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OPEN

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The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Management of Glomerular Diseases is an update to the KDIGO 2012 guideline. The aim is to assist clinicians caring for individuals with glomerulonephritis (GN), both adults and children. The scope includes various glomerular diseases, including IgA nephropathy and IgA vasculitis, membranous nephropathy, nephrotic syndrome, minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), infection-related GN, antineutrophil cytoplasmic antibody (ANCA) vasculitis, lupus nephritis, and anti–glomerular basement membrane antibody GN. In addition, this guideline will be the first to address the subtype of complement-mediated diseases. Each chapter follows the same format providing guidance related to diagnosis, prognosis, treatment, and special situations. The goal of the guideline is to generate a useful resource for clinicians and patients by providing actionable recommendations based on evidence syntheses, with useful infographics incorporating views from experts in the field. Another aim is to propose research recommendations for areas where

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Received 14 March 2021; revised 18 May 2021; accepted 20 May 2021

there are gaps in knowledge. The guideline targets a broad global audience of clinicians treating GN while being mindful of implications for policy and cost. Development of this guideline update followed an explicit process whereby treatment approaches and guideline recommendations are based on systematic reviews of relevant studies, and appraisal of the quality of the evidence and the strength of recommendations followed the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) approach. Limitations of the evidence are discussed, with areas of future research also presented.

Kidney International (2021) **100,** 753–779; https://doi.org/10.1016/j.kint.2021.05.015

KEYWORDS: AAV; ANCA; anti-GBM; C3; complement; evidence-based; FSGS; glomerular diseases; glomerulonephritis; guideline; IgA nephropathy; IgA vasculitis; infection-related glomerulonephritis; KDIGO; lupus nephritis; membranous nephropathy; minimal change disease; MPGN; nephrotic syndrome; systematic review

We are pleased to present the second edition of Kidney Disease: Improving Global Outcomes (KDIGO) Guideline for the Management of Glomerular Diseases to the providers who care for patients with glomerular diseases and the patients and families who live with glomerular diseases. This guideline is the culmination of a dedicated process that began in 2017, at which time a Controversies Conference was convened to identify important updates and ongoing needs in the field of glomerular diseases and resulted in 2 summary documents (Part 1: https://kdigo.org/wp-content/uploads/2017/02/KDIGO-GN-Conference-Report-Part-1.pdf; Part 2: https://kdigo.org/wp-content/uploads/2017/02/KDIGO-GN-Conference-Report-Part-2.pdf). Based on these conference conclusions, an extensive review of available literature on glomerular diseases was undertaken by the Cochrane Kidney and Transplant Evidence Review Team. This enabled a Work Group of experts in glomerular diseases to craft a data-driven series of recommendations, and practice points to facilitate the care and treatment of patients with glomerular diseases. This guideline supplants the KDIGO 2012 Guideline for Glomerulonephritis (GN). In addition to this guideline, there are other groups examining trial designs for glomerular diseases and how best to incorporate patient preferences and outcomes of relevance to patients and families in trials. Such efforts, like Standardized Outcomes in Nephrology-Glomerular Diseases (SONG-GD) should be used in conjunction with the KDIGO guideline.

The guideline is organized into 11 chapters, 10 of which cover a specific primary or secondary glomerular disease or group of diseases. The first chapter is an extensive review of general management principles that should be considered for patients with any type of glomerular disease. The chapters provide recommendations that are evidence-based and actionable. The recommendations are graded to provide the reader with an idea of the strength of a given recommendation and quality of the evidence underpinning it. In the many instances where high-confidence data, for example from randomized, controlled clinical trials (RCTs), are lacking, practice points informed by observational studies, cohort studies, uncontrolled or open-label studies, and expert consensus have been provided. Practice points should be considered as suggestions to assist clinicians in managing patients when there is a lack of or gaps in high-quality evidence for a given topic or issue.

This Executive Summary provides highlights of the KDIGO 2021 guideline and in general, summarizes what is the same, what is new, and what remains in need of more evidence in comparison to the 2012 guideline. The summary is organized into chapter discussions that follow the outline of the guideline. Given the extensive scope of this guideline, this summary is not comprehensive and the reader is referred to the full guideline for details and discussion of the flow of evidence and logic leading to the recommendations and practice points (https://kdigo.org/guidelines/gd/). We have not included references in the Executive Summary as the guideline itself is extensively referenced. The evidence used to generate the guideline is available in the Data Supplement published alongside the guideline and will be published on the MAGICapp platform (https://kdigo.org/guidelines/gd/).

Chapter 1: General principles for the management of glomerular disease

This chapter emphasizes the role of the kidney biopsy, which is still considered the "gold standard" for the diagnostic evaluation of glomerular diseases. Repeat kidney biopsy should be performed if the information will potentially alter the diagnosis, the therapeutic plan, or contribute to the estimation of prognosis. Serologic studies and genetic testing (e.g., whole exome sequencing) in selected cases may enhance the interpretation and the utility of the kidney biopsy in the future.

To assess total urinary protein excretion in patients with GN, a 24-hour urine collection should be obtained. In children, a first morning protein-creatinine ratio (PCR) is more appropriate. When feasible, a reasonable compromise is to collect an "intended" 24-hour urine sample and measure PCR in an aliquot of the collection. To assess estimated glomerular filtration rate (eGFR), the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation is preferred in adult patients with GN and the modified Schwartz equation in children. The Full Age Spectrum (FAS) equation may be used in both adults and children. Issues of race in these formulae are now being clarified by the National Kidney Foundation-American Society of Nephrology Task Force. Routine evaluation of urine sediment for erythrocyte morphology and the presence of red cell casts and/or acanthocytes is indicated in all forms of GN.

Edema management in nephrotic syndrome (NS) has not changed significantly from the 2012 guideline version. Loop

Practice Point 1.13.1. Choose a glomerulonephritis treatment regimen that averts the immediate morbidity of the primary disease process	• Intensity of induction therapy is predicated on the severity of presenting symptoms and type of glomerulonephritis • The level of GFR needs to be taken into account for determining safe dosage
Practice Point 1.13.2. Choose a glomerulonephritis treatment regimen that prevents disease progression	• Complete clinical remission may not be possible in all forms of chronic glomerulonephritis • Prolonged immunosuppression or multiple rounds of immunosuppression may be required to prevent or delay chronic kidney disease progression or the development of kidney failure • Proteinuria reduction is a surrogate endpoint in the treatment of glomerulonephritis
Practice Point 1.13.3. Choose a glomerulonephritis treatment regimen that minimizes harmful side effects from immunosuppression	• Disclose individual drug side effects (both short- and long-term) • Consider the patient's point of view in shared decision-making • Screen for latent infections, where appropriate, prior to initiation of certain immunosuppression protocols • Monitor therapeutic drug levels where clinically indicated • Prescribe prophylaxis for specific immunosuppressive drug side effects • Review vaccination status and update as required • Offer fertility preservation, where indicated • Monitor for development of cancers or infections • Prolonged immunosuppression or multiple rounds of immunosuppression is associated with more toxic drug exposure over time

Figure 1 | Minimization of immunosuppression-related adverse effects. GFR, glomerular filtration rate.

diuretics are the preferred agents, as is restriction of dietary sodium intake. If diuretic response is insufficient, other mechanistically different diuretics should be added. In such cases, particular attention to adverse effects of the diuretics is necessary, including hyponatremia, hypokalemia, glomerular filtration rate (GFR) reduction, and volume depletion.

Management of hypertension and proteinuria in GN also has experienced few changes. Angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARBs) should be used at maximally tolerated or allowed dose as first-line in treating patients with both hypertension and proteinuria. Target systolic blood pressure in most adult patients is $<$120 mm Hg using standardized office BP measurement (https://kdigo.org/guidelines/blood-pressure-in-ckd/). Target 24-hour mean arterial pressure in children is $\leq$50th percentile for age, sex, and height by ambulatory blood pressure monitoring. Clinicians should up-titrate an ACEi or ARB to maximally tolerated or allowed daily dose as first-line in treating patients with GN and proteinuria alone and advise on sodium restriction, but counsel patients to hold renin-angiotensin system (RAS) inhibitors and diuretics if they are at risk for volume depletion such as an intercurrent illness. Proteinuria goal is variable depending on the GN-type (see individual chapters). If needed, potassium-wasting diuretics and/or potassium-binding agents can be used to reduce serum potassium to normal, in order to allow the use of RAS inhibitors for blood pressure control and proteinuria reduction. Metabolic acidosis should be treated if serum bicarbonate is $<$22 mmol/l. Lifestyle modifications should be employed in all GN patients as synergistic means for improving control of hypertension and proteinuria.

Treatment of dyslipidemia may be considered in patients with the NS, particularly for patients with other cardiovascular risk factors, including hypertension and diabetes. Lifestyle modifications are important in all patients with persistent dyslipidemia and glomerular disease. Consider starting a statin drug as first-line therapy for persistent dyslipidemia in patients with glomerular disease and consider initiation of non-statin therapy in those individuals who cannot tolerate a statin, or who are at high atherosclerotic cardiovascular disease risk and fail to achieve low-density lipoprotein cholesterol or triglyceride goals despite maximally tolerated statin dose.

Full anticoagulation is indicated for patients with thromboembolic events occurring in the context of NS.

Prophylactic anticoagulation should be employed in patients with NS when the risk of thromboembolism exceeds the estimated patient-specific risks of an anticoagulation-induced serious bleeding event. A particular high-risk situation is membranous nephropathy (MN) with NS; a decision algorithm in this situation is shown in the section related to Chapter 3 (see below).

To prevent infections in GN patients with impaired immunity, pneumococcal vaccine should be administered to those with NS and/or chronic kidney disease (CKD). Patients and household contacts should receive the influenza vaccine. Screening for tuberculosis (TB), hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and syphilis in clinically appropriate patients is suggested. Prophylactic trimethoprim-sulfamethoxazole should be considered in patients receiving high-dose prednisone or other immunosuppressive agents (rituximab, cyclophosphamide). Meningococcal vaccine and prophylaxis are necessary in patients with complement deficiencies or treated with complement inhibitors.

Outcome measures, such as treatment goals for proteinuria reduction, vary between the specific causes of GN. A reduction in the slope of decline in GFR can be taken as a favorable surrogate outcome of treatment. A 40% or greater decline in eGFR from baseline over a 2- to 3-year period has been suggested as a surrogate outcome measure for kidney failure in clinical trials.

Figure 1 shows options for minimization of immunosuppression-related adverse effects.

Dietary modifications and regular physical activity to normalize body mass index, limit central obesity, and decrease cardiovascular disease risk factors are appropriate. Patients should be counseled to restrict dietary sodium to <2.0 g/d (<90 mmol/d). Dietary protein restriction may be considered in adults based on the degree of proteinuria and level of kidney function, with replacement of nephrotic losses.

Care for pregnant patients with GN needs coordination between nephrology and obstetrics, and ideally, planning for pregnancy should be considered.

Patients with GN should be offered participation in a disease registry and clinical trials, whenever available.

Chapter 2: Immunoglobulin A nephropathy (IgAN)/ immunoglobulin A vasculitis (IgAV)

Following the biopsy-confirmed diagnosis of IgAN, including histologic scoring via the MEST-C (mesangial [M] and endocapillary [E] hypercellularity, segmental glomerulosclerosis [S], interstitial fibrosis/tubular atrophy [T], and crescents [C]) system, it is essential to assess disease prognosis. A valuable resource is the International IgAN Prediction Tool available at Calculate by QxMD. It is important to realize however that neither this calculator nor the MEST-C score nor the presence or number of crescents can presently be used to determine the likely impact of any particular treatment regimen.

As in the 2012 guideline version, the primary focus of IgAN management should be multifaceted, optimized supportive care, including RAS blockade as much as tolerated or allowed, blood pressure control, cardiovascular risk minimization, adherence to lifestyle advice, including dietary counselling, smoking cessation, weight control, and exercise as appropriate. RAS blockade should be instituted irrespective of hypertension if the patient has proteinuria >0.5 g/d (*Grade 1B*).

If proteinuria stays above 0.75–1 g/d despite at least 90 days of optimized supportive care, the patient has a high risk of progressive loss of kidney function and may be considered for a 6-month course of glucocorticoid therapy (*Grade 2B*), or preferably, the opportunity to take part in a therapeutic clinical trial. Because the clinical benefit of glucocorticoids in IgAN is not established, they should be given with extreme caution or avoided entirely in patients with:

- an eGFR <30 ml/min per 1.73 m^2,
- diabetes,
- obesity (defined as body mass index >30 kg/m^2),
- latent infections (e.g., viral hepatitis, tuberculosis),
- secondary disease (e.g., liver cirrhosis),
- active peptic ulceration,
- uncontrolled psychiatric disease, or
- severe osteoporosis.

Management of the patient with IgAN who remains at high risk for progression after maximal supportive care is illustrated in Figure 2. Proteinuria reduction to under 1 g/d is a surrogate marker of improved kidney outcome in IgAN, and hence a reasonable treatment target.

Beyond glucocorticoids, other immunosuppressive therapies are not recommended in IgAN, including azathioprine, cyclophosphamide (except in the setting of rapidly progressive IgAN), calcineurin inhibitors (CNIs), and rituximab. The use of mycophenolate mofetil (MMF) in IgAN is not recommended in non-Chinese patients, whereas it may be used as a glucocorticoid-sparing agent in Chinese patients. Similarly, in non-Japanese patients there are no data to support the routine use of tonsillectomy in high risk IgAN patients. If 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.

A number of new therapies for high-risk IgAN patients are currently being evaluated, including drugs that may augment the supportive care approach (sodium-glucose co-transporter-2 [SGLT2] inhibitors, sparsentan, atrasentan, hydroxychloroquine) or more specific approaches (e.g., enteric-coated budesonide, various complement inhibitors, therapies targeting B-cell development).

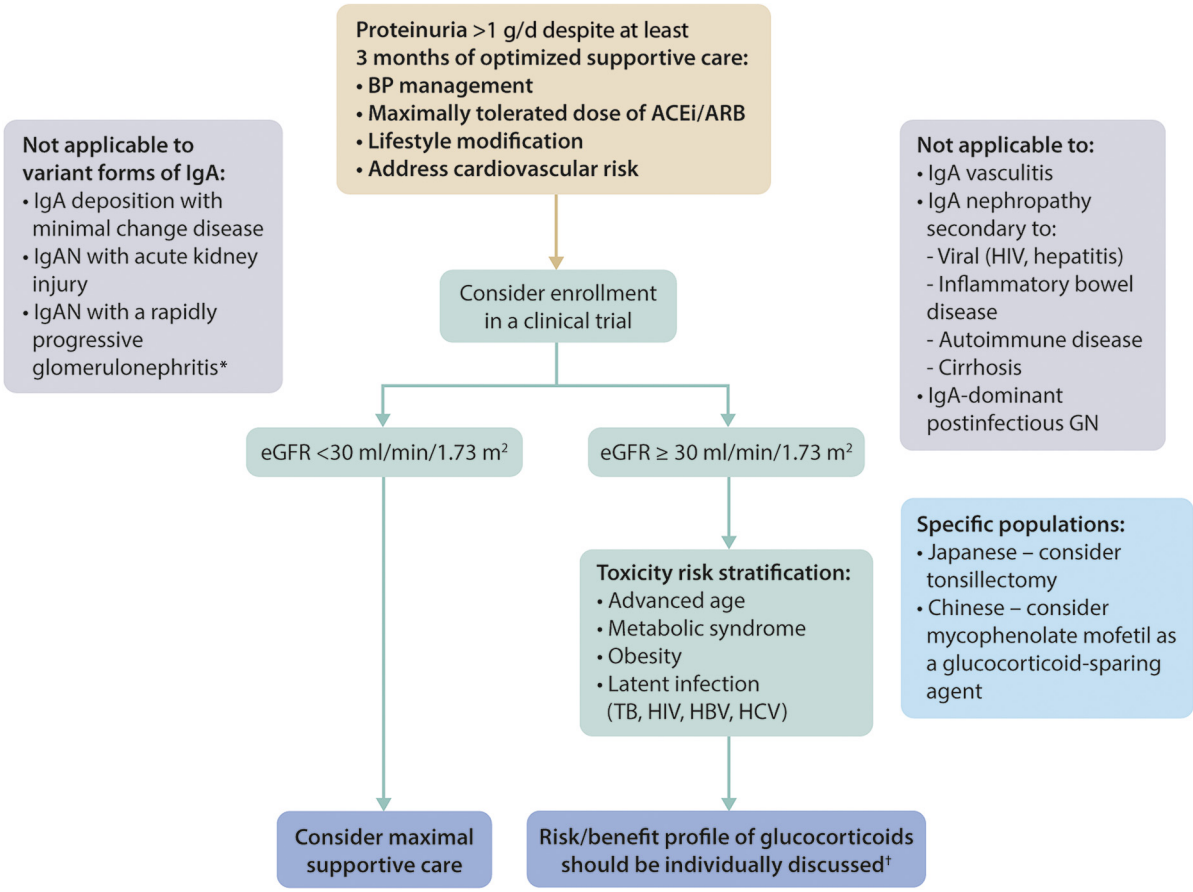

Figure 2 | Management of patients with IgAN who remain at high risk for progression after maximal supportive care. *IgAN with rapidly progressive glomerulonephritis is covered in Practice Point 2.4.3. †The Therapeutic Evaluation of Steroids in IgA Nephropathy Global (TESTING) study shows early evidence of efficacy in patients who had marked proteinuria (2.4 g/d average) at the expense of treatment-associated morbidity and mortality. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; eGFR, estimated glomerular filtration rate; GN, glomerulonephritis; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IgAN, immunoglobulin A nephropathy; TB, tuberculosis.

Special situations in IgAN include the presence of NS. Patients with a kidney biopsy demonstrating mesangial IgA deposition and histologic features consistent otherwise with minimal change disease (MCD) should be treated in accordance with the guidelines for MCD (Chapter 5). Patients with NS whose kidney biopsy has coexistent features of a mesangioproliferative GN should be managed in the same way as high-risk IgAN patients. Finally, nephrotic range proteinuria without NS may be seen in IgAN, and this commonly reflects coexistent secondary focal segmental glomerulosclerosis (FSGS) (e.g., obesity, uncontrolled hypertension) or development of extensive glomerulosclerosis and tubulointerstitial fibrosis.

IgAN can also lead to acute kidney injury (AKI) from severe visible hematuria, in which case management should focus on supportive care for AKI. A repeat kidney biopsy should be considered in patients who fail to show improvement in kidney function within 2 weeks following cessation of the hematuria. Alternatively, AKI can result from a rapidly progressive glomerulonephritis (RPGN) IgAN course with extensive crescent formation (usually >50% of glomeruli), commonly in the absence of visible hematuria. Importantly, the presence of crescents in a kidney biopsy in the absence of a concomitant change in GFR does not constitute rapidly progressive IgAN; however, these patients require close follow-up to ensure prompt detection of any GFR decline. Patients with true rapidly progressive IgAN should be offered treatment with cyclophosphamide and glucocorticoids in accordance with the guidelines for antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV; Chapter 9).

There are insufficient data currently to recommend that post-pubertal children be managed as adults with IgAN. There is strong evidence suggesting a benefit of RAS blockade in children. In children the use of immunosuppressants is more widespread, particularly the early use of glucocorticoids, but trial-based evidence that may inform recommendations is absent.

Unlike children, there are no internationally agreed-upon criteria for the diagnosis of IgAV in adults, although a clinical diagnosis of IgAV is often made in adults based on the criteria described for children. Adult patients with IgAV should be assessed for secondary causes and for malignancy with age- and sex-appropriate screening tests. Neither the MEST-C classification nor the International IgAN Prediction Tool has been validated in IgAV. Supportive care measures do not differ from those in patients with IgAN.

Glucocorticoids should not be used to prevent nephritis in patients with isolated extrarenal IgAV (*Grade 1B*). In those patients who wish to try immunosuppressive therapy, treatment with glucocorticoids is as described above for IgAN. IgAV nephropathy (IgAVN) with RPGN may also be associated with significant extrarenal involvement (e.g., pulmonary, gastrointestinal, and skin), which may dictate alternative immunosuppressive strategies. Uncontrolled case series describe the potential role for the addition of plasma exchange to glucocorticoid therapy to accelerate recovery in patients with life- or organ-threatening extrarenal complications of IgAV. The majority of IgAV children who will develop nephritis will do so within 3 months of presentation. Oral prednisone/prednisolone or pulsed intravenous methylprednisolone should be used in children with mild or moderate IgAVN. Children with IgAVN and NS and/or rapidly deteriorating kidney function are treated in the same way as rapidly progressive IgAN.

Chapter 3: Membranous nephropathy

In contrast to the KDIGO 2012 guidelines, a kidney biopsy is no longer required to confirm the diagnosis of MN in patients with NS and a positive anti-M-type phospholipase A2 receptor (PLA2R) antibody test. Nevertheless, a kidney biopsy can provide important additional information even under these circumstances. Patients with MN should be evaluated for associated conditions (e.g., malignancy, infections, lupus, drugs), regardless of whether anti-PLA2R antibodies and/or anti–thrombospondin type-1 domain-containing 7A (THSD7A) or other antibodies are present or absent. Clinical and laboratory criteria should then be used to assess the risk of progressive loss of kidney function (Figure 3).

Low risk	Moderate risk	High risk	Very high risk
• Normal eGFR, proteinuria <3.5 g/d and serum albumin >30 g/l OR • Normal eGFR, proteinuria <3.5 g/d or a decrease >50% after 6 months of conservative therapy with ACEi/ARB	• Normal eGFR, proteinuria >3.5 g/d and no decrease >50% after 6 months of conservative therapy with ACEi/ARB AND • Not fulfilling high-risk criteria	• eGFR <60 ml/min/1.73 m^{2}* and/or proteinuria >8 g/d for >6 months OR • Normal eGFR, proteinuria >3.5 g/d and no decrease >50% after 6 months of conservative therapy with ACEi/ARB AND at least one of the following: • Serum albumin <25 g/l† • PLA2Rab >50 RU/ml‡ • Urinary α_1-microglobulin >40 µg/min • Urinary IgG >1 µg/min • Urinary β_2-microglobulin >250 mg/d • Selectivity index >0.20§	• Life-threatening nephrotic syndrome OR • Rapid deterioration of kidney function not otherwise explained

Figure 3 | Clinical criteria for assessing risk of progressive loss of kidney function. eGFR and PCR are used in routine clinical care. Other biomarkers may not be available in all centers; this table provides an overview of useful biomarkers. *Most studies have used serum creatine (SCr) values to guide management, and SCr values >1.5 mg/dl (133 µmol/l) are often used to define kidney insufficiency. An eGFR value of 60 ml/min per 1.73 m^2 defines kidney insufficiency in a young adult. It is important to realize that eGFR decreases with age, and an SCr value of 1.5 mg/dl (133 µmol/l) reflects an eGFR of 50 ml/min per 1.73 m^2 in a 60-year-old male patient and 37 ml/min per 1.73 m^2 in a 60-year-old female patient. Thus, when using eGFR in risk estimation, age should be taken into account. †Serum albumin should be measured by BCP or immunometric assay. ‡Cutoff values are not validated. Anti-PLA2R antibodies should be measured at 3–6-month intervals, the shorter interval being performed in patients with high anti-PLA2R antibodies levels at baseline. Changes in anti-PLA2R antibodies levels during follow-up likely add to risk estimation. Disappearance of anti-PLA2R antibodies precedes clinical remission and should lead to refraining from additional therapy. Detailed data are lacking. §Selectivity index is calculated as clearance of IgG/clearance of albumin. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BCP, bromocresol purple; eGFR, estimated glomerular filtration rate; IgG, immunoglobulin G; PLA2Rab, antibodies against the M-type phospholipase A2 receptor.

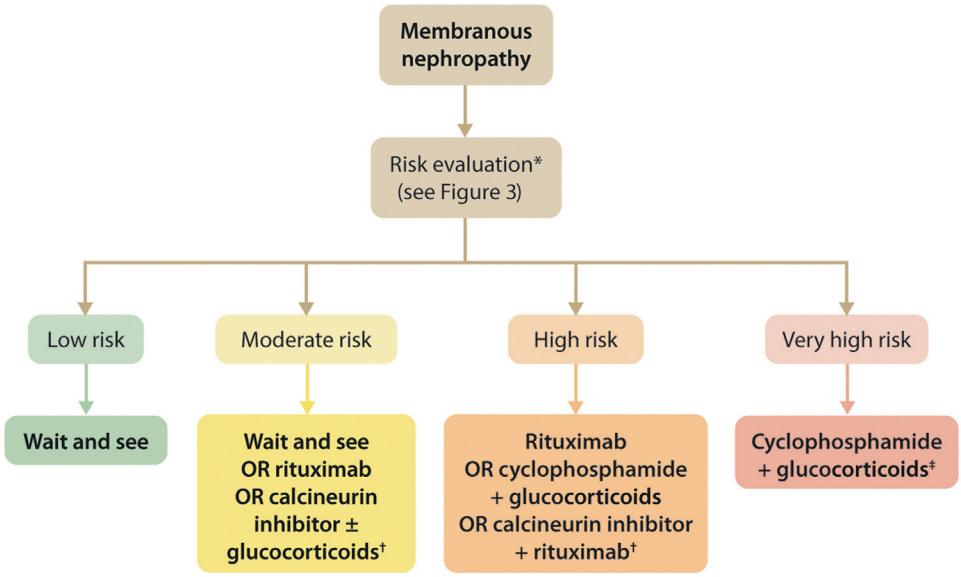

Figure 4 | Risk-based treatment of MN. *See Practice Point 3.2.1 and Figure 3 for a detailed description of risk evaluation. †Calcineurin inhibitor (CNI) monotherapy is considered less efficient. Treatment with CNI for 6–12 months with rapid withdrawal is associated with a high relapse rate. Still, its use may be considered in patients with normal eGFR and moderate risk of progression, since many of these patients will develop a spontaneous remission. The use of CNI will shorten the period of proteinuria. In patients with high risk of progression, addition of rituximab after 6 months of treatment with CNI is advised, with the possible exception of patients with documented disappearance of anti-PLA2R antibodies after CNI treatment. ‡There is insufficient evidence that rituximab used in standard doses prevents development of kidney failure. If eGFR falls below 50 ml/min per 1.73 m^2, the doses of cyclophosphamide should be halved. In patients who do not tolerate or can no longer use cyclophosphamide, rituximab could be offered. Consultation with an expert center is advised. eGFR, estimated glomerular filtration rate; MN, membranous nephropathy; PLA2R, M-type phospholipase A2 receptor.

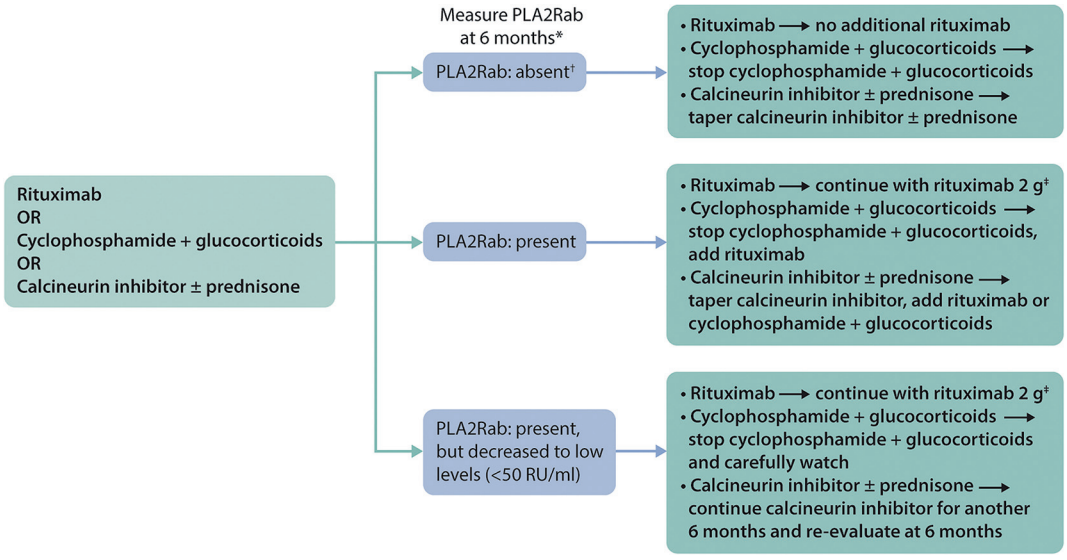

Figure 5 | Immunologic monitoring in MN after start of therapy. See text for current treatment schedules. Note: The cumulative dose of cyclophosphamide should not exceed 36 g in view of the risk of malignancy (Chapter 1). To stay on the safe side, we usually limit the cumulative dose to 25 g (in an 80 kg male: 6 months cyclical cyclophosphamide at a dose of 2.5 mg/kg/d equals 18 g and 6 months daily cyclophosphamide at a dose of 1.5 mg/kg/d equals 22 g). Lower doses (maximum 10 g) must be used in patients who wish to conceive. CNIs are unlikely to induce late immunologic remission; in patients with persistent anti-PLA2R antibodies, these drugs may be used in combination with rituximab. B cell depletion is insufficient to judge the efficacy of rituximab therapy; extra doses may be considered even if B cells in the peripheral blood are absent or very low. However, in these patients, consultation with an expert center is advised. eGFR should be stable; if not, then it is always necessary to evaluate for other causes; and if eGFR decrease is attributed to MN activity, always provide additional therapy. *Some centers will measure anti-PLA2R antibodies at month 3, and adapt treatment at that time. In most patients, response occurs within 3 months after start of therapy. †A negative immunofluorescence test indicates immunologic remission. If measured by enzyme-linked immunosorbent assay, a cutoff value of 2 RU/ml should be used to define complete immunologic remission. ‡Retreatment with rituximab should be given similarly to the initial treatment with 1 or 2 infusions of 1 g rituximab each administered 2 weeks apart (Fervenza FC, Appel GB, Barbour SJ, et al. Rituximab or cyclosporine in the treatment of membranous nephropathy. *N Engl J Med*. 2019;381:36–46). CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; MN, membranous nephropathy; PLA2Rab, antibodies against the M-type phospholipase A2 receptor.

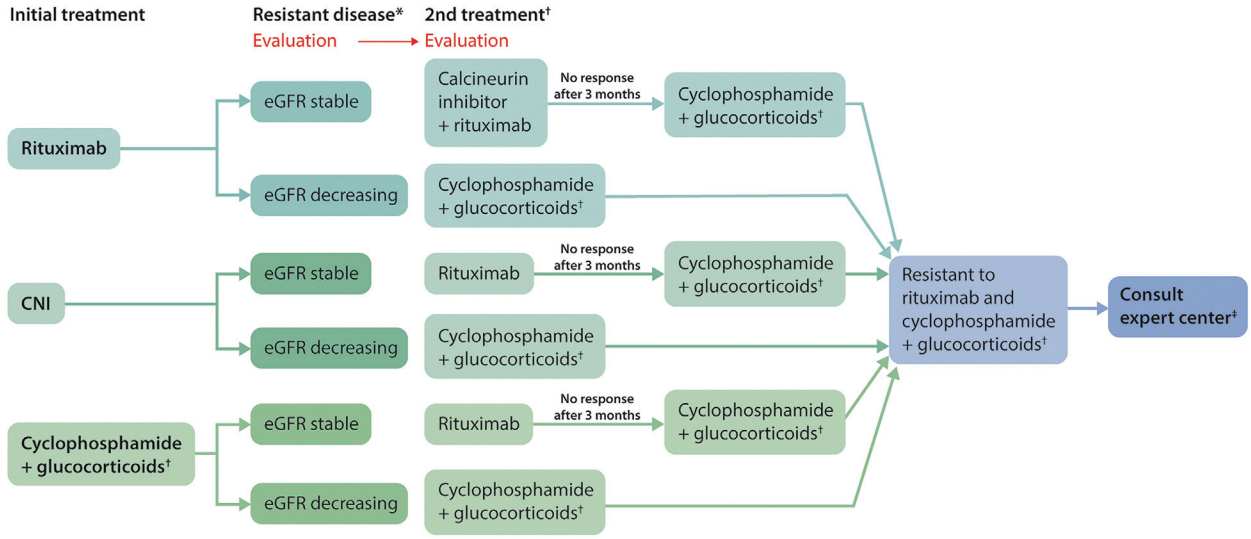

Figure 6 | Management of resistant disease in MN. Details of commonly used treatment regimens are shown in Figure 32 of the full guideline text. *Evaluation: In patients with resistant disease, compliance should be checked and efficacy monitored (e.g., B-cell response, anti-rituximab antibodies, IgG levels, leukocytopenia during cyclophosphamide, CNI levels). Persistent proteinuria is not sufficient to define resistance. If proteinuria persists, while serum albumin has increased, one should also consider secondary FSGS. This would be further supported by the disappearance of anti-PLA2R antibodies. In patients with persistent proteinuria with normal or near-normal serum albumin levels or patients with persistent proteinuria despite loss of anti-PLA2R antibodies, a kidney biopsy should be considered to document active MN. †Second treatment is dependent on the severity of deterioration of eGFR as indicated. When rituximab is chosen as second treatment, the response of proteinuria and anti-PLA2R antibodies should be evaluated after 3 months. Cyclophosphamide treatment should take into account the maximal tolerable dose: The cumulative dose should not exceed 10 g if preservation of fertility is required. The cumulative dose should not exceed 36 g to limit risk of malignancies. Expert centers may still use more, based on weighing risk and benefits. ‡Patients who did not respond to rituximab or cyclophosphamide should have a consultation with an expert center. These centers may choose experimental therapies (bortezomib, anti-CD38 therapy, and belimumab) or a higher dose of conventional immunosuppressive therapy. CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; MN, membranous nephropathy; PLA2R, M-type phospholipase A2 receptor.

All patients with primary MN and proteinuria should receive optimal supportive care. Immunosuppressive therapy is not required in patients with 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. Immunosuppressive therapy should be considered when at least one risk factor for disease progression is present or when serious complications of NS (e.g., AKI, infections, thromboembolic events) have occurred (Figure 4). For patients with MN and at least one risk factor for disease progression, consider using rituximab or cyclophosphamide and alternate month glucocorticoids for 6 months, or tacrolimus-based therapy for ≥6 months, depending on the estimate of risk (Figures 3 and 4) (*Grade 1B*). Longitudinal monitoring of anti-PLA2R antibody levels after starting therapy may be useful for evaluating treatment response in patients with MN, and can be used to guide adjustments to therapy (Figure 5).

In patients with MN and initial relapse of the NS after therapy, the initial therapy can be repeated or treatment may be switched to rituximab in those initially treated with CNIs or cyclophosphamide. Management suggestions for the patient with treatment-resistant MN are shown in Figure 6.

Evaluation of a kidney transplant recipient with MN should include maximal efforts to ascertain if MN is associated with PLA2R antibodies, including staining the native kidney biopsy for PLA2R expression in immune deposits (enhanced PLA2R staining). The risk of recurrence increases if PLA2R antibodies persist in the circulation despite kidney failure. After transplantation, patients with known PLA2R antibody-associated MN should be monitored for the kinetics of antibody levels every 1–3 months with a liberal transplant biopsy in case of increasing antibodies. Rituximab can be used in case of documented recurrent MN.

MN in children is very rare and no evidence to guide management exists. Such children should be referred to an expert center.

Prophylactic anticoagulant therapy in patients with MN and NS should be based on an estimate of the risk of

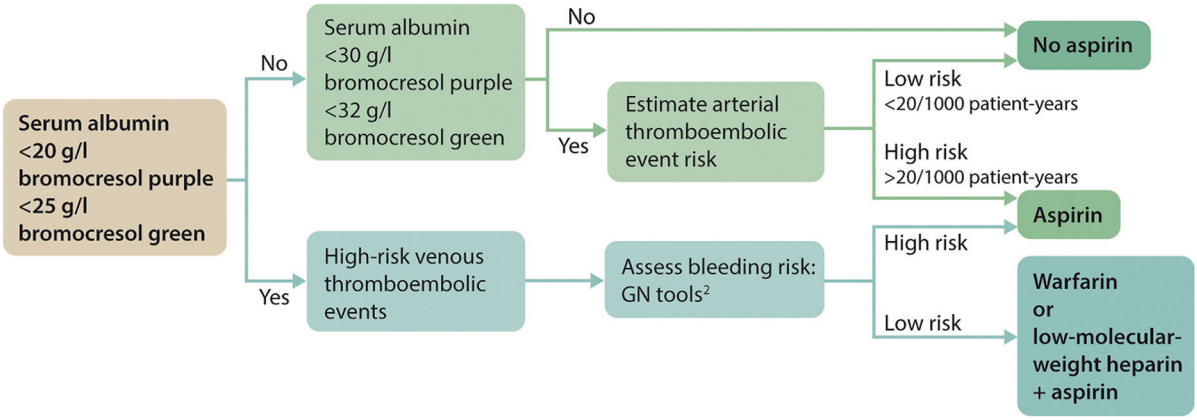

Figure 7 | Anticoagulant therapy in patients with MN. Adapted from *Kidney International*, volume 89, issue 5, Hofstra JM, Wetzels JFM. Should aspirin be used for primary prevention of thrombotic events in patients with membranous nephropathy? Pages 981–983, Copyright © 2016, with permission from the International Society of Nephrology. Proposed algorithm for anticoagulant therapy in patients with membranous nephropathy (MN). This algorithm provides guidance for the clinicians. The proposed cutoff values are based on expert opinion. When considering anticoagulant therapy, it is important to balance benefits and risks. The following are important considerations:

1. The risk of thrombotic events is related to the level of serum albumin. It is important to note that there is a large difference among the serum albumin assays. A serum albumin concentration of 25 g/l [2.5 g/dl] with bromocresol green (BCG) equals a concentration of ~20 g/l [2.0 g/dl] with bromocresol purple (BCP), or immunonephelometry. It is likely that most studies have used the BCG assay. Consider using 25 g/l [2.5 g/dl] as a threshold when using BCG and 20 g/l [2.0 g/dl] when using BCP or immunonephelometry.
2. Assess risk of venous thrombosis and risk of bleeding (http://www.med.unc.edu/gntools/).
3. Patients with MN and nephrotic syndrome are also at risk of developing arterial thrombotic events. The risk of arterial thrombotic event (ATE) is dependent on age, history of previous events, diabetes, estimated glomerular filtration rate (eGFR), smoking, and severity of nephrotic syndrome (NS). Risk assessment can be done using the Framingham risk score, and including previous events and proteinuria.
4. Use of aspirin is insufficient to prevent venous thromboembolism (VTE); use of warfarin is sufficient to prevent ATE.
5. Treatment with warfarin: There is more international normalized ratio (INR) variability in patients with NS and low eGFR; there is increased risk of thrombosis immediately after starting high-dose warfarin. Consider starting anticoagulation therapy with low-dose low-molecular-weight heparin and then folding in warfarin and, when therapeutic, stopping the heparin. A good alternative is to use low-dose low-molecular-weight heparin + aspirin for a period of 3 months before switching to warfarin, allowing for judgment on the course of proteinuria.
6. Glucocorticoids increase the risk of thrombosis; thus, anticoagulant therapy should not be omitted in patients who start prednisone therapy.
7. ATE risk is estimated using the Framingham risk score, with added risk in case of low eGFR or higher proteinuria. The Framingham risk score takes into account age, smoking, serum cholesterol, and blood pressure.

thrombotic events and the risk of bleeding complications, as illustrated in Figure 7.

Chapter 4: Nephrotic syndrome in children

In contrast to the management of NS in adults, a diagnostic kidney biopsy is generally not performed at presentation in children to establish a diagnosis. Children who develop NS are generally assumed to have MCD that will respond to glucocorticoids (steroid-sensitive nephrotic syndrome [SSNS]). Patients who are glucocorticoid-resistant (steroid-resistant nephrotic syndrome [SRNS]) have poor long-term kidney survival, and should undergo a more extensive evaluation, including a kidney biopsy and genetic testing (Figure 8).

Since the 2012 guideline, several trials demonstrated that a shorter initial course of glucocorticoids has comparable efficacy to a 6-month course, leading to the updated recommendation that children be treated with high-dose glucocorticoids for a total of 8–12 weeks instead of 24 weeks (*Grade 1B*). This will help to decrease treatment toxicity, especially given that SSNS often relapses and multiple glucocorticoid courses may be given to an individual. Building on the theme of lowering glucocorticoid burden, the Work Group also recommended that children who frequently relapse or who have become glucocorticoid-dependent be treated for a week with 0.5 mg/kg/d of prednisone (or prednisolone) during upper respiratory infections to reduce relapse risk and the need for restarting

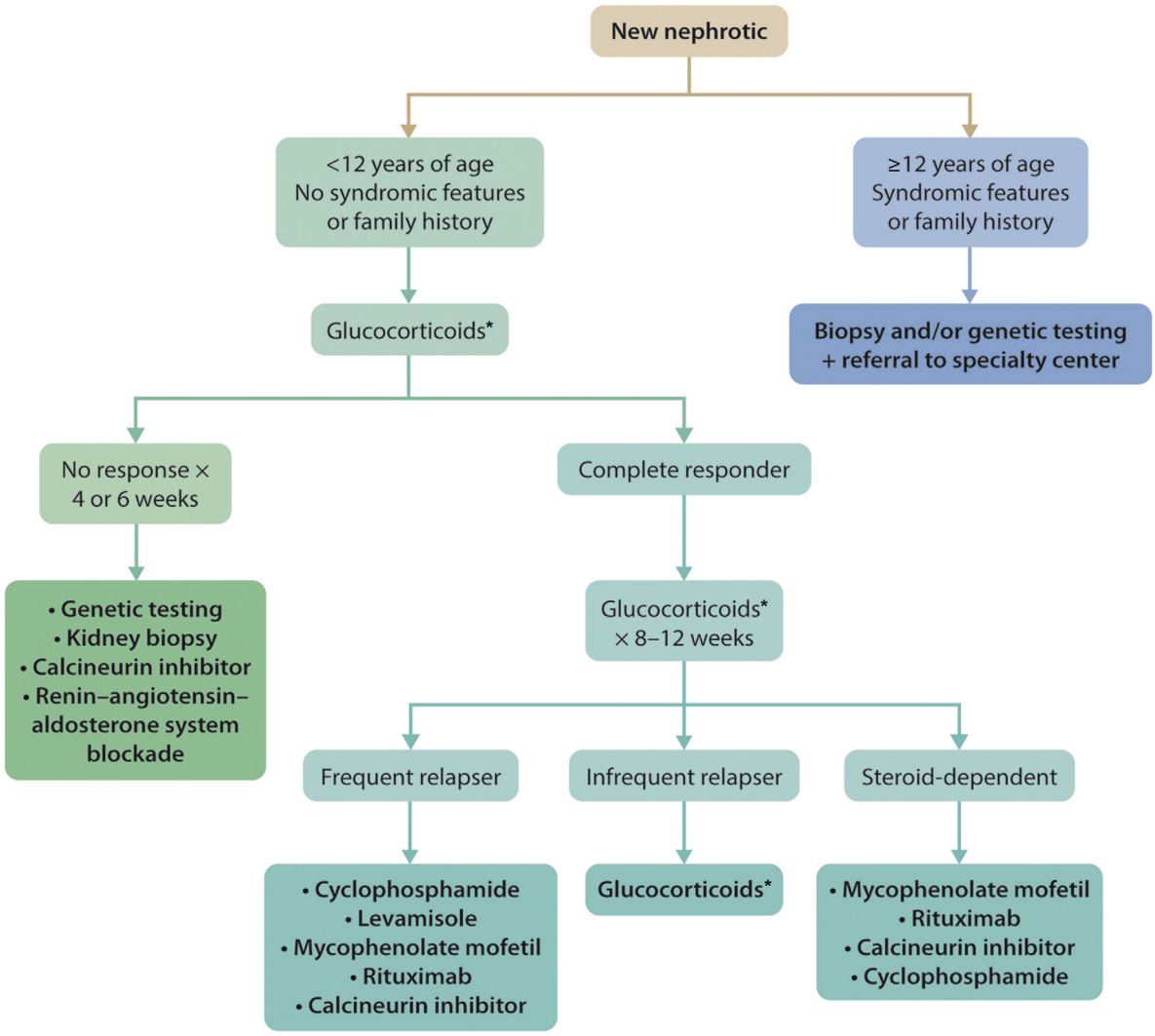

Figure 8 | Treatment algorithm for NS in a newly nephrotic child. Therapeutic approach to NS in children from onset. Refer to clinical trial where appropriate. *Glucocorticoids: p.o. prednisone or prednisolone. NS, nephrotic syndrome.

high-dose glucocorticoids (*Grade 1C*). Additionally, for SSNS patients who frequently relapse and have glucocorticoid-related side effects, and all glucocorticoid-dependent patients, consideration should be given to switching the patients to a glucocorticoid-sparing agent (*Grade 1B*). A variety of glucocorticoid-sparing agents have been used in SSNS (Figure 9). Recent encouraging results have indicated that a therapeutic agent that is unavailable in many countries, levamisole, may be an effective, safe, and inexpensive option, especially in frequently relapsing forms of NS, and the effectiveness of rituximab in both frequently relapsing and steroid-dependent forms suggests a pivotal role of B cells in this disease.

For children with SRNS, CNIs are recommended as the initial therapy after glucocorticoid failure (*Grade 1C*). Cyclophosphamide should be used only if CNIs are not available in low-resource settings, and the role of rituximab seems to be limited. For patients who do respond to a CNI, a switch to MMF to maintain remission should be considered to avoid long-term CNI toxicity. Importantly, genetic testing may help clarify the use of immunosuppressive agents in SRNS. Although some podocyte mutations may respond to a CNI or other interventions, the vast majority will not, and knowing this may provide justification to reduce the exposure of a child to a potentially toxic medication.

Treatment	Dose and duration	Clinical tips
First line:		
• **Oral cyclophosphamide**	2 mg/kg/d for 12 weeks (maximum cumulative dose 168 mg/kg)	Cyclophosphamide should not be started until the child has achieved remission with glucocorticoids. Moreover, second courses of alkylating agents should not be given. Weekly CBCs are recommended during the treatment course to assess for severe leukopenia or overall bone marrow suppression prompting dose reduction or treatment cessation
• **Oral levamisole**	2.5 mg/kg on alternate days, with a maximum dose of 150 mg	Monitor CBC every 2–3 months and alanine and aspartate aminotransferases every 3–6 months during therapy with levamisole. Check ANCA titers every 6 months, if possible, and interrupt treatment in case of ANCA positivity, skin rash or agranulocytosis. Maintaining low-dose alternate-day glucocorticoid dosing on the days not taking levamisole may be effective in some children. Levamisole should be continued for at least 12 months
Alternative agents:		
• **Mycophenolate mofetil**	Starting dose of 1200 mg/m^2/d (given in two divided doses)	Target area under the curve >50 μg•h/ml.[†] Mycophenolate mofetil should be continued for at least 12 months, as most children will relapse when it is stopped. In children experiencing significant abdominal pain on mycophenolate mofetil, other mycophenolic acid analogs (MPAAs), such as sodium mycophenolate, may be employed at equivalent doses (360 mg of sodium mycophenolate corresponds to 500 mg of mycophenolate mofetil)
• **Rituximab**	375 mg/m^2 i.v. × 1–4 doses	Rituximab may be used as a treatment for steroid-sensitive nephrotic syndrome in children who have continuing frequent relapses despite optimal combinations of prednisone and glucocorticoid-sparing oral agents, and/or who have serious adverse effects of therapy. Current trials report 1 to 4 doses of rituximab. There are insufficient data to make a recommendation for specific number of needed doses. Where available, CD20 levels should be monitored. Hepatitis B surface antigen, hepatitis B core antibody, and a QuantiFERON test for tuberculosis must be checked prior to rituximab administration. Monitoring IgG levels both before and after rituximab therapy may allow for earlier identification of risk for developing significant infection and identify patients who may benefit from immunoglobulin replacement
• **Calcineurin inhibitors***		CNI should be continued for at least 12 months as most children will relapse upon discontinuation. Monitor CNI levels during therapy to limit toxicity
– **Cyclosporine**	4 to 5 mg/kg/d (starting dose) in two divided doses	Cyclosporine may be preferable in patients at risk for diabetic complications. Target 12 hour trough level of 60–150 ng/ml [50–125 nmol/l] aiming for lowest levels to maintain remission and avoid toxicity
– **Tacrolimus**	0.1 mg/kg/d (starting dose) given in two divided doses	Tacrolimus may be preferred over cyclosporine in patients for whom the cosmetic side effects of cyclosporine are unacceptable. Target 12 hour trough level of 5–10 ng/ml [6–12 nmol/l] aiming for lowest levels to maintain remission and avoid toxicity

Figure 9| | Glucocorticoid-sparing therapies in children with SSNS. [†]Gellermann J, Weber L, Pape L, *et al.* Mycophenolate mofetil versus cyclosporin A in children with frequently relapsing nephrotic syndrome. *J Am Soc Nephrol*. 2013;24:1689–1697. *The CNI, while often used twice daily, may be dosed once a day, depending on individual formulations. Blood levels of CNI do not provide information on intracellular levels. The target ranges for CNIs have been based on the transplant literature. The KDIGO Work Group acknowledges that targets for glomerular diseases are not known. Most clinicians check these levels to verify adherence and avoid CNI toxicity. At present, 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 serum creatinine and reducing the dose if serum creatinine increases but does not plateau or increases over 30% of baseline. If the serum creatinine level does not fall after dose reduction, the CNI should be discontinued. ANCA, antineutrophil cytoplasmic antibody; CBC, complete blood count; CNI, calcineurin inhibitor; SSNS, steroid-sensitive nephrotic syndrome.

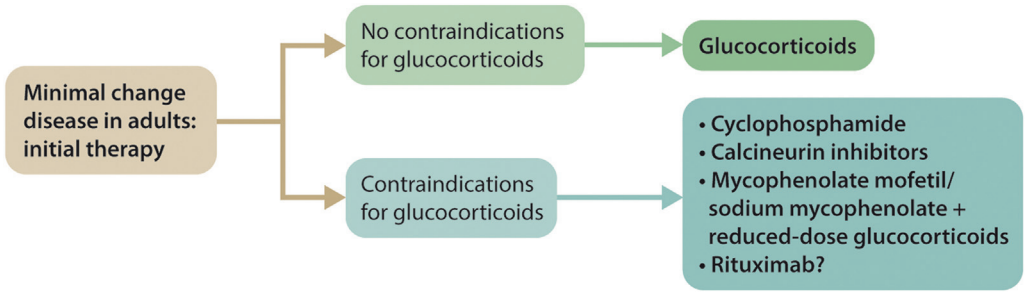

Figure 10 | Initial treatment of MCD in adults. The optimal glucocorticoid regimen is not well defined; however, suggested doses are outlined in Figure 45 of the full guideline. The choice of medication should be based on physician and patient preference. MCD, minimal change disease.

Chapter 5: Minimal change disease in adults

In contrast to children, MCD in adults requires biopsy confirmation. Long-term kidney survival is excellent in MCD patients who respond to glucocorticoids, but less certain for patients who do not respond. High-dose oral glucocorticoids constitute initial treatment for MCD (*Grade 1C*) unless there are contraindications to glucocorticoids, in which case alternatives include cyclophosphamide, CNIs, MMF, and, possibly, rituximab (Figure 10). The optimal glucocorticoid regimen is not well-defined; however, high-dose glucocorticoid treatment for MCD should be given for no longer than 16 weeks. Tapering of glucocorticoids should start 2 weeks after remission.

Infrequent relapses should be treated with glucocorticoids. Cyclophosphamide, rituximab, CNIs, or mycophenolic acid analogs (MPAA) should be employed for the treatment of frequently relapsing/glucocorticoid-dependent MCD (*Grade 1C*). An algorithm for treatment of frequently relapsing/glucocorticoid-dependent MCD in adults is shown in Figure 11.

Chapter 6: Focal segmental glomerulosclerosis

Advances in the management of glomerular diseases that demonstrate FSGS lesions on light microscopy have been confounded by the absence of a rigorous classification of the diseases that lead to an FSGS pattern of injury, coupled with a poor understanding of the molecular pathways involved in disease pathogenesis. To clearly illustrate the heterogeneity of the processes that can result in FSGS histology, the Work Group proposed a revised classification of FSGS (Figure 12).

An important suggestion of the proposed classification system is to eliminate the term *idiopathic* from the FSGS lexicon, and to only use *primary* FSGS for the disease entity presumably caused by an as of yet unidentified podocyte-toxic factor that is often amenable to treatment. The new system adds a category of FSGS of undetermined cause (FSGS-UC). These patients have an FSGS lesion on kidney biopsy, but do not have an identifiable underlying cause of FSGS or the clinicopathologic features of primary FSGS. FSGS-UC patients bear careful scrutiny as changes in their clinical characteristics may prompt a second biopsy, supporting a need for treatment.

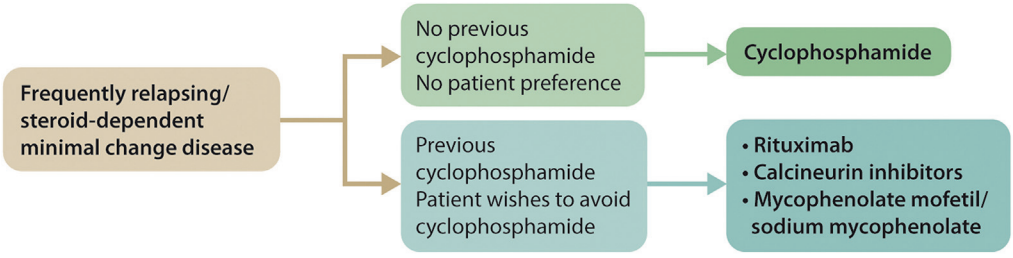

Figure 11 | Treatment of frequently relapsing/steroid-dependent MCD in adults. The choice of medication should be based on physician and patient preference. MCD, minimal change disease.

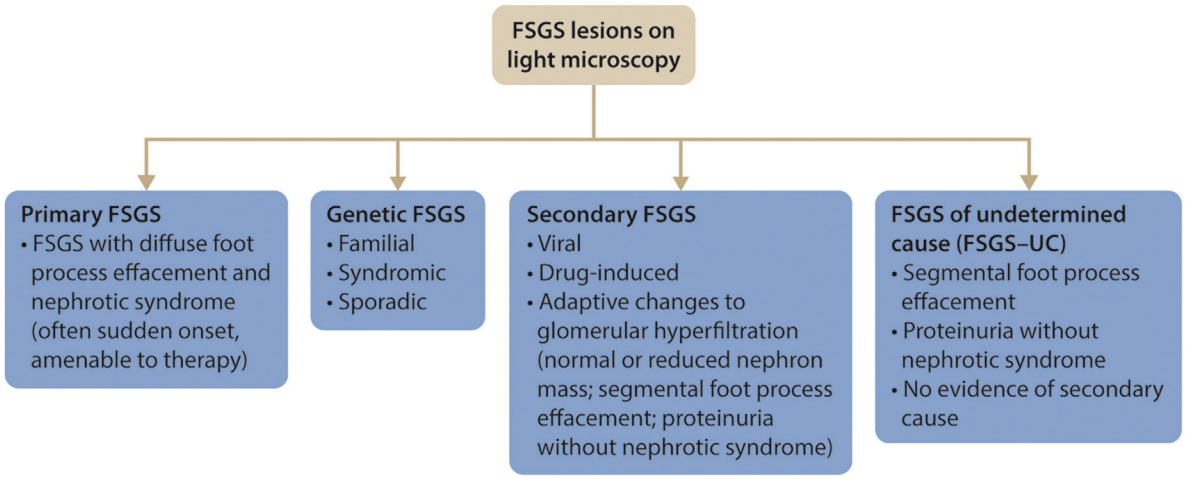

Figure 12| Proposed classification of FSGS. FSGS, focal segmental glomerulosclerosis.

This revised classification leads to a diagnostic and treatment algorithm designed to focus immunosuppressive therapies only to those patients likely to benefit and avoid their use in patients not likely to respond (Figure 13). The classification scheme and treatment algorithm also demonstrate the important gaps in knowledge and resources that need to be addressed by the nephrology community for the proper management of FSGS. For example, without knowing the podocyte-toxic factor(s) that mediates primary FSGS, diagnosis of primary FSGS is based on a clinical presentation of full-blown nephrotic syndrome often of sudden onset, and diffuse foot process effacement by electron microscopy, a technology that is not routinely available throughout the world. The appropriate use of genetic evaluation in adults with FSGS remains unclear, and even when indicated requires an often unavailable or costly expertise to interpret the results.

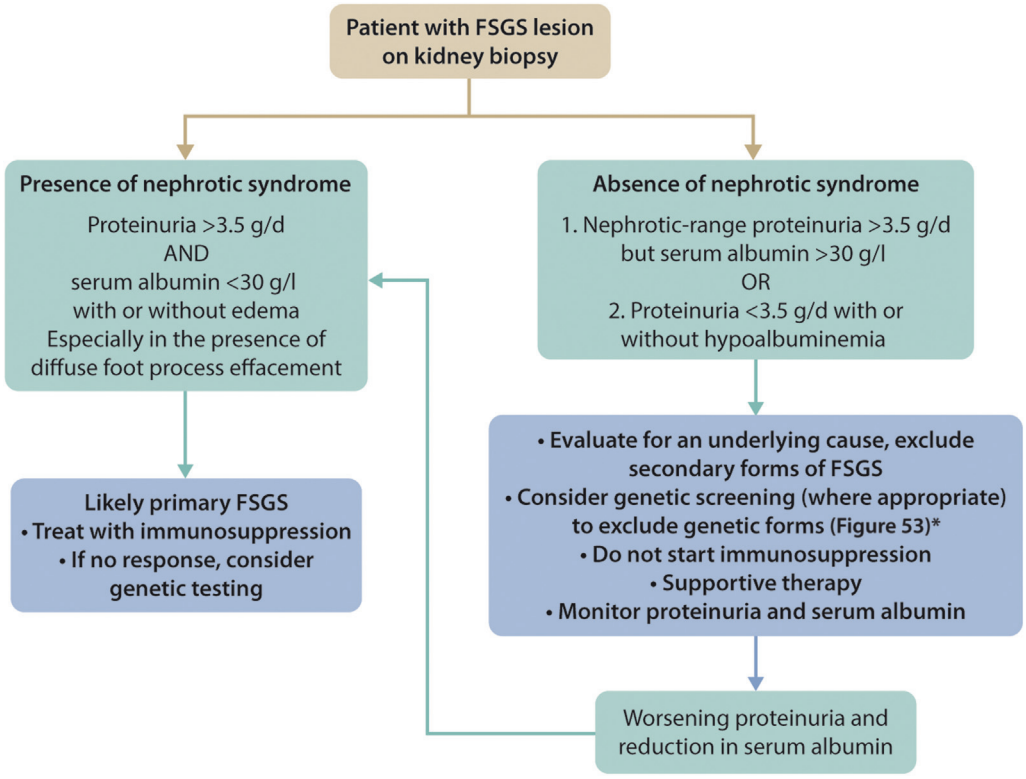

Figure 13| Evaluation of a patient with FSGS lesion on the kidney biopsy and no evidence of other glomerular pathology. *For Figure 53, please see full guideline. FSGS, focal segmental glomerulosclerosis.

Treatment	Dose and duration
Glucocorticoids	**Starting dose:** • High-dose glucocorticoid therapy with prednisone at daily single dose of 1 mg/kg (maximum 80 mg) or alternate-day dose of 2 mg/kg (maximum 120 mg)
	High-dose glucocorticoid treatment duration: • Continue high-dose glucocorticoid therapy for at least 4 weeks and until complete remission is achieved, or a maximum of 16 weeks, whichever is earlier • Patients who are likely to remit will show some degree of proteinuria reduction before 16 weeks of high-dose treatment • It may not be necessary to persist with high-dose glucocorticoid therapy until 16 weeks if the proteinuria is persistent and unremitting, especially in patients who are experiencing side effects
	Glucocorticoid tapering: • If complete remission is achieved rapidly, continue high-dose glucocorticoid treatment for 2 weeks or after the disappearance of proteinuria, whichever is longer. Reduce prednisone by 5 mg every 1–2 weeks to complete a total duration of 6 months • If partial remission is achieved within 8 to 12 weeks of high-dose glucocorticoid treatment, continue until 16 weeks to ascertain whether further reduction of proteinuria and complete remission may occur. Thereafter, reduce the dose of prednisone by 5 mg every 1–2 weeks to complete a total duration of 6 months • If the patient proves to be steroid-resistant or develops significant toxicities, glucocorticoids should be rapidly tapered as tolerated and treatment with alternative immunosuppression like a CNI should be considered
Calcineurin inhibitors*	**Starting dose:** • Cyclosporine 3–5 mg/kg/d in 2 divided doses OR tacrolimus 0.05–0.1 mg/kg/d in 2 divided doses • Target trough levels could be measured to minimize nephrotoxicity • Cyclosporine target trough level: 100–175 ng/ml (83–146 nmol/l) • Tacrolimus target trough level: 5–10 ng/ml (6–12 nmol/l)
	Treatment duration for determining CNI efficacy: • Cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 4–6 months, before considering the patient to be resistant to CNI treatment
	Total CNI treatment duration: • In patients with partial or complete remissions, cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 12 months to minimize relapses • The dose of cyclosporine or tacrolimus can be slowly tapered over a course of 6–12 months as tolerated

Figure 14 | Treatment protocols for FSGS. *The target ranges for CNIs have been based on the transplant literature. The KDIGO Work Group acknowledge that targets for glomerular diseases are not known. Most clinicians check these levels to verify adherence and avoid CNI toxicity. At present, 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 serum creatinine and reducing the dose if serum creatinine increases but does not plateau or increases over 30% of baseline. If the serum creatinine level does not fall after dose reduction, the CNI should be discontinued. CNI, calcineurin inhibitor; FSGS, focal segmental glomerulosclerosis.

The 2 key recommendations for the treatment of primary FSGS remain the same as the 2012 recommendations. High-dose glucocorticoids are recommended as first-line therapy (*Grade 1D*), and for glucocorticoid-resistant or intolerant patients, a trial of a CNI is recommended (*Grade 1C*). The use of oral predniso(lo)ne at a dose of 1 mg/kg/d has the potential for severe toxicity, so application of this recommendation requires close supervision for side effects and a maximum duration of 16 weeks is suggested. Additionally, patients who are expected to respond to glucocorticoids usually show at least some improvement in proteinuria within 4–8 weeks. In the setting of no indication of response and/or severe glucocorticoid side effects, it is prudent to move patients to second-line therapy with a CNI. The overall duration of glucocorticoids should be 6 months (high-dose period plus taper), and the overall duration of CNIs should be 12 months. Suggested treatment protocols are outlined in Figure 14. If patients have not responded to glucocorticoids or a CNI, the therapeutic choices for primary FSGS are limited. Several other immunosuppressive agents have been tried, but there are no high-quality data supporting their use (Figure 14). This speaks to the importance of considering FSGS patients for clinical trials, and for trying to identify

the circulating factor(s) mediating FSGS, as this may lead to more targeted therapies with less toxicity than long-term, high-dose glucocorticoids or CNIs.

Chapter 7: Infection-related glomerulonephritis

Bacterial infection-related GN. Kidney biopsy can be useful in suspected bacterial infection-related 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 at arriving at the correct diagnosis, as comorbidities contribute to difficulty in making the diagnosis (Figure 15).

Prognosis and therapy of classic bacterial infection-related GN syndromes depends on the underlying infection. In general, prognosis is good with early diagnosis and antibiotic treatment of the infection. However, in IgA-dominant infection-related GN, dialysis is frequently required in the acute phase and <20% of the patients return to their premorbid levels of kidney function. The utility of immunosuppression, even in cases of crescentic GN, is uncertain and carries substantial potential risks, in particular in the elderly. In classical postinfectious GN, persistently low C3 in serum beyond week 12 may be an indication for kidney biopsy to particularly exclude complement C3 glomerulonephritis (C3GN).

Hepatitis C infection-related GN. The Work Group concurs fully with Recommendations 5.1 through 5.2.3 of the *KDIGO 2018 Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney*

	Postinfectious GN	Shunt nephritis	Endocarditis-related GN	IgA-dominant infection-related GN
Risk and risk features	Children, elderly, immunocompromised hosts, subsanitary living conditions	Highest: Ventriculo-atrial Mid: Ventriculo-jugular Least: Ventriculo-peritoneal	Prosthetic valve or structural heart valve lesion; substance abuse; elderly; diabetes mellitus; hepatitis C; HIV; immunocompromised host	Diabetes mellitus, hypertension, heart disease, malignancy, alcohol or substance abuse, or kidney transplantation
History	Seek evidence of antecedent resolved pharyngitis (1–2 wks) or impetigo (4–6 wks)	May present within months or decades of shunt placement, sometimes after shunt revision. Diagnosis may be confounded and difficult in the 40% with occult infection	Echocardiographic evidence of cardiac valvular vegetations	Demonstration of active blood or tissue infection in a patient with acute GN
Physical exam	In some, active skin or tonsil infections present	Non-specific signs/symptoms of infection, lethargy, fever, clinical signs of bacteremia	Fever, new or changed cardiac murmur; splenomegaly; characteristic skin lesions	Frequent hypertension. Exam mostly reflects the location/severity of the infection
Laboratory kidney	• Urinalysis (assess for glomerular hematuria and red blood cell casts); ACR; PCR • Measure serum creatinine/eGFR			
Laboratory infection	Culture skin or tonsils if infected Measure anti-streptolysin O, anti-DNAse B, and anti-hyaluronidase antibodies	Organism culture in blood, cerebrospinal fluid, shunt tip (after removal)	Blood culture positive 90–98%; negative 2–10%. Fastidious infections, such as *Candida, Coxiella burnetii*, *Borrelia*, and *Bartonella* may be difficult to culture. Serological tools for diagnosis may be required in such cases	Culture blood/tissues to identify bacterial infection (mostly staphylococcal)
Laboratory immunology	• Assess for low complement (C3, C4), rheumatoid factor, cryoglobulins, factor B antibody levels • Rule out other causes of nephritis if diagnosis in doubt: ANA, ANCA (occasionally PR3-ANCA in shunt nephritis and endocarditis), anti-GBM antibody			
				Serum IgA may be high

Figure 15| Evaluation of classic bacterial infection-related GN syndromes. ACR, albumin-creatinine ratio; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; eGFR, estimated glomerular filtration rate; GBM, glomerular basement membrane; GN, glomerulonephritis; HIV, human immunodeficiency virus; PCR, protein-creatinine ratio; PR3, proteinase 3.

Disease. Please refer to this publication for specific recommendations, selection and dosing of specific therapeutic agents, and research recommendations (https://kdigo.org/wp-content/uploads/2017/02/KDIGO-2018-Hep-C-GL.pdf).

Hepatitis B infection-related GN. Patients with proteinuric glomerular disease should undergo testing for HBV infection, and adult patients with chronic HBV infection should be considered at risk for the development of kidney failure. 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 (*Grade 1C*). Immunosuppressive agents, such as cyclophosphamide or rituximab, may accelerate HBV replication and should be avoided in patients with untreated replicative HBV infection and GN.

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. Plasma exchange may be tried in patients with accompanying cryoglobulinemic vasculitis.

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

Human immunodeficiency virus (HIV)–related GN. HIV-related kidney disease is a global problem contributing significantly to CKD rates (Figure 16). 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. The spectrum of kidney biopsy findings in HIV-infected patients in the modern era is shown in Figure 17.

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., apolipoprotein L1 [*APOL1*] risk alleles), coinfection with other viruses, and development of immune complex (IC) disease or thrombotic microangiopathy. Thus, the estimation of prognosis in individual patients can be very difficult.

We recommend that antiretroviral therapy (ART) should 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 (*Grade 1C*). 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. The presence of CKD is not a contraindication for ART of HIV infection. Current consensus data, based on 2 large RCTs on the time to initiate ART, Strategic Timing of AntiRetroviral Treatment (START) and Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis Against Tuberculosis in HIV-infected Adults (TEMPRANO), demonstrate benefit of early initiation of ART at the time of diagnosis, regardless of CD4 count.

Schistosomal nephropathy. 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. A kidney biopsy should be obtained

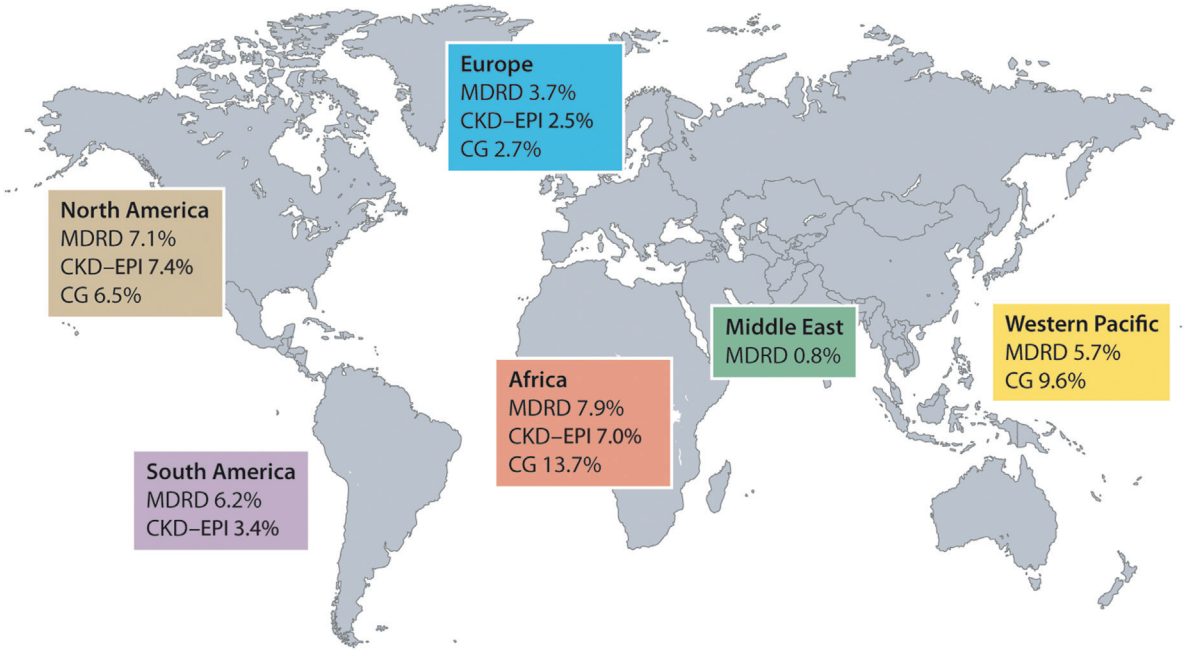

Figure 16 | The global distribution of CKD associated with HIV infection. Reproduced from Ekrikpo UE, Kengne AP, Bello AK, et al. Chronic kidney disease in the global adult HIV-infected population: a systematic review and meta-analysis. *PLoS One*. 2018;13:e0195443. Copyright © 2018 Ekrikpo *et al.* This is an open access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/). CG, Cockcroft-Gault; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; HIV, human immunodeficiency virus; MDRD, Modification of Diet in Renal Disease.

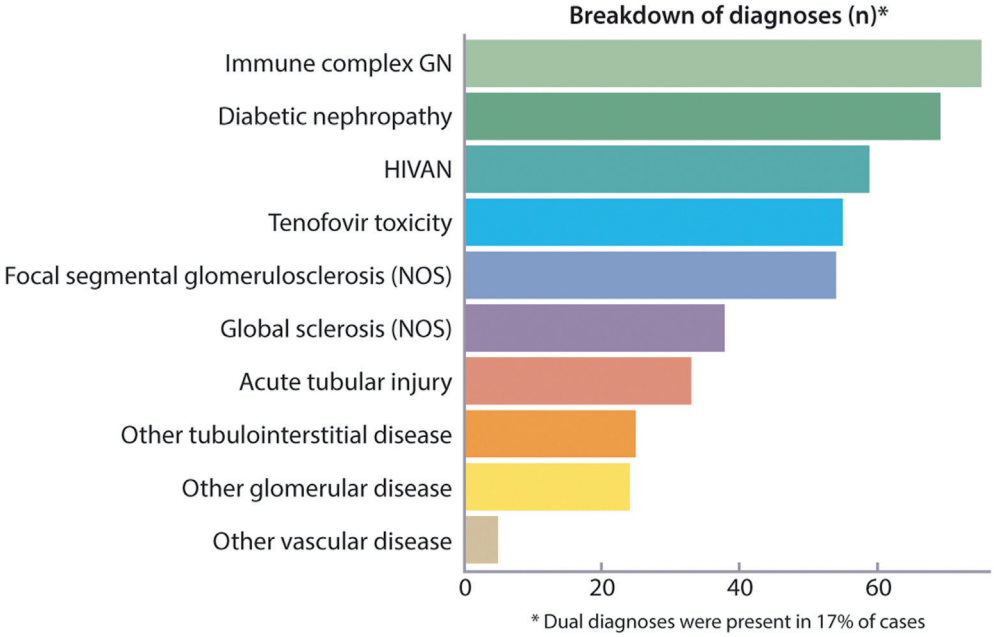

Figure 17 | The spectrum of kidney biopsy findings in patients with HIV in the modern era. Reproduced from *Kidney International*, volume 97, issue 5, Kudose S, Santoriello D, Bomback AS, et al. The spectrum of kidney biopsy findings in HIV-infected patients in the modern era, pages 1006–1016, Copyright © 2020, with permission from the International Society of Nephrology. A total of 26,737 native biopsies from 2010–2018 were retrospectively reviewed; 437 (1.6%) from patients with HIV-infected patients (mean age: 53 years; 66% male; 58% black; 25% white; 17% Hispanic; <1% Asian; 80% on antiretroviral therapy [ART]; comorbidities included: 57% hypertension, 31% diabetes, 27% hepatitis C coinfection). Conclusion from the study: ART has changed the landscape of HIV-associated kidney disease toward diverse immune complex GN, diabetic nephropathy, and non-collapsing glomerulosclerosis, but it has not eradicated HIV-associated nephropathy. GN, glomerulonephritis; HIV, human immunodeficiency virus; HIVAN, human immunodeficiency virus-associated nephropathy; NOS, not otherwise specified.

in patients suspected of having schistosomal GN in the presence of a viral coinfection (HCV, HBV, HIV). Patients with schistosomal infection and GN should be treated 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.

Monitor patients with hepatic fibrosis from schistosomiasis for the development of kidney disease and evaluate patients with a history of schistosomiasis and an elevated serum creatinine and/or hematuria for bladder cancer and/or urinary obstruction.

Filariasis and glomerular disease. Patients with filarial infection and GN should be treated with an appropriate antiparasitic agent in sufficient dosage and duration to eradicate the organism.

Malarial nephropathy. Malaria-related kidney disease mostly manifests as AKI, but GN can also occur. Patients with malarial infection and GN should be treated 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.

Chapter 8: Immunoglobulin- and complement-mediated glomerular diseases with a membranoproliferative glomerulonephritis pattern of injury

A membranoproliferative pattern of injury on a kidney biopsy does not reflect a specific disease, but is a histologic finding that often occurs in the setting of aberrant complement activation and/or IC deposition. This led the Work Group to suggest eliminating the term membranoproliferative glomerulonephritis (MPGN) from the new glomerular diseases guideline, in favor of a more pathophysiologic classification of these diseases. The diseases that can result in an MPGN pattern are heterogeneous and require distinct therapies; they must be properly identified beyond their histologic characteristics (Figure 18). Fortuitously, the immunofluorescence findings on biopsy can be used to move the work-up of these patients in the correct direction (Figure 19). If the biopsy is positive for immunoglobulins, with or without complement components, the evaluation should be focused on distinguishing between monoclonal deposition diseases, autoimmune IC diseases, and infection-associated diseases. In adults, idiopathic immune complex glomerulonephritis (ICGN) is rare, and all other diagnostic possibilities should be exhausted before making this diagnosis. If immunofluorescence microscopy shows a complement-dominant pattern, C3 or C4 glomerulopathy (C3G, C4G) should be considered, and an appropriate evaluation of the complement system should be undertaken. Negative immunofluorescence should raise the possibility of several diseases (Figure 18), but especially various types of thrombotic microangiopathy (TMA).

Like most classification schemes, caveats apply. Complement dysregulation may occur in IC glomerular

Immunoglobulin-/ immune complex-mediated	**Deposition of antigen–antibody immune complexes as a result of an infection:** • Viral: hepatitis C (including HCV-associated mixed cryoglobulinemia), hepatitis B • Bacterial: endocarditis, infected ventriculo-atrial shunt, visceral abscesses, leprosy, meningococcal meningitis • Protozoa/other infections: malaria, schistosomiasis, mycoplasma, leishmaniasis, filariasis, histoplasmosis **Deposition of immune complexes as a result of an autoimmune disease:** • SLE • Sjögren's syndrome • Rheumatoid arthritis • Mixed connective tissue disease **Deposition of monoclonal Ig as a result of a monoclonal gammopathy due to a plasma cell or B cell disorder** **Fibrillary glomerulonephritis** **Idiopathic** • None of the conditions above are present
Complement-mediated	**C3 glomerulonephritis and C3 DDD:** • Mutations in complement regulatory proteins: CFH, CFI, CFHR5 • Mutations in complement factors: C3 • Antibodies to complement factors: C3, C4, and C5 nephritic factors • Antibodies to complement regulatory proteins: CFH, CFI, CFB **C4 glomerulonephritis and C4 DDD**
Membranoproliferative pattern without immune complexes or complement	• Healing phase of HUS/TTP • Antiphospholipid (anticardiolipin) antibody syndrome • POEMS syndrome • Radiation nephritis • Nephropathy associated with bone marrow transplantation • Drug-associated thrombotic microangiopathies • Sickle cell anemia and polycythemia • Dysfibrinogenemia and other pro-thrombotic states • Antitrypsin deficiency

Figure 18| Causes of a membranoproliferative pattern of injury. CFB, complement factor B; CFH, complement factor H; CFHR5, complement factor H–related protein 5; CFI, complement factor I; DDD, dense deposit disease; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HUS, hemolytic-uremic syndrome; Ig, immunoglobulin; MPGN, membranoproliferative glomerulonephritis; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes; SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenic purpura.

diseases. Conversely, C3G may look like an ICGN, especially if it is triggered by an infection. Therefore, in any case of an apparent idiopathic ICGN, it is prudent to exclude a complement-mediated process. Similarly, before assigning a diagnosis of C3G, concurrent or preceding infection should be excluded. It may be necessary to use proteolytic digestion on paraffin-embedded biopsy tissue to detect monoclonal immunoglobulins that may be masked during routine immunofluorescence investigation. Monoclonal gammopathies can initiate C3G, without glomerular deposition of immunoglobulin, and should be considered, especially in patients who present with C3G over the age of 50 years.

Treatment for monoclonal immunoglobulin-associated diseases focuses on controlling the clone of B cells or plasma cells responsible for production of the monoclonal immunoglobulin. Autoimmune diseases are most often treated with immunosuppression, and infection-associated glomerular diseases generally respond to controlling the infection. The management of idiopathic ICGN and C3G/C4G is less clear, and because of the absence of any RCT data, the Work Group was able to offer only practice points in these areas and no specific recommendations.

In contrast to the 2012 guideline, the current approach to idiopathic ICGN is more nuanced, as opposed to immediately committing to an immunosuppressive drug (Figure 20). This approach tailors therapy to severity of disease presentation and histology. Importantly, the approach suggests restraint in treating patients aggressively

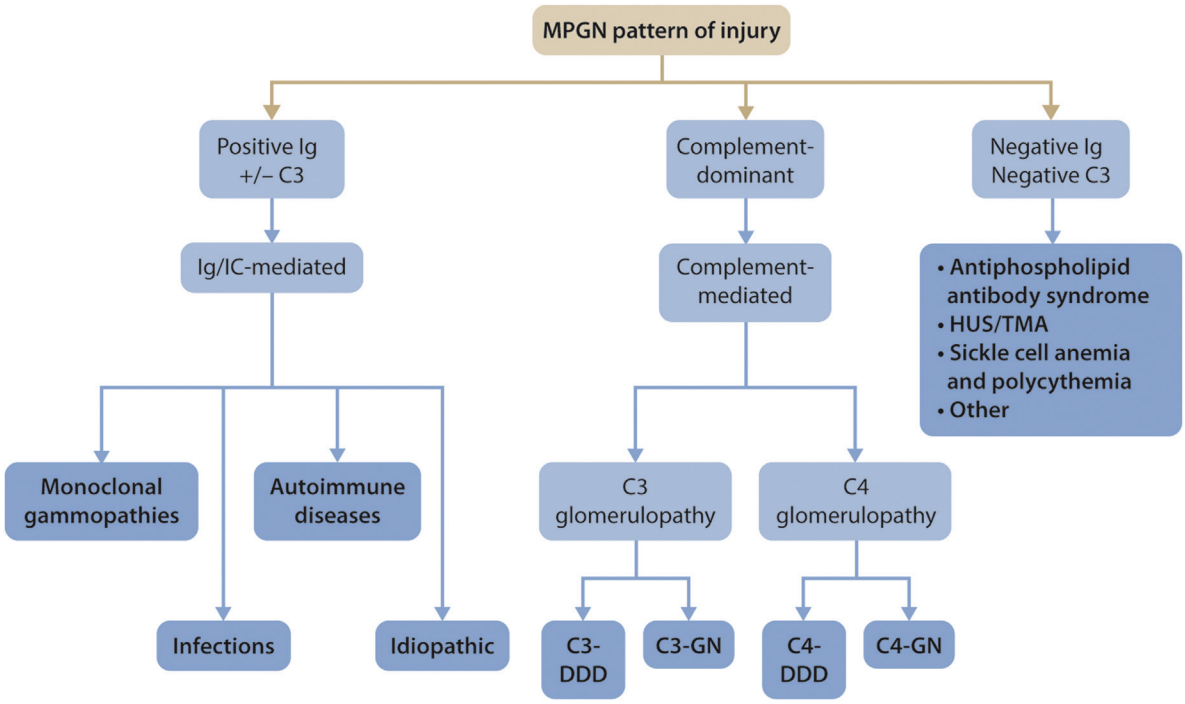

Figure 19 | Pathophysiology of membranoproliferative lesions. DDD, dense deposit disease; GN, glomerulonephritis; HUS, hemolytic-uremic syndrome; IC, immune complex; Ig, immunoglobulin; MPGN, membranoproliferative glomerulonephritis; TMA, thrombotic microangiopathy.

who have a chronic and significant impairment of kidney function.

For patients with C3G in whom a monoclonal gammopathy has been excluded, and who have moderate-to-severe disease (proteinuria >1 g/d and/or declining kidney function over several months), MMF is suggested as first-line therapy. Observational data showed that MMF decreased progression to kidney failure compared to other immunosuppressives. After MMF, the direction of treatment is not clear. Because C3G is a complement-mediated disease, eculizumab has been used in a small number of patients with variable results. While eculizumab can be tried in patients who fail to respond to MMF, such

Presentation of idiopathic ICGN	Suggested approach to management
• Proteinuria <3.5 g/d • Absence of nephrotic syndrome • Normal eGFR	• Supportive care • RAS blockade
• Nephrotic syndrome • Normal or near-normal eGFR	• Supportive care • RAS blockade • Limited course of glucocorticoids
• Abnormal eGFR • Active urine sediment • No crescents • Any level of proteinuria	• Supportive care • RAS blockade • Glucocorticoids • Immunosuppressive therapy
• Rapidly progressive disease • Crescents present	• Supportive care • RAS blockade • Glucocorticoids • Cyclophosphamide
• eGFR <30 ml/min/1.73 m^2	• Supportive care • RAS blockade

Figure 20 | Approach to idiopathic ICGN. eGFR, estimated glomerular filtration rate; ICGN, immune complex glomerulonephritis; RAS, renin-angiotensin system.

patients should be considered for clinical trials to begin to address this unmet need by gathering controlled study data.

Chapter 9: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis

ANCA-associated vasculitis (AAV) is the most common cause for rapidly progressive kidney failure, with other important causes being anti–glomerular basement membrane (GBM) antibody GN and lupus nephritis (LN). The diagnostic strategy for evaluating patients presenting with RPGN is shown in Figure 21.

Because of the potential severity of AAV, if a patient's clinical presentation is compatible with a small-vessel vasculitis and myeloperoxidase (MPO)- or proteinase 3 (PR3)-ANCA serology is positive, waiting for a kidney biopsy to be done or reported to verify diagnosis should not delay starting immunosuppressive therapy (Figure 22). The same consideration is true if anti-GBM antibody GN or lupus nephritis is suspected in a patient with RPGN. Besides confirming diagnosis, the kidney biopsy provides prognostic information so it should be done when feasible. In all cases, however, infection must be excluded with as much certainty as possible before significant immunosuppression is given.

The initial therapy of new-onset AAV has been updated to include induction with cyclophosphamide or rituximab combined with glucocorticoids. Recent trials, such as Plasma Exchange and Glucocorticoids for the Treatment of ANCA-Associated Vasculitis (PEXIVAS), have demonstrated that glucocorticoid dosing can safely be reduced from the high-dose regimens traditionally used in AAV. As a caveat, it was emphasized that there are only limited data for rituximab induction in the setting of severely impaired kidney function (serum creatinine >4 mg/dl [>354 μmol/l]). Cyclophosphamide remains the preferred immunosuppressive for such patients, although the combination of cyclophosphamide plus rituximab can be considered. To help in choosing whether to use cyclophosphamide or rituximab, the Work Group provided several suggestions (Figure 23). As noted in Figure 23, for relapsing disease, patients should be re-induced and the treatment of choice is rituximab, especially if patients have already reached a cumulative dose of cyclophosphamide over 36 g, as this may increase chances for developing a malignancy.

One of the more controversial aspects of the initial management of AAV is the role of plasma exchange in patients who present with severe kidney failure and/or require dialysis. Older studies suggested a benefit, but the recently reported PEXIVAS trial did not show that plasma exchange delayed time to kidney failure or death in AAV patients who presented with eGFR <50 ml/min per 1.73 m^2 or alveolar hemorrhage.

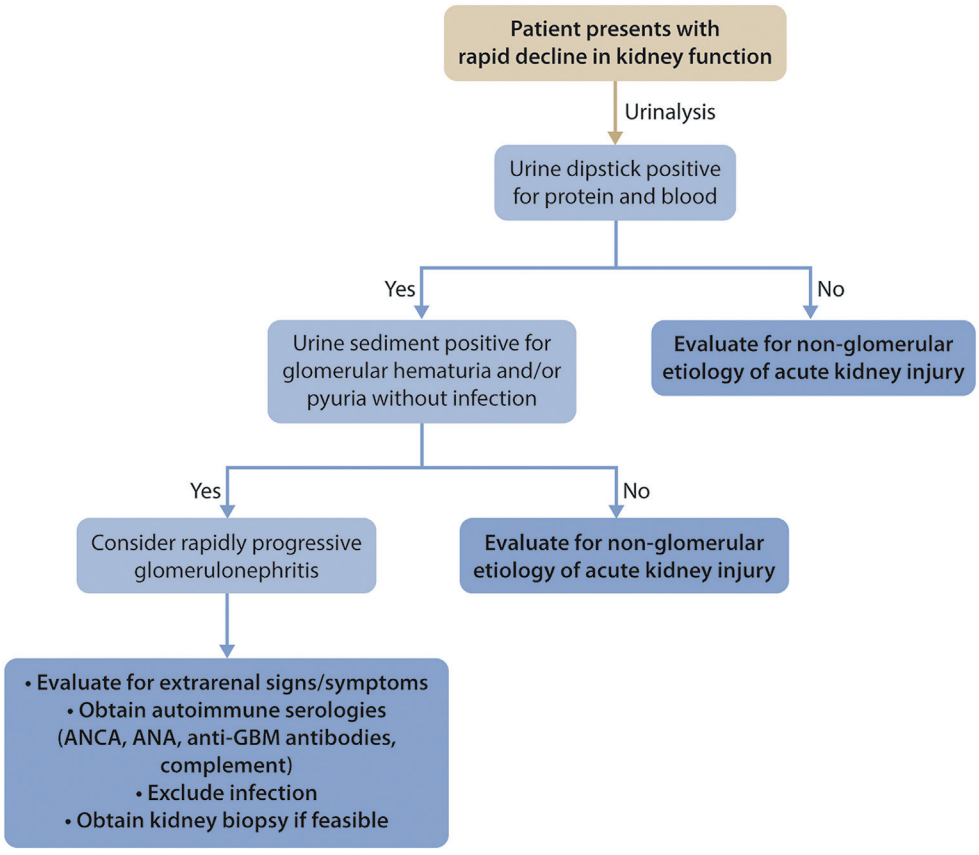

Figure 21 | Diagnostic strategy in rapidly progressive glomerulonephritis. ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane.

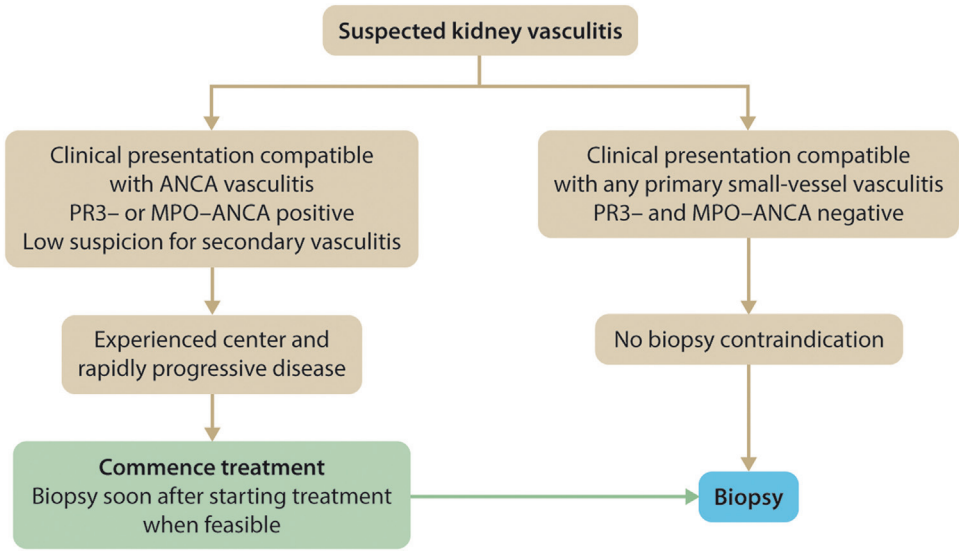

Figure 22 | Biopsy strategy in suspected kidney vasculitis. ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3.

Rituximab preferred	Cyclophosphamide preferred
• Children and adolescents • Pre-menopausal women and men concerned about their fertility • Frail older adults • Glucocorticoid-sparing especially important • Relapsing disease • PR3–ANCA disease	• Rituximab difficult to access • Severe GN (SCr >4 mg/dl [354 μmol/l]), combination of two intravenous pulses of cyclophosphamide with rituximab can be considered

Figure 23 | Factors for consideration when choosing between rituximab and cyclophosphamide for induction therapy of AAV. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; GN, glomerulonephritis; PR3, proteinase 3; SCr, serum creatinine.

It is therefore suggested that plasma exchange not be used routinely in AAV. However, if AAV overlaps with anti-GBM antibody GN, plasma exchange should be used.

Finally, because the treatment of AAV uses therapies that come with considerable risk for adverse events, therapeutic futility should be considered. The Work Group suggested that immunosuppression be discontinued in patients who have no extrarenal disease manifestations if after 3 months they remain dialysis-dependent.

After induction therapy, patients with AAV require maintenance immunosuppression because of their high likelihood of relapse, especially those with PR3-ANCA disease. The updated recommendations for AAV maintenance include rituximab or azathioprine plus low-dose glucocorticoids, although the Work Group preferred rituximab for maintenance. Considerations for using rituximab or azathioprine are outlined in Figure 24.

The duration of maintenance immunosuppression in AAV is not clear. Both rituximab and azathioprine have been used for a minimum of 18 months, and up to 4 years for azathioprine. It is therefore suggested that the duration of maintenance therapy be at least 18 months. Withdrawal can then

Rituximab preferred	Azathioprine preferred
• Relapsing disease • PR3–ANCA disease • Frail older adults • Glucocorticoid-sparing especially important • Azathioprine allergy	• Low baseline IgG <300 mg/dl • Hepatitis B exposure (HBsAg positive) • Limited availability of rituximab

Figure 24 | Considerations for using rituximab or azathioprine for AAV maintenance therapy. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; HBsAg, hepatitis B surface antigen; IgG, immunoglobulin G; PR3, proteinase 3.

Baseline factors	Factors after diagnosis	Treatment factors
• Diagnosis of granulomatosis with polyangiitis • PR3–ANCA subgroup • Lower serum creatinine • More extensive disease • Ear, nose, and throat disease	• History of relapse • ANCA positive at the end of induction • Rise in ANCA	• Lower cyclophosphamide exposure • Immunosuppressive withdrawal • Glucocorticoid withdrawal

Figure 25| Factors that increase relapse risk for AAV. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; PR3, proteinase 3.

be considered, after factoring in the risk of disease relapse (Figure 25).

Unfortunately, the commonly monitored serologies in ANCA vasculitis are imperfect biomarkers of disease relapse. Persistence of ANCA positivity after treatment, rising titers of ANCA, and conversion from ANCA negativity to ANCA positivity are only modestly predictive of future relapse; therefore, removing maintenance therapy remains a clinical decision, as opposed to a biomarker-driven decision for now.

Finally, if patients progress to require long-term kidney replacement therapy, kidney transplantation should be delayed until patients are in clinical remission for ≥6 months. Importantly, persistent ANCA positivity should not delay kidney transplantation.

Chapter 10: Lupus nephritis

The management recommendations for LN are poised to change significantly in the coming months because several high-quality RCTs of novel therapies have recently been successfully completed. These approaches will be incorporated into the guideline as the community understands how best to apply the new agents in the context of existing regimens. However, as the 2021 guideline was being established, details of these new data were not yet available, so

Risk	Risk attenuation
Cardiovascular risk	• Lifestyle modifications – smoking cessation, body weight optimization, exercise • Dyslipidemia management • Low-dose aspirin during pregnancy
Proteinuria (Chapter 1)	• Avoidance of high-sodium diet • Blood pressure control • RAS blockade
Infection risk	• Assess medical history of herpes zoster and tuberculosis • Screening for HBV, HCV, HIV, and HBV vaccination • *Pneumocystis jirovecii* prophylaxis (issue of potential adverse drug reaction discussed below) • Influenza and pneumococcal vaccination • Individualized consideration for recombinant zoster vaccine • Individualized consideration for other infectious organisms as dictated by public health concerns at the time of treatment
Bone injury	• Bone mineral density and fracture risk assessment • Calcium and vitamin D supplementation • Bisphosphonates when appropriate
Ultraviolet light exposure	• Broad-spectrum sunscreen • Limit ultraviolet light exposure
Premature ovarian failure	• Gonadotropin-releasing hormone agonists (i.e., leuprolide) • Sperm/oocyte cryopreservation
Unplanned pregnancy	• Individual evaluation and counselling for contraception type (preference, thrombosis risk, age)
Cancer	• Evaluate individual risk factors for malignancies • Age-specific malignancy screening • Limit lifetime cyclophosphamide exposure to <36 g

Figure 26| Measures to minimize the risk of complications related to LN or its treatment. HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LN, lupus nephritis; RAS, renin-angiotensin system.

that the recommendations on choice of treatment may appear not too dissimilar to the 2012 guideline. Nonetheless, some new management themes for LN have emerged, and management guidelines are presented in the current context.

It is recommended that antimalarials be given to patients with systemic lupus erythematosus (SLE) if there are no contraindications. Antimalarials are generally well-tolerated and have several benefits that include reducing flare rates (including kidney flares), decreasing organ damage, and enhancing responsiveness to immunosuppression.

Given the systemic nature of SLE and the potential adverse effects of therapies used to treat LN, the Work Group noted that a holistic approach to the management of LN be considered. Several relevant suggestions to improve the health and well-being of LN patients are described in Figure 26.

Considering the specific treatment of LN, there has been an increasing realization that for proliferative forms of LN (Class III/IV ± Class V) many patients may need less intense immunosuppression, especially with regard to glucocorticoid exposure, than previously thought. This is reflected in the new recommendation for the initial treatment of proliferative LN (Figure 27). Although glucocorticoids plus either MMF or cyclophosphamide are still recommended, the dosing goals have been reduced compared to the prior recommendations.

Intravenous methylprednisolone is still recommended to initiate therapy, but the cumulative dose has been reduced, followed by a lower starting dose of oral prednisone that is tapered fairly rapidly. MMF and cyclophosphamide remain the 2 recommended first-line immunosuppressive drugs. Initial MMF dosing has not changed, but low-dose intravenous cyclophosphamide (the Euro-Lupus regimen, Figure 27 lower panel) has replaced high-dose cyclophosphamide (the National Institutes of Health regimen) and oral cyclophosphamide as the method of choice to give an alkylating agent. In contrast, for patients with very severe proliferative LN, either histologically (abundant crescents, glomerular capillary necrosis) and/or clinically (rapid deterioration of kidney function), treating physicians may elect to use more traditional intense immunosuppression up-front. This recommendation and associated practice points provide sufficient latitude to individualize initial therapy.

The combination of a glucocorticoid, MMF, and a CNI, the so-called "multitarget" regimen, shows good efficacy compared to cyclophosphamide. Because the multitarget regimen had not been studied in diverse lupus populations, it was not recommended as first-line treatment, but suggested as an alternative for MMF and cyclophosphamide. However,

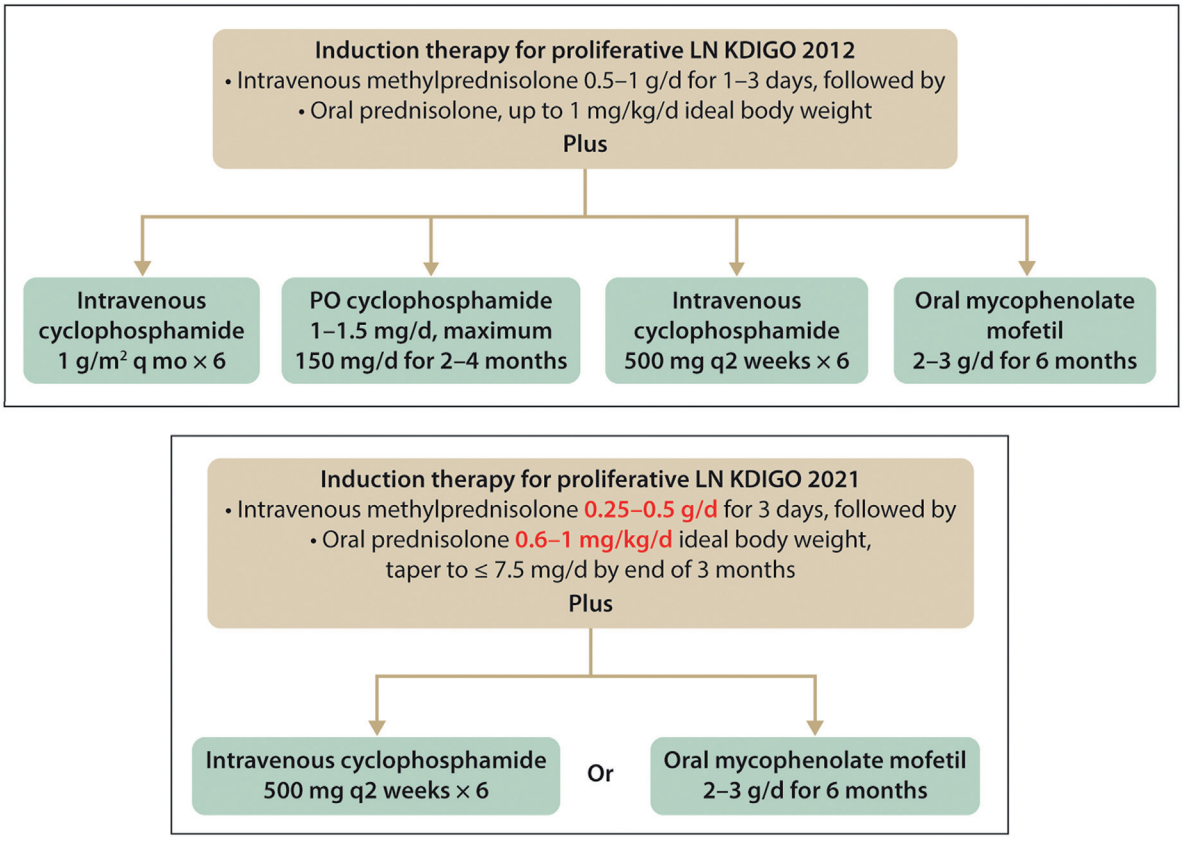

Figure 27 | Comparison of recommended initial first-line treatment of proliferative LN in the 2012 versus KDIGO 2021 guideline. LN, lupus nephritis; mo, month; q2, every 2.

in January 2021, the US Food and Drug Administration approved the addition of the novel CNI, voclosporin, to prednisone and MMF for the treatment of adults with active LN (Classes III, IV, V, and mixed) based on the results of a positive multicenter, multinational phase 3 trial. Voclosporin has not been studied with cyclophosphamide. After these data have been systematically reviewed, multitarget therapy will be reassessed for recommendation. Of likely importance to patients, the voclosporin regimen is significantly glucocorticoid-sparing, and will hopefully reduce the glucocorticoid adverse events often seen during LN treatment.

Biologics such as rituximab, which targets a B-cell surface marker, or belimumab, a monoclonal antibody to the B-cell growth and survival factor, B-cell activating factor (BAFF), are not included in the recommendation of first-line treatment. Biologics are, however, discussed in a practice point, noting that there are positive data from recent clinical trials demonstrating that biologics are effective in LN, and have favorable safety profiles.

The history of biologics for the treatment of LN is storied. Although the initial trials of rituximab and abatacept held considerable promise for modifying LN treatment, neither agent proved better when added to standard of care than placebo. Despite these negative trials, rituximab enjoys considerable off-label use, and in uncontrolled but real-world patient settings, is frequently reported to be effective. At the same time, clinical trialists, having learned lessons from failed trials, designed new trials that have been successful.

Regulatory approval from the US Food and Drug Administration of a biologic for LN came in December 2020 after the Efficacy and Safety of Belimumab in Patients with Active Lupus Nephritis (BLISS-LN) trial demonstrated that belimumab was more effective than placebo in achieving a primary efficacy renal response (PERR) at 2 years (43% vs. 32%; odds ratio 1.6; $P = 0.03$) when added to background therapy of glucocorticoids plus either MMF or low-dose cyclophosphamide. The PERR is a novel endpoint for LN trials and was defined as a PCR <0.7, an eGFR that was no worse than 20% below baseline or at least 60 ml/min per 1.73 m^2, and no treatment failure. The optimal use of belimumab in LN will become clear as its use increases, and the BLISS-LN data will be incorporated into the evidence review.

After completion of initial therapy for proliferative LN, a MPAA is recommended for ongoing immunosuppression (Figure 28). As shown, alternative long-term treatments are available and may be used in cases of intolerance to a specific therapy or if other special circumstances arise. For example, MPAA should not be used during pregnancy, but azathioprine and CNIs can be given.

One of the critical and as yet unsettled questions in the management of LN is the overall duration of immunosuppression. The pros and cons of prolonged immunosuppression hinge on balancing the risk of lupus relapse with the risk of adverse events secondary to immunosuppressive drugs. There are few high-quality data to support a specific duration of immunosuppression, although it is suggested that for patients who have achieved a complete kidney response and have no ongoing extrarenal SLE manifestations, the total duration of immunosuppression (initial plus maintenance) should not be <36 months. In the overall context of withdrawal of immunosuppression, it is suggested that glucocorticoid discontinuation may be considered after patients have maintained a complete clinical response for about a year, and have no extrarenal disease requiring glucocorticoids. These suggestions imply that patients who do not achieve a complete kidney remission, but only a partial remission, would

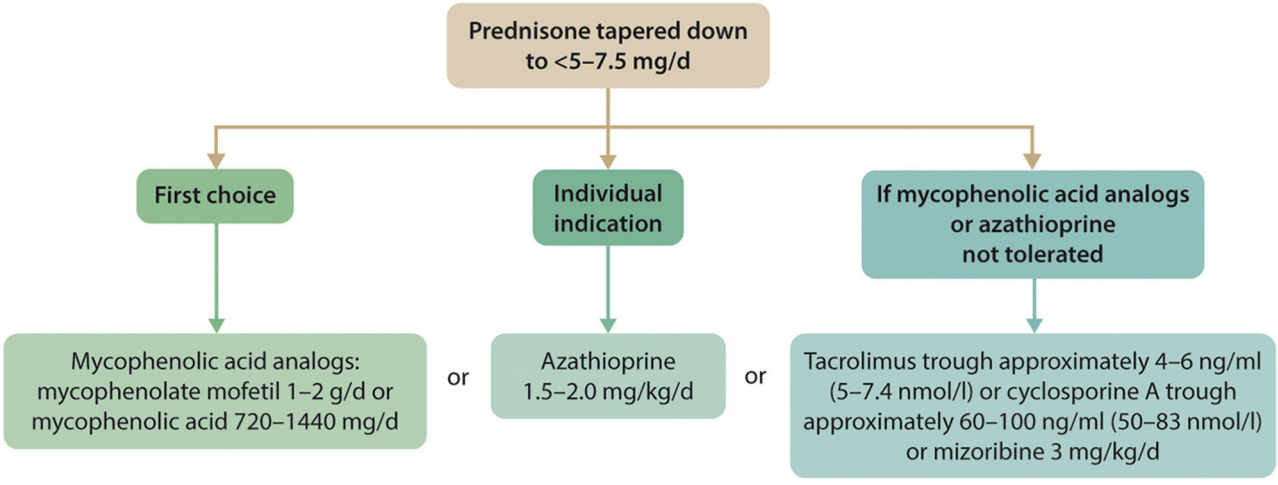

Figure 28 | Maintenance therapy for Class III and Class IV LN. The target ranges for CNIs have been based on the transplant literature. The KDIGO Work Group acknowledges that targets for glomerular diseases are not known. Most clinicians check these levels to verify adherence and avoid CNI toxicity. At present, 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 serum creatinine and reducing the dose if serum creatinine increases but does not plateau or increases over 30% of baseline. If the serum creatinine level does not fall after dose reduction, the CNI should be discontinued. CNI, calcineurin inhibitor; LN, lupus nephritis.

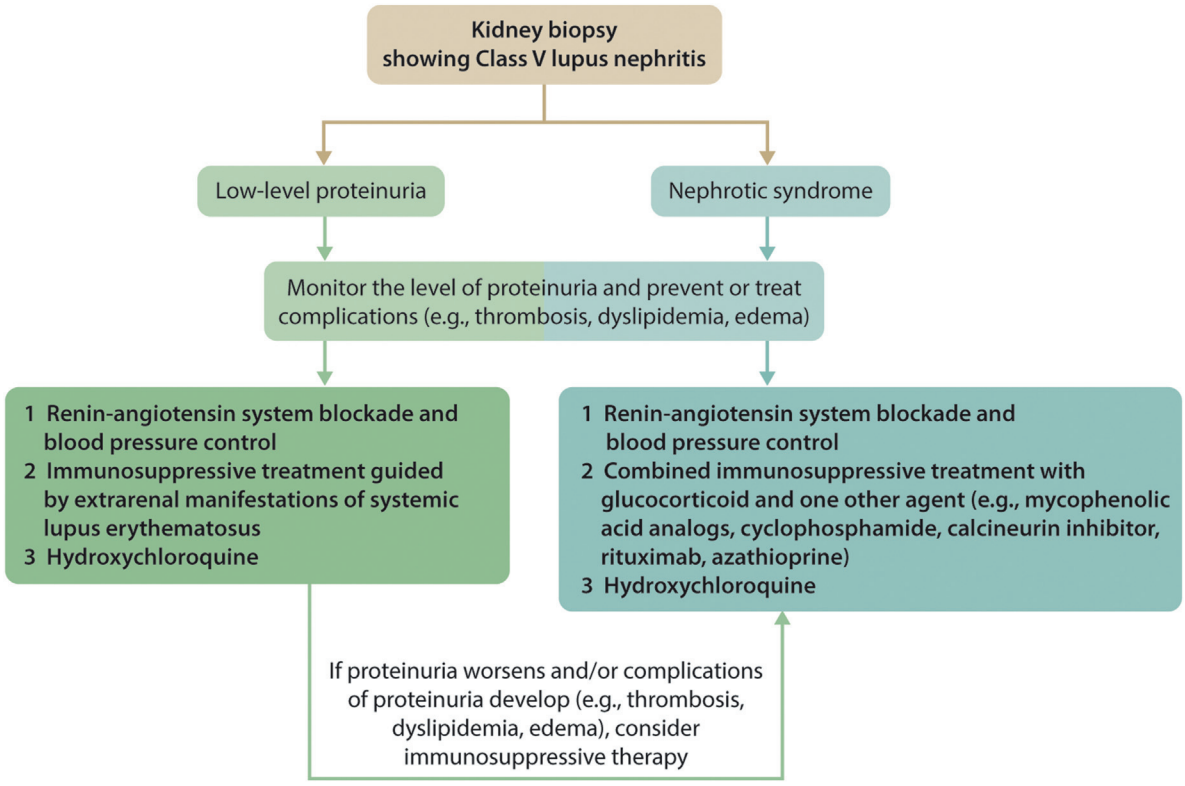

Figure 29| Management of patients with pure Class V LN. LN, lupus nephritis.

need to be kept on immunosuppression indefinitely. However, repeat biopsy studies have shown that while persistent histologic activity is a risk factor for LN relapse, many patients who have achieved only a partial clinical remission have no remaining activity on kidney biopsy. Thus, a more focused use of repeat kidney biopsies may help in managing the duration of immunosuppression.

Of the histologic types of LN, the membranous form (Class V) has received the least attention in terms of specific clinical trials. However, several of the newer trials evaluating novel treatments included patients with pure Class V LN. Subgroup analyses will help in understanding if these new agents have a role in Class V management. Until then, the suggested approach to pure Class V LN (Figure 29) has not materially changed since the last glomerular disease guideline.

One of the issues facing the evaluation of novel LN therapies is defining a meaningful response to treatment. The common definitions (Figure 30) are based on clinical thresholds and timelines that may be optimistic and used more to keep trial costs under control than for pathophysiologic reasons. Protocol repeat biopsy studies have shown that clinical responses and histologic improvement of the kidneys may be discordant.

The biomarkers used clinically for the evaluation of LN activity, such as complement levels and anti–double-stranded DNA titers, also have limitations. Therefore, the Work Group suggested that if patients are improving, allowing 18–24

Criteria	Definition
Complete response*	• Reduction in proteinuria <0.5 g/g (50 mg/mmol) measured as the PCR from a 24-h urine collection • Stabilization or improvement in kidney function (±10%–15% of baseline) • Within 6–12 mo of starting therapy, but could take more than 12 mo
Partial response	• Reduction in proteinuria by at least 50% and to <3 g/g (300 mg/mmol) measured as the PCR from a 24-h urine collection • Stabilization or improvement in kidney function (±10%–15% of baseline) • Within 6–12 mo of starting therapy
No kidney response	• Failure to achieve a partial or complete response within 6–12 mo of starting therapy

Figure 30| Commonly used definitions of response to therapy in LN. *For children <18 years old, complete response is defined as proteinuria <0.5 g/1.73 m^2/d or <300 mg/m^2/d based on a 24-hour urine specimen. LN, lupus nephritis; PCR, protein-creatinine ratio.

months to achieve a complete response is reasonable in the clinic and outside of the clinical trial setting. Importantly, many of the new trial designs are incorporating a longer timeline to assess clinical response.

Chapter 11: Anti-GBM antibody GN

The recommended therapy for anti-GBM antibody GN had not changed from the 2012 Glomerulonephritis guideline. Patients should be treated with glucocorticoids, cyclophosphamide, and plasmapheresis (*Grade 1C*). However, in the absence of pulmonary hemorrhage, if a patient requires dialysis at presentation and their kidney biopsy shows 100% crescents or more than 50% global glomerulosclerosis, the risk of this intense immunosuppressive protocol is difficult to justify given the very poor prognosis for sufficient recovery of kidney function to discontinue dialysis. Because anti-GBM disease may progress rapidly, if there is a high degree of suspicion for the diagnosis, treatment should not be delayed by the logistics of performing or interpreting a kidney biopsy. The biopsy can be done after treatment has been initiated. Importantly, for patients who do respond to therapy and recover, maintenance therapy with an immunosuppressive is not required as anti-GBM disease only rarely relapses. However, if a patient is positive for both anti-GBM antibodies and ANCA (up to 30% of patients), they should be given maintenance immunosuppression, as would be done for patients with AAV.

Other therapies have been tried for anti-GBM disease, but these have been mainly in the context of case reports or small, uncontrolled series. For example, rituximab has been successfully used for patients who have incompletely responded to the recommended approach. There have also been reports successfully substituting MMF for cyclophosphamide in the treatment of anti-GBM disease. Given the rarity of anti-GBM GN and its severity, it is understandable why progress toward new treatments has been limited.

Conclusion

The KDIGO 2021 Guideline for the Management of Glomerular Diseases is an extensive evaluation of literature and data supporting the management of patients with glomerular diseases. Although there has been significant progress made in treatment since the first guideline in 2012, it is clear that practice points greatly outnumber recommendations in the guideline. It is the hope of all those involved in the generation of this guideline that the document will serve as impetus to move clinical research in glomerular diseases forward so the unanswered questions raised here can be addressed and new evidence be made available to incorporate into the next iteration of recommendations. This guideline is intended to be a "living document" that will be updated as the nephrology community generates new high-quality data.

DISCLOSURE

The development of this guideline is strictly funded by KDIGO, and neither KDIGO nor its guideline Work Group members sought or received monies or fees from corporate or commercial entities in connection with this work.

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reports consultancy for Bayer, Chinook, Chugai, Daiichi Sankyo, Kyowa Kirin, Mitsubishi Tanabe Pharma, MorphoSys, Novartis, Travere (formerly Retrophin), and Visterra; grant/research support from Astellas*, Bayer*, Chinook, Chugai*, Daiichi Sankyo*, the Japan Agency for Medical Research and Development*, the Japan Society for the Promotion of Science*, Kyowa Kirin*, the Ministry of Health, Labour and Welfare in Japan*, Moderna, MSD K.K.*, Ono*, Sanwa Kagaku Kenkyusho*, Sumitomo Dainippon Pharma*, Sunstar*, Suzuken Memorial Foundation*, Takeda*, Teijin Pharma*, Torii Pharmaceutical*, Travere (formerly Retrophin), and Visterra; speakers bureaus for Asahi Kasei Pharma, Astellas, Bayer, Chugai, Daiichi Sankyo, Kissei, Kowa, Kyowa Kirin, Mitsubishi Tanabe Pharma, MSD K.K., Novartis, Ono, and Sumitomo Dainippon Pharma; and manuscript preparation for Chugai-Igakusha, Fuji Medical Publishing, Japan Medical Journal, Kagaku Hyoronsha Co., Ltd., Medicus Shuppan, Publishers Co., Ltd., Nankodo Co., Ltd., Shindan to Chiryo Sha, Inc., and Tokyo-Igakusha. SCWT reports consultancy for Novartis and Travere (formerly Retrophin); grants/research support from Sanofi; and speaker bureaus for AstraZeneca. VT reports consultancy for Abbvie, Amgen, Baxter, Bayer, Boehringer Ingelheim, ChemoCentryx, and Fresenius Medical Care; speaker bureaus for Bayer and Boehringer Ingelheim; and travel expenses from AbbVie. MV reports consultancy for Apellis, Novartis, Roche, and Travere (formerly Retrophin). JFMW reports serving as an international scientific advisory board member for Alexion*; consultancy for MorphoSys, Novartis, and Travere (formerly Retrophin); grant/research support from Alexion, MorphoSys*, and Novartis; and speaker bureaus for Novartis*. MAT reports honoraria from AstraZeneca and Travere (formerly Retrophin) with monies donated to charity. JF reports consultancy for Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Calliditas, MorphoSys, Novo Nordisk, Omeros, Travere (formerly Retrophin), and Visterra; and speaker bureaus for Amgen and Fresenius-Vifor. All the other authors declared no competing interests.

*Monies paid to institution.

ACKNOWLEDGMENTS

A special debt of gratitude is owed to following people for their contribution to this important guideline effort: Melissa Thompson, Debbie Maizels, Suetonia C. Palmer, Giovanni F.M. Strippoli, Fiona Russell, Gail Y. Higgins, Brydee Cashmore, Michel Jadoul, Wolfgang C. Winkelmayer, Kathleen Conn, Danielle Green, Tanya Green, and John Davis.