alleles are at increased risk for worse renal outcomes;[91] however, *APOL1*

Table 2 | KDIGO clinical practice guideline on the treatment of HCV-associated glomerulonephritis

Renal presentation	Treatment
Stable kidney function and/or nonnephrotic proteinuria	Direct-acting antiviral therapy
Cryoglobulinemic flare, nephrotic syndrome, or rapidly progressive kidney failure	Direct-acting antiviral therapy with immunosuppressive treatment, with or without plasma exchange
Histologically active HCV-associated glomerulonephritis that does not respond to direct-acting antiviral therapy	Rituximab as first-line immunosuppressive treatment

HCV, hepatitis C virus; KDIGO, Kidney Disease: Improving Global Outcomes.
From the KDIGO Hepatitis C Work Group.[63]

Table 3 | Examples of future directions in studying C3 glomerulopathy, immune complex glomerulonephritis, and monoclonal gammopathies of renal significance

C3 glomerulopathy
- Establish trends in complement abnormalities with repeated testing and in the setting of treatment
- Evaluate the association of baseline kidney biopsy findings with clinical outcomes and subsequent changes in kidney biopsy histology
- Explore the association of complement testing abnormalities with response to specific anticomplement therapies

Immune complex glomerulonephritis
- Determine the diagnostic, prognostic and therapeutic value of complement testing
- Determine whether complement abnormalities are pathogenic or reflective of disease activity
- Identify glomerular antigens involved in pathogenesis

Monoclonal gammopathies of renal significance
- Define the value of performing bone marrow biopsies in patients without detectable paraproteinemia
- Perform randomized controlled trials comparing the efficacy and safety of clone-directed therapies
- Elucidate the role of autologous stem cell transplantation
- Determine optimal treatment for patients without detectable clones
- Ascertain the role for maintenance therapy

testing is not routinely available and the risks and benefits of *APOL1* testing need to be clarified.

Biomarkers and prediction of prognosis

Proteinuria, hematuria, urinary sediment, and estimated GFR. No single biomarker predicts the development of LN in patients with SLE or of LN flares in patients with quiescent disease. Proteinuria, hematuria, urinary sediment analysis, and serum creatinine (with estimated GFR)[92] remain important to diagnose LN and monitor response to therapy. The diagnosis of LN should be confirmed by biopsy.

There are limitations to these clinical markers. Repeat kidney biopsy studies have shown that patients with resolution of proteinuria and normalization of serum creatinine can still have histologic activity on biopsy and vice versa.[93–97] Studies are needed to evaluate the clinical relevance of this discordance.

Proteinuria at 1 year was the best predictor of long-term renal outcome.[98–100] Random spot urine protein-to-creatinine ratios are not sufficiently accurate to direct therapeutic changes. Such changes should be based on 24-hour urine collections for proteinuria or the urine protein-to-creatinine ratios from a 24-hour urine.[101]

Anti–double-stranded DNA, complement C3, C4, anti-C1q testing. The combination of elevated anti–double-stranded DNA, low serum complement, and anti-C1q autoantibody levels, if available, is strongly associated with renal involvement in SLE and should be monitored in patients at risk for LN or LN flare.[102,103] Levels may change several months prior to LN flare, and how these changes relate to flare prediction needs to be validated in prospective studies.

Novel urine/serum biomarkers. Several putative novel serum and urine biomarkers have been studied in LN.[104–107] These candidate markers must be studied in a prospective fashion, ideally in clinical trials. It is likely that biomarker panels will be required to accurately stratify risk, predict flare, determine treatment, monitor response to treatment, and predict prognosis. Molecular interrogation of the kidney biopsy may help in these processes.[108–110]

Treatment

Antimalarials. Antimalarial treatment is recommended for all patients with LN. Observational and cohort studies have demonstrated that antimalarials reduce the odds of developing LN in patients with SLE and are associated with a higher likelihood of a complete renal response to treatment and a reduced likelihood of developing end-stage kidney disease.[111–114]

Corticosteroids. Corticosteroids, although almost universal in LN regimens, are associated with significant short- and long-term adverse effects. Patients with LN are more likely to develop corticosteroid-associated organ damage than are SLE patients without nephritis.[115] Moderate doses are not safer and are associated with as many adverse effects as high doses are.[116] Therefore, although not possible for all patients, an attempt to minimize corticosteroids (e.g., prednisone equivalent $\leq$5 mg/d) during LN maintenance therapy, should be made. Regimens with reduced or no oral corticosteroids and rapid tapering protocols are under investigation[93,117,118] (Aurinia Renal Response in Active Lupus With Voclosporin [AURORA], NCT03021499; Safety and Efficacy of Two Doses of Anifrolumab Compared to Placebo in Adult Subjects With Active Proliferative Lupus Nephritis [TULIP-LN1], NCT02547922).

Immunosuppressive therapy. While CYC- or MMF-based regimens for remission induction remain the gold standard therapy for most patients, CNI-based regimens have been studied in Asia, and they often combine MMF and corticosteroids with a CNI.[119] A large Chinese multicenter RCT compared low-dose MMF, tacrolimus, and corticosteroids with monthly i.v. CYC and corticosteroids for induction therapy of LN. The CNI-based regimen was superior at achieving 24-week complete and partial renal remissions.[119] However, the cumulative response rates were similar in the 2 treatment arms with extended follow-up.[120] Ongoing studies are addressing the role and toxicity of CNI-based regimens in ethnically diverse populations. Protocol biopsies in clinical trials using CNIs will help clarify immunologic responses as CNIs can reduce proteinuria by nonimmunologic mechanisms.

Maintenance treatment. Maintenance treatment after induction typically consists of MMF or azathioprine (AZA) with or without low-dose corticosteroids. It is not clear how long to continue maintenance. In recent clinical trials, the duration of maintenance has been 3 to 5 years, and many patients remained on maintenance therapy for 10 years.[121,122] A minimum of 3 years of maintenance is suggested. A maintenance withdrawal trial is underway (Randomized MMF Withdrawal in Systemic Lupus Erythematosus [ALE06]; NCT01946880). Prolonged maintenance for "high-risk" groups (Table 4) may be considered.

Preliminary studies suggest that intensive B-cell depletion with a RTX plus CYC-based regimen may avoid the need for maintenance therapy.[117] This must be verified in large studies.

Table 4 | | Lupus nephritis patients at high risk for poor renal outcome (risk increases with the number of risk factors present)

Patient characteristics	Serologic characteristics	Histologic characteristics
• African or Hispanic ancestry • Male • Pediatric onset • Frequent relapses • Incomplete remission • Neuropsychiatric lupus • Proteinuria >4 g/d at diagnosis	• Antiphospholipid antibodies or antiphospholipid syndrome • Persistent hypocomplementemia • High titer dsDNA antibodies • High titer C1q antibodies	• Crescentic glomerulonephritis • Thrombotic microangiopathy • Extensive tubulointerstitial damage

dsDNA, double-stranded DNA.

Slowly withdrawing immunosuppression could be considered in patients with complete clinical remission. A repeat kidney biopsy may be helpful to exclude persistent but clinically silent histologic activity. Patients should be closely monitored for relapse after decreasing or discontinuing maintenance therapy.[123–127]

Refractory disease. LN may be considered refractory if a patient does not respond to either of the currently standard induction therapies (CYC or MMF) used sequentially. A suggested algorithm for refractory disease is illustrated in Figure 1. Medication adherence should always be evaluated. Repeat kidney biopsy to distinguish active LN from scarring and/or identify new lesions could be considered. For persistently active LN, if MMF was used for induction, consider switching to CYC or vice versa. After this, RTX or CNI-based regimens could be tried.[117,119,128–131]

Special circumstances

Class V LN. There is consensus that class V LN with persistent nephrotic proteinuria should receive immunosuppression, but some would also treat patients with lower levels of proteinuria.[132] The level of proteinuria at which immunosuppressive therapy may provide benefit therefore needs to be established. Class V LN is often treated initially with MMF, but if not effective, CYC may be used. Some investigators also suggest using CNIs for class V LN. RTX may be considered in the treatment options for class V LN.[133]

TMA. TMA with LN on kidney biopsy may be due to antiphospholipid antibodies/syndrome ([APS], anti-cardiolipin antibodies, anti-β2 glycoprotein I, and lupus anticoagulant), thrombotic thrombocytopenic purpura, or atypical hemolytic uremic syndrome.[134,135] Treatment should be guided by the underlying etiology of TMA.[134] Plasma exchange is indicated for thrombocytopenic purpura, but it may also be beneficial in cases of refractory APS.[136,137] Anti-complement therapies may be considered in catastrophic APS, thrombocytopenic purpura, complement-mediated TMA, and recurrent TMA in an allograft.[138–141] Anti-coagulation remains the standard of care when APS is present.[142] However, the impact of anticoagulation on renal

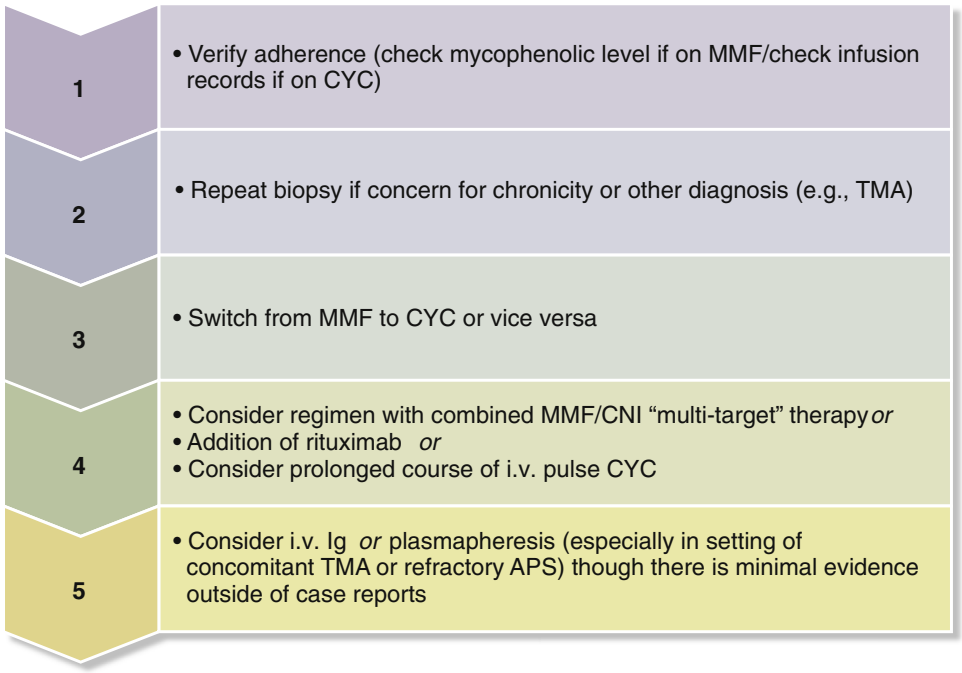

Figure 1 | Algorithm for refractory disease in lupus nephritis. APS, antiphospholipid syndrome; CNI, calcineurin inhibitor; CYC, cyclophosphamide; MMF, mycophenolate mofetil; TMA, thrombotic microangiopathy.

lesions is unclear, and many patients experience a decline in kidney function despite therapeutic anticoagulation.[143] Mammalian target of rapamycin inhibition increased kidney transplant survival in patients with a history of APS nephropathy, but further studies are needed in native kidneys.[144]

Pregnancy. Patients who are on MMF maintenance and wish to become pregnant should be switched to AZA, as MMF is teratogenic. Similarly, renin-angiotensin system blockers should be stopped before conception. CNIs may be considered for treatment of LN in pregnancy if AZA cannot be tolerated, as adjunct therapy with AZA in severe cases or as primary therapy for class V LN with nephrotic syndrome.[145]

Posttransplant. Patients with LN have equivalent or better outcomes following kidney transplantation compared with other primary glomerular diseases.[146] Clinically significant LN posttransplant recurs in <20% of patients.[147–151] Patients should remain on hydroxychloroquine posttransplant and be on MMF/CNI-based immunosuppressive regimen. Patients with mild flares can be treated with oral corticosteroids alone. Patients with moderate flares should be treated with i.v. corticosteroids and increased MMF. Patients with crescentic disease/severe flare should be treated with i.v. corticosteroids and CYC. MMF should be held while patient is on CYC therapy.

Pediatric-onset disease. Pediatric-onset LN, occurring before age 16, needs further study but children are excluded from adult LN trials. Children often have few comorbidities, but they exhibit more severe disease with a higher genetic contribution. There is consensus for response, relapse, and treatment for children with proliferative LN.[152] Children with class V LN tend to need additional immunosuppression even with subnephrotic proteinuria.[153,154] The Single Hub and Access Point for Paediatric Rheumatology in Europe initiative has recently published recommendations for the treatment of children with LN.[155]

Future studies

Class III/IV LN should be studied separately from class V LN in view of their different disease courses. Data are needed to assess benefits of treating class V LN patients with subnephrotic proteinuria. Validated histological activity indices are also needed. Clinical trials should require a recent (≤3 months) kidney biopsy, and trial duration should be at least 12 months for induction therapies and longer to assess relapse rates. Patient-reported outcomes should be integrated into future studies and biomarkers of prognosis and response are needed. Recommendations from the 2012 guideline that should be revisited are outlined in Supplementary Table S3.

ANCA-ASSOCIATED VASCULITIS

Terminology

ANCA-associated vasculitis (AAV) represents a group of small vessel vasculitides that include granulomatosis with polyangiitis (GPA), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis.[156] Renal-limited vasculitis can also occur. Kidney histology shows pauci-immune, focal necrotizing, and crescentic GN. Pauci-immune refers to the paucity but not absence of immune and complement deposits.

AAV is characterized by ANCA specific for myeloperoxidase (MPO-ANCA) or proteinase 3 (PR3-ANCA). Rare patients with pauci-immune GN are negative for ANCA, but they are considered in the same spectrum of diseases. There is some evidence that a percentage of these cases may vary in ANCA detectability when tested by different assays.[157]

Classifying patients as having GPA or microscopic polyangiitis might some provide prognostic information, but ANCA serology (MPO- or PR3-ANCA) is more relevant as it seems to predict outcomes and risk of relapse better.[158,159] A genetic component exists in AAV and genetic distinctions between GPA and microscopic polyangiitis are associated with ANCA specificity.[160]

Pathogenesis

The pathogenesis of AAV involves genetic, epigenetic, immunoregulatory, hormonal, and environmental phenomena. The relative contribution of each of these factors may vary in an individual patient. Polymorphisms associated with an increased risk of AAV particularly involve the human leukocyte antigen system (immune regulation) and target antigen (in anti-PR3 disease).[160] A role for complement activation in the pathogenesis of ANCA-associated nephritis (AAN) has emerged from therapeutic studies with complement inhibitors.[161,162]

Biomarkers and prediction of prognosis

Proteinuria, hematuria, urinary sediment, and estimated GFR. Proteinuria, hematuria, urinalysis, estimated GFR, and kidney biopsy are important clinical tools for the diagnosis and management of AAN.[163] At present, there is no biomarker that can be used to predict the development of AAN or disease flares.

ANCA. Both an increase in ANCA titer and persistently positive ANCA are modestly but significantly associated with disease relapse, although serial ANCA testing is not sufficiently robust to trigger changes in therapy.[164] Disease relapse is more frequent in PR3-ANCA than in those who are MPO-ANCA, and relapse may be predicted by PR3-ANCA levels.[158,159]

Novel urine/serum biomarkers. The Birmingham Vasculitis Activity Score and the Vasculitis Damage Index utilize traditional clinical and laboratory biomarkers to evaluate vasculitis activity and are valuable research tools.[165,166] However, traditional laboratory measures do not differentiate between active disease and chronic damage very well. In a *post hoc* analysis of the Rituximab for ANCA-Associated Vasculitis (RAVE) study, chemokine C-X-C motif chemokine ligand 13, matrix metalloproteinase-3, and tissue inhibitor of metalloproteinases-1 discriminated active from inactive AAV better than erythrocyte sedimentation rate and C-reactive protein did.[167] Tissue inhibitor of metalloproteinases-1 was the best marker of AAV activity as reported in the Remission Induction Therapy in Japanese Patients With AAV and Rapidly Progressive Glomerulonephritis (RemIT-JAV-RPGN) study.[168] Urinary soluble CD163 levels are also promising for identifying active renal vasculitis.[169] These biomarkers need independent and, ideally, prospective validation.

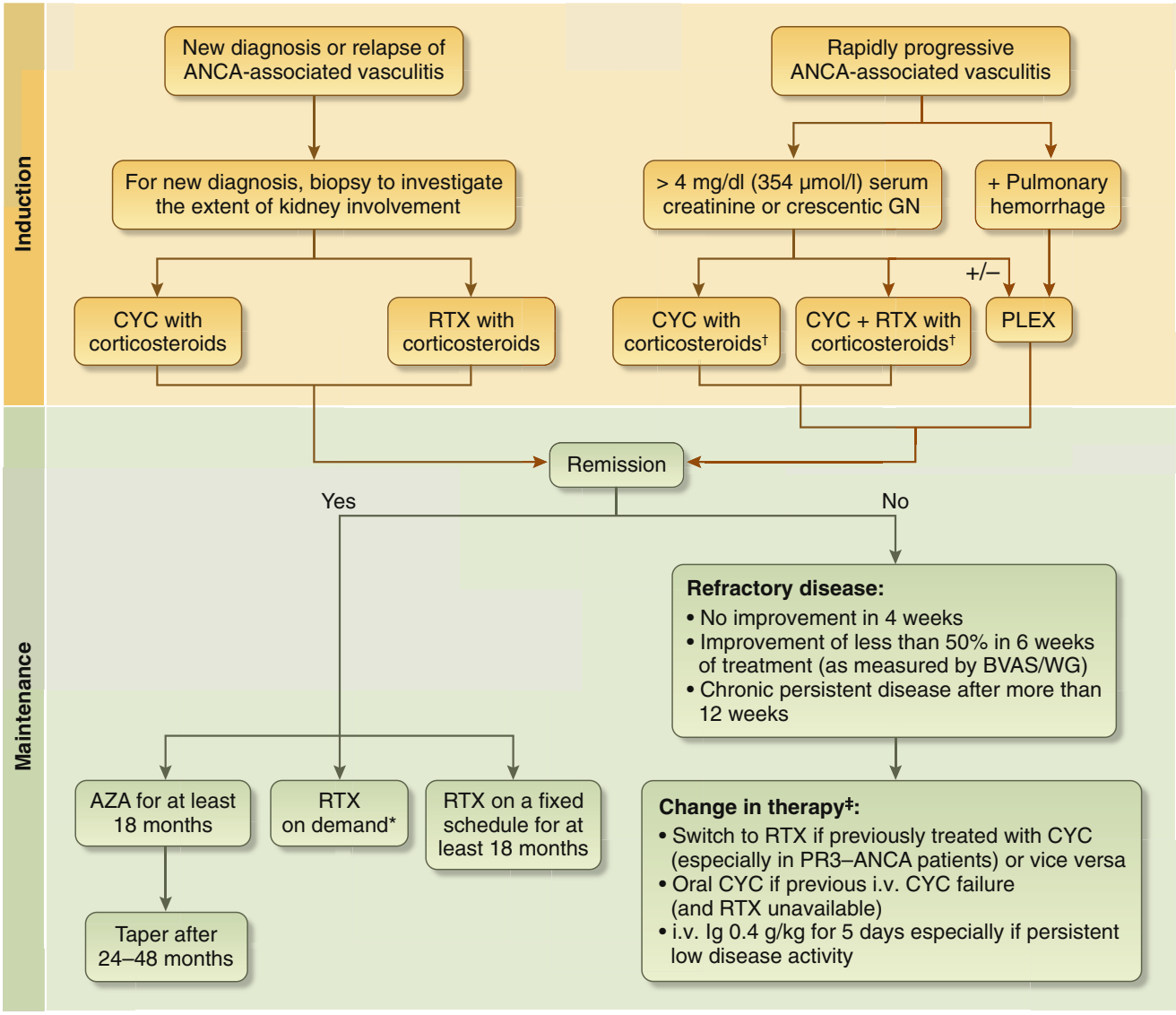

Figure 2 | Treatment algorithm for anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitis. Remission is defined by the absence of manifestations of vasculitis and glomerulonephritis disease activity (Birmingham Vasculitis Activity Score for Wegner granulomatosis [BVAS/WG] of 0). For glomerulonephritis (GN), remission is considered as absence of microscopic hematuria and improved proteinuria and glomerular filtration rate. *Based on peripheral B-cell repopulation plus ANCA reappearance. †In patients with rapidly deteriorating kidney function, corticosteriods are often initiated i.v. as pulse doses of 500 to 1000 mg/d methylprednisone and given for 1 to 3 days before converting to an oral formulation. ‡Consider re-biopsy in order to guide second-line therapy. AZA, azathioprine; CYC, cyclophosphamide; PLEX, plasma exchange; PR3, proteinase 3; RTX, rituximab.

Treatment

An algorithm for the treatment of AAV is given in Figure 2.

Corticosteroids. Corticosteroids are used almost universally for AAV and are often given as 500- to 1000-mg i.v. pulses daily for 1 to 3 days at the initiation of treatment, especially in patients with a clinical picture of rapidly progressive GN. However, corticosteroid monotherapy is not effective and corticosteroids are associated with significant short- and long-term adverse effects. However complement inhibition is on the horizon as an adjunct/steroid-sparing therapy in AAV/AAN.[170]

Induction. CYC has been the immunosuppressant of choice for decades. Despite its efficacy in the management of AAV, its safety profile has required the need for testing the value of alternative options. Recently, RTX has been proven to be as effective as CYC induction/AZA maintenance for AAN patients with serum creatinine <4 mg/dl (354 µmol/l).[171–173] An alternative approach includes the use of CYC for the induction phase and considers RTX for maintenance. It is unknown whether treatment should be different for MPO-ANCA and PR3-ANCA, however a *post hoc* analysis of RAVE suggested RTX was superior to CYC for PR3-ANCA and as effective as CYC for MPO-ANCA.[174] In a pooled analysis of the Comparison of Methotrexate or Azathioprine as Maintenance Therapy for ANCA-Associated Vasculitides (WEGENT) and RAVE trials, clinical differences between

MPO- and PR3-ANCA-positive patients with GPA were not obvious. The risk of relapse was associated more closely with disease type than ANCA subset.[175]

In patients with median GFR <20 ml/min per 1.73 m^2, a RTX-based regimen (An International, Randomized, Open Label Trial Comparing a Rituximab-based Regimen With a Standard Cyclophosphamide/Azathioprine-based Regimen in the Treatment of Active, Generalized ANCA-Associated Vasculitis [RITUXVAS] trial) consisting of a combination of corticosteroids, RTX 375 mg/m^2 per week for 4 weeks, and 2 i.v. CYC pulses followed by low-dose corticosteroids was found to be equal to the administration of standard corticosteroids with i.v. CYC for 3 to 6 months followed by AZA.[176] At 24 months, the composite outcome of death, end-stage kidney disease, and relapse did not differ between groups. Relapses occurred in 21% of patients in the RTX group and 18% of the control group.[177]

Maintenance treatment. In AAN, maintenance therapy is initiated after remission is achieved, usually within 3 to 6 months after beginning induction and typically consists of AZA or RTX. There is no consensus regarding the length of maintenance therapy in AAV. Duration may be different depending on the underlying ANCA serology as well as treatment, but this has not been adequately studied.

For conventional therapy with CYC induction and AZA maintenance, the relapse rate was lower if maintenance was continued for 48 as opposed to 24 months.[178] Alternatively, patients with MPO-ANCA who achieve remission and ANCA negativity at end of induction might require a shorter course of maintenance. This is based on the observation that most patients with MPO–microscopic polyangiitis given a single course of 6 rituximab infusions without any maintenance therapy did not relapse for a mean of 66 months.[179] However, it is unlikely that this observation applies to MPO-GPA.[175] Retrospective and prospective studies have used RTX for remission maintenance in AAV, but there has been no consensus on dosing for maintenance or even induction therapy (Table 5).[172,177,180-186] It is also not clear whether rituximab should be given as a fixed regimen or only when B cells reappear, but this is being tested by the Comparison Study of Two Rituximab Regimens in the Remission of ANCA-Associated Vasculitis (MAINRITSAN 2; NCT01731561).

Refractory disease. In a patient with worsening creatinine and/or proteinuria after initial therapy, medication adherence should be evaluated. Additionally, a repeat kidney biopsy to distinguish active AAV from scarring and/or identify new lesions could be considered. For continued active AAV lesions, initial treatment should change to the other standard-of-care regimen (i.e., switch from CYC to RTX or vice versa).

Special circumstances

Role of plasma exchange. Plasma exchange should be considered in AAN with severe renal impairment (serum creatinine >5.6 mg/dl [495 μmol/l]) and/or diffuse crescents. Plasma exchange may also have a role in AAV with pulmonary hemorrhage. The role of plasma exchange in patients with pulmonary hemorrhage and/or less severe renal impairment is being studied in the Plasma Exchange and Glucocorticoids for Treatment of Antineutrophil Cytoplasm Antibody–Associated Vasculitis (PEXIVAS) trial (NCT00987389).

Table 5 | Examples of various rituximab-based regimens for induction and remission in AAV that have been used in the literature

Induction
Four weekly i.v. doses of 375 mg/m^2,[171,172] or 2 biweekly doses of 750 mg/m^2 (maximum dose 1000 mg)[182]
Four weekly i.v. doses of 375 mg/m^2 and 1 monthly infusion 1 and 2 months apart[179,186]
Maintenance
750 mg/m^2 (maximum dose 1000 mg) every 6 months[180–183]
750 mg/m^2 (maximum dose 1000 mg) every 4 months[181]
750 mg/m^2 (maximum dose 1000 mg) every 6 months for 24 months[184]
750 mg/m^2 (maximum dose 1000 mg) every 12 months[183]
375 mg/m^2 every 6 months[183]
500 mg on days 1 and 15, then 5.5 months later, and again every 6 months for a total of 5 doses over 18 months[185]

AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis.

Childhood-onset disease. AAV in children should be studied separately from AAV in adults.[187] Pediatric scoring tools for disease activity and damage have been developed. There is a high frequency of kidney disease (75%) among pediatric AAV patients and a predominance of female subjects (65%, compared with 40%–45% in adult cohorts).[188] There have not been any randomized controlled trials in children, but cohort studies support efficacy of both CYC and RTX.[189,190]

Future studies

Future studies should further investigate the CYC-sparing effect of biological agents (e.g., anti-B-cell therapies) and the steroid-sparing effect of newer agents, such as complement inhibitors.

The clinical role and the cost-effectiveness of RTX in severe kidney disease and optimal maintenance regimens remain undefined.

Future clinical trials in AAV should target subgroups of patients stratified according to ANCA subtype, identification of high-risk patients (e.g., with comorbidities), and differentiation between active versus chronic disease by noninvasive biomarkers.

The choice of appropriate endpoints is crucial and should be addressed in future research. Similarly, determining optimal time for assessing primary endpoint and the minimum duration of clinical trial/follow-up has to be further investigated (expert consensus has suggested a minimum of 12 to 24 months). Moreover, patient-reported outcome measures and side effects need to be incorporated. Recommendations from the 2012 guideline that should be revisited are outlined in Supplementary Table S4.

CONCLUSIONS

Since the first KDIGO GN guideline published in 2012, important progress has been made in defining diseases

(e.g., C3G), improving diagnostics (e.g., antiphospholipase A2 receptor), identifying relevant biomarkers (e.g., DNA J homolog subfamily B member 9), and applying new therapies (e.g., rituximab in AAN). However, for any single glomerular disease, we are still missing 1 or more crucial pieces necessary for optimal clinical management. Considerations around treatment futility and patient-centered outcomes, which are important for all glomerular diseases, are just emerging. This Controversies Conference may be best summarized as an honest assessment of where we are currently and a roadmap of where we need to be.

APPENDIX

Other Conference Participants

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DISCLOSURE

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SUPPLEMENTARY MATERIAL

Table S1. 2012 Kidney Disease: Improving Global Outcomes (KDIGO) glomerulonephritis (GN) guideline recommendations related to minimal change disease, focal segmental glomerulosclerosis (FSGS), steroid-sensitive nephrotic syndrome (SSNS), and steroid-resistant nephrotic syndrome (SRNS): Need to be revisited?

Table S2. 2012 Kidney Disease: Improving Global Outcomes (KDIGO) glomerulonephritis (GN) guideline recommendations related to idiopathic membranoproliferative glomerulonephritis: Need to be revisited?

Table S3. 2012 Kidney Disease: Improving Global Outcomes (KDIGO) glomerulonephritis (GN) guideline recommendations related to lupus nephritis: Need to be revisited?

Table S4. 2012 Kidney Disease: Improving Global Outcomes (KDIGO) glomerulonephritis (GN) guideline recommendations related to anti-neutrophil cytoplasmic antibody–associated vasculitis (AAV): Need to be revisited?

Supplementary material is linked to the online version of the paper at www.kidney-international.org.

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