KDOQI US Commentary on the 2021 KDIGO Clinical Practice Guideline for the Management of Glomerular Diseases

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The KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases represents the first update to this set of recommendations since the initial set of KDIGO guideline recommendations was published in 2012. The pace of growth in our molecular understanding of glomerular disease has quickened and a number of newer immunosuppressive and targeted therapies have been introduced since the original set of guideline recommendations, making such an update necessary. Despite these updates, many areas of controversy remain. In addition, further updates since the publication of KDIGO 2021 have occurred which this guideline does not encompass. With this commentary, the KDOQI work group has generated a chapter-by-chapter companion opinion article that provides commentary specific to the implementation of the KDIGO 2021 guideline in the United States.

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Because they are designed to reflect the views and recommendations of the responsible KDOQI Commentary work group and they are reviewed and approved by KDOQI and NKF leadership KDOQI Commentaries are not peer reviewed by AJKD. *This article was prepared by a KDOQI Commentary work group comprising the authors and cochaired by Drs William Whittier and Laurence Beck. It was reviewed and approved by the NKF Scientific Advisory Board and the KDOQI Chair and Vice Chairs for Commentaries and Education.*

Introduction

The *KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases* represents a substantial and important update to the initial 2012 guideline. The past 10 years have witnessed an increasing understanding about the molecular underpinnings of and distinctions between categories of glomerular disease, as well as novel immunosuppressive therapies and others such as sodium/glucose cotransporter 2 (SGLT2) inhibitors. These advances are ongoing, and the 2021 KDIGO guideline is designed to be a living document, responsive to important new findings in the fields. In this KDOQI Commentary, we have placed the 2021 KDIGO guideline into perspective for a US audience and have provided our commentary reflecting updates, clarifications, challenges, and additional considerations as a companion to the KDIGO guideline.

Review and Approval Process for This Commentary

The KDOQI Steering Committee selected co-chairs and members of the KDOQI Work Group based on their clinical and research expertise as well as interest in the guideline process or familiarity with kidney disease quality metrics. During the selection process, particular emphasis was placed on identifying individuals with diverse perspectives and with experience in taking care of adult and pediatric patients with chronic kidney disease (CKD) and glomerulonephritis (GN).

KDOQI Work Group members worked in groups of 2 to review recent literature and provide commentary on the KDIGO guideline practice points and recommendations, focusing on their clinical utility and implementation in the United States. The work group discussed the guideline via teleconference, and all work group members and KDOQI leadership reviewed and approved the commentary. Our review and commentary follow the same order and numbering scheme that was used in the guideline. All material quoted from the KDIGO guideline is reproduced with permission of KDIGO and is reproduced verbatim, except that any reference numbers included in the original were omitted.

Guideline Statements and Commentary: General Principles for the Management of Glomerular Disease

The lead-off chapter of the KDIGO guideline is an important reference chapter, as it broadly covers aspects in the treatment of glomerular diseases that should be considered in all patients.[1] Most practitioners diagnosing and treating glomerular diseases should be familiar with these topics, which are not typically duplicated in more specific, disease-centered chapters that follow.

This chapter contains no evidence-based recommendations but is filled with practice points that cover 18 topics matching the headings of the following sections, with the exception that dietary management in glomerular disease is discussed in the guideline but not commented on here.

Further, there is not space in this commentary to list or comment on all practice points, or even most, and the reader is referred to the actual KDIGO chapter to understand the scope and content of the information presented. However, we have selected what we feel are the most impactful or controversial points for commentary herein.

Kidney Biopsy

The first 4 sections focus on diagnosis and assessment of kidney function, proteinuria, and hematuria. The guideline contains a discussion of the need for kidney biopsy and the minimum standards for adequacy, pathologic assessment, and consideration of repeat biopsy. Importantly, the guideline indicates that while kidney biopsy is still the gold standard for diagnosing the overall type of glomerular disease and can give important information about activity versus chronicity or dual diagnoses, there are certain situations in which a biopsy might not be necessary (ie, with childhood nephrotic syndrome, in the presence of certain serological markers such as antineutrophil cytoplasmic antibody [ANCA] or anti–M-type phospholipase A_2 receptor [anti-PLA_2R] antibodies, or with a known familial genetic nephropathy).

Assessment of Kidney Function

The next section relates to assessment of kidney function in terms of proteinuria and estimated glomerular filtration rate (eGFR). These 2 assessments are singled out since they are used for prognosis, treatment decisions, and are key outcomes for individual patients and in clinical trials.

Proteinuria

Practice Point 1.2.1: Obtain 24-hour urine collection to determine total protein excretion in patients with glomerular disease for whom initiation or intensification of immunosuppression is necessary, or who have a change in clinical status.

The guideline discourages random (spot) urinary protein-creatinine (UPCR) assessments in patients with glomerular disease. While we agree that a properly performed 24-hour urine collection is a more accurate quantitation of daily proteinuria, its standard use for clinical care is center dependent and may not be feasible in some situations. In addition, in clinical practice, 24-hour urine collections are cumbersome and prone to error. We agree that timed collections may be the gold standard in a clinical trial, in which different patients are compared with each other, to delineate proteinuria cut points and determine relative or absolute remission rates. In clinical practice, however, a trend in spot UPCR in an individual patient over time provides meaningful input about improving or worsening glomerular disease. This trend in spot UPCR, coupled with trends in serum albumin in an individualized patient is considered informative in clinical practice to initiate, intensify, or de-escalate therapy without confirming with a timed urine collection.[2] If using the spot UPCR, efforts should be made to collect samples at the same time of day with similar activity, often with the first morning sample providing the most consistency.

In Figure 4, which appears on page S91 of the guideline, there is a typographical error in the non–nephrotic-range proteinuria section. Instead of "<300 mg/g (<30 mg/mmol)" for UPCR, the values should be <3,000 mg/g (<300 mg/mmol) or <3,500 mg/g in order to correspond to the traditional thresholds for nephrotic-range proteinuria.

Estimation of GFR

The section on assessment of eGFR was written prior to the recent deliberations about the use of race in GFR estimation questions, and the reader is referred to several articles about this topic.[3–5] Outside of this guideline, it has been recommended that only age- and sex-based formulas are appropriate (eg, 2021 CKD-EPI creatinine equation), as opposed to the MDRD Study or 2009 CKD-EPI creatinine equations that include a race factor. Cystatin C may also add benefit, although obtaining this test is more difficult and is often a send-out test, delaying time-sensitive information. Although not affected by muscle mass, cystatin C levels may be increased by glucocorticoids and inflammation. Implementation may initially be a challenge as electronic medical records replace old formulas with the new one(s).

In children, KDIGO recommends use of the modified Schwartz formula or Full Age Spectrum formulas.[6,7]

We agree with the KDIGO guideline highlighting that all eGFR formulas, including non–race-based or cystatin C–based formulas, have not been established or validated in patients with glomerular disease. In addition, equations based on serum creatinine (Scr) may overestimate eGFR in the nephrotic syndrome with hypoalbuminemia.

Evaluation of Hematuria

While KDIGO recommends microscopic evaluation of hematuria and discusses both dysmorphic/small red blood cells (RBCs) (>50%-80% of RBCs), acanthocytes (>5%), and RBC casts as markers for inflammatory glomerular disease, there is little discussion of the clinical utility or significance of white blood cell (WBC) casts (which are admittedly not specific to glomerular disease) or lipiduria. Due to the variable presence of appropriate clinical centrifuges and microscopes, such inspection of the urine sediment is not always available, and the practitioner is left relying on a description of a central laboratory, with variable accuracy. Certification for examination of the urinary sediment also limits its use by some nephrologists. However, we feel that examination of the urinary sediment is an essential tool for the nephrologist with an interest in glomerular disease, and all attempts should be made to allow routine performance and teaching of this skill. Therefore, we agree with Practice Points 1.3.1, which calls for routine evaluation of urine sediment for dysmorphic

RBC and RBC casts in all forms of GN, and 1.3.2, which discusses the possible prognostic value of periodic monitoring of "magnitude and persistence" of hematuria in many forms of glomerular disease, especially in immunoglobulin A nephropathy (IgAN) and IgA vasculitis (IgAV).

Management of Complications of Glomerular Disease

This section identifies edema, proteinuria, and hypertension as the main complications that require general supportive therapy. Figure 6 in the guideline provides a reasonable overview and "checklist" of general and disease specific recommendations that should be considered for a patient with glomerular disease.

The focus is on sodium retention and volume overload, use of diuretics, including mechanisms of resistance, classes, routes, specific circumstances (eg, intravenous albumin), and dietary sodium restriction. We agree with these general recommendations.

Management of Hypertension and Proteinuria Reduction in Glomerular Disease

We agree with these practice points about the use of diuretics and renin-angiotensin-aldosterone system (RAAS) inhibitors. We would like to particularly emphasize 2 points in this section.

> Practice Point 1.5.6. Counsel patients to hold ACEi or ARB and diuretics when at risk for volume depletion.

As most patients with glomerular disease are treated with these agents, it is important to discuss and reinforce these "sick day rules" to avoid hemodynamic- and volume-related acute kidney injury (AKI) in settings of diarrhea, vomiting, excessive sweating, or inadequate fluid intake. We acknowledge that this routine practice has been challenged and that controversy remains due to lack of clinical evidence.[8]

Within the text of the guideline, it is also noted that the widely used dihydropyridine calcium channel blockers (eg, amlodipine and nifedipine) not only exacerbate edema but also have little impact on proteinuria and may even increase proteinuria. Therefore, in the event of increasing proteinuria in a patient on one of these agents, discontinuation and/or substitution with another antihypertensive should be considered prior to concluding that immunosuppression is necessary.

Management of Hyperlipidemia in Glomerular Disease

Hyperlipidemia is often a consequence of the nephrotic syndrome, but may also be impacted by genetics, diet, and the effects of immunosuppression (corticosteroids, mammalian target of rapamycin [mTOR] inhibitors, and calcineurin inhibitors [CNIs]). We agree with the general discussion and points made about this topic.

Hypercoagulability and Thrombosis

Venous thromboembolic disease is another cause of morbidity in the nephrotic syndrome, more common in membranous nephropathy (MN) than other nephrotic disorders. This often occurs within the first 6 months of diagnosis, and at increasing frequency with a serum albumin level of less than 2.9 g/dL. Treatment doses of unfractionated or low-molecular-weight heparin or warfarin are the preferred agents for treatment or prevention in those felt to have thromboembolic risk greater than bleeding risk (based on the online tool at www.med.unc.edu/gntools/bleedrisk.html). It is noted that factor Xa inhibitors and direct thrombin inhibitors have significant/moderate albumin binding and are therefore lost in nephrotic urine, and pharmacokinetics are not well studied. Despite several favorable clinical case reports detailing the use of factor Xa inhibitors in the nephrotic syndrome, these popular agents are not recommended at this time.

Risks of Infection

Infection risk is heightened in glomerular disease, due both to the underlying disease and loss of immune factors in the urine and more importantly to the potent immunosuppressive agents used in the treatment of many glomerular diseases.

Screening for latent diseases such as tuberculosis, hepatitis B and C viruses (HBV and HCV), human immunodeficiency virus (HIV), and syphilis (Practice Point 1.8.2) is an important consideration, as is ruling out *Strongyloides* infection in patients with increased risk and an elevated peripheral eosinophil count (Practice Point 1.8.3). Gathering a travel history, especially in those who have recently immigrated to the United States, is essential to assessing risk.

We agree with the recommendations for vaccinating against encapsulated organisms, especially when using complement inhibitors, and the use of trimethoprim-sulfamethoxazole or equivalent for *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis when using a daily prednisone equivalent dose of ≥20 mg as well as other immunosuppression such as cyclophosphamide or rituximab.

Practice Point 1.8.1 recommends influenza, pneumococcal,[9] and varicella vaccines[10] for all patients with nephrotic syndrome, a practice that may be utilized more often in children. We would additionally recommend that all eligible and willing patients be immunized against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Outcome Measures

The specific practice points in this section are limited: Practice Point 1.9.1 states that goals for proteinuria reduction vary by disease and Practice Point 1.9.2 reports that a drop in eGFR > 40% over 2-3 years may be a surrogate outcome measure for kidney failure. This particular outcome has been used in clinical trials; however, its use in

practice for guiding initiation or withdrawal of immunosuppression is unclear.

The text provides a good discussion of topics beyond these 2 practice points. One notable statement is that most clinical trials are of insufficient duration to assess many traditional or even newer outcome measures; most focus instead on the surrogate outcome measures mentioned above. Outcome measures also vary based on disease and tend to undervalue patient-reported outcomes such as quality of life.

Impact of Age, Sex, Ethnicity, and Genetic Background

This section comments on the uncertainty about the generalizability of clinical trial results across the age spectrum and across different ethnicities and genetic backgrounds, suggesting that additional research is needed to assess for differences in treatment or outcomes.

Genomics, Transcriptomics, Proteomics, Metabolomics

The guideline acknowledges that the ultimate goal in the treatment of glomerular disease will be personalized or precision medicine using omics data. We are perhaps closest to this goal in the recent appearance of genetic test kits that can screen for proteinuric disorders. However, this is clearly still an evolving field.

Use of Glucocorticoids and Immunosuppressive Therapy

The Practice Points detailed in this section (1.13.1-1.13.3; Figure 15) guide the practitioner and patient to choose an immunosuppressive regimen that (1) averts immediate morbidity from the glomerular disease, (2) prevents the disease process from progressing, while (3) minimizing adverse effects from the treatment itself. Figure 14 provides a reasonable checklist of factors to screen or provide prophylaxis for prior to choosing a particular immunosuppressive regimen.

The guideline emphasizes that a discussion between practitioner and patient should include a full disclosure of the early and late risks specific to each potential drug regimen. Discussion of infection and malignancy risk is particularly important when the immediate risk from disease is low or the evidence for treatment is weak, but there is strong evidence for adverse effects of therapy.

We agree with the general discussion of risks of corticosteroids, CNIs, and cyclophosphamide. Discussion of risks of mTOR inhibitors, mycophenolate, azathioprine, eculizumab, or other new drugs for lupus are not included in this general overview.

Pharmacologic Aspects of Immunosuppression

This section discusses the rationale for following levels of CNIs, although no specific guidance is provided. We agree with the recommendation to follow levels when initially starting therapy to find an effective dose that allows trough levels in the desired therapeutic range. We also agree that it is necessary to monitor drug levels at regular intervals, especially if new medications are added that might impact CNI metabolism or if Scr becomes elevated above baseline.

Pregnancy and Reproductive Health in Women With Glomerular Disease

> Practice Point 1.15.1: Care for the pregnant patient with glomerular disease needs coordination between nephrology and obstetrics, and ideally, such planning should be considered before pregnancy.

We strongly agree with the suggestion that close collaboration is necessary with an obstetrician familiar with high-risk maternal-fetal medicine (OB/MFM). Reference tables in this section provide suggestions and considerations for: coordinated care during the prepregnancy, antenatal, delivery, and postnatal phases; birth control method options to avoid unwanted pregnancy in patients with glomerular disease; and the known impacts of glomerular disease on maternal-fetal outcomes. We agree that both nephrotic diseases and pregnancy are thrombophilic states, and discussion of anticoagulation with low-molecular-weight heparin should be considered with OB/MFM in pregnant patients with proteinuria. Care should be given to avoid common medications with known teratogenicity, such as coumadin, angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blockers (ARBs), and mycophenolate mofetil (MMF).

Treatment Costs and Related Issues

This section addresses the important issues of cost and availability for the medications recommended for the treatment of glomerular disease, especially considering the availability and affordability of certain agents across countries. However, even in the United States, a patient's medical insurance and Food and Drug Administration (FDA) approval is likely to dictate which options are open for consideration in each scenario.

> Practice Point 1.16.1: Patients with glomerular disease should be offered participation in a disease registry and clinical trials, whenever available.

Registries, such as NephCure Kidney Patient Network and Kidney Health Gateway, and society-based registries and portals are important for future studies into the epidemiology, treatment, and pathophysiology of glomerular diseases. Registries can be useful to patients and families by linking patients with certain diseases with ongoing clinical trials.

Goals of Glomerular Disease Treatment

This section re-emphasizes the earlier Practice Points 1.13.1-1.13.3 but also focuses attention on the maximization of patient comfort and quality of life when

balancing benefits and risks of treatment. The consideration of patient-reported outcomes in ongoing and upcoming clinical trials may draw more attention to these important quality of life issues.

Posttransplantation GN

This brief section acknowledges that glomerular diseases can recur in the kidney allograft. There are more details provided in the disease-specific chapters.

Guideline Statements and Commentary: IgA Nephropathy

Diagnosis of IgAN

Practice Point 2.1.1: Considerations for the diagnosis of immunoglobulin A nephropathy (IgAN):

- IgAN can only be diagnosed with a kidney biopsy.
- Determine the MEST-C score (mesangial [M] and endocapillary [E] hypercellularity, segmental sclerosis [S], interstitial fibrosis/tubular atrophy [T], and crescents [C]) according to the revised Oxford Classification.
- There are no validated *diagnostic* serum or urine biomarkers for IgAN.
- Assess all patients with IgAN for secondary causes.

Commentary

IgAN is a heterogeneous disease with varying clinical and histologic manifestations. We agree with the practice point that given the lack of serum or urine biomarkers validated for the diagnosis of IgAN, a kidney biopsy is necessary to establish the diagnosis as well as to identify specific histologic findings that correlate with disease progression. The Oxford classification of IgAN was originally published in 2009[11] and underwent revision in 2016[12] to include crescents in their scoring description. The MEST-C scoring of the Oxford classification has been validated in several cohorts and provides valuable prognostic information independent of clinical characteristics.

Clinical Utility

Patients with suspected IgAN with higher levels of proteinuria or diminished or worsening eGFR warrant a kidney biopsy to confirm the diagnosis and determine risk stratification and treatment options. Patients with preserved eGFR, lower levels of proteinuria (<500 mg/g) and a low suspicion for other glomerular disorders based on serologic evaluation for glomerular disease require a patient-centered discussion on the utility of a kidney biopsy for definitive diagnosis. Reasonable alternatives include a combination of watchful waiting, trial of antiproteinuric therapy, and serial monitoring of urine protein excretion, blood pressure, and eGFR.

Implementation and Challenges

Kidney biopsy may not be initially pursued when the kidney function is normal. Instead, some patients may be suspected of having IgAN based on clinical presentation without a biopsy-proven diagnosis. Empiric therapy with ACEIs or ARBs can be started in most low-risk patients without an established histologic diagnosis, but treatment with more aggressive immunosuppressive therapy usually warrants a kidney biopsy for diagnostic and prognostic purposes.

Prognosis of Primary IgAN

Practice Point 2.2.1: Considerations for the prognostication of primary IgAN:

- Clinical and histologic data at the time of biopsy can be used to risk stratify patients.
- The International IgAN Prediction Tool is a valuable resource to quantify risk of progression and inform shared decision-making with patients.
  - Calculate by QxMD
- The International IgAN Prediction Tool incorporates clinical information at the time of biopsy and cannot be used to determine the likely impact of any particular treatment regimen.
- There are no validated *prognostic* serum or urine biomarkers for IgAN other than eGFR and proteinuria.

Commentary

New in the 2021 guideline is a practice point regarding risk stratification in IgAN. Whereas the 2012 guideline acknowledged the importance of risk assessment to determine progression of disease, there was no guidance available as to how this should be accomplished. The previous guideline noted that patients with >1 g/d proteinuria were at high risk of progression, but there were no tools to quantify this risk and guide management.

Given the aforementioned heterogeneity of IgAN and the importance of other parameters, including demographic, laboratory, clinical, and pathology data, the International IgAN Network derived and externally validated a prediction tool (Figure 20). This tool allows for 5-year risk prediction of 50% decline in eGFR or progression to kidney failure using data collected at the time of kidney biopsy.[13] An updated prediction tool has also been validated using data at 1 or 2 years after biopsy.[14] An important consideration, however, is that it is not known how this risk may be modified by choice of and response to treatment. It is also notable that this tool uses the original MEST, not the revised MEST-C score of the Oxford scoring system, as crescents were not found to be a significant predictor in model derivation.

Clinical Utility

The International IgAN Prediction Tool is freely available, can be accessed via an app or a webpage,[15] and can provide important prognostic information at the time of biopsy for both health care providers and patients. It can be used to help patients understand the common gradual progression of disease over years or decades. Lower risk

patients can be counseled on how control of factors such as blood pressure and urinary protein excretion positively impact long-term kidney health. Alternatively, in patients with more severe or advanced disease the prediction tool can be used to emphasize the need to prepare for kidney replacement therapy.

Implementation and Challenges

As acknowledged in the practice point, the IgAN Prediction Tool should not be used to determine or monitor response to therapy. Additionally, patients with variant forms of IgAN (eg, nephrotic range proteinuria, rapidly progressive GN, etc) were not included in the original cohort of patients from which the tool was derived. These special situations warrant a unique approach that is outlined in Section 2.4.

Treatment of IgAN

Practice Point 2.3.1: Considerations for treatment of all patients with IgAN who do not have a variant form of primary IgAN:

- The primary focus of management should be optimized supportive care.
- Assess cardiovascular risk and commence appropriate interventions as necessary.
- Give lifestyle advice, including information on dietary sodium restriction, smoking cessation, weight control, and exercise, as appropriate.
- Other than dietary sodium restriction, no specific dietary intervention has been shown to alter outcomes in IgAN.
- Variant forms of IgAN: IgA deposition with minimal change disease (MCD), IgAN with acute kidney injury (AKI), and IgAN with rapidly progressive glomerulonephritis (RPGN) may require specific immediate treatment.

Practice Point 2.3.2: Algorithm for the initial assessment and management of the patient with IgAN (Figure 21).

Recommendation 2.3.1: We recommend that all patients have their blood pressure managed, as described in Chapter 1. If the patient has proteinuria >0.5 g/d, we recommend that initial therapy be with either an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) *(1B)*.

Commentary

Supportive care with antiproteinuric and antihypertensive therapy has evolved substantially over the past decade. The KDIGO guideline from 2012 recommended long-term ACEI or ARB treatment for patients with IgAN and proteinuria > 1 g/d, whereas the 2021 guideline lowered the proteinuria threshold to 0.5 g/d. Perhaps even more important, the addition of drugs such as SGLT2 inhibitors to ACEI or ARB has positive long-term potential for kidney outcomes. Although there are no randomized controlled trials specific to IgAN, studies such as DAPA-CKD included many patients with GN without diabetes (16%, 695 patients) and showed that the addition of dapagliflozin to baseline treatment with ACEI or ARBs led to a significant decrease (hazard ratio, 0.64) in the primary outcome of 50% reduction in eGFR or onset of kidney failure.[16] Similarly, the EMPA-KIDNEY trial also showed promise and included >800 patients with IgAN and patients with eGFR as low as 20 mL/min.[17]

As addressed in the guideline, there are no data to support dual ACEI and ARB therapy for patients with IgAN. Subgroup analyses of STOP-IgAN demonstrated no additional benefit with dual blockade, and safety issues pertaining to hyperkalemia are a potential concern.[18]

Clinical Utility

The section of the guideline pertaining to supportive treatment for IgAN is comprehensive and thorough. The challenge for practitioners is to identify outliers that either warrant additional immunosuppressive therapy or are past the "point of no return."[19] Patients may also have mild increases in albuminuria (30-300 mg/d) with normal blood pressure, and the benefit of using an ACEI or ARB in this population is unclear given the lack of data.

Implementation and Challenges

Despite the encouraging data and excitement surrounding the kidney benefits of SGLT2 inhibitors in nondiabetic kidney disease, utilization uptake has been slow. Barriers include not only health care education but also cost, as insurance coverage for this class of medications is not universal.

Treatment: Patients With IgAN at High Risk of Progressive CKD Despite Maximal Supportive Care

Practice Point 2.3.1.1: Considerations for treatment of patients with IgAN who are at high risk of progressive CKD despite maximal supportive care.

- High risk of progression in IgAN is currently defined as proteinuria >0.75–1 g/d despite ≥90 days of optimized supportive care.
- Immunosuppressive drugs should be considered only in patients with IgAN who remain at high risk of progressive CKD despite maximal supportive care (The patients enrolled in the only large randomized controlled trial [RCT] suggesting benefit of immunosuppression had an average of 2.4 g/d of proteinuria).
- In view of the current uncertainty over the safety and efficacy of existing immunosuppressive treatment choices, all patients who remain at high risk of progressive CKD despite maximal supportive care should be offered the opportunity to take part in a clinical trial.
- In all patients in whom immunosuppression is being considered, a detailed discussion of the risks and benefits of each drug should be undertaken with the patient recognizing that adverse treatment effects are more likely in patients with an eGFR <50 ml/min per 1.73 m^2.
- There is insufficient evidence to support the use of the Oxford Classification MEST-C score in determining whether immunosuppression should be commenced in IgAN.
- There is insufficient evidence to base treatment decisions on the presence and number of crescents in the kidney biopsy.
- The International IgAN Prediction Tool cannot be used to determine the likely impact of any particular treatment regimen.

- Dynamic assessment of patient risk over time should be performed, as decisions regarding immunosuppression may change.

Practice Point 2.3.1.2: Proteinuria reduction to under 1 g/d is a surrogate marker of improved kidney outcome in IgAN, and reduction to under 1 g/d is a reasonable treatment target.

Commentary

Practice Points 2.3.1.1-2.3.1.2 establish several tenets that clinicians can use to determine a potential need for more aggressive treatment for IgAN. Numerous studies have suggested that proteinuria is the most powerful predictor of poor long-term kidney outcomes, and this is now even reflected in clinical trial design after the FDA established proteinuria as a surrogate marker. The guideline notes that proteinuria > 0.75 g/d despite optimized supportive care correlates with high risk of disease progression, yet at the same time suggests that a value of <1 g/d should be the target. The guideline makes no definitive recommendations regarding indication for or type of immunosuppression in high-risk patients and, new in the 2021 guideline, suggests appropriate patients be considered for clinical trials. We agree with the guideline that an individualized patient-oriented discussion is needed for each case as management cannot be based solely on a histologic finding, a prediction tool calculation, or a single clinical or laboratory factor at the time of biopsy. Rather, a combination of all these factors must be considered with multiple assessments over time.

Recommendation 2.3.1.1: We suggest that patients who remain at high risk of progressive CKD despite maximal supportive care be considered for a 6-month course of glucocorticoid therapy. The important risk of treatment-emergent toxicity must be discussed with patients, particularly those who have an eGFR <50 ml/min per 1.73 m^2 *(2B)*.

Practice Point 2.3.1.3: Use of glucocorticoids in IgAN:

- Clinical benefit of glucocorticoids in IgAN is not established and should be given with extreme caution or avoided entirely in situations listed in Figure 23.
- There is insufficient evidence to support the use of the Oxford Classification MEST-C score in determining when any glucocorticoid therapy should be commenced.
- There are no data to support efficacy or reduced toxicity or alternate-day glucocorticoid regimens, or dose-reduced protocols.
- Where appropriate, treatment with glucocorticoid (prednisone equivalent ≥ 0.5 mg/kg/d) should incorporate prophylaxis against *Pneumocystis* pneumonia along with gastroprotection and bone protection, according to local guidelines.

Practice Point 2.3.1.4: Management of patients with IgAN who remain at high risk for progression after maximal supportive care (Figure 24).

Commentary

Initiating glucocorticoid therapy in IgAN patients with high-risk features is based on relatively weak evidence from 2 trials, each with several limitations outlined below. Special situations such as nephrotic syndrome, AKI, and RPGN are discussed separately in the guideline, but this recommendation applies specifically to patients who have persistent levels of proteinuria > 1 g/d despite maximal supportive therapy and a preserved eGFR. While we agree that these patients can be considered for a 6-month course of glucocorticoids, it should be emphasized that the benefit of immunosuppression in this high-risk group has not been demonstrated.

The STOP-IgAN trial evaluated 309 patients with IgAN who had a 6-month run-in phase to optimize proteinuria levels using renin-angiotensin system blockade.[18] At the end of the run-in phase, patients with sustained proteinuria (mean of 1.7 g/d in this trial) were randomized to continue supportive care alone versus supportive care plus immunosuppression; those with an eGFR of at least 60 mL/min per 1.73 m^2 received 6 months of corticosteroid monotherapy (0.5 mg/kg of prednisolone every 48 hours, with 3 daily 1-gram doses of intravenous methylprednisolone at the start of months 1, 3, and 5). Those with a lower eGFR received a complicated regimen of glucocorticoids, cyclophosphamide, and azathioprine. Although proteinuria was significantly reduced (mean of 0.7 g/d) in those treated with immunosuppression, the decline in kidney function did not differ between the groups over the 3-year follow-up period. Additionally, the reduction in proteinuria came at a cost of higher infections in the immunosuppression group, of which 25% were considered by the investigators to be related to the study treatment. Outcomes over 10 years from STOP-IgAN subsequently demonstrated no long-term differences in the 2 groups.[20] STOP-IgAN was unique in its incorporation of a strict run-in to optimize renin-angiotensin system (RAS) blockade, which has become standard for all IgAN clinical trials. However, the trial had substantial limitations, including the use of 2 differing and unusual immunosuppressive regimens, a lack of baseline histologic data, and a slow rate of kidney function decline.

The TESTING study was similar in scope but opted to test full-dose corticosteroid therapy at 1 mg/kg.[21] A similar run-in period was performed, and several of the limitations of STOP-IgAN were addressed with this trial—a uniform immunosuppressive regimen, kidney biopsy finding reporting, and higher levels of baseline proteinuria (2.4 g/d despite maximal supportive therapy). However, the trial was terminated early due to a high level of serious adverse events (mostly infections) in the immunosuppressive group. A post hoc analysis revealed that the steroid arm did have a benefit on kidney outcomes with longer follow-up. The second TESTING trial evaluated both a full-dose and reduced-dose steroid regimen in conjunction with PJP prophylaxis versus placebo and showed a significant reduction in composite outcome with steroid treatment over a median 4.2-year follow-up.[22] Although the effect of steroids on urinary protein excretion was not sustained over time, there was a significant reduction in

primary outcome in patients treated with steroids compared with placebo (28.8% vs 43.1%). However, serious adverse events remained significantly higher in the steroid group, including 4 fatalities in the methylprednisolone arm despite the use of pneumocystis prophylaxis.

A targeted-release glucocorticoid, budesonide, has potential to allow for the immunosuppressive effect of steroids without significant adverse events. In December 2021, the FDA granted accelerated approval of delayed-release budesonide for primary IgA nephropathy with a UPCR > 1.5 g/g. Preliminary results revealed a statistically significant 34% reduction in proteinuria from baseline at 9 months in patients in the intervention arm. It remains to be seen whether this reduction translates into long-term kidney survival outcomes.[23]

In the guideline, Figure 24 outlines an algorithm for management of patients with IgAN who remain at high risk for progression after maximal supportive care. We feel it falls short in addressing the complexities of this heterogeneous disease. With the availability of SGLT2 inhibitors, the positive results of TESTING trial, and now FDA approval of budesonide delayed-release capsules, the algorithm will need further revision. In this ever-changing landscape, there are more treatment choices but many unanswered questions.

Clinical Utility

It is critical to keep in mind that the typical progression of IgAN is gradual and measured over years or decades. The utility of 6 months of immunosuppression to reduce proteinuria to more acceptable levels is established by STOP-IgAN,[18] but a legacy effect has not been proven. The often slow rate of disease progression makes it challenging to demonstrate this kidney outcome over the course of a 2- to 3-year trial. Additionally, as both STOP-IgAN and TESTING demonstrated a higher incidence of adverse events in those treated with immunosuppression, a thorough discussion of potential adverse events for each individual case is necessary.[18,21]

Implementation and Challenges

Although IgAN is commonly labeled the most common GN in the world, studies in this patient population are challenging. The variable histologic findings, the time point at which IgAN is diagnosed, and the long progression of disease lead to small numbers and challenging clinical trial design. What little data we have on treating patients with higher levels of proteinuria leave more questions than answers. Additionally, while glucocorticoids are globally available and inexpensive, resources for monitoring infections and other side effects of prolonged steroid use may not be universally accessible.

Other Pharmacologic Therapies Evaluated in IgAN

Practice Point 2.3.1.5: Other pharmacologic therapies evaluated in IgAN (Figure 25).

Commentary

We agree with Figure 25, which discourages the general use of many additional immunosuppressive agents for IgAN. The majority of agents listed have either demonstrated no benefit or have been shown to be useful in small populations under special circumstances. For patients in whom higher dose glucocorticoids are a relative contraindication, MMF has successfully been used in the People's Republic of China for patients with high proteinuria (>1 g/d) and histologic features of activity (crescents, endocapillary proliferation, or segmental necrotizing lesions).[24] Using an MMF dose of 1.5 g/d in conjunction with a prednisone dose of 0.4-0.6 mg/kg/d provided similar outcomes to prednisone 0.8-1.0 mg/kg/d. Other trials, however, have not shown any benefit to using MMF as monotherapy for IgAN.

Fish oil is another agent that often falls under supportive therapy, but unlike the previous KDIGO guideline, it is no longer recommended. Despite an abundance of research in animal models demonstrating the effect of omega-3 fatty acids on kidney function, anti-inflammatory effects, and free radical inhibition, human trials have not been consistent. Given the variability in clinical efficacy, we agree that patients who wish to take fish oil should be advised on the doses from the positive studies that have shown benefit.[25]

Special Situations Relevant to IgAN

For the special situations listed in Practice Points 2.4.1 and onward that pertain to patients with IgAN who present with nephrotic syndrome, AKI, or RPGN, we agree with the recommendations. Similarly, we agree with the recommendations pertaining to IgAN presentations in pregnant individuals and children as outlined in Practice Points 2.4.4 and 2.4.5.

Guideline Statements and Commentary: Membranous Nephropathy

This chapter has been updated from the 2012 version and highlights the clinical utility of anti-PLA_2R antibody testing in the management of primary MN, as well as recent clinical trial evidence supporting the use of the anti-CD20 B-cell–depleting agent rituximab.

Diagnosis of MN

Practice Point 3.1.1: A kidney biopsy is not required to confirm the diagnosis of membranous nephropathy (MN) in patients with nephrotic syndrome and a positive anti-PLA2R antibody test.

Commentary

This striking initial practice point, suggesting that a positive anti-PLA_2R antibody test can obviate the need for

kidney biopsy in certain situations, is an example of the heightened role that serologic testing now plays in the diagnosis and monitoring of MN. We feel that this practice point and the overall interpretation of what represents a positive (and negative) anti-PLA_2R antibody test deserve further commentary.

Despite the increasing use and availability of serologic testing, the kidney biopsy remains the gold standard for the diagnosis of MN. However, the high specificity[26] of a positive anti-PLA_2R antibody test allows a high-confidence diagnosis of primary MN without exposing the patient to risks, costs, and inconvenience inherent to the kidney biopsy procedure. It is important to note that autoantibodies other than anti-PLA_2R antibodies—for example, anti-THSD7A antibodies[27] and anti-NELL1[28] antibodies—do not yet carry the same level of accuracy and should not be used as the sole diagnostic test in the absence of a biopsy.

Certain situations may warrant a confirmatory kidney biopsy even in the face of a positive anti-PLA_2R antibody. These include scenarios where a secondary MN remains a suspicion or if there is a rapidly progressive eGFR decline that is out of proportion to the disease. Kidney biopsy should also be considered to evaluate for alternative or additional diseases in patients who are initially treated for MN based on seropositivity for anti-PLA2R antibody but do not follow the expected course. Kidney biopsy allows immunofluorescence staining of the tissue to determine the presence of the PLA_2R (or other) antigen within the immune deposits; this can provide critical information in the setting of seronegativity for anti-PLA_2R antibodies to determine if a patient has entered immunological remission. Furthermore, there are rare cases of dual autoantibodies, which can be missed both serologically and histopathologically when the focus is only on PLA_2R. The kidney biopsy also provides clinical utility beyond diagnostic information; for example, the degree of chronic interstitial fibrosis and tubular atrophy is a major adverse prognostic factor for all glomerular disorders and may also help to guide conservative or more aggressive therapy.

It is essential to consider what is meant by the presence, absence, or disappearance of anti-PLA_2R antibodies, as determination of what constitutes a positive test is nuanced and warrants further discussion. While the immunofluorescence test is the most sensitive clinically available test for detection of anti-PLA_2R antibodies and can be reported as positive or negative, many laboratories provide instead a numerical titer based on enzyme-linked immunosorbent assay (ELISA). A threshold of 14 RU/mL, below which the test is negative, was chosen by the manufacturer to maximize specificity. Other studies (eg, Bobart et al[29]) have used a higher cutoff value of 20 RU/mL to clearly define a positive test. ELISA titers in the 2-14 RU/mL range are denoted as "ambiguous" in the guideline but may represent true seropositivity for anti-PLA_2R antibodies when confirmed by immunofluorescence test.[29] Whether one uses a cutoff of 14 or 20 RU/mL to determine seropositivity, and even with a specificity as high as 99%, there exists potential for false positives, and ideal clinical use would include one or more confirmatory tests. Therefore, it may be reasonable to confirm a weakly positive result upon testing for PLA_2R autoantibodies with the more sensitive immunofluorescence test or consider kidney biopsy before further management decisions are made.

The disappearance of anti-PLA_2R antibodies can help guide the duration of treatment. When assessing disappearance, the ELISA titer should be <2 RU/mL (some clinical laboratories report <4 RU/mL) and/or the immunofluorescence test reported as negative.

Clinical Utility

Testing for anti-PLA_2R antibodies has become more widely available, both for primary care providers and for nephrologists. It is often included in a standard work-up for unexplained proteinuria, in which case a confirmed positive result would indicate primary MN. Decisions about whether to perform kidney biopsy in the setting of seropositivity are more nuanced and should be considered on an individual basis, especially if immunosuppression is being considered. A positive test can be considered sufficient for diagnosis if confirmed in 2 assays and as the basis for starting treatment, if needed, when kidney biopsy cannot be safely performed. Other situations in which this serologic test may be the preferred method of diagnosis are in practices that are unable to obtain a biopsy in a timely manner. On the other hand, kidney biopsy may be readily available and practical while assaying for anti-PLA_2R antibodies might prove to be more difficult.

Implementation

The type of anti-PLA_2R antibody testing available to an individual practitioner is variable: some centers routinely get ELISA results, some get immunofluorescence tests, and a few get both results. The caveats to the more commonly reported ELISA test are outlined above. The ideal diagnostic approach utilizes accessible resources to the health care team and accounts for patient risks, costs, and preferences.

Practice Point 3.1.2: Patients with MN should be evaluated for associated conditions, regardless of whether anti-PLA2R antibodies and/or anti-THSD7A antibodies are present or absent (Figure 29).

Commentary

We agree with this statement. The presence of anti-PLA_2R antibodies can occasionally occur in the presence of other diseases or infections that have historically been reported to be secondary causes of MN. Thus, a positive test does not necessarily rule out these other disorders, although it is sometimes difficult to assess causality versus coincidence. Autoantibodies to several newer antigens such as THSD7A and NELL1 may be more often associated with malignancy as compared to anti-PLA_2R antibodies.[30,31] The potential presence of latent infections should certainly be assessed

since initial treatment of the underlying infection would be warranted rather than giving immunosuppression, which might rapidly worsen the infectious process.

Prognosis of MN

Practice Point 3.2.1: In patients with MN, use clinical and laboratory criteria to assess the risk of progressive loss of kidney function (Figure 30).

Commentary

The initial presentation of MN can range from asymptomatic proteinuria to severe nephrotic syndrome with thromboembolic complications, and the disease course and outcome are unpredictable. Risk stratification for this disease has historically relied on the degree of proteinuria, eGFR at the time of kidney biopsy, and the extent of irreversible histologic damage as measured by interstitial fibrosis and tubular atrophy. More recent prognostication continues to rely on proteinuria and kidney function but may use anti-PLA_2R antibody titers in lieu of traditional kidney biopsy findings (see Practice Point 3.1.1). Over the last decade, several studies have validated the use of anti-PLA_2R antibodies as a useful clinical tool in the prognosis of MN in 2 main ways. First, changes in the level of circulating antibodies against podocyte antigens precede and predict changes in proteinuria, which then impacts long-term prognosis. Early studies demonstrated that a decrease in antibody levels (ie, immunologic remission) preceded a decline in proteinuria (ie, clinical remission) by 6 or more months.[32] Second, the likelihood of spontaneous remission is inversely related to the degree of detectable antibody at the time of diagnosis.[33,34] Spontaneous remission rates are consistently highest among patients with low anti-PLA_2R antibody levels, whereas the opposite is true for those with severely elevated antibody titers. This may reflect the duration of disease that is expected following the test, as those with high levels may have longer duration of heavy proteinuria than those who are likely closer to an immunological remission. It is difficult to assign risk based on a single autoantibody measurement, as peak levels associated with severe nephrotic syndrome may differ among individual patients. More important is the trajectory over the course of several serial measurements, with increasing levels conferring greater risk of prolonged disease than decreasing levels. Patients in whom the diagnosis of MN is made by kidney biopsy and do not have a defined autoantibody-antigen system are more heterogeneous, and their prognosis relies on traditional markers such as eGFR and proteinuria.

Clinical Utility

The addition of anti-PLA_2R antibody testing in the prognostic algorithm of MN is welcome and is the most important addition to the initial Toronto risk algorithm.[35] Measurement of urinary high- and low-molecular-weight proteins has long been known to associate with risk but generally is not a test performed or relied on in the United States. Kidney function (estimated by Scr), urinary protein excretion, and serum albumin are traditional risk factors that oftentimes take many months after treatment to demonstrate improvement due to immunologic damage to the basement membrane, and sometimes these values conflict with the trend in anti-PLA_2R antibody titers. Unlike IgAN, there is no universally accepted prediction tool for MN that combines clinical, serologic, and histologic factors to assess prognosis. The guideline briefly mentions the importance of anti-PLA_2R antibody trajectory, which we feel needs further emphasis as opposed to an arbitrary threshold (>50 RU/mL) for risk assessment. Any individual measurement is a snapshot, and the change over time is more clinically meaningful than any single value. Increasing levels portend a longer disease course with worsening proteinuria whereas decreasing levels are associated with a better chance for remission.

Treatment of MN

Recommendation 3.3.1: For patients with MN and at least one risk factor for disease progression, we recommend using rituximab or cyclophosphamide and alternate month glucocorticoids for 6 months, or CNI-based therapy for ≥6 months, with the choice of treatment depending on the risk estimate (Figure 30 and Figure 31) *(1B).*

Commentary

This is the only evidence-based recommendation in the chapter and is based on a collection of studies and observational data with differing levels of evidence and outcomes for each agent. The general premise is that one should use immunosuppression to bring about immunological, followed by clinical, remission in those patients with serious disease that is unlikely to spontaneously remit, and in those at higher risk of adverse kidney outcomes or other consequences of the nephrotic syndrome. However, despite the provision of clinical and laboratory risk criteria alluded to in Practice Point 3.2.1, the decision of when to treat, and with which agent, remains difficult and must be individualized based on risk-benefit analysis, patient preference, and local availability. A risk prediction tool similar to what is available for IgAN would be welcome.

Regimens combining alkylating agents with glucocorticoids (eg, the modified Ponticelli regimen) are very effective, represent the only therapies that have been shown to preserve kidney function over long-term follow-up, and can achieve rapid immunologic remission with sustainable reduction of anti-PLA_2R antibodies. However, the possibility of short- and long-term toxicity has limited the use of such agents to the highest risk patients due to increasing evidence that anti-CD20 agents such as rituximab are also effective agents for the induction of immunological and clinical remission.

CNIs can reduce proteinuria through multiple mechanisms that lead to high partial remission rates but often are less effective at reducing autoantibodies. In long-term follow-up, both proteinuria and PLA_2R autoantibodies can rebound after the drug is discontinued, and kidney failure end points are less encouraging with CNI than with alkylating agents. We cannot provide further commentary for or against the individual treatment options, but the reader is directed to the discussion provided in chapter 3 of the guideline as well as a recent review of the topic.[36]

The specific practice points in this treatment section provide suggestions for when immunosuppressive therapy might be avoided and/or unnecessary.

Practice Point 3.3.1: Considerations for treatment of patients with primary MN:
- All patients with primary MN and proteinuria should receive optimal supportive care.
- Immunosuppressive therapy should be restricted to patients considered at risk for progressive kidney injury (Figure 31).

Commentary

We agree with these statements. It is important to optimize therapy with the nonimmunosuppressive drugs discussed in chapter 1 of the guideline and restrict potentially harmful immunosuppressive therapy to those with immediate complications or those whose risk factors suggest that they are at high risk for future loss of kidney function.

Practice Point 3.3.2: Immunosuppressive therapy is not required in patients with MN, proteinuria <3.5 g/d, serum albumin >30 g/l by bromocresol purple (BCP) or immunometric assay, and eGFR >60 ml/min per 1.73 m^2.

Commentary

We agree that individuals with subnephrotic levels of proteinuria and serum albumin levels that are above 3.0 g/dL should receive optimal supportive care and be followed closely. However, increasing proteinuria or titer of anti-PLA_2R antibodies over time could change their risk estimate.

Practice Point 3.3.3: Immunosuppressive therapy is not required in patients with MN, nephrotic syndrome, and normal eGFR, unless at least one risk factor for disease progression is present or serious complications of nephrotic syndrome (e.g., AKI, infections, thromboembolic events) have occurred.

Commentary

This point is more subjective and relates to the interpretation of an individual's risk factors as described in the prognosis section. As mentioned previously, anti-PLA_2R antibody levels should not be interpreted at a single time point; thus, a single value above 50 RU/mL in the presence of the nephrotic syndrome does not necessarily indicate a need for immunosuppressive treatment.

Practice Point 3.3.4: Longitudinal monitoring of anti-PLA2R antibody levels at 6 months after start of therapy may be useful for evaluating treatment response in patients with MN, and can be used to guide adjustments to therapy (Figure 33).

Commentary

This point likely represents one of the most important advances in the management of MN, as changes in anti-PLA_2R antibody levels precede and predict changes in clinical parameters (ie, proteinuria) that can limit immunosuppressive treatment to the shortest duration necessary to achieve an immunologic remission. This important point has been borne out by observational studies[37] and now by randomized trials such as MENTOR,[38] which showed rituximab to be superior to cyclosporine for causing remission in MN. While decline and disappearance of anti-PLA_2R antibodies by 6 months should be an indication to limit further immunosuppression, their persistence should lead the treating physician to continue therapy or ultimately change to another agent. Note that a disappearance of PLA_2R autoantibodies (ie, immunologic remission) is defined by either a negative immunofluorescence test or an ELISA titer < 2 RU/mL (some laboratories report <4 RU/mL, which is also reasonable). The field has not generated sufficient data to confidently assess if other antipodocyte antibodies such as those to THSD7A can be used in a similar manner, although declining titers of such antibodies are also suspected to show a response to therapy.

Special Situations Relevant to MN

Practice Point 3.4.1: Algorithm for the treatment of patients with MN and initial relapse after therapy (Figure 34).

Practice Point 3.4.2: Algorithm for management of patients with treatment-resistant MN (Figure 35).

Commentary

We agree with the algorithm given in Figure 34. Regarding Figure 35, management of treatment-resistant MN is challenging and is hindered by a paucity of robust clinical data. Preservation of kidney function while attaining a timely immunologic and clinical remission are the goals of treatment. Failure to achieve any or all these end points after an adequate period should prompt reconsideration of the current regimen. The decision to move from one class of agents to another should not be based on eGFR alone and should take into account the trends in eGFR, proteinuria, and serum antipodocyte antibodies.

In patients who are worsening quickly and would benefit from urgent clinical and immunologic remission, the regimen of cyclophosphamide and corticosteroids is most appropriate regardless of initial treatment choice of rituximab or CNI. In patients who initially received cyclophosphamide and corticosteroids and for whom treatment is failing, the current treatment can be prolonged at the risk of cumulative toxicity, or a trial of rituximab can be considered. Patients for whom both therapies fail should be referred to GN centers where experimental or unconventional therapies may be considered. Future agents with ongoing investigations include more potent anti-CD20 agents (eg, obinutuzumab), anti-CD38 therapy, and proteasome inhibitors.

An essential point is what constitutes resistant disease, and the text thoughtfully explains that the persistence of high level or unchanged anti-PLA_2R antibody levels after one line of immunosuppression is one example. However, the persistence of proteinuria for 12-24 months after disappearance of anti-PLA_2R antibodies is expected and does not constitute resistant disease. For patients without autoantibodies that can be followed, persistent or worsening nephrotic syndrome without any substantial improvement in serum albumin could constitute resistant disease.

We generally agree with the succession of choices for immunosuppression as a second treatment option in this algorithm, although there are situations in which one might consider alkylating agents as second-line therapy even with a stable eGFR. Treatment choices should always be individualized, as above.

Practice Point 3.4.3: Evaluation of a kidney transplant recipient with MN (Figure 36).

Commentary

We agree with this approach. Patients who are known to have developed kidney failure due to MN or who have an unknown etiology should be screened for the presence of anti-PLA_2R antibodies before transplant. The presence of circulating anti-PLA2R antibodies at the time of transplantation will quickly initiate a process of recurrent MN in the allograft. However, this initially subclinical process may be curtailed if the transplant immunosuppression alone is sufficient to cause a decline and disappearance of PLA_2R autoantibodies and thus may never be of clinical consequence. However, if a recipient is transplanted in the presence of very high anti-PLA_2R antibody levels, or if significant levels persist or increase after transplantation, that recipient will likely develop clinically apparent recurrent MN that may need additional immunosuppressive treatment with anti-CD20 agents. There are no data about whether to postpone transplant until anti-PLA_2R antibody levels can be reduced or at what threshold titer it would be acceptable to proceed. At the moment, each case should be considered on an individual basis. This is an important area for future research in the field. As clinical tests for the other relevant antipodocyte antibodies become available, it will likely be possible to test for and monitor these less frequently occurring antibodies in a similar manner.

Practice Point 3.4.4: Algorithm for management of children with MN (Figure 37).

Commentary

There is virtually no evidence to guide the management of MN in children since it is a relatively rare cause of the nephrotic syndrome in this population. We agree with attempting to ascertain etiology (eg, primary, infectious, lupus-associated) with serologies when available or from clues in the kidney biopsy itself. PLA_2R-associated MN can be seen in preadolescents and adolescents, but is rare before the age of 10 years. Staining of pediatric kidney biopsy registries[39] has shown a variety of additional target antigens, most of which were first described in adults. Semaphorin-3B (Sema3B) is a newer autoantigen in a subtype of MN that seems to be enriched in the pediatric population. There are no clinically available tests for anti-Sema3B antibodies, although certain specialized centers can stain for the presence of the antigen in the biopsy tissue. We would favor investigation of this antigen over a search for the infrequently encountered cationic bovine serum albumin (BSA) antibodies as suggested in the algorithm in young children with MN.

Practice Point 3.4.5: Prophylactic anticoagulant therapy in patients with MN and nephrotic syndrome should be based on an estimate of the risk of thrombotic events and the risk of bleeding complications (Figure 38).

Commentary

The risk of venous thromboembolic events (VTE) in MN is higher than in other causes of the nephrotic syndrome and increases when serum albumin falls below 2.9 g/dL.[40] As highlighted in the algorithm, this threshold will vary depending on the albumin assay used: bromocresol green (BCG) or bromocresol purple (BCP). BCG is more common but overestimates serum albumin in the nephrotic syndrome. In determining risk for VTE, it is therefore important for physicians to know the assay and normal range reported by their local laboratory.

Despite the growing use of direct oral anticoagulants such as apixaban, they are largely untested for prophylactic treatment of VTE in the nephrotic syndrome, and their use is not recommended based on available data. When anticoagulation is used for known VTE or prophylaxis of such in the nephrotic syndrome, the dose recommended is that for known VTE.

Guideline Statements and Commentary: Nephrotic Syndrome in Children

Diagnosis of Nephrotic Syndrome in Children

Practice Point 4.1.1: The definitions relating to nephrotic syndrome in children are based on the clinical characteristics outlined in Figure 39.

Commentary

The definition of pediatric nephrotic syndrome was initially set by the International Study of Kidney Disease in Children as proteinuria (≥40 mg/h/m^2) and hypoalbuminemia (≤2.5 g/dL) and was used to determine enrollment eligibility for this seminal 1978 study that established the currently used treatments as well as for future clinical trials and other studies of children with nephrotic syndrome.[41,42] The substitution of spot UPCR for the 24-hour urine collection has been established as the standard of care for children due to good correlation between the 2 results and the ease of collection in children, with nephrotic-range proteinuria defined as first morning UPCR of ≥2 g/g.[43] Whereas the 2012 KDIGO guideline maintained the definition of nephrotic syndrome as requiring albumin ≤2.5 g/dL, the current guideline suggests a definition of <3 g/dL; however, a rationale for this change was not provided. We suggest continuing to use serum albumin of ≤2.5 g/dL as a component of the definition of nephrotic syndrome for children in the absence of evidence to support a change to a higher cutoff.

Clinical Utility

It is unknown whether children with nephrotic-range proteinuria and less severe hypoalbuminemia (albumin of 2.6-2.9 g/dL) have similar underlying kidney pathology findings or will respond to treatment in a similar manner as those with classically defined nephrotic syndrome. This has not been studied in prospective clinical trials.

Implementation and Challenges

Changing the definition of childhood nephrotic syndrome after 50 years of clinical trials utilizing a standard definition may make future clinical trials difficult to compare to historical trials if different populations of children are included. Future studies showing the equivalence of these 2 populations (nephrotic range proteinuria + albumin ≤2.5 g/dL vs nephrotic range proteinuria + albumin <3 g/dL) are needed prior to supporting a change in the definition.

Treatment of Nephrotic Syndrome in Children

Recommendation 4.3.1.1: We recommend that oral glucocorticoids be given for 8 weeks (4 weeks of daily glucocorticoids followed by 4 weeks of alternate-day glucocorticoids) or 12 weeks (6 weeks of daily glucocorticoids followed by 6 weeks of alternate-day glucocorticoids) *(1B)*.

Commentary

In the 1960s and 1970s, the International Study of Kidney Disease in Children established a consensus initial corticosteroid treatment regimen for children with nephrotic syndrome of 60 mg/m^2/d for 4 weeks followed by 40 mg/m^2/d for 3 consecutive days per week for 4 weeks.[44] The follow-up dose was changed to every other day corticosteroids in the late 1970s for ease of administration, although head-to-head comparisons of the 2 regimens are not available. Since then, numerous studies have attempted to fine-tune this regimen to minimize the risk of frequently relapsing disease and avoid complications of corticosteroid treatment. While some early RCTs demonstrated a benefit of longer corticosteroid treatment (12-24 weeks) versus 8 weeks on risk of relapse,[42] more recent studies have not consistently shown a benefit for extending the initial treatment course beyond 12 weeks.[45,46] Given the limitations of the available evidence, we agree with the initial treatment recommendations for 8 or 12 weeks of initial glucocorticoid treatment.

Clinical Utility

It is beneficial for patients to have some flexibility in the initial treatment course of steroids depending on their response and clinical characteristics. For example, a child who enters remission rapidly (within 7 days) or those at highest risk for complications of corticosteroids (obesity, diabetes, or psychiatric illness) may benefit from fewer side effects from treatment with 8 versus 12 weeks of therapy with likely little effect on long-term disease course.

Implementation and Challenges

These treatment recommendations are the current standard of care for children with nephrotic syndrome. Corticosteroids are widely available, inexpensive, and available in liquid formulations to allow for use by the youngest of children. Future clinical avenues of research should include determining whether lower initial steroid doses are adequate to induce remission while maintaining a similar risk of frequently relapsing or steroid-dependent nephrotic syndrome and identifying whether alternative initial therapies such as MMF or CNIs may induce remission with an improved safety profile compared with corticosteroids.

Recommendation 4.3.2.1: For children with frequently relapsing and steroid-dependent nephrotic syndrome who are currently taking alternate-day glucocorticoids or are off glucocorticoids, we recommend that daily glucocorticoids 0.5 mg/kg/d be given during episodes of upper respiratory tract and other infections for 5–7 days to reduce the risk of relapse *(1C)*.

Commentary

Infections are a well-known trigger for relapses of nephrotic syndrome in children. Given the toxicity of

corticosteroids and significant risks associated with relapse itself, strategies to prevent relapses and avoid full-relapse treatment courses of glucocorticoids are needed. Several prior RCTs demonstrated that daily glucocorticoids at the onset of an upper respiratory infection may prevent relapse.[47-50] These studies had several potential sources of bias, and the generalizability of the findings was limited. However, since the publication of the 2021 KDIGO guideline, a large, well-conducted RCT was published (PREDNOS 2) that did not support the use of daily corticosteroids at the time of upper respiratory infection to prevent relapses. In the trial, 365 children in the United Kingdom with relapsing steroid-sensitive nephrotic syndrome were randomized to treatment with prednisolone 15 mg/m^2 daily or matching placebo for 6 days at the onset of an upper respiratory infection.[51] There was no significant difference between the groups in the primary outcome of incidence of first upper respiratory infection–related relapse or in a number of relevant secondary outcomes, including overall rate of relapse, cumulative dose of prednisolone, incidence of corticosteroid adverse effects, and quality of life. Given the updated RCT data, we do not support the recommendation to provide corticosteroids at onset of upper respiratory infection to prevent nephrotic syndrome relapses.

Implementation and Challenges

There are several challenges to implementing a preventive treatment at the onset of an upper respiratory infection to prevent relapse. First, education should be given to parents to help recognize subtle clinical symptoms in their child and have corticosteroids available to initiate rapidly. Second, as the COVID-19 pandemic has taught us, a significant number of children may have subclinical infection with viruses that would limit our ability to preemptively treat to prevent relapse.[52] The role of subclinical viral infection on risk of nephrotic syndrome relapse is unknown. Finally, by the time children demonstrate symptoms of an upper respiratory tract infection, it may be too late to prevent a relapse of nephrotic syndrome.

Recommendation 4.3.2.2: For children with frequently relapsing nephrotic syndrome who develop serious glucocorticoid-related adverse effects and for all children with steroid-dependent nephrotic syndrome, we recommend that glucocorticoid-sparing agents be prescribed, rather than no treatment or continuation with glucocorticoid treatment alone *(1B)*.

Commentary

Children with frequently relapsing nephrotic syndrome, defined as those with ≥4 relapses in a 12-month period, will have significant exposure to high-dose corticosteroids throughout their disease course. The majority of these children will have at least 1 severe steroid side effect, including growth failure, obesity, hypertension, diabetes, osteoporosis, behavioral concerns, or cataracts.[53,54] We agree with the recommendation that children with frequently relapsing nephrotic syndrome be offered a glucocorticoid-sparing agent. The prior KDIGO guideline included only cyclophosphamide, chlorambucil, CNIs, levamisole, or mycophenolate as potential agents and specifically suggested rituximab only in those settings where children with steroid-dependent nephrotic syndrome had failed treatment with other options. Since the publication of the 2012 guideline, several large pediatric clinical trials have shown a favorable response to rituximab infusion in children with frequently relapsing or steroid-dependent nephrotic syndrome. Thus, it is appropriate that this has been added to the recommended list of potential corticosteroid-sparing therapies.[55,56]

Clinical Utility

The choice of glucocorticoid-sparing agent will depend on family and nephrologist choice and includes consideration of such factors as route of administration (eg, intravenous vs oral), drug-monitoring requirements, side-effect profile, and length of treatment. Given that there is no clear therapeutic benefit to any of the named drugs compared to the others, it is appropriate that the guideline leaves room for shared decision making regarding corticosteroid-sparing treatment choice.

Implementation and Challenges

Choice of agent may depend on geographic region and/or insurance coverage. Most corticosteroid-sparing agents used for the treatment of children with frequently relapsing nephrotic syndrome are used off-label; that is, there is no specific FDA indication for nephrotic syndrome on the drug label. For that reason, these treatments are often denied by insurance carriers due to expense, which may limit options for therapy for some children. Levamisole is an antihelminthic agent with immunomodulatory effects that was withdrawn from the US market in 2000 due to concerns for severe adverse effects including agranulocytosis.[57] There remain significant concerns about immunosuppressive side effects in children who require corticosteroid-sparing therapies, and future studies of novel strategies to maintain remission in children with frequently relapsing nephrotic syndrome are needed.

Treatment of Steroid-resistant Nephrotic Syndrome in Children

Recommendation 4.4.1: We recommend using cyclosporine or tacrolimus as initial second-line therapy for children with steroid-resistant nephrotic syndrome *(1C)*.

Commentary

We agree with the use of CNIs as initial treatment of steroid-resistant nephrotic syndrome. These drugs may induce remission via their immunosuppressive properties

or via direct stabilization of the podocyte actin cytoskeleton.[58]

We recommend genetic testing for monogenic causes of nephrotic syndrome in parallel with initiation of treatment with cyclosporine or tacrolimus for children who are steroid resistant. Between 11% and 30% of children with steroid-resistant disease will have a monogenic cause of disease.[59,60] A clear recommendation from the KDIGO Work Group for genetic testing in this population is needed to support insurance coverage and family acceptance of genetic testing in these situations. Identification of a genetic cause of nephrotic syndrome is required to identify those individuals who may not respond to immunosuppression, thus minimizing their exposure to these drugs and their potential side effects.

Clinical Utility

Cyclosporine and tacrolimus have not been tested head-to-head to determine whether one drug is more efficacious in children with steroid-resistant nephrotic syndrome. Thus, the decision to use one drug or the other often comes down to provider experience and side-effect profile. Patients treated with cyclosporine may have more risk of gingival hypertrophy and hypertrichosis whereas patients treated with tacrolimus may demonstrate more diabetes or glucose intolerance. Both drugs have risks of kidney scarring with long-term use.

Implementation and Challenges

Given variable drug metabolism, both cyclosporine and tacrolimus require drug-level monitoring to avoid toxicity. This can be challenging for patients and caregivers given the timing of blood draw that is required just before a dose is given, which is typically in the early morning or evening. Optimal drug levels to induce initial remission are not supported by evidence and this should be a priority for future clinical trials.

Guideline Statements and Commentary: Minimal Change Disease (MCD) in Adults

Diagnosis of MCD in Adults

Practice Point 5.1.1: MCD in adults can be diagnosed only with a kidney biopsy.

Practice Point 5.2.1: Long-term kidney survival is excellent in patients with MCD who respond to glucocorticoids, but less certain for patients who do not respond.

Recommendation 5.3.1: We recommend high-dose oral glucocorticoids for initial treatment of MCD *(1C)*.

Commentary

We agree with these 2 practice points. We agree with Recommendation 5.3.1 and the associated algorithm (Figure 44) for the initial treatment of primary MCD in adults, which recommends the initial use of corticosteroids for all individuals without absolute or relative contraindications to their use. The 2012 guideline provided additional insight on the use of supportive care in the initial nephrotic syndrome episode of adult MCD patients, which included avoiding the use of a statin as well as avoiding RAS blockade in normotensive patients. The 2021 guideline does not specifically include these recommendations; however, we want to highlight and agree with these older recommendations because oftentimes these MCD patients can obtain remission quickly without the need of those agents. In addition, we would like to acknowledge the need to rule out secondary causes of MCD in adults such as malignancy, nonsteroidal anti-inflammatory drug (NSAID) use, and systemic lupus erythematosus (SLE) (lupus podocytopathy).

Treatment of MCD in Adults

Practice Point 5.3.2: High-dose glucocorticoid treatment for MCD should be given for no longer than 16 weeks.

Commentary

We agree with this practice point.

Implementation and Challenges

A trial of high-dose glucocorticoid therapy for a maximum of 16 weeks stems from observational studies of adult MCD patients that showed an increase in remission in patients who received high-dose glucocorticoid therapy for up to 16 weeks.[61]

Practice Point 5.3.3: Begin tapering of glucocorticoids 2 weeks after complete remission.

Commentary

This practice point represents a change from the 2012 recommendation of a 4-week minimum of high-dose glucocorticoids even if remission is achieved earlier. We agree with this change in the KDIGO guideline because of the deleterious side effects of glucocorticoids, and thus it is best to reduce dosing as soon as possible without sacrificing clinical benefits in adults with MCD.

Implementation and Challenges

Studies examining a rapid taper of glucocorticoids were performed in childhood nephrotic syndrome cohorts, and it is not clear if the same regimens would be safe in an adult population of biopsy-proven MCD.[46,62] More data are needed in the adult MCD population at this time, and we agree with the guideline to perform a slow taper over a total of 24 weeks.

Practice Point 5.3.4: Although daily oral glucocorticoids are used most often to treat MCD, the route and frequency of administration can be individualized to patient needs.

Clinical Utility

We agree that daily oral glucocorticoids or every-other-day oral glucocorticoids can be used safely in adult MCD patients. In addition, intravenous steroids may be beneficial in the presence of bowel edema.

Practice Point 5.3.5: For patients in whom glucocorticoids may be relatively contraindicated, consider initial therapy with cyclophosphamide, a CNI, or MMF.

Commentary

This practice point has been modified for the 2021 guideline. In 2012, KDIGO recommended oral cyclophosphamide or CNIs in patients with intolerance of or contraindication to glucocorticoids. Most alternative therapy studies in adults with MCD or focal segmental glomerulosclerosis (FSGS) have focused on patients who have already exhibited steroid resistance and therefore not on their use as initial therapy.

Clinical Utility

One must weigh the relative adverse effect profiles of any potential agent considered for treatment in these patients. There are a good deal of observational data in adult FSGS patients to support the 2021 KDIGO Work Group recommending CNIs as the preferred alternative therapy in this patient population. Therefore, we recommend a trial of CNIs, mycophenolic acid analogues, or rituximab, if available, prior to the use of cyclophosphamide due to their safer side-effect profiles. The potential for gonadal suppression, risk of serious infection, and late malignancy should be considered prior to using cyclophosphamide.

Implementation and Challenges

Research studies examining these alternative therapies as first-line treatment options in adults with MCD are needed.

The definitions surrounding remission, relapse, resistance, and dependency can vary across studies, sometimes hindering direct comparisons. We appreciate the inclusion of Figure 46, which provides clear definitions for standardization.

Practice Point 5.3.1.1 Algorithm for treatment of frequently relapsing (FR)/steroid-dependent (SD) MCD in adults (Figure 47).

Recommendation 5.3.1.1: We recommend cyclophosphamide, rituximab, CNIs, or mycophenolic acid analogs (MPAA) for the treatment of frequently relapsing/steroid-dependent MCD, rather than prednisone alone or no treatment *(1C).*

Commentary

This section of the guideline has been modified since the 2012 version, which recommended the use of oral cyclophosphamide for adult patients with FR/SD MCD and use of CNIs if a patient relapsed despite oral cyclophosphamide or was of childbearing age. We agree that repeated or prolonged exposure to glucocorticoids should be avoided in patients relapsing more than infrequently and that alternative therapies, which now include cyclophosphamide, rituximab, CNIs, or mycophenolic acid analogs, should be used instead. Again, we emphasize considering the adverse effect profile of any agent in the context of the individual patient and remembering the limited data supporting the efficacy of any of these medications.

Implementation and Challenges

Cost and/or insurance coverage of these alternative therapies, as well as patient preferences, need to be considered. Another challenge is clinical inertia, since cyclophosphamide had previously been the preferred agent for FR/SD MCD, and education of the nephrology workforce about these updated KDIGO 2021 guideline recommendations, which have added rituximab and mycophenolic acid analogs as alternative therapies, will take time. Emerging data have shown encouraging responses to rituximab[63,64] and mycophenolic acid analogs in adults with FR/SD MCD.[65,66]

Practice Point 5.3.1.2: Treat infrequent relapses with glucocorticoids (Figure 46).

Commentary

We agree with this point, with the understanding that the overall duration of corticosteroids should be minimized. The dose and duration of glucocorticoid therapy is patient dependent, and a patient's previous response can provide helpful guidance for both treatment efficacy and adverse effects.

Guideline Statements and Commentary: Focal Segmental Glomerulosclerosis (FSGS) in Adults

Diagnosis: Differentiating Between Primary and Secondary FSGS

Practice Point 6.1.1.1: Adults with FSGS who do not have nephrotic syndrome should be evaluated for a secondary cause (Figure 51; Figure 52).

Commentary

The term FSGS has long been used to represent an etiology of the nephrotic syndrome with a specific (partially scarred) appearance of the glomerulus on light microscopy. However, it has become clear that this general finding on biopsy can be the result of a number of disparate causes of injury that include genetic, viral, medications, immunologic, or unknown etiologies, may respond differently to treatment, and may have variable prognoses. Prior KDIGO guidelines suggested classifying patients with FSGS as having either a "primary" or "secondary" cause. Due to the inadequacies of this classification system, the 2021

guideline proposes a novel classification system that divides patients with FSGS into 4 subclasses: (1) primary FSGS, which is typically immunologically mediated and responsive to treatment with immunosuppression; (2) genetic FSGS; (3) secondary FSGS, which is mediated by viral injury, medication-related injury, or adaptive changes; and (4) FSGS of undetermined cause (FSGS-UC). Workup for secondary causes should occur in patients with non–nephrotic-range proteinuria (<3.5 g/d) or with nephrotic-range proteinuria but albumin > 3.0 g/dL. We recommend also adding history of prematurity as a potential etiology for those with secondary FSGS due to reduced nephron number.[67]

Clinical Utility

The initial classification of patients with the FSGS lesion on biopsy as "likely primary FSGS" (ie, those with proteinuria > 3.5 g/d, serum albumin < 3.0 g/dL, and diffuse podocyte foot-process effacement) is useful in that it identifies patients who are most likely to respond to treatment with immunosuppressive therapy. Unfortunately, such patients do not always respond to therapy or may have an underlying genetic cause of disease, and there remains much overlap between this and the other 3 categories. To add to the complexity, patients may move from one category to another as more information about their individual disease is uncovered. We agree that patients without clear "primary FSGS" deserve further evaluation for secondary, including genetic, causes (see below).

Implementation and Challenges

This guideline is in keeping with current standard clinical practice in the United States. To truly advance the field, nephrologists must be able to classify patients at the time of presentation with nephrotic syndrome due to FSGS into those who would benefit from immunosuppression versus those who will not. Biomarkers identified via proteomic or metabolomic studies may provide noninvasive strategies in the future to better determine the etiology of disease at presentation with implications for treatment.[68,69] The classification of FSGS is likely to evolve further over time.

Diagnosis: Genetic Testing

Practice Point 6.1.2.1: Genetic testing may be beneficial for selected patients with FSGS who should be referred to specialized centers with such expertise (Figure 53).

Commentary

This recommendation is a change from the 2012 guideline that specifically suggested that nephrologists "not perform genetic testing" in adults with FSGS.[70] Genetic testing is now specifically recommended for patients with familial kidney disease or syndromic features. We agree with this practice point. In addition, we suggest that patients with steroid-resistant FSGS receive genetic testing. Over the past 10 years, there has continued to be an explosion of new information about the genetic causes of FSGS. For adults with steroid-resistant nephrotic syndrome and FSGS on biopsy, up to 11% to 24% will have disease-causing variants primarily in type IV collagen or podocyte genes.[71-73] These results have implications for treatment and prognosis.

Clinical Utility

Identification of a causative variant in a patient with FSGS has a number of potential clinical benefits. First, patients with genetic causes of FSGS are much less likely to respond to immunosuppression, thus this knowledge can spare individuals exposure to potentially toxic therapies with significant risk for complications. Second, patients with a genetic cause of FSGS are much less likely to have disease recurrence after kidney transplantation, although there have been some reported exceptions.[74] Patients without a genetic cause should receive counseling about the risk of recurrent disease. Next, results of genetic testing may impact enrollment in clinical trials as novel molecular therapies are currently being tested. Finally, identification of an FSGS-causing variant in a patient can help to identify other family members who may be at risk so that they can be diagnosed and treated early.[75]

Implementation and Challenges

Access to genetic testing in the United States is limited by insurance coverage in many cases. Even if some of the cost of testing is covered by insurance, there may be significant co-pays for patients, thus there remain significant barriers to testing. Additionally, the suggestion that such patients should be referred to a specialized center for genetic testing may limit access for patients who do not have the resources to travel to a referral center. The availability of low-cost testing options offered through various commercial companies may improve access for patients.[76]

Treatment: Management of FSGS-UC and Secondary FSGS

Practice Point 6.2.1.1: Immunosuppression should not be used in adults with FSGS of undetermined cause (FSGS-UC) or in those with secondary FSGS.

Commentary

It is important to remember FSGS is not a specific disease process but a morphologic lesion described from kidney pathology. The kidney biopsy is pivotal in differentiating primary and secondary causes of FSGS. A proposed classification system for FSGS divides patients into primary FSGS, genetic FSGS, secondary FSGS, and FSGS-UC (see Practice Point 6.1.1.1 at the beginning of this section). FSGS-UC is a new addition in the 2021 guideline, and this category has features similar to a maladaptive secondary FSGS.[77]

Clinical Utility

We agree immunosuppressive medications are unlikely to be beneficial in FSGS-UC or in those with secondary FSGS, and a limited case-by-case trial of glucocorticoid therapy may be warranted in HIV-associated nephropathy (HIVAN). We agree that RAS blockade, blood pressure control, sodium restriction, and treating secondary causes of FSGS is most important in FSGS-UC and secondary FSGS.

Implementation and Challenges

In general, there is a consensus that secondary FSGS does not need immunosuppression. FSGS-UC will need more research in determining the underlying etiology and prognosis. Also, more education is needed for nephrology providers about this new category FSGS-UC that has features similar to a maladaptive secondary FSGS.

Treatment: Initial Treatment of primary FSGS

Recommendation 6.2.2.1: We recommend that high-dose oral glucocorticoids be used as the first-line immunosuppressive treatment for primary FSGS *(1D)*.

Commentary

We agree with this recommendation (and Figure 54 on initial treatment of primary FSGS, which is referred to by some of the underlying practice points) and that the risks of using glucocorticoids are outweighed by the ongoing effects of the nephrotic syndrome and the high risk of CKD progression and kidney failure if the disease is left untreated. A large observational study of 281 patients with nephrotic FSGS demonstrated a high rate of complete and partial remission in patients treated with high-dose prednisone.[78] Also, a large retrospective study with 458 patients with FSGS comparing glucocorticoids to CNI in early FSGS treatment showed glucocorticoids and CNI with improved renal outcomes, but it did not demonstrate a superiority of CNI over glucocorticoids.[79]

Clinical Utility

In patients with *primary* FSGS, high-dose oral glucocorticoid therapy should be the first-line therapy. Glucocorticoids are inexpensive and widely available medications in comparison to alternatives. Considerations should be made to patient choice when discussing the side-effect profile of glucocorticoids, particularly those with comorbid conditions such as uncontrolled diabetes which could worsen with glucocorticoid use, or those with psychiatric disorders whereby the psychological side effects of glucocorticoids may be severe.

Implementation and Challenges

The recommendation of glucocorticoids as the first-line therapy in primary FSGS is consistent with the previous 2012 guideline. The side-effect profile is the great challenge with glucocorticoids, and we agree with the precautions and prophylaxis measures as discussed in chapter 1 of the guideline. We agree that more research is needed in dosing and duration of glucocorticoid therapy. More investigation is needed on differentiating glucocorticoid treatment response in pathological subtypes of FSGS. Furthermore, more research is needed to develop novel and specific therapies for primary FSGS.

Practice Point 6.2.2.1: Suggested dosing schedule for glucocorticoids in the initial treatment of primary FSGS is outlined in Figure 54 below.

Practice Point 6.2.2.2: Initial high-dose glucocorticoids should be continued until complete remission is achieved, or as tolerated by patients up to a maximum of 16 weeks, whichever is earlier.

Practice Point 6.2.2.3: Adults with primary FSGS who respond to glucocorticoid treatment should receive glucocorticoids for ≥6 months.

Commentary and Clinical Utility

We agree with the dosing recommendations for glucocorticoids. We agree that it is not necessary to persist with high-dose glucocorticoid therapy for a full 16 weeks if the proteinuria is resistant to treatment, especially in patients who are experiencing glucocorticoid side effects. We agree that if a partial remission is achieved, a continuation of high-dose steroids up to 16 weeks, if tolerated, is reasonable. At 16 weeks, providers should begin to titrate down the dose of the glucocorticoid, and patients should receive glucocorticoid for at least 6 months of total duration.

Implementation and Challenges

This recommendation is consistent with the previous recommendation from 2012. Challenges in implementation include the side-effect profile of glucocorticoids and patient tolerance of those medications at a high dose and prolonged duration. The data for a goal of 16 weeks of high-dose glucocorticoid therapy are extrapolated from observational studies in patients with FSGS that demonstrated an increase in remission in patients who received high-dose glucocorticoid therapy for at least 16 weeks.[61,80-82] We agree any added benefit after 16 weeks of high-dose glucocorticoid in primary FSGS is unlikely, especially since FSGS patients are generally less likely to respond to therapy than MCD patients. More studies are needed in the FSGS population.

Practice Point 6.2.2.4: In adults with relative contraindications or intolerance to glucocorticoids, alternative immunosuppression with CNIs should be considered as the initial therapy in patients with primary FSGS (Figure 54).

Commentary

We agree with this practice point on CNI use.

Clinical Utility

We specifically agree with the text in the legend to Figure 54, which states "the most reasonable dosing of a CNI may be to titrate in the individual patient to obtain the desired effect on proteinuria, balancing dose escalation against Scr and reducing the dose if Scr increases but does not plateau or increases over 30% of baseline. If the Scr does not fall after dose reduction, the CNI should be discontinued."

Implementation and Challenges

There is a paucity of data on the optimal dosing of CNIs for FSGS, and most data are extrapolated from the kidney transplant literature. The kidney transplant data do provide a clinical range to use to prevent nephrotoxicity, but this may not correlate with clinical optimization in primary FSGS patients.

Special Situations: Steroid-resistant Primary FSGS

Recommendation 6.3.1.1: For adults with steroid-resistant primary FSGS, we recommend that cyclosporine or tacrolimus be given for ≥6 months rather than continuing with glucocorticoid monotherapy or not treating *(1C)*.

Commentary

We agree with this recommendation due to the side effects of glucocorticoid. Also, if the patient is not responding to glucocorticoid therapy within 16 weeks that patient should be considered to be steroid-resistant. CNIs have the most data and should be the preferred second-line agent for primary FSGS. We agree with the importance the KDIGO Work Group assigns to proteinuria reduction, the benefits of which may outweigh the potential negative side effects of CNI with close monitoring of kidney function and drug levels. The recommendation is updated in comparison to the 2012 guideline, which recommended cyclosporine only and an initial trial of at least 4-6 months with continuation for at least 12 months as long as the patient develops a partial or complete remission followed by a slow taper.

Clinical Utility

The accumulation of data for CNIs as the preferred option for steroid-resistant primary FSGS is strong in comparison to other agents. There have been RCTs comparing cyclosporine versus supportive therapy or continued glucocorticoid in patients with steroid-resistant FSGS, with improved renal outcomes in the cyclosporine group. The use of tacrolimus has not been studied in an RCT, but observational data show tacrolimus to be a comparable alternative. Providers must consider the side-effect profiles of these drugs, whereby tacrolimus might have more glucose intolerance and cyclosporine might have higher rates of dyslipidemia and hypertension.

Implementation and Challenges

The kidney transplant literature has shown a preference for tacrolimus over cyclosporine due to better graft outcomes, and thus more nephrology providers are familiar with the use of tacrolimus. These drugs are more expensive compared to glucocorticoids and are associated with long-term ischemic damage, thus increasing Scr in patients. However, the use of CNIs for 12 months with close monitoring of kidney function outweighs the negative effects of not treating patients with steroid-resistant FSGS, which has a high risk of progression of kidney disease and kidney failure if left untreated. Another challenge is the need for drug monitoring in these patients, which leads to an even further increase in the cost associated with CNI use.

Special Situations: CNI Dosing Schedule and Duration of Treatment

Practice Point 6.3.2.1: Treatment of steroid-resistant primary FSGS: Suggested dosing schedule for cyclosporine and tacrolimus (Figure 55).

Practice Point 6.3.3.1: Adults with steroid-resistant primary FSGS who respond to CNI treatment should receive CNIs for a minimum of 12 months to minimize the risk of relapse (Figure 55).

Commentary

We agree with the CNI dosing regimen. The duration recommendations are the same for initial treatment of primary FSGS.

Special Situations: Patients Resistant to or Intolerant of CNIs

Practice Point 6.3.4.1: Adults who have steroid-resistant primary FSGS with resistance to or intolerance of CNIs should be referred to specialized centers for consideration of rebiopsy, alternative treatment, or enrollment in a clinical trial (Figure 55).

Commentary

We agree that a rebiopsy, alternative treatment, or enrollment in a clinical trial is needed in a patient with steroid-resistant primary FSGS who is also resistant or intolerant to CNIs, especially as more easily obtained genetic data (eg, variants in *COL4A* or *APOL1*) may direct patients to specific clinical trials. This is new to the 2021 guideline; by contrast, the 2012 guideline suggested that patients with steroid-resistant FSGS who are unable to tolerate cyclosporine receive a combination of MMF and high-dose dexamethasone.

Clinical Utility

Limited data exist for all the alternative therapies, and we cannot recommend 1 therapy as a first-line therapy or

preferred agent in steroid or CNI-resistant or CNI-dependent patients.

Limitations and Challenges

More research is needed in the use of alternative therapies such as rituximab, corticotropin (ACTH), MMF with high-dose dexamethasone, cyclophosphamide, and low-density lipoprotein apheresis.

Special Situations: Management of Relapse

Practice Point 6.3.5.1: Adults with previous steroid-sensitive primary FSGS who experience a relapse can be treated using the same approach as that for adults with relapsing MCD (Figure 47).

Commentary

See the MCD information.

Guideline Statements and Commentary: Infection-related Glomerulonephritis

Bacterial Infection-related GN: Diagnosis

Practice Point 7.1.1.1: Kidney biopsy can be useful in suspected bacterial infection-related glomerulonephritis (GN), particularly when culture evidence of infection is elusive or the diagnosis is in doubt, to assess prognosis, and/or for potential therapeutic reasons. In some cases, biopsy may be critical for arriving at the correct diagnosis, as comorbidities may contribute to confounding effects (Figure 56).

Commentary

We generally agree with this practice point. The diagnosis of infection-related GN can be challenging, and kidney biopsy remains the gold standard. Just as the epidemiology and infecting organisms have grown beyond the traditional nomenclature of "poststreptococcal GN," the histology has evolved as well. The classic neutrophilic infiltrate and subepithelial dome-like humps of classic poststreptococcal GN can still be seen, but entities such as IgA-dominant infection-related GN are increasingly more common in older patients with staphylococcal infections.[83]

Clinical Utility

Despite the kidney biopsy's diagnostic utility, treatment is geared toward the clinical picture rather than the tissue-specific findings, regardless of the histologic lesion. A presumptive diagnosis also can be made with positive cultures and/or serologic markers in patients with glomerular injury, particularly in children. Even with an elusive infection, confirming a diagnosis of infection-related GN with a kidney biopsy rarely affects treatment and may not be necessary unless there is high suspicion for alternative diseases.

Implementation and Challenges

There is a broad range of histologic findings seen in bacterial-infection related GN. The spectrum is heterogeneous and evolving, and standardization between various case series is challenging. It should also be noted that some immune- or complement-mediated kidney diseases can be unmasked or triggered by infections.

Bacterial Infection-related GN: Prognosis and Treatment

Practice Point 7.1.2.1: Prognosis and suggested therapy of bacterial infection-related GN (Figure 57).

Commentary

We agree with Figure 57, as there are no randomized data to guide our treatment, and that antibiotics should universally be given for treatment of the underlying infection.

Clinical Utility

The decision to use glucocorticoids in these disorders should weigh the potential risk of worsening infection versus the potential kidney benefit. Immunosuppressive agents should only be considered in those with rapidly progressive disease such as crescentic GN, and should account for the possibility of exacerbating the infection. Every attempt should be made to initiate specific antibiotic therapy and control the source of infection whenever possible prior to using steroids.[84]

HBV Infection-related GN: Diagnosis

Practice Point 7.2.2.1.1: Patients with proteinuric glomerular disease should undergo testing for HBV infection.

Commentary

We agree with this practice point given the prevalence of chronic HBV infection affecting more than 5% of the world's population,[85] in addition to the increased incidence of co-infections with HIV and HCV.

Clinical Utility

Given the relatively low cost and wide availability, serologic testing for HBV should be performed in all patients with proteinuric glomerular disease.

HBV Infection-related GN: Prognosis

Practice Point 7.2.2.2.1: Adult patients with chronic HBV infection should be considered at risk for the development of kidney failure.

Commentary

We agree with this practice point as it pertains to glomerular diseases related to chronic infection such as

MN, where it has been shown that HBV co-infection increases the likelihood of kidney failure and warrants antiviral treatment to preserve kidney function.[86] However, this statement is a generalization that does not apply to all forms of chronic kidney disease. While treatment of chronic HBV infection in CKD has benefits related to viral complications (eg, cirrhosis and hepatocellular carcinoma), coexisting HBV infections are a controversial independent risk factor for the development of kidney failure.[87]

Clinical Utility

Despite the lack of clear causative data, nearly all patients should be considered candidates for antiviral treatment as outlined in Recommendation 7.2.2.3.1.

HBV Infection-related GN: Treatment

Recommendation 7.2.2.3.1: We recommend that patients with replicative HBV infection (as denoted by HBV DNA levels >2000 IU/ml) and GN receive treatment with nucleos(t)ide analogues as recommended for the general population by standard clinical practice guidelines for HBV infection *(1C)*.

Commentary

We agree with this recommendation.

Clinical Utility

The guideline makes note of many older agents such as interferon α that were poorly tolerated and had low efficacy in addition to having unique nephrotoxic side effects. The newer nucleos(t)ide analogues are oral agents that have higher efficacy and a lower rate of nephrotoxic side effects.

Implementation and Challenges

Despite higher efficacy and improved tolerability, the newer nucleos(t)ide analogues are also more costly. There are very few RCTs comparing the several drugs available to treat chronic HBV infection. Some analogues such as adefovir and tenofovir have higher rates of nephrotoxicity than others, and serial monitoring of kidney function and dose-adjustment based on GFR is necessary for all patients undergoing treatment.

Practice Point 7.2.2.3.1: Pegylated interferon regimens should not be used to treat patients with replicative HBV infection and GN.

Practice Point 7.2.2.3.2: Immunosuppressive agents, such as cyclophosphamide or rituximab, may accelerate HBV replication and should be avoided in patients with untreated replicative HBV infection and GN.

Practice Point 7.2.2.4.1: Rituximab and cyclophosphamide should be avoided in patients with simultaneous HBV infection and anti-PLA2R antibody-mediated MN until a sustained virologic remission has been obtained by nucleos(t)ide analogue therapy.

Commentary

We agree with Practice Points 7.2.2.3.1-7.2.2.3.2 and generally agree with Practice Point 7.2.2.4.1. HBV reactivation is a serious disorder that can be induced by immunosuppressive agents such as B-cell–depleting and alkylating agents, which are first-line agents for severe primary MN.[88] Although serum anti-PLA_2R antibodies are highly specific for primary MN, they cannot be used to differentiate primary MN from HBV-associated MN, as some studies have shown high rates of double positivity with overlap of PLA_2R and hepatitis B surface antigen (HBsAg) along the capillary loop.[89]

Clinical Utility

Given the high efficacy of nucleo(s/t)ide analogue therapy in suppressing viral replication, it is most reasonable to initiate antiviral agents in nonemergent scenarios prior to utilizing immunosuppressive therapy in patients with simultaneous HBV infection and also anti-PLA_2R antibody-mediated MN. This allows the clinician not only to determine if the MN was secondary to the HBV infection, but also to minimize the amount of virus in the body prior to immunosuppression. Although data are limited, it would not be unreasonable to initiate rituximab or cyclophosphamide in conjunction with antiviral HBV treatment in rare extenuating circumstances. MN with RPGN or severely nephrotic disease may not be able to wait until virologic remission is obtained prior to initiating higher risk immunosuppression. In these unusual scenarios, we recommend a multidisciplinary approach in conjunction with hepatology to determine the ideal treatment approach.

HBV Infection-related GN: Special Situations

Practice Point 7.2.2.4.2: Plasma exchange may be tried in patients with accompanying cryoglobulinemic vasculitis.

Practice Point 7.2.2.4.3: Children with HBV infection and MN should be managed conservatively without immunosuppression due to a high likelihood of spontaneous remission of the kidney disease.

Commentary

We agree with these practice points.

HIV-related GN: Diagnosis

Practice Point 7.2.3.1.1: A kidney biopsy should be performed, when feasible, to evaluate the morphology of HIV-related kidney disease. A pathology-based description of HIV-related kidney disease should be used to help define and guide therapy.

Commentary

We endorse the recommendation of a kidney biopsy being performed when considered necessary and feasible to

evaluate HIV-related kidney disease. HIV directly infects the kidney, with pathological changes seen in the glomerulus, interstitial space, and vasculature, along with side effects from medications including antiretroviral agents and prophylactic therapy for opportunistic infections, and pathology from chronic comorbidities such as diabetes and hypertension. The pathological diagnosis obtained from a kidney biopsy is essential in guiding therapy, and this topic was evaluated extensively in a KDIGO Controversies Conference.[90]

Glomerular podocytopathy in the form of a collapsing FSGS is considered classic HIVAN and is predominantly seen in patients of African ancestry. High-risk variants of *APOL1* have been associated with increased risks of classic HIVAN and FSGS (Figure 60 in the guideline). This entity is now being distinguished from FSGS not otherwise specified (NOS) (ie, FSGS without collapsing features) in the guideline; this differs from the 2012 guideline, which did not make a clear distinction in the terminology for HIVAN. In the 2012 guideline, morphological changes likely due to interferon changes associated with HIV are brought to attention, such as microcystic dilatation and tubuloreticular inclusions. The term HIV-associated immune complex kidney disease (HIVICK) has been used to classify a number of HIV immune complex diseases such as IgAN, lupus-like GN, MN, and membranoproliferative glomerulonephritis (MPGN). HIVICK was not used in the 2012 guideline but has since gained popularity in the nephrology community. The 2021 work group recommends eliminating the term HIVICK because there is a lack of certainty that HIV is responsible for those pathological changes.

Clinical Utility

We understand that uncertainty exists, and we do believe that providers should consider a complete clinical evaluation of HIV patients with the understanding that treating comorbid conditions and infections such as HCV are important for patient care. The differential diagnosis in HIV-related kidney disease is broad and includes HIVAN, FSGS NOS, and immune complex GN, which is sometimes referred to as HIVICK. But tubulointerstitial diseases such as diffuse infiltrative lymphocytosis syndrome and diseases affecting the vasculature like thrombotic microangiopathy can also be seen.[91]

Implementation and Challenges

The differential diagnosis for HIV-related kidney disease is broad, and providers should consider a kidney biopsy when indicated and feasible. A pathological diagnosis will guide treatment plans. Due to a dearth of research, there are still controversies about HIV and its role in certain conditions such as the addition of FSGS NOS and about differentiating it from HIVAN with collapsing FSGS features. The lack of data also applies to HIV immune complex–related diseases such as IgAN and MPGN.

HIV-related GN: Prognosis

Practice Point 7.2.3.2.1: The factors contributing to the long-term outcome of HIV infection associated with GN are numerous and include persistence of viral replication, response to antiviral treatment, genetic predisposition to glomerular injury (e.g., *APOL1* risk alleles), coinfection with other viruses, and development of immune complex disease or thrombotic microangiopathy. Thus, the estimation of prognosis in individual patients can be very difficult.

Commentary

The practice point acknowledges the lack of data in outcomes and prognosis of patients with HIV-related kidney disease. Factors that contribute to the prognosis in these patients include genetics such as *APOL1* high-risk variants and possibly sickle cell trait, along with age, race and ethnicity, concomitant substance abuse, history of AKI, and the presence of comorbid conditions such as diabetes, hypertension, and malignancy. Also contributing are infection-related risk factors such as CD4 count and HIV viral load, and the presence of co-infections such as HBV, HCV, and syphilis.[90] *APOL1* high-risk variants (G1, G2) are being recognized as a strong predictor of adverse kidney outcomes from HIVAN, FSGS, and COVID-19–associated nephropathy in patients infected with SARS-CoV-2.[92,93]

Patients infected with SARS-CoV-2 may develop associated glomerular disease, with reports ranging from immune complex-related disease such as a diffuse proliferative GN and ANCA-associated GN, but the most commonly reported cases are of a nephrotic syndrome due to FSGS. A number of the reports have been a collapsing FSGS[92,93] that resembles other virus-associated FSGS such as HIV-associated nephropathy, which has led some to refer to this as COVAN (COVID-19–associated nephropathy).[94] Also, similar to HIVAN, COVAN has been associated with high-risk *APOL1* genotype with 50% to 100% of patients with high-risk alleles.[92,93] These case series have described severe kidney disease, with one series having two-thirds of patients requiring dialysis[92]; long-term data in patients with COVAN are needed.

Clinical Utility

The factors contributing to the long-term outcome of HIV-related kidney diseases are copious, and the estimation of prognosis is challenging in these patients.

Implementation and Challenges

There is a need for more research examining the prognosis of HIV-related kidney disease. Also, more studies are needed examining the role of *APOL1* in patients of African ancestry with HIV-related kidney disease, and testing for *APOL1* high-risk variants in patients is not universally recommended. Novel treatments for *APOL1* are currently being tested[95]; future *APOL1* testing in the general HIV

population may become beneficial if a therapeutic agent becomes available.

HIV-related GN: Treatment

Recommendation 7.2.3.3.1: We recommend that antiretroviral therapy be initiated in all patients with HIV and CKD, especially biopsy-proven HIV-associated nephropathy (HIVAN), regardless of CD4 count, adjusted to the degree of kidney function *(1C)*.

Commentary

We agree with this strong recommendation that antiretroviral therapy be initiated in all patients with HIV and CKD regardless of CD4 count. This recommendation is broader in comparison to the KDIGO 2015 recommendation to start antiretroviral therapy immediately in patients with kidney biopsy-proven HIVAN only. The side-effect profile of antiretroviral medications has improved, and the benefits outweigh potential side effects in our patients with HIV-related kidney disease. This approach is supported by 2 large trials, and this approach has expanded to all patients with HIV. The TEMPRANO ANRS 12136 Study Group examined the benefits of early antiretroviral therapy, isoniazid preventive therapy, or both among HIV-infected adults with high CD4 cell counts in sub-Saharan Africa.[96] A total of 2,056 patients with a CD4 count < 800/μL were followed for 4,757 patient-years. Immediate (early) antiretroviral therapy and isoniazid preventive therapy led to lower rates of severe illness than deferred antiretroviral therapy and no isoniazid preventive therapy, and this effect was also seen among patients with CD4 cell counts > 500/μL. The INSIGHT START Study Group randomized 4,685 patients who were followed for a mean of 3 years with a median CD4 count of 651/μL. Interim analysis determined the patients in the deferred-initiation group be offered antiretroviral therapy because of the net benefits seen in the early asymptomatic treatment arm.[97]

Clinical Utility

Early treatment of HIV has become the standard of care in the treatment of HIV-positive patients, with the 2016 International Antiviral Society-USA Panel recommending all individuals with HIV infection with detectable viremia to be treated with antiretroviral therapy.[98] This will be a change for certain providers who are accustomed to treating patients with HIV when they have a lower CD4 count, opportunistic infection, or classic HIVAN. There is likely a consensus due to data showing less HIVAN in the modern era of antiretroviral therapy and improvement in HIVAN patients' kidney outcomes with treatment. Uncertainty remains about HIV's direct role in HIVICK and the role of antiretrovirals in improving kidney outcomes in those patients. A retrospective cohort study of 47 patients with lesions other than HIVAN did not demonstrate a beneficial effect among HIV patients with kidney diseases other than HIVAN.[99] A nested case control study of 751 HIV-infected patients showed that both HIVICK and HIVAN were predominant in patients of African ancestry and more advanced HIV disease, but antiretroviral therapy use was not associated with lowering risk of kidney failure.[100] Another study did demonstrate a benefit in renal outcomes with antiretrovirals, but it was a small cohort (n = 16) of HIVICK patients and not statistically significant.[101]

Implementation and Challenges

There are no randomized clinical trials to assess concrete kidney outcomes in this early treatment method in HIVAN and other HIV-related kidney diseases, and these recommendations are based on strong clinical data, including randomized controlled trials from the overall HIV-positive population. Consideration was given to the side effects and costs of antiretroviral agents, but these potential deleterious effects are lower than the costly risks of needing kidney replacement therapy, especially in resource-poor areas. HIV patients who do not receive treatment have more severe CKD and a higher risk of kidney failure. A clear benefit has been shown in HIVAN patients, but more research is needed in other HIV-related kidney diseases.

Practice Point 7.2.3.3.1: A decision for the use of glucocorticoids as an adjunct therapy for HIVAN must be made on a case-by-case basis, as the risks and benefits long-term are uncertain.

Commentary

Early observational studies demonstrated a benefit from additional therapy besides antiretroviral therapy in HIVAN, including ACEI and glucocorticoid therapy. There is uncertainty in the risk versus benefits profile of glucocorticoid therapy in HIVAN, and this practice point recommends a case-by-case determination of glucocorticoid therapy use. We also bring to attention other issues such as co-infection with HBV or HCV, or the risk of other infections such as SARS-CoV-2 that must be considered when using glucocorticoid therapy in HIV patients and especially those untreated with antiviral agents.

Clinical Utility

Providers must weigh the risk-benefit profile in each patient when determining the need for glucocorticoid therapy in HIVAN, such as co-infection, degree of CKD, furthering immunosuppression in an immunocompromised patient, and patient adherence to therapy.

Implementation and Challenges

We agree with the guideline that more research is needed in HIVAN and immune-complex GN in HIV to determine

benefits of antiretroviral therapy, RAAS inhibition, and glucocorticoids.

Schistosomal Nephropathy: Diagnosis

Practice Point 7.3.1.1.1: Test for appropriate endemic coinfections (*Salmonella*, HBV, HCV, HIV), as targeted treatment may alter the aggressiveness of an underlying GN or the sequela of schistosomiasis.

Practice Point 7.3.1.1.2: Obtain a kidney biopsy in patients suspected of having schistosomal GN in the presence of a viral coinfection (HCV, HBV, HIV).

Commentary

We agree with Practice Point 7.3.1.1.1. In the guideline, the explanatory text under Practice Point 7.3.1.1.2 provides a general recommendation for kidney biopsy in a schistosome-infected patient with a GN with overt or progressive kidney disease (proteinuria > 1 g/d, hypocomplementemia, hematuria, reduced GFR) but offers that a kidney biopsy can reasonably be deferred in mild disease with the recommendation of empirical treatment of schistosomal infection with antiparasitic therapy.

Clinical Utility

The ability to detect parasitic antigens in the glomeruli can only be done in specialized laboratories, and that should be taken into consideration when considering the utility of kidney biopsy in schistosomal GN.

Schistosomal Nephropathy: Treatment and Special Situations

Practice Point 7.3.1.2.1: Treat patients with schistosomal infection and GN with an appropriate antiparasitic agent in sufficient dosage and duration to eradicate the organism. There are no indications for use of immunosuppressive agents in schistosomal nephropathy.

Practice Point 7.3.1.3.1: Monitor patients with hepatic fibrosis from schistosomiasis for the development of kidney disease.

Practice Point 7.3.1.3.2: Evaluate patients with a history of schistosomiasis and an elevated SCr and/or hematuria for bladder cancer and/or urinary obstruction.

Commentary

We agree with these practice points.

Filariasis and Glomerular Disease: Treatment

Practice Point 7.3.2.1.1: Treat patients with filarial infection and GN with an appropriate antiparasitic agent in sufficient dosage and duration to eradicate the organism.

Commentary

We agree with this practice point.

Malarial Nephropathy: Treatment

Practice Point 7.3.3.1.1: Treat patients with malarial infection and GN with an appropriate antiparasitic agent in sufficient dosage and duration to eradicate the organism from blood and hepatosplenic sites. There are no indications for use of immunosuppressive agents in malarial nephropathy.

Commentary

Malarial infection can be associated with AKI, acute GN, or a chronic progressive GN. Treating patients with appropriate antiparasitic agents is important, but unfortunately patients can still have progressive disease or develop malaria-associated kidney disease even after treatment of a malarial infection. At this time, there is insufficient evidence to recommend glucocorticoid therapy.

Clinical Utility

Appropriate treatment of malarial infection is needed for malaria-associated kidney disease. Malarial infection in the United States is unlikely but must be considered in patients with international travel to at-risk countries.

Implementation

If malarial infection is suspected, an infectious disease expert is suggested for specific malarial treatment as treatment differs depending on malarial subtype, and some treatments require G6PD deficiency testing and pregnancy-related dosing.

Guideline Statements and Commentary: Immunoglobulin- and Complement-mediated Glomerular Diseases With a Membranoproliferative Glomerulonephritis (MPGN) Pattern of Injury

Since the 2012 guideline, the concept of MPGN as a single diagnosis or disease has been rendered obsolete, and this is well represented in the title and text of the current chapter. The term MPGN merely reflects a characteristic pattern of injury with multiple different causes; the specific etiologies can be narrowed down by correlating clinical associations with the patterns of immunoglobulin and complement immunofluorescence staining on biopsy.[102,103]

Historically, during the era when this pattern was labeled as a disease, the renal presentation was typically one of hypertension, hematuria, proteinuria (often nephrotic), and hypocomplementemia. On biopsy, the light microscopy findings classically had basement membrane duplication, "tram-tracking," and a lobular appearance. MPGN was further classified on the presence and location of deposits on the electron microscopy. Etiologies of MPGN were attributed to either HCV or "idiopathic" causes. However, neither the clinical renal presentation nor electron microscopy biopsy classification were found to be helpful to delineate the underlying cause.[102-104]

Due to a growing understanding of the distinct pathogenetic mechanisms underlying the MPGN pattern of injury, and since light microscopy and electron microscopy findings lack specificity for an underlying diagnosis, a modern biopsy classification scheme has been developed that correlates the immunofluorescence findings to more specific disease processes. Three distinct patterns of immunofluorescence exist: (1) immune complex–mediated (immunoglobulin-positive with or without complement), (2) complement dominant (immunoglobulin-negative complement-positive), or (3) immunofluorescence-negative (immunoglobulin-negative complement-negative). Figures 68 and 69 in chapter 8 of the guideline describe distinct diseases that can give rise to these immunofluorescence findings. For (1) immune complex–mediated MPGN, the classification is split into whether the immunofluorescence has monoclonal restriction (in which case, plasma cell disorders or monoclonal gammopathy of renal significance [MGRS] are considered),[105,106] or polyclonal immune complex deposition (due to either infections or autoimmune disorders[107]). For (2) complement dominant MPGN, C3/C4 GN and dense deposit disease (DDD) are etiologies due to immune or genetic complement activation.[108-110] Finally, for (3) negative immunofluorescence MPGN, vascular diseases predominate such as thrombotic microangiopathies or sickle cell disease. Rarely, some patients will still be considered idiopathic if none of the above are found.[104]

As there are essentially no high-quality trials that have enrolled patients according to this new classification (ie, limiting the trial to a single etiologic cause), there are no formal evidence-based recommendations in this chapter. Practice points are given to guide clinical decision making until more evidence exists. We therefore stress the importance of enrolling patients with these diseases into clinical trials where available.

The chapter is appropriately divided between diagnosis and treatment, with the guiding principle being that treatment must be targeted to the specific disease subtype.

Diagnosis of Immune Complex-Mediated GN

The suggestions for diagnostic workup are algorithmic and proceed from the most common, easiest to detect to the rarer disorders that may require a difficult and expensive workup. We agree in general with this approach.

Practice Point 8.1.1: Evaluate patients with immune complex-mediated GN (ICGN) for underlying disease (Figure 68).

Commentary

A pattern of MPGN with dominance of polyclonal immunoglobulin and complement is most often due to infectious or autoimmune disease, and thus the practitioner should screen for underlying infections (eg, HBV or HCV, bacterial or parasitic disease) or autoimmune disease with appropriate serologies. In rare cases, malignancy should be considered as a source of chronic antigenemia. Treatment should focus on the underlying cause.

Practice Point 8.1.2: Evaluate patients with GN and monoclonal immunoglobulin deposits for a hematologic malignancy.

Commentary

The finding of immunoglobulin subclass or light chain restriction by immunofluorescence warrants workup for a paraprotein with serum and urine electrophoresis and immunofixation and free light chain analysis. Involvement of a hematologist is often useful for diagnosis of the clonal process (although a B-cell clone may not ultimately be found) as well as treatment of the MGRS. Additionally, a finding of an otherwise unexplained MPGN pattern of injury with or without the presence of a paraprotein in plasma or urine may require further tissue interrogation with antigen retrieval or further subclass-specific stains that could reveal proliferative GN with monoclonal immune deposits (PGNMID).[111] Of note, a clonal process is only found in about 30% of cases with PGNMID, and novel immunofluorescence methods have detected a polyclonal process in some cases.[112]

Practice Point 8.1.3: If no underlying etiology is found for ICGN after extensive workup, evaluate for both complement dysregulation and drivers of complement dysregulation (Figure 70).

Commentary

Before labeling the cause of ICGN as idiopathic, evaluation for genetic and immune complement dysregulation should be performed, as well as work up for plasma cell dyscrasias (as above). Such a workup should occur even in the absence of hypocomplementemia.[109]

Practice Point 8.1.4: Rule out infection-related GN or post-infectious GN prior to assigning the diagnosis of C3 glomerulopathy (C3G).

Commentary

We agree that prior or active infection be ruled out before a diagnosis of C3GN can be given. However, this process is often difficult as often an infection can be a trigger for an underlying complement abnormality. In addition to clinically evaluating for an infection, a comprehensive complement analysis is necessary to assist with the diagnosis of C3GN.[109]

Practice Point 8.1.5: Evaluate for the presence of a monoclonal protein in patients who present for the first time with a C3G diagnosis at ≥50 years of age (Figure 69).

Commentary

We agree with this important suggestion based on the fact that certain monoclonal proteins can activate the complement pathway without necessarily leading to immunoglobulin deposition.[113,114] This is more common in older adults but can occur at lower frequencies in younger adults. Therefore, we disagree with the strict age cutoff and would

recommend that a search for a paraprotein should be considered in any adult patient with complement-dominant MPGN. As monoclonal proteins are known to affect the complement cascade and can even clinically present as a complement-mediated hemolytic uremic syndrome (HUS),[115,116] we recommend serum and urine immunoelectrophoresis and immunofixation as well as a serum free light chain analysis for all adult patients with C3GN.

Clinical Utility and Implementation

We strongly agree that every effort should be made to ascertain the etiology of the MPGN pattern. Screening for viral infections with HBV and HCV serologies or autoimmune disease with antinuclear antibody (ANA) or more specific autoantibodies are routinely available in most settings, as are general tests for paraproteins.

Figure 70 of the guideline lists the specialized complement tests that could be considered in looking for a cause of complement dysregulation. However, many of these tests are not routinely available with commercial laboratories, and thus sending samples to specialized laboratories should be considered when this is feasible. Collecting and storing the sample for specific complement tests may also be labor intensive, and practitioners should speak with their clinical laboratories about how best to collect and send these specialized tests to one of a number of centers able to do these specialized tests.

Treatment of Immune-Complex GN

We agree that the specific treatment should be focused on the underlying process, with major considerations including treating an underlying infectious, malignant, or clonal process;[117] controlling inflammation with broadly immunosuppressive agents; or focusing on complement inhibition, a growing field in therapeutics for glomerular disease. This treatment section is largely devoted to immune complex–mediated MPGN, with the next section pertaining to complement-dominant disease (ie, C3GN).

Practice Point 8.2.1.1: When the cause of ICGN is determined, the initial approach to treatment should focus on the underlying pathologic process.

Commentary

We agree that the underlying etiology responsible for the immune complex GN should be targeted.[118] If infection is deemed to the causal or initiating factor and the kidney disease is still progressing despite control of the infection, concomitant immunosuppression can be considered.[119] An example of this would be a patient who has achieved a sustained viral response in HCV-associated MPGN but continues to have active GN and nephrotic-nephritic syndrome. In this case, corticosteroids and/or other immunosuppression could be considered.

The next few practice points offer guidance on immunosuppression for differing severities of glomerular disease according to a risk-benefit analysis. We agree with these points with additional commentary as noted below.

Practice Point 8.2.1.2: Indolent ICGN, whether idiopathic or linked to a primary disease process, is best managed with supportive care and carefully considered use of immunosuppression.

Practice Point 8.2.1.3: For patients with idiopathic ICGN and proteinuria <3.5 g/d, the absence of the nephrotic syndrome, and a normal eGFR, we suggest supportive therapy with RAS inhibition alone.

Commentary

This is also a reasonable suggestion with the caveat that severe inflammation on biopsy (eg, cellular crescents or focal necrosis) would warrant immunosuppressive treatment in the absence of active infection.

Practice Point 8.2.1.4: For patients with idiopathic ICGN, a nephrotic syndrome, and normal or near-normal SCr, try a limited treatment course of glucocorticoids.

Commentary

We agree that glucocorticoids could be considered in this situation as initial immunosuppressive treatment. In the absence of robust data, if a patient has an absolute or relative contraindication to glucocorticoids, is unwilling to take them, or has a less than satisfactory initial response, we would instead consider therapy with MMF, anti-CD20 agents such as rituximab[120] or cyclophosphamide, but not CNIs. Long-term use of CNIs is associated with immune complex-negative MPGN and thrombotic microangiopathy[121] and should be avoided if possible as a treatment until further data exist.

Practice Point 8.2.1.5: For patients with idiopathic ICGN, abnormal kidney function (but without crescentic involvement), active urine sediment, with or without nephrotic-range proteinuria, add glucocorticoids and immunosuppressive therapy to supportive care.

Commentary

We agree that the presence of abnormal kidney function with nephritic syndrome and proteinuria, in the absence of crescents, should be treated with immunosuppressive therapy and supportive care. Similar to above, we agree with prednisone as an initial therapy, but if there are contraindications, reluctance, or lack of efficacy, we would instead recommend therapy with MMF, anti-CD20 agents, or cyclophosphamide.

Practice Point 8.2.1.6: For patients presenting with a rapidly progressive crescentic idiopathic ICGN, treat with high-dose glucocorticoids and cyclophosphamide.

Commentary

Severe forms of MPGN with crescents, focal necrosis, and/or RPGN warrants the most aggressive treatment, and we agree with prompt initiation of a regimen similar to that used to treat ANCA-associated vasculitis (see chapter 9 of the guideline) with either cyclophosphamide or rituximab along with pulse dose intravenous methylprednisolone followed by oral prednisone.

Practice Point 8.2.1.7: For most patients with idiopathic ICGN presenting with an eGFR <30 ml/min per 1.73 m^2, treat with supportive care alone.

Commentary

We need to highlight the subtext for this suggestion that limiting to supportive care does not apply to cases in which there is an active necrotizing or crescentic GN (or additional cause of active tubulointerstitial inflammation) as the cause of the low GFR. Cases with otherwise preserved renal parenchyma, significant acute tubular necrosis, and/or no significant fibrosis or atrophy also would not fall into this category. The choice for withholding immunosuppressive therapy should be based on overall renal viability, which can be assessed by a persistently (not acutely) low eGFR and biopsy findings of a high degree of interstitial fibrosis and tubular atrophy and/or glomerular sclerosis.

Practice Point 8.2.1.8: Patients who fail to respond to the treatment approaches discussed in 8.2.1.4 and 8.2.1.5 should be considered for a clinical trial where available.

Commentary

We agree that a clinical trial, where available, should be considered for refractory disease, but patients also should be considered for initial therapy if there are clinical trials recruiting in the area, since clinical trials with modern immunosuppressive therapies are still needed to find effective therapies for the subtypes of MPGN as categorized in the present classification system.

Treatment of C3 Glomerulopathy

This section encompasses glomerular diseases due primarily to complement dysregulation that results in discrete deposits of C3 or C4 in the glomerulus, as opposed to other C-dysregulatory disorders that result in endothelial injury alone such as "atypical" or complement-mediated HUS.[122] "C3 glomerulopathy" is a catch-all term that includes C3GN and the morphologically distinct C3DDD. One should also consider C4GN and C4DDD as related diseases in this treatment section.

Practice Point 8.2.2.1: In the absence of a monoclonal gammopathy, C3G in patients with moderate-to-severe disease should be treated initially with MMF plus glucocorticoids, and if this fails, eculizumab should be considered.

Commentary

We agree with this empirical approach based on the available literature.

Practice Point 8.2.2.2: Patients who fail to respond to the treatment approaches discussed in 8.2.2.1 should be considered for a clinical trial where available.

Commentary

All patients with C3GN, not only those who prove refractory to the initial therapy, should be considered for and offered participation a clinical trial in the recruiting phase when feasible, given the paucity of evidence to treat this condition, even prior to attempting empirical immunosuppression as recommended above. Many medications are under investigation that block the alternative pathway at specific sites (-copans) and are purported to block specific complement factors as opposed to the final common pathway blockade by eculizumab. This may one day give rise to targeted therapy based on individualized analysis of the complement cascade. Updated trials can be found at ClinicalTrials.gov.

Guideline Statements and Commentary: ANCA-associated Vasculitis

The clinical phenotypes of ANCA-associated vasculitis (AAV) include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). Kidney involvement is present in up to 75% of patients, often presenting clinically as RPGN with pauci-immune necrotizing and crescentic GN as the histologic hallmark.[123] Treatment choice in AAV is influenced by the presence of renal as well as extrarenal vasculitis. The pivotal AAV trials discussed in the guideline excluded patients with EGPA, so these recommendations are limited to patients with GPA and MPA.

Diagnosis of AAV

Practice Point 9.1.1: In the case of a clinical presentation compatible with small-vessel vasculitis in combination with positive myeloperoxidase (MPO)- or proteinase 3 (PR3)-ANCA serology, waiting for a kidney biopsy to be performed or reported should not delay starting immunosuppressive therapy, especially in patients who are rapidly deteriorating (Figure 71).

Commentary and Clinical Utility

This is a new practice point in the 2021 guideline and highlights the urgency in treating ANCA-associated glomerulonephritis (ANCA-GN). ANCA-GN often presents as RPGN, and timely initiation of immunosuppressive therapy is of utmost importance to swiftly control inflammation and preserve nephron function. While kidney biopsy remains the gold standard with

diagnostic and prognostic value in AAV, the combined presence of a clinical presentation compatible with small vessel vasculitis and a positive MPO/PR3 ANCA serology is sufficient to begin immunosuppressive therapy while awaiting kidney biopsy to be performed or reported. ANCA directed to either PR3 or MPO is present in 90% of patients with GPA and MPA,[124] so testing is recommended to screen for AAV.[125] The 2021 guideline lacks a discussion of the diagnosis of drug-induced vasculitis, which has important implications for the management of AAV. A number of therapeutic agents are associated with AAV, including hydralazine, propylthiouracil, cocaine adulterated with levamisole, and minocycline. The drug-induced AAVs are characterized by high-titre MPO ANCA positivity, dual MPO and PR3 ANCA positivity, and discordance of ANCA type by immunofluorescence and ELISA. They are often associated with positivity for ANA and antihistone antibodies, and in the case of levamisole-induced AAV, neutropenia and retiform purpuric rash are often present. In these individuals, discontinuation of the offending agent is critical to control AAV and to prevent relapses. Vasculitis mimics due to infection, malignancy, and other rheumatologic diseases can have similar presentation. In ANCA-negative patients, diagnostic kidney biopsy should be performed before starting immunosuppressive therapy.

Implementation and Challenges

The clinical course of ANCA-GN is characterized by rapid progression over days to weeks, with a significant proportion of patients requiring dialysis at presentation. With timely institution of therapy, more than 50% of ANCA-GN patients requiring dialysis experience renal recovery.[126] A multitude of patient- and treatment center-related factors can cause delays in performing and reporting a kidney biopsy. However, we should be cognizant of the fact that immunoassays for PR3 ANCA and MPO ANCA are not universally available and are poorly standardized. The turnaround time for the ANCA serology is variable, and where there is an anticipated delay in ANCA assays a kidney biopsy should be expedited to confirm the diagnosis.

Practice Point 9.1.2: Patients with ANCA-associated vasculitis (AAV) should be treated at centers with experience in AAV management.

Commentary and Clinical Utility

This is a new practice point in the 2021 guideline and emphasizes the need for specialized and collaborative care. Delays in diagnosis and treatment can have devastating consequences,[127,128] so AAV patients should be managed in centers with expertise in managing AAV. Physicians caring for AAV patients should be able to recognize vasculitis mimics and overlap syndromes of AAV with other connective tissue diseases, distinguish disease activity from infection and vasculitis damage, and diagnose and manage refractory vasculitis. Expertise in knowledge of immunosuppressives and therapy-related complications is needed considering the long-term use of immunosuppressives and changes in the therapeutic landscape in AAV. Finally, research in AAV is critically important, and vasculitis centers play an integral role in the execution of clinical trials.

Implementation and Challenges

Expertise in diagnosis and management of AAV is crucial; however, gaining such expertise may be difficult due to the rarity of the disease. The majority of the clinical practices in the United States have access to diagnostic procedures like computed tomography scans, magnetic resonance imaging, kidney biopsy, and lung biopsy. In terms of treatment modalities, dialysis, glucocorticoids, cyclophosphamide, and rituximab are widely available while access to plasma exchange may be limited to teaching hospitals. Furthermore, only a handful of dedicated vasculitis centers exist in the United States, and there is a need to develop care pathways to coordinate the care of AAV patients between vasculitis centers, academic centers, and community practices.

Prognosis of AAV

Practice Point 9.2.3.1: The persistence of ANCA positivity, an increase in ANCA levels, and a change in ANCA from negative to positive are only modestly predictive of future disease relapse and should not be used to guide treatment decisions.

Commentary

We agree with this point, which has been retained from the 2012 guideline. The association of an increase in ANCA titer with subsequent disease relapse is complex and is influenced by disease phenotype, ANCA type, and induction agent. Persistence of ANCA, rise in ANCA titer, and change in ANCA from negative to positive are not solely reliable predictors of disease relapse at an individual level, and treatment decisions should be informed by the clinical status of the patient in conjunction with other pertinent diagnostic studies confirming disease activity.

Clinical Utility

Although the diagnostic utility of ANCA is undisputed, its disappearance is not a prerequisite for defining complete remission, and the role of ANCA monitoring as a predictor of relapse remains controversial. ANCA titers decline with immunosuppressive therapy and may disappear in a proportion of patients. In PR3 ANCA patients treated with rituximab, disappearance of ANCA was associated with long-lasting remission.[129] An increase in ANCA titer or persistent ANCA is only modestly predictive of relapse.[130]

Nevertheless, in a single-center study, the rise in ANCA titer was a strong predictor of subsequent relapse in patients with kidney disease.[131] Analysis from the RAVE trial demonstrated that the rise in ANCA titer was predictive of relapse in patients treated with rituximab but only in patients with renal disease and alveolar hemorrhage.[132] In a Japanese study, reappearance of MPO ANCA but not ANCA persistence was significantly associated with relapse.[133] While ANCA monitoring alone is not helpful to guide treatment decisions, these data suggest that monitoring ANCA during remission can help in relapse prediction and identify patients who need close monitoring for relapse.

Implementation and Challenges

The utility of serial ANCA monitoring has considerable challenges, including definitions and tools to capture active disease and remission, method of ANCA testing, definition of increase in titer, and frequency of monitoring. Since the assays used vary between laboratories, standardization of the ANCA immunoassay is necessary for meaningful interpretation and utility.

Treatment: Induction Therapy

Recommendation 9.3.1.1: We recommend that glucocorticoids in combination with cyclophosphamide or rituximab be used as initial treatment of new-onset AAV *(1B)*.

Commentary and Clinical Utility

This recommendation is one of the most noticeable revisions from the 2012 guideline, which recommended cyclophosphamide as the initial induction therapy choice. We agree with this updated recommendation with the following clarification. Achievement of remission inversely correlates with risk of kidney failure and death.[134] Complete remission has been an important primary outcome in AAV induction trials, with all except the WGET and RAVE trials including only newly diagnosed patients.[135-137]

Cyclophosphamide in combination with glucocorticoids has the longest experience in treatment of AAV. This treatment regimen is associated with high remission rates, but with this remission comes the attendant risks of prolonged exposure, including infertility and increased risk of infection and malignancies.[138] CYCAZAREM[139] demonstrated that cyclophosphamide use for remission induction could be shortened, and CYCLOPS[140] demonstrated no difference in remission rates between intravenous and oral cyclophosphamide. Although the cumulative cyclophosphamide dose was higher in the oral group in CYCLOPS, it was associated with less disease relapse over the long-term follow-up.[141]

The RAVE and RITUXVAS trials demonstrated equivalence of rituximab to cyclophosphamide for achieving remission with a similar rate of severe adverse events.[137,142] In patients with relapsing disease and PR3 ANCA positivity, rituximab was superior to cyclophosphamide for remission induction.[137,143] It is important to note that the RAVE trial excluded patients with Scr > 4.0 mg/dL while the RITUXVAS trial enrolled patients with a median eGFR of 20 mL/min/1.73 m^2 and additionally included 2 doses of intravenous cyclophosphamide in the rituximab arm, reinforcing cyclophosphamide as the preferred induction agent in severe disease. On the basis of these trial results, cyclophosphamide and rituximab are both effective for remission induction in AAV, with rituximab preferred for relapsing disease and those with PR3 ANCA, and cyclophosphamide preferred for those presenting with severe kidney failure. It would be important to clarify the dosing of rituximab for remission induction. The FDA approved 4 weekly doses of 375 mg/m^2, but 2 doses of 1,000 mg rituximab given 2 weeks apart has been shown to be equally effective in retrospective studies; the choice between these 2 dosing regimens should be guided by patient preference. Importantly, a patient panel on the American College of Rheumatology ANCA guideline committee preferred rituximab over cyclophosphamide.[144]

While the 2012 guideline did not make suggestions or recommendations for use of MMF for induction therapy, Figure 76 of the 2021 guideline considers its use in mild to moderate disease. The MMF trials showed that this drug was as effective as cyclophosphamide for remission induction,[145,146] but it resulted in a higher relapse rate in the MYCYC trial, especially in PR3 ANCA patients, suggesting that MMF can be an alternative to cyclophosphamide in MPO ANCA patients with mild to moderate renal disease in whom avoidance of cyclophosphamide and rituximab is desirable.[145] Methotrexate was also noninferior to cyclophosphamide for remission induction of nonsevere extrarenal disease, but methotrexate also resulted in a higher relapse rate.[147] Lastly, avacopan, an oral C5a receptor inhibitor, was recently approved as an adjunct treatment for remission induction in AAV, and future algorithms for induction therapy will need incorporation of avacopan. The induction therapy of choice should therefore be guided by patient age, severity of renal dysfunction, alveolar hemorrhage, and ANCA serotype, as well as patient preference.

Implementation and Challenges

Rituximab is the most prescribed induction agent and cyclophosphamide the least prescribed induction agent, based on a recent analysis of AAV treatment patterns in patients from the Rheumatology Informatics System for Effectiveness (RISE) Registry, who are treated mainly by community rheumatologists.[148] However, delays may be anticipated in rituximab administration depending on medical insurance. The wide availability of glucocorticoids and cyclophosphamide is reassuring, and delays in treatment initiation are not anticipated.

Practice Point 9.3.1.1: A recommended treatment algorithm for AAV with kidney involvement is given in Figure 76.

Commentary and Clinical Utility

This algorithm stratifies treatment based on severity of organ involvement, but as presented needs some clarification. For patients with vital organ/life-threatening active AAV and Scr > 5.7 mg/dL, in addition to the consideration of plasma exchange, cyclophosphamide plus glucocorticoids should be added as the preferred induction regimen. With regard to maintenance therapy, the algorithm seems to suggest that azathioprine and rituximab are equivalent for remission maintenance. Based on results of the MAINRITSAN trial, rituximab would be preferred after cyclophosphamide induction,[149] and observational studies suggest effectiveness of rituximab for remission maintenance after rituximab induction.[150] Additionally, the preliminary results of the RITAZAREM trial suggested superiority of rituximab compared with azathioprine for remission maintenance in patients with relapsing AAV induced with rituximab.[151] Thus, we suggest using rituximab as the first-line maintenance agent and azathioprine as the second line.

Implementation and Challenges

While the goal of induction therapy is to achieve remission, we lack a robust and uniform definition of remission. The Birmingham Vasculitis Activity Score (BVAS)[152] is used in clinical trials to assess disease activity, with BVAS of 0 or 1 used to define remission. However, to a large extent we rely on a clinical definition of remission in day-to-day care of AAV patients, which is stabilization or improvement in Scr, resolution of hematuria, and absence of extrarenal signs of vasculitis. Laboratory data for disease activity should be monitored both to identify refractory disease and to evaluate treatment response. It is important to note, however, that the significance of persistent hematuria is unclear, and more than 40% of patients who are in clinical remission can have hematuria. There is a clear need for better biomarkers of disease activity to help customize therapy for patients.

Practice Point 9.3.1.2: In patients presenting with markedly reduced or rapidly declining GFR (SCr >4.0 mg/dl [>354 mmol/l], there are limited data to support rituximab and glucocorticoids. Cyclophosphamide and glucocorticoids are preferred for induction therapy. The combination of rituximab and cyclophosphamide can also be considered in this setting.

Commentary

We agree with this recommendation. Given the high risk of progression to kidney failure and the high mortality rate in this cohort, combination of glucocorticoids and cyclophosphamide is preferred due to their rapid onset of action. Observational studies conducted in the United Kingdom and United States using a combination of glucocorticoids, cyclophosphamide, and rituximab for treatment of such patients demonstrate excellent rates of remission and renal and patient survival. This combination regimen could be a reasonable option for patients presenting with severe kidney disease.[153,154]

Implementation and Challenges

This group of patients represents the most severe AAV phenotype and should be managed in dedicated vasculitis or GN clinics. In hospitalized patients, the therapies described above can be implemented without major hurdles. However, when the patient is discharged home, follow-up with physicians with expertise in management of AAV is critical due to the need for close monitoring for renal recovery, identify refractory or relapsing disease, therapy-related adverse events, and for adjustment of immunosuppressive dosing.

Practice Point 9.3.1.3: Considerations for choosing between rituximab and cyclophosphamide for induction therapy are given in Figure 77.

Commentary and Clinical Utility

This practice point is a new addition to the 2021 guideline that lists situations in which either rituximab or cyclophosphamide might be preferred. We would like to comment and clarify a few points here. Patient preference should be considered for treatment with both rituximab or cyclophosphamide. Glucocorticoid sparing is mentioned as a reason for rituximab preference. However, in the RAVE trial the glucocorticoid dosing was not different between the cyclophosphamide and rituximab arms, and in the PEXIVAS trial the subgroup analyses showed that use of standard-dose steroids compared with reduced-dose steroids in rituximab-treated patients had a favorable effect on the primary outcome of death and kidney failure. Additionally, one could consider preferential use of rituximab in patients when nonadherence to medical care is a concern. In the United States, rituximab is easily accessible as an FDA-approved medication, so preferring cyclophosphamide due to lack of rituximab access is not applicable. Although no definitive conclusion can be made regarding induction therapy choice in the elderly based on the current literature, we should be cognizant of the need for cyclophosphamide dose adjustment and monitoring for bone marrow suppression in the elderly population.[155]

Figure 78, which depicts considerations for choosing the route of administration of cyclophosphamide, lists factors that might influence the choice of providing cyclophosphamide intravenously or as an oral formulation. Both intravenous and oral cyclophosphamide are effective for remission induction and need meticulous monitoring for adverse events. We agree with the listed factors that consider the higher cumulative dose and higher incidence of leukopenia with daily oral cyclophosphamide. In addition, it might be beneficial to use intravenous cyclophosphamide for younger individuals to limit toxicity. The advantage of intravenous cyclophosphamide is its lower cumulative dose while the main limitation is often access

to an infusion center. Lastly, individual physician and patient preferences should be taken into consideration.

Practice Point 9.3.1.5: Discontinue immunosuppressive therapy after 3 months in patients who remain on dialysis and who do not have any extrarenal manifestations of disease.

Commentary and Clinical Utility

This practice point is consistent with the 2012 guideline. We agree that in patients with renal-limited vasculitis who remain on dialysis the decision to discontinue induction immunosuppression needs to be made given the high risk for infection and related mortality while relapse risk is low.[156] We would suggest that minimum treatment duration could be extended to 6 months, a time point for primary outcome of remission used in a majority of clinical trials. We would suggest that these patients should be monitored closely for emergence of extrarenal disease or treatment-related complications. Additionally, it is important to remember that rituximab-treated patients may have B-cell depletion for more than 8 to 12 months.

Implementation and Challenges

AAV patients requiring dialysis at entry almost always require hospitalization and may not be followed by the same nephrologist after discharge from the hospitalization. Care pathways for discharge disposition and follow-up should be established, and referral to nephrologists with expertise in AAV is required to monitor for extrarenal relapse.

Practice Point 9.3.1.6: Recommendations for oral glucocorticoid tapering are given in Figure 79.

Commentary and Clinical Utility

This is a new practice point for the 2021 guideline that offers reduced-dose corticosteroid tapering schedules for patients based on body weight. Glucocorticoids are reviled by physicians and patients alike. Glucocorticoid use is a major contributing factor for serious infections in the first year of treatment. A major unmet need in AAV is reducing glucocorticoid burden, and the results of PEXIVAS and LoVAS trials are promising steps toward accomplishing this goal.[157,158] The use of pulse glucocorticoids continues with dosing based on local practice in the absence of evidence-based guidelines. The adoption of a reduced-dose glucocorticoid algorithm will be a step to standardize oral glucocorticoid tapering and to decrease glucocorticoid toxicity. A recent clinical practice guideline update recommended the use of reduced-dose glucocorticoids based on a systematic review of comparative efficacy and safety of alternate glucocorticoid dosing regimens which demonstrated a decrease in serious infection and death without increasing the risk of kidney failure.[159,160] We agree with this recommendation to adopt the reduced-dose glucocorticoid dosing of the PEXIVAS trial with 2 comments. In the PEXIVAS trial, only 15% of the patients received rituximab for remission induction; therefore, the efficacy and safety of reduced-dose glucocorticoid in this group requires further study. For this reason, if using reduced-dose glucocorticoids, we suggest close monitoring of kidney function during the first 4 weeks for patients receiving rituximab for induction therapy and in those presenting with organ-threatening kidney involvement.

The ADVOCATE trial demonstrated that avacopan, a C5a receptor blocker, had similar efficacy to high-dose glucocorticoids at week 26 and superior efficacy at week 52 when used in combination with either rituximab or cyclophosphamide. Furthermore, it was associated with a decreased relapse rate, better preservation of GFR, reduced glucocorticoid toxicity, and improved quality of life.[161] It should be noted that the avacopan group received glucocorticoids, although the mean daily dose was one-third of the prednisone arm. Avacopan was FDA-approved as an adjunct therapy for AAV in 2021. Given the glucocorticoid-sparing effects of avacopan, further modifications in steroid-tapering algorithms with drastic reduction of cumulative glucocorticoid dose can be anticipated. We agree with the immunosuppressive dosing recommendations provided in Figure 80 with a comment that the cyclophosphamide dose needs to be adjusted based on follow-up WBC count and GFR.

Practice Point 9.3.1.8: Consider plasma exchange for patients with SCr >5.7 mg/dl (>500 μmol/l) requiring dialysis or with rapidly increasing SCr, and in patients with diffuse alveolar hemorrhage who have hypoxemia.

Commentary

We agree with this practice point.

Implementation and Challenges

The prescribed regimen is 7 exchanges over 14 days. Although a majority of patients require prolonged hospitalization due to disease severity, plasma exchange can also be performed in outpatient settings. Plasma exchange is not readily available in many community hospitals, thereby requiring transfer to a tertiary academic center. Expertise in pheresis procedure and knowledge of its applications and complications are needed, and plasma exchange can be performed by hematologists or nephrologists. Plasma exchange can be associated with hemodynamic shifts, coagulation disorders, electrolyte imbalances, and line-related bacteremia and requires a careful risk-benefit analysis. Furthermore, it can remove certain medications, which may complicate induction therapy. With the use of intravenous cyclophosphamide, the infusion is given after a plasma exchange session; and when using rituximab, plasma exchange should be held for 48 to 72 hours after rituximab infusion.

Practice Point 9.3.1.9: Add plasma exchange for patients with an overlap syndrome of ANCA vasculitis and anti-GBM.

Commentary

This is consistent with the 2012 guideline. We agree with this practice point to add plasma exchange daily for 14 days or until anti–glomerular basement membrane (anti-GBM) antibodies are undetectable. Patients who have double positive disease with positivity for both ANCA and anti-GBM have a poor kidney prognosis more like those with anti-GBM antibodies compared with those who are positive only for ANCA. However, unlike anti-GBM disease, those who are double positive for ANCA and anti-GBM tend to relapse and require maintenance immunosuppression.[162]

Treatment: Maintenance therapy

Recommendation 9.3.2.1: We recommend maintenance therapy with either rituximab or azathioprine and low-dose glucocorticoids after induction of remission *(1C)*.

Commentary

There is a striking difference in maintenance therapy options between the 2012 guideline, which recommended azathioprine for remission maintenance, and the 2021 guideline, which recommends either rituximab or azathioprine. We agree with this recommendation and would like to provide further clarification. Despite major treatment advances and effective disease control, relapse and consequential disease- and therapy-related complications occur in up to 50% of patients over 5 years.[163] All patients should receive maintenance immunosuppressive therapy, with the exception of those with renal-limited disease who remain on dialysis after completing induction therapy. The role of maintenance therapy for MPO ANCA patients after remission induction with rituximab has been controversial given the low relapse rate noted in the RAVE trial where no maintenance therapy was used. However, MPO ANCA patients are not impervious to relapse, and one needs to be cognizant of the facts that not only do MPO ANCA patients have a higher frequency of kidney disease but also any renal relapse is associated with an increased risk of kidney failure. We therefore suggest that maintenance immunosuppression should be considered for MPO ANCA patients after rituximab-induced remission. With regard to the choice of immunosuppressive agent, while azathioprine and rituximab have been tested in clinical trials, the role of low-dose prednisone for maintaining remission has not been rigorously tested and cannot be universally recommended. A meta-analysis of randomized trials and observational studies demonstrated that a prolonged duration of prednisone therapy was favorable for relapse prevention, but this analysis did not include rituximab-treated patients.[164] Furthermore, prednisone therapy beyond 6 months is associated with increased infection risk.[165]

Clinical Utility

Relapse consequences include morbidity related to relapse and its treatment, with a significant increase in risk of kidney failure after a kidney relapse. Monitoring for therapy-related adverse events is critical during the remission maintenance phase: for rituximab, serum immunoglobulins should be monitored every 6 months, and PJP prophylaxis is advised. For azathioprine, thiopurine methyltransferase activity should be tested to identify patients at risk for bone marrow suppression and complete blood cell count and liver function tests should be monitored along with surveillance for skin cancer.

Implementation and Challenges

Balancing the relapse risk with long-term effects of immunosuppression remains a challenge, and patients should be managed by physicians with expertise in AAV. The choice of immunosuppressive agent needs to be individualized based on patient risk factors and patient choice. While relapse can occur, a proportion of patients demonstrate prolonged disease-free remission off immunosuppression.[166] The optimal duration of maintenance therapy remains uncertain and should be individualized based on the presence of risk factors for relapse.

Practice Point 9.3.2.1: Following cyclophosphamide induction, either azathioprine plus low-dose glucocorticoids or rituximab without glucocorticoids should be used to prevent relapse.

Commentary

We agree with this statement with the following clarifications. Both prior relapsing disease and PR3 ANCA serotype have been consistently shown to have an increased rate of future relapses.[167,168] In patients with new-onset AAV after cyclophosphamide induction of remission, azathioprine was shown to be an effective maintenance agent in multiple clinical trials. However, in patients with relapsing disease and PR3 ANCA serotype, rituximab is superior to azathioprine for relapse prevention.[149,169]

Practice Point 9.3.2.2: Following rituximab induction, maintenance immunosuppressive therapy should be given to most patients.

Commentary

We suggest maintenance therapy be given to all patients following successful rituximab induction for reasons highlighted under Recommendation 9.3.2.1. Both rituximab and azathioprine are reasonable choices for patients with new-onset AAV and MPO ANCA serotype while rituximab is preferred for those with relapsing disease and PR3 ANCA serotype.

Practice Point 9.3.2.3: The optimal duration of azathioprine plus low-dose glucocorticoids is not known but should be between 18 months and 4 years after induction of remission.

Commentary

This differs from the 2012 guideline, which recommended at least 18 months of treatment with azathioprine. We

would like to clarify this statement further. The recommendation for an extended period of remission maintenance is based on the REMAIN study, which demonstrated that extending maintenance azathioprine therapy to 48 months was associated with significantly lower relapse risk and better renal survival compared with withdrawal of azathioprine at 24 months.[170] However, two-thirds of the patients in the withdrawal group did not experience any major relapse, highlighting the need to personalize the maintenance therapy duration based on individual risk factors for relapse and tolerance to immunosuppressive therapy.

Implementation and Challenges

Long-term use of azathioprine is not without adverse events, and a proportion of patients have durable remission off immunosuppressive therapy. For these reasons, a decision to extend the duration of maintenance therapy should be individualized, with ongoing vigilance for treatment-related adverse events. Patients at high risk of relapse should be followed at vasculitis centers.

Practice Point 9.3.2.4: The optimal duration of rituximab maintenance is not known, but studies to date have evaluated a duration of 18 months after remission. There is no role for the routine use of an oral glucocorticoid or an oral immunosuppressive with rituximab maintenance.

Commentary

This is a new practice point for the 2021 guideline. An extended course of rituximab for a total of 46 months was tested in the MAINRITSAN3 trial, which enrolled 97 patients who completed the MAINRITSAN2 trial and randomized them to receive rituximab or placebo. Relapse-free survival was superior in the rituximab arm (96%) compared with placebo (74%).[171] Nonetheless, 74% of patients receiving placebo enjoyed extended periods of disease remission after cessation of rituximab, and there are safety concerns of long-term B-cell depletion, including hypogammaglobulinemia, impaired response to vaccines, and increased infection risk. More research on biomarkers is needed to guide pre-emptive treatment in this low-risk group.

Practice Point 9.3.2.5: When considering withdrawal of maintenance therapy, the risk of relapse should be considered, and patients should be informed of the need for prompt attention if symptoms recur (Figure 82).

Commentary

This practice point is new for the 2021 guideline and Figure 82 lists factors that increase relapse risk in AAV, highlighting a need for personalized maintenance therapy. We agree with the relapse risk factors noted. A number of cohort studies and long-term follow-up of randomized controlled trials have revealed 5-year relapse rates varying from 21% to 89%.[172] A recent systematic review and meta-analysis demonstrated that the 1-year, 3-year, and 5-year cumulative incidence of relapse in AAV patients receiving cyclophosphamide for remission induction was 12%, 33%, and 47%, respectively.[173] Relapse is also common in patients induced with rituximab, occurring in 40% of patients in a series.[174] Most guidelines recommend a 2-year course of maintenance rituximab. Data from the MAINRITSAN3 demonstrated a lower relapse rate in patients receiving extended treatment with rituximab for 46 months, suggesting that in patients with high relapse risk, extended treatment may be beneficial.[171]

Implementation and Challenges

Patients at high risk of relapse should be followed at vasculitis centers to decide on the duration of therapy and management of comorbidities related to disease and treatment. Similarly, patients in whom immunosuppressive therapy is stopped should be followed at vasculitis centers for close monitoring for disease relapse, and such patients should be educated to recognize the symptoms of early relapse and to use home monitoring for detection of proteinuria and hematuria.

Practice Point 9.3.2.6: Consider methotrexate for maintenance therapy in patients, after induction with methotrexate or for those who are intolerant of azathioprine and MMF, but not if GFR is <60 ml/min per 1.73 m^2.

Commentary

We agree with this practice point.

Practice Point 9.3.2.7: Considerations for choosing rituximab or azathioprine for maintenance therapy are presented in Figure 83.

Commentary

This is a new practice point to the 2021 guideline and provides guidance on choosing between rituximab and azathioprine as the appropriate maintenance therapy. We agree with the factors listed and would add that rituximab would be preferred for patients with deficiency of TMPT enzyme or a history of skin cancer.

Figure 84 provides guidance on dose and duration of the different maintenance therapy options, namely rituximab, azathioprine, and MMF. The duration of maintenance therapy should be individualized by taking into account the risk factors for relapse. We suggest adding extended duration of rituximab for 46 months in patients who are at high risk of relapse.

Treatment: Relapsing Disease

Practice Point 9.3.3.1: Patients with relapsing disease (life- or organ-threatening) should be reinduced (Recommendation 9.3.1.1), preferably with rituximab.

Commentary

This differs from the 2012 guideline, which recommends treating relapses similar to the initial disease presentation. Rituximab is superior to cyclophosphamide for induction of remission in patients with relapsing disease.[137] For relapses occurring after the first course of rituximab, post hoc analysis of the RAVE trial comparing rituximab to cyclophosphamide for remission demonstrated that retreatment with rituximab induced remission in 88% of patients.[175] The RITAZAREM trial demonstrated that rituximab induced remission in 91% of patients with relapsing GPA/MPA.[169] However, if a relapse occurs early (less than 6 months after remission is achieved after an induction course of rituximab), alternate induction regimens using cyclophosphamide or MMF could be used.

Special Situations: Refractory Disease

Practice Point 9.4.1.1: Refractory disease can be treated by an increase in glucocorticoids (intravenous or oral), by the addition of rituximab if cyclophosphamide induction has been used previously, or vice versa. Plasma exchange can be considered.

Commentary

This differs from 2012 guideline, which focused on cyclophosphamide-induced patients only and recommended using rituximab for these patients, with the suggestion of intravenous immunoglobulin and plasma exchange as alternatives. Refractory disease is defined as unchanged or increased disease activity after 4 weeks of treatment with standard induction therapy or less than 50% improvement in the BVAS score after 6 weeks. Patients with refractory disease encompass those who have inadequate control of disease activity or disease progression despite optimal induction therapy. Post hoc analysis of the RAVE trial found that in patients who did not achieve remission, blinded cross-over or treatment according to the best medical judgment by the physician led to disease control in the majority.[176] In addition to re-evaluating the primary diagnosis and excluding medication nonadherence, it is crucial to exclude other vasculitis mimics such as infection, medications, and malignancy. Intravenous immunoglobulin therapy by neutralizing ANCA may be used as an adjunct to treat refractory vasculitis.[177]

Implementation and Challenges

It is important to ensure that immunosuppression has been optimized, both with regards to the choice and dose of immunosuppressants before concluding that the patient has refractory disease. Patients with refractory disease should be referred to centers of expertise both to confirm refractory vasculitis and for treatment decisions.

Practice Point 9.4.1.2: In the setting of diffuse alveolar bleeding with hypoxemia, plasma exchange should be considered in addition to glucocorticoids with either cyclophosphamide or rituximab.

Commentary

Diffuse alveolar hemorrhage (DAH) is one of the life-threatening manifestations of AAV, occurring in 25% of patients with AAV.[178] Older age, severe kidney failure, degree of hypoxemia, and involvement of >50% of lung area at presentation are independent predictors of mortality.[179] Aggressive treatment of alveolar hemorrhage with combination of glucocorticoids with either cyclophosphamide or rituximab is the standard of care. Addition of plasma exchange is recommended by the American Society of Apheresis. There has not been an adequate trial designed to evaluate the role of plasma exchange in patients with severe DAH. The PEXIVAS trial did not demonstrate any observed effect of plasma exchange on the primary composite outcome in patients with alveolar hemorrhage. Subgroup analysis however showed a trend toward benefit in patients with nonsevere and severe alveolar hemorrhage.[158] A recent clinical practice guideline update recommended against the use of plasma exchange in patients with DAH without kidney involvement due to an increased infection risk and no mortality benefit.[159,180] Nonetheless, given the high mortality associated with DAH, plasma exchange should be considered as part of induction therapy until a trial dedicated to patients with alveolar hemorrhage is conducted.

Special Situations: Transplantation

Practice Point 9.4.2.1: Delay transplantation until patients are in clinical complete remission for ≥6 months. Persistence of ANCA should not delay transplantation.

Commentary

The 2012 guideline recommended delaying transplant until the patient has been in extrarenal remission for 12 months, and we agree with this recommendation. In the current era of modern immunosuppressants, the risk of recurrent disease in the allograft and extrarenal flares is low, ranging from 0.006 to 0.1 per patient per year.[181] The timing of kidney transplantation is an important point to consider. Transplantation less than 1 year after remission is associated with an increased risk of death, and it is recommended to wait for 1 year after disease remission to proceed with transplantation.[182] Although in the general population ANCA positivity is not always associated with disease activity, persistent elevation in ANCA is a risk factor for relapse, especially in PR3 ANCA patients. In the setting of kidney transplant, the relationship between ANCA and relapse is less clear, with earlier studies finding no correlation between ANCA positivity and posttransplant relapse and a subsequent pooled analysis demonstrating a higher relapse rate in patients who were ANCA positive at the time of transplant.[183] We agree, based on the available evidence, that ANCA positivity at the time of transplant should not delay transplant, but this finding should not be negated, and these patients should be monitored closely for disease relapse.

Guideline Statements and Commentary: Systemic Lupus Erythematosus

Diagnosis of Lupus Nephritis

Practice Point 10.1.1: Approach to the diagnosis of kidney involvement in systemic lupus erythematosus (SLE) (Figure 85).

Commentary and Clinical Utility

Figure 85 is an algorithm that suggests testing kidney markers at time of initial SLE presentation or flares and recommends consideration of biopsy if proteinuria is >500 mg/d or if eGFR is worsening. The threshold level for isolated proteinuria is lower than the American College of Rheumatology (ACR) 2012 lupus nephritis (LN) guidelines. This is consistent with increasing evidence that patients can have significant LN even at low levels of proteinuria.[184,185] A recent study demonstrated that 92% of patients with <1 g/g proteinuria biopsied in their cohort had histology showing International Society of Nephrology/Renal Pathology Society (ISN/RPS) class III, IV, V, or mixed histology.[184] We generally agree with this algorithm, but would also consider kidney biopsy in some patients with persistent glomerular hematuria even with <0.5 g/d proteinuria, especially in high-risk populations with evidence of high SLE activity, as is recommended by the EULAR/ERA-EDTA guidelines.[186] De Rosa et al[185] demonstrated ~85% of patients with proteinuria < 0.5 g/d and ~75% of patients with proteinuria < 0.25 g/d had ISN/RPS class III, IV, or mixed histology in a cohort of SLE patients undergoing kidney biopsy.

Implementation and Challenges

The algorithm does not provide clear guidance on how frequently to monitor for kidney involvement in patients with SLE. High-risk patients require frequent monitoring, especially in the first 5 years of SLE diagnosis. It is important to recognize that LN is frequently asymptomatic. SLE patients should be monitored every 3-6 months with creatinine, urinalysis, and UPCR.[186]

Increased awareness of screening for urine abnormalities in patients with SLE is critical to early diagnosis. Inadequate follow-up and screening can lead to delays in diagnosis and treatment. Referrals to nephrology are often delayed, especially when kidney function is preserved.

Treatment: General Management of Patients With SLE

Recommendation 10.2.1.1: We recommend that patients with SLE, including those with lupus nephritis (LN), be treated with hydroxychloroquine or an equivalent antimalarial unless contraindicated *(1C)*.

Commentary and Clinical Utility

We agree with this recommendation although the supporting data are mostly observational. Antimalarial use reduces flares, including kidney flares, and is associated with higher response rates and reduced risk of CKD or kidney failure.[187] A starting dose of up to 6.5 mg/kg ideal body weight (up to 400 mg/d) followed by 4-5 mg/kg/d for maintenance is recommended. We recommend a maximum dose of 5 mg/kg/d based on risk of toxicity at higher doses. This is consistent with recent recommendations by 2 major ophthalmology societies.[188-190]

Implementation and Challenges

Retinal toxicity is low at 5 and 10 years (1% and 2%, respectively) but increases over time.[189] KDIGO recommends baseline and annual retinal examinations. A baseline examination may delay the initiation of therapy and is not necessary according to the latest guidelines of the Royal College of Ophthalmologists.[190] Yearly monitoring should begin after 1 year of therapy in high-risk patients (ie, patients with concomitant tamoxifen use, daily dose > 5mg/kg/d, chloroquine use, or eGFR < 60 mL/min/1.73 m^2) and after 5 years of therapy in low-risk patients.[189,190]

Practice Point 10.2.1.1: Adjunctive therapies to manage LN and attenuate complications of the disease or its treatments should be considered for all patients, as outlined in Figure 87.

Commentary and Clinical Utility

We generally agree with these recommendations for risk attenuation presented in Figure 87, despite limited data in some areas. There is limited data on the risk of *P jirovecii* in immunosuppressed patients with SLE. Observational data suggest the risk in patients treated with cyclophosphamide is low (0.1588%).[191] The guidelines do not give clear recommendations as to what level of immunosuppression to consider therapy. The risk is highest in patients receiving prednisone ≥20 mg/d for >1 month and patients receiving concomitant cyclophosphamide therapy, and these are the populations who would benefit the most from prophylaxis.[192]

Regarding premature ovarian failure and gonadal toxicity, patients receiving cyclophosphamide should be counseled about the risk of infertility and shared decision making should guide therapy and interventions. The risk of gonadal toxicity increases with cumulative dose and the age of the patient.[193] The risk of infertility from the Euro-Lupus cyclophosphamide regimen (total cyclophosphamide dose: 3 grams) is much lower than oral or National Institutes of Health (NIH) cyclophosphamide regimens.[194]

Implementation and Challenges

Sulfa allergies are common in patients with SLE and may limit who can receive *P jirovecii* prophylaxis with

trimethoprim-sulfamethoxazole (TMP-SMX). Kidney function and hyperkalemia may also limit use. Alternatives, such as atovaquone, dapsone (often used for skin manifestations in SLE), or pentamidine may be considered in patients unable to take TMP-SMX.

For patients receiving cyclophosphamide, gonadotropin-releasing hormone agonists and sperm or oocyte cryopreservation should be considered, but some of these therapies require fertility specialists, may not be covered by many insurance plans, and could lead to unacceptable delays in LN treatment. Shared decision making, with discussion of the risks and benefits of treatment, should guide therapy.

Treatment: Class I or Class II LN

Practice Point 10.2.2.1: Approach to immunosuppressive treatment for patients with Class I or Class II LN (Figure 88).

Commentary and Clinical Utility

The 2 recommendations on class I and II LN from the 2012 guideline were updated by Figure 88, which suggests that immunosuppression in such patients with only low-grade proteinuria should be guided by extrarenal SLE manifestations, while those with nephrotic syndrome should specifically be treated for lupus podocytopathy similar to MCD. The guideline does not address the management of class I/II patients with proteinuria between low-grade and nephrotic range. We agree that, beyond proteinuric kidney disease recommendations, patients with class I/II and nonnephrotic proteinuria should not receive immunosuppression unless needed for extrarenal lupus. However, in the absence of immunosuppression, we suggest close monitoring for increased disease activity since class transformation may occur within 1 to 5 years of LN I/II diagnosis.[195]

Patients with SLE and biopsy-proven MCD or FSGS, with or without LN I/II are considered to have lupus podocytopathy, which is a different entity than proliferative and/or membranous LN. Clinically they present with nephrotic-range proteinuria or nephrotic syndrome, have diffuse effacement of the podocytes on electron microscopy, and respond to therapy in a similar manner to patients with primary MCD/FSGS. Although the data on management of lupus podocytopathy are retrospective or observational, we agree with the use of steroids and/or steroid-sparing immunosuppressants if needed.

Implementation and Challenges

Overt clinical kidney involvement in SLE patients, regardless of its severity, does not necessarily signify an active immune complex–mediated kidney process that requires escalation of immunosuppressive therapy for LN.[196] As stated above, LN I/II and lupus podocytopathies are managed differently, and therefore the kidney biopsy is critical to define the histologic lesion and confirm diagnosis to avoid erroneous therapeutic exposures. Furthermore, non-LN glomerular disease occurs only in about 1% to 5% of SLE patients with kidney manifestations, making prospective trials difficult to pursue in lupus podocytopathies.

Treatment: Initial Therapy of Active Class III/IV Lupus Nephritis

Recommendation 10.2.3.1.1: We recommend that patients with active Class III or IV LN, with or without a membranous component, be treated initially with glucocorticoids plus either low-dose intravenous cyclophosphamide or MPAA *(1B)*.

Commentary and Clinical Utility

The algorithm presented as Figure 89 in this section provides standard dosing recommendations for these agents, and adds additional possibilities of CNIs or B-cell–targeting therapeutics in combination with corticosteroids. We agree with Recommendation 10.2.3.1.1 that active class III or IV LN should be initially treated with glucocorticoids plus either cyclophosphamide or MPAA (mycophenolic acid analogs). Please note that, compared to 2012, the 2021 guidelines have updated the wording to specify MPAA. MPAA incorporates the use of MMF or enteric-coated mycophenolate sodium (EC-MPS), which has been shown to have a reduced gastrointestinal symptom burden.[197]

While cyclophosphamide and MPAA remain the recommended remission-inducing therapies in active LN, the guideline limits its recommendation for cyclophosphamide to low-dose intravenous cyclophosphamide, stating immediately afterward that high value is placed on data demonstrating that steroids in combination with "standard dose" cyclophosphamide will improve kidney outcomes in active severe LN. Recommending the use of low-dose intravenous cyclophosphamide by using data from standard cyclophosphamide dosing regimens in LN is confusing. In the United States, both high- and low-dose (Euro-Lupus) intravenous cyclophosphamide have been used with success in preserving kidney function and attenuating LN flares. Oral cyclophosphamide is also effective in active LN and less expensive than intravenous cyclophosphamide.[198,199] Given the lack of sufficient evidence to support the recommendation of one cyclophosphamide dosing regimen over the others and in all active LN scenarios, we suggest removing "low dose" from the recommendation. This would place an emphasis on the importance of personalized considerations for each patient that are discussed under practice points.

The ALMS trial established a role for MPAA in LN induction therapy.[200] Although the study did not meet its primary end point of showing that MPAA was superior to intravenous cyclophosphamide in active LN (III, IV, V), it showed similar renal response rates in both groups.

Adverse events attributed to MPAA might not necessarily be less frequent but occur with a different profile than those related to cyclophosphamide. Based on this study and the concerns for cyclophosphamide-related toxicity, MPAA has become a preferred induction therapy in active LN. It is worth noting that in the ALMS, MPAA had numerically higher rates of disease relapse compared with those treated with intravenous cyclophosphamide.

We agree with all considerations regarding the implementation of Recommendation 10.2.3.1.1, which will be discussed with the upcoming practice points.

Practice Point 10.2.3.1.1: A regimen of reduced-dose glucocorticoids following a short course of methylprednisolone pulses may be considered during the initial treatment of active LN when both the kidney and extrarenal disease manifestations show satisfactory improvement (Figure 90).

Commentary and Clinical Utility

This practice point replaces a 1A-graded recommendation in the 2012 guideline for use of corticosteroids as initial therapy for active LN classes III and IV. The practice point is supplemented by Figure 90, which provides dosing schedules for standard-, moderate-, and reduced-dose glucocorticoid regimens.

We agree that the role of intravenous methylprednisolone at the start of treatment is not well studied. However, this is often given as up to 3 daily doses of 0.5 g each followed by an oral steroid taper. Figure 90 reports on 3 different glucocorticoid schemes: standard-, moderate-, and reduced-dose regimens based on published literature and recent clinical trials, without including supporting citations. In the standard-dose scheme, the use of intravenous methylprednisolone was optional, and the starting oral steroid taper was high-dose prednisone. Even the reduced-dose scheme continues to recommend high (up to 40 mg/d) initial dosing instead of a more moderate starting dose of prednisone prior to the taper. The early anti-inflammatory and immunosuppressive effects of glucocorticoids dramatically improved survival in patients with active LN; however, this was associated with significant adverse events.[201] We suggest further reduction of the peak of oral glucocorticoid dose along with a rapid tapering schedule, following a short course of methylprednisolone pulses, as a safer strategy while maintaining efficacy.[202]

Implementation and Challenges

A small clinical trial in SLE suggested similar clinical outcomes when using 3 daily 100 mg versus 3 daily 1,000 mg methylprednisolone doses.[203] Another LN study suggested that repeated pulses of methylprednisolone allowed a lower starting oral prednisone dose at ≤30 mg/d.[204] Recently, the implementation of less toxic steroid regimens with reduced or no oral steroid have been explored successfully or are under investigation. This was facilitated by the addition of new immunosuppressants or biologics. For example, the addition of voclosporin (recently approved for LN by the FDA) to MPAA and quicker steroid taper in active LN improved renal response (41% at 52 weeks) with an acceptable safety profile.[205] In a propensity analysis of 63 matched pairs of patients from the control arm of the phase 2 RCT testing voclosporin in LN (AURA)[206] and both arms of the ALMS,[200] the dose of immunosuppressives in AURA was lower than in ALMS (mean dose of total glucocorticoid 2,631 vs 3,709 and mean dose of MPAA 1.9 vs 2.6 g/d) without compromised efficacy and with less adverse events.[202] In another steroid minimization study, the Rituxilup scheme consisted of 2 doses of rituximab 1 g along with 0.5 g methylprednisolone followed by MPAA without oral steroids in active LN. In this observational study, renal response was 86% at 52 weeks.[207] An ongoing clinical question is how much steroid minimization can be achieved in initial LN therapy. The OBILUP clinical trial is ongoing and will compare MPAA plus oral steroids versus MPAA plus obinutuzumab (NCT04702256); both arms will receive intravenous methylprednisolone pulses.

Practice Point 10.2.3.1.2: Intravenous cyclophosphamide should be used as the initial therapy for active Class III and Class IV LN in patients who may have difficulty adhering to an oral regimen.

Commentary and Clinical Utility

We agree that an intravenous immunosuppressive regimen is a better option for induction in LN when adherence to an oral regimen is an issue. Both high-dose and low-dose intravenous cyclophosphamide are effective in diverse racial and ethnic populations.[208-211] To avoid longer duration and higher cumulative exposure to intravenous cyclophosphamide, the Euro-Lupus regimen would be a preferred option unless there are other factors such as either central nervous system or cardiac involvement or the presence of RPGN in which a higher dose might be indicated.

When cyclophosphamide is prescribed and adherence to oral regimen is not an issue, oral cyclophosphamide remains an underused option,[199] especially when patients are struggling financially. Oral cyclophosphamide is easy to administer, can be discontinued anytime during LN induction, is as effective as high-dose intravenous cyclophosphamide including in Black patients, and is cheaper than intravenous cyclophosphamide and MPAA. We suggest that a short, 2- to 4-month course of oral cyclophosphamide has a comparable adverse event profile to MPAA.[199] Although the 2021 guideline has extended the duration of oral cyclophosphamide to 6 months (Figures 89 and 91), we propose going back to a shorter course of 2-4 months (as per the 2012 guideline) to minimize cyclophosphamide-related toxicity.

Most studies of MPAA and cyclophosphamide as treatment for LN lack long-term outcomes. Based on a meta-

analysis examining the use of MMF versus cyclophosphamide in severe LN,[212] intravenous cyclophosphamide was equally effective in inducing remission in the short term and was superior to MPAA in maintaining long-term outcomes, such as preservation of kidney function and fewer relapses.

Due to the widespread acceptance of MPAA as induction therapy, many new therapies are specifically being tested as "add-on" to MPAA. However, as mentioned above, cyclophosphamide is still an acceptable induction agent and, as such, should also be included in future trials. Furthermore, relevant areas for future research could be to compare MPAA with oral cyclophosphamide (2-4 months), Euro-Lupus cyclophosphamide with oral cyclophosphamide (2-4 months), and intravenous Euro-Lupus with oral Euro-Lupus (500 mg orally every 2 weeks for 6 doses).

Practice Point 10.2.3.1.3: An MPAA-based regimen is the preferred initial therapy of proliferative LN for patients at high risk of infertility, patients who have a moderate to high prior cyclophosphamide exposure, and patients of Asian, Hispanic, or African ancestry.

Commentary

We agree with this statement. However, it is unclear why KDIGO is suggesting MPAA-based regimen as a preferred initial therapy in Asian patients with active LN while referring to the ALMS post hoc study results. In the post hoc analysis of ALMS looking at the influence of race and ethnicity on response to LN,[213] the response rate to MPAA versus cyclophosphamide was higher in Hispanics and patients from Latin America and numerically higher without reaching statistical significance in Black patients. On the other hand, the response rate to cyclophosphamide versus MPAA was numerically higher in Asian patients (63.9 vs 53.2%, $P = 0.24$). Furthermore, patients in the Asian group had lower tolerability to MPAA, which led to a higher withdrawal rate due to adverse events compared with other racial groups. A meta-analysis showed that MPAA is more effective than intravenous cyclophosphamide in Asian patients with LN.[214] However, cyclophosphamide followed by azathioprine had a comparable complete response rate to not only MPAA alone but also the multitarget therapy (MPAA plus tacrolimus) at 12 through 18 months of therapy in a Chinese LN RCT.[215,216] We propose removing "Asian" from the practice point.

Practice Point 10.2.3.1.4: Initial therapy with a triple immunosuppressive regimen that includes a CNI (tacrolimus or cyclosporine) with reduced-dose MPAA and glucocorticoids is reserved for patients who cannot tolerate standard-dose MPAA or are unfit for or will not use cyclophosphamide-based regimens.

Commentary

We agree with this practice point but would clarify that this recommendation might be more applicable to Asian populations based on evidence from the available studies. Additionally, the recommendation of multitarget therapy in those unable to tolerate standard-dose MPAA is a practical point that is not evidence based, since this was never part of the inclusion criteria for these multitarget therapy studies. Furthermore, this practice point indirectly limits multitarget therapy to always requiring a reduced dose of MPAA.

This practice point stems from a Chinese multicenter RCT that compared multitarget therapy consisting of tacrolimus (4 mg/d) plus MMF (1 g/d) with standard of care cyclophosphamide (intravenous 0.5-1.0 g/m^2/month for 6 months) for initial therapy in active LN.[215] Patients who achieved complete or partial renal response at 6 months were followed for 18 more months. At 6 months, complete renal response was attained in 46% of the multitarget therapy group compared with 26% of the cyclophosphamide group ($P < 0.001$) and more quickly. At 24 months, following 6 months in the induction phase and 18 months in the maintenance phase, there was no difference in complete renal response rates and in cumulative LN flare rates between both groups.[215,216] Thus, the multitarget therapy was successful at achieving an earlier remission, yet long-term remission was no different and without a meaningful difference in side effects.

The 2021 guideline briefly mentions the use of glucocorticoids combined with CNI alone, without MPAA or cyclophosphamide, for induction in active LN. In the Cyclofa-Lune study, with mean follow up of 40 months, glucocorticoids combined with cyclosporine given over 18 months had comparable efficacy to glucocorticoids combined with cyclophosphamide and without adversely affecting kidney function.[217] Patients with Scr ≥ 1.5 mg/dL were excluded from the study. Data mainly from studies in Asian patients reported similarly on the efficacy of cyclosporine without MPAA or cyclophosphamide.[218] A meta-analysis showed that in active LN tacrolimus is more effective at achieving complete renal response than cyclophosphamide.[219] The 10-year outcome of an RCT comparing tacrolimus with MPAA given during induction in active LN over a 6-month period showed that tacrolimus was noninferior to MPAA as induction agent, including in terms of relapse rates and time to relapses. Patients with Scr ≥ 2.2 mg/dL and/or chronicity index on histology > 3 were excluded from the study.[220]

Although primary end point definitions vary between studies, they all use proteinuria as a criterion of kidney response. Beyond T-cell inhibition, CNIs can decrease proteinuria through nonimmune mechanisms such as reduction of glomerular perfusion pressure and stabilization of the podocyte cytoskeleton. Thus, it is possible that CNIs reduce proteinuria while LN remains active with ongoing kidney damage at the molecular and histologic levels. In addition, the improvement in proteinuria is often transient, and proteinuria often increases once the CNI has been stopped. Therefore, confirming the short-term and long-term

efficacy of CNIs at the histologic level is a challenge unless repeat biopsies are used as components of response in the studies. Furthermore, surprisingly there is not much interest in testing the regimen of combined glucocorticoids and CNIs (tacrolimus or cyclosporine) alone in other ethnic groups or in multinational RCTs to bring stronger evidence for its "solo" indication in active LN. Instead, the use of CNIs has been embraced in a multitarget regimen adapted from therapies in kidney transplantation that was studied initially and extensively in Asia.

Implementation and Challenges

As mentioned earlier and as will be discussed in the next practice point, multitarget therapy not only has higher and faster short-term response but also may facilitate the use of lower glucocorticoid doses for LN management. Lower doses of CNI, MMF, and steroids may potentially minimize adverse events, especially those caused by corticosteroids, and consequently improve adherence to therapy.

Beyond what is stated in the practice point, to whom and when multitarget therapy should be offered in active LN remains to be determined. Most CNI-based studies, whether alone or in combination with MPAA or cyclophosphamide, excluded patients with baseline Scr > 2 mg/dL and/or chronicity index on histology > 3.

Future trials should involve ethnically diverse populations and focus on response to CNI versus multitarget regimens, as well as compare different formulations of CNI (including voclosporin) alone or as a component of multitarget therapy. In addition, studies of duration of CNI use, taking into consideration potential nephrotoxicity with appropriate follow-up after withdrawal, are all needed in order to expand the indication of these therapies. Finally, drug-drug interaction when using cyclosporine with MMF is important to consider in order to adjust the dose of medications to maintain appropriate exposure and efficacy.[221]

Practice Point 10.2.3.1.5: In patients with baseline eGFR of at least 45 ml/min per 1.73 m², voclosporin can be added to MPAA and glucocorticoids as initial therapy for 1 year.

Commentary and Clinical Utility

Voclosporin is a novel CNI modified from cyclosporine A by a single carbon extension on the first amino acid. This modification increases its potency of calcineurin inhibition and leads to faster elimination of its metabolites, resulting in a more consistent pharmacokinetic and pharmacodynamic predictability than cyclosporine A.

Voclosporin was recently FDA approved for the treatment of adults with active LN following 2 positive international RCTs, the phase 2b AURA-LV[206] and the phase 3 AURORA-1,[205] that compared voclosporin with placebo on a background of MMF and reduced steroid regimen (intravenous methylprednisolone 0.5-1.0 g in total followed by 20-25 mg/d prednisone that was tapered down to 2.5 mg/d by week 16) in active LN. In both LN studies, patients with eGFR ≤ 45 mL/min were excluded. Kidney biopsy showing active LN was required within 6 months of screening for AURA-LV and within 24 months of screening for AURORA-1. Primary end points were met in both studies: in AURA-LV the patients treated with voclosporin 23.7 mg twice a day plus MMF and steroids had significantly higher complete remission rates at 6 months than controls (32.6% vs 19.3%; $P = 0.049$), and in AURORA-1 complete remission rates at 12 months were higher in the voclosporin arm compared with controls (41% vs 23%; $P < 0.0001$) while adverse events were balanced between groups. Importantly, long-term outcomes of relapses were not reported.

We agree with the addition of the voclosporin-based regimen as an option for initial therapy in active LN. This indication was listed as a practice point and was not graded, awaiting more supportive systematic data.

From a clinical standpoint, the use of voclosporin does not require drug monitoring.[205] Furthermore, it is suggested that exposure to voclosporin might induce less metabolic adverse events commonly seen with other CNIs.[205]

Implementation and Challenges

The addition of voclosporin to MMF and steroids in active LN improved response (chiefly proteinuria) at 6 and 12 months while exposing patients to lower peak and cumulative glucocorticoid doses. However, there are questions about how to most appropriately use voclosporin. With the caveat that neither trial was designed to investigate responses between LN subgroups, several observations are worth noting. In phase 2, only patients who were "MMF naïve" had significant superior outcomes in the voclosporin arm (odds ratio [OR], 2.7 [95% CI, 1.15-6.44]). The opposite occurred in phase 3: only patients who were on MMF at screening (duration not disclosed) had significantly superior outcomes with voclosporin (OR, 5.8 [95% CI, 2.8-11.9]). However, those who received MMF > 2 g/d during the phase 3 study did not benefit from the addition of voclosporin (OR, 1.6 [95% CI, 0.3-8.4]). Future studies will help determine if the addition of voclosporin is most useful for the MMF-naïve patient and/or one who has not been able to achieve or tolerate the maximal induction dose of 2.5 or 3 g/d of MMF.

The relative benefit of voclosporin compared with other CNIs remains to be determined. Although it is difficult to compare agents across studies, the voclosporin-based multitarget therapy regimen yielded a complete renal response rate of 32% at 6 months while the Chinese RCT that used tacrolimus-based multitarget therapy[215] demonstrated a higher rate of 46% at 6 months, despite use of a lower dose of MMF (1 g/d). Therefore, other CNIs when added to MMF can also be efficacious, which is important when considering availability and cost.[222] It is also not clear if there might be race and ethnicity differences in response. While White patients seemed to benefit

the most from voclosporin based on the initial phase 2 study (OR, 3.8 [95% CI, 1.38-10.95), this was not reproduced in phase 3 where the main significant benefit of voclosporin use was driven by Asian and Black patients.

The more favorable response in the voclosporin arm of AURORA-1 was driven by a superior and faster drop in proteinuria, as SLEDAI scores and other serologies were comparable in both arms. It is likely that reduction in proteinuria is in part due to nonimmunosuppressive effects such as decreased glomerular filtration pressure and stabilization of the podocyte cytoskeleton, similar to cyclosporine. Biopsy data are anticipated that should provide information about the relative effects of voclosporin on immunological/histologic remission versus chronic damage that could reflect CNI-induced nephrotoxicity. Thus, it remains to be known whether the initial CNI-induced reduction in proteinuria will translate into improved long-term kidney outcomes and survival.

A small increase in proteinuria was noted 2 weeks after voclosporin withdrawal in AURA-LV, consistent with CNI discontinuation when used for other proteinuric glomerular diseases. Duration of treatment and decisions about when it would be safe to taper voclosporin are unresolved questions that could potentially be answered by repeat kidney biopsy to assess the presence of ongoing inflammation or the development of more chronic CNI toxicity. It is reassuring that the interim analysis of AURORA-2 (2-year extension study of AURORA-1) showed that the mean UPCR at 30 months was 0.58 mg/g in the voclosporin arm and 1.34 g/g in the control arm with stable eGFR and acceptable safety profile, but in the absence of additional data such as histopathology the need for such extended treatment is not clear.

The efficacy and acceptable metabolic profile of voclosporin use along with far less corticosteroid exposure brings a potentially exciting advancement in the management of active LN. However, many challenging issues remain for voclosporin that hopefully can be answered with more clinical trials in the future.

Practice Point 10.2.3.1.6: There is an emerging role for B-lymphocyte targeting biologics in the treatment of LN. Belimumab can be added to standard therapy in the treatment of active LN. Rituximab may be considered for patients with persistent disease activity or repeated flares.

We will divide our commentary according to therapies focused on B-cell depletion (eg, the anti-CD20 monoclonal antibody rituximab) or inhibition of B-cell activation (eg, belimumab).

Commentary on B-Cell Depletion

We agree with Practice Point 10.2.3.1.6. B-cell therapies are not included yet as first-line treatment in the recommendations but rather are discussed as a practice point in the management of active LN class III/IV.

Despite the established role of B cells in SLE/LN, initial anti-CD20 trials (LUNAR and BELONG) failed.[223,224] That said, in both studies add-on rituximab and ocrelizumab arms demonstrated numerically better overall renal response at 1 year compared with placebo. BELONG was terminated early due to higher ocrelizumab-induced serious infection rates. In the exploratory analysis of LUNAR, the rituximab group had more significant complete or partial response with respect to proteinuria at week 78 ($P = 0.04$), as well as improvement in kidney function and less need for rescue therapy at both 52 and 78 weeks. A post hoc analysis of LUNAR revealed variability in B-cell depletion in the rituximab arm, with only 78% achieving complete peripheral B-cell depletion (0 cells/μL) within 365 days.[225] Complete peripheral depletion, longer duration of complete peripheral depletion, and shorter time to achieve complete peripheral depletion of B cells were associated with complete renal response at week 78. Although only 40% of rituximab participants who achieved a complete peripheral B-cell depletion had a complete response at week 52, this increased to 47% at week 78, showing that long-term remission can be achieved and should be evaluated in future studies of B-cell–depleting agents.

These findings, along with uncontrolled and observational studies with positive results including in patients with treatment refractory LN,[207,226] suggest that optimizing treatment protocols for peripheral B-cell depletion remains a viable treatment option for active LN

Implementation and Clinical Utility of B-Cell Depletion

The need for a more potent B-cell–depleting therapy in LN combined with the superiority of obinutuzumab to rituximab in leukemia and lymphoma[227,228] as well as in murine LN[229] led to NOBILITY: a phase 2 RCT that compared the humanized type II anti-CD20 antibody obinutuzumab with placebo as an add-on to standard of care (MPAA/steroids) in active LN III, IV, or mixed.[230] A total of 125 patients were randomized to obinutuzumab 1,000 mg plus methylprednisolone 80 mg versus placebo given on day 1 and weeks 2, 24, and 26, and they were followed through week 104. Complete renal response was higher in the obinutuzumab group at week 52 (35% vs 23%; $P = 0.115$) and week 104 (41% vs 23%; $P = 0.026$). The benefit of obinutuzumab was greatest among patients with a baseline UPCR ≥ 3 g/g and with class IV LN. Adverse events were balanced between both groups. REGENCY (NCT04221477), a phase 3 study of obinutuzumab in LN, is currently under investigation.

Commentary on Inhibition of B-Cell Activation

Currently, belimumab, a recombinant human monoclonal antibody that inhibits B-cell–activating factor, is the only FDA-approved drug for both SLE and LN. It was evaluated in BLISS-LN, the largest RCT of LN induction, as an add-on to standard of care therapy (steroids plus cyclophosphamide-azathioprine [26%] or MPAA [74% of patients]) in active LN.[231] The revised primary end point of primary efficacy renal response (PERR) and complete

renal response were higher in the belimumab arm compared with the placebo arm at week 104 (OR, 1.6 [95% CI, 1.0-2.3], and OR, 1.7 [95% CI, 1.1-2.7], respectively), but the positive effect was limited to those treated with MPAA. The risk of renal-related event or death was significantly lower in the belimumab group. The safely profile of belimumab was acceptable with balanced adverse events between groups.

Despite these favorable results, limitations exist. The cohort was predominantly Asian with underrepresentation of Black and Hispanic participants and predominantly treated with MPAA as the standard of care. The selection of background therapy was nonrandom and was determined by the investigators. This design introduces potential bias to the study as patients with "more severe LN" may have been more likely to be treated with cyclophosphamide and may explain, beyond sample size, a more favorable response in the subgroup of belimumab-MPAA treated patients. LN status at randomization, such as new flare, relapse, or therapy failure, was not reported.

Based on lessons learned from previous studies in LN,[232-234] the primary end point of the study was revised after enrollment to include PERR. Despite this relaxation in end points, the PERR was achieved in less than 50% of patients by week 104. Using the initial prerevision end points, the responses were not significantly different between groups and would have resulted in a negative study. Instead, this study led to belimumab approval for the treatment of active LN in the United States and European Union.

Implementation and Clinical Utility of Inhibition of B-Cell Activation

A post hoc analysis of the 2-year BLISS-LN study showed that add-on belimumab was more effective in relapsed, proliferative LN and patients with baseline UPCR < 3 g/g.[235] More importantly, belimumab reduced the risk of a sustained 30% to 40% decrease in eGFR and reduced the annual rate of eGFR decline in those who remained in the study from week 24 through week 104. Belimumab also reduced the risk of LN flare in the overall population,[235] and this effect has been validated in other studies.[236,237] Despite this success, new LN diagnoses have been reported to occur in patients who were started on belimumab for nonrenal SLE.[238-240] In summary, use of this agent will certainly improve the care of patients with LN, but future studies and experience can help to delineate its specific role.

A limitation with all of the newer agents is cost and access, and individualization of care must remain a priority.

Practice Point 10.2.3.1.7: Other therapies, such as azathioprine or leflunomide combined with glucocorticoids, may be considered in lieu of the recommended initial drugs for proliferative LN in situations of patient intolerance, lack of availability, and/or excessive cost of standard drugs, but these alternatives may be associated with inferior efficacy, including increased rate of disease flares and/or increased incidence of drug toxicities.

Commentary

We agree with this practice point.

Treatment: Maintenance Therapy for Class III and Class IV LN

Recommendation 10.2.3.2.1: We recommend that after completion of initial therapy, patients should be placed on MPAA for maintenance *(1B)*.

Commentary and Clinical Utility

We agree that MPAA should be first line for maintenance therapy in the US population. This is based on the results of the ALMS maintenance trial in which MMF showed superiority to azathioprine. The ALMS maintenance trial included a multiethnic cohort, which better represents the US population.[241] If MMF is not tolerated due to gastrointestinal side effects, we would consider changing to EC-MPS before going to a second-line agent.

Implementation and Challenges

In the United States, MPAA have been widely used for both initial and maintenance therapies. A new challenge is how to best utilize adjunct therapies such as belimumab and voclosporin, which have recently been FDA approved for adjunctive treatment of LN. Both trials extended into the maintenance phase, but it is unclear at this point how long each therapy should be used. The BLISS LN trial evaluated belimumab in addition to standard of care regimens with aforementioned efficacy and safety over 24 months[231] and was effective at reducing flares. The AURORA trial also demonstrated the efficacy and safety of voclosporin in addition to standard of care over 12 months.[205] As discussed above, both therapies add substantial expense to the standard of care. Identifying patients who will benefit the most from these adjunct therapies will be valuable.

Practice Point 10.2.3.2.1: Azathioprine is an alternative to MPAA after completion of initial therapy in patients who do not tolerate MPAA, who do not have access to MPAA, or who are considering pregnancy.

Commentary and Clinical Utility

We generally agree with this recommendation. Access to MPAA should not be an issue in the United States. Azathioprine is a reasonable alternative. There was no difference in terms of kidney flares in the 10-year follow-up of the MAINTAIN trial.[242,243]

Practice Point 10.2.3.2.4: If MPAA and azathioprine cannot be used for maintenance, CNIs or mizoribine should be considered.

Commentary and Clinical Utility

We agree that CNIs should be considered in this setting, although there are limited data on CNI monotherapy for maintenance of proliferative LN in US populations and nephrotoxicity needs to be considered. If low-dose MPAA can be tolerated, low-dose MPAA combined with CNI therapy may be a reasonable alternative. The multitarget maintenance trial that evaluated tacrolimus 2-3 mg/d, MMF 0.5-0.75 g/d, and prednisone 10 mg/d compared with azathioprine (2 mg/kg/d) and prednisone 10 mg/d showed similar relapse rates with lower adverse events in the multitarget group.[216] The AURORA study evaluated multitarget therapy in an ethnically diverse cohort with MMF 2 g/d and voclosporin 23.7 mg twice a day. The study did allow for dose adjustments of MMF, with a small number of patients on less than the target dose. Voclosporin, however, has not been evaluated as a monotherapy. Mizoribine is not available in the United States. Other maintenance therapies to consider in patients unable to tolerate first-line therapies include B-cell–depleting agents such as rituximab, which have been successfully used in case series.[244]

Implementation and Challenges

Long-term use of CNIs can lead to nephrotoxicity. The risk is dose dependent, and all CNIs require close monitoring of blood pressure, kidney function, and electrolytes. Traditional CNIs cyclosporine and tacrolimus require drug level monitoring, which can be difficult for patients. Voclosporin does not require drug level monitoring but has not been studied as a monotherapy. CNIs can reduce proteinuria through nonimmunological mechanisms, and response to CNIs may not reflect histologic quiescence. Studies that incorporate repeat biopsies are needed to evaluate the response.

Point 10.2.3.2.5: The total duration of initial immunosuppression plus combination maintenance immunosuppression for proliferative LN should not be <36 months.

Commentary and Clinical Utility

We agree that the immunosuppression should not be <36 months, and in the vast majority of cases a longer duration of therapy is necessary. Multiple studies have demonstrated an increased risk of disease flare with shorter duration of maintenance therapy.[245,246] Prolonged therapy is necessary in high-risk populations (patients with African or Hispanic ancestry, pediatric onset disease, incomplete remission, and history of frequent disease flares).[247]

Implementation and Challenges

The optimal duration of maintenance therapy remains uncertain. The ideal regimen would minimize immunosuppressive risk while preventing kidney flare. The long-term goal is to preserve kidney function and prevent disease flares. Every time a patient experiences an LN flare, there is irreversible nephron loss, which shortens the life span of the kidney.[248] At this time, there are no adequate disease activity biomarkers, and there is often discordance of clinical and biopsy findings. Repeat kidney biopsies are helpful to assess for continued histologic activity when considering dose de-escalation.[249,250]

Treatment of Class V LN

Practice Point 10.2.4.1: A suggested approach to the management of patients with pure Class V LN is described in Figure 94.

Commentary and Clinical Utility

The algorithm in Figure 94 divides patients into those with low-level proteinuria, whose treatment should be guided by extrarenal manifestations of SLE, and those with nephrotic syndrome, for whom corticosteroids in combination with another immunosuppressive agent may be more appropriate.

We generally agree with recommendations in the outline. Immunosuppressive therapy for isolated membranous LN (class V) depends on the level of proteinuria and should be given universally in patients with nephrotic syndrome. There are very few clinical trials for pure class V, and many of the suggested treatments are based on small RCTs or the inclusion of pure class V patients in larger trials. It is not clear which agent is best in pure class V, nor is it clear if it should be treated similarly to other classes of LN or similarly to primary MGN. The algorithm lumps all immunosuppressive therapy together, which may be misleading. This is clarified in the chapter with MPAA suggested as first-line therapy.

Implementation and Challenges

The treatment cutoffs for subnephrotic proteinuria are not clear. EULAR/ERA-EDTA guidelines recommend consideration of immunosuppression for persistent proteinuria > 1 g/g despite maximal supportive therapy.[186] This is reasonable given the general risk of CKD progression and cardiovascular disease with proteinuria, but there are no studies comparing long-term kidney outcomes in subnephrotic class V treated with conservative therapy versus immunosuppression.

Assessing Treatment Response in LN

Practice Point 10.2.4.1.1: Definitions of response to therapy in LN are provided in Figure 95.

Commentary and Clinical Utility

We agree with the definitions of response as outlined in Figure 95.

Implementation and Challenges

The main goal in defining a response is to guide therapy that will preserve long-term kidney outcomes. There are

fewer data on patients with nephrotic syndrome from class V or mixed lesions. If proteinuria is improving, there may not need to be a change in therapy, as complete remission may take longer to be achieved. A more relaxed goal (0.7-0.8 g/d) has been proposed based on data from long-term follow-up suggesting that long-term kidney outcomes are achieved at this level.[232,243] Unfortunately, proteinuria is not always indicative of active disease, and the resolution of proteinuria does not always indicate quiescence. Patients with active disease based on clinical findings may have little activity on biopsy, and patients in clinical remission may still have active disease,[249] highlighting the need for research for biomarkers of active disease.

Management of Unsatisfactory Response to Treatment of LN

Practice Point 10.2.4.2.1: An algorithmic approach to patients whose response to therapy is deemed unsatisfactory is provided in Figure 96.

Commentary and Clinical Utility

The algorithm depicts a stepwise assessment of verifying adherence to treatment; ensuring adequate dosing by drug level; consideration of repeat biopsy; switching to an alternative first-line agent; and consideration of combination therapy, adjunctive rituximab, or an extended cyclophosphamide course. We agree with the algorithm as there are limited data on treatment for resistant disease.

Implementation and Challenges

The importance of adherence to immunosuppressive therapy cannot be understated. It is important to utilize shared decision making when choosing an initial therapy. For example, patients who are reluctant or unable to tolerate a large pill burden may benefit from an intravenous-based regimen.

Treatment of LN Relapse

Practice Point 10.2.4.3.1: After a complete or partial remission has been achieved, LN relapse should be treated with the same initial therapy used to achieve the original response, or an alternative recommended first-line therapy.

Commentary and Clinical Utility

We generally agree with this. Alternative first line may be preferred if cyclophosphamide was used initially to limit cumulative exposure and associated toxicities.

Implementation and Challenges

Any time a patient has a relapse, it is critical to evaluate for nonadherence. Flare is not clearly defined. Laboratory fluctuations in proteinuria, especially with random UPCR, can be significant. Flares that are defined by increase in proteinuria alone should be validated with repeat testing.

Practice Point 10.3.1.1: Patients with LN and thrombotic microangiopathy (TMA) should be managed according to the underlying etiology of TMA, as shown in Figure 97.

Commentary and Clinical Utility

We agree with management of TMA based on the algorithm provided in Figure 97. In addition to testing for ADAMTS13, complement-mediated TMA, and APL when TMA is suspected, we additionally suggest that every SLE be screened for APL antibodies at the time of diagnosis of lupus itself.[251]

Implementation and Challenges

The evaluation and treatment of TMA is very specialized, requiring specific testing that may not be available at some centers and may require treatment with plasma exchange, which may not be widely available. Patients with severe TMA need to be evaluated at centers familiar with diagnosis and treatment of TMA.

Special Situations: Pregnancy in Patients With LN

Practice Point 10.3.2.1: Patients with active LN should be counseled to avoid pregnancy while the disease is active or when treatment with potentially teratogenic drugs is ongoing, and for ≥6 months after LN becomes inactive.

Commentary and Clinical Utility

We agree with this statement. Patients should be counseled that pregnancy with active LN is associated with increased maternal risk and inferior fetal outcomes, including increased risk of miscarriage, still birth, preeclampsia, intrauterine growth restriction, preterm labor, and low birthweight.[252,253]

Implementation and Challenges

Contraception failure is common. Patients should be counseled on what to do should they become pregnant or are contemplating pregnancy. Ensuring an alternative to RAS blockade and MPAA is paramount as they have known teratogenicity.

Practice Point 10.3.2.2: To reduce the risk of pregnancy complications, hydroxychloroquine should be continued during pregnancy, and low-dose aspirin should be started before 16 weeks of gestation.

Commentary and Clinical Utility

We agree with this statement with the clarification that low-dose aspirin should be started after 12 weeks'

gestation (and before 16 weeks' gestation) as a preventative medication for pre-eclampsia.[254] Patients with a history of antiphospholipid antibody syndrome require anticoagulation with therapeutic doses of low-molecular-weight or unfractionated heparin in addition to low-dose aspirin.[253] Although not specifically studied for LN, patients with the nephrotic syndrome with hypoalbuminemia should be considered for prophylactic anticoagulation because of the known thrombophilic states of nephrosis and pregnancy.

Implementation and Challenges

Community obstetrician/gynecologists often have limited experience in the care of LN patients. These patients would benefit from OB/MFM referral and care at an experienced center if available.

Practice Point 10.3.2.3: Only glucocorticoids, hydroxychloroquine, azathioprine, and CNIs are considered safe immunosuppressive treatments during pregnancy.

Commentary and Clinical Utility

We agree, but to avoid confusion need to clarify that the legacy CNIs, tacrolimus and cyclosporine, are considered safe in pregnancy. There are no data on the safety of voclosporin in pregnancy, and the capsules contain alcohol, which should be avoided.[253,255]

Implementation and Challenges

Ideally, immunosuppression would be changed prior to pregnancy to ensure tolerance and continued disease remission after changing therapy. We would consider azathioprine as first line for proliferative LN in pregnancy, while CNIs may be considered as adjunct therapy in severe disease, nephrotic syndrome, or monotherapy in pure class V. Pregnant LN patients need frequent monitoring by obstetrics/gynecology and nephrology throughout pregnancy.

Special Situations: Treatment of LN in Children

Practice Point 10.3.3.1: Treat pediatric patients with LN using immunosuppression regimens similar to those used in adults, but consider issues relevant to this population, such as dose adjustment, growth, fertility, and psychosocial factors, when devising the therapy plan.

Commentary and Clinical Utility

We agree with this practice point.

Implementation and Challenges

Steroid reduction is critical in this population, but there are no studies evaluating reduced-dose regimens in pediatric LN.

Special Situations: Management of Lupus Patients With Kidney Failure

Practice Point 10.3.4.1: Patients with LN who develop kidney failure may be treated with hemodialysis, peritoneal dialysis, or kidney transplantation; and kidney transplantation is preferred to long-term dialysis.

Commentary and Clinical Utility

We agree with this practice point.

Guideline Statements and Commentary: Anti–glomerular Basement Membrane Antibody Glomerulonephritis

Introduction

Anti-GBM antibody GN is a rare but important cause of small vessel vasculitis, classically presenting as a pulmonary-renal syndrome (Goodpasture syndrome, anti-GBM disease), but can also be renal limited (anti-GBM nephritis). It is most often a result of antibodies directed against an intrinsic antigen in the noncollagenous (NC1) domain of the α3 chain of type IV collagen[256] which is present in the glomerular and alveolar basement membranes.[257] The chapter focuses on prompt recognition and early treatment because kidney failure is inevitable and the mortality rate is up to 96% in untreated patients.

Diagnosis of Anti-GBM GN

Practice Point 11.1.1: Diagnosis of anti-glomerular basement membrane (GBM) disease should be made without delay in all patients with suspected RPGN (Figure 98).

Commentary

We agree with the prompt workup of RPGN as delineated in Figure 98, including sending serologies for anti-GBM, ANA, and ANCA. As the anti-GBM antibodies can be falsely negative in approximately 10% of cases,[258] tissue diagnosis with a kidney biopsy is crucial when considered safe and feasible.

Treatment of Anti-GBM GN

Recommendation 11.2.1: We recommend initiating immunosuppression with cyclophosphamide and glucocorticoids plus plasmapheresis in all patients with anti-GBM GN except those who are treated with dialysis at presentation, have 100% crescents or > 50% global glomerulosclerosis in an adequate biopsy sample, and do not have pulmonary hemorrhage *(1C)*.

Commentary

As there are essentially no high-quality trials that have enrolled patients with anti-GBM GN, this recommendation

is based on low-quality evidence. However, as this is a rare disease, a well-performed RCT is unlikely to be completed. In addition, because the untreated disease causes a high morbidity and mortality, we agree with the recommendation to treat aggressively with the above regimen even in the absence of alveolar hemorrhage unless there is limited renal viability.

Assessment of renal viability with greater likelihood of response to immunosuppression can be split into clinical and pathologic features. First, patient assessment of the tolerability of aggressive immunosuppression should be considered, regarding age, frailty, and infection risk. Clinically, alveolar hemorrhage and/or AKI not requiring dialysis should be an indication for immediate therapy.[259] Long-term outcome of patients presenting on dialysis had a mortality rate of 35%, and >90% remained on dialysis at 1 year,[4] so these patients should be considered for treatment only if the presentation is acute, nonoliguric, and/or the biopsy has features of acuity such as acute tubular injury, <50% glomerulosclerosis, tubular atrophy and interstitial fibrosis, and <100% crescents.

Of note, even those who present with Scr > 500 mmol/L (5.7 mg/dL) but do not require dialysis within 72 hours of presentation benefit from immunosuppression.[259] Additionally, a phase 2 study of imlifidase, an IgG-degrading enzyme of *Streptococcus pyogenes*, demonstrated that a single dose of imlifidase when given in combination with plasma exchange and corticosteroids resulted in a rapid decline of antibody levels within 6 hours, with a 67% dialysis-free survival at 6 months.[260]

The following practice points are given to guide clinical decision making in the nuanced areas of this disease until more evidence exists.

Practice Point 11.2.1: Treatment for anti-GBM disease should start without delay if this diagnosis is suspected, even before the diagnosis is confirmed.

Commentary

We agree that empirical solumedrol and plasma exchange should begin immediately when anti-GBM disease is suspected. This will result in rapid removal of the pathogenic antibodies and can enhance renal survival.[5] Plasma exchange with albumin replacement is sufficient, but if there is alveolar hemorrhage or a recent kidney biopsy, replacement with fresh frozen plasma is preferred.[259] Cyclophosphamide administration could be considered empirically once infection has been sufficiently ruled out, but ideally should be given after the disease has been confirmed.

A kidney biopsy is helpful not only to confirm the diagnosis but also to give valuable prognostic information that can help guide the need for continued therapy. Important features on biopsy to assist in this decision are degree of acute tubular necrosis, percentage of crescents, and percent of tubular atrophy/interstitial fibrosis.

Practice Point 11.2.2: Plasma exchange should be performed until anti-GBM titers are no longer detectable.

Commentary

Most cases (97%) have undetectable anti-GBM antibodies within 8 weeks of immunosuppression and plasma exchange initiation.[261] As long as there is renal viability, extended plasma exchange should be continued until the anti-GBM antibody levels are negative on 2 consecutive tests.

Practice Point 11.2.3: Cyclophosphamide should be administered for 2-3 months and glucocorticoids for about 6 months (Figure 99).

Commentary

We agree with oral cyclophosphamide at a dose of 2-3 mg/kg for 2-3 months, dose adjusted for reduced GFR or older age. Glucocorticoids can be tapered to be completed by 6 months. Pneumocystis prophylaxis with trimethoprim-sulfamethoxazole should continue until cyclophosphamide is complete, and the prednisone dose is <20 mg daily.[262]

Practice Point 11.2.4: No maintenance therapy of anti-GBM disease is necessary.

Commentary

As the relapse rate is <5% in treated anti-GBM disease, maintenance therapy is unnecessary. As hydrocarbon exposure is associated with disease activity, smoking cessation should be strongly recommended.[263]

Practice Point 11.2.5: Patients with GN who are anti-GBM- and ANCA-positive should be treated with maintenance therapy as for patients with AAV.

Commentary

In patients with double positivity for ANCA and anti-GBM disease, relapse rates are equivalent to those of patients with AAV, as opposed to isolated anti-GBM disease.[162,264] Thus, maintenance immunosuppression as in patients treated for AAV is required for those patients who are double positive.

Practice Point 11.2.6: In refractory anti-GBM disease, rituximab may be tried.

Commentary

We agree that in addition to referring for a clinical trial where available, refractory anti-GBM should be treated with rituximab[265,266] or MMF.[267-269]

Practice Point 11.2.7: Kidney transplantation in patients with kidney failure due to anti-GBM disease should be postponed until anti-GBM antibodies remain undetectable for ≥6 months.

Commentary

Recurrence of anti-GBM disease after transplantation is very low in patients without detectable antibodies, and thus we agree that they should be negative for 6 months prior to transplantation.[270] In patients with Alport syndrome, anti-GBM antibodies to the foreign collagen chain in the transplanted kidney can occur approximately 2% to 3% of cases and can be detected by transplant kidney biopsy.[271]

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