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Canadian Society of Nephrology Commentary on the Evolving Kidney Disease Improving Global Outcomes Adult Glomerulonephritis Guidelines

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Abstract

Purpose of review: The purpose of this commentary is to address the challenges of implementing the evolving Kidney Disease Improving Global Outcomes (KDIGO) glomerulonephritis (GN) guidelines within the Canadian health care context, highlighting barriers to adoption of the guidelines and discussing contextual issues unique to Canada.
Sources of information: The KDIGO 2021 guidelines with 2024 updates in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis and lupus nephritis, as well as the 2025 updated guideline for immunoglobulin A (IgA) nephropathy.
Methods: A Canadian Society of Nephrology (CSN) working group with expertise in GN was formed, representing nephrologists, pathologists, pharmacists, and patient partners with geographic representation from across Canada. Recommendations and practice points were reviewed by member surveys, with discussions to reach consensus and frame the commentary.
Key findings: The commentary highlights diagnostic investigations, the role of immune treatments for primary glomerular diseases, and the growing role of conservative kidney therapies.
Limitations: A review of the quality of evidence was not undertaken. Implementation and uptake of the guidelines will vary across each province given drug availability and cost.
Implications: The commentary aims to provide tailored guidance to enhance the care of Canadians living with glomerular disease.

Abrégé

Motif de la revue: Ce commentaire examine les difficultés associées à l'application des lignes directrices en constante évolution de KDIGO (Kidney Disease Improving Global Outcomes) sur la glomérulonéphrite dans le contexte des soins de santé au Canada. Il met en lumière les obstacles à l'adoption des recommandations, ainsi que les enjeux contextuels propres au pays.
Sources de l'information: Les recommandations KDIGO 2021, incluant les mises à jour de 2024 concernant la vascularite associée aux anticorps anticytoplasme des neutrophiles (ANCA) et la néphrite lupique, et la mise à jour de 2025 sur la néphropathie à immunoglobuline A (IgA).
Méthodologie: Un groupe de travail de la Société canadienne de néphrologie (SCN), spécialisé en glomérulonéphrite, a été formé. Le groupe rassemblait des néphrologues, des pathologistes, des pharmaciens et des partenaires patients, avec une représentation géographique couvrant l'ensemble du Canada. Les recommandations et points de pratique ont été évalués par sondage des membres et discussions en vue d'un consensus structurant le commentaire.
Principaux résultats: Ce commentaire met en évidence les démarches diagnostiques, le rôle des traitements immunomodulateurs dans la prise en charge des glomérulopathies primitives, et l'essor des stratégies conservatrices en néphrologie.

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Limites: La qualité des données n'a pas été évaluée. La mise en œuvre et l'adoption des recommandations varieront d'une province à l'autre, selon l'accès aux traitements et leur coût.
Conclusion: Ce commentaire vise à fournir des orientations ciblées pour optimiser les soins prodigués aux Canadiens atteints de glomérulopathie.

Keywords
glomerulonephritis, KDIGO, clinical guidelines, Canadian Society of Nephrology

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Introduction

Reflective of the rapidly emerging molecular research underpinning our understanding of the pathophysiology of glomerular diseases as well as the multitude of clinical trials in the field, Kidney Disease Improving Global Outcomes (KDIGO) released new guidelines in 2021[1] with subsequent chapters already receiving updates, including antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis,[2] lupus nephritis (LN),[3] and most recently immunoglobulin A (IgA) nephropathy.[4] Despite this expanded knowledge for diagnostic testing as well as the many new, but often expensive treatment options, implementation and uptake of the guidelines will vary globally given drug availability as well as cost implications.

Canada is unique among countries with universal health care, in that it does not have a universal national pharmacare program. Instead, drug coverage varies significantly by province or territory. Furthermore, Canada's small market share and proximity to the United States serves to disincentivize pharmaceutical companies from seeking Health Canada Approval. As such, the Canadian Society of Nephrology (CSN) has again established a Canadian glomerulonephritis (GN) working group to create a guideline commentary,[5] highlighting barriers to guideline uptake given our local contextual factors while providing guidance aimed to improve the care of Canadians living with glomerular diseases.

Methods

The 2021 KDIGO GN Guideline consists of evidence-based recommendations formulated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE)[6] approach and practice points. First included in these guidelines, practice points represent expert consensus statements to provide guidance when there is insufficient or inconclusive evidence to warrant a recommendation, but do not include an explicit discussion about benefits, harms, patient values, or resource considerations, and are not graded for strength of evidence.[7] To provide context to the 2021 KDIGO GN guideline relevant to the Canadian kidney community, a commentary was developed and written using the recently updated CSN methods.[8]

The Canadian Society of Nephrology's Clinical Practice Guideline Committee (CSN-CPGC) appointed a multidisciplinary working group, consisting of a chair and co-chair,

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adult nephrologists with clinical and content expertise, renal pathologists, renal pharmacists, and people with lived experience. Consistent with CSN policy, consideration was given to geographical representation from across Canada and other equity factors, such as age, gender, and career stage. The 2021 KDIGO GN guidelines were reviewed except for Chapter 4 (Pediatric Nephrotic Syndrome) and Chapter 7 (Infection-Related Glomerulonephritis). In addition, the 2024 ANCA-associated vasculitis[2] and LN[3] updates were reviewed, as well as the 2025 IgA nephropathy (IgAN) guidelines' update.[4]

The working group systematically reviewed all recommendations and practice points, identifying those to be included in the commentary. To determine inclusion, the following criteria were considered: (1) high yield for clinical practice, (2) resource constraints (frequently excluded from guideline development), (3) potential for targeted knowledge translation activities relevant to the local, regional, and national context, (4) factors specific to delivery of health care in Canada, and (5) recommendations wherein the working group questioned the strength of the evidence (Table 1).

Prior to the first working group meeting, each member completed a survey, indicating whether each recommendation: (1) required discussion regarding the supporting evidence, (2) required discussion for Canadian implications, and (3) did not require further discussion. The survey also allowed participants to abstain from responding and included an accompanying free text field for each question. Responses from the survey, including free text comments, were collated and disseminated in advance of the first working group meeting, and were used to frame meeting discussions. With respect to practice points, chapters were assigned to working group members tasked to identify those requiring discussion. These identified practice points were also presented and discussed at working group meetings. While the group did not perform or conduct systematic reviews to inform the commentary, any new studies since the publication of the guideline were incorporated into the discussion per the working group discretion. The chairs provided a chapter template to all working group members in advance who then utilized meeting minutes and survey results to draft their assigned chapters.

Dissemination of this commentary will be done through a variety of approaches, including publication in peer-reviewed nephrology journals as well as posting of the full document on partner websites, including the CSN, Kidney Foundation of Canada, Ontario Renal Agency, BC Renal Agency, and Can-SOLVE along with relevant commentaries in appropriate local, national, and international forums.

Chapter 1: General Principals for the Management of Glomerular Disease

Given that immunosuppression may be required for months to years, the same care that is afforded our transplant population should be applied to those with glomerular diseases, including cardiovascular risk reduction strategies to treat concomitant hypertension and hyperlipidemia (Practice Points 1.5.1 and 1.6.4), maintenance of vaccination schedules (Practice Point 1.8.1), age-appropriate cancer screening, as well as attention to reproductive health with coordinated multidisciplinary pregnancy planning (Practice Point 1.15.1).

SGLT2 Inhibitors and Conservative Therapies (Practice Point 1.5.1). In addition to the use of renin-angiotensin-aldosterone system (RAAS) blockade to manage hypertension and lower proteinuria, sodium-glucose cotransport-2 inhibitor (SGLT-2i) use has become widespread in select glomerular diseases, such as IgAN. While the balance of efficacy and safety are still being investigated, clinicians are now prescribing SGLT-2i in other glomerular diseases with proteinuria.[9,10] However, more research is needed before recommending SGLT-2i with concomitant immunosuppression, including safety data regarding infectious complications, risk of euglycemic diabetic ketoacidosis with simultaneous glucocorticoid use, and the risk of acute kidney injury (AKI) in patients with nephrotic syndrome (NS).

The benefit from SGLT-2i is from time accrued while on the medication, and therefore, risk likely outweighs benefit in those receiving induction immunosuppression regimens and SGLT-2i should not be concomitantly prescribed in this patient population. The priority for treatment of glomerular diseases remains addressing the underlying immunological issue. This is an important consideration if there is a "masked" decrease in proteinuria, which may exclude patients from clinical trials or disease-targeted treatment. Given the current data, it may be reasonable, however, to consider SGLT-2i for patients with glomerular diseases with residual proteinuria or those with chronic kidney disease (CKD) regardless of the degree of proteinuria who are on no or stable maintenance immunosuppression regimens.

Both dapagliflozin and empagliflozin are approved by Health Canada for non-diabetic CKD. Although a recent cross-sectional study from Alberta noted many adults with CKD would derive both cardiac and renal benefits with SGLT-2i,[11] many did not have access for various reasons, including being of a low socio-economic class. Hopefully the availability of generic options will limit cost as a reason for decreased uptake of SGLT-2i.

Chapter 2: Immunoglobulin A Nephropathy

An updated 2025 guideline for the treatment of IgAN[4] highlighted the role of novel therapies that impact disease pathogenesis (eg, nefecon) and progression (eg, sparsentan). Given the emergence of more targeted and less toxic therapies, the importance of prioritizing treatment of the underlying immunologic and inflammatory components was emphasized. To date, none of the novel therapies that have received full or conditional approval in the United States are

Table 1. Discussion Criteria for Recommendations.

Recommendation	Clinical practice	Resource constraints	Knowledge translation	Canadian health care	Evidence strength
2.3.1: In patients with IgAN, blood pressure should be managed by RAAS blockade (1B)	X		X		
2.3.2: In patients with IgAN, proteinuria $>$ 0.5 g/day, irrespective of BP, should be managed by RAAS blockade (1B)	X		X		
2.3.1.1: Patients with IgAN at risk for progression despite six months of conservative therapy should be considered for a six-month course of glucocorticoid therapy after risk assessment with special attention to the potential for toxicity in those with as GFR $<$ 50 ml/min (2B)	X		X		X
3.3.1: Patients with MN and at least one risk factor for disease progression should receive rituximab or cyclophosphamide and alternate month glucocorticoids or CNI-based therapy for six months, with treatment choice depending on the risk estimate (1B)	X	X		X	
5.3.1: High-dose oral glucocorticoids should be the initial treatment of MCD (1C).	X				X
5.3.1.1: Cyclophosphamide, rituximab, CNIs, or mycophenolic acid analogs should be used for the treatment of frequently relapsing/steroid-dependent MCD, rather than prednisone alone or no treatment (1C).	X	X		X	X
6.2.2.1: High-dose oral glucocorticoids should be used as the first-line immunosuppressive treatment for primary FSGS (1D)	X				X
6.3.1.1: For adults with steroid-resistant primary FSGS, cyclosporine or tacrolimus should be given for $\geq$ six months rather than continuing with glucocorticoid monotherapy or not treating (1C)	X	X		X	X
9.3.1.1: Glucocorticoids in combination with cyclophosphamide or rituximab should be used as initial treatment of new-onset AAV (1B)	X		X		
9.3.2.1: Maintenance therapy with either rituximab or azathioprine and low-dose glucocorticoids should be used after induction of remission (1C)	X		X		
10.2.1.1: Patients with SLE, including those with lupus nephritis (LN), should be treated with hydroxychloroquine or an equivalent antimalarial unless contraindicated (1C)	X				X
10.2.3.1.1: Patients with active Class III or IV LN, with or without a membranous component, be treated initially with glucocorticoids plus any one of the following: i. mycophenolic acid analogs (MPAA) (1B); or ii. low-dose intravenous cyclophosphamide (1B); or iii. belimumab and eitherMPAA or low-dose intravenous cyclophosphamide (1B); or iv. MPAA and a calcineurin inhibitor (CNI) when kidney function is not severely impaired (1B)	X	X	X	X	X
11.2.1: Immunosuppression with cyclophosphamide and glucocorticoids plus plasmapheresis should be used in all patients with anti-GBM GN except those who are treated with dialysis at presentation, have 100% crescents or $>$ 50% global glomerulosclerosis in an adequate biopsy sample, and do not have pulmonary hemorrhage (1C)	X	X			X

approved or funded in Canada (ie, nefecon, sparsentan, and iptacopan). Looking to the future, immunosuppression is an explosive area of research in the IgAN space with ongoing phase 3 trials investigating complement inhibitors as well as anti-A Proliferating-Inducing Ligand (APRIL) and B-cell Activating Factor (BAFF) therapies. Unfortunately, the high costs of these medications will certainly be barriers to use in Canada, requiring ongoing physician and patient advocacy.

Assessment of Risk of Progression (Practice Point 2.2.1). As was recently demonstrated in a study examining the UK National Registry of Rare Kidney Diseases (RaDaR),[12] long-term kidney outcomes in patient with IgAN are poor; even in those who are traditionally stratified as being low risk of short-term progression. Similarly, a study within Kaiser Permanante Southern California showed increased rates of adverse kidney outcomes with proteinuria levels $\geq$0.5 g/g.[13] As it remains clinically challenging to determine which patients should be treated, and furthermore, how they should be treated, the KDIGO guideline highlights the IgA Nephropathy Prediction Tool as an important resource that incorporates pathologic information along with clinical and biochemical data, at the time of biopsy to quantify the risk of

progression.[14] More recently, it was shown that this tool is valid one to two years post-biopsy.[15] The authors highlight that this tool cannot help with the selection of therapy, nor does it inform the impact of therapy. However, importantly, it presents an opportunity for shared decision making with patients whereby the personalized risk of disease progression can be weighed against therapy related toxicity in the context of patient preferences. In addition, this can serve as a standardized means of communicating amongst care providers. The tool is readily accessible online (https://qxmd.com/calculate/calculator_499/international-igan-prediction-tool-at-biopsy-adults) and there should be minimal barriers to consistent utilization by Canadian nephrologists.[16]

Conservative or Supportive Therapy (Recommendations 2.3.1 and 2.3.2). The KDIGO guideline authors highlight the importance of blood pressure (BP) management in patients with IgAN, selecting RAAS blockade as the preferred agents in patients with $>$ 0.5 g/day of proteinuria. These recommendations are foundational to the care of hypertensive patients, while in those without hypertension, dose titration should be based on tolerability. When reflecting upon on the balance of harm versus benefit, the application of these therapies is evaluated as being heavily in favor of benefit, with little harm and thus, should be applied broadly.

Since the publication of the KDIGO guidelines, sub-analysis of DAPA-CKD[10] (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) and Empagliflozin in Patients with Chronic Kidney Disease (EMPA-Kidney[17]) have suggested that SGLT-2i therapy may also provide significant benefit as it pertains to reducing the progression of kidney disease in patients with IgAN. This represents an area requiring further research in terms of the sequencing of therapy and how to interpret SGLT-2i-mediated proteinuria reduction when assessing risk, as well as making decisions about immunotherapy. Importantly, SGLT-2i therapy is not disease modifying and should not replace immunotherapy but should instead augment supportive therapy in addition to RAAS blockade.

Recently, phase 3 data have been published investigating the utilization of the dual endothelin angiotensin receptor antagonist (DEARA), sparsentan,[18] which resulted in proteinuria reduction, but provided only modest benefit on the rate of estimated glomerular filtration decline. Similarly, the selective endothelin receptor agonist (SERA), atrasentan demonstrated proteinuria reduction in IgAN, but estimated glomerular filtration rate (eGFR) data are yet to be reported.[19] Both medications carry a significant financial cost relative to SGLT-2i. Furthermore, whether there is added benefit as well as an acceptable risk profile when used with SGLT-2i remains unknown. In Canada, we presently cannot access these medications, but efforts are ongoing to make these medications more readily available for select patient populations.

Glucocorticoids (Recommendation 2.3.1.1). Despite the prevalence of IgAN, the role and application of glucocorticoid therapy remains controversial.[20] Kidney Disease Improving Global Outcomes suggested that patients who remain high risk after 6 months of conservative therapy should be considered for glucocorticoids. This recommendation remains problematic for several reasons. Care providers, but more importantly, patients may perceive the toxicity of glucocorticoids differently and may be less willing to accept these risks, in the setting of a largely asymptomatic disease. In patients with active lesions on biopsy, conservative therapies may reduce proteinuria to less than 1 g/day but not modify disease activity. As such, these patients may remain at risk of disease progression from untreated active disease despite having lower proteinuria. Notably, this has been rectified in the update wherein the importance of targeting inflammatory disease activity with immunosuppression simultaneously with the initiation of supportive therapies is emphasized.[4]

At the time of publication of the 2021 guidelines, the complete Therapeutic Evaluation of Steroids in IgA Nephropathy Global (TESTING) trial, including the lower-dose protocol results, was not known. The trial suggested that lower-dose steroids do improve renal outcomes as effectively as higher-dose steroids, while reducing the risk of adverse events relative to higher doses.[21] Given the balance of benefit compared with harm in patients who are at high risk of progression, the lower-dose glucocorticoid regimen is a logical first choice for those patients deemed to require immunosuppression. The KDIGO guidelines suggested that more caution should be applied in those with glomerular filtration rates (GFRs) $<$ 50 ml/min. However, those patients are also at a high risk to develop end-stage kidney disease (ESKD) and were enrolled in the TESTING trial (GFR $>$ 20 ml/min in the high-dose protocol and 30 ml/min in the low-dose protocol).[21] Consideration of only one factor, such as GFR, in a disease as complex as IgAN, can lead to errors in decision making, as it pertains to treatment. In Canada, the adoption of lower-dose glucocorticoid regimens may present challenges. Due to the clinical equipoise that existed in this therapeutic domain, altering clinical inertia will be difficult. The addition of newer agents in the realm of supportive care, such as SGLT-2i, will further blur these lines, due to their anti-proteinuric effects. Also, application of these protocols to Indigenous populations and other equity deserving populations, who may be at higher risk of adverse events, is not well studied. Finally, there is no established immune therapy in patients who relapse or do not respond to glucocorticoid therapy. Acknowledging the above, glucocorticoids remain the only available immunosuppressive therapy in Canada with robust evidence.

In the recent KDIGO IgAN guideline revision,[4] it was suggested that targeted-release oral budesonide could be considered as an alternative to oral prednisone. The Efficacy and Safety of Nefecon in Patients with Primary IgA Nephropathy (NEFIgARD) trial was recently published along with 2-year durability results,[22,23] demonstrating that targeted-release oral budesonide was effective at lowering proteinuria and reducing the progression of kidney disease as

compared with standard of care, and was associated with less side-effects than high-dose systemic glucocorticoids. However, the relative tolerability of targeted-release budesonide compared with the low-dose steroid protocol from the TESTING trial remains unknown, and presently, targeted-release oral budesonide is not available in Canada.

Chapter 3: Membranous Nephropathy

Immunosuppression (Recommendation 3.3.1). The KDIGO treatment guidelines for membranous nephropathy (MN) are based on a risk stratification for progression that includes low-risk patients with low-grade proteinuria and normal eGFR on one end of the spectrum who do not require immunosuppression to those at very high risk who have life-threatening NS or rapidly progressive loss of kidney function. In those deemed to be at either moderate or high risk of progression, either rituximab, cyclophosphamide, or calcineurin inhibitors (CNIs) can be utilized, as all three first-line treatments are thought to be of equal efficacy for inducing remission in MN. However, in patients deemed to be very high risk, cyclophosphamide and steroids should be the first-line therapy. This is graded as 1B level evidence, as only oral alkylating agents have data demonstrating long-term reduction in kidney failure and benefit in those with declining kidney function.[24,25] Distinguishing patients who may be high risk as opposed to very high risk is a subjective clinical evaluation. Furthermore, data are emerging noting the benefit of rituximab in reducing the rate of eGFR decline.[26]

Typically, the side-effect profile becomes the determining factor for the choice of first-line immunosuppression. For moderate- and high-risk MN patients, the preferred adverse effect profile of CNIs and rituximab may favor their use over cyclophosphamide-based regimens (eg, fertility and malignancy risk).[27] The oral dosing of CNIs may make treatment initiation easier, while vascular disease or a rising serum creatinine may be a contraindication for their use. In addition, data from the MENTOR trial, which compared rituximab with CNIs, suggested patients with very elevated serum anti-phospholipase A2 receptor (PLA2R) levels may respond better to rituximab, suggesting biomarkers may also guide the initial choice of immunosuppression.[28] Finally, higher relapse rates upon CNI discontinuation may be reason for concern for moderate-high risk patients with MN.[29] As the quality of remission determines risk factors for relapse (high residual proteinuria and low serum albumin), additional treatment may be needed with CNI therapy to reduce the risk of relapse. Combination therapy of CNI and rituximab has been described.[30] One possible advantage of this combination therapy is the faster initial proteinuria reduction with CNI therapy and the sustained reduction with rituximab.[31] Although combination therapy with rituximab and cyclophosphamide is being investigated, there remain concerns about the adverse side-effect profile and larger studies are needed for efficacy.[32,33] Unfortunately, there is significant provincial variability with respect to rituximab coverage for MN,[34] limiting accessibility when rituximab is deemed the most appropriate immunosuppressive option. Based on the current guidelines, it is no longer appropriate for a patient to have to fail cyclophosphamide to gain access to rituximab.

Diagnosis and Biomarkers (Practice Points 3.1.1 and 3.2.1). Serum anti-PLA2R alone is now considered sufficiently sensitive and specific to diagnose MN,[35] and it has now become acceptable to consider treatment for serum anti-PLA2R positive, nephrotic patients with preserved eGFR without a confirmatory kidney biopsy. Risk factors for bleeding or the imminent need for anticoagulation would be reasons to extend this guideline to those with more advanced kidney disease.

Beyond diagnosis quantifying the anti-PLA2R level can guide treatment decisions. For example, a serum anti-PLA2R $>$ 50 RU/ml is also listed as a feature of high-risk MN, while Barbour et al[36] have evaluated the change in serum anti-PLA2R at three and six months from baseline as a predictor of treatment response. The KDIGO working group identified changes in serum titers as a research priority to aid in risk assessment and treatment decisions. If further data continue to support changes in serum anti-PLA2R titers as correlating with disease progression, this biomarker will become an even more valuable tool in disease management.

Although this serological investigation is becoming more widely available outside of academic centers in Canada, the test is not available in all provinces, and the costs are not covered in any province. In addition, there is variability in the type of testing being used (eg, quantitative vs semi-quantitative), limiting its utilization.

Anticoagulation (Practice Point 3.4.5). Venous thromboembolic (VTE) events occur in less than 10% of patients with MN, typically presenting within the first six months.[37] Though infrequent, there are clinically significant complications associated with VTE events. The analysis by Lionaki et al[37] is referenced as a tool to aid in the decision for anticoagulation with hypoalbuminemia being the single strongest predictor of risk. Hypoalbuminemia also affects the pharmacokinetics of warfarin and the newer direct acting oral anticoagulants (DOAC), impacting both efficacy and bleeding risk. Emerging evidence from retrospective studies, however, does suggest DOAC use in NS may be both efficacious and safe.[38,39] Furthermore, DOACs may be preferred by patients and providers given lack of necessary blood work. Despite these knowledge gaps regarding the optimal prophylactic anticoagulant of choice, warfarin remains the preferred agent by many providers for the highest risk patients given the ability to monitor international normalized ratios.

Chapter 5: Minimal Change Disease

Immunosuppression (Recommendations 5.3.1 and 5.3.1.1; Practice Points 5.3.3 and 5.3.5). Despite the scarcity of high-quality data, high-dose corticosteroids remain first-line treatment for the initial presentation of minimal change disease (MCD), provided there are no contraindications. However, shorter treatment courses are now favored with tapering to begin two weeks after complete remission. This differs from the 2012 recommendation wherein a minimum of four weeks of high-dose glucocorticoids was recommended irrespective of remission status. Given these guidelines have been largely extrapolated from studies in children[40,41] as well as the higher potential toxicity of steroid use in adults, both the induction dose and tapering schedule should be applied with caution.

When choosing therapy for patients with contraindications to corticosteroids, clinicians should carefully consider patient demographics and medication safety profiles with particular attention given to baseline myelosuppression, propensity for malignancy, reproductive plans, and ability to monitor blood work. There are no studies to date elucidating a superior steroid-sparing agent for the treatment of MCD, but CNIs and mycophenolate mofetil (MMF) generally have a favorable safety profile compared with cyclophosphamide. Given the recent discovery of anti-nephrin antibodies, a marker of disease activity, among a sizable proportion of patients with MCD, including 44% of adults,[42] there is growing evidence to support the use of rituximab in the initial management of MCD in adults. Rituximab has been shown to clear anti-nephrin antibodies, resulting in sustained remission,[42] but further study is required to compare efficacy with that of glucocorticoids.[43,44]

Up to 33% of patients with MCD will become frequent relapsers (FRs) (> three per year) or steroid dependent (SD). Cyclophosphamide, rituximab, CNIs, and mycophenolic acid analogs (MPAAs) have been used as glucocorticoid-sparing agents to treat FR/SD MCD. These agents are supported by low-quality evidence for efficacy and questionable long-term benefit in adults with MCD. Furthermore, there is limited evidence to favor one drug class over another. However, the avoidance of prolonged or repeated glucocorticoid-associated morbidity supports their use. Unfortunately, the choice of therapy for FR/SD (frequently relapsing/steroid-dependent) MCD is impacted by accessibility and cost for non-glucocorticoid drugs in Canada, some of which are not covered by publicly funded provincial health care plans or restricted in access with rituximab typically being the drug most difficult to access despite the noted benefits in this patient population. Further studies, including economic analyses of maintenance rituximab given every six months compared with daily oral therapy of combination immunosuppression, should be prioritized to ensure similar access and coverage across all Canadian provinces.

Chapter 6: Focal and Segmental Glomerulosclerosis

Classification (Practice Point 6.2.1.1). Focal segmental glomerulosclerosis (FSGS) is a histological diagnosis, and it is incumbent upon the nephrologist to unmask the etiology. Clinicians must assess whether the patient has a full NS as opposed to only nephrotic or sub-nephrotic range proteinuria, and any potential underlying causes. The 2021 KDIGO guidelines support a classification system to aid with management, with a new term, FSGS of undetermined cause (FSGS-UC), for patients without NS or an identifiable etiology. Although Practice Point 6.2.1.1 suggests that FSGS-UC, a diagnosis of exclusion, should be treated conservatively, recent findings show that FSGS-UC with nephrotic-range proteinuria but without hypoalbuminemia can obtain a remission in the setting of immunosuppression and behave like primary FSGS, with a similar relapse rate.[45] Some cases of FSGS-UC also evolve to a full NS over time. As such, there are instances wherein immunosuppression may be indicated in those presenting with FSGS-UC.

Genetic Testing (Practice Point 6.1.2.1). Although the 2012 guidelines recommended against genetic testing in patients with FSGS, this recommendation was revised in the 2021 version for patients who fail immunosuppressive therapy, as well as for those with a positive family history of kidney diseases. Since genetic forms are typically less responsive to immunosuppression, these patients should be identified to avoid side effects associated with escalating immunosuppression. Furthermore, collagen IV mutations can cause FSGS lesions on biopsy and treatment with immunosuppression would be deemed inappropriate in these patients.[46] Finally, genetic forms of FSGS rarely recur post-transplant, which may affect transplant candidacy and management, particularly when a related donor is being considered. With newer screening methods, costs have considerably dropped in recent years, and current exome sequencing of over 70 genes is available for under 1000 USD. As such, genetic testing should be considered for any FSGS patient without a new-onset NS or a plausible secondary cause.[46] Genetic testing will also allow for the development of more precision-based therapies, particularly for APOL1-associated disease or mutations affecting coenzyme Q10 synthesis.[47,48] Hampering adherence to this practice point is the variable funding for genetic testing by province as well as the lack of counseling resources, which affects all Canadian provinces. Ontario's new framework for genetic testing may provide a roadmap to address this pan-Canadian issue.[49]

Immunosuppression (Recommendations 6.2.2.1 and 6.3.1.1; Practice Point 6.2.2.2). The recommendation for prednisone as first-line immunosuppressive therapy for primary FSGS, which is extrapolated from pediatric studies, remains unchanged. The suggested maximum duration of 16 weeks for high-dose glucocorticoid therapy is long, and

likely intolerable for patients given the side-effect profile. The lack of response to high-dose glucocorticoids will likely present within the initial months, allowing the clinician to introduce second-line immunosuppression well before the 16-week mark to allow the earlier tapering of glucocorticoids. In addition, the recommended total duration of glucocorticoids in prednisone responsive patients is six months. This is a long duration, and it is uncertain if this prolonged treatment translates into long-term benefit.[50] Calcineurin inhibitors are the preferred second–line therapy when there is intolerance or resistance to glucocorticoids, and/or relapsing disease. Given the limited published series, therapies other than glucocorticoids and CNIs are only briefly discussed in the new guidelines. Nevertheless, physicians are often tasked to consider long-term immunosuppressive therapy in primary FSGS. Without solid evidence, MMF and rituximab are the two most used additional regimens.[51-54] Contrary to Practice Point 6.3.5.1, the use cyclophosphamide should be reserved to individuals who have failed these regimens. Further research is urgently needed to identify more effective and less toxic therapies.

Conservative Treatment (Practice Point 6.1.1.1). Focal segmental glomerulosclerosis patients require conservative therapy starting with RAAS blockade, BP control, and dietary measures. The 2021 guidelines do not comment on the potential use of SGLT-2i, mineralocorticoid receptor antagonists (MRAs), DEARAs, or SERAs specifically for FSGS. However, evidence for the use of SGLT-2i is also emerging in patients with FSGS. A sub-analysis of the DAPA-CKD study demonstrated that the addition of an SGLT-2i to a maximally tolerated dose of RAAS blockade benefited patients with biopsy-proven FSGS in terms of proteinuria reduction, reduced risk of sustained eGFR decline or ESKD, and death from cardiovascular or renal causes.[55] These results, however, did not reach statistical significance, due to the small number of events. There is also potential for DEARA use. A large, recently published, phase 3 study found a greater reduction in proteinuria and greater complete remission with sparsentan compared with irbesartan, although the eGFR slopes over 108 weeks were not different between the two treatment groups.[56] This, combined with the associated costs, makes sparsentan an unlikely treatment option for FSGS in Canada, pending further data.

Chapter 8: Immunoglobulin- and Complement-Mediated Glomerular Diseases With a Membranoproliferative Glomerulonephritis Pattern of Injury

Diagnosis and Histopathology (Practice Point 8.1.1). There have been significant advancements in the diagnosis and management of patients with membranoproliferative glomerulonephritis (MPGN). Membranoproliferative glomerulonephritis is no longer considered a disease but instead a pattern of glomerular injury, and a new classification scheme has replaced the older classification, which was based on the location of deposits on electron microscopy.[57] The newer classification system is based on advances in pathophysiology and relies on immunofluorescence patterns to classify the injury. Membranoproliferative glomerulonephritis can be subdivided into C3 glomerulopathy (C3G) and immune-complex MPGN (IC-MPGN). With C3G, immunofluorescence is predominantly C3 positive, whereas in IC-MPGN, there are both polyclonal immunoglobulins and C3 deposits.[57] In adults, most cases of IC-MPGN are due to infections, autoimmune conditions, or monoclonal immunoglobulins.[58-60] Immune-complex membranoproliferative glomerulonephritis may also evolve to C3G over time.[61-63] Therefore, it is thought that idiopathic IC-MPGN may be a complement driven process.

Hematology Assessment (Practice Point 8.1.2). Working with a hematologist with knowledge of monoclonal gammopathies of renal significance (MGRS) is important for evaluation and treatment of patients with an MPGN pattern on kidney biopsy as C3G/IC-MPGN may be associated with a monoclonal protein, even in the absence of restricted free light-chain staining on kidney biopsy. Discovery of a monoclonal protein in the blood or serum in the context of C3G/IC-MPGN warrants exclusion of multiple myeloma. When a paraprotein is identified, treatment should be directed at the underlying hematological disease.[64] Developing specialized hematology expertise in the diagnosis and management of MGRS requires collaborative investment to improve care across the country.

Complement Dysregulation (Practice Point 8.1.3). Research into mechanisms of complement dysregulation continues to evolve and assays to evaluate complement activation have matured in parallel. Assessment of complement dysregulation is recommended for C3G and cases of idiopathic IC-MPGN. This includes both genetic testing and functional antibody assays. Up to 20% of patients may have mutations in complement genes. The most common rare pathogenic complement variants, including mutations in CFH, CFI, C3, and CFB.[65-67]

Nephritic factors are autoantibodies that bind to and stabilize C3 or C5 convertases and are thought to be present in most patients with C3G.[68,69] Of these, C3 nephritic factor is the most prevalent. Nephritic factors also define the site of complement dysregulation and may suggest treatment response to complement inhibitors. Additional autoantibodies to complement proteins, including anti-factor B autoantibodies, have been reported particularly in response to infections.[70,71] The degree of terminal complement pathway activation has also been associated with worse renal prognosis in C3G/IC-MPGN.[72]

Despite their ability to provide important insights into disease mechanisms that may alter treatment choices, these emerging complement assays are not Health Canada approved for clinical use, and are therefore not routinely

available in most Canadian centers and provinces. Funding to send blood samples out of province or out of country is also not consistently available. Furthermore, some provinces rely on pharmaceutical industry funding for complement genetic testing and functional assays, which creates inconsistent access to these tests and the potential for a conflict of interest. Given IC-MPGN and C3G are rare diseases, expert Canadian centers for complement testing should be developed for clinical use and research, and these assays should be funded by provincial health authorities.

Therapy (Practice Point 8.2.2.1). The natural history and prognosis of C3G and IC-MPGN are not well described.[57] Treatment decisions are still predominantly made on the basis of proteinuria and eGFR, but immunohistological features, genetics and functional complement assays should additionally factor into treatment decisions. For mild cases, RAAS blockade has been associated with improved renal survival.[73] For patients with proteinuria >1 to 2g/day, various immunosuppressive therapies have been described with mycophenolate and prednisone having the strongest retrospective data.[74] Despite initial optimism, the use of complement inhibition has not demonstrated consistent benefits. Currently the use of eculizumab or ravulizumab to treat C3G or IC-MPGN is off-label. Due to the cost of the medication, access is unequal across provinces and may not be available compassionately. However, with the changing landscape in C3G/idiopathic IC-MPGN, novel complement blockade treatment options are emerging, and there is an opportunity for the Canadian nephrology community to participate in research trials.

Clinical Trials (Practice Point 8.2.2.2). The results of novel upstream complement inhibitor trials are starting to emerge for C3G, noting good safety profiles without reports of serious infections. Pegcetacoplan, a C3 inhibitor, demonstrated 50% proteinuria reduction over 48 weeks in their phase 2 study compared with placebo, with improvement in serum C3 and sCb5 to sCb59 levels.[75] Their phase 3 study results, which were announced at ASN Kidney Week 2024, demonstrated a 68% relative proteinuria reduction in the treatment group compared with placebo at 6 months.[76] Iptacopan, a factor B inhibitor, has also demonstrated impressive phase 2 results with 45% proteinuria reduction at 12 weeks versus placebo for patients along with improvements in serum C3 levels.[77] The results of their phase 3 study demonstrated a 35% relative reduction in proteinuria compared with placebo at 6 months.[78] Both treatments had a positive impact on eGFR slope. Treatment recommendations and funding criteria once these medications become available for these rare renal diseases will continue to evolve with some provinces now able to access these medications through the company for select patients. Additional small molecule inhibitors, RNAi and monoclonal antibodies against complement activation are in early-stage clinical trials. There is an opportunity for the Canadian GN community to participate in research trials to evaluate the efficacy of complement blockade in IC-MPGN and C3G.

Chapter 9: Antineutrophil Cytoplasmic Antibody-Associated Vasculitis

Induction Therapy (Recommendation 9.3.1.1 and Practice Point 9.3.1.6). Advances in the last several years continue to refine the treatment of ANCA-associated vasculitis to improve disease control more safely, with the pillars of induction therapy remaining cyclophosphamide or rituximab with glucocorticoid therapy albeit at significantly reduced doses relative to previous treatment regimens based on the results of the "Plasma exchange and glucocorticoids for ANCA-associated vasculitis" (PEXIVAS) trial.[79] Since then, a meta-analysis incorporating detailed information from PEXIVAS as well as other trials substantially improved our understanding of the effects of these treatments.[80] Two additional, randomized controlled trials have also informed oral glucocorticoid reduction strategies, including the "Low-dose glucocorticoids plus rituximab versus high-dose glucocorticoids plus rituximab for remission induction in ANCA-associated vasculitis" (LoVAS) trial and the "Avacopan for the treatment of ANCA-associated vasculitis (ADVOCATE) trial.[81,82] Taken together, the use of the PEXIVAS trial's "reduced-dose" regimen for oral glucocorticoids and early withdrawal of prednisone is reasonable for clinicians to consider during induction treatment of ANCA-associated vasculitis with either cyclophosphamide or rituximab.

Treatment in Patients With Reduced eGFR (Practice Point 9.3.1.2). In patients presenting with markedly reduced or rapidly declining GFR/serum creatinine > 354 μmol/L, the guidelines highlight that there are limited data to support rituximab and glucocorticoids, suggesting that cyclophosphamide and glucocorticoids are preferred for induction therapy. The combination of rituximab and cyclophosphamide can also be considered in this setting; however, this is largely based on published case series, experts' anecdotal use of combination regimens, and, to a degree, the RITUXVAS trial.[83] This remains an area of controversy that is further complicated by new treatment regimens that may also include avacopan, which exploratory data suggest may further improve kidney outcomes.[84] Given ANCA-associated vasculitis is a rare disease, many nephrologists will have limited experience with novel therapeutic regimens and care should be led by centers with substantial experience and expertise.

Glucocorticoid Dosing and Avacopan (Practice Points 9.3.1.6 and 9.3.1.7). In the 2024 update, avacopan emerged as an additional therapy to reduce glucocorticoid burden.[82] Because the ADVOCATE trial design resulted in many participants in the avacopan arm also treated with a substantial amount of prednisone, there is some uncertainty as to the independent effect of avacopan and when prednisone should

be withdrawn. This uncertainty appeared to be a major consideration in the Canada's Drug and Health Technology Agency's unfavorable review of avacopan. In addition, the use of avacopan in patients with life or organ threatening manifestations of vasculitis remains limited to case series and very small subgroups in the ADVOCATE trial, requiring further, systematic study to optimize its use in clinical practice.[85] Finally, health care providers also face uncertainty as to whether the maintenance regimen should be modified at all for the use of avacopan since no rituximab maintenance was used in ADVOCATE and there was no study of outcomes after 1 year when avacopan was withdrawn. However, its use may be considered in patients with a strong contraindication to glucocorticoids. A Canada-specific discussion on the role of avacopan was published in 2023 providing guidance on the use of avacopan in our health care system.[86] Presently, despite guideline recommendations, public reimbursement is not available.[87] Avacopan is currently funded by private insurance or by compassionate release from the pharmaceutical company on a case-by-case basis.

Plasma Exchange (Practice Point 9.3.1.9). Initially, plasma exchange was suggested appropriate to consider in patients with a serum creatinine $>$ 500 μmol/L, rapidly increasing creatinine, requiring dialysis or with hypoxemia from diffuse alveolar hemorrhage. The updated guidelines, however, suggested reducing the creatinine threshold for consideration to 300 μmol/L on the basis of (1) the relative reduction in kidney failure effect of plasma exchange being similar regardless of baseline risk and (2) the risk of kidney failure being appreciable for patients with less extreme presentations. This working group would like to highlight that patients presenting with severe AKI also be considered for plasmapheresis.

Maintenance Therapy (Recommendation 9.3.2.1; Practice Points 9.3.2.2, 9.3.2.5, and 9.3.2.6). Trials comparing rituximab, whether every four months, six months, or on the basis of reconstituted biomarkers and whether dosed at 500 or 1000 mg, consistently demonstrate superiority to the combination of azathioprine and prednisone suggesting that it is the preferred agent for patients with ANCA-associated vasculitis who are at risk of relapse.[88-90] There remains uncertainty about the efficacy of the individual components of azathioprine and prednisone (ie, does each contribute to remission maintenance and to what degree). In addition, there is no commonly accepted method of estimating the risk of relapse for these patients which would help determine the degree to which rituximab is preferred over azathioprine and prednisone for some patients and the degree of residual risk of relapse some patients may have despite maintenance therapy. There is a wide variation in the optimal duration of maintenance therapy, ranging between 18 months and four years. It is important to note that even after four years of maintenance, the risk of relapse appears to increase substantially after the withdrawal of maintenance therapy.[89,91] This should be considered in both the duration of therapy and the monitoring strategy employed after withdrawal.

The utility of maintenance therapy in patients with renal-limited disease who remain dialysis-dependent is dependent on the individual patient. Vasculitis is a systemic disease, and extrarenal manifestations may occur in dialysis-dependent patients. The relapse risk is lower in patients with ESKD than patients not on dialysis, and infectious complications are higher, making individual decision-making important.[92] Individual factors that may be important in weighing the risks versus benefits of maintenance therapy include the vasculitis subtype, comorbid conditions, and feasibility and timing of future transplantation.

Chapter 10: Lupus Nephritis

General Therapy (Recommendation 10.2.1.1). Every patient with LN should be started and remain on hydroxychloroquine. Hydroxychloroquine has been shown to increase rates of complete remission, lower the incidence of flares, and reduce progression to ESKD.[93] Additional reported benefits include lower incidence of cardiovascular and thrombotic events in patients with anti-phospholipid antibodies,[94] improved lipid profiles,[95] and better preservation of bone health.[96] At weight based recommended doses (5 mg/kg), benefits clearly outweigh risk. Doses though should be decreased by 25% in those with a GFR $<$ 30 ml/min.

The guidelines also detailed recommendations for risk attenuation strategies spanning infection prevention to bone health, all critical in patients on prolonged courses of immunosuppression, and at times neglected. Proteinuria reduction using RAAS blockade, BP control, and avoiding a high-sodium diet was emphasized. Presently, the role of SGLT2 inhibitors to prevent renal progression is unclear, but is reasonable to consider in those on stable maintenance immunosuppression who are at less risk for AKI, pending further studies.[97]

Proliferative Lupus Nephritis (Recommendation 10.2.3.1.1 and Practice Point 10.2.3.1.1). The 2023 guidelines suggested that patients with Class III or IV LN with or without a membranous component can be treated with glucocorticoids plus one of the four following regimens as induction therapy, providing individualized treatment options: (1) MPAA, (2) low-dose intravenous cyclophosphamide, (3) belimumab and either MPAA or low-dose intravenous cyclophosphamide, or (4) MPAA and a CNI when kidney function is not severely impaired.

Although the clinical trials introduced belimumab and CNIs immediately at induction, the optimal timing of initiation is still debated. Post hoc studies have also highlighted that belimumab may not be effective in nephrotic patients or those with class 5 disease.[98] Furthermore, some patients may not require these add-on therapies to achieve complete

remission, thereby exposing them to possible medication side effects. One alternative to adding on the new therapies to standard of care at induction is to consider triple therapy in the presence of clinical risk factors for poor kidney outcomes (eg, African or Hispanic ancestry, decreased eGFR, relapsing disease, or high-grade proteinuria). If add-on therapy is not started upfront, early assessment of treatment response at two to three months should be pursued to reassess the decision.[99]

This add-on approach to therapy, however, is complicated by the Canadian funding structure and drug availability. Criteria for the use of belimumab, for example, directly mirror the inclusion criteria of the clinical trial. It is recommended that belimumab only be used within 60 days of initiating induction therapy even though other patient populations, such as those with relapsing disease could benefit from it as a steroid-sparing agent. Furthermore, it is only funded for one year thereafter, requiring yearly review by the funding agency to determine whether treatment can be continued, which is not aligned with the recommendation for 2.5 years of induction therapy.

Also contrary to the guidelines, voclosporin is not presently available in Canada, and therefore, cannot be used as first-line therapy. The benefits of voclosporin include no requirement for drug monitoring, no interaction with MPAA and less metabolic and electrolyte impacts. Tacrolimus and cyclosporine mandate drug levels, which are not universally reimbursed across Canada. Furthermore, some provinces also have restrictions on available CNI options. In Ontario, for example, cyclosporine is funded as first-line therapy. Through inhibition of enterohepatic recirculation, cyclosporine can reduce MPAA levels by 40%, which can result in undertreatment of severe disease.[100] Monitoring of MPAA levels is also typically not available in Canada potentially having a significant impact on patient outcomes. Therefore where available, tacrolimus is preferred pending approval of voclosporin. More recently, the phase 3 REGENCY trial investigated the addition of obinutuzumab to MMF versus placebo for patients with proliferative LN.[101] A greater rate of complete renal response was seen in the obinutuzumab group versus placebo (46.4% vs 33.1%). Presently, Health Canada approval is pending.

Canadian physicians are also reminded to use reduced-dose glucocorticoid regimens for initial treatment of LN. The AURA-LV trial involved participants receiving prednisone 0.4 mg/kg/day with a taper over three months to 2.5 mg/day.[102] This has led to an update for both KDIGO and the European League Against Rheumatism (EULAR) guidelines on corticosteroid dosing,[99] mirroring recommendations for other glomerular diseases wherein prolonged courses of high-dose steroids result in excessive risk. Although steroid pulses remain appropriate for patients presenting acutely with aggressive disease, subsequent oral steroid doses have been lowered and courses abbreviated.

Chapter 11: Anti-Glomerular Basement Membrane Disease

Treatment (Recommendation 11.2.1; Practice Points 11.2.1, 11.2.6, and 11.2.7). Anti-glomerular basement membrane (GBM) disease is rare, limiting advances in the diagnosis and treatment with recommendations largely based on observational data compared with historical controls. As anti-GBM antibodies are pathogenic, treatment should begin even before kidney biopsy to limit renal damage. The turnaround time for serum anti-GBM titres is particularly important as this prompts referral to Canadian centers with plasmapheresis. Although this has become a standard test in most larger centers, access and turnaround time remain significant issues in smaller centers. Furthermore, plasmapheresis is a geographically constrained resource due to its specialized nature, adding an additional barrier to expedited treatment of this potentially fatal disease.

In addition to plasmapheresis, the mainstay of management for anti-GBM disease remains glucocorticoids and cyclophosphamide. Although rituximab instead of cyclophosphamide has been described, its use should be reserved for those with refractory anti-GBM disease ($<$10% of cases) given the low quality of evidence.[103-105] However, in patients who decline treatment with cyclophosphamide or wherein there is a contraindication (eg, due to fertility concerns), rituximab in conjunction with corticosteroids and plasmapheresis can be offered. Alternatives to plasmapheresis, such as imlifidase, an IgG-degrading endopeptidase able to clear anti-GBM antibodies from the circulation, may help reduce barriers to plasmapheresis in the future.[106]

Not present in the 2012 guidelines were recommendations with respect to the futility of treatment when there is advanced glomerulosclerosis. The 2021 guidelines note that the risks associated with immunosuppression may outweigh the benefit in those without pulmonary hemorrhage on dialysis at presentation with 100% crescents or $>$50% global glomerulosclerosis. Other histological features consistent with severe scarring such as interstitial fibrosis and tubular atrophy are not considered. In a study of 174 patients with anti-GBM disease, the renal risk score originally developed for ANCA-associated vasculitis was applied to predict kidney outcomes.[107] The study demonstrated that stratifying patients according to two key factors, the need for renal replacement therapy at diagnosis and the percentage of normal glomeruli in kidney biopsy (using a 10% cutoff), provided superior outcome prediction, creating four distinct risk groups with 36-month renal survival rates ranging from 96.4% (best prognosis: no dialysis needed, $\geq$10% normal glomeruli) to 14.1% (worst prognosis: dialysis needed, $<$10% normal glomeruli). As the quality of evidence supporting this recommendation is very low, a shared decision-making approach is necessary. Furthermore, plans for future kidney transplantation may also guide immunosuppressive therapies, as the

recurrence rate is up to 50% in those with detectable anti-GBM antibodies compared with very low rates (<3%) in those with undetectable antibody titers at the time of transplantation.[108] With the evolution of glomerular disease registries, higher-quality risk estimation for both the prognosis of anti-GBM disease and the associated harms of treatment may help clinical decision-making even in the absence of further trials.

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Supplemental Material

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