KDIGO 2021 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF GLOMERULAR DISEASES

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KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases

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Reference keys

NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

Within each recommendation, the strength of recommendation is indicated as **Level 1** or **Level 2**, and the quality of the supporting evidence is shown as **A**, **B**, **C**, or **D**.

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

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

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health. CKD is classified based on Cause, GFR category (G1–G5), and Albuminuria category (A1–A3), abbreviated as CGA.

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (ml/min/1.73 m²) Description and range			Persistent albuminuria categories Description and range		
			A1	A2	A3
			Normal to mildly increased	Moderately increased	Severely increased
			< 30 mg/g < 3 mg/mmol	30–300 mg/g 3–30 mg/mmol	> 300 mg/g > 30 mg/mmol
G1	Normal or high	≥ 90			
G2	Mildly decreased	60–89			
G3a	Mildly to moderately decreased	45–59			
G3b	Moderately to severely decreased	30–44			
G4	Severely decreased	15–29			
G5	Kidney failure	< 15			

Green, low risk (if no other markers of kidney disease, no CKD); yellow, moderately increased risk; orange, high risk; red, very high risk.
GFR, glomerular filtration rate

CONVERSION FACTORS OF CONVENTIONAL UNITS TO SI UNITS

	Conventional unit	Conversion factor	SI unit
Albumin	g/dl	10	g/l
Creatinine	mg/dl	88.4	μmol/l
Creatinine clearance	ml/min	0.01667	ml/s
Cyclosporine	ng/ml	0.832	nmol/l
Mycophenolic acid	μg/ml	3.12	μmol/l
Protein-creatinine ratio	mg/g	0.113	mg/mmol
Tacrolimus	ng/ml	1.24	nmol/l

Note: Conventional unit × conversion factor = SI unit.

RELATIONSHIP AMONG CATEGORIES FOR ALBUMINURIA AND PROTEINURIA

	Categories		
Measure	Normal to mildly increased (A1)	Moderately increased (A2)	Severely increased (A3)
AER (mg/d)	<30	30–300	>300
PER (mg/d)	<150	150–500	>500
ACR			
(mg/mmol)	<3	3–30	>30
(mg/g)	<30	30–300	>300
PCR			
(mg/mmol)	<15	15–50	>50
(mg/g)	<150	150–500	>500
Protein reagent strip	Negative to trace	Trace to +	+ or greater

Relationships among measurement methods within a category are not exact. For example, the relationships between AER and ACR and between PER and PCR are based on the assumption that average creatinine excretion rate is approximately 1.0 g/d or 10 mmol/d. The conversions are rounded for pragmatic reasons. (For an exact conversion from mg/g of creatinine to mg/mmol of creatinine, multiply by 0.113.) Creatinine excretion varies with age, sex, race and diet; therefore, the relationship among these categories is approximate only. The relationship between urine reagent strip results and other measures depends on urine concentration. ACR, albumin-to-creatinine ratio; AER, albumin excretion rate; PCR, protein-creatinine ratio; PER, protein excretion rate.

Abbreviations and acronyms

AAV	ANCA-associated vasculitis
ACEi	angiotensin-converting enzyme inhibitor(s)
ACR	albumin–creatinine ratio
ACT	artemisinin-based combination therapy
AFRAN	African Association of Nephrology
aHUS	atypical hemolytic uremic syndrome
AIDS	acquired immunodeficiency syndrome
AKI	acute kidney injury
ANCA	antineutrophil cytoplasmic antibody
aPLA	antiphospholipid antibodies
APS	antiphospholipid syndrome
ARB	angiotensin II receptor blocker
ART	antiretroviral therapy
ATE	arterial thromboembolism
AUC	area under the curve
BCG	bromocresol green
BCP	bromocresol purple
BMI	body mass index
BP	blood pressure
C3G	C3 glomerulopathy
C4G	C4 glomerulopathy
C3GN	C3 glomerulonephritis
CCB	calcium channel blocker
CFH	Complement Factor H
CFHR	Complement Factor H–related
CI	confidence interval
CKD	chronic kidney disease
CNI	calcineurin inhibitor
CrCl	creatinine clearance
CV	cardiovascular
DDD	dense deposit disease
DNA	deoxyribonucleic acid
DNAJB9	DnaJ homolog subfamily B member 9
DOAC	direct oral anticoagulant
DRI	direct renin inhibitor
dsDNA	double-stranded DNA
DVT	deep vein thrombosis
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
ERT	Evidence Review Team
ESKD	end-stage kidney disease
FAS	Full Age Spectrum
FDA	Food and Drug Administration
FR	frequently relapsing
FRNS	frequently relapsing nephrotic syndrome
FSGS	focal segmental glomerulosclerosis
FSGS-UC	FSGS of undetermined cause
G6PD	glucose-6-phosphate dehydrogenase
GBM	glomerular basement membrane
GFR	glomerular filtration rate
GN	glomerulonephritis
GPA	granulomatosis with polyangiitis
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIVAN	HIV-associated nephropathy
HR	hazard ratio
ICGN	immune complex–mediated glomerulonephritis
IFN	interferon
IgADIRGN	IgA-dominant infection-related GN
IgAN	immunoglobulin A nephropathy
IgAV	immunoglobulin A vasculitis
IgAVN	immunoglobulin A vasculitis–associated nephritis
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
ISN/RPS	International Society of Nephrology and the Renal Pathology Society
IOM	Institute of Medicine
IQR	interquartile range
i.v.	intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
LDL-C	low-density lipoprotein cholesterol
LN	lupus nephritis
MCD	minimal change disease
MD	mean difference
MDRD	Modification of Diet in Renal Disease
MPA	mycophenolic acid
MPAA	mycophenolic acid analogs
MMF	mycophenolate mofetil
MN	membranous nephropathy
MPGN	membranoproliferative glomerulonephritis
MPO	myeloperoxidase
MRA	mineralocorticoid receptor antagonist
mTOR	mammalian target of rapamycin
NCGN	necrotizing crescentic glomerulonephritis
NIH	National Institutes of Health, USA
NS	nephrotic syndrome
NSAIDS	nonsteroidal anti-inflammatory drugs
OR	odds ratio
PCR	protein–creatinine ratio
PE	pulmonary embolism
PER	protein excretion rate
PERR	primary efficacy renal response
PGNMID	proliferative GN with monoclonal Ig deposits
PICOM	Population, Intervention, Comparator, Outcome, Methods

PLA2R	M-type phospholipase A2 receptor
p.o.	oral
PPI	proton pump inhibitor(s)
PR3	proteinase 3
QMN	quartan malarial nephropathy
RAS	renin–angiotensin system
RASi	renin–angiotensin system inhibitor(s)
RBC	red blood cell
RCT	randomized controlled trial
RPGN	rapidly progressive glomerulonephritis
RR	relative risk
RVT	renal vein thrombosis
SCr	serum creatinine
SD	steroid-dependent
SLE	systemic lupus erythematosus
SMP	sodium mycophenolate
SoF	Summary of Findings
SRNS	steroid-resistant nephrotic syndrome
SSNS	steroid-sensitive nephrotic syndrome
TB	tuberculosis
THSD7A	thrombospondin type-1 domain-containing 7A
TMA	thrombotic microangiopathy
TMP-SMX	trimethoprim–sulfamethoxazole
TTP	thrombotic thrombocytopenic purpura
UK	United Kingdom
UPE	urine protein excretion
US	United States
VTE	venous thromboembolism
WHO	World Health Organization

Notice

SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINE

This Clinical Practice Guideline document is based upon literature searches last conducted in October 2018, supplemented with additional evidence through September 2019. The search was updated in June 2020. It is designed to assist decision-making. It is not intended to define a standard of care and should not be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians consider the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Healthcare professionals using these recommendations should decide how to apply them to their own clinical practice.

SECTION II: DISCLOSURE

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Foreword

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With the growing awareness that chronic kidney disease (CKD) is a major global health problem, Kidney Disease: Improving Global Outcomes (KDIGO) was established in 2003 with the stated mission "to improve the care and outcomes of patients with kidney disease worldwide through promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines."

Since 2003, KDIGO has developed a catalog of clinical practice guidelines informing the care of patients with, or at risk of developing, kidney diseases. Recently, KDIGO published one new guideline on Diabetes Management in CKD and updated their Management of Blood Pressure in CKD guideline. The last in the series is the update to the Management of Glomerular Diseases guideline. All 3 guidelines will be presented using a new guideline format.

Glomerular diseases, excluding diabetic nephropathy, account for about 25% of the cases of CKD worldwide. Given the magnitude of long-term morbidity from glomerular diseases, and in particular, their frequent manifestation in younger patients, it is critical that they be diagnosed efficiently, and that management is optimized to control disease and prevent progressive kidney disease.

KDIGO published its Clinical Practice Guideline for Glomerulonephritis (GN) in 2012. The guideline was derived from a significant effort by the Work Group to summarize recommendations for 12 distinct diseases based on evidence available through November 2011. Since that time, substantial new evidence has emerged with important implications for the recommendation statements made in this original guideline.

In 2017, KDIGO convened a Controversies Conference on Glomerular Diseases. The objective of the conference was to gather a global panel of multidisciplinary clinical and scientific experts to identify key issues relevant to the optimal management of primary and secondary glomerular disease. The goal was to determine best practice treatment and areas of uncertainties in the treatment of glomerular disease, review key relevant literature published since the KDIGO 2012 GN Guideline, identify topics or issues that warrant revisiting for future guideline updating, and outline research needed to improve GN management. The conclusions from this Controversies Conference were published in *Kidney International* last year.[1,2] Based on this conference, a guideline update was recommended.

In keeping with KDIGO's policy for transparency and rigorous public review during the guideline development process, the scope of the 2017 Controversies Conference was made available for open commenting prior to the conference. The guideline Work Group members carefully considered both the feedback received on the Scope of Work and the output of the conference. This guideline was made available for public review, too, and the Work Group has critically reviewed the public input and revised the guideline as appropriate for the final publication.

We thank Jürgen Floege, MD, and Brad H. Rovin, MD, for leading this important initiative, and we are especially grateful to all Work Group members who provided a considerable amount of their time and expertise to this endeavor. In addition, this Work Group was ably assisted by colleagues from the independent Evidence Review Team (ERT) led by Jonathan C. Craig, MBChB, DipCH, FRACP, M Med (Clin Epi), PhD, Martin Howell, PhD, and David J. Tunnicliffe, PhD, who made this guideline possible.

KDIGO recently appointed Marcello A. Tonelli, MD, SM, MSc, FRCPC as its first Guideline Methods Chair. He was tasked with improving KDIGO guideline methodology by reinforcing the linkage between the recommendations and the corresponding evidence, standardizing the guideline format, reducing unnecessary length, and strengthening the utility of the guideline for its users.

To meet these goals, Dr. Tonelli suggested KDIGO work with MAGICapp, a web-based publishing platform for evidence-based guidelines. The program uses a predefined format and allows for direct linkage of the evidence to the recommendation statement, and the generation of patient decision aids directly from the evidence syntheses used to support the guideline. In addition, he introduced the concept of practice points, a new form of guidance produced in addition to recommendations. When a systematic review was not done or was done but did not find sufficient evidence to warrant a recommendation, a practice point was used to provide guidance to clinicians. Practice points do not necessarily follow the same format as recommendations—for example, they may be formatted as tables, figures, or algorithms—and are not graded for strength or evidence quality.

With Dr. Tonelli's guidance and expertise, the use of MAGICapp, and the adoption of practice points, KDIGO has seen the update of the Glomerular Diseases Guideline develop into a highly useful document that is rich in guidance while maintaining the high-quality standards and rigor for which KDIGO is best known. The update to the KDIGO guideline format is discussed in greater detail below by Dr. Tonelli (Figure 1).

In summary, we are confident that this guideline will prove useful to clinicians treating people with glomerular disease throughout the world. Once again, we thank the Work Group Co-Chairs and members and all those who contributed to this very important KDIGO activity.

Michel Jadoul, MD
Wolfgang C. Winkelmayer, MD, ScD
KDIGO Co-Chairs

Updates to the KDIGO guideline format

KDIGO guidelines continue to use the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology, but we have strengthened the link between the recommendation statements and underlying evidence base.

Guidelines now include a mix of recommendations and "practice points" to help clinicians better evaluate and implement the guidance from the expert Work Group.

All recommendations follow a consistent and structured format and are similar in style to previous KDIGO recommendations.

Practice points are a new addition to KDIGO guidance, and may be formatted as a table, a figure, or an algorithm to make them easier to use in clinical practice.

Guidelines will be published in print form and posted online in MAGICapp; the online format will facilitate rapid updates as new evidence emerges.

Below are frequently asked questions outlining the rationale for this shift along with an example recommendation in the new format.

Practice Points are used when	Recommendations are provided when
• No systematic review was conducted	• Systematic review was conducted
• There is insufficient evidence	• Ample/significant evidence is available
• Evidence is inconclusive	• Evidence shows a clear preference for one action over the alternatives
• The alternative option is illogical	
• Guidance is discretionary for the physician	• Guidance is always actionable
• Consensus statements providing guidance are needed in the absence of evidence. Benefits and harms will not be explicitly discussed	• Consensus statements are supported with evidence and explicit discussion of their balance of benefits and harms, values and preferences is necessary
• Guidance does not require an explicit discussion of values and preferences or of resource considerations, although it is implied that these factors were considered	• Application of guidance requires explicit discussion of values and preferences or resource considerations
• The guidance may be more useful as a table, figure, or algorithm	• The guidance requires a more thorough explanation in text (i.e., rationale)

Information on Guideline Development Process

Who

- A Work Group of experts is convened to develop KDIGO guidelines based on evidence and clinical judgment.
- A designated Evidence Review Team systematically reviews and analyzes the evidence.
- The GRADE approach is used to analyze certainty in the evidence and strength of guideline recommendations.

Figure 1 | Updates to the KDIGO guideline format. CNI, calcineurin inhibitors; eGFR, estimated glomerular filtration rate; FAQ, frequently asked questions; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; KDIGO, Kidney Disease: Improving Global Outcomes; MN, membranous nephropathy, PLA2R, M-type phospholipase A2 receptor; RCT, randomized controlled trial. (Continued)

How

- Where the Work Group determines that the quality of evidence or strength/importance of the statement warrants a graded recommendation, the text will be organized into structured sections (see below).
- Strength, quality, and magnitude of evidence (published or empirical) will indicate grading of the recommendation.
- Where the Work Group judges that there is a lack of evidence or consensus-based clinical practice statements are more appropriate, they may choose to develop a practice point.

What are the structured sections that are included in a recommendation?

Following each recommendation, there is a short remark of one to two sentences **summarizing the most important factors** considered when making the recommendation statement.

Next, the **Key Information** write-up consists of five specific subsections representing factors that the Work Group considered both in developing and grading the recommendation. The sections are:

1. Balance of benefits and harms,
2. Quality of evidence,
3. Values and preferences,
4. Resource use and costs, and
5. Considerations for implementation.

The final section of the write-up is a **Rationale** section which serves two purposes. First, the rationale expands on the short remark that immediately follows the recommendation summarizing how the Work Group considered the five factors of the Key Information section when drafting the recommendation.

Second, the rationale may be used to describe any key differences between the current KDIGO recommendation and recommendations made in the previous guideline or by other guideline producers.

How should I use practice points when caring for my patients?

- As noted, practice points are consensus statements about a specific aspect of care, and supplement recommendations for which a larger quantity of evidence was identified.
- Note that practice points represent the expert judgment of the guideline Work Group, but may also be based on limited evidence.
- Unlike recommendations, practice points are not graded for strength of recommendation or quality of evidence.
- Users should consider the practice point as expert guidance, and use it as they see fit to inform the care of patients.

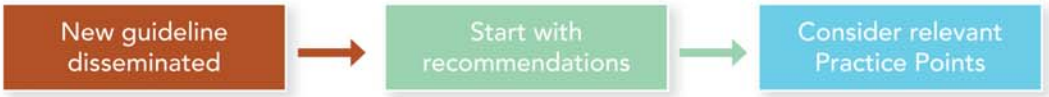


Figure 1 | (Continued)

What happened to the previous "ungraded statements"?

Ungraded statements were often useful to clinicians, but some were not strictly necessary, and their format (i.e., as imperative statements) was not suitable for every situation.

The added flexibility to present practice points in alternative formats such as tables, figures, and algorithms should make them more useful to clinicians. Since shorter documents are easier to use, we have tried to eliminate superfluous statements from the guideline and to retain only those that are necessary for providing patient care.

Why did KDIGO make these changes?

The main rationale for the changes was to improve rigor (better linkage of evidence to recommendations; standardized and consistent format), reduce unnecessary length, and enhance utility to practitioners (clinically useful guidance through practice points; visually appealing tables, figures and algorithms that are easier to use at point of care).

Example of new recommendation and practice point format

Treatment

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

Why was this formatted as a recommendation?

- Balance of benefits and harms (all based on published, scientific studies):
  - Benefits: Prevention of progressive kidney failure, complete and partial remission, reduction in the complications and risk of nephrotic syndrome.
  - Harms: Severe short- and long-term side effects with alkylating agents.
- Quality of evidence: This recommendation was based on clinical data extracted from RCTs and outcomes from observational studies were considered.
- Values and preferences: Most physicians and patients will prefer initial treatment with rituximab or CNI over treatment with cyclophosphamide and most well-informed patients with (very high risk of) kidney failure would choose to be treated with cyclophosphamide as compared to conservative treatment only.
- Resources and other costs: This recommendation is likely to be cost-effective to the extent that immunosuppressive treatment prevents progressive loss of kidney function and kidney failure. Cost-efficacy is less likely in patients with a predicted uneventful disease course.
- Considerations for implementation: The recommendation holds for all patients.

Practice Point 1. Immunosuppressive therapy is not required in patients with MN, proteinuria <3.5 g/d, serum albumin >30 g/l, and eGFR >60 ml/min per 1.73 m^2.

Why was this formatted as a practice point?

- Less robust data than recommendation; no systematic review was conducted.
- Few studies found; clinical experience and data from cohort studies show

Figure 1 | (Continued)

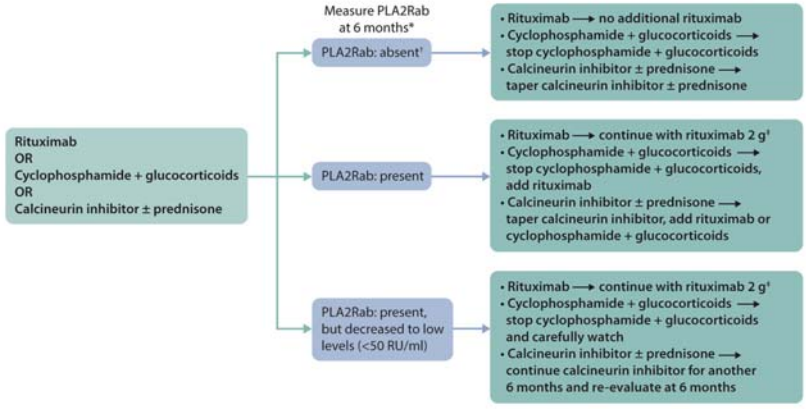
favorable kidney outcomes in patients with MN who are persistently non-nephrotic, despite the absence of immunosuppressive treatment. This evidence cannot be considered conclusive.

- Based on the limited evidence available, the Work Group decided to base their guidance on the observation that immunosuppressive therapy adds risks without potential benefits for this population.

Practice Points may also have accompanying algorithms to aid in implementation

For example:

Practice Point 2. Longitudinal monitoring of anti-PLA2R antibody levels at 6 months after start of therapy may be useful for evaluating treatment response in patients with membranous nephropathy, and can be used to guide adjustments to therapy.



Why was this formatted as a practice point?

- Limited evidence to support the guidance but monitoring anti-PLA2R antibody levels in these patients can be beneficial.
- No systematic review was conducted.
- The Work Group believes a graphic would be more useful to the reader since an algorithm offers a clearer visual presentation of the approach to monitoring than a series of statements.

Figure 1 | (Continued)

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Abstract

The *Kidney Disease: Improving Global Outcomes (KDIGO) 2021 Clinical Practice Guideline for the Management of Glomerular Diseases* is an update to the KDIGO 2012 guideline on the topic. The aim is to assist clinicians caring for individuals with glomerular disease, both adults and children. The scope includes various glomerular diseases, including IgA nephropathy (IgAN) and IgA vasculitis (IgAV), membranous nephropathy, nephrotic syndrome in children, minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), infection-related glomerulonephritis (GN), antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, lupus nephritis, and anti-glomerular basement membrane (anti-GBM) 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 with valuable infographics based on a rigorous formal systematic literature review. Another aim is to propose research recommendations for areas where there are gaps in knowledge. The guideline targets a broad audience of clinicians treating glomerular disease while being mindful of implications for policy and cost. Development of this guideline update followed an explicit process of evidence review. Treatment approaches and guideline recommendations are based on systematic reviews and evidence synthesis 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.

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

CITATION

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This guideline, including all statements and evidence, will also be published on MAGICapp (https://kdigo.org/guidelines/gd/). This online format will facilitate rapid updates as new evidence emerges.

Introduction

Glomerular disease, be it primary or secondary, occurring in the setting of systemic autoimmune diseases, infections, drugs, or malignancy, affects individuals of all ages. In most kidney failure registries, glomerular diseases account for about 20%–25% of the prevalent cases. However, in children, teenagers, and young adults, glomerular disease is one of the most common causes of irreversible kidney damage and, as such, is not only a source of personal suffering but also a major socioeconomic problem.

In 2012, KDIGO published its first-ever guideline on the management of glomerular diseases. In the 8 years that have passed, several major discoveries have been made that relate to our understanding of the pathogenesis, diagnosis, and therapy of glomerular disease. The unequivocal proof that primary membranous nephropathy is an autoimmune disease, the uncovering of the role of complement in glomerulopathies from dense deposit disease to ANCA-associated vasculitis, and the demonstration that targeting B cells is effective for treating diseases mediated by pathogenic (auto) antibodies are examples of some of the most important advances. Thus, an update of the 2012 guideline is appropriate and more urgent as ever.

In this guideline, we have largely maintained the topics covered in the first edition, focusing on the most common adult and pediatric glomerulonephritides (i.e., IgAN, membranous nephropathy, nephrotic syndrome including minimal change disease and FSGS, and infection-related glomerulonephritis [GN]), as well as systemic immunologic diseases (i.e., lupus nephritis, ANCA-associated vasculitis, and anti-GBM antibody GN). We have expanded the chapter on *General principles for the management of glomerular disease* that discusses supportive therapies appropriate for all glomerular diseases that supplement the more specific immunosuppressive treatments for each disease. Consistent with new findings on disease pathogenesis, the updated *Membranous nephropathy* chapter now provides an in-depth discussion of monitoring pathogenic autoantibodies in disease management. We have replaced the chapter heading on membranoproliferative GN (MPGN) with a new chapter entitled *Immunoglobulin- and complement-mediated glomerular diseases with an MPGN pattern of injury*. The chapter on *Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis* compares and contrasts B cell–targeted therapies with traditional cytotoxic drugs. The chapter on *Focal segmental glomerulosclerosis* (FSGS) has been reorganized to help clinicians more accurately differentiate between FSGS mediated by a soluble factor that may be amenable to immunosuppression, and conditions with FSGS-like histology, for which immunosuppression should not be used. *Nephrotic syndrome in children* takes advantage of several new trials that have defined duration of immunosuppression, and this chapter has been written to closely align with recommendations from the International Pediatric Nephrology Association (IPNA).

Although the present guideline is the most extensive KDIGO guideline to date, covering a large array of diseases, there are a few remaining glomerular diseases not addressed. Specifically, very rare GN types, such as fibrillary GN, immunotactoid GN, and IgM GN, for example, are not covered, related in part to space and resource restrictions, but particularly because of the lack of controlled trials to guide treatment. Our focus on immune-mediated glomerular disease has led to the exclusion of other important entities, such as amyloidosis and immunoglobulin deposition diseases, Alport syndrome, and thrombotic microangiopathies.

The guideline primarily considers questions of clinical management for which high-quality scientific evidence is available. It is not meant to replace textbooks. Rather, in collaboration with an Evidence Review Team, the Work Group reassessed questions posed in the 2012 guideline version and identified several issues that have remained clinically pressing and for which there is now at least some evidence base from which to make defensible recommendations. The chapter on *General principles for the management of glomerular disease* links this guideline with other KDIGO guidelines, the most important of which cover the management of hypertension associated with chronic kidney disease (KDIGO Guideline for the Management of Blood Pressure in CKD: https://kdigo.org/guidelines/blood-pressure-in-ckd/). At the end of each chapter, a research agenda has also been included and is intended to provide a roadmap for future investigation based on our comprehensive review of the current state of clinical evidence.

The majority of glomerular diseases are classified as rare diseases, and consequently, there is a paucity of randomized controlled trials on which to base firm recommendations. Given this situation, evidence-based recommendations have been supplemented with practice points, based on retrospective analyses, registry data, and consensus of expert opinion to fill in management gaps when there was insufficient evidence to make a formal recommendation. The reader will notice that most of this guideline is comprised of practice points. This should be taken as a challenge to the clinical investigators of the nephrology community to develop novel clinical trial designs, such as basket trials, umbrella trials, biomarker-driven trials, and n-of-1 trials, to implement the proposed research agenda in the absence of a sufficient number of patients to carry out traditional prospective randomized controlled trials.

As Co-Chairs, we are more than grateful to the Work Group, Evidence Review Team, and KDIGO staff for their outstanding contributions to the creation of this extensive

guideline. The Work Group was diverse, multinational, multidisciplinary, experienced, thoughtful, and dedicated, and volunteered countless hours of their time to developing this guideline. Finally, we owe a special debt of gratitude to the KDIGO Executive Committee, in particular Marcello Tonelli, who reviewed the guideline and made very helpful suggestions on methodological aspects of this project.

We hope that the guidance provided here will lead to better and more standardized care and improved outcomes for patients with immune-mediated glomerular diseases.

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Glomerular Disease Guideline Co-Chairs

Summary of recommendation statements and practice points

Chapter 1: General principles for the management of glomerular disease

1.1. Kidney biopsy

Practice Point 1.1.1: The kidney biopsy is the "gold standard" for the diagnostic evaluation of glomerular diseases. However, under some circumstances, treatment may proceed without a kidney biopsy confirmation of diagnosis (Figure 2).

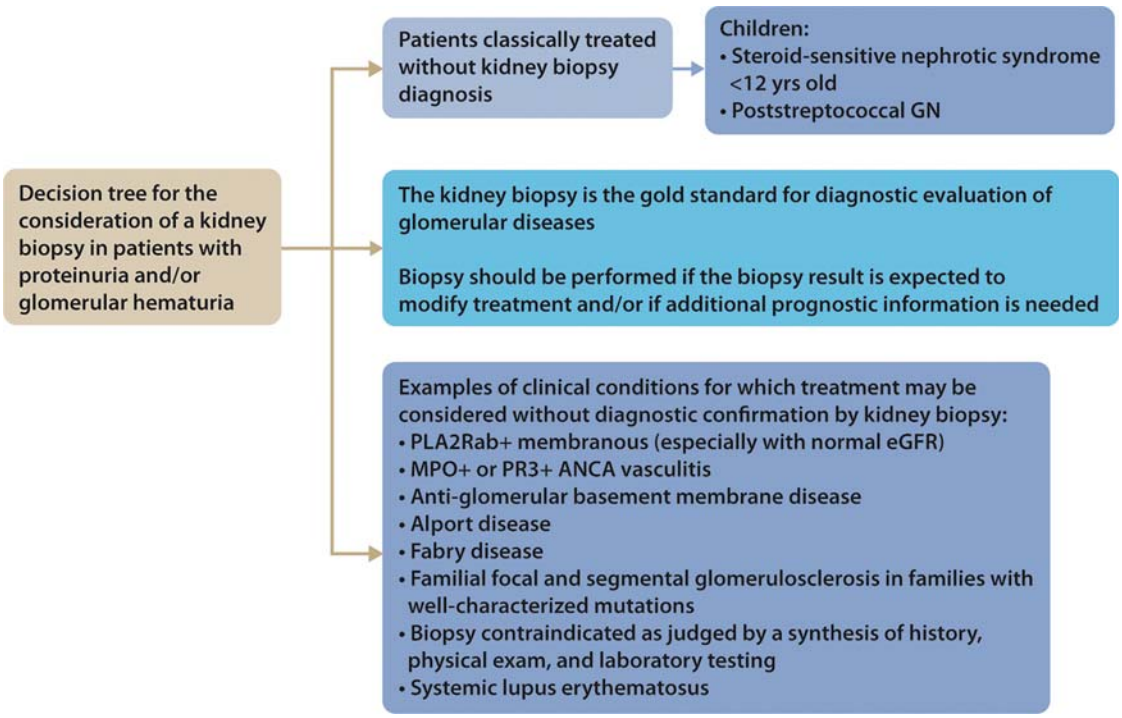

Figure 2 | Considerations for a kidney biopsy in patients with proteinuria and/or glomerular hematuria. ANCA, antineutrophil cytoplasmic antibody; eGFR, estimated glomerular filtration rate; GN, glomerulonephritis; MPO, myeloperoxidase; PLA2Rab+, M-type phospholipase A2 receptor antibody positive; PR3, proteinase 3.

Practice Point 1.1.2: The evaluation of kidney tissue should meet standards of biopsy adequacy (Figure 3).

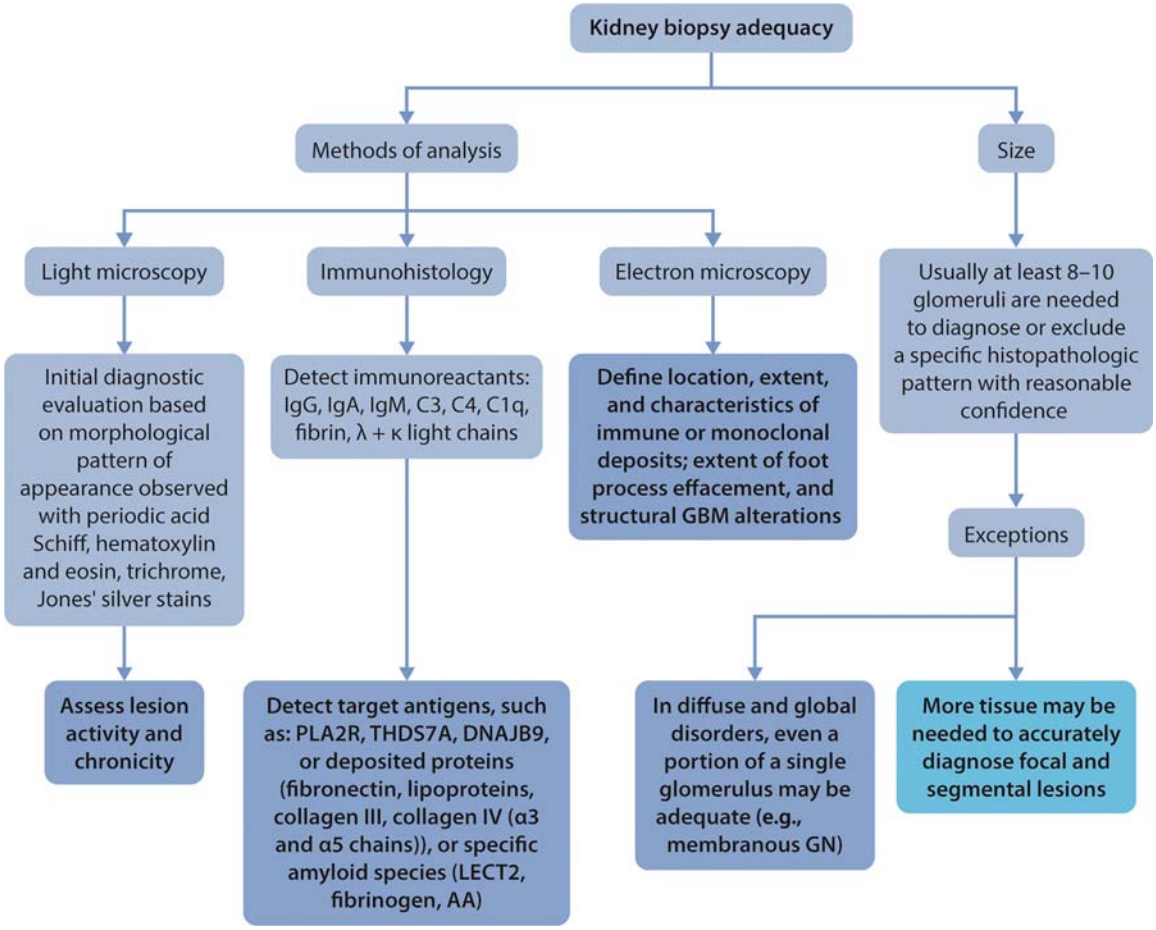

Figure 3 | Evaluation of kidney tissue. AA, amyloid A; GBM, glomerular basement membrane; DNAJB9, DnaJ homolog subfamily B member 9; GN, glomerulonephritis; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; LECT2, leukocyte cell-derived chemotaxin-2; PLA2R, M-type phospholipase A2 receptor; THDS7A, thrombospondin type-I domain-containing 7A.

Practice Point 1.1.3: Repeat kidney biopsy should be performed if the information will potentially alter the therapeutic plan or contribute to the estimation of prognosis.

1.2. Assessment of kidney function

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

Practice Point 1.2.2: For pediatrics, 24-hour urine collection is not ideal as it may not be accurate and is cumbersome to collect. Instead, monitor first morning protein–creatinine ratio (PCR).

Practice Point 1.2.3: Random "spot" urine collections for PCR are not ideal as there is variation over time in both protein and creatinine excretion.

Practice Point 1.2.4: First morning urine collections may underestimate 24-hour protein excretion in orthostatic proteinuria.

Practice Point 1.2.5: When feasible, a reasonable compromise is to collect an "intended" 24-hour urine sample and measure PCR in an aliquot of the collection.

Practice Point 1.2.6: There is no need to simultaneously and routinely quantify sodium excretion on each timed urinary collection, unless there is reason to suspect a failure to adhere to suggestions regarding dietary sodium restriction (Figure 5 and Practice Points 1.4.2 and 1.5.9).

Direct measures of kidney function	Indirect measures of kidney function: estimating equations	Limitations
• Creatinine clearance - 24 h urine creatinine	• eGFR	• No estimate of kidney function has been specifically validated for glomerular diseases and/or nephrotic syndrome • Ethnicity is often a confounding influence • In creatinine-based formulas, hypoalbuminemia may lead to overestimation of true GFR due to increased tubular creatinine secretion[8] • Glucocorticoids may increase serum cystatin C, potentially underestimating eGFR[9] • Low muscle mass overestimates eGFR using creatinine-based formulae[10] • AKI confounds all estimates, which are valid only in steady-state
• Measured GFR* - Inulin clearance (gold standard) - Radioisotopic plasma clearance[1] • ^{125}Iothalamate; ^{99m}Tc-DTPA; ^{51}Cr-EDTA - Non-radioisotopic plasma clearance • Iohexol[2]	**Adults** • Cockcroft–Gault[3] (140-age) (wt [kg]) x 0.85, if female/serum creatinine (mg/dl) x 72 • Modification of diet in renal disease (MDRD) equations[4] (not valid for eGFR >60 ml/min/1.73 m^2) - CKD-EPI creatinine equation (preferred) • Valid with eGFR >60 ml/min/1.73 m^2 - CKD-EPI-cystatin C equations[5] (valid for eGFR >60 ml/min/1.73 m^2) - Full Age Spectrum (FAS) equation[7] • Valid even in eGFR >60 ml/min/1.73 m^2 **Children** • Schwartz equation and its modifications[6] • Full-age spectrum (FAS) formulae[7]	

Figure 5 | Assessment of kidney function in glomerular disease. *In ml/min per 1.73 m^2. The correction coefficient for race in GFR estimating equations is controversial, and discussions about this topic are ongoing.[20] Please refer to the KDIGO CKD guideline for more information.[18] [1]Perrone *et al.*[13], [2]Gaspari *et al.*[12], [3]Cockcroft and Gault.[11], [4]Stevens *et al.*[16], [5]Stevens *et al.*[17], [6]Schwartz *et al.*[15], [7]Pottel *et al.*[14], [8]Branten *et al.*[19], [9]Zhai *et al.*[21], [10]Levey *et al.*[22] AKI, acute kidney injury; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; ^{51}Cr-EDTA, chromium-51 labeled ethylenediamine tetraacetic acid; eGFR, estimated glomerular filtration rate in ml/min per 1.73 m^2; ^{99m}Tc-DTPA, technetium-diethylenetriamine pentaacetic acid.

Practice Point 1.2.7: Quantify proteinuria in glomerular disease, as it has disease-specific relevance for prognosis and treatment decision-making. Qualitative assessment of proteinuria may be useful in selected instances.

Practice Point 1.2.8: In children, quantify proteinuria, but goals of treatment should not be different between disease etiologies. A PCR of <200 mg/g (<20 mg/mmol) or <8 mg/m^2/hour in a 24-hour urine should be the goal for any child with glomerular disease. Acceptance of a baseline higher than this should come only with kidney biopsy evidence of kidney scarring.

Practice Point 1.2.9: The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) estimated glomerular filtration rate (eGFR) creatinine equation is preferred in adult patients with glomerular disease, and the modified Schwartz equation is preferred in children. The Full Age Spectrum (FAS) equation may be used in both adults and children (Figure 5).

1.3. Evaluation of hematuria

Practice Point 1.3.1: Routine evaluation of urine sediment for erythrocyte morphology and the presence of red cell casts and/or acanthocytes is indicated in all forms of glomerular disease.

Practice Point 1.3.2: Monitoring of hematuria (magnitude and persistence) may have prognostic value in many forms of glomerular disease. This is particularly applicable to immunoglobulin A nephropathy (IgAN) and vasculitis (IgAV; Chapter 2).

1.4. Management of complications of glomerular disease (Figure 7)

Practice Point 1.4.1. Use loop diuretics as first-line therapy for treatment of edema in the nephrotic syndrome	• Twice daily dosing preferred over once daily dosing; daily dosing may be acceptable for reduced GFR • Increase dose of loop diuretic to cause clinically significant diuresis or until maximally effective dose has been reached • Switch to longer acting loop diuretic such as bumetanide or torsemide/torasemide if concerned about treatment failure with furosemide, or if concerned about oral drug bioavailability
Practice Point 1.4.2. Restrict dietary sodium intake	• Restrict dietary sodium to <2.0 g/d (<90 mmol/d)
Practice Point 1.4.3. Use loop diuretics with other mechanistically different diuretics as synergistic treatment of resistant edema in the nephrotic syndrome	• All thiazide-like diuretics in high doses are equally effective. None is preferred. • Thiazide diuretics, administered with an oral or i.v. loop diuretic, will impair distal sodium reabsorption and improve diuretic response • Amiloride may provide improvement in edema/hypertension, and counter hypokalemia from loop or thiazide diuretics • Acetazolamide may be helpful for the metabolic alkalosis of diuresis • Spironolactone may provide improvement in edema/hypertension, and counter hypokalemia from loop or thiazide diuretics
Practice Point 1.4.4. Monitor for adverse effects of diuretics	• Hyponatremia with thiazide diuretics • Hypokalemia with thiazide and loop diuretics • Impaired GFR • Volume depletion, especially in pediatric/elderly patients • Hyperkalemia with spironolactone and eplerenone especially if combined with RAS blockade
Practice Point 1.4.5. Strategies for diuretic-resistant patient	• Amiloride • Acetazolamide • i.v. loop diuretics (bolus or infusion) alone • i.v. loop diuretics in combination with i.v. albumin • Ultrafiltration • Hemodialysis • Amiloride may reduce potassium loss and improve diuresis. Acetazolamide may help to treat metabolic alkalosis but is a weak diuretic

Figure 7 | Edema management in NS. GFR, glomerular filtration rate; i.v., intravenous; NS, nephrotic syndrome; RAS, renin–angiotensin system.

1.5. Management of hypertension and proteinuria reduction in glomerular disease (Figure 8)

Practice Point 1.5.1.	Use an ACEi or ARB to maximally tolerated or allowed dose as first-line therapy in treating patients with both hypertension and proteinuria	• Do not stop ACEi or ARB with modest and stable increase in serum creatinine (up to 30%) • Stop ACEi or ARB if kidney function continues to worsen, and/or refractory hyperkalemia • Combinations of ACEi and ARB may be used in young adults without diabetes or cardiovascular disease, but benefits and safety are uncertain Caveat: do not start ACEi/ARB in patients who present with abrupt onset of NS. These drugs can cause AKI especially in patients with MCD
Practice Point 1.5.2.	Target systolic blood pressure in most adult patients is <120 mm Hg using standardized office BP measurement. Target 24 h mean arterial pressure in children is ≤50th percentile for age, sex, and height by ambulatory blood pressure monitoring	• Refer to KDIGO BP Guideline (https://kdigo.org/guidelines/blood-pressure-in-ckd/) • Formally speaking, SBP <120 mm Hg has not been validated in GN. In practicality, we are able to achieve an SBP of 120–130 mm Hg in most patients with glomerular disease
Practice Point 1.5.3.	Uptitrate an ACEi or ARB to maximally tolerated or allowed daily dose as first-line therapy in treating patients with GN and proteinuria alone	• Indicated for persistent proteinuria despite treatment of primary GN with immunosuppression (where indicated) • Avoid use of an ACEi or ARB if kidney function is rapidly changing
Practice Point 1.5.4.	Proteinuria goal is variable depending on primary disease process; typically, <1 g/d	• It may be reasonable to delay initiation of ACEi or ARB for patients without hypertension with podocytopathy (MCD, SSNS, or primary FSGS) expected to be rapidly responsive to immunosuppression • Proteinuria goal is disease-specific in adults with GN
Practice Point 1.5.5.	Monitor labs frequently if on ACEi or ARB	• Titration of ACEi or ARB may cause acute kidney injury or hyperkalemia
Practice Point 1.5.6.	Counsel patients to hold ACEi or ARB and diuretics when at risk for volume depletion	• Increased risk for acute kidney injury and hyperkalemia • Counsel patients according to level of education in a culturally sensitive manner • Consider transiently stopping RASi during sick days
Practice Point 1.5.7.	Use potassium-wasting diuretics and/or potassium-binding agents to reduce serum potassium to normal, in order to use RAS blocking medications for BP control and proteinuria reduction Treat metabolic acidosis (serum bicarbonate <22 mmol/l)	• Loop diuretics • Thiazide diuretics • Patiromer • Sodium zirconium cyclosilicate (each 10 g of sodium zirconium cyclosilicate contains 800 mg of sodium) • Supplement with oral sodium bicarbonate
Practice Point 1.5.8.	Employ lifestyle modifications in all GN patients as synergistic means for improving control of hypertension and proteinuria	• Restrict dietary sodium to <2.0 g/d (<90 mmol/d) • Normalize weight • Exercise regularly • Stop smoking
Practice Point 1.5.9.	Intensify dietary sodium restriction in those patients who fail to achieve proteinuria reductions, and who are on maximally tolerated medical therapy	• Restrict dietary sodium to <2.0 g/d (<90 mmol/d). Consider using mineralocorticoid receptor antagonists in refractory cases (monitor for hyperkalemia)

Figure 8 | Management of hypertension and proteinuria in glomerular disease. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; KDIGO, Kidney Disease: Improving Global Outcomes; MCD, minimal change disease; NS, nephrotic syndrome; RAS, renin–angiotensin system; RASi, renin–angiotensin system inhibitors; SBP, systolic blood pressure; SSNS, steroid-sensitive nephrotic syndrome.

1.6. Management of hyperlipidemia in glomerular disease (Figure 10)

Practice Point 1.6.1.	Treatment of hyperlipidemia may be considered in patients with the nephrotic syndrome, particularly for patients with other cardiovascular risk factors, including hypertension and diabetes	High quality data are lacking to guide treatment in these patients
Practice Point 1.6.2.	Use lifestyle modifications in all patients with persistent hyperlipidemia and glomerular disease: • Heart-healthy diet • Increased physical activity • Weight reduction • Smoking cessation	• Not well studied as primary means of reducing lipids in nephrotic syndrome • Can be used as primary therapy in low-risk individuals with mild to moderate hyperlipidemia • Additive to pharmacologic treatment of hyperlipidemia • Considered first-line treatment of hyperlipidemia in children • Consider a plant-based diet • Avoid red meat
Practice Point 1.6.3.	Consider starting a statin drug as first-line therapy for persistent hyperlipidemia in patients with glomerular disease: • Assess ASCVD risk based on LDL-C, Apo B, triglyceride and Lp (a) levels, age group, and ASCVD 'risk enhancers' • Align statin dosage intensity to ASCVD risk • Statins can be initiated in children aged > 8 years with concerning family history, extremely elevated LDL-C or Lp(a), in the context of informed shared decision-making and counselling with patient and family	• Reduced eGFR (<60 ml/min/1.73 m^2 not on dialysis) and albuminuria (ACR >30 mg/g) are independently associated with an elevated risk of ASCVD • ASCVD risk enhancers include chronic inflammatory conditions such as systemic lupus erythematosus, rheumatoid arthritis, history of preeclampsia, early menopause, South Asian ancestry, chronic kidney disease and human immunodeficiency virus/AIDS (accuracy of ASCVD risk estimators have not been well validated for adults with chronic inflammatory disorders or human immunodeficiency virus) • Adherence to changes in lifestyle and effects of LDL-C lowering medication should be assessed by measurement of fasting lipids and appropriate safety indicators 4–12 weeks after statin initiation/dose adjustment or inflammatory disease-modifying therapy/antiretroviral therapy, and every 3–12 months thereafter based on need to assess adherence or safety
Practice Point 1.6.4.	Consider initiation of non-statin therapy in those individuals who cannot tolerate a statin, or who are at high ASCVD risk and fail to achieve LDL-C or triglyceride goals despite maximally tolerated statin dose: • Bile acid sequestrants • Fibrates • Nicotinic acid • Ezetimibe • PCSK9 inhibitor • Lipid apheresis	• Bile acid sequestrants have a high rate of gastrointestinal side effects limiting their use • Bile acid sequestrants and fibrates have been shown in small studies to reduce serum cholesterol in nephrotic syndrome • Fibrates will increase serum creatinine level due to direct action on the kidney • Ezetimibe has limited vascular and clinical benefits, but is used in statin-intolerant patients as salvage therapy • Nicotinic acid and ezetimibe have not been studied in patients with nephrotic syndrome • PCSK9 inhibitors may be beneficial in nephrotic syndrome; trials ongoing

Figure 10 | Management of hyperlipidemia in glomerular disease. ACR, albumin–creatinine ratio; AIDS, acquired immunodeficiency syndrome; Apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; Lp, lipoprotein; PCSK9, proprotein convertase subtilisin/kexin type 9.

1.7. Hypercoagulability and thrombosis

Practice Point 1.7.1: Full anticoagulation is indicated for patients with thromboembolic events occurring in the context of nephrotic syndrome. Prophylactic anticoagulation should be employed in patients with nephrotic syndrome when the risk of thromboembolism exceeds the estimated patient-specific risks of an anticoagulation-induced serious bleeding event (Figure 11).

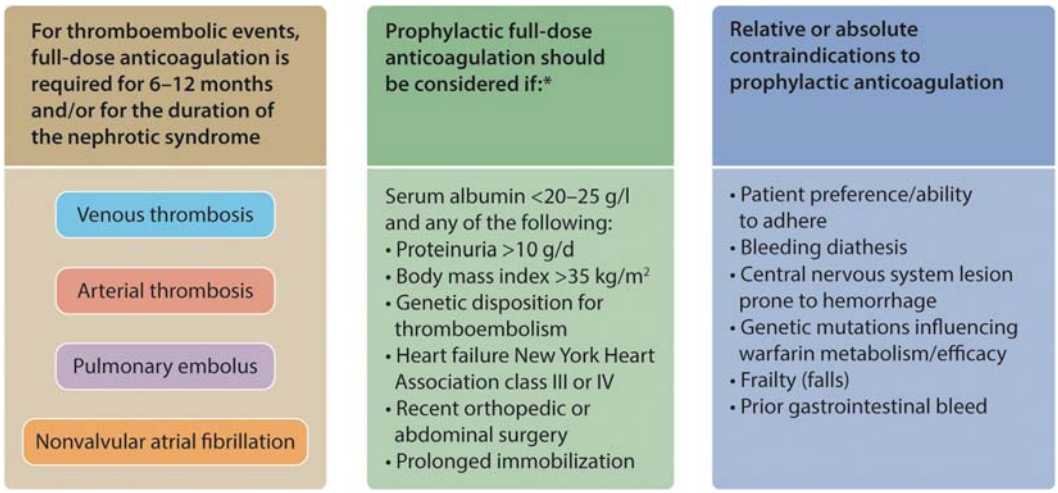

Figure 11 | Anticoagulation in NS. *Membranous GN carries a particularly high risk of thromboembolic events. NS, nephrotic syndrome.

Practice Point 1.7.2: Anticoagulant dosing considerations in patients with nephrotic syndrome (Figure 12 and Figure 13[44]).

Prophylactic anticoagulation during transient high-risk events

- Low-dose anticoagulation (e.g., unfractionated heparin 5000 U subcutaneous twice per day)
- Low–molecular-weight heparin: dose reduction may be advised with creatinine clearance <30 ml/min (unadjusted for body surface area); avoid in kidney failure

Full warfarin anticoagulation for thromboembolic events

- Intravenous heparin followed by bridging to warfarin is preferred
- Higher than usual heparin dosing may be required in nephrotic syndrome due to antithrombin III urinary loss
- Long-term experience with warfarin makes it the anticoagulant of choice until pharmacokinetic studies are performed with newer agents
- International normalized ratio should be monitored frequently, since warfarin–protein binding may fluctuate with changing serum albumin
- Target international normalized ratio is 2–3
- These recommendations are not supported by randomized controlled trials
- Be watchful of interactions of warfarin with other medications

Factor Xa inhibitors (Xai): not systematically studied in patients with nephrotic syndrome

- Dosing in the general population is adjusted according to serum creatinine, creatinine clearance (estimated by Cockcroft–Gault equation), age, and weight. Urinary clearance of the Xa inhibitors varies:
  - Apixaban, 27%
  - Edoxaban, 50%
  - Rivaroxaban, 66%
- The effects of hypoalbuminemia on drug dosing have not been studied, and these drugs are heavily albumin-bound, which is likely to substantially affect their half-lives
- Protein binding:
  - Apixaban, 92%–94%
  - Edoxaban, 55%
  - Rivaroxaban, 92%–95%
- Despite a few favorable case reports, the pharmacokinetic properties of these drugs require additional study for both safety and efficacy before they can be generally recommended in nephrotic patients

Direct thrombin inhibitors (DTI): not systematically studied in patients with nephrotic syndrome

- Dosing in the general population is adjusted according to creatinine clearance for dabigatran. No adjustment is required for argatroban. The urinary clearance of the DTI varies:
  - Argatroban, 22% (6% metabolites; 16% unchanged drug)
  - Dabigatran etexilate, 7%
- The effects of hypoalbuminemia on drug dosing have not been studied, and these drugs are modestly albumin-bound, which is likely to affect their half-lives
- Protein binding:
  - Argatroban, 54%
  - Dabigatran etexilate, 35%
- Despite improved safety in the general population, the pharmacokinetic properties of these drugs require additional study for both safety and efficacy before they can be recommended in nephrotic patients

Figure 12 | Anticoagulant dosing considerations in patients with NS. NS, nephrotic syndrome.

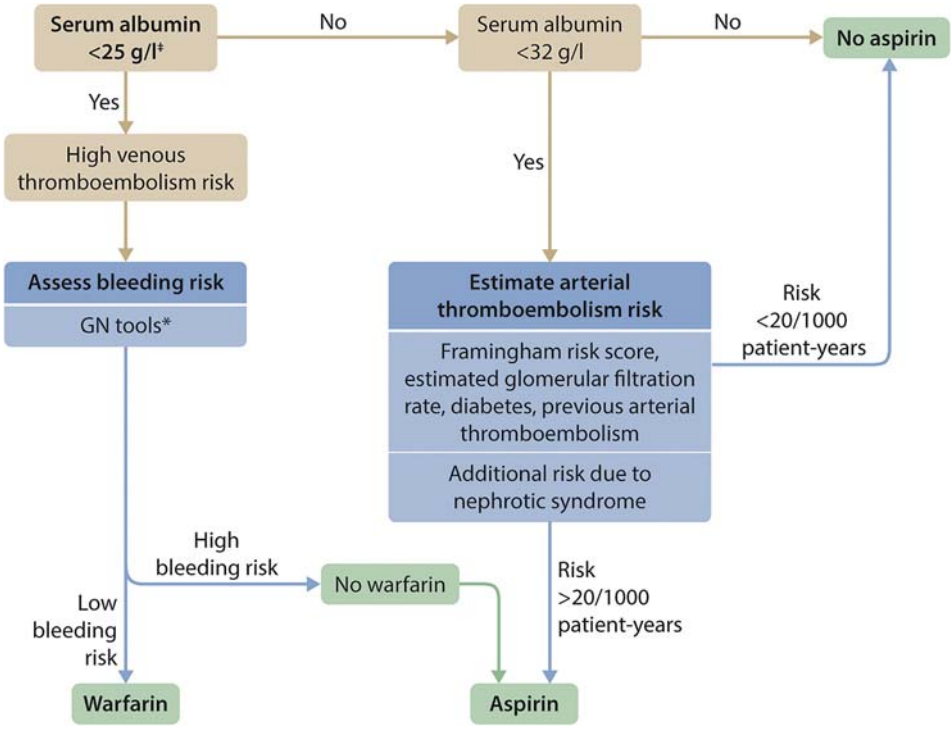

Figure 13 | Prophylactic anticoagulation in adults with GN/nephrotic syndrome. Reproduced from *Kidney International*, volume 89, issue 5, Hofstra JM, Wetzels JFM. Should aspirin be used for primary prevention of thrombotic events in patients with membranous nephropathy? Pages 981–983, Copyright © 2016, with permission from the International Society of Nephrology.[44] Note: This algorithm was developed for patients with membranous nephropathy. Its value is unknown for patients with nephrotic syndrome (NS) due to other underlying diseases. In pediatric patients with glomerulonephritis (GN), consider formal hematology consultation for evaluation of venous thromboembolism (VTE) and bleeding risk. Framingham Risk Score is not available for pediatric patients. ‡Albumin value of 25 g/l or 32 g/l (2.5 g/dl or 3.2 g/dl) is measured using bromocresol green (BCG). A value of 20 g/l or 30 g/l (2 g/dl or 3 g/dl) should be used when bromocresol purple (BCP) or immunoassays for serum albumin levels are used. *Please go to https://www.med.unc.edu/gntools/bleedrisk.html.

1.8. Risks of infection

Practice Point 1.8.1: Use pneumococcal vaccine in patients with glomerular disease and nephrotic syndrome, as well as patients with chronic kidney disease (CKD). Patients and household contacts should receive the influenza vaccine. Patients should receive herpes zoster vaccination (Shingrix).

Practice Point 1.8.2: Screen for tuberculosis (TB), hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and syphilis in clinically appropriate patients (Chapter 7).

Practice Point 1.8.3: Strongyloides superinfection should be considered in patients receiving immunosuppression who once resided in endemic tropical environments and who have eosinophilia and elevated serum immunoglobulin E (IgE) levels.

Practice Point 1.8.4: Prophylactic trimethoprim–sulfamethoxazole (TMP-SMX) should be considered in patients receiving high-dose prednisone or other immunosuppressive agents (rituximab, cyclophosphamide).

1.9. Outcome measures

Practice Point 1.9.1: Goals for proteinuria reduction with treatment vary among the various specific causes of glomerular disease.

Practice Point 1.9.2: A ≥40% decline in eGFR from baseline over a 2–3-year period has been suggested as a surrogate outcome measure for kidney failure.

1.10. Impact of age, sex, ethnicity, and genetic background

[No recommendations or practice points]

1.11. Genomics, transcriptomics, proteomics, metabolomics

[No recommendations or practice points]

1.12. Use of glucocorticoids and immunosuppressive therapy

[Please refer to individual chapters for further information.]

1.13. Pharmacologic aspects of immunosuppression (Figure 15)

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

1.14. Dietary management in glomerular disease (Figure 16)

Practice Point 1.14.1.	Restrict dietary sodium to reduce edema, control blood pressure, and control proteinuria	• Dietary sodium <2.0 g/d (<90 mmol/d)
Practice Point 1.14.2.	Restrict dietary protein based on degree of proteinuria	• Nephrotic-range proteinuria: 0.8–1 g/kg/d protein intake* • Add 1 g per g of protein losses (up to 5 g/d) • The safety of protein restriction in GN has not been established in children • Plant-based diets may be preferred
Practice Point 1.14.3.	Restrict dietary protein based on kidney function	• Estimated glomerular filtration rate <60 ml/min/1.73 m^2 with nephrotic-range proteinuria • Limit or target intake to 0.8 g/kg/d • Avoid <0.6 g/kg/d due to safety concerns and risk of malnutrition • Emphasis on vegetable (plant) sources of protein is appropriate
Practice Point 1.14.4.	Restrict caloric intake to achieve normal body mass index and limit central adiposity in order to reduce chronic kidney disease progression, development of kidney failure, cardiovascular events, and mortality	• Target caloric intake 35 kcal/kg/d • Estimated glomerular filtration rate <60 ml/min/1.73 m^2: 30–35 kcal/kg/d
Practice Point 1.14.5.	Restrict dietary fats in patients with elevated serum cholesterol to prevent cardiovascular complications	• Heart-healthy diet • Dietary fat <30% of total calories • Mono- or polyunsaturated fat 7%–10% of total calories

Figure 16 | Dietary suggestions in glomerular disease. *Ideal body weight. GN, glomerulonephritis.

1.15. Pregnancy and reproductive health in women with glomerular disease

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

1.16. Treatment costs and related issues

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

1.17. Goals of glomerular disease treatment

[No recommendations or practice points]

1.18. Post-transplantation GN

[Please refer to individual chapters for further information.]

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

Immunoglobulin A nephropathy

2.1 Diagnosis

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

- **IgAN can only be diagnosed with a kidney biopsy.**
- **Determine the MEST-C score (mesangial [M] and endocapillary [E] hypercellularity, segmental sclerosis [S], interstitial fibrosis/tubular atrophy [T], and crescents [C]) according to the revised Oxford Classification.[80]**
- **There are no validated *diagnostic* serum or urine biomarkers for IgAN.**
- **Assess all patients with IgAN for secondary causes.**

2.2 Prognosis

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

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

2.3 Treatment

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

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

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

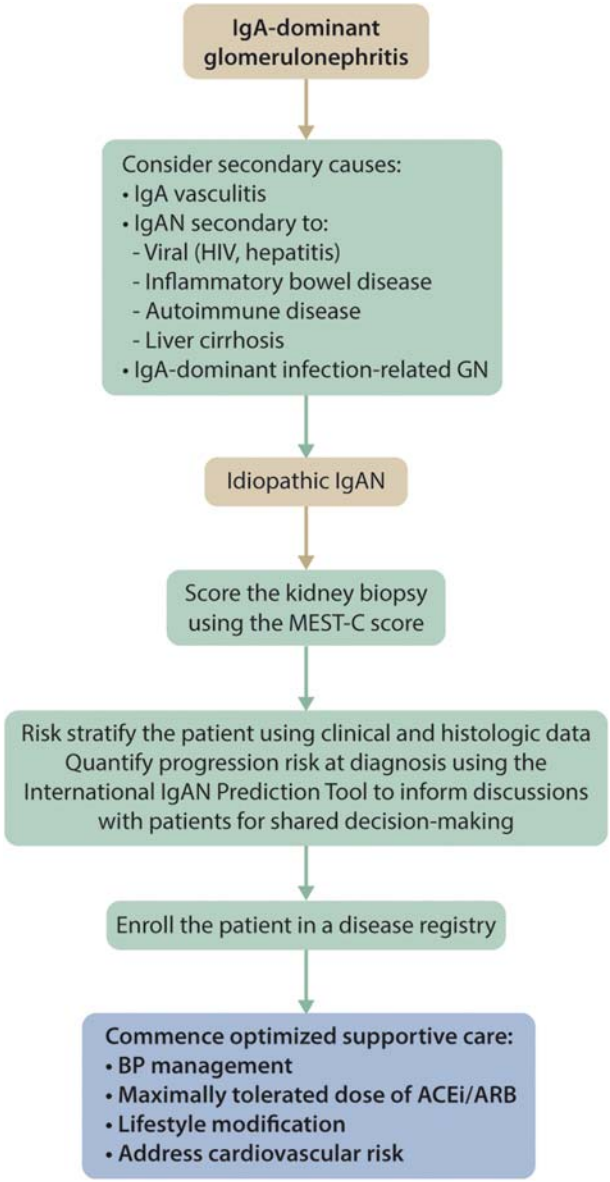

Figure 21 | Initial assessment and management of the patient with IgAN. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; GN, glomerulonephritis; HIV, human immunodeficiency virus; IgAN, immunoglobulin A nephropathy; MEST-C, mesangial (M) and endocapillary (E) hypercellularity, segmental sclerosis (S), interstitial fibrosis/tubular atrophy (T), and crescents (C).

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

Recommendation 2.3.2: We recommend that all patients with proteinuria >0.5 g/d, irrespective of whether they have hypertension, be treated with either an ACEi or ARB *(1B)*.

2.3.1 Patients with IgAN who are at high risk of progressive CKD despite maximal supportive care

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

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

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

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

Practice Point 2.3.1.3: Use of glucocorticoids in IgAN:

- **Clinical benefit of glucocorticoids in IgAN is not established and should be given with extreme caution or avoided entirely in situations listed in Figure 23:**

eGFR <30 ml/min/1.73 m^2 *
Diabetes
Obesity (BMI >30 kg/m^2)†
Latent infections (e.g., viral hepatitis, TB)
Secondary disease (e.g., cirrhosis)
Active peptic ulceration
Uncontrolled psychiatric illness
Severe osteoporosis

Figure 23 | Situations when glucocorticoids should be avoided, or administered with great caution. *The Therapeutic Evaluation of Steroids in IgA Nephropathy Global (TESTING)[109] study included patients with eGFR 20–30 ml/min per 1.73 m^2, but only 26 patients in total had this range of kidney function. Prespecified subgroup analyses for signals of efficacy and toxicity were underpowered and did not distinguish patients with eGFR <30 ml/min per 1.73 m^2. †High BMI in the TESTING study was not specifically considered an exclusion, but the mean BMI was <24 kg/m^2. BMI, body mass index; eGFR, estimated glomerular filtration rate; TB, tuberculosis.

- **There is insufficient evidence to support the use of the Oxford Classification MEST-C score in determining when any glucocorticoid therapy should be commenced.**
- **There are no data to support efficacy or reduced toxicity of alternate-day glucocorticoid regimens, or dose-reduced protocols.**
- **Where appropriate, treatment with glucocorticoid (prednisone equivalent ≥0.5 mg/kg/d) should incorporate prophylaxis against *Pneumocystis* pneumonia along with gastroprotection and bone protection, according to local guidelines.**

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

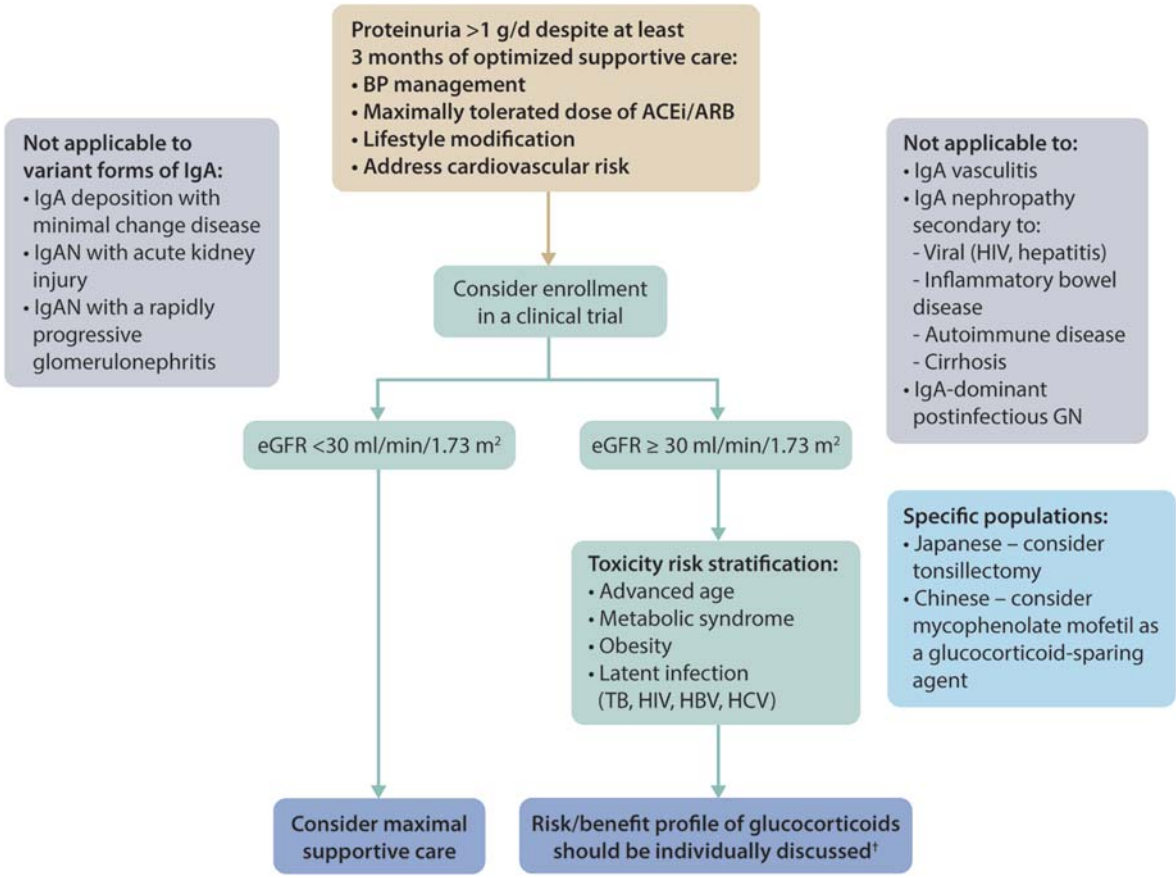

Figure 24 | Management of patients with IgAN who remain at high risk for progression after maximal supportive care. *IgAN with rapidly progressive glomerulonephritis is covered in Practice Point 2.4.3. †The TESTING study[109] shows early evidence of efficacy in patients who had marked proteinuria (2.4 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.

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

Agent	Suggested usage	Remarks
Antiplatelet agents	Not recommended	No documented evidence of efficacy
Anticoagulants	Not recommended	No documented evidence of efficacy
Azathioprine	Not recommended	No evidence for efficacy as monotherapy or when combined with glucocorticoids
Cyclophosphamide	Not recommended	Unless in the setting of rapidly progressive IgAN
Calcineurin inhibitors	Not recommended	No documented evidence of efficacy
Rituximab	Not recommended	No documented evidence of efficacy
Fish oil	Not recommended	Patients who wish to take fish oil should be advised of the dose and formulation used in the published clinical trials that reported efficacy.
Mycophenolate mofetil (MMF)	**Chinese patients** In those patients in whom glucocorticoids are being considered MMF may be used as a glucocorticoid-sparing agent	In a single RCT conducted in China, MMF with low-dose glucocorticoids was noninferior to standard-dose glucocorticoids for the treatment of incident IgAN presenting with proliferative histologic lesions (E or C lesions with or without necrosis) on kidney biopsy and proteinuria >1.0 g/d. There were significantly fewer glucocorticoid-related side effects in the combination-therapy arm.[1,5]
	Non-Chinese patients There is insufficient evidence to support the use of MMF	In the RCTs of MMF in non-Chinese patients there was no evidence for efficacy of MMF monotherapy.[2–5]
Hydroxychloroquine	**Chinese patients** In those patients who remain at high risk of progression in spite of optimized supportive care	In a small, short-term RCT conducted in China, hydroxychloroquine introduced to patients with proteinuria of 0.75–3.5 g/d despite optimized ACEi/ARB reduced proteinuria by 48% versus 10% in the placebo group at 6 months.[6]
	Non-Chinese patients There is insufficient evidence to support the use in those patients	Hydroxychloroquine has not been evaluated in non-Chinese patients.

Figure 25 | Other pharmacologic therapies evaluated in IgAN. [1]Hou *et al.*[115], [2]Hogg *et al.*[116], [3]Frisch *et al.*[117], [4]Maes *et al.*[118], [5]Vecchio *et al.*[119], [6]Liu *et al.*[120] ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; IgAN, immunoglobulin A nephropathy; MMF, mycophenolate mofetil; RCT, randomized controlled trial.

Practice Point 2.3.1.6: Tonsillectomy in IgAN:

- **Tonsillectomy should not be performed as a treatment for IgAN in Caucasian patients.**
- **Tonsillectomy is suggested in some national guidelines for the treatment of recurrent tonsillitis in patients with IgAN.**
- **Multiple studies from Japan have reported improved kidney survival and partial or complete remission of hematuria and proteinuria following tonsillectomy alone or with pulsed glucocorticoids (Figure 26; Supplementary Table S7[95,121–124]).**

	Japanese IgAN	Chinese IgAN	Caucasian IgAN
Clinical practice	Performed routinely (often with pulsed glucocorticoids)	Not routinely performed	Not performed
Remarks	Multiple cohort studies,[1–5] including a large retrospective study with propensity matching,[5] report improved kidney survival following tonsillectomy. A single RCT failed to show a difference in eGFR at 1 year comparing tonsillectomy vs. tonsillectomy and pulsed glucocorticoids, and no longer term data are available from this study.[6]	Inconsistent data from small retrospective cohort studies and a small single-center RCT	Very few data available in this population. Available data do not support the efficacy of tonsillectomy as a treatment for IgAN in Caucasian patients

Figure 26 | Regional use of tonsillectomy as a treatment for IgAN. [1]Yang *et al.*[124], [2]Kawasaki *et al.*[123], [3]Hotta *et al.*[121], [4]Reid *et al.*[95], [5]Hirano *et al.*[125], [6]Kawamura *et al.*[122] eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; RCT, randomized controlled trial.

2.4. Special situations

Practice Point 2.4.1: IgAN with nephrotic syndrome:

- **Rarely, patients with IgAN present with nephrotic syndrome (including edema and both hypoalbuminemia and nephrotic-range proteinuria >3.5 g/d).**
- **In these cases, mesangial IgA deposition can be associated with light and electron microscopy features otherwise consistent with a podocytopathy resembling MCD.**
- **It is unclear whether this is a specific podocytopathic variant of IgAN or the existence of MCD in a patient with IgAN.**
- **Patients with a kidney biopsy demonstrating mesangial IgA deposition and light and electron microscopy features otherwise consistent with MCD should be treated in accordance with the guidelines for MCD (Chapter 5).**
- **Patients with nephrotic syndrome whose kidney biopsy has coexistent features of a mesangioproliferative glomerulonephritis (MPGN) should be managed in the same way as those patients at high risk of progressive CKD despite maximal supportive care.**
- **Nephrotic-range proteinuria without nephrotic syndrome may also 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.**

Practice Point 2.4.2: IgAN with AKI:

- **AKI can occur in patients with IgAN in the context of severe visible hematuria, commonly in association with an upper respiratory tract infection. 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. Immediate management of AKI with visible hematuria should focus on supportive care for AKI.**
- **IgAN may also present with AKI either *de novo* or during its natural history due to an RPGN with extensive crescent formation, commonly in the absence of visible hematuria. In the absence of visible hematuria and when other causes of an RPGN (e.g., antineutrophil cytoplasmic antibody [ANCA]-associated vasculitis [AAV], anti-glomerular basement membrane [GBM] disease) and reversible causes (e.g., drug toxicity, common pre- and post-kidney causes) have been excluded, a kidney biopsy should be performed as soon as possible.**

Practice Point 2.4.3: IgAN with RPGN:

- **Rapidly progressive IgAN is defined as a ≥50% decline in eGFR over ≤3 months, where other causes of an RPGN (e.g., AAV, anti-GBM disease) and reversible causes (e.g., drug toxicity, common pre- and post-kidney causes) have been excluded.**
- **A kidney biopsy is essential in these cases and will commonly demonstrate mesangial and endocapillary hypercellularity, and a high proportion of glomeruli affected by crescents with areas of focal necrosis.**
- **The presence of crescents in a kidney biopsy in the absence of a concomitant change in serum creatinine (SCr) does not constitute rapidly progressive IgAN; however, these patients require close follow-up to ensure prompt detection of any GFR decline. If this occurs, a second kidney biopsy may be considered.**
- **Patients with rapidly progressive IgAN should be offered treatment with cyclophosphamide and glucocorticoids in accordance with the guidelines for AAV (Chapter 9).**

- Prophylactic measures that should accompany immunosuppression are discussed in Chapter 1.
- There is insufficient evidence to support the use of rituximab for the treatment of rapidly progressive IgAN.

Practice Point 2.4.4: IgAN and pregnancy planning:

- IgAN is a disease predominantly of young adults, and all women of childbearing potential should be offered preconception counseling when appropriate.
- Preconception counseling should include a discussion on cessation of renin–angiotensin system (RAS) blockade. Blood pressure control should be optimized with alternative antihypertensive medications prior to conception.
- In those women at high risk of progressive CKD (Recommendation 2.3.1.1) despite maximal supportive care, a trial of immunosuppression to optimize immunologic activity and reduce proteinuria prior to conception may be preferable to emergent initiation of immunosuppression during pregnancy.

Practice Point 2.4.5: IgAN in children:

General considerations

- For the purposes of this practice point, children are defined as those aged <18 years. It is acknowledged that postpubertal children in some respects may have a similar course and response to treatment as adults with IgAN, but there are insufficient data currently to recommend that they be managed as adults with IgAN.
- Visible hematuria is more frequent in children than in adults, and this may account for earlier diagnosis in children.[126]
- Children generally have higher eGFR, lower urine protein excretion, and more hematuria than adults at diagnosis.[127]

Kidney biopsy in children

- A kidney biopsy is usually performed at presentation of symptoms (hematuria, proteinuria, normal C3) in order to confirm the diagnosis (and rule out other diagnoses) and assess the degree of inflammation/presence of necrosis.
- Inflammation, mesangial, and endocapillary hypercellularity tend to be more prevalent in kidney biopsies of IgAN in children than in those of adults.[128–131]

Treatment

- There is strong evidence suggesting a benefit of RAS blockade in children.[132] All children with IgAN and proteinuria >200 mg/d or PCR >200 mg/g (>0.2 g/g [20 mg/mmol]) should receive ACEi or ARB blockade, advice on a low-sodium diet, and optimal lifestyle and blood pressure control (systolic blood pressure [SBP] <90th percentile for age, sex, and height).
- It is widely acknowledged that treatment of IgAN with immunosuppression differs between adults and children, and that in children, the use of immunosuppressants is more widespread, particularly the use of glucocorticoids. However, RCTs and specific expert consensus-driven indications are lacking.
- Evidence derived mostly from retrospective studies suggests that treatment with glucocorticoids (plus second-line immunosuppression) leads to improved kidney survival.[126,133]
- In children with proteinuria >1 g/d or PCR >1 g/g (100 mg/mmol) and/or mesangial hypercellularity, most pediatric nephrologists will treat with glucocorticoids in addition to RAS blockade from time of diagnosis. Duration of treatment is not established, but usually 4 weeks of 1–2 mg/kg/d of oral prednisolone (or equivalent) followed by alternate-day tapering over 4-6 months is employed. Regimens including intravenous methylprednisolone are also used.[127,128,130,134]
- Evidence for the use of non-glucocorticoid immunosuppressants in addition to glucocorticoids is scarce, but this approach may be considered in more severe cases.
- As for adults, IgAN with MCD may be found, and it should be treated as steroid-sensitive nephrotic syndrome (SSNS; Chapter 4).
- As in adults, children with rapidly progressive IgAN have a poor outcome, and despite limited evidence, this subgroup should be offered treatment with glucocorticoids (usually as methylprednisolone pulses) and cyclophosphamide.[128,130,135]

Follow-up

- Aim for proteinuria ≤200 mg/d (≤400 mg/1.73 m^2/d) or PCR ≤200 mg/g (≤0.2 g/g [≤20 mg/mmol]).
- Aim for blood pressure at SBP <90th percentile for age, sex, and height.
- Continue to follow patients even after complete remission, as they can relapse even after many years.[136]

Immunoglobulin A vasculitis

2.5 Diagnosis

Practice Point 2.5.1: Considerations for the diagnosis of immunoglobulin A vasculitis (IgAV):

- **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 based on the criteria described for children.[140,141]**
- **In adults with a vasculitic rash typical of IgAV, a kidney biopsy should be performed in the setting of features consistent with a persistent and/or significant nephritis, RPGN, proteinuria >1g/d, and/or impaired kidney function.**
- **Assess all adult patients with IgAV for secondary causes.**
- **Assess all adult patients with IgAV for malignancy, with age- and sex-appropriate screening tests.**

2.6 Prognosis

Practice Point 2.6.1: Considerations for the prognostication of IgAV:

- **Retrospective data from a limited number of small registries have identified uncontrolled hypertension and the amount of proteinuria at presentation, and hypertension and mean proteinuria during follow-up, as predictors of a poor kidney outcome in adults with IgAV.[142–144]**
- **The Oxford Classification has not been validated for IgAV.**
- **The International IgAN Prediction Tool[88] is not designed for prognostication in IgAV.**

2.7 Treatment

2.7.1 Prevention of nephritis in IgAV

Recommendation 2.7.1.1: We recommend not using glucocorticoids to prevent nephritis in patients with isolated extrarenal IgAV *(1B)*.

Practice Point 2.7.1.1: Considerations for the treatment of all patients with IgAV-associated nephritis (IgAVN) who do not have an RPGN:

- **Assess cardiovascular risk and commence appropriate interventions as necessary.**
- **Give lifestyle advice, including information on smoking cessation, weight control, and exercise, as appropriate.**
- **No specific dietary intervention has been shown to alter outcomes in IgAVN.**
- **Treat to nationally agreed-upon blood pressure targets. KDIGO suggests treating to an SBP target of <120 mm Hg measured using standardized office blood pressure measurement (Figure 8).**
- **Treat with maximally tolerated dose of ACEi or ARB if proteinuria >0.5 g/d.**
- **Offer participation in a clinical trial if one is available.**

2.7.2 Patients with IgAVN who are at high risk of progressive CKD despite maximal supportive care

Practice Point 2.7.2.1: Considerations for the treatment of patients with IgAVN who are at high risk of progressive CKD despite maximal supportive care:

- **There is insufficient evidence to support the use of the Oxford Classification MEST-C score in determining whether immunosuppression should be commenced in patients with IgAVN.**
- **The presence of crescents in the kidney biopsy is not in itself an automatic indication for commencement of immunosuppression.**
- **In all patients in whom immunosuppression is being considered, a detailed discussion of the risks and benefits of each drug should be undertaken with the patient with a recognition that adverse treatment effects are more likely in patients with an eGFR <50 ml/min per 1.73 m^2.**
- **In those patients who wish to try immunosuppressive therapy, treatment with glucocorticoids is as described above for IgAN.**

2.8 Special situations

Practice Point 2.8.1: IgAV with RPGN:

- **The potential risks and benefits of immunosuppression should be evaluated at the individual patient level and discussed with the patient.**
- **Patients agreeing to treatment should be treated in accordance with the guidelines for AAV (Chapter 9).**
- **IgAV with RPGN as well as other IgAVN may be associated with significant extrarenal involvement (pulmonary, gastrointestinal, and skin), which may dictate alternative immunosuppressive strategies.**
- **There are insufficient data to determine the efficacy of plasma exchange in IgAVN with RPGN. However, 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.[151] Clinicians are**

referred to the guidelines of the American Society for Apheresis regarding recommendations regarding plasma exchange for IgAV.[152]

2.8.1 IgAV-associated nephritis in children

Practice Point 2.8.1.1: For the purposes of this practice point, children are defined as those aged <18 years. It is acknowledged that post-pubertal children in some respects may have a similar course and response to treatment as adults with IgAN, but there are insufficient data currently to recommend that they be managed as adults with IgAN. Indications for management of IgAVN in children have recently been published as the result of a European consortium initiative.[140] Briefly:

- There are no data supporting the use of glucocorticoids to prevent nephritis in children with IgAV but mild or absent evidence of kidney involvement.[153,154]
- Children >10 years of age more often present with non-nephrotic-range proteinuria and impaired kidney function, and they may suffer more chronic histologic lesions with delay in biopsy and delay in treatment longer than 30 days.[155]
- The majority of children who will develop nephritis will do so within 3 months of presentation. Urinary monitoring is necessary for ≥6 months and optimally 12 months from initial presentation of systemic disease.
- Children with IgAVN and persistent proteinuria for >3 months should be treated with an ACEi or ARB. A pediatric nephrologist should be consulted.
- A kidney biopsy should be performed in children with nephrotic-range proteinuria, impaired GFR, or persistent moderate (>1 g/d) proteinuria.
- Oral prednisone/prednisolone or pulsed intravenous methylprednisolone should be used in children with mild or moderate IgAVN.
- Children with IgAVN with nephrotic syndrome and/or rapidly deteriorating kidney function are treated in the same way as those with rapidly progressive IgAN.

Chapter 3: Membranous nephropathy

3.1 Diagnosis

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

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

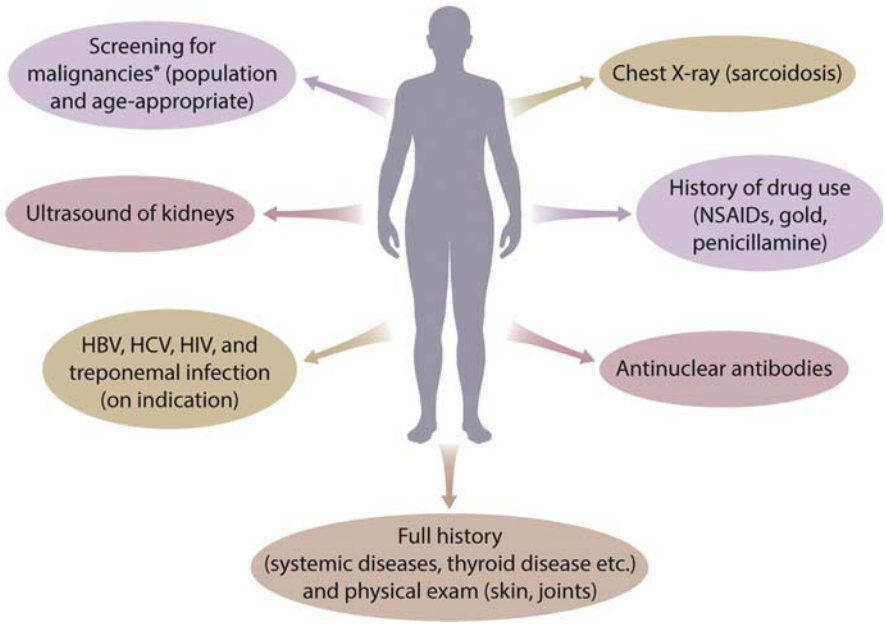

Figure 29 | Evaluation of patients with MN for associated conditions. Patient with MN should be evaluated for associated conditions, independent of the presence or absence of anti-PLA2R antibodies or anti-THSD7A antibodies. *Varies per country; the yield of cancer screening is not very high, especially in younger patients. Many centers will perform chest X-ray or computed tomography (CT) scan, look for iron deficiency, and require the patients to participate in the national screening program for breast and colon cancer; a prostate-specific antigen (PSA) test is done in adult males aged >50–60 years. HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NSAIDs, nonsteroidal anti-inflammatory drugs.

3.2 Prognosis

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

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 30 | 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 creatinine (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-to-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.

3.3 Treatment

Practice Point 3.3.1: Considerations for treatment of patients with primary MN:

- **All patients with primary MN and proteinuria should receive optimal supportive care.**
- **Immunosuppressive therapy should be restricted to patients considered at risk for progressive kidney injury (Figure 31).**

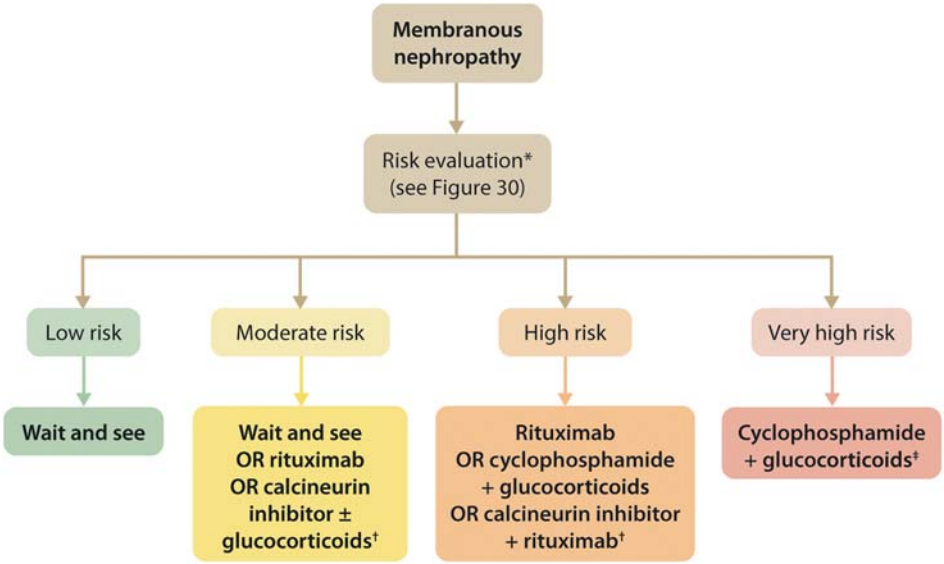

Figure 31 | Risk-based treatment of MN. *See Practice Point 3.2.1 and Figure 30 for a detailed description of risk evaluation. †Calcineurin inhibitor (CNI) monotherapy is considered less efficient. Treatment with CNI for 6–12 months with rapid withdrawal is associated with a high relapse rate. Still, 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.

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

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

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

Practice Point 3.3.4: Longitudinal monitoring of anti-PLA2R antibody levels at 6 months after start of therapy may be useful for evaluating treatment response in patients with MN, and can be used to guide adjustments to therapy (Figure 33[193]).

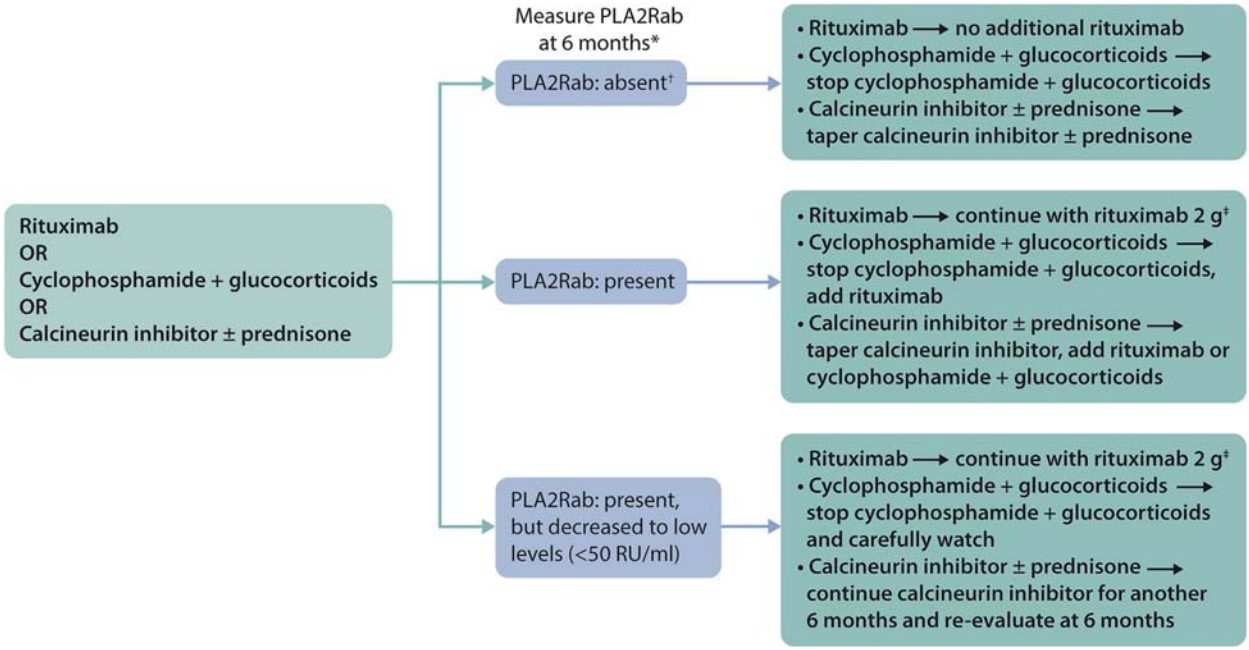

Figure 33 | Immunologic monitoring in MN after start of therapy. See text for current treatment schedules. Note: The cumulative dose of cyclophosphamide should not exceed 36 g in view of the risk of malignancy (Chapter 1). To stay on the safe side, we usually limit the cumulative dose to 25 g (in an 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. CNI 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.[182] CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; MN, membranous nephropathy; PLA2Rab, antibodies against the M-type phospholipase A2 receptor.

3.4 Special situations

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

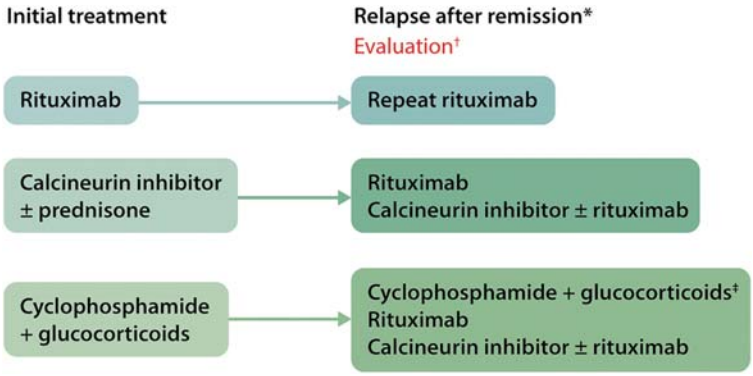

Figure 34 | Management of initial relapse after therapy in MN. Details of commonly used treatment regimens are shown in Figure 32. *The definition of relapse is variable. Some authors define relapse after remission as an increase in proteinuria >3.5 g/d in patients who developed a partial or complete remission. We suggest that the course of serum albumin and PCR should be used in the evaluation. If PCR decreased to values between 2–3.5 g/d without an increase of serum albumin to normal, the subsequent rise in PCR should be considered resistant disease rather than relapse after remission. In patients with a partial remission (characterized by normalization of serum albumin), a relapse should be defined by an increase of proteinuria paralleled by a decrease in serum albumin levels. †Immunologic monitoring is of particularly great value in these situations. If, in the period of "clinical remission," anti-PLA2R antibodies were still positive, this would be evidence for resistant disease. Therefore, in patients with positive anti-PLA2R antibodies, it is advised that anti-PLA2R antibodies be evaluated at the time of remission and relapse. The course of anti-PLA2R antibodies should precede the clinical course. In patients with very early relapse, it is important to consider reasons for the failure of the previous therapy (e.g., compliance, low drug levels, insufficient B cell depletion, presence of anti-rituximab antibodies). ‡Cyclophosphamide can be repeated; however, physicians must 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. MN, membranous nephropathy; PCR, protein-creatinine ratio; PLA2R, M-type phospholipase A2 receptor.

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

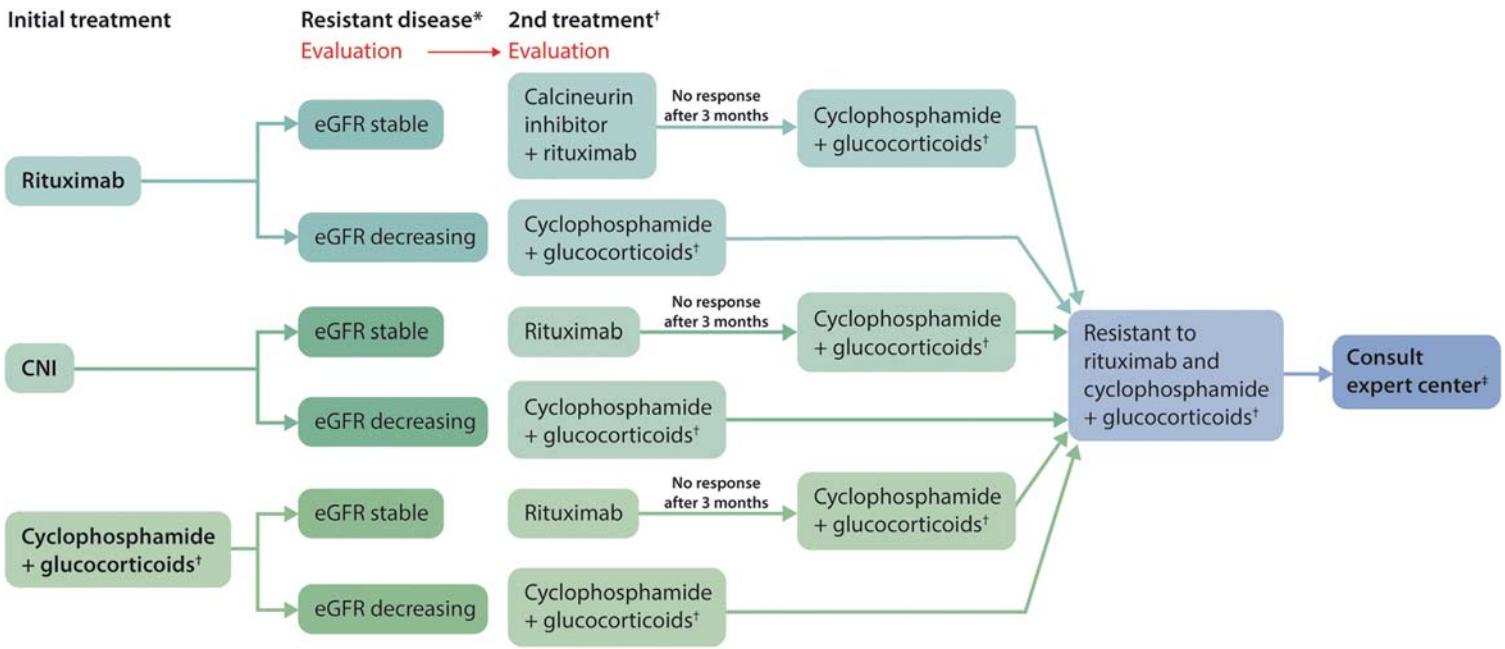

Figure 35 | Management of resistant disease in MN. Details of commonly used treatment regimens are shown in Figure 32. *Evaluation: In patients with resistant disease, compliance should be checked and efficacy monitored (e.g., B cell response, anti-rituximab antibodies, IgG levels, leukocytopenia during cyclophosphamide, CNI levels). Persistent proteinuria is not sufficient to define resistance. If proteinuria persists, while serum albumin has increased, one should consider secondary focal segmental glomerulosclerosis (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 glomerlosclerosis; MN, membranous nephropathy; PLA2R, M-type phospholipase A2 receptor.

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

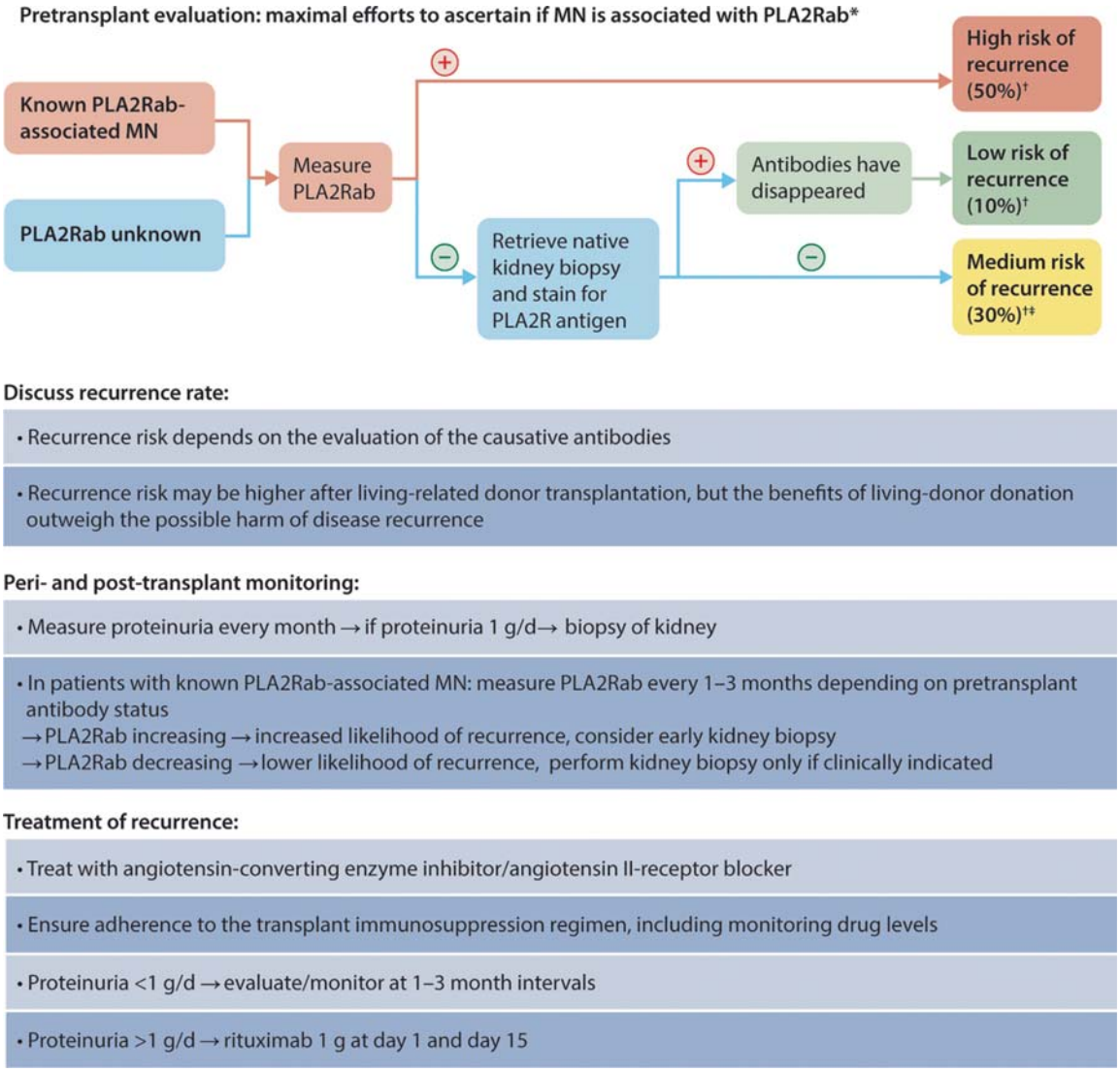

Figure 36 | Evaluation of a kidney transplant recipient with MN. *Limited data available, but the same algorithm likely applies to anti-THSD7A-associated MN. †Clinical recurrence. ‡This is the estimated average recurrence rate for patients with MN and unidentified antigen. We suggest that in these patients the recurrence rate can be better estimated by evaluating the patient for THSD7A antigen/antibodies. MN, membranous nephropathy; PLA2Rab, antibodies against the M-type phospholipase A2 receptor; THSD7A, thrombospondin type-1 domain-containing 7A.

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

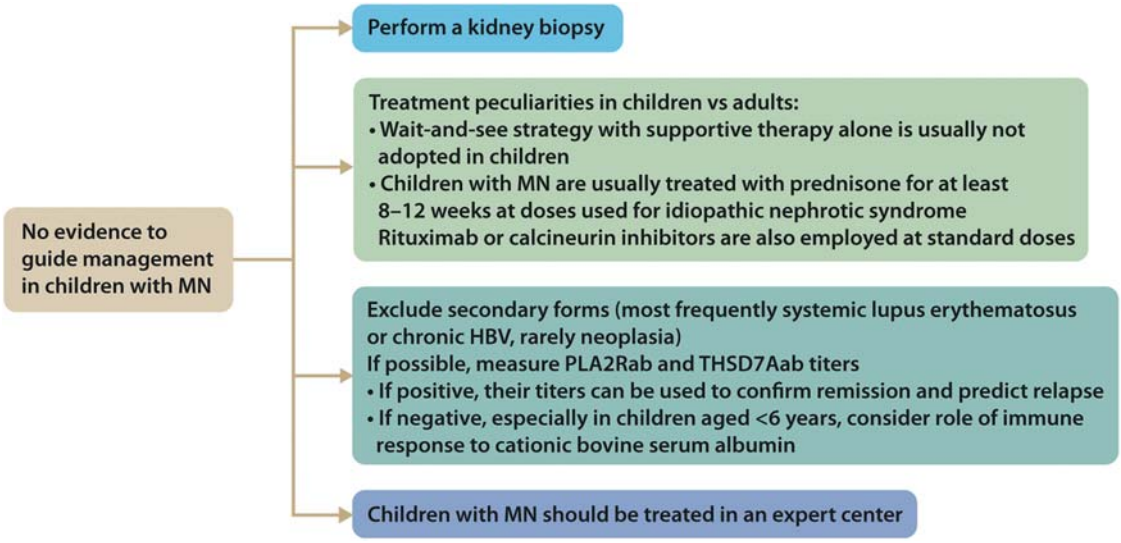

Figure 37 | Management of children with MN. HBV, hepatitis B virus; MN, membranous nephropathy; PLA2Rab, antibodies against the M-type phospholipase A2 receptor; THSD7Aab, antibodies against thrombospondin type-1 domain-containing 7A.

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

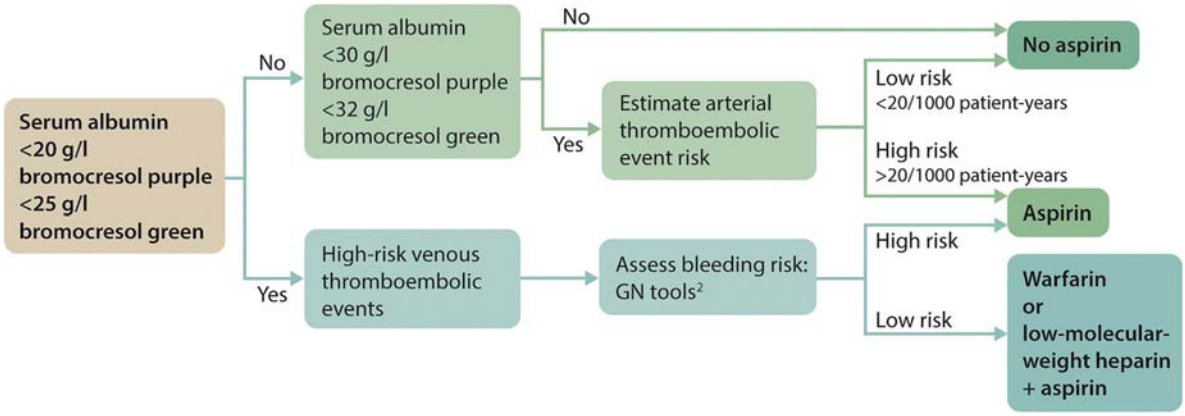

Figure 38 | Anticoagulant therapy in patients with MN. Adapted from *Kidney International*, volume 89, issue 5, Hofstra JM, Wetzels JFM. Should aspirin be used for primary prevention of thrombotic events in patients with membranous nephropathy? Pages 981–983, Copyright Copyright 2016, with permission from the International Society of Nephrology.[44] 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.[204] 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 (https://www.med.unc.edu/gntools/bleedrisk.html).
3. Patients with MN and nephrotic syndrome are also at risk of developing arterial thrombotic events. The risk of arterial thromboembolism (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.[44]
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 nephrotic syndrome 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.[205]
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.

Chapter 4: Nephrotic syndrome in children

4.1 Diagnosis

Practice Point 4.1.1: The definitions relating to nephrotic syndrome in children are based on the clinical characteristics outlined in Figure 39[206].

- **Nephrotic-range proteinuria:** First morning or *24-h PCR ≥2 g/g (or 200 mg/mmol or ≥3+ dipstick)
- **NS:** Nephrotic-range proteinuria and either hypoalbuminemia (serum albumin <30 g/l (3 g/dl)) or edema when albumin level is not available
- **Complete remission:** First morning or *24-h PCR ≤200 mg/g (or 20 mg/mmol or negative or trace dipstick) on three or more consecutive occasions
- **Partial remission:** First morning or *24-h PCR >200 mg/g but <2 g/g (or >20 and <200 mg/mmol) and, if available, serum albumin ≥30 g/l (3 g/dl)
- **Relapse:** Recurrence of nephrotic-range proteinuria. In children, relapse is commonly assessed by urine dipstick and is thus defined as dipstick ≥3+ for 3 consecutive days
- Typical dipstick results are expressed semiquantitatively as follows†, or as stated by manufacturer:
  Negative: 0 to <15 mg/dl
  Trace: 15 to <30 mg/dl
  1+: 30 to <100 mg/dl
  2+: 100 to <300 mg/dl
  3+: 300 to <1000 mg/dl
  4+: ≥1000 mg/dl

- **SSNS:** Complete remission after 4 weeks of prednisone or prednisolone at standard dose
- **Infrequent relapsing NS:** <2 relapses per 6 months within 6 months of disease onset or <4 relapses per 12 months in any subsequent 12-month period
- **Frequent relapsing NS:** ≥2 relapses per 6 months within 6 months of disease onset or ≥4 relapses per 12 months in any subsequent 12-month period
- **Steroid-dependent NS:** Two consecutive relapses during therapy with prednisone or prednisolone (either at full dose or during tapering) or within 15 days of prednisone or prednisolone discontinuation
- **SRNS:** Lack of complete remission at 4 weeks of therapy with daily prednisone or prednisolone at standard dose
- **Late responder:** Complete remission at 6 weeks.
- **Calcineurin inhibitor-responsive SRNS:** Partial remission after 6 months of treatment and/or complete remission after 12 months of treatment with a calcineurin inhibitor at adequate doses and/or levels
- **Calcineurin inhibitor-resistant SRNS:** Absence of partial remission after at least 6 months of treatment with a calcineurin inhibitor at adequate doses and/or levels
- **Multi-drug resistant SRNS:** Absence of complete remission after 12 months of treatment with 2 mechanistically distinct glucocorticoid-sparing agents at standard doses (see below)
- **Secondary SRNS:** A SSNS patient at disease onset who at a subsequent relapse fails to achieve remission after 4 weeks of therapy with daily prednisone or prednisolone at standard dose

Figure 39 | Definitions relating to NS in children aged 1–18 years. *To rule out orthostatic proteinuria, the first morning urine should be collected separately for assessment. †van der Watt *et al.*[206] NS, nephrotic syndrome; PCR, protein-creatinine ratio; SRNS, steroid-resistant nephrotic syndrome; SSNS, steroid-sensitive nephrotic syndrome.

4.2 Prognosis

Practice Point 4.2.1: The prognosis for childhood nephrotic syndrome is best predicted by the patient's response to initial treatment and frequency of relapse during the first year after treatment. Therefore, a kidney biopsy is not usually needed at initial presentation, and instead is reserved for children with resistance to therapy or an atypical clinical course.

4.3 Treatment

4.3.1 Initial treatment of NS in children

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

Practice Point 4.3.1.1: The standard dosing regimen for the initial treatment of nephrotic syndrome is daily oral prednisone/prednisolone 60 mg/m^2/d or 2 mg/kg/d (maximum 60 mg/d) for 4 weeks followed by alternate day prednisone/prednisolone, 40 mg/m^2, or 1.5 mg/kg (maximum of 50 mg) for other 4 weeks, or prednisone/prednisolone 60 mg/m^2/d (maximum 60 mg/d) for 6 weeks followed by alternate day prednisone/prednisolone, 40 mg/m^2, or 1.5 mg/kg (maximum of 50 mg), for other 6 weeks.

4.3.2 Prevention and treatment of relapses of NS in children

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

Practice Point 4.3.2.1: The initial approach to relapse should include oral prednisone/prednisolone as a single daily dose of 60 mg/m^2/d or 2 mg/kg/d (maximum 60 mg/d) until the child remits completely for ≥3 days.

Practice Point 4.3.2.2: After achieving complete remission, reduce oral prednisone/prednisolone to 40 mg/m^2 or 1.5 mg/kg (maximum 50 mg) on alternate days for ≥4 weeks.

Practice Point 4.3.2.3: For children with frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome without glucocorticoid toxicity, the same glucocorticoid regimen may be employed in subsequent relapses.

Practice Point 4.3.2.4: For children with frequently relapsing nephrotic syndrome without serious glucocorticoid-related adverse effects, low-dose alternate-day oral prednisone/prednisolone (optimally ≤0.5 mg/kg/d) can be prescribed to prevent relapse.

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

Practice Point 4.3.2.5: Patients should ideally be in remission with glucocorticoids prior to the initiation of glucocorticoid-sparing agents such as oral cyclophosphamide, levamisole, mycophenolate mofetil (MMF), rituximab, or calcineurin inhibitors (CNIs). Coadministration of glucocorticoids is recommended for ≥2 weeks following initiation of glucocorticoid-sparing treatment.

Practice Point 4.3.2.6: Choosing the most appropriate glucocorticoid-sparing agent from among oral cyclophosphamide, levamisole, MMF, rituximab, and CNI is a decision that requires careful consideration of specific patient-related issues such as resources, adherence, adverse effects, and patient preferences. Oral cyclophosphamide and levamisole may be preferable glucocorticoid-sparing therapies in frequently relapsing nephrotic syndrome. MMF, rituximab, CNIs, and to a lesser extent, oral cyclophosphamide may be preferable to glucocorticoid-sparing therapies in children with steroid-dependent nephrotic syndrome (Figure 41[178]).

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 41 | Glucocorticoid-sparing therapies in children with SSNS. *Gellermann *et al.*[178] †The CNI, while often used twice daily, may be dosed once a day, depending on individual formulations. In smaller children (<6 years of age), daily dose of cyclosporine can be divided into 3 doses (every 8 hour) to obtain steady hematic levels. 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.

Steroid-resistant nephrotic syndrome in children

4.4 Treatment

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

4.5 Special situations

Practice Point 4.5.1: Figure 43[301,302] outlines the general principles in children with nephrotic syndrome.

Indication for kidney biopsy*	• Children presenting with nephrotic syndrome ≥ 12 years of age • Steroid-resistant nephrotic syndrome or subsequent failure to respond to glucocorticoids in steroid-sensitive nephrotic syndrome (secondary steroid-sensitive nephrotic syndrome) • A high index of suspicion for a different underlying pathology (macroscopic hematuria, systemic symptoms of vasculitis, hypocomplementemia, etc.) • At onset, kidney failure not related to hypovolemia. Subsequently, decreasing kidney function in children receiving calcineurin inhibitors or prolonged exposure to calcineurin inhibitors (2 to 3 years)
Genetic testing	• Steroid-resistant nephrotic syndrome • Congenital and infantile forms of nephrotic syndrome (<1 year of age) • Nephrotic syndrome associated with syndromic features • Family history of steroid-resistant nephrotic syndrome or focal segmental glomerulosclerosis
Vitamin D/calcium	In patients with steroid-sensitive nephrotic syndrome and normal vitamin D levels, supplementation is not required. However, in frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome in children or in the presence of a known vitamin D deficiency, a reduction in bone mineral content can be prevented by oral supplementation with oral calcium and vitamin D.[1,2]
Gastroprotection	There is insufficient evidence of benefit to recommend prophylactic use of proton-pump inhibitors in children with nephrotic syndrome in the absence of risk factors for gastrotoxicity or of gastric symptoms.

Figure 43 | General principles in children with NS. *If there is an evident extrarenal cause for proteinuria (i.e., lymphoma, monoclonal antibody treatment in ulcerative colitis, human immunodeficiency virus), a kidney biopsy may not be warranted. NS, nephrotic syndrome. [1]Gulati *et al.*[301], [2]Gruppen *et al.*[302]

Chapter 5: Minimal change disease (MCD) in adults

5.1 Diagnosis

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

5.2 Prognosis

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

5.3 Treatment

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

Practice Point 5.3.1: Algorithm for the initial treatment of MCD in adults (Figure 44)

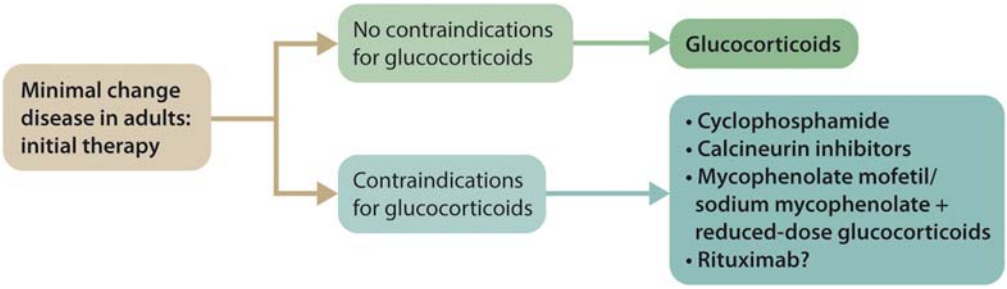

Figure 44 | Initial treatment of MCD in adults. The optimal glucocorticoid regimen is not well-defined; however, suggested doses are outlined in Figure 45. The choice of medication should be based on physician and patient preference. MCD, minimal change disease.

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

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

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

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

5.3.1 Treatment of relapses (Figure 46)

Complete remission
Reduction of proteinuria to <0.3 g/d or PCR <300 mg/g (or <30 mg/mmol), stable serum creatinine and serum albumin >3.5 g/dl (or 35 g/l)
Partial remission
Reduction of proteinuria to 0.3–3.5 g/d or PCR 300–3500 mg/g (or 30–350 mg/mmol) and a decrease >50% from baseline
Relapse
Proteinuria >3.5 g/d or PCR >3500 mg/g (or 350 mg/mmol) after complete remission has been achieved
Steroid-resistant MCD
Persistence of proteinuria >3.5 g/d or PCR >3500 mg/g (or 350 mg/mmol) with <50% reduction from baseline despite prednisone 1 mg/kg/d or 2 mg/kg every other day for >16 weeks
Frequently relapsing MCD
Two or more relapses per 6 months (or four or more relapses per 12 months)
Steroid-dependent MCD
Relapse occurring during, or within 2 weeks of completing glucocorticoid therapy

Figure 46 | Definition of remission, relapse, resistance, and dependence for MCD. MCD, minimal change disease; PCR, protein–creatinine ratio.

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

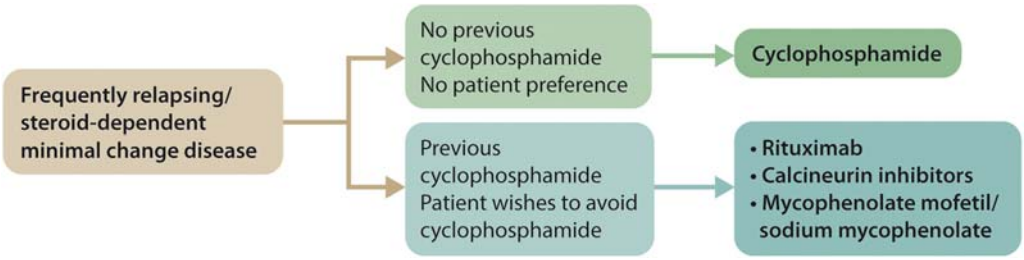

Figure 47 | Treatment of FR/SD MCD in adults. The choice of medication should be based on physician and patient preference. FR/SD, frequently relapsing/steroid-dependent.

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

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

Chapter 6: Focal segmental glomerulosclerosis (FSGS) in adults

6.1 Diagnosis

6.1.1 Differentiating between primary and secondary FSGS

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

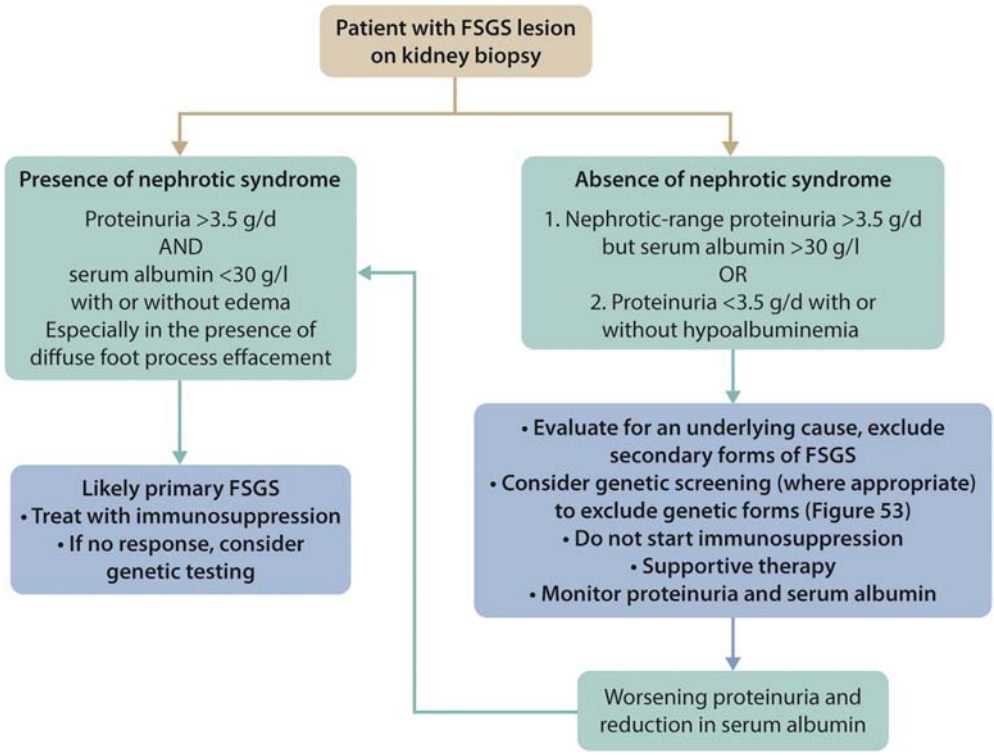

Figure 51 | Evaluation of a patient with FSGS lesion on the kidney biopsy and no evidence of other glomerular pathology. FSGS, focal segmental glomerulosclerosis.

Secondary to alterations of glomerular epithelial cells	
Viral infections	HIV (established) CMV (probably) Parvovirus B19, EBV, HCV (possibly) Hemophagocytic syndrome (possibly) SARS-COV-2 (with *APOL1* risk genotype)
Drug-induced	Direct-acting antiviral therapy mTOR inhibitors, CNIs Anthracyclines Heroin (adulterants) Lithium Interferon Anabolic steroids NSAIDs
Secondary to adaptive changes with glomerular hypertension	
Reduced nephron number	Reflux nephropathy Renal dysplasia Oligomeganephronia Sickle cell disease Age-related FSGS
Normal nephron number	Obesity-related glomerulopathy Primary glomerular diseases Systemic conditions, e.g., diabetic nephropathy, hypertensive nephrosclerosis

Figure 52 | Causes of secondary FSGS. *APOL1*, apolipoprotein L1; CMV, cytomegalovirus; CNI, calcineurin inhibitor; EBV, Epstein-Barr virus; FSGS, focal segmental glomerulosclerosis; HCV, hepatitis C virus; HIV, human immunodeficiency virus; mTOR, mammalian target of rapamycin; NSAID, nonsteroidal anti-inflammatory drug; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

6.1.2 Genetic testing

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

Genetic forms of FSGS	
Genetic mutations of podocyte and glomerular basement membrane proteins	• Familial • Sporadic • Syndromic
Considerations for genetic testing in adults with FSGS	
• When there is a strong family history and/or clinical features suggestive of a syndromal disease • Aiding in diagnosis, especially if the clinical features are not representative of a particular disease phenotype • Limiting immunosuppression exposure, especially in situations where patients appear to be resistant to treatment • Determining the risk of recurrent disease in kidney transplantation • Allowing for risk assessment in living-related kidney donor candidate, or where there is a high suspicion for *APOL1* risk variants • Aiding in prenatal diagnosis	

Figure 53 | Utility of genetic testing in patients with FSGS. *APOL1*, apolipoprotein-L1; FSGS, focal segmental glomerulosclerosis.

6.2 Treatment

6.2.1 Management of FSGS-UC and secondary FSGS

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

6.2.2 Initial treatment of primary FSGS

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

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

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

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

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

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 54 | Initial treatment of primary FSGS. *The CNI, while often used twice daily, may be dosed once a day, depending on individual formulations. Blood levels of CNIs 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. CNI, calcineurin inhibitor; FSGS, focal segmental glomerulosclerosis.

6.3 Special situations

6.3.1 Steroid-resistant primary FSGS

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

6.3.2 Dosing schedule for cyclosporine and tacrolimus

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

Treatment	Dose and duration
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 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 • Consider discontinuing cyclosporine or tacrolimus if the eGFR continues to decline to <30 ml/min per 1.73 m^2
Inability to tolerate or contraindications to calcineurin inhibitors	• Lack of quality evidence for any specific alternative agents • Mycophenolate mofetil and high-dose dexamethasone, rituximab, and ACTH have been considered • Treatment will need to be personalized and is dependent on availability of drugs and resources, as well as the benefits of further treatment and risks of adverse effects of immunosuppression • Patients should be referred to specialized centers with the appropriate expertise, and should be evaluated on the appropriate use of alternative treatment agents or to discontinue further immunosuppression

Figure 55 | Treatment of glucocorticoid-resistant primary FSGS. *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. ACTH, adrenocorticotropic hormone; CNI, calcineurin inhibitors; eGFR, estimated glomerular filtration rate.

6.3.3 Duration of CNI treatment

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

6.3.4 Patients resistant to or intolerant of CNIs

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

6.3.5 Management of relapse

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

Chapter 7: Infection-related glomerulonephritis

7.1 Bacterial infection-related GN

7.1.1 Diagnosis

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

	Postinfectious GN	Shunt nephritis	Endocarditis-related GN	IgA-dominant infection-related GN
Risk and risk features	Children, elderly, immuno-compromised hosts, sub-sanitary 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; immuno-compromised 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 56 | 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.

7.1.2 Prognosis and treatment

Practice Point 7.1.2.1: Prognosis and suggested therapy of bacterial infection–related GN (Figure 57[401–403])

	Postinfectious GN	Shunt nephritis	Endocarditis-related GN	IgA-dominant infection-related GN
Prognosis	Short-term prognosis in children is excellent. In endemic regions, persistent albuminuria may occur and some adults develop low eGFR. In the elderly, kidney prognosis is poor for those who develop persistent albuminuria; mortality may be up to 20%	Outcome is good with early diagnosis and treatment of infection. Most patients recover some kidney function but are left with residual chronic kidney disease	Immediate prognosis is good with prompt infection eradication. Some may require valve replacement	Dialysis is frequently required in the acute setting. Recovery is guarded, with <20% returning to pre-morbid levels of kidney function
Treatment	• No randomized controlled trials guide the treatment in any of these conditions • Antibiotics for underlying infection (although this will not alter GN course in postinfectious GN) per local guidelines. Antibiotics can be given in poststreptococcal GN if streptococci are cultured from any site. This is primarily done to prevent the spread of infection within community sites • Treat edema, hypertension, etc. as well as persistent proteinuria and/or progressive GFR decline as per Chapter 1			
	Value of high dose glucocorticoids remains unproven [(1)]	Most shunts have been replaced with a shunt with a lesser likelihood of infection. Rarely ventriculocisternostomy has been performed after shunt removal	Utility of glucocorticoids and immunosuppression unproven and carries serious potential risks, even in cases with crescentic GN [(2)]	For severe kidney functional impairment, weigh risks and benefits of immunosuppression. The risk of infection and glucocorticoid-induced complications in this often elderly population with comorbidities can be substantial. A role for immunosuppression remains unproven and these agents should generally not be used
Course	• Follow kidney function, serum C3 and C4, urinalysis, ACR, and proteinuria at appropriate intervals until complete remission or return to baseline			
	Persistently low C3 beyond 12 weeks may be an indication for kidney biopsy to particularly exclude C3GN.[(3)] Prevention of epidemic poststreptococcal GN may include socioeconomic interventions and mass antimicrobial use to improve living conditions and limit the spread of infection in populations where Group A streptococcus infection and scabies are highly prevalent	The natural history of the PR3-ANCA seen in some patients is unclear and requires follow-up	If the infection can be identified and promptly eradicated, the prognosis is favorable	The prognosis for recovery is poor, especially in diabetic subjects

Figure 57 | Prognosis and therapy of classic bacterial infection–related GN syndromes. [1]Kapadia *et al.*[401], [2]Okuyama *et al.*[402], [3]Khalighi *et al.*[403] ACR, albumin–creatinine ratio; ANCA, antineutrophil cytoplasmic antibody; C3GN, C3 glomerulonephritis; eGFR, estimated glomerular filtration rate; GN, glomerulonephritis; PR3, proteinase 3; RCT, randomized controlled trial.

7.2 Viral infection-related GN

7.2.1 Hepatitis C virus (HCV) infection–related GN

The Work Group concurs fully with Recommendations 5.1–5.2.3 of the *KDIGO 2018 Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease*.[405] Please refer to this publication for specific recommendations, selection, and dosing of specific therapeutic agents, and research recommendations.

7.2.2 Hepatitis B virus (HBV) infection–related GN

7.2.2.1 Diagnosis

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

7.2.2.2 Prognosis

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

7.2.2.3 Treatment

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

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

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

7.2.2.4 Special situations

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

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

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

7.2.3 Human immunodeficiency virus (HIV)–related GN

7.2.3.1 Diagnosis

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

7.2.3.2 Prognosis

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

7.2.3.3 Treatment

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

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

7.3 Nephropathies due to infections with schistosomiasis, filariasis, and malaria

7.3.1 Schistosomal nephropathy

7.3.1.1 Diagnosis

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

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

7.3.1.2 Treatment

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

7.3.1.3 Special situations

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

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

7.3.2 Filariasis and glomerular disease

7.3.2.1 Treatment

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

7.3.3 Malarial nephropathy

7.3.3.1 Treatment

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

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

8.1 Diagnosis

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

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 68 | 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; 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.

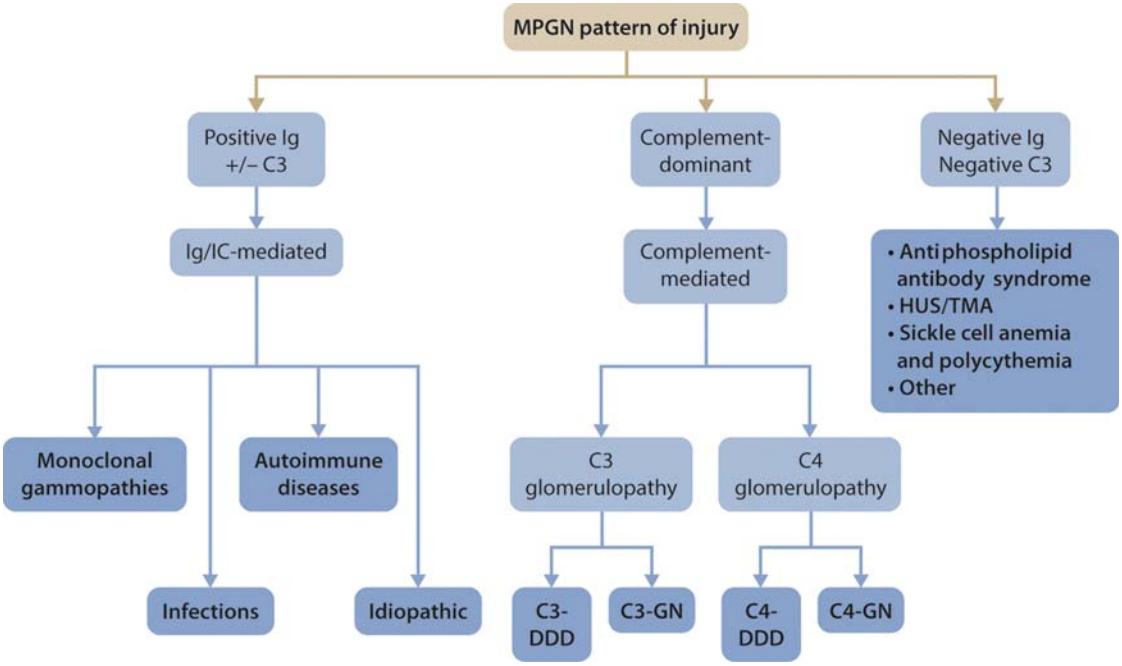

Figure 69 | Pathophysiology of membranoproliferative lesions. DDD, dense deposit disease; GN, glomerulonephritis; HUS, hemolytic–uremic syndrome; IC, immune complex; Ig, immunoglobulin(s); MPGN, membranoproliferative glomerulonephritis; TMA, thrombotic microangiopathy.

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

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

Functional assays	CH50, AP50, FH function
Quantification of complement components and regulators	C3, C4, FI, FH, FB, Properdin
Measurement of complement activation	C3d, Bb, sMAC
Autoantibodies	Anti-FH, anti-FB, nephritic factors (C3, C4, C5)
Genetic testing	C3, CFH, CFI, CFB, and CFHR1-5 MLPA
Plasma cell disorders‡	Serum free light chains, serum and urine electrophoresis, and immunofixation†
Immunofluorescence studies on kidney biopsy specimen	IgA, IgG, IgM, C1q, C3, fibrinogen, kappa, lambda, C4d (usually bright C3, negative or minimal Ig, negative C4d)

Figure 70 | Evaluation of abnormalities of the alternative pathway of complement. Adapted from *Kidney International*, volume 89, issue 2, Angioi A, Fervenza FC, Sethi S, et al. Diagnosis of complement alternative pathway disorders, pages 278–288, Copyright © 2016, with permission from the International Society of Nephrology.[539] ‡The presence of a circulating monoclonal gammopathy is less common below the age of 50 years. Ability to detect a monoclonal protein will depend on the sensitivity of the assay used. †Some complement assays may require referral to specialist/research laboratories, and interpretation of complement assays may require expert consultation. AP50, complement alternate pathway activation 50%; Bb, activated factor B; C3d, complement component 3d; C4d, complement component 4d; CFB, complement factor B; CFH, complement factor H; CFHR1-5, complement factor H–related protein 1-5; CFI, complement factor I; CH50, complement hemolytic activity 50%; FB, factor B; FH, factor H; FI, factor I; Ig, immunoglobulin; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; MLPA, multiplex ligation-dependent probe amplification; sMAC, soluble membrane attack complex.

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

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

8.2 Treatment

8.2.1 ICGN

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

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

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

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

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

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

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

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

8.2.2 C3 glomerulopathy

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

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

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

9.1 Diagnosis

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

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

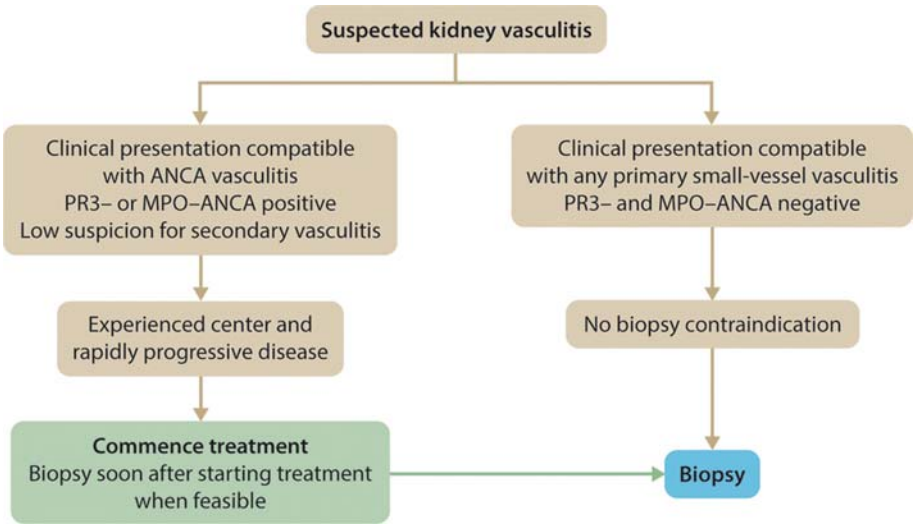

Figure 71 | Biopsy strategy in suspected kidney vasculitis. ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3.

9.2 Prognosis

9.2.1. Survival

[No recommendations or practice points]

9.2.2. Kidney prognosis and treatment response

[No recommendations or practice points]

9.2.3 Relapses

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

9.3 Treatment

9.3.1 Induction

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

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

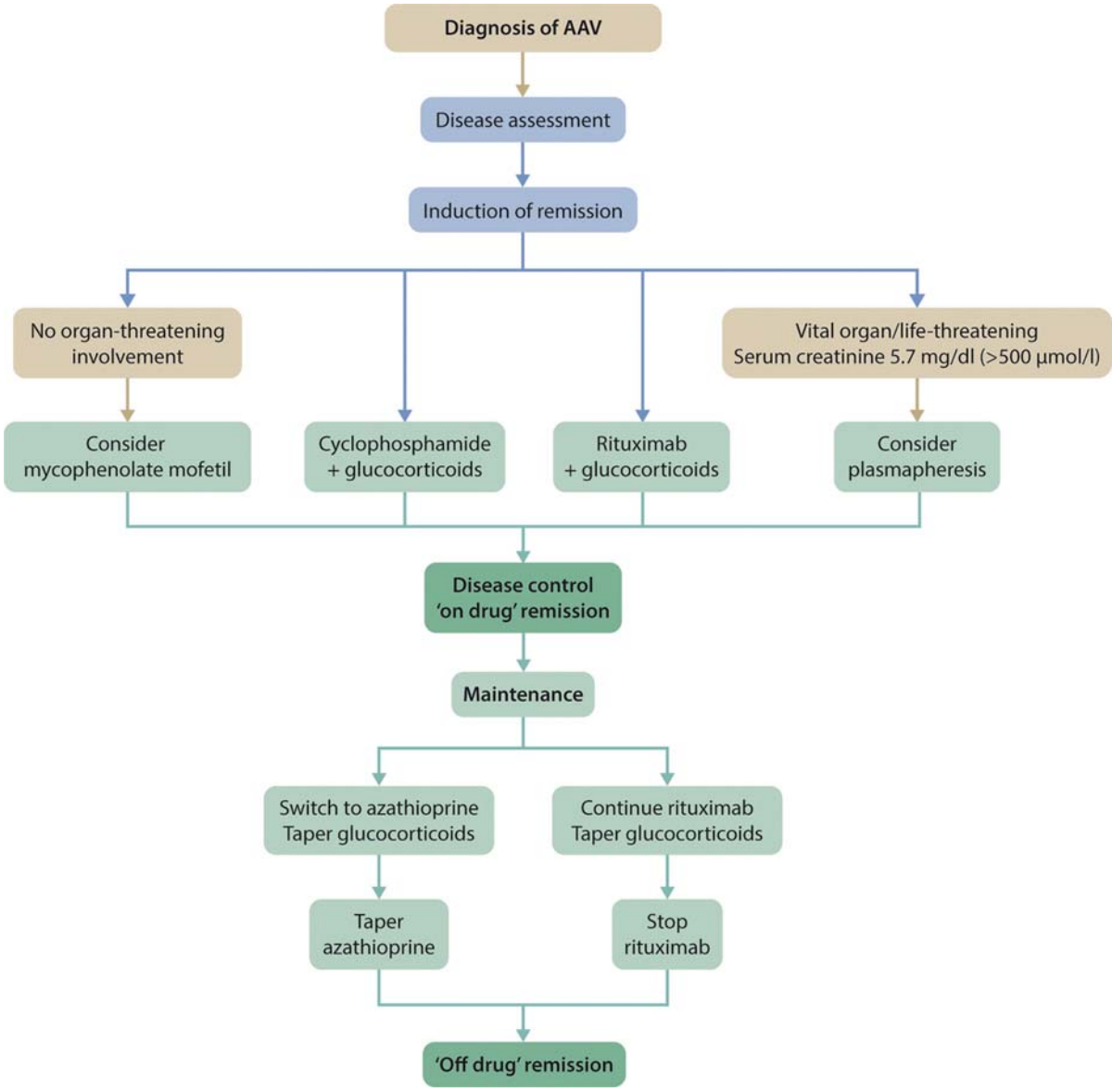

Figure 76 | Recommended treatment regimen for AAV. AAV, ANCA-associated vasculitis.

Practice Point 9.3.1.2: In patients presenting with markedly reduced or rapidly declining GFR (SCr >4 mg/dl [>354 μmol/l]), there are limited data to support rituximab and glucocorticoids. Cyclophosphamide and glucocorticoids are preferred for induction therapy. The combination of rituximab and cyclophosphamide can also be considered in this setting.

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

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 77 | 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.

Practice Point 9.3.1.4: Considerations for choosing the route of administration of cyclophosphamide are given in Figure 78.

Intravenous cyclophosphamide	Oral cyclophosphamide
• Patients who already have a moderate cumulative dose of cyclophosphamide • Patients with lower white blood cell counts • Ready access to an infusion center • Adherence may be an issue	• Cost is an important factor • Access to an infusion center difficult • Adherence is not an issue

Figure 78 | Considerations for the route of administration of cyclophosphamide for AAV. AAV, ANCA-associated vasculitis.

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

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

Week	'Reduced-corticosteroid dose' in PEXIVAS trial		
	<50 kg	50–75 kg	>75 kg
1	50	60	75
2	25	30	40
3–4	20	25	30
5–6	15	20	25
7–8	12.5	15	20
9–10	10	12.5	15
11–12	7.5	10	12.5
13–14	6	7.5	10
15–16	5	5	7.5
17–18	5	5	7.5
19–20	5	5	5
21–22	5	5	5
23–52	5	5	5
>52	Investigators' local practice		

Figure 79 | Prednisolone tapering regimen for AAV. AAV, ANCA-associated vasculitis.

Practice Point 9.3.1.7: Recommendations for immunosuppressive dosing are given in Figure 80.

Oral cyclophosphamide	Intravenous cyclophosphamide	Rituximab	Rituximab and i.v. cyclophosphamide	MMF
2 mg/kg/d for 3 months, continue for ongoing activity to a maximum of 6 months	15 mg/kg at weeks 0, 2, 4, 7, 10, 13 (16, 19, 21, 24 if required)	375 mg/m²/week × 4 weeks OR 1 g at weeks 0 and 2	Rituximab 375 mg/m²/week × 4 weeks, with i.v. cyclophosphamide 15 mg/kg at weeks 0 and 2 OR Rituximab 1 g at 0 and 2 weeks with cyclophosphamide 500 mg/2 weeks × 6	2000 mg/d (divided doses), may be increased to 3000 mg/d for poor treatment response
Reduction for age: • 60 yr, 1.5 mg/kg/d • 70 yr, 1.0 mg/kg/d Reduce by 0.5 mg/kg/day for GFR <30 ml/min/1.73 m²	Reduction for age: • 60 yr 12.5 mg/kg • 70 yr, 10 mg/kg Reduce by 2.5 mg/kg for GFR <30 ml/min/1.73 m²			

Figure 80 | Immunosuppressive drug dosing for AAV. AAV, ANCA-associated vasculitis; GFR, glomerular filtration rate; i.v., intravenous; MMF, mycophenolate mofetil.

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

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

9.3.2 Maintenance therapy

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

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

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

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

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

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

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

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

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

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 83 | 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.

Practice Point 9.3.2.8: Recommendations for dosing and duration of maintenance therapy are given in Figure 84.

Rituximab	Azathioprine	MMF
Scheduled dosing protocol: **1.** 500 mg × 2 at complete remission, and 500 mg at months 6, 12 and 18 thereafter (MAINRITSAN scheme) OR **2.** 1000 mg infusion after induction of remission, and at months 4, 8, 12, and 16 after the first infusion (RITAZAREM* scheme)	1.5–2 mg/kg/d at complete remission until one yr after diagnosis then decrease by 25 mg every 3 mo	2000 mg/d (divided doses) at complete remission for 2 yrs
	Extend azathioprine at complete remission until 4 yrs after diagnosis; start at 1.5–2 mg/kg/d for 18–24 mo, then decrease to a dose of 1 mg/kg/d until 4 yrs after diagnosis, then taper by 25 mg every 3 mo. Glucocorticoids should also be continued at 5–7.5 mg/d for 2 yrs and then slowly reduced by 1 mg every 2 mo	

Figure 84 | Immunosuppressive dosing and duration of AAV maintenance therapy. *RITAZAREM was in relapsing AAV. MAINRITSAN, MAINtenance of Remission Using RITuximab in Systemic ANCA-associated Vasculitis; MMF, mycophenolate mofetil; RITAZAREM, Rituximab versus azathioprine as therapy for maintenance of remission for antineutrophil cytoplasm antibody-associated vasculitis (AAV).

9.3.3 Relapsing disease

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

9.4 Special situations

9.4.1 Refractory disease

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

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

9.4.2 Transplantation

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

Chapter 10: Lupus nephritis

10.1 Diagnosis

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

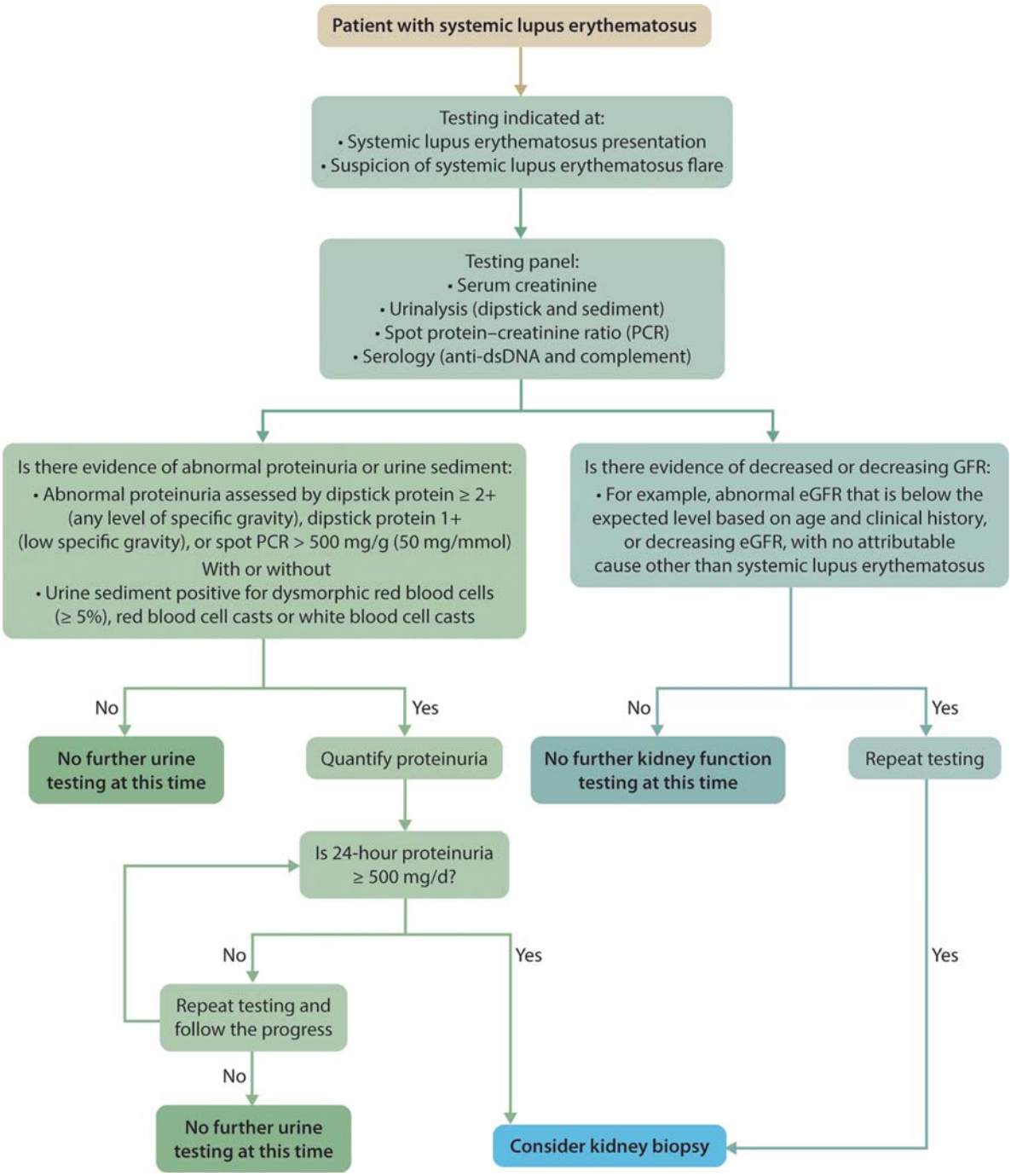

Figure 85 | Diagnosis of kidney involvement in SLE. eGFR, estimated glomerular filtration rate.

10.2 Treatment

10.2.1 General management of patients with lupus nephritis

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

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

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 87 | 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.

10.2.2 Class I or Class II lupus nephritis

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

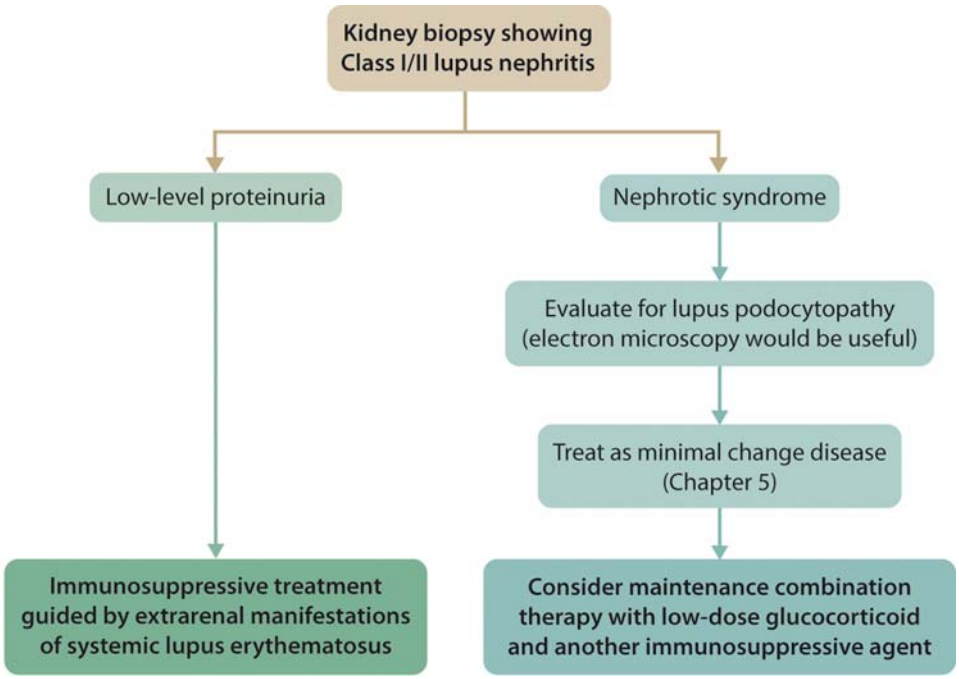

Figure 88 | Immunosuppressive treatment for patients with Class I or Class II LN. LN, lupus nephritis.

10.2.3 Class III or Class IV lupus nephritis

10.2.3.1 Initial therapy of active Class III/IV lupus nephritis

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

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

	Standard-dose scheme	Moderate-dose scheme	Reduced-dose scheme
Methylprednisolone intravenous pulses	Nil or 0.25–0.5 g/day up to 3 days as initial treatment	0.25–0.5 g/day up to 3 days often included as initial treatment	0.25–0.5 g/day up to 3 days usually included as initial treatment
Oral prednisone equivalent (/day)			
Week 0–2	0.8–1.0 mg/kg (max 80 mg)	0.6–0.7 mg/kg (max 50 mg)	0.5–0.6 mg/kg (max 40 mg)
Week 3–4	0.6–0.7 mg/kg	0.5–0.6 mg/kg	0.3–0.4 mg/kg
Week 5–6	30 mg	20 mg	15 mg
Week 7–8	25 mg	15 mg	10 mg
Week 9–10	20 mg	12.5 mg	7.5 mg
Week 11–12	15 mg	10 mg	5 mg
Week 13–14	12.5 mg	7.5 mg	2.5 mg
Week 15–16	10 mg	7.5 mg	2.5 mg
Week 17–18	7.5 mg	5 mg	2.5 mg
Week 19–20	7.5 mg	5 mg	2.5 mg
Week 21–24	5 mg	<5 mg	2.5 mg
Week >25	<5 mg	<5 mg	<2.5 mg

Figure 90 | Example of glucocorticoid regimens for LN. LN, lupus nephritis.

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

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

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

Practice Point 10.2.3.1.5: In patients with baseline eGFR of at least 45 ml/min per 1.73 m^2, voclosporin can be added to MPAA and glucocorticoids as initial therapy for 1 year.

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

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

10.2.3.2 Maintenance therapy for Class III and Class IV lupus nephritis

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

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

Practice Point 10.2.3.2.2: Glucocorticoids should be tapered to the lowest possible dose during maintenance, except when glucocorticoids are required for extrarenal lupus manifestations; discontinuation of glucocorticoids can be considered after patients have maintained a complete clinical renal response for ≥12 months.

Practice Point 10.2.3.2.3: The dose of MMF in the early maintenance phase is approximately 750–1000 mg twice daily, and for MPA, approximately 540–720 mg twice daily.

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

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

10.2.4 Class V lupus nephritis

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

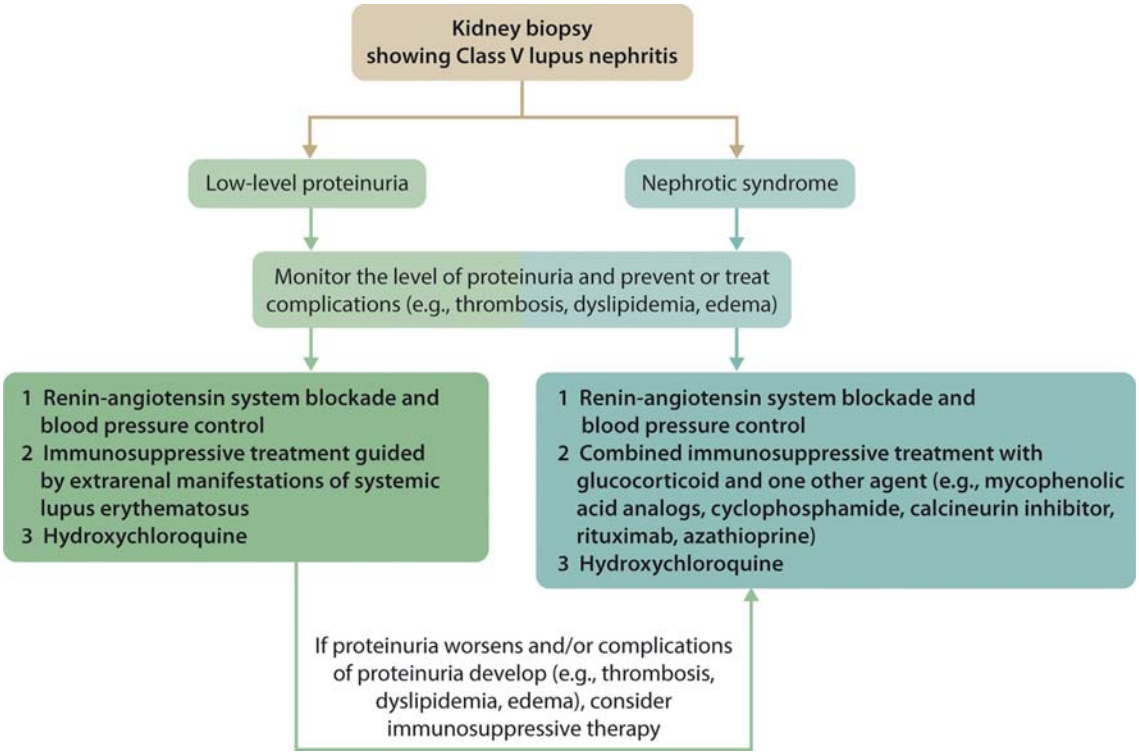

Figure 94 | Management of patients with pure Class V LN. LN, lupus nephritis.

10.2.4.1 Assessing treatment response in LN

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

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 95 | 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-h urine specimen. LN, lupus nephritis; PCR, protein–creatinine ratio.

10.2.4.2 Management of unsatisfactory response to treatment

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

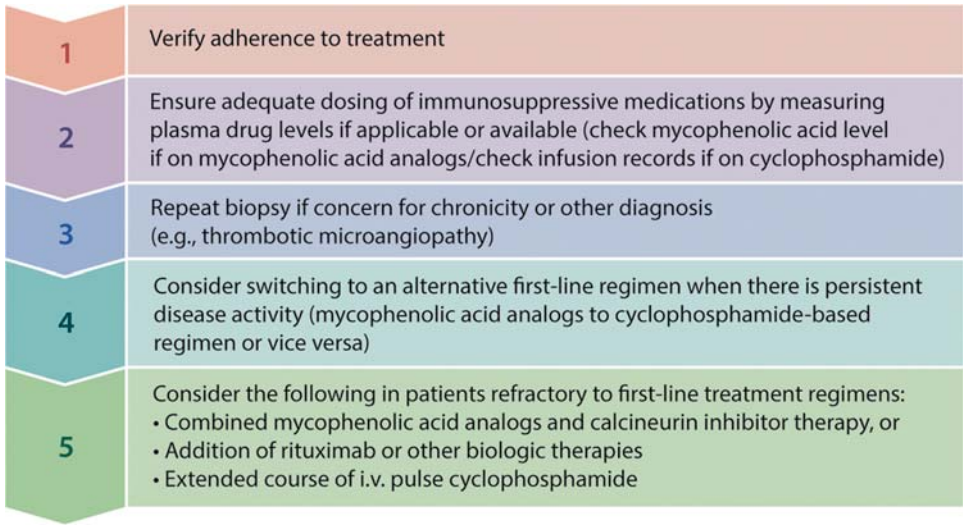

Figure 96 | Management of patients who show unsatisfactory response to initial therapy for active LN. i.v., intravenous; LN, lupus nephritis.

10.2.4.3 Treatment of LN relapse

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

10.3 Special situations

10.3.1 Lupus nephritis and thrombotic microangiopathy

Practice Point 10.3.1.1: Patients with LN and thrombotic microangiopathy (TMA) should be managed according to the underlying etiology of TMA, as shown in Figure 97[864].

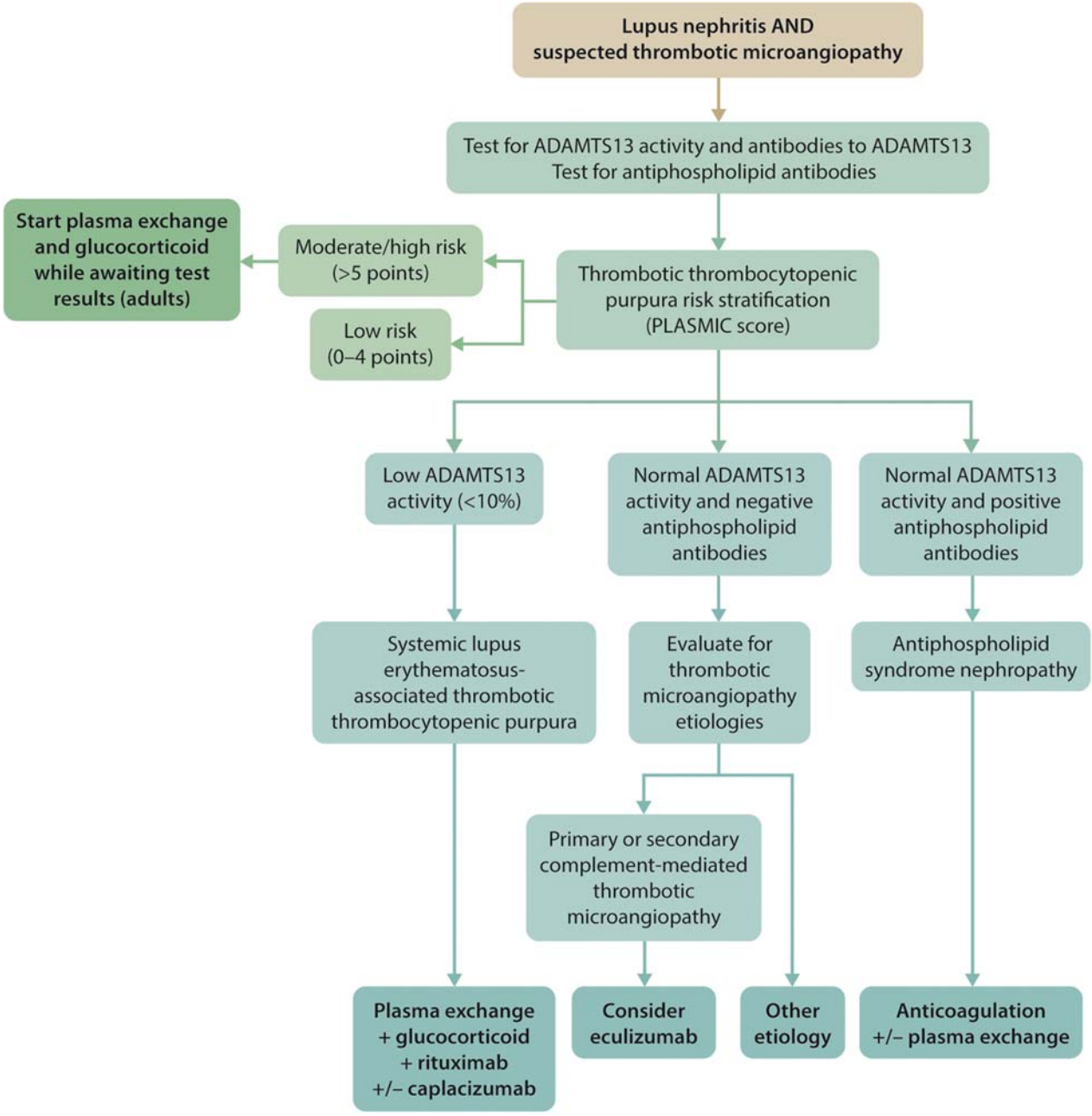

Figure 97 | Management of patients with LN and TMA. Bendapudi PK, Hurwitz S, Fry A, et al. Derivation and external validation of the PLASMIC score for rapid assessment of adults with thrombotic microangiopathies: a cohort study. *Lancet Haematol.* 2017;4:e157–e164.[864] ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; PLASMIC, Platelet count, combined hemoLysis variable, absence of Active cancer, absence of Stem-cell or solid-organ transplant, MCV, INR, Creatinine.

10.3.2 Pregnancy in patients with lupus nephritis

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

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

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

10.3.3 Treatment of lupus nephritis in children

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

10.3.4 Management of lupus patients with kidney failure

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

Chapter 11: Anti-glomerular basement membrane (Anti-GBM) antibody glomerulonephritis

11.1 Diagnosis

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

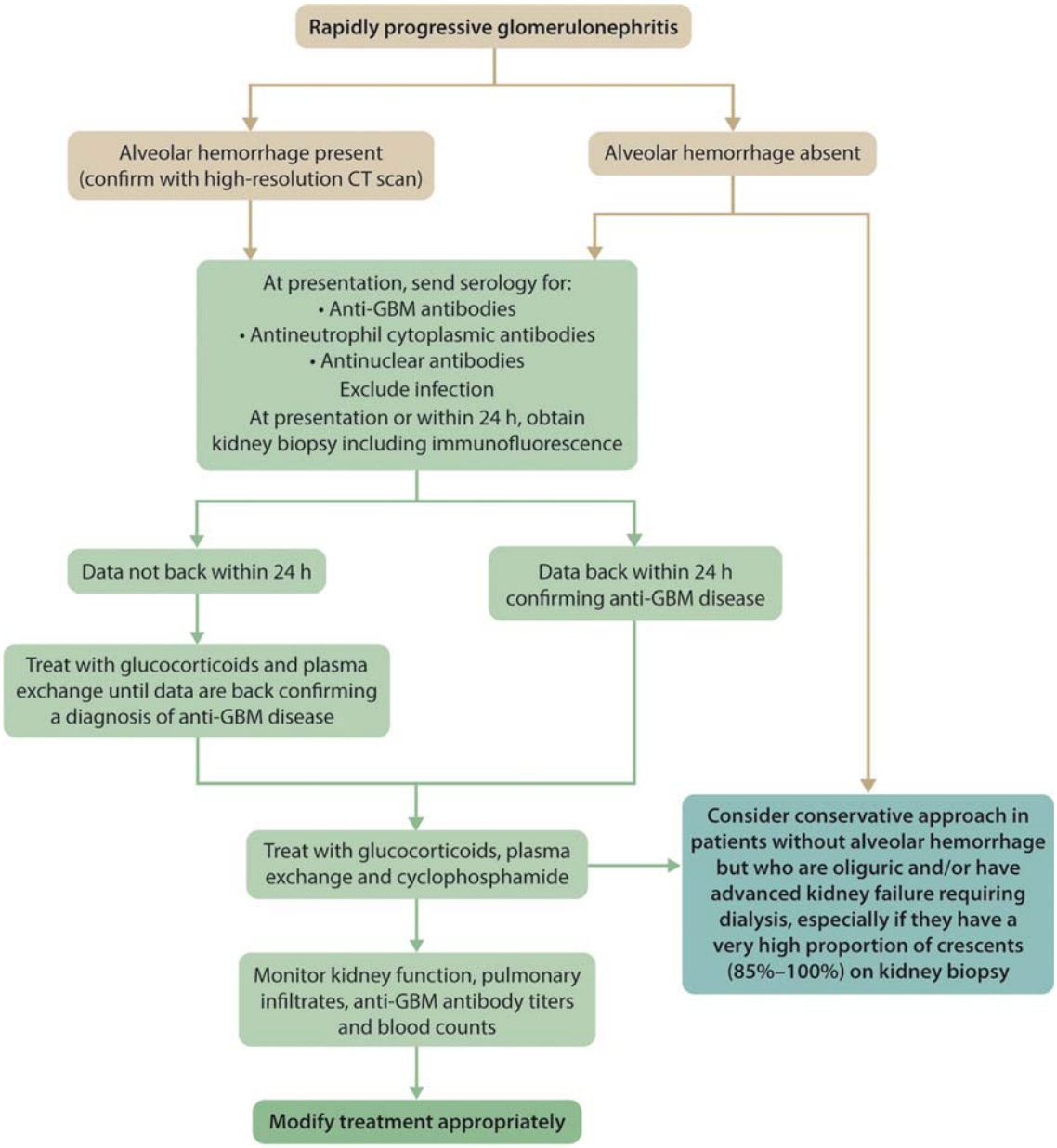

Figure 98 | Diagnosis and therapy in anti-GBM disease. CT, computed tomography; GBM, glomerular basement membrane.

11.2 Treatment

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

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

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

Practice Point 11.2.3: Cyclophosphamide should be administered for 2–3 months and glucocorticoids for about 6 months (Figure 99[931,945,946]).

Intervention	Dosing	Duration of treatment
Plasma exchange	• 40–50 ml/kg ideal body weight exchange daily against 5% albumin • Add fresh frozen plasma at the end of plasma exchange in patients with alveolar hemorrhage and/or after kidney biopsy	Until circulating anti-GBM antibodies can no longer be detected; usually 14 days
Cyclophosphamide	• 2–3 mg/kg orally (reduce to 2 mg/kg in patients >55 years); experience with pulse intravenous cyclophosphamide is limited and efficacy is uncertain • Cyclophosphamide dosing should be reduced (or treatment interrupted) in cases of leukopenia • In patients not tolerating (or not responding to) cyclophosphamide, rituximab or mycophenolate mofetil may be tried but experience is limited and efficacy uncertain	3 months
Glucocorticoids	• Pulse methylprednisolone may be given initially up to 1000 mg/d on 3 consecutive days • Prednisone 1 mg/kg orally • Reduce to 20 mg/d by 6 weeks	6 months

Figure 99 | Treatment of anti-GBM disease. Adapted from *Journal of the American Society of Nephrology*, volume 10, issue 11, Kluth DC, Rees AJ. Anti-glomerular basement membrane disease, pages 2446–2453, Copyright © 1999, with permission from the American Society of Nephrology.[946] Adapted from *Clinical Journal of the American Society of Nephrology*, volume 12, issue 7, McAdoo SP, Pusey CD. Anti-glomerular basement membrane disease, pages 1162–1172, Copyright © 2017, with permission from the American Society of Nephrology.[931] Adapted from Kaplan AA, Appel GB, Pusey CE, et al. Anti-GBM (Goodpasture) disease: treatment and prognosis. UpToDate: Evidence-based Clinical Decision Support. Available at: www.uptodate.com. Accessed September 7, 2021.[945]

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

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

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

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

Chapter 1: General principles for the management of glomerular disease

The general management principles covered in this Chapter apply to most or all of the histologic forms of glomerular disease. We broadly discuss these general principles in order to minimize repetition in the individual disease-specific guidelines that follow. Where specific applications or exceptions to these general statements exist, an expansion and rationale for these variations and/or recommendations are given in each disease-specific Chapter. The evidence underlying these general principles is varied and often of low or moderate quality, as relevant randomized clinical trials (RCTs) are infrequent or have been conducted only in subjects with a variety of glomerular diseases (including diabetic nephropathy) and in specific diseases, as enumerated in the Chapters that follow. Thus, the general principles outlined in this section are not usually accompanied by specific evidence-based graded recommendations.

1.1 Kidney biopsy

Kidney biopsy has been mandatory for diagnosis in adults with nephrotic syndrome (NS) when the cause is not evident from the initial evaluation, and in most circumstances, it remains so. However, in children younger than 12 years, in steroid-sensitive NS (SSNS; Chapter 4), and in post-streptococcal glomerulonephritis (GN; Chapter 7), clinical presentations are usually sufficiently characteristic to direct initial treatment without a biopsy. In adults, the wider spectrum of possible underlying glomerular disease had often necessitated a kidney biopsy prior to treatment in most patients without diabetes. In recent years, advances in serologic testing for some glomerular diseases have become sufficiently sensitive and specific, when interpreted in the context of the clinical presentation and ancillary laboratory studies, to make a presumptive diagnosis and guide therapy, even in adults, without a kidney biopsy (an example is membranous nephropathy; Chapter 3).[3] Although this approach has not been analyzed formally for all conditions, in the presence of a contraindication or a patient objection to biopsy, it may be reasonable to waive the requirement that a morphologic diagnosis be known prior to treatment.

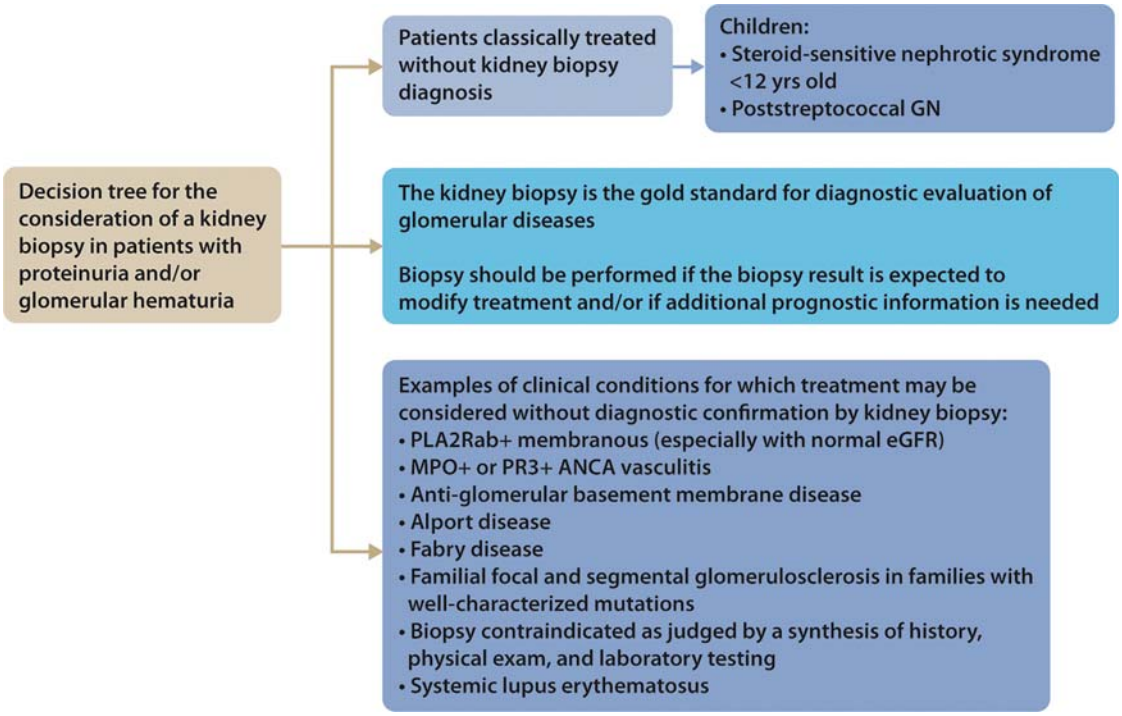

Figure 2 | Considerations for a kidney biopsy in patients with proteinuria and/or glomerular hematuria. ANCA, antineutrophil cytoplasmic antibody; eGFR, estimated glomerular filtration rate; GN, glomerulonephritis; MPO, myeloperoxidase; PLA2Rab+, M-type phospholipase A2 receptor antibody positive; PR3, proteinase 3.

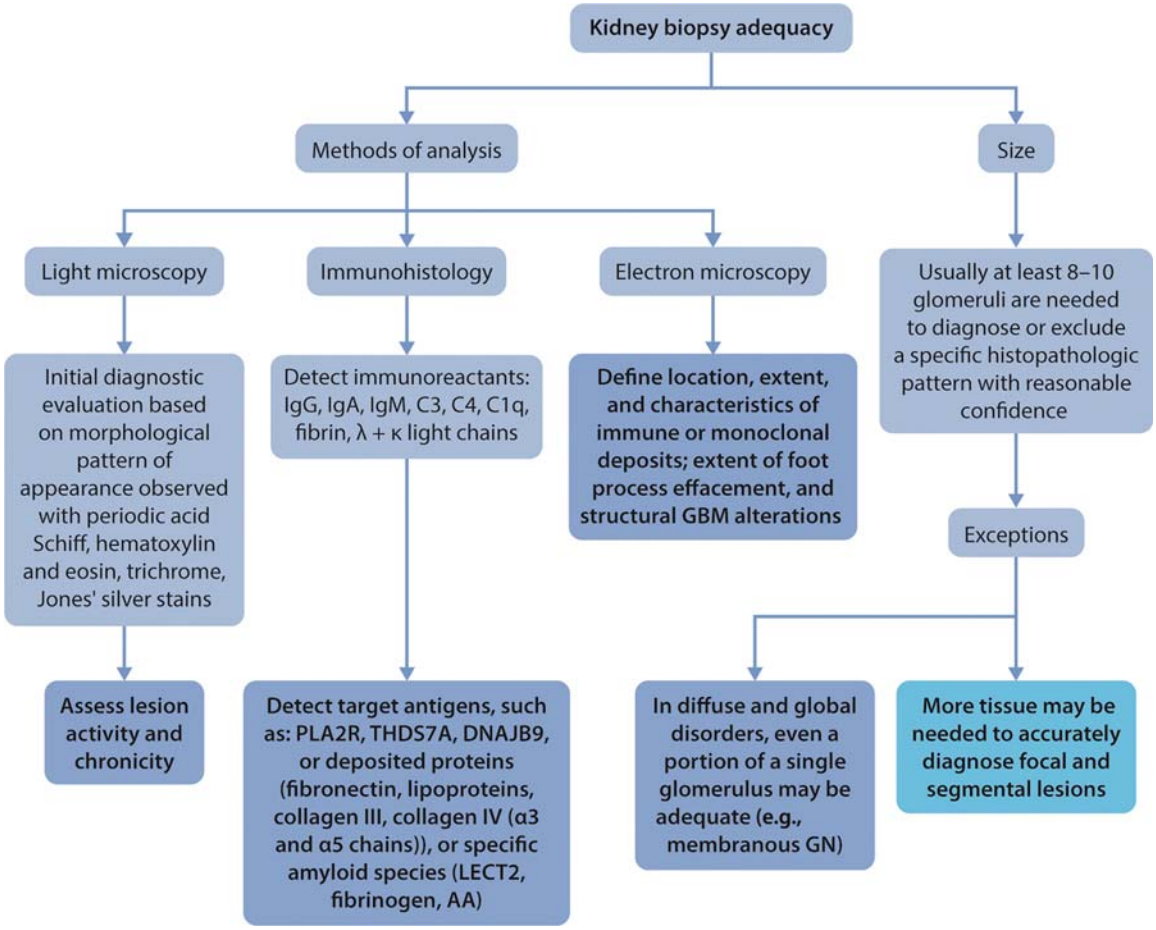

Figure 3 | Evaluation of kidney tissue. AA, amyloid A; GBM, glomerular basement membrane; DNAJB9, DnaJ homolog subfamily B member 9; GN, glomerulonephritis; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; LECT2, leukocyte cell-derived chemotaxin-2; PLA2R, M-type phospholipase A2 receptor; THDS7A, thrombospondin type-I domain-containing 7A.

Practice Point 1.1.1: The kidney biopsy is the "gold standard" for the diagnostic evaluation of glomerular diseases. However, under some circumstances, treatment may proceed without a kidney biopsy confirmation of diagnosis (Figure 2).

Treating without morphologic analysis forgoes other information obtained from kidney biopsies, including activity, chronicity, and other unsuspected glomerular, vascular, and/or tubulointerstitial diseases and injuries (such as thrombotic microangiopathy or interstitial nephritis), which may have prognostic or even therapeutic significance.

Kidney biopsies should be performed when the value of the information obtained from the biopsy exceeds the risks entailed. Patients (or parents) may also place varying values on the increased certainty of diagnosis and prognosis before embarking on a treatment plan, often involving medications with significant side effects, versus the potential complications of the biopsy itself. Local resources are also likely to determine prevailing practice.

Practice Point 1.1.2: The evaluation of kidney tissue should meet standards of biopsy adequacy (Figure 3).

The size of the biopsy necessary to diagnose or exclude a specific histopathologic pattern with reasonable confidence (assessed by the number of glomeruli present in the sample) usually is at least 8–10 glomeruli.[4,5] In some diseases, for example, focal segmental glomerulosclerosis (FSGS) and necrotizing GN associated with antineutrophil cytoplasmic antibodies (ANCA), lesions are only seen in some segments of some glomeruli. In these cases, it is important that the biopsy be examined by light microscopy at several levels, if lesions are not to be missed. Fewer glomeruli may be acceptable for diffuse and global disorders, such as membranous nephropathy, where even a portion of a single glomerulus may be adequate.

Optimally, samples should be studied by light, immunofluorescence, and electron microscopy and evaluated by an experienced nephropathologist. Light microscopy examination should minimally provide an initial diagnostic evaluation based on the morphologic pattern of appearance observed on tissue sections stained with periodic acid Schiff, hematoxylin and eosin, trichrome, and Jones' silver stains. Immunofluorescence microscopy and/or immunoperoxidase analyses are required to detect immune-reactants immunoglobulin G (IgG), immunoglobulin A (IgA), immunoglobulin M (IgM), C3, C4, C1q, fibrin, and λ and κ light chains. These methodologies may be further used to detect target antigens,

such as M-type phospholipase A2 receptor (PLA2R), thrombospondin type-1 domain-containing 7A (THSD7A), DnaJ homolog subfamily B member 9 (DNAJB9—seen in fibrillary GN), fibronectin, lipoproteins, collagen III, collagen IV α3 and α5 chains, and specific amyloid species. Antigen retrieval methods, such as protease digestion of paraffin-embedded tissue, can be helpful diagnostically.

Ideally, all kidney biopsies should be assessed by light microscopy, immune-histology, and electron microscopy. Due to cost and equipment limitations, it is recognized that electron microscopy may not be available everywhere. Electron microscopy defines the location, extent, and specific characteristics, including organized substructure, of the immune or monoclonal deposits, the extent of foot process effacement, structural glomerular basement membrane (GBM) alterations, and glycoprotein or lipid deposition. Some diagnoses, including minimal change disease (MCD) and immunotactoid deposition disease, are dependent on electron microscopy. In others, electron microscopy contributes significant descriptive and semi-quantitative information about podocytes and GBM, adding to diagnostic certainty. In centers where electron microscopy is not available, consideration should be given to the development of consultative relationships to obtain microscopy assessment in such instances.

"Active" lesions are acute and potentially responsive to specific therapy. "Chronic" lesions are usually not reversible or treatable. Glomerular scarring is associated with downstream tubular atrophy and interstitial fibrosis. The degree of chronic irreversible damage is most easily assessed from the amount of interstitial fibrosis and tubular atrophy. The assessment of chronic damage from the biopsy must always be interpreted together with the clinical data to avoid misinterpretation if the biopsy is taken (by chance) from a focal cortical scar. The amount of information derived from kidney pathology varies substantially in the different types of glomerular diseases; when of particular relevance, this issue is addressed specifically within the appropriate Chapters.

Clinicians should pay attention to the contents and detailed descriptions of active or chronic histopathologic features, and not just the diagnosis, in the biopsy report. Internationally validated scoring systems have been developed for some entities (e.g., MEST-C—mesangial (M) and endocapillary (E) hypercellularity, segmental sclerosis (S); interstitial fibrosis/tubular atrophy (T), and crescents (C) scoring in IgA nephropathy [IgAN; International Society of Nephrology and the Renal Pathology Society [ISN/RPS] classes in lupus nephritis [LN]), which should also be taken into account when discussing treatment.

Practice Point 1.1.3: Repeat kidney biopsy should be performed if the information will potentially alter the therapeutic plan or contribute to the estimation of prognosis.

Repeat kidney biopsy may be needed when the initial biopsy is inadequate to arrive at a diagnosis. Occasionally, sufficient uncertainty regarding the response to management or the progression of kidney disease may be present to warrant a repeat biopsy, even in patients with a well-established diagnosis.

Repeat kidney biopsies are often considered in diseases that have a tendency for a relapsing course or transformations to other histopathologic forms, such as MCD/FSGS. However, there is no evidence that repeat kidney biopsy in SSNS with an initial kidney biopsy showing MCD or FSGS has any material benefit for management (Chapters 5 and 6). A repeat kidney biopsy might be considered, even when the original biopsy was adequate for diagnosis, in the following circumstances:

- when evaluation of a cause for an unexpected deterioration in kidney function is not compatible with the known natural history;
- when the response to treatment is unsatisfactory, especially when a change of therapy is considered;
- in evaluating changes in clinical or laboratory parameters that suggest a change of injury pattern within the same diagnosis (e.g., conversion of membranous to diffuse proliferative LN[6]);
- in reaffirming the morphologic diagnosis and re-evaluating the relative contributions of disease activity and chronicity, to determine whether to intensify, maintain, reduce, or otherwise modify therapy; or
- when defining a "point of no return/therapeutic futility."

Given the invasive nature of the procedure, repeat kidney biopsies should be used when the information expected cannot be obtained from the synthesis of the available clinical information, and when the result is likely to change therapy. Local cost–benefit analysis applied to the clinical decision-making for the care of individual patients may be necessary. There are no RCTs to support recommendations for when or how often a repeat biopsy is necessary.

Research recommendation

- Determine whether proteomics, mass spectroscopy, and/or RNA sequencing analyses on kidney biopsy material can supplement or replace therapeutic decision-making based on morphologic characterizations alone.

1.2 Assessment of kidney function

Key measures for the diagnosis, evaluation of prognosis, and management decision in patients with glomerular disease include assessment of kidney function, particularly measurement (or estimation) of proteinuria and glomerular filtration rate (GFR).

Proteinuria

Assessment of urine total protein excretion rate (PER) using timed urine collections is the preferred method for patients with glomerular disease, particularly when marked proteinuria is present on qualitative testing.[7] It averages the variation of proteinuria due to the circadian rhythm, physical activity, and posture, and avoids the errors introduced by using a random "spot" protein–creatinine ratio (PCR). However, 24-hour urine collection can also be subject to error due to overcollection or undercollection. Simultaneous measurement of urine creatinine and protein in an aliquot of an intended 12–24-hour urine collection is a good compromise

Nephrotic syndrome	Nephrotic-range proteinuria	Non-nephrotic-range proteinuria
Proteinuria (adults)* • ≥3.5 g per 24 h • PCR ≥3000 mg/g (≥300 mg/mmol)	Proteinuria (adults) • ≥3.5 g per 24 h • PCR ≥3000 mg/g (≥300 mg/mmol)	Variable levels of proteinuria • 0.3–3.4 g per 24 h • PCR <300 mg/g (<30 mg/mmol)
Proteinuria (children)* • ≥40 mg/m^2/h • ≥300 mg/dl • 3+ on urine dipstick • PCR ≥2000 mg/g (≥200 mg/mmol)	Proteinuria (children) • ≥40 mg/m^2/h • ≥300 mg/dl • 3+ on urine dipstick • PCR ≥2000 mg/g (≥200 mg/mmol)	• Serum albumin normal • No clinical symptoms
• Hypoalbuminemia† • Edema‡ • Hyperlipidemia‡	• Serum albumin usually normal • Edema is usually absent or minor • Serum lipids usually normal or only mildly elevated	

Figure 4 | Definition of "nephrotic syndrome," "nephrotic-range proteinuria," and "non-nephrotic-range proteinuria." *Essential. †Laboratory-specific values: Serum albumin should be measured by bromocresol purple (BCP; colorimetric) capillary electrophoresis (CE), or immunonephelometric (iMN) methods. Bromocresol green (BCG) methods can give erroneously high results (Clase *et al.*[10]). The values of serum albumin measured by BCG are about 5.5 g/l higher than those measured by the BCP, CE, or iMN methods, so the definition of the degree of hypoalbuminemia required to meet a definition of NS varies according to the method used for quantifying serum albumin concentration. ‡Variable.

that yields useful and reasonably consistent results. A first morning void and determination of PCR, which in effect is an overnight collection of urine, can also be used but tends to underestimate 24-hour PER by about 20% due to the effects of overnight recumbency. This effect is seen to a lesser extent when marked (nephrotic-range) proteinuria is present.

The albumin excretion rate and the albumin–creatinine ratio (ACR) are not commonly used in nondiabetic forms of glomerular disease, even though these measurements are recommended for the categorization of chronic kidney disease (CKD) and for estimation of prognosis via the Kidney Failure Risk Equations.[8]

Prediction of albumin excretion rate or ACR from PER or PCR values can be made using prediction formulas, but these are rather unreliable at low PER values (<500 mg/d), perhaps because of the presence of tubular proteinuria, in which PER can consist of nonalbumin low–molecular weight proteins.[9] On average, albumin accounts for about 65% of total urinary protein in GN, although higher values can be observed in some diseases (such as MCD). Sex, diet, race, and physical condition variations can modify creatinine generation, and may also contribute to discrepancies between values for PCR/ACR and PER/ACR from timed urinary collections.

Simultaneous measurement of urine sodium using the 24-hour urine collection can help determine whether high sodium intake contributed to worsening proteinuria.

Nephrotic-range proteinuria is not always associated with "nephrotic syndrome," in that hypoalbuminemia may not be present. This form of proteinuria is commonly seen in patients with secondary FSGS and IgAN. NS can be present in some patients whose urine protein quantification does not quite meet the traditional definition of nephrotic-range proteinuria but whose clinical symptoms match a classic presentation (Figure 4[10]).

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

Quantification of proteinuria is an important measure in the assessment of the patient with GN and is relevant in almost all the primary and secondary glomerular diseases discussed in this guideline. Separate from MCD, proteinuria in GN is typically heterogeneous and consists of both albumin and other proteins. Most clinical trials for GN incorporate 24-hour urine collections to assess response to therapy.

If a 24-hour urine collection cannot be obtained, use an alternative method to quantify proteinuria. The best option is to determine PCR on an aliquot of an attempted 12-24-hour urine collection at first presentation or on a first morning void. Random "spot" PCR assessments are discouraged for evaluation of patients with GN, unless urine is collected at the same time of day and under similar conditions of physical activity and when the patients are otherwise stable.

Practice Point 1.2.2: For pediatrics, 24-hour urine collection is not ideal as it may not be accurate and is cumbersome to collect. Instead, monitor first morning protein–creatinine ratio (PCR).

Direct measures of kidney function	Indirect measures of kidney function: estimating equations	Limitations
• Creatinine clearance - 24 h urine creatinine	• eGFR	• No estimate of kidney function has been specifically validated for glomerular diseases and/or nephrotic syndrome • Ethnicity is often a confounding influence • In creatinine-based formulas, hypoalbuminemia may lead to overestimation of true GFR due to increased tubular creatinine secretion[8] • Glucocorticoids may increase serum cystatin C, potentially underestimating eGFR[9] • Low muscle mass overestimates eGFR using creatinine-based formulae[10] • AKI confounds all estimates, which are valid only in steady-state
• Measured GFR* - Inulin clearance (gold standard) - Radioisotopic plasma clearance[1] • ^{125}Iothalamate; ^{99m}Tc-DTPA; ^{51}Cr-EDTA - Non-radioisotopic plasma clearance • Iohexol[2]	**Adults** • Cockcroft–Gault[3] (140-age) (wt [kg]) x 0.85, if female/serum creatinine (mg/dl) x 72 • Modification of diet in renal disease (MDRD) equations[4] (not valid for eGFR >60 ml/min/1.73 m^2) - CKD-EPI creatinine equation (preferred) • Valid with eGFR >60 ml/min/1.73 m^2 - CKD-EPI-cystatin C equations[5] (valid for eGFR >60 ml/min/1.73 m^2) - Full Age Spectrum (FAS) equation[7] • Valid even in eGFR >60 ml/min/1.73 m^2 **Children** • Schwartz equation and its modifications[6] • Full-age spectrum (FAS) formulae[7]	

Figure 5 | Assessment of kidney function in glomerular disease. *In ml/min per 1.73 m^2. The correction coefficient for race in GFR estimating equations is controversial, and discussions about this topic are ongoing.[20] Please refer to the KDIGO CKD guideline for more information.[18] [1]Perrone *et al.*[13], [2]Gaspari *et al.*[12], [3]Cockcroft and Gault.[11], [4]Stevens *et al.*[16], [5]Stevens *et al.*[17], [6]Schwartz *et al.*[15], [7]Pottel *et al.*[14], [8]Branten *et al.*[19], [9]Zhai *et al.*[21], [10]Levey *et al.*[22] AKI, acute kidney injury; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; ^{51}Cr-EDTA, chromium-51 labeled ethylenediamine tetraacetic acid; eGFR, estimated glomerular filtration rate in ml/min per 1.73 m^2; ^{99m}Tc-DTPA, technetium-diethylenetriamine pentaacetic acid.

Practice Point 1.2.3: Random "spot" urine collections for PCR are not ideal as there is variation over time in both protein and creatinine excretion.

Practice Point 1.2.4: First morning urine collections may underestimate 24-hour protein excretion in orthostatic proteinuria.

Practice Point 1.2.5: When feasible, a reasonable compromise is to collect an "intended" 24-hour urine sample and measure PCR in an aliquot of the collection.

Practice Point 1.2.6: There is no need to simultaneously and routinely quantify sodium excretion on each timed urinary collection, unless there is reason to suspect a failure to adhere to suggestions regarding dietary sodium restriction (Figure 5 and Practice Points 1.4.2 and 1.5.9).

Practice Point 1.2.7: Quantify proteinuria in glomerular disease, as it has disease-specific relevance for prognosis and treatment decision-making. Qualitative assessment of proteinuria may be useful in selected instances.

Refer to subsequent glomerular disease Chapters for the levels and changes in proteinuria (PER or PCR as defined above) that have been used to categorize both the risk of disease progression and the definition of clinical response. These parameters are not uniform and vary widely across the spectrum of glomerular disease and even within individual glomerular disease types.

Currently, there is insufficient evidence to recommend basing treatment decisions on more detailed qualitative analysis of proteinuria, such as urine electrophoresis (outside of MCD in children) or the measurement of fractional urinary excretion of IgG, β-2 microglobulin, retinol-binding protein, or α-1 microglobulin, but in specific diseases (such as membranous nephropathy [MN] and FSGS), these latter low–molecular weight proteins may have clinical and prognostic utility.

Estimation of GFR

Most of the available evidence for treatment of GN has been based on estimations of excretory kidney function using serum creatinine (SCr) or creatinine clearance (CrCl) requiring a 24-hour urine collection. Very few studies have reported gold-standard measurements of GFR using urinary clearance of inulin, radioisotopic iothalamate, or plasma disappearance of iohexol, nonradioisotopic iothalamate, ^{99m}Tc-DTPA, or ^{51}Cr-EDTA techniques. Other techniques include adjustment of SCr for age, weight, and sex, using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) or other formulas and reciprocal or log transformation of SCr. Serum cystatin C, as an alternative to SCr, has not been well validated in subjects with GN. All these methods have limitations but are informative when sequential measurements are made in each subject.[11–17] The details of GFR assessment can be found in the *KDIGO Clinical Practice Guideline for the Evaluation and Management of CKD* (Figure 5[11–22]).[18]

Estimation of GFR using the CKD-EPI formula based on SCr has gained increasing acceptance, although it has not been validated specifically in those patients with GN. It may be more accurate than earlier equations, especially at values >60 ml/min per 1.73 m^2. Ethnicity, muscle bulk, sarcopenia, and the method used for creatinine measurement may influence the accuracy of estimated glomerular filtration rate (eGFR) based on SCr. This is less true when one uses a serum cystatin C biomarker to estimate GFR. In NS and hypoalbuminemia, tubular creatinine handling is altered, and CrCl- and eGFR-creatinine-based equations may overestimate true GFR by 50% or more.[16,19] GFR estimations are also unreliable during episodes of acute kidney injury (AKI) and possibly are influenced by altered creatinine generation in patients with chronic glucocorticoid-related myopathy.

In children, there are alternative validated formulas for eGFR, notably the Schwartz or Full Age Spectrum (FAS) formulas.

Practice Point 1.2.8: In children, quantify proteinuria, but goals of treatment should not be different between disease etiologies. A PCR of <200 mg/g (<20 mg/mmol) or <8 mg/m^2/hour in a 24-hour urine should be the goal for any child with glomerular disease. Acceptance of a baseline higher than this should come only with kidney biopsy evidence of kidney scarring.

Practice Point 1.2.9: The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) estimated glomerular filtration rate (eGFR) creatinine equation is preferred in adult patients with glomerular disease, and the modified Schwartz equation is preferred in children. The Full Age Spectrum (FAS) equation may be used in both adults and children (Figure 5).

All creatinine-based eGFR equations tend to overestimate true GFR in patients with NS and hypoalbuminemia. eGFR, cystatin C, or combinations of eGFR, cystatin C, and creatinine may be used in special circumstances when disturbances in creatinine generation are suspected.

Research recommendations

- Evaluation of "spot" versus "timed" urine collections in evaluation of proteinuria in specific kidney diseases
- Evaluation of urine proteomics for diagnosis and prognosis of specific forms of GN
- Evaluation of urinary biomarkers for detection and quantification of kidney fibrosis in GN
- Evaluation of whether validated GFR-estimating equations in patients with marked proteinuria can improve clinical trial outcomes and patient management

1.3 Evaluation of hematuria

Hematuria is one of the cardinal manifestations of glomerular disease. The initial detection of hematuria is often by "dipstick" analysis of a random urine specimen. Dipstick tests are very sensitive for detection of hemoglobin in urine (free or erythrocyte-related) with very few false negatives (except in patients taking large amounts of vitamin C), but with false positives in myoglobinuria or hemoglobinuria. Macroscopic or gross hematuria usually imparts a reddish or brownish "smoky" appearance to voided urine, depending on urine pH. In visible hematuria due to GN, clots do not occur. Typically, hematuria in GN is not accompanied by urinary tract symptoms.

An abnormal dipstick test for blood should be confirmed by a microscopical examination of fresh, centrifuged urine sediment by phase-contrast microscopy or brightfield optics under low- and high-power magnification. Staining of the urine sediment (Sternheimer-Malbin) can aid in the recognition of cells and formed elements. Flow-assisted cell-sorting techniques can greatly aid automated analysis of hematuria.

In patients with GN, the erythrocytes are commonly (50%–80%) misshapen (dysmorphic) and small (microcytic). The presence of casts containing red blood cells or the presence of acanthocytes (>5% of all red blood cells) usually indicates an inflammatory glomerular disease. It should be noted that among the few erythrocytes seen in a normal, properly collected urine, all are of a glomerular (dysmorphic) type.

The prognostic implications of the persistence and magnitude of hematuria can have a very significant impact on long-term outcomes of glomerular disease. Given this, findings often represent continued "low-grade" activity of the underlying glomerular inflammatory process. This aspect of hematuria as a "biomarker" of progression, for example, in IgAN,[23] is now receiving long-overdue attention. Periodic monitoring of the presence and magnitude of hematuria should be a part of the care process for all forms of glomerular disease, in our opinion.

Practice Point 1.3.1: Routine evaluation of urine sediment for erythrocyte morphology and the presence of red cell casts and/or acanthocytes is indicated in all forms of glomerular disease.

Practice Point 1.3.2: Monitoring of hematuria (magnitude and persistence) may have prognostic value in many forms of glomerular disease. This is particularly applicable to immunoglobulin A nephropathy (IgAN) and vasculitis (IgAV; Chapter 2).

Research recommendation

- Further prospective studies of the impact of persistent hematuria on prognosis for specific forms of glomerular disease and its therapeutic implications

1.4 Management of complications of glomerular disease

A number of complications of glomerular disease are a consequence of the clinical presentation rather than the specific histopathologic pattern. Active management of such complications should always be considered to have a positive impact on the natural history of the disease and to significantly improve morbidity and even mortality. These include measures to control edema, reduce proteinuria, treat elevated systemic arterial blood pressure (BP), slow disease progression, and

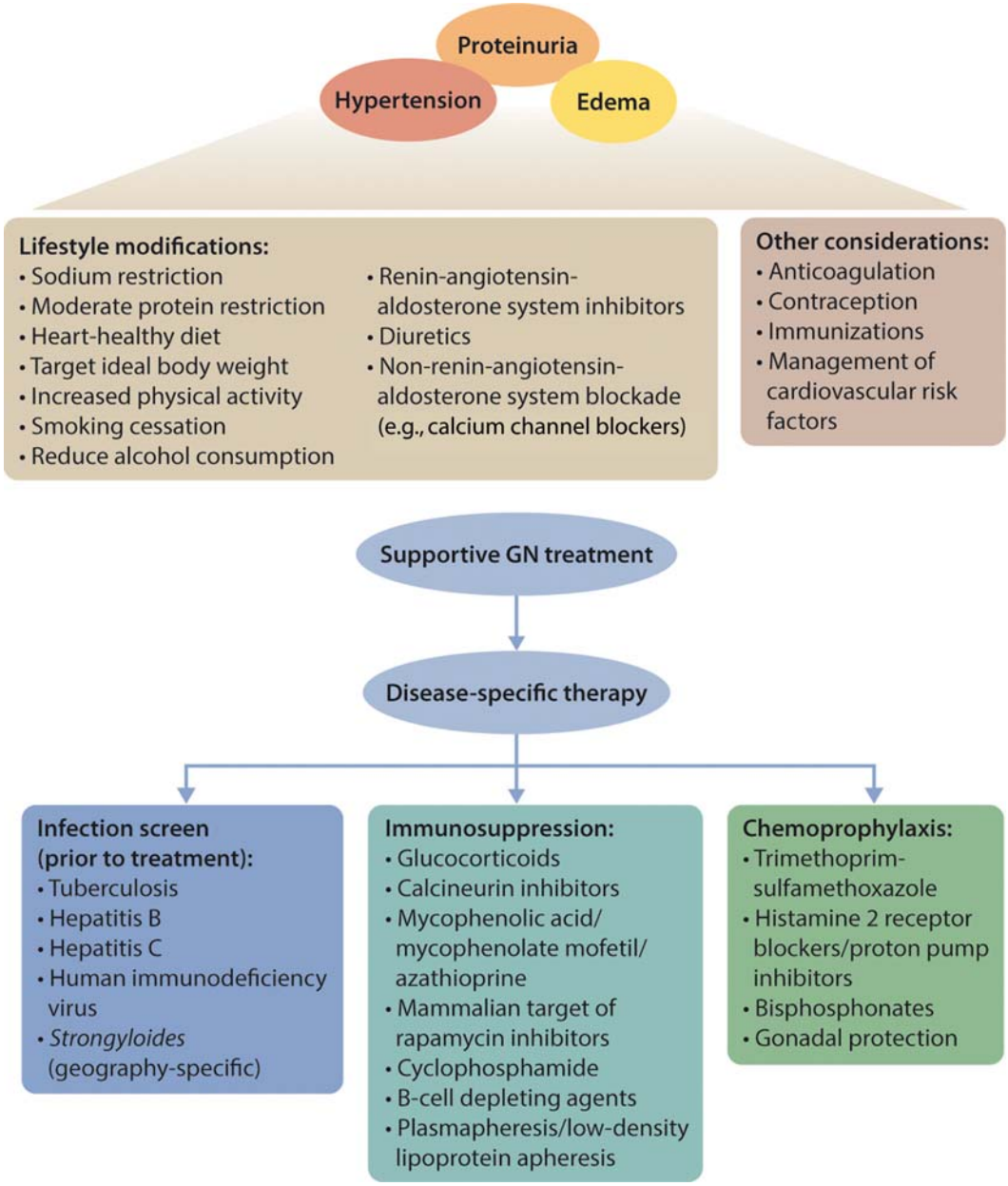

Figure 6 | Summary of supportive management of glomerular disease. Note: Prednisone and prednisolone are equivalent, used in the same dosage, and have both been used in RCTs, depending on the country of origin. All later usages of "prednisone" in this guideline refer to prednisone or prednisolone. All later usages of "glucocorticoids" refer to prednisone or prednisolone, unless otherwise specified. GN, glomerulonephritis; RCT, randomized controlled trial.

address other metabolic and thrombophilic consequences of the NS (Figure 6). These relatively nontoxic therapies may prevent, or at least modulate, the need for immunosuppressive drugs, which have potential adverse effects. Such supportive therapy may not be necessary in steroid-sensitive MCD with rapid remission, or in patients with GN and only microscopic hematuria, preserved GFR, and neither proteinuria nor hypertension (commonly seen in early IgAN).

Practice Point 1.4.1. Use loop diuretics as first-line therapy for treatment of edema in the nephrotic syndrome	• Twice daily dosing preferred over once daily dosing; daily dosing may be acceptable for reduced GFR • Increase dose of loop diuretic to cause clinically significant diuresis or until maximally effective dose has been reached • Switch to longer acting loop diuretic such as bumetanide or torsemide/torasemide if concerned about treatment failure with furosemide, or if concerned about oral drug bioavailability
Practice Point 1.4.2. Restrict dietary sodium intake	• Restrict dietary sodium to <2.0 g/d (<90 mmol/d)
Practice Point 1.4.3. Use loop diuretics with other mechanistically different diuretics as synergistic treatment of resistant edema in the nephrotic syndrome	• All thiazide-like diuretics in high doses are equally effective. None is preferred. • Thiazide diuretics, administered with an oral or i.v. loop diuretic, will impair distal sodium reabsorption and improve diuretic response • Amiloride may provide improvement in edema/hypertension, and counter hypokalemia from loop or thiazide diuretics • Acetazolamide may be helpful for the metabolic alkalosis of diuresis • Spironolactone may provide improvement in edema/hypertension, and counter hypokalemia from loop or thiazide diuretics
Practice Point 1.4.4. Monitor for adverse effects of diuretics	• Hyponatremia with thiazide diuretics • Hypokalemia with thiazide and loop diuretics • Impaired GFR • Volume depletion, especially in pediatric/elderly patients • Hyperkalemia with spironolactone and eplerenone especially if combined with RAS blockade
Practice Point 1.4.5. Strategies for diuretic-resistant patient	• Amiloride • Acetazolamide • i.v. loop diuretics (bolus or infusion) alone • i.v. loop diuretics in combination with i.v. albumin • Ultrafiltration • Hemodialysis • Amiloride may reduce potassium loss and improve diuresis. Acetazolamide may help to treat metabolic alkalosis but is a weak diuretic

Figure 7 | Edema management in NS. GFR, glomerular filtration rate; i.v., intravenous; NS, nephrotic syndrome; RAS, renin–angiotensin system.

Nephrotic edema

Significant edema and weight gain are common with the NS. This clinical presentation can complicate a patient's symptoms and control of BP and may be mediated by an intrinsic defect in sodium excretion by the kidney.[24] The mainstays of treatment are diuretics accompanied by moderate dietary sodium restriction (1.5–2 g/d or 60–90 mmol/d of sodium; Figure 7).

Nephrotic patients are often diuretic resistant, even if the GFR is normal. Loop diuretics are considered first-line in treating nephrotic edema, and twice daily administration is usually preferred. Higher doses of loop diuretics are typically required, due to decreased delivery of the drugs to the loop of Henle (larger volume of distribution with hypoalbuminemia), or to binding of the filtered drug with filtered albumin. However, repetitive administration of furosemide can induce short-term (braking phenomenon, acute diuretic resistance) and long-term (compensatory tubular sodium absorption, chronic diuretic resistance) adaptations, of which the mechanisms are not well known. Some evidence demonstrates more favorable pharmacokinetic profiles and more consistent oral bioavailability with longer-acting torsemide and bumetanide, compared with furosemide (at least in heart failure studies).[25]

Combining a loop diuretic with a thiazide-like diuretic (hydrochlorothiazide, metolazone, chlorthalidone) can be an effective oral regimen to overcome diuretic resistance, by blocking sodium resorption at several sites within the nephron. In high doses, the efficacy of thiazide-like diuretics is similar. It is recommended to give the thiazide diuretic 2–5 hours prior to loop diuretic infusion for peak drug levels, and to maximize the blockade of distal sodium reabsorption.

Plasmin in nephrotic urine can activate the epithelial sodium channel, potentially contributing to diuretic resistance. Amiloride blocks the epithelial sodium channel and may be a potentially useful add-on therapy for edema/hypertension and hypokalemia management in NS.[26] The use of amiloride has not been validated in RCTs.

Acetazolamide is a weaker diuretic, but as a carbonic anhydrase inhibitor, it may be helpful if severe metabolic alkalosis is present.

If a patient fails with maximally dosed oral loop diuretic, then it is reasonable to transition to intravenous loop diuretics, with individual practice preference for intravenous bolus versus continuous infusion. Avoid administration of loop diuretics as a rapid intravenous "push," as toxicity can occur (hearing loss and/or tinnitus). The administration of a loop diuretic as a continuous infusion may mitigate the toxic effects and provide sustained diuretic excretion.

Gastrointestinal absorption of diuretics may be uncertain in severe NS because of intestinal wall edema, and intravenous loop diuretics (by bolus injection or infusion) may be necessary to provoke an effective diuresis. A blunted response to intravenous diuretics may be due to decreased intravascular volume with associated activation of the neurohumoral and renin–angiotensin systems (RAS). For the intravenous diuretic-resistant patient with hypoalbuminemia, intravenous albumin can be added to intravenous diuretic therapy to improve intravascular volume, diuresis, and natriuresis. Several studies of intravenous (salt-poor) albumin with intravenous furosemide have shown transient clinical benefit from combination therapy, but comparison of the data is difficult due to differences in study design. There is not a lot of significant research evidence that albumin is effective in reducing edema in the NS in adults. The clinical effects of albumin in children may be more promising. It may be reasonable to consider intravenous albumin in the diuretic-resistant patient who fails to respond to maximal dosing of intravenous diuretic alone or in diuretic combinations, and whose serum albumin is <2.0 g/dl (20 g/l). Albumin can be administered by premixing with a loop diuretic, or by giving 25–50 g albumin solution 30–60 minutes prior to the intravenous loop diuretic (maximal effect of intravascular volume expansion).[27] However, in nephrotic patients, most of the administered albumin will be rapidly excreted in the urine, and any effect on plasma albumin level will be transient at best. Occasionally, mechanical ultrafiltration and/or hemodialysis are required for resistant edema, especially if the GN is accompanied by AKI.

Potassium-sparing diuretics (such as spironolactone or amiloride) are helpful for maintaining blood potassium levels in the normal range and might have additive effects to thiazides or loop-acting diuretics in terms of natriuresis for management of hypertension or edema.[28]

Water restriction is usually not necessary in the management of edema in the NS, as patients are often intravascularly volume depleted and more prone to dehydration with intensive diuretics. However, water restriction may be necessary in patients who develop hyponatremia.

Research recommendations

- RCT to:
  - evaluate the efficacy of intravenous albumin plus diuretics versus diuretics alone for the management of edema in diuretic-resistant patients with severe NS[29]
  - test the efficacy of amiloride versus other diuretic classes for nephrotic edema
  - compare loop diuretics in NS (furosemide vs. bumetanide vs. torsemide) for efficacy and optimal dose administration
  - compare oral versus i.v. bolus versus i.v. continuous infusion of diuretics in NS
  - evaluate when it is clinically most appropriate to treat a diuretic-resistant patient with ultrafiltration or hemodialysis

1.5 Management of hypertension and proteinuria reduction in glomerular disease

As in all chronic kidney disease (CKD), the aim of BP control is to both protect against the cardiovascular (CV) risks of hypertension (stroke, heart failure, coronary artery disease) and delay progressive loss of GFR. Lifestyle modification (salt restriction, weight normalization, regular exercise, reduction in alcohol intake, and smoking cessation) should be an integral part of the therapy for BP control. Antihypertensive therapy may not be necessary in all patients with glomerular disease (i.e., steroid-sensitive MCD; Figure 8 and Figure 9).

Reduction in proteinuria is important, as it reflects control of the primary disease, reduction of glomerular hypertension, and also reduction of podocyte damage (likely a major factor in glomerular scarring). Most studies suggest that the loss of kidney function in the progressive histologic patterns discussed in this guideline largely can be prevented if proteinuria can be reduced to levels below 0.5 g/d, and progression slowed if reduced to levels below 1–1.5 g/d. The exceptions are MCD and SSNS, for which complete remission defines the disease course. Proteinuria (or plasma factors present in proteinuric urine) may also be toxic to the tubulointerstitium. In NS, a reduction of proteinuria to a non-nephrotic range often results in an elevation of serum proteins (particularly albumin) to normal levels. This elevation in serum albumin reduces thromboembolic and infection risk and often alleviates many of the patient's symptoms, and the metabolic complications of the NS, and thereby improves quality of life.

The antiproteinuric agents of choice are angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARBs), which may reduce proteinuria by up to 40%–50% in a dose-dependent manner, particularly if the patient complies with dietary salt restriction. There is little evidence to suggest that ACEi differ from ARBs in this respect. Although concomitant use of ACEi or ARBs may result in additive antiproteinuric activity, the combination has been associated with an increase in AKI and hyperkalemia events in RCTs involving diabetic subjects.[30,31]

Although this has not been demonstrated directly in large RCTs involving patients without diabetes, the data are sufficient to advise caution. Even as monotherapy, ACEi and/or ARBs lower GFR, and a 10%–20% increase in SCr is often observed. Unless creatinine continues to rise, this moderate increase reflects their effect on kidney hemodynamics and not worsening intrinsic kidney disease, and should not prompt withdrawal of the medication. However, if a patient's GFR is rapidly changing, an ACEi or ARB may further contribute to kidney insufficiency and should not be used. If antiproteinuric medication dosing is limited by clinically significant hyperkalemia, this may be countermanded by the use of potassium-wasting diuretics, correction of metabolic acidosis, or oral potassium-binding agents. Liberalization of sodium intake may also help to some extent.

Alternatively, if the patient is unable to tolerate an ACEi or ARB, a direct renin inhibitor (DRI) or mineralocorticoid

Practice Point 1.5.1.	Use an ACEi or ARB to maximally tolerated or allowed dose as first-line therapy in treating patients with both hypertension and proteinuria	• Do not stop ACEi or ARB with modest and stable increase in serum creatinine (up to 30%) • Stop ACEi or ARB if kidney function continues to worsen, and/or refractory hyperkalemia • Combinations of ACEi and ARB may be used in young adults without diabetes or cardiovascular disease, but benefits and safety are uncertain Caveat: do not start ACEi/ARB in patients who present with abrupt onset of NS. These drugs can cause AKI especially in patients with MCD
Practice Point 1.5.2.	Target systolic blood pressure in most adult patients is <120 mm Hg using standardized office BP measurement. Target 24 h mean arterial pressure in children is ≤50th percentile for age, sex, and height by ambulatory blood pressure monitoring	• Refer to KDIGO BP Guideline (https://kdigo.org/guidelines/blood-pressure-in-ckd/) • Formally speaking, SBP <120 mm Hg has not been validated in GN. In practicality, we are able to achieve an SBP of 120–130 mm Hg in most patients with glomerular disease
Practice Point 1.5.3.	Uptitrate an ACEi or ARB to maximally tolerated or allowed daily dose as first-line therapy in treating patients with GN and proteinuria alone	• Indicated for persistent proteinuria despite treatment of primary GN with immunosuppression (where indicated) • Avoid use of an ACEi or ARB if kidney function is rapidly changing
Practice Point 1.5.4.	Proteinuria goal is variable depending on primary disease process; typically, <1 g/d	• It may be reasonable to delay initiation of ACEi or ARB for patients without hypertension with podocytopathy (MCD, SSNS, or primary FSGS) expected to be rapidly responsive to immunosuppression • Proteinuria goal is disease-specific in adults with GN
Practice Point 1.5.5.	Monitor labs frequently if on ACEi or ARB	• Titration of ACEi or ARB may cause acute kidney injury or hyperkalemia
Practice Point 1.5.6.	Counsel patients to hold ACEi or ARB and diuretics when at risk for volume depletion	• Increased risk for acute kidney injury and hyperkalemia • Counsel patients according to level of education in a culturally sensitive manner • Consider transiently stopping RASi during sick days
Practice Point 1.5.7.	Use potassium-wasting diuretics and/or potassium-binding agents to reduce serum potassium to normal, in order to use RAS blocking medications for BP control and proteinuria reduction Treat metabolic acidosis (serum bicarbonate <22 mmol/l)	• Loop diuretics • Thiazide diuretics • Patiromer • Sodium zirconium cyclosilicate (each 10 g of sodium zirconium cyclosilicate contains 800 mg of sodium) • Supplement with oral sodium bicarbonate
Practice Point 1.5.8.	Employ lifestyle modifications in all GN patients as synergistic means for improving control of hypertension and proteinuria	• Restrict dietary sodium to <2.0 g/d (<90 mmol/d) • Normalize weight • Exercise regularly • Stop smoking
Practice Point 1.5.9.	Intensify dietary sodium restriction in those patients who fail to achieve proteinuria reductions, and who are on maximally tolerated medical therapy	• Restrict dietary sodium to <2.0 g/d (<90 mmol/d). Consider using mineralocorticoid receptor antagonists in refractory cases (monitor for hyperkalemia)

Figure 8 | Management of hypertension and proteinuria in glomerular disease. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; KDIGO, Kidney Disease: Improving Global Outcomes; MCD, minimal change disease; NS, nephrotic syndrome; RAS, renin–angiotensin system; RASi, renin–angiotensin system inhibitors; SBP, systolic blood pressure; SSNS, steroid-sensitive nephrotic syndrome.

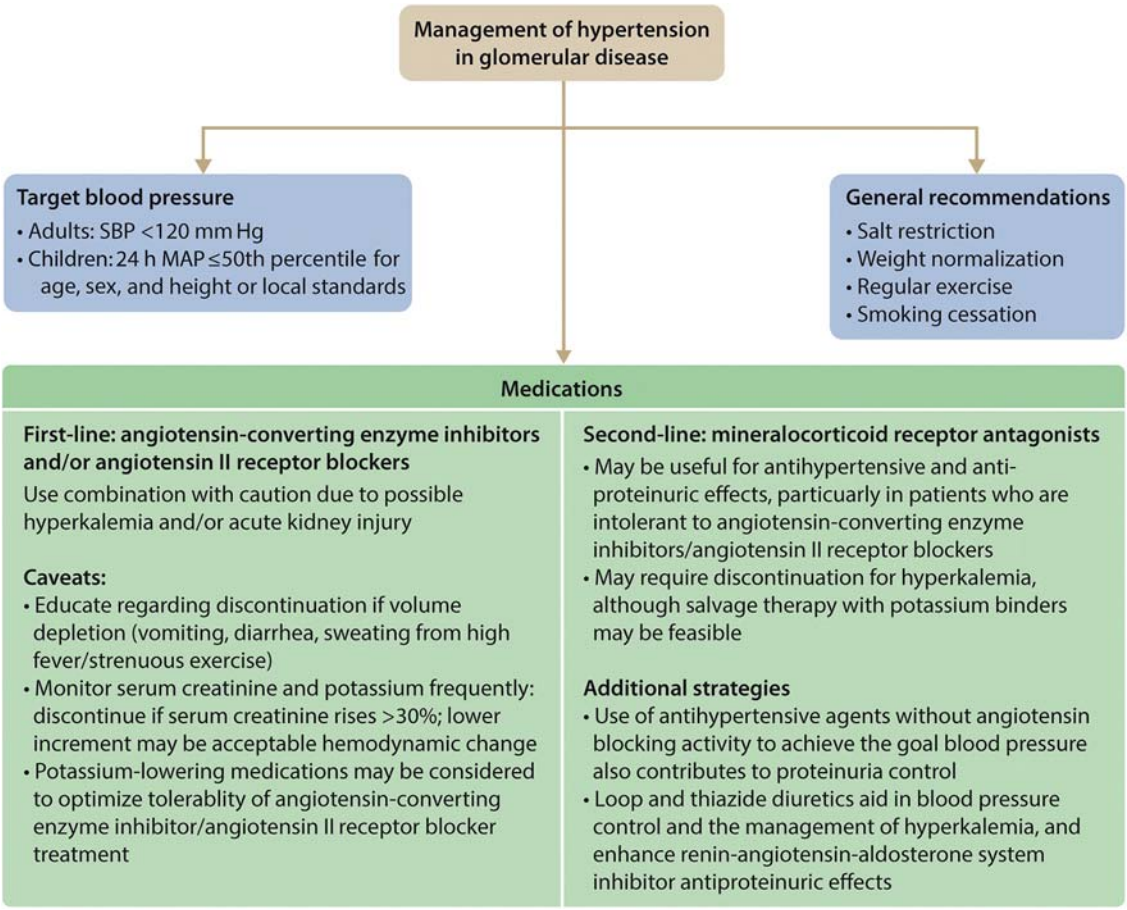

Figure 9 | Management of hypertension in glomerular disease. MAP, mean arterial pressure; SBP, systolic blood pressure.

receptor antagonist (MRA) can be used.[32] As with ACEi/ARBs, hyperkalemia and reduction in GFR are side effects of these medications, so routine laboratory monitoring is recommended. However, the use of combination ACEi or ARBs with DRI is not recommended due to an increased risk of hyperkalemia,[33] at least as described in a trial involving subjects with diabetes.

Some patients are unable to tolerate even low-dose ACEi, ARB, MRA, or DRI. In this circumstance, alternative antihypertensive agents are recommended for both control of BP and improvement in urine protein excretion. Nondihydropyridine calcium channel blockers (CCB), such as diltiazem and verapamil, modestly reduce proteinuria. Beta blockers, diuretics, and α-1 blockers also reduce proteinuria, but to a lesser degree. Dihydropyridine CCB, methyldopa and guanfacine, have little impact on proteinuria and may even increase proteinuria. Patients who fail to achieve adequate reduction in urine protein (despite control of BP) should be counseled to further restrict dietary sodium as a nonpharmacologic means of reducing proteinuria.

Meta-analyses have suggested that a sustained decline of 30% from baseline for albumin excretion rate or total PER may be an acceptable surrogate outcome for eventual doubling of SCr or kidney failure as hard outcome criteria for a favorable impact on CKD progression.[34–36]

The evidence for kidney protective therapy is the subject of a *KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease*.[18]

Research recommendations

- RCTs to determine the safety and efficacy of the addition of MRAs to RAS inhibitor (RASi) monotherapy in the treatment of nondiabetic proteinuric kidney diseases
- RCTs to determine the safety and efficacy of using newer potassium-lowering agents to maximize RASi therapy in nondiabetic proteinuric kidney diseases

1.6 Management of hyperlipidemia in glomerular disease

Hyperlipidemia in patients with glomerular disease reflects the impact of diet, the patient's underlying genetic predisposition, the presence of NS, and the complications of treatment for the glomerular disease including glucocorticoids, mammalian target of rapamycin (mTOR) inhibitors

(sirolimus and everolimus), and calcineurin inhibitors (CNI; cyclosporine A more often than tacrolimus).[37,38] Treatment of hyperlipidemia in patients with NS may follow the guidelines that apply to the general population and use the same lipid-lowering agents, but demonstration of CV event reduction or quality-of-life improvement is lacking in patients with hyperlipidemia from glomerular disease or its treatment (Figure 10).[39] Risk factors include family history, obesity,

Practice Point 1.6.1.	Treatment of hyperlipidemia may be considered in patients with the nephrotic syndrome, particularly for patients with other cardiovascular risk factors, including hypertension and diabetes	High quality data are lacking to guide treatment in these patients
Practice Point 1.6.2.	Use lifestyle modifications in all patients with persistent hyperlipidemia and glomerular disease: • Heart-healthy diet • Increased physical activity • Weight reduction • Smoking cessation	• Not well studied as primary means of reducing lipids in nephrotic syndrome • Can be used as primary therapy in low-risk individuals with mild to moderate hyperlipidemia • Additive to pharmacologic treatment of hyperlipidemia • Considered first-line treatment of hyperlipidemia in children • Consider a plant-based diet • Avoid red meat
Practice Point 1.6.3.	Consider starting a statin drug as first-line therapy for persistent hyperlipidemia in patients with glomerular disease: • Assess ASCVD risk based on LDL-C, Apo B, triglyceride and Lp (a) levels, age group, and ASCVD 'risk enhancers' • Align statin dosage intensity to ASCVD risk • Statins can be initiated in children aged > 8 years with concerning family history, extremely elevated LDL-C or Lp(a), in the context of informed shared decision-making and counselling with patient and family	• Reduced eGFR (<60 ml/min/1.73 m^2 not on dialysis) and albuminuria (ACR >30 mg/g) are independently associated with an elevated risk of ASCVD • ASCVD risk enhancers include chronic inflammatory conditions such as systemic lupus erythematosus, rheumatoid arthritis, history of preeclampsia, early menopause, South Asian ancestry, chronic kidney disease and human immunodeficiency virus/AIDS (accuracy of ASCVD risk estimators have not been well validated for adults with chronic inflammatory disorders or human immunodeficiency virus) • Adherence to changes in lifestyle and effects of LDL-C lowering medication should be assessed by measurement of fasting lipids and appropriate safety indicators 4–12 weeks after statin initiation/dose adjustment or inflammatory disease-modifying therapy/antiretroviral therapy, and every 3–12 months thereafter based on need to assess adherence or safety
Practice Point 1.6.4.	Consider initiation of non-statin therapy in those individuals who cannot tolerate a statin, or who are at high ASCVD risk and fail to achieve LDL-C or triglyceride goals despite maximally tolerated statin dose: • Bile acid sequestrants • Fibrates • Nicotinic acid • Ezetimibe • PCSK9 inhibitor • Lipid apheresis	• Bile acid sequestrants have a high rate of gastrointestinal side effects limiting their use • Bile acid sequestrants and fibrates have been shown in small studies to reduce serum cholesterol in nephrotic syndrome • Fibrates will increase serum creatinine level due to direct action on the kidney • Ezetimibe has limited vascular and clinical benefits, but is used in statin-intolerant patients as salvage therapy • Nicotinic acid and ezetimibe have not been studied in patients with nephrotic syndrome • PCSK9 inhibitors may be beneficial in nephrotic syndrome; trials ongoing

Figure 10 | Management of hyperlipidemia in glomerular disease. ACR, albumin–creatinine ratio; AIDS, acquired immunodeficiency syndrome; Apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; Lp, lipoprotein; PCSK9, proprotein convertase subtilisin/kexin type 9.

diabetes, concomitant hypertension, impaired GFR, persistent albuminuria, prior cardiovascular disease, and current smoking. Management of hyperlipidemia is most relevant in patients for whom GN cannot be completely ameliorated, and when other risk factors for cardiovascular disease coexist, most commonly hypertension and proteinuria. Persistence of hyperlipidemia can lead to acceleration of atherogenesis in both children and adults.

Dietary restriction of fats and cholesterol alone has only inconsistent and minimal effects on hyperlipidemia in glomerular disease, in particular in NS, and lifestyle modifications (diet, exercise, and weight reduction) have been incompletely studied in glomerular disease.

Statins are well-tolerated and effective in correcting, at least partially, the abnormal lipid profile in NS. Whether statin therapy protects from a decline in GFR has not been established. Some data suggest that certain statins, particularly atorvastatin, may reduce albuminuria. Care is needed when statins are used in combination with other drugs; there is an increased risk of myalgia/myositis when statins are combined with CNI. Extremely limited data are available regarding the efficacy of ezetimibe or fibrates for lowering low-density lipoprotein (LDL) in NS. A recent meta-analysis concluded that the limited information available does not support the use of these agents as monotherapy.[39]

Lipid apheresis, approved to treat familial hyperlipidemia, has also been used to treat hyperlipidemia in patients with steroid-resistant NS (SRNS). In treated patients with NS, cholesterol and triglyceride levels were reduced, and in some, remission of NS was observed. The rationale for the use of PCSK9 inhibitors in NS is reasonably compelling,[38,40] but to date, only a few case reports support the use of these agents. More data are needed concerning the utility of PCSK9 inhibitors in nephrotic hyperlipidemia before they can be broadly recommended.

Research recommendations

- RCTs to assess the safety and efficacy of pharmacologic treatment for the hyperlipidemia accompanying nephrotic and non-nephrotic glomerular disease
- Studies on the impact of lifestyle modifications for reduction of hyperlipidemia in the NS
- Impact of statin drugs on reduction of CV events in patients with the NS; many RCTs show reduction in CV events in the general population who are treated with statin drugs
- Utility of hyperlipidemia treatment in the older patient with NS (>76 years old)
- RCTs for pharmacologic reduction of hyperlipidemia and risks of treatment in children with NS
- RCTs for pharmacologic reduction of hyperlipidemia in the NS with anti-PCSK9 monoclonal antibodies
- Studies to better understand low-density lipoprotein cholesterol (LDL-C) goals of therapy with statins in patients with persisting NS

1.7 Hypercoagulability and thrombosis

The risk of arterial or venous thrombotic events in the NS for both children and adults is higher than that in the general population, especially within the first 6 months of diagnosis. Thrombosis is more common in adults than children, is more often venous than arterial, and differs in frequency according to the underlying histopathology. Deep venous thrombosis (DVT) and renal vein thrombosis (RVT) are the most common. Pulmonary embolism (PE) is also relatively common and may occur without symptoms. Thrombotic events are most common in MN but can occur with other lesions such as MCD or complement-related glomerulopathies. Histologic diagnosis, degree of proteinuria, and serum albumin <2.5 g/dl (25 g/l; Figure 4) remain the best predictors for thrombotic risk. Independently, a low serum albumin level (regardless of degree of proteinuria) can increase the thrombotic event risk. Arterial thrombosis is uncommon in both adults and children, but it had been reported in virtually all arterial vascular beds, including aorta, mesenteric, axillary, pulmonary, iliac, renal, femoral, popliteal, ophthalmic, and cerebral circulations.

Additional risk factors include prior thrombosis, genetic predisposition to thrombosis, antiphospholipid antibodies, immobility, obesity, malignancy, pregnancy, or surgery. An online tool to help calculate bleeding risk versus benefits of anticoagulation in NS is available at https://www.med.unc.edu/gntools/bleedrisk.html. Heparin or its derivatives and/or coumarin agents (vitamin K antagonists or warfarin) are the current agents of choice for prophylaxis and/or treatment of venous or arterial thromboembolic events occurring in the context of NS. There are no RCTs comparing the efficacy and/or safety of low-molecular-weight heparin to warfarin in NS. There are many drug–drug interactions with warfarin, especially with immunosuppressive agents, such as CNIs, so the physician should be mindful when the patient is on multiple drugs.

Direct oral anticoagulant (DOACs) have not been systematically studied in nephrotic patients for prophylaxis or treatment of thrombosis. In August 2018, the literature consisted only of 4 case reports and 3 conference proceedings.[41,42] An open-label pharmacokinetic study of apixaban is underway in nephrotic patients without diabetes, with a primary outcome for dosing information, not clinical outcomes (NCT02599532). DOACs may have fewer drug interactions than warfarin, but their safety and efficacy for both treatment and prophylaxis of venous thromboembolism (VTE), arterial thromboembolism (ATE), and PE in NS require additional study. DOAC use in atrial fibrillation was associated with lower bleeding and all-cause mortality when compared to warfarin (CKD G1–G5D).[41,43]

The efficacy and safety of DOACs in pediatric patients is not established. Pediatric VTE is uncommon; however, its

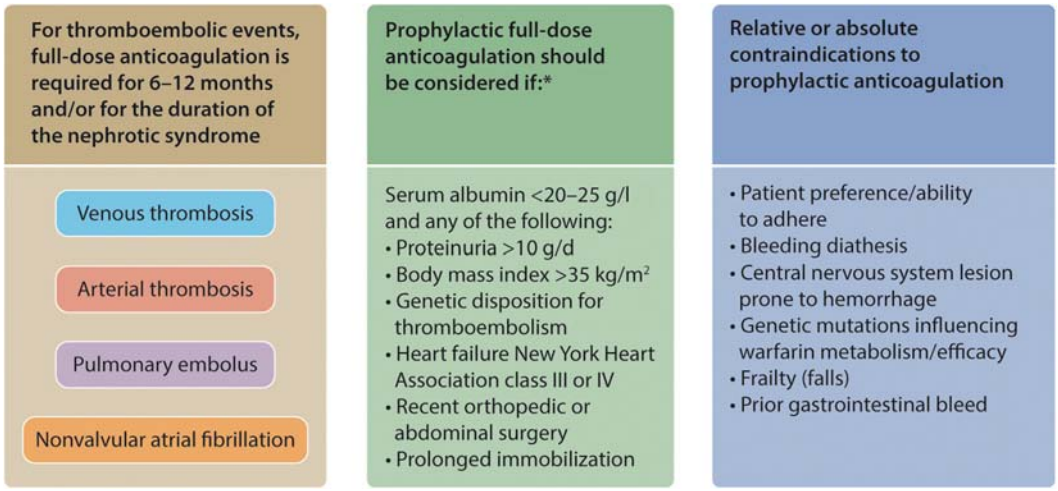

Figure 11 | Anticoagulation in NS. *Membranous GN carries a particularly high risk of thromboembolic events. NS, nephrotic syndrome.

incidence has been increasing over the past 2 decades. Heparin and warfarin traditionally have been used in this population, mostly based on extrapolation of results of studies in adults.

Practice Point 1.7.1: Full anticoagulation is indicated for patients with thromboembolic events occurring in the context of nephrotic syndrome. Prophylactic anticoagulation should be employed in patients with nephrotic syndrome when the risk of thromboembolism exceeds the estimated patient-specific risks of an anticoagulation-induced serious bleeding event (Figure 11).

Practice Point 1.7.2: Anticoagulant dosing considerations in patients with nephrotic syndrome (Figure 12 **and** Figure 13[44]).

Research recommendations

- RCTs of prophylactic anticoagulation in the nephrotic patient with GN: These RCTs should examine the safety and efficacy of heparin (low- or high-molecular-weight), warfarin, DOAC versus no anticoagulant therapy for prophylaxis of VTE or ATE in such patients.
- Robust estimates of absolute thrombosis risk-adjusted for glomerular disease type, serum albumin, PCR, ACR, eGFR, age, comorbidities (e.g., obesity, genetic thrombophilia, immobilization, prior DVT/PE)
- RCTs to test the efficacy and safety of DOACs versus warfarin for prophylaxis and treatment in NS
- Studies to determine whether high protein-binding of DOACs leads to urinary losses and lower drug efficacy
- Observational data to ascertain current practice in prescribing DOACs in patients with NS
- Observational study comparing rates of arterial thrombosis in nephrotic patients who are untreated versus receiving anticoagulation
- Further research to determine whether the biochemical profile used to estimate risk of VTE differs between adults and children
- Clinical trials to define the optimal duration of anticoagulation in patients with venous or arterial thrombosis or PE
- A clinical trial to determine the efficacy and safety of inferior vena cava filters for PE in patients with NS

Prophylactic anticoagulation during transient high-risk events

- Low-dose anticoagulation (e.g., unfractionated heparin 5000 U subcutaneous twice per day)
- Low–molecular-weight heparin: dose reduction may be advised with creatinine clearance <30 ml/min (unadjusted for body surface area); avoid in kidney failure

Full warfarin anticoagulation for thromboembolic events

- Intravenous heparin followed by bridging to warfarin is preferred
- Higher than usual heparin dosing may be required in nephrotic syndrome due to antithrombin III urinary loss
- Long-term experience with warfarin makes it the anticoagulant of choice until pharmacokinetic studies are performed with newer agents
- International normalized ratio should be monitored frequently, since warfarin–protein binding may fluctuate with changing serum albumin
- Target international normalized ratio is 2–3
- These recommendations are not supported by randomized controlled trials
- Be watchful of interactions of warfarin with other medications

Factor Xa inhibitors (Xai): not systematically studied in patients with nephrotic syndrome

- Dosing in the general population is adjusted according to serum creatinine, creatinine clearance (estimated by Cockcroft–Gault equation), age, and weight. Urinary clearance of the Xa inhibitors varies:
  - Apixaban, 27%
  - Edoxaban, 50%
  - Rivaroxaban, 66%
- The effects of hypoalbuminemia on drug dosing have not been studied, and these drugs are heavily albumin-bound, which is likely to substantially affect their half-lives
- Protein binding:
  - Apixaban, 92%–94%
  - Edoxaban, 55%
  - Rivaroxaban, 92%–95%
- Despite a few favorable case reports, the pharmacokinetic properties of these drugs require additional study for both safety and efficacy before they can be generally recommended in nephrotic patients

Direct thrombin inhibitors (DTI): not systematically studied in patients with nephrotic syndrome

- Dosing in the general population is adjusted according to creatinine clearance for dabigatran. No adjustment is required for argatroban. The urinary clearance of the DTI varies:
  - Argatroban, 22% (6% metabolites; 16% unchanged drug)
  - Dabigatran etexilate, 7%
- The effects of hypoalbuminemia on drug dosing have not been studied, and these drugs are modestly albumin-bound, which is likely to affect their half-lives
- Protein binding:
  - Argatroban, 54%
  - Dabigatran etexilate, 35%
- Despite improved safety in the general population, the pharmacokinetic properties of these drugs require additional study for both safety and efficacy before they can be recommended in nephrotic patients

Figure 12 | Anticoagulant dosing considerations in patients with NS. NS, nephrotic syndrome.

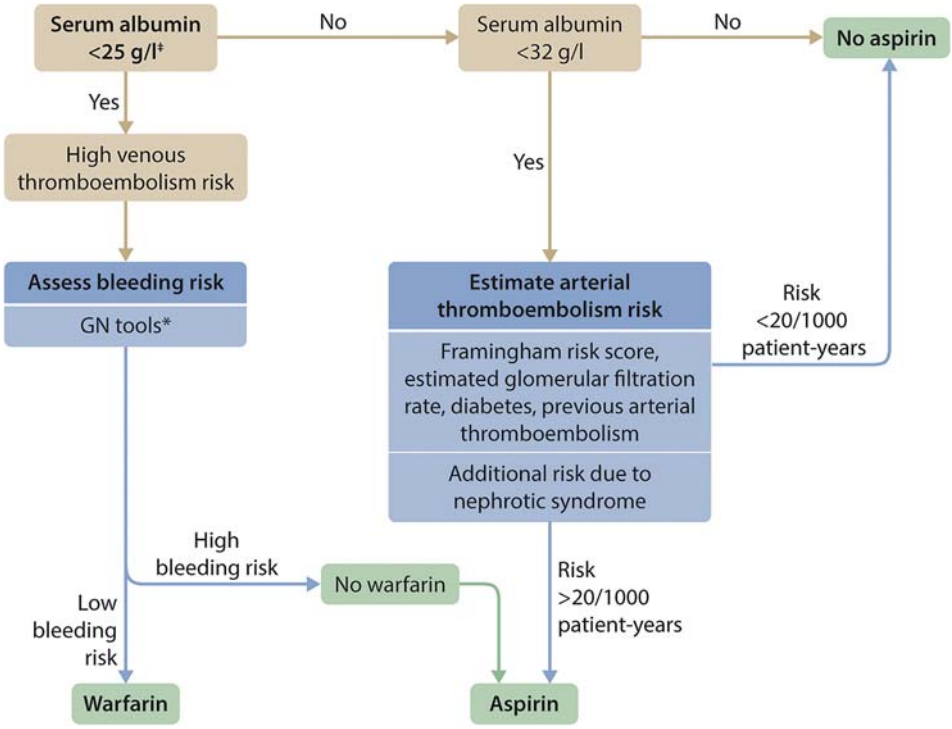

Figure 13 | Prophylactic anticoagulation in adults with GN/nephrotic syndrome. Reproduced from *Kidney International*, volume 89, issue 5, Hofstra JM, Wetzels JFM. Should aspirin be used for primary prevention of thrombotic events in patients with membranous nephropathy? Pages 981–983, Copyright © 2016, with permission from the International Society of Nephrology.[44] Note: This algorithm was developed for patients with membranous nephropathy. Its value is unknown for patients with nephrotic syndrome (NS) due to other underlying diseases. In pediatric patients with glomerulonephritis (GN), consider formal hematology consultation for evaluation of venous thromboembolism (VTE) and bleeding risk. Framingham Risk Score is not available for pediatric patients. ‡Albumin value of 25 g/l or 32 g/l (2.5 g/dl or 3.2 g/dl) is measured using bromocresol green (BCG). A value of 20 g/l or 30 g/l (2 g/dl or 3 g/dl) should be used when bromocresol purple (BCP) or immunoassays for serum albumin levels are used. *Please go to https://www.med.unc.edu/gntools/bleedrisk.html.

1.8 Risks of infection

Epidemiology

A high order of clinical vigilance for bacterial infection is vital in patients with glomerular disease, including nephrotic patients. This is particularly important in nephrotic children with ascites, in whom the fluid should be examined microscopically and cultured for spontaneous bacterial peritonitis. Bacteremia can occur even if clinical signs are localized to the abdomen. Erythrocyte sedimentation rate is unhelpful, but an elevated C-reactive protein level may be informative.

Parenteral antibiotics should be started once cultures are taken. If repeated infections occur, serum immunoglobulins should be measured. If serum IgG is <600 mg/dl (6 g/l), there is limited evidence that infection risk is reduced by monthly administration of intravenous immunoglobulin 400 mg/kg to keep serum IgG >600 mg/dl (>6 g/l). Patients with glomerular disease receiving immunosuppressive agents are at increased risk for a variety of infections, including community-acquired pneumonia, sepsis, and other infectious diseases.

Screening for unrecognized, latent infectious disease

Unrecognized, untreated latent disease may flare when immunosuppression for glomerular disease is initiated. Diagnostic evaluations to disclose and treat these prior to or concomitant with the initiation of therapy can reduce morbidity and mortality. Appropriate screening is clearly dependent on exposures that may be unique in particular geographic regions and/or occupations. Although we cannot provide exhaustive coverage of these issues, a few caveats are provided.

- Serologic tests for syphilis, HIV, hepatitis B (HBV), and hepatitis C (HCV) are commonly sought as potential underlying causes for glomerular disease (Chapter 7). If identified, either related to or independent of the glomerular disease diagnosed, treatment should be considered either preceding or concomitant with immunosuppressive therapy, depending on the urgency of the timing of immunosuppression. Immunosuppressive therapy (glucocorticoids and or cytotoxic/immunomodulating agents, rituximab) can induce a serious exacerbation of HBV replication and thus aggravate liver disease (Chapter 7).
- Latent tuberculosis (TB), common in many populations, should be screened for if appropriate by QuantiFERON testing and/or purified protein derivative skin testing and treated concomitantly with immunosuppression. A recent study demonstrated that 4 months of rifampin is noninferior to 9 months of isoniazid and pyridoxine for treatment of

latent TB.[45] Some caution should be exercised in prescribing rifampin in patients receiving glucocorticoids, as rifampin may decrease the bioavailability of glucocorticoids.

- Infection with the helminth *Strongyloides stercoralis* should be screened for and treated in at-risk individuals prior to the initiation of immunosuppression, especially glucocorticoids. The diagnosis, treatment, and prevention of hyperinfection from *Strongyloides* has recently been reviewed.[46] Eosinophilia, and high serum IgE levels, may raise suspicion in an otherwise asymptomatic individual from an endemic area. *Strongyloides* may be transformed from an asymptomatic infection to a potentially lethal systemic disease (hyperinfection syndrome) by exposure to as little as a few days of glucocorticoid therapy. In patients at risk of harboring asymptomatic *Strongyloides* in whom glucocorticoid therapy is contemplated, screening is advised. The least expensive type is stool examination for ova and parasites. In the event that screening is unavailable or delayed in a high-risk patient, some have advocated for empiric treatment with ivermectin or second-line agents if ivermectin is contraindicated or unavailable.

Vaccinations and prophylaxis

Adults and children with GN and NS (as well as CKD in general) are at increased risk of invasive pneumococcal infection, and they as well as their household contacts should receive pneumococcal vaccination with the heptavalent conjugate vaccine (7vPCV) and the 23-valent polysaccharide vaccine (23vPPV) as well as the annual influenza vaccination. The response does not seem to be impaired by concurrent glucocorticoid therapy. Vaccination with live vaccines (measles, mumps, rubella, varicella, rotavirus, yellow fever) is contraindicated while on immunosuppressive or cytotoxic agents and should be deferred until prednisone dose is <20 mg/d and/or immunosuppressive agents have been stopped for at least 1–3 months. Following treatment of the first episode of SSNS, nonimmunized children should be vaccinated with live vaccines as soon as possible, especially varicella zoster virus.

Patients receiving complement antagonists should be vaccinated with both a meningococcal conjugate vaccine (MenACWY) and a serogroup B meningococcal vaccine (MenB). As these vaccinations may confer only partial protection from meningococcal infection, the Centers for Disease Control recommend consideration of concomitant meningococcal antibiotic prophylaxis (https://www.cdc.gov/meningococcal/clinical/eculizumab.html).

Exposure to varicella can be life-threatening, especially in children. Treatment should be given with zoster immune globulin if exposure does occur, and antiviral therapy with acyclovir or valaciclovir begun at the first sign of chickenpox lesions (see Chapter 4, SSNS for additional details on management in children). Herpes zoster prevention is recommended. The live, attenuated Zostavax® vaccine is contraindicated in patients who are immunosuppressed and immunodeficient. The newer recombinant Shingrix vaccine is safe, but immunosuppression may reduce its efficacy.

Immunize healthy household contacts with live vaccines to minimize the risk of transfer of infection to an immunosuppressed child, but avoid direct exposure of the child to gastrointestinal, urinary, or respiratory secretions of vaccinated contacts for 3–6 weeks after vaccination.

As noted below, prophylactic trimethoprim–sulfamethoxazole (TMP-SMX) should be administered during periods of high-dose prednisone therapy to prevent *Pneumocystis* infection. This strategy may also apply to other immunosuppressive agents such as rituximab.

Practice Point 1.8.1: Use pneumococcal vaccine in patients with glomerular disease and nephrotic syndrome, as well as patients with chronic kidney disease (CKD). Patients and household contacts should receive the influenza vaccine. Patients should receive herpes zoster vaccination (Shingrix).

Practice Point 1.8.2: Screen for tuberculosis (TB), hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and syphilis in clinically appropriate patients (Chapter 7).

Practice Point 1.8.3: Strongyloides superinfection should be considered in patients receiving immunosuppression who once resided in endemic tropical environments and who have eosinophilia and elevated serum immunoglobulin E (IgE) levels.

Practice Point 1.8.4: Prophylactic trimethoprim–sulfamethoxazole (TMP-SMX) should be considered in patients receiving high-dose prednisone or other immunosuppressive agents (rituximab, cyclophosphamide).

Atovaquone or pentamidine may be substituted for the sulfa-allergic. This suggestion is mainly based on studies of immunosuppressed patients without glomerular disease.

Research recommendations

- Further studies concerning prevention and treatment of infections developing in patients with glomerular disease receiving immunosuppressive agents
- Additional research to better understand the management of immunosuppression-induced hypogammaglobulinemia

1.9 Outcome measures

Remissions, kidney failure, mortality

A definitive assessment of the efficacy of a treatment for GN requires the demonstration that kidney failure has been prevented or substantially delayed, mortality reduced, or quality of life improved. The Standardised Outcomes in Nephrology

(SONG) initiative is focusing on these issues from both the patient and provider perspectives.[47] Safety is also an important component of evaluation of treatment effects. Very few studies in glomerular disease have been of sufficient duration or have analyzed sufficient numbers of patients to accurately assess these outcomes. This is not surprising, given the slow natural history of many of the histologic variants of glomerular disease in this guideline. The other accepted outcome measure for many of these disorders is complete remission, assessed by the complete disappearance of abnormal proteinuria (<300 mg/24 hours). However, most studies rely on other surrogates as predictors of clinical outcomes. These surrogate outcome measures include changes in proteinuria (e.g., partial remission of proteinuria), change in kidney function, "point of no return," quality of life, and quality of health.

Changes in proteinuria

A quantitative change in proteinuria (or albuminuria) is presented in most studies. This is often categorized as complete remission, usually defined as proteinuria <0.3 g per 24 hours (PCR <300 mg/g [<30 mg/mmol]), or partial remission, defined as proteinuria >0.3 g but <3.5 g per 24 hours or a decrease in proteinuria by ≥50% from the initial value and <3.5 g per 24 hours. However, definitions vary and are not used consistently, even within a specific GN pattern. The variations in these definitions will be discussed in each disease-specific Chapter. A percentage decline in proteinuria or albuminuria of >30% is also predictive of protection from progression to kidney failure with moderate reliability.[35,48]

Changes in kidney function

Changes in kidney function are usually measured by changes in SCr, eGFR, or endogenous CrCl. These need to be substantial to indicate true disease progression (e.g., doubling of SCr, or halving of CrCl or eGFR). This is because most patients with GN have gradual changes in kidney function, and there are many factors that may modify the SCr value besides progression of kidney disease (see *Evaluation of GFR* above). In more recent studies, changes over time in eGFR have been reported to predict harder outcome measures, such as kidney failure. A ≥40% decline in eGFR from baseline over a 2–3-year period has been suggested as a surrogate outcome measure for kidney failure in clinical trials. Its utility in general management of patients with various forms of glomerular disease needs further testing. In the absence of kidney failure as a defined adverse outcome, the slope of eGFR over time may also be an adequate and reliable marker of change in kidney function, provided that sufficient data at sequential time points are available, the slope is sufficiently linear, and there are no acute effects of the agent used for treatment of GN.[49,50]

Changes in GFR are often described qualitatively as "deteriorating" or "rapidly deteriorating" kidney function. These terms have no precise definitions, but they are in common usage, especially in certain histologic categories such as vasculitis and LN. These are descriptive terms, and the value of a particular therapy can be properly evaluated only when it is compared to treatment of another group with similar clinical and histologic characterizations and in the setting of an RCT. Where available, these are presented in each Chapter.

"Point of no return"

This concept has no precise definition but describes a situation in the natural history of a chronic glomerular disease where severe loss of kidney function (to an eGFR <20–30 ml/min per 1.73 m^2) is accompanied by such extensive and irreversible kidney injury (primarily interstitial fibrosis and tubular atrophy, and/or bilateral renal atrophy) that any therapeutic strategy being tested cannot reasonably be expected to alter the natural history of progressive deterioration in kidney function (therapeutic futility). The presumption is that such patients should be excluded from clinical trials since they are expected to be "non-responders," and therefore may dilute any treatment effect and adversely affect the power of the study. Furthermore, these subjects with reduced kidney function may be at higher risk of adverse effects of the therapies being tested. In the absence of precise definitions of the "point of no return," it is not possible to know, in most of the published trials, whether the inclusion or exclusion of such patients has masked any therapeutic benefit. Even among patients who have reached a point at which specific interventions are likely futile, continuation of therapies directed at avoidance of non-kidney complications such as coronary artery disease, stroke, and congestive heart failure is highly appropriate.

Quality of life and quality of health

Patients' own perceptions of their quality of life and quality of health, and their preferences, are extremely important elements of the assessment of therapy, but they are often an underappreciated and/or unmeasured parameter in the evaluation of many of the clinical trials reviewed in this guideline. These factors are particularly relevant when considering the risk–benefit ratio analysis of interventions, which may include the short- and long-term risks of immunosuppressive treatments, but they often do not account for the patient's perspective in relationship to real or perceived impact on their quality of life. These unassessed elements have the potential to significantly obfuscate outcomes (e.g., concerns about body image in young women/girls treated with glucocorticoids could impact adherence to therapy). The recent introduction of patient-related outcomes (Patient-Reported Outcomes Measurement Information System [PROMIS]) that allows a more rapid assessment has the potential to provide a more uniform

quality-of-life determination that is standard across all chronic diseases (see SONG-GN initiative[47]).

The lack of such data is a substantial evidence gap in the evaluation of studies relating to the management of glomerular disease.

Practice Point 1.9.1: Goals for proteinuria reduction with treatment vary among the various specific causes of glomerular disease.

Practice Point 1.9.2: A ≥40% decline in eGFR from baseline over a 2–3-year period has been suggested as a surrogate outcome measure for kidney failure.

This threshold has mainly been examined in the context of clinical trials, and its utility in a nonclinical trial setting needs to be better understood.

Research recommendations

- Further analysis of disease-specific surrogate outcome measures, such as slope of GFR, in the specific forms of glomerular disease
- Additional data on impact of treatments on quality of life in glomerular disease

1.10 Impact of age, sex, ethnicity, and genetic background

The infrequency of RCTs of treatment for GN resulted in uncertainty about generalizability (i.e., whether the demonstrated benefits [or lack of efficacy] of any treatments will still emerge if patients are then treated who come from different ethnic groups and/or are of different age or sex) compared to those included in the published studies. Examples of this issue are: whether it is reasonable to extrapolate treatment recommendations from children to adults with MCD, and vice versa; whether expectations of effectiveness of regimens for LN proven in Caucasians can be appropriately extended to those of other ethnicities; and whether the safety observed with a course of immunosuppression in the young applies equally to the elderly.

Furthermore, few available RCTs are statistically powered to examine less-common adverse effects of therapy. It is not yet clear if new insights into these and other issues will emerge from a better understanding of the pharmacogenetic variations that can substantially alter the pharmacokinetics and/or pharmacodynamics of immunosuppressive and other agents, such as thiopurine transferase activity assessment in subjects chosen to receive azathioprine or assessment of genetic variants that affect the anticoagulant properties of warfarin. Although early evidence suggests that such genetic traits may alter clinical outcome, the cost of such pharmacogenetic testing also needs consideration, and, as yet, there is little robust evidence that these factors should modify the treatment of glomerular disease.

Research recommendation

- Additional research concerning the impact of ethnicity and ancestry on treatment and outcomes of GN

1.11 Genomics, transcriptomics, proteomics, metabolomics

The evolving focus on "personalized" or "precision" medicine has brought the diverse fields of genomics, transcriptomics, proteomics, and metabolomics to center stage in the field of management of glomerular disease. As yet, these developments are preliminary and at a "proof-of concept" stage. Nevertheless, the evidence for an important impact on management and treatment decisions is emerging and rapidly growing, both in quality and quantity. In some glomerular diseases, such as the FSGS lesions, targeted whole-genome or whole-exome sequencing is likely to have value in the assessment of the phenotype of steroid-resistant forms of FSGS (Chapter 6).[51] Transcriptomic patterns of what appears to be the phenotype of glomerular pathology may yet reveal new promising targets for novel therapeutics.[52] The proteomic and metabolomic patterns of serum or urine may also provide important insights into the prognostic and therapeutic variations in human glomerular disease. The recent observations that serum soluble urokinase plasminogen activator receptor (suPAR) levels and urinary proteomic patterns predict outcome of CKD are examples of these studies.[53,54]

Research recommendations

- Continued research into the genetic origins of specific glomerular lesions (especially in FSGS)
- Continued search for serum and/or urine biomarkers that predict prognosis and lesions of interstitial fibrosis
- Continued search through transcriptomics for novel pathways of glomerular injury that are potentially modifiable

1.12 Use of glucocorticoids and immunosuppressive therapy

The physician ideally seeks a treatment regimen that averts the immediate morbidity of the primary disease process (e.g., achieving remission of NS) and prevents disease progression, while minimizing harmful side effects from immunosuppression. However, physicians must also recognize that prolonged immunosuppressive treatment may be required in order to prevent/delay CKD progression or the development of kidney failure. The focus in the management of chronic patterns of glomerular disease has shifted from cure to control, exemplified by recognition of the short- and long-term benefits of a reduction in proteinuria. This paradigm has translated into use of more extended (or repeated) treatment regimens, with the corollary of more toxic drug exposure over time.

The specific adverse effects of the recommended immunosuppressive agents and the need for routine prophylactic measures are beyond the scope of this guideline, but are familiar in clinical practice, and have been reviewed.[55] Specific regimens that potentially require prolonged exposure to these immunosuppressive agents are identified in the Chapters to follow.

Adverse effects

The potential adverse effects of immunosuppressive therapy must always be discussed with the patient and family before treatment is initiated; this part of the management cannot be overemphasized. The patient should be counseled about the risks that are specific to individual drugs, as well as an overall increased risk for infection and certain cancers. The risks of treatment with many of the agents are significant and may have a substantial latent period (e.g., cyclophosphamide). It is sometimes difficult to reconcile the immediate risks of immunosuppression in the otherwise clinically well patient versus the potential for progression to advanced CKD and kidney failure, both of which are associated with a significant shortening of life expectancy (even with dialysis or transplantation). The physician should be aware of this conundrum; where the evidence for treatment is weak (but potentially life-altering) and the risk for harm is strong, a full disclosure is mandatory.

Individual patient perceptions of the acceptability of any adverse effect may strongly influence the decision (e.g., the possibility of hirsutism with cyclosporine therapy may be perceived as less tolerable in a young woman than in an older man). What might be seen as an acceptable trade-off by the physician may not be viewed similarly by the patient, leading to an issue with therapy compliance.

With more intensive immunosuppressive regimens, prophylaxis may be required to minimize possible adverse effects (Figure 14[62]). Specific recommendations are beyond the scope of this guideline and are without an evidence base specific to the treatment of glomerular disease. It is reasonable to consider potential complications of long-term immunosuppression in glomerular disease based on kidney transplantation data.

Other long-term side effects of immunosuppression include the risk for infection, as well as bone marrow inhibition. Certain immunosuppression increases the risk for cancers. The patient should be offered the opportunity for sperm or ovum storage/preservation (where available) before treatment with the gonadotoxic agents, cyclophosphamide, and chlorambucil. To protect against gonadal toxicity, for

Assessment	Measures
Peptic ulcer disease	H_2 blockers Proton pump inhibitors
Bone health and protection	Individual fracture risk assessment/bone mineral density Calcium and vitamin D supplementation Bisphosphonates Growth hormone (pediatric population)
Infection risk	Assess medical history of herpes zoster infection Screening for hepatitis B virus, hepatitis C virus, human immunodeficiency virus Hepatitis B virus vaccination Zoster vaccination Screening for tuberculosis Screening for strongyloides Pneumocystis prophylaxis Influenza and pneumococcal vaccination* Meningococcal vaccination (if C5 antagonists are used) Monitor gammaglobulin levels and white blood cells levels (rituximab, cyclophosphamide)
Ultraviolet light protection	Limit ultraviolet exposure Broad-spectrum sunscreen
Fertility protection	Gonadotropin receptor hormone agonists (i.e., leuprolide) in cyclophosphamide Sperm/oocyte cryopreservation in cyclophosphamide
Effective contraception	Individual evaluation (preference, thrombosis risk, age)
Cancer screening	Evaluate individual risk factors for malignancy Age-specific malignancy screening Annual dermatology exam Bladder cancer (cyclophosphamide cumulative dose >36 g)

Figure 14 | Screening/prophylaxis for all patients with glomerular disease on immunosuppression. *Not recommended while being treated with moderate to high immunosuppression (e.g., prednisone 10 mg/d) because of reduced antibody response (Salemi and D'Amelio[62]).

example, during cyclophosphamide therapy, women may be offered prophylaxis with gonadotropin-releasing hormone analog (leuprolide) treatment and men may be offered testosterone treatment.[56] Screening for latent infections prior to initiation of some forms of immunosuppression is discussed above.

Glucocorticoids

Chronic glucocorticoid use in both high and low dose is associated with physical changes (weight gain, buffalo hump, acne, thinning skin, purpura, muscle atrophy, growth retardation) and metabolic complications (hyperglycemia or development of overt diabetes, hypertension, hyperlipidemia, bone loss, gastric ulcers). Common long-term glucocorticoid prophylaxis includes the use of antimicrobials to minimize opportunistic infection, and H2-receptor antagonists or proton pump inhibitors (PPI) to prevent peptic ulceration. However, due to recent retrospective data implicating long-term PPI use in unexplained CKD, as well as case reports linking PPI use to AKI and interstitial nephritis, PPI use as first-line peptic ulcer prophylaxis may need to be reconsidered.[55,57,58] Bisphosphonates (except in the presence of kidney failure) are used to minimize loss of bone density during prolonged treatment with glucocorticoids. Please refer to *KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease—Mineral and Bone Disorder*.[59]

Calcineurin inhibitors

CNIs are potentially nephrotoxic, but with lower serum trough levels used in MCD and other glomerular diseases, this side effect is uncommon.[60] Risk factors for tubulointerstitial lesions in childhood MCD included cyclosporine use for >24 months and presence of heavy proteinuria for >30 days during cyclosporine therapy.[61] Susceptibility to CNI nephrotoxicity is also increased in patients with impaired kidney function. Calcineurin agents are also commonly associated with metabolic side effects, including hypertension (cyclosporine [CSA] > tacrolimus [TAC]), hyperlipidemia (CSA > TAC), and diabetes (TAC > CSA). In addition, the CNI side effect profile includes hair growth (CSA), gingival hyperplasia (CSA), and tremors (TAC > CSA).

Cyclophosphamide

The dose of cyclophosphamide should be reduced (by ≥30%) in patients with eGFR <30 ml/min per 1.73 m^2, and by 50% in patients on dialysis, with close monitoring of its marrow-suppressive effect. To reduce bladder toxicity, the duration of cyclophosphamide treatment should not exceed 6 months, and in patients treated with oral cyclophosphamide, the drug should be taken in the morning, and patients should be instructed to have copious fluid intake. Sodium-2-mercaptoethane sulfonate (Mesna) can be prescribed as appropriate if the dosage of cyclophosphamide is considered high. The risk of bladder cancer (and other cancers) is greater if the total cumulative dose of cyclophosphamide exceeds 36 grams (about 500 mg/kg in adults) in a patient's lifetime. Dosing above this threshold should be scrupulously avoided. Yearly urologic screening is recommended in high-risk individuals.

Rituximab (anti-CD20 agents)

Rituximab is associated with infusion reactions, which may sometimes be severe, including anaphylaxis. Prolonged use of rituximab may be associated with hypogammaglobulinemia, especially in older age and preexisting hypogammaglobulinemia. Hypogammaglobulinemia, when severe (<200–400 mg/dl), can promote risk of bacterial infection. Administration of polyclonal intravenous immunoglobulin (sucrose-free) may be indicated, but efficacy is not proven by an RCT. Late-onset leukopenia or pancytopenia can be observed in rituximab-treated patients. Granulocyte colony stimulating factor (G-CSF) may be indicated in patients at high risk of infection.

1.13 Pharmacologic aspects of immunosuppression

Immunosuppressive agents with a narrow therapeutic index include the CNI, cyclosporine, and tacrolimus, as well as the mTOR inhibitors sirolimus and everolimus. Unfortunately, there are no RCTs that compare response to treatment in glomerular disease and different achieved blood levels of these immunosuppressant agents. Dosing and target blood levels are based on established practice in kidney transplantation. The main goal of blood level monitoring is to avoid toxicity due to high drug levels while still maintaining efficacy. Therapeutic drug monitoring can also be used to assess compliance. Response to therapy can often be assessed by proteinuria reduction, which can sometimes be achieved with trough blood levels of CNIs that would be considered sub-therapeutic for solid-organ transplantation.

Although it is not necessary to measure mycophenolic acid (MPA) exposure in most patients, measurement of trough MPA level or its area under the concentration-versus-time curve may provide useful information in selected patients, such as those with LN and repeated flares, or those who develop drug-related complications despite being treated with conventional mycophenolate dosage. It is a good tool to assess compliance, and should be used more frequently (Figure 15).

Research recommendations

- Identify specific target drug levels best suited for achieving remission in GN
- Develop guidelines for bone-loss screening/prophylaxis for short-term use of high-dose glucocorticoids in patients with GN
- RCT of prophylactic intravenous immunoglobulin (i.v. Ig) in hypogammaglobulinemic subjects treated with rituximab

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

1.14 Dietary management in glomerular disease

As mentioned above, dietary restriction of sodium to <2 g/d (<90 mmol/d) is a primary tenet for control of BP and edema (especially in the nephrotic patient) and to improve urinary protein excretion (UPE) independently of medications that reduce proteinuria (Figure 16).

Ensure adequate dietary protein intake in the patient with proteinuria (0.8–1.0 g/kg daily), with a high carbohydrate intake (35 kcal/kg ideal body weight, unless obese) to maximize utilization of that protein. In the MDRD study, up to 5 g dietary protein was added back to the prescription, gram per gram, to compensate in part for the heavy proteinuria of nephrotic patients. Caution is advised regarding a very high–protein diet in the NS, as this can worsen proteinuria. In patients with GFR <60 ml/min per 1.73 m^2, further protein restriction can positively impact kidney function and metabolic acidosis. However, a very low–protein diet should be avoided, as the risk of malnutrition increases. Vegetable (plant) sources of protein should be encouraged whenever possible.

Calorie restriction in patients with reduced GFR and body mass index (BMI) higher than ideal is recommended to facilitate weight loss and to prevent CV and kidney complications (i.e., faster rate of progression of CKD and kidney failure). Patients with GFR <60 ml/min per 1.73 m^2 should consume 30–35 kcal/kg/d. Patients with elevated serum cholesterol who are at risk for CV complications should follow a heart-healthy diet. In addition, fats should be restricted to <30% of total calories, with saturated fats <10%.

Research recommendations

- Further studies on the beneficial effects of diet on progression of disease in glomerular disease and upon quality of life
- RCTs of plant-based low-protein diets in patients with glomerular disease

Practice Point 1.14.1.	Restrict dietary sodium to reduce edema, control blood pressure, and control proteinuria	• Dietary sodium <2.0 g/d (<90 mmol/d)
Practice Point 1.14.2.	Restrict dietary protein based on degree of proteinuria	• Nephrotic-range proteinuria: 0.8–1 g/kg/d protein intake* • Add 1 g per g of protein losses (up to 5 g/d) • The safety of protein restriction in GN has not been established in children • Plant-based diets may be preferred
Practice Point 1.14.3.	Restrict dietary protein based on kidney function	• Estimated glomerular filtration rate <60 ml/min/1.73 m^2 with nephrotic-range proteinuria • Limit or target intake to 0.8 g/kg/d • Avoid <0.6 g/kg/d due to safety concerns and risk of malnutrition • Emphasis on vegetable (plant) sources of protein is appropriate
Practice Point 1.14.4.	Restrict caloric intake to achieve normal body mass index and limit central adiposity in order to reduce chronic kidney disease progression, development of kidney failure, cardiovascular events, and mortality	• Target caloric intake 35 kcal/kg/d • Estimated glomerular filtration rate <60 ml/min/1.73 m^2: 30–35 kcal/kg/d
Practice Point 1.14.5.	Restrict dietary fats in patients with elevated serum cholesterol to prevent cardiovascular complications	• Heart-healthy diet • Dietary fat <30% of total calories • Mono- or polyunsaturated fat 7%–10% of total calories

Figure 16 | Dietary suggestions in glomerular disease. *Ideal body weight. GN, glomerulonephritis.

1.15 Pregnancy and reproductive health in women with glomerular disease

In women of childbearing potential, the risks of pregnancy on the patient, on the fetus, and on the underlying kidney disease must be considered. The care of pregnant patients with GN requires coordination and planning with an obstetrician-gynecologist (OB-GYN) and maternal fetal medicine, as detailed in Figure 17.[63,64] A review of women diagnosed with GN showed that many patients presented during pregnancy with complications, and this may be an opportunity for healthcare providers to act early in the disease process.[65]

Contraception is also an important consideration. RASi and many GN therapies are known to be Category X (potentially teratogenic or embryotoxic) medications. Additionally, immunosuppression, such as cyclophosphamide, can have an impact on long-term fertility. Birth control should continue for a minimum of 6 weeks after stopping mycophenolate. In men treated with mycophenolate, condom use is recommended during intercourse with a woman who might become pregnant and this practice should continue for a minimum of 90 days after stopping mycophenolate. These issues and the psychological impact of these treatments on the patient have to be considered. A summary is provided below on glomerular disease considerations with contraception subtypes (Figure 18[64,66] and Figure 19[64]).

The frequency of glomerular disease present during pregnancy varies by specific disease. IgAN was the most commonly reported GN, with smaller numbers for FSGS, MCD, and MN. The number of patients in many of these

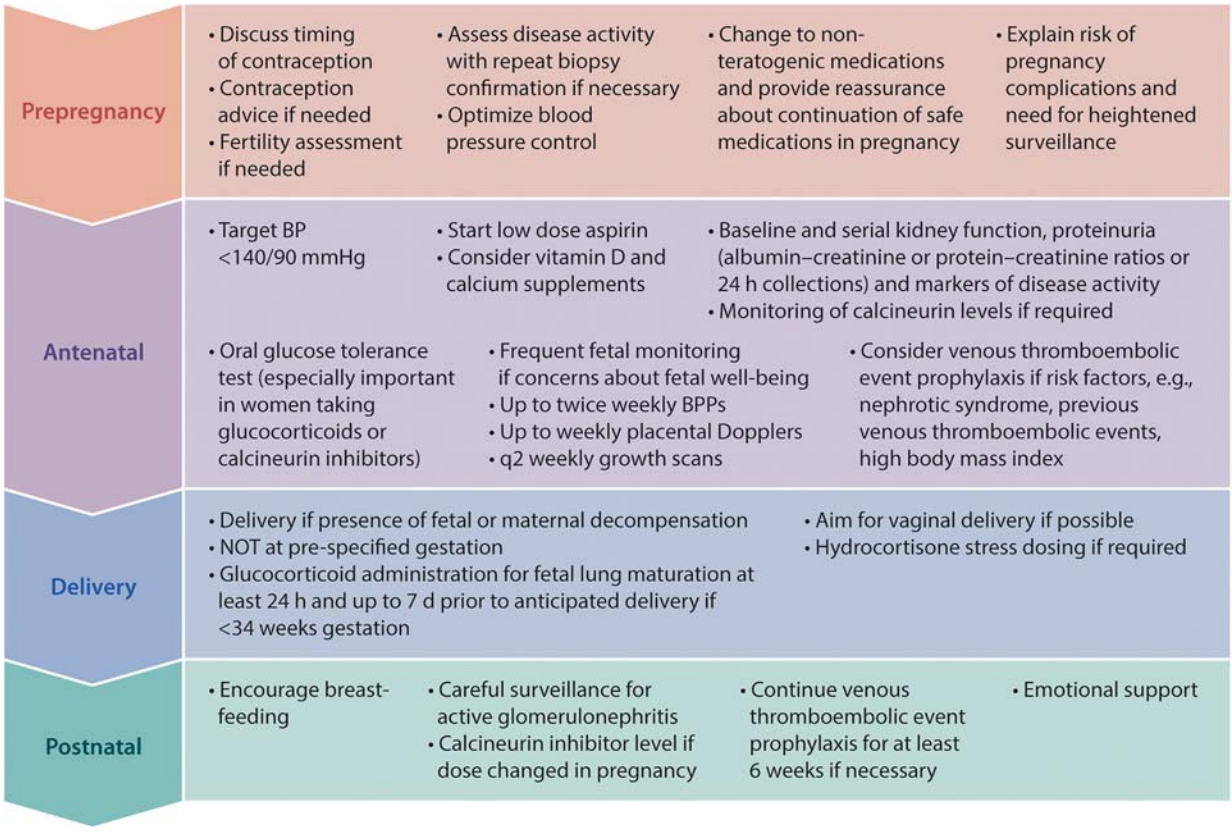

Figure 17 | Coordinated care of pregnant patients with glomerular disease. Adapted with permission from Blom K, Odutayo A, Bramham K, et al. Pregnancy and glomerular disease: a systematic review of the literature with management guidelines. *Clin J Am Soc Nephrol.* 2017;12:1862–1872.[63] Copyright © 2017 by the American Society of Nephrology. BP, blood pressure; BPP, biophysical profile; q2, every 2.

review studies is small.[63] Control of glomerular disease and BP are recommended prior to planning pregnancy. A major predictor of pregnancy outcome is the GFR at time of conception[67–69] and during mid-pregnancy.[70]

Because of the suggested high risk of preeclampsia in patients with glomerular disease, low-dose aspirin (60–150 mg) should be considered after the first trimester to reduce risk and the occurrence of important adverse perinatal health outcomes, but no large trials have been conducted.[71]

Risk to mother and fetus in pregnancy may vary by glomerular disease type. A recent review demonstrated no maternal risk of progression in IgAN, but an increased risk of adverse pregnancy-related outcomes and adverse fetal outcomes.

Risk has been shown to be high in systemic lupus erythematosus (SLE) and antiphospholipid syndrome, but exact risk is not known.[72] In patients with SLE, meta-regression analysis showed positive associations between premature birth rate and active nephritis, and increased hypertension and preeclampsia rates in subjects with active nephritis or a history of nephritis.[73] Antiphospholipid antibodies were associated with hypertension, premature birth, and an increased rate of induced abortion. Stable disease seemed to predict the best outcomes.[74,75] The take-home message from all of these

Contraceptive method	Unintended pregnancy rate within 1st year of use (%)†		Contraindications in glomerular disease	Other considerations
	Perfect use	Typical use		
Estrogen-containing methods (pill, patch, ring)	0.3	9	• Lupus • Venous thromboembolism • Vascular disease	• Breast cancer risk • Cervical cancer risk with immunosuppression • Venous thromboembolism risk in nephrotic syndrome
Progesterone-only pill	0.3	9	• None	• Longest re-dosing interval with desogestrel (may improve typical use) • Possible breast cancer risk, especially >40 yr
Progesterone intrauterine device (Mirena)	0.2	0.2	• None	• Possible breast cancer risk, especially >40 yr • Effective with immuno-suppression, no evidence of increased infection
Progesterone implant (Nexplanon)	0.05	0.05	• None	• Possible breast cancer risk, especially >40 yr
Copper intrauterine device	0.6	0.8	• None	• No associated hormonal risk
Male condom	2	18	• Ineffective for long-term use	• Protects against human immunodeficiency virus and sexually transmitted infection
Female condom	5	21		
None	85	85		

Figure 18 | Contraception in women with glomerular disease. Reproduced from *Kidney International Reports*, volume 3, issue 2, Wiles K, Lightstone L. Glomerular disease in women, pages 258–270, https://www.kireports.org/article/S2468-0249(18)30017-2/fulltext, Copyright © 2018, International Society of Nephrology.[64] This is an open access article under the CC BY NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). †Trussell.[66]

studies is that women with active disease should be strongly discouraged from conceiving until their lupus is controlled.[76–79]

Testosterone use should be discouraged in men with GN.

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

Research recommendation

- Further studies on the specific effects of each glomerular disease on maternal and fetal outcomes

Aspect of health	Glomerular etiology	Impact	Details
Disease prevalence	All	Increased opportunities for diagnosis in women	Higher use of primary care by women, with opportunities for urine and blood pressure screening
	SLE	Female preponderance	Hypothesized modulation of immune system by sex steroids
	Preeclampsia	Affects 3%–5% of women	Estimated to be the most common glomerular disease worldwide. Prevalence underestimated by histological data as biopsy is rare
Fertility	All	Reduced	Effects of CKD on reproductive hormone profile. Voluntary childlessness may contribute
	SLE	Reduced	Active disease, anti-corpus luteum antibodies, endometriosis, reduced ovarian reserve
	SLE, vasculitis, rapidly progressive GN	Reduced	Dose- and age-dependent premature ovarian failure secondary to cyclophosphamide. Consider fertility preservation in premenopausal women
	All	Need for artificial reproductive techniques	Risk of VTE and ovarian hyperstimulation. Single-embryo transfer in CKD
Contraception	All	Required with teratogenic medication	Includes mycophenolate, cyclophosphamide, methotrexate. Progesterone-only preparations are safe and effective in SLE and CKD
Pregnancy	All	Remove teratogens in advance of pregnancy	Advise 3 months for washout and to ensure disease stability. CNI, AZA, HCQ, glucocorticoids are considered safe for pregnancy
	All	Adverse pregnancy outcomes	Increased risk with CKD, hypertension, and proteinuria
	All	Preeclampsia	Prophylaxis with low-dose aspirin (75–150 mg). No diagnostic criteria for superimposed preeclampsia. Clinical overlap with GN signs and symptoms. Surveillance by an expert clinical team. Future use of anti/angiogenic biomarkers predicted
	All	VTE risk in pregnancy increased if proteinuria	Threshold for LMWH prophylaxis unknown
	All	BP	Aim <140/90 mm Hg
	All	Vitamin D deficiency	Replacement if 25-hydroxyvitamin D is <20 ng/ml (50 nmol/l). Continue activated vitamin D analogs as pre-pregnancy
	All	Anemia	Increased erythropoietin requirement. May need synthetic replacement
	All relapsing-remitting GN	Disease activity associated with adverse pregnancy outcome	Aim remission for 6 months before conception. HCQ for all women with lupus nephritis
	SLE	Risk of flare	Risk of ~15% during pregnancy and ~15% in 1-year postpartum
	SLE	Placental transfer of maternal antibodies	Risk of neonatal cutaneous lupus and congenital heart block with anti-SSA (Ro)/SSB (La). Thromboprophylaxis in antiphospholipid syndrome.
	Membranous	Anti-PLA2R	Role in maternal diagnosis/prognosis and fetal effects unknown
Long-term outcomes	Membranous and FSGS	Slower rate of decline in kidney function	Lower levels of BP and proteinuria in women contribute. Additional protective effect also measured in women
	All with a history of preeclampsia	Increased future vascular and kidney disease risk	Causality versus association not determined
	IgA	Kidney disease progression	Not affected by pregnancy if kidney function preserved

Figure 19 | An overview of the impact of glomerular disease in women. Adapted from from *Kidney International Reports*, volume 3, issue 2, Wiles K, Lightstone L. Glomerular disease in women, pages 258–270, https://www.kireports.org/article/S2468-0249(18)30017-2/fulltext, Copyright © 2018, International Society of Nephrology.[64] This is an open access article under the CC BY NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). AZA, azathioprine; BP, blood pressure; CKD, chronic kidney disease; CNI, calcineurin inhibitor; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis, HCQ, hydroxychloroquine; LMWH, low-molecular-weight heparin; PLA2R, M-type phospholipase A2 receptor; SLE, systemic lupus erythematosus; SSA/SSB, Sjögren syndrome antibodies; VTE, venous thromboembolism.

1.16 Treatment costs and related issues

These guidelines have been developed with the goal of providing evidence-based treatment recommendations for glomerular disease that can be used by physicians in all parts of the world. Most of the medications recommended are available at low cost in many parts of the world. These include prednisone, azathioprine, and cyclophosphamide tablets. Monitoring (e.g., by regular checks of blood count) is also cheap and widely available.

The cost of some agents (e.g., CNIs, mycophenolate, rituximab, Acthar® gel, and eculizumab) remains high, but the development and marketing of generic agents and biosimilars is now rapidly reducing costs. However, care must be taken to ensure that variations in bioavailability with these less-expensive generic agents do not compromise effectiveness or safety.

Plasmapheresis remains unavailable in some parts of the world, related to not only the high cost and limited availability of replacement fluids (including human albumin and fresh frozen plasma) but also equipment and staffing costs.

Some treatments suggested as potential "rescue" therapies in this guideline (e.g., rituximab) remain prohibitively expensive in most parts of the world and, as such, are another indication of the urgent need for developing trials that will provide robust evidence of the efficacy of these therapies. Uncertainty about the value of such high-cost agents would also be mitigated if there were comprehensive national or international registries collecting comprehensive observational data on their use; unfortunately, no such registry exists. Research has started in this topic area, but the data are still sparse.

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

Research recommendation

- Further analyses of cost-effectiveness of therapeutic agents, including biosimilars, in glomerular disease

1.17 Goals of glomerular disease treatment

The overall goals of treatment of glomerular disease are:

1. To secure a lasting remission of the clinical manifestations of glomerular disease. A complete remission is more desirable, but a partial remission may suffice in many cases. For those diseases that have a tendency to relapse, the goal is to minimize the frequency and severity of relapses to the maximum extent possible. Treatment choice should take into account the risks of kidney failure and extrarenal complications, and estimates of both likely efficacy and futility.
2. To secure the above benefits in ways that avoid or minimize the development of treatment-related adverse events, particularly those that are potentially life-threatening or those that can adversely affect the patient's quality of life.
3. To administer therapy in ways that maximize patient comfort and quality of life.

1.18 Post-transplantation GN

Virtually all of the histologic variants discussed in this guideline (with the possible exception of MCD) may recur after transplantation. Recurrent disease is recognized as the second or third most common cause of kidney transplant failure. Attempts should be made to assess the risk of recurrent disease prior to transplantation, as this might influence the choice of donor and post-transplant management. A few situations might warrant avoidance of live-donor transplants due to an extremely high risk of recurrent diseases (see specific disease Chapters). Currently, there are no proven strategies to prevent recurrent glomerular disease in kidney transplant recipients. Despite the high rate of recurrent disease, long-term graft survival is still very good in most cases, and transplantation remains the best treatment option for patients with kidney failure secondary to glomerular disease. Where there are specific recommendations in particular variants of glomerular disease that relate to management before transplantation, they are discussed in each relevant Chapter.

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

IMMUNOGLOBULIN A NEPHROPATHY

IgA nephropathy (IgAN) is the most common pattern of primary glomerular disease worldwide and remains a leading cause of CKD and kidney failure. Most commonly, IgAN is asymptomatic and follows a slowly progressive course with approximately 25%–30% of any cohort developing kidney failure within 20–25 years of presentation. Unlike the majority of glomerular disease included in this guideline, management of IgAN is focused on nonimmunosuppressive-based strategies, so-called supportive care, to slow the rate of progression of the disease. This encompasses rigorous BP control, optimal inhibition of the RAS, and lifestyle modification, including weight reduction, exercise, smoking cessation, and dietary sodium restriction (Chapter 1).

Although IgAN is characterized by a single histopathologic criterion of predominant or codominant IgA deposits on kidney biopsy, it is now well recognized that this "disease" exhibits marked heterogeneity in its clinical and pathological features. There is good evidence that the epidemiology, clinical presentation, disease progression, and long-term outcome of IgAN differ across ethnic populations around the world. IgAN is most prevalent and more likely to cause kidney failure in people of East Asian ancestry, followed by Caucasians, and is relatively rare in individuals of African descent. It is unclear if these observations are due to differences in pathogenesis and/or the contribution of varying genetic and environmental influences.

This Chapter makes treatment recommendations for adults with IgAN and provides a practice point on how to apply these recommendations to children aged 1–18 years. Where possible, we have highlighted possible racial differences in response to particular treatment regimens.

IgA vasculitis (Henoch–Schönlein purpura) is dealt with later in this Chapter.

2.1 Diagnosis

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

- **IgAN can only be diagnosed with a kidney biopsy.**
- **Determine the MEST-C score (mesangial [M] and endocapillary [E] hypercellularity, segmental sclerosis [S], interstitial fibrosis/tubular atrophy [T], and crescents [C]) according to the revised Oxford Classification.[80]**
- **There are no validated *diagnostic* serum or urine biomarkers for IgAN.**
- **Assess all patients with IgAN for secondary causes.**

2.2 Prognosis

Several prognostic scores have been developed to assist in predicting kidney outcomes in IgAN. Earlier scoring systems included a variety of pathologic classification schema in cohorts of uniform racial and geographic origin.[80–85] More recently, the standardized MEST-C score as defined in the revised Oxford Classification has been incorporated into development of prognostic scoring systems[86] and machine-learning used to select predictive variables.[87] The largest study to date developed a prognostic score in a multinational and multiracial cohort, including sizeable training and validation populations, including over 4000 subjects.[88] The 5-year risk of halving of a kidney function or kidney failure prediction score incorporates the MEST-C histologic scores and clinical variables measured at the time of kidney biopsy. The tool is available as an online calculator to assist in discussions with patients regarding outcome. Future work will be required to determine if clinical data measured more remotely from the time of biopsy can be used in a similar manner. In addition, one cannot use the tool to make inferences about treatment. However, one can envision using the tool for clinical trial design and analysis in the future. Variables in this prediction algorithm are listed in Figure 20.

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

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

2.3 Treatment

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

- **The primary focus of management should be optimized supportive care.**

Estimated GFR at biopsy.....ml/min/1.73 m²

Systolic blood pressure at biopsy.....mm Hg

Diastolic blood pressure at biopsy.....mm Hg

Proteinuria at biopsy.....g/day

Age at biopsy.....years

Race
- Caucasian
- Chinese
- Japanese
- Other

Use of ACE inhibitor or ARB at the time of biopsy
- No
- Yes

MEST M-score
- 0
- 1

MEST E-score
- 0
- 1

MEST S-score
- 0
- 1

MEST T-score
- 0
- 1
- 2

Immunosuppression use at or prior to biopsy
- No
- Yes

Figure 20 | The data elements included in the International IgAN Prediction Tool. Using clinical and histologic data at biopsy, users can determine a 50% decline in eGFR or kidney failure at selected time intervals. The tool is not validated for use with data obtained remotely from the time of biopsy. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; GFR, glomerular filtration rate; MEST, mesangial (M) and endocapillary (E) hypercellularity, segmental sclerosis (S), and interstitial fibrosis/tubular atrophy (T).

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

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

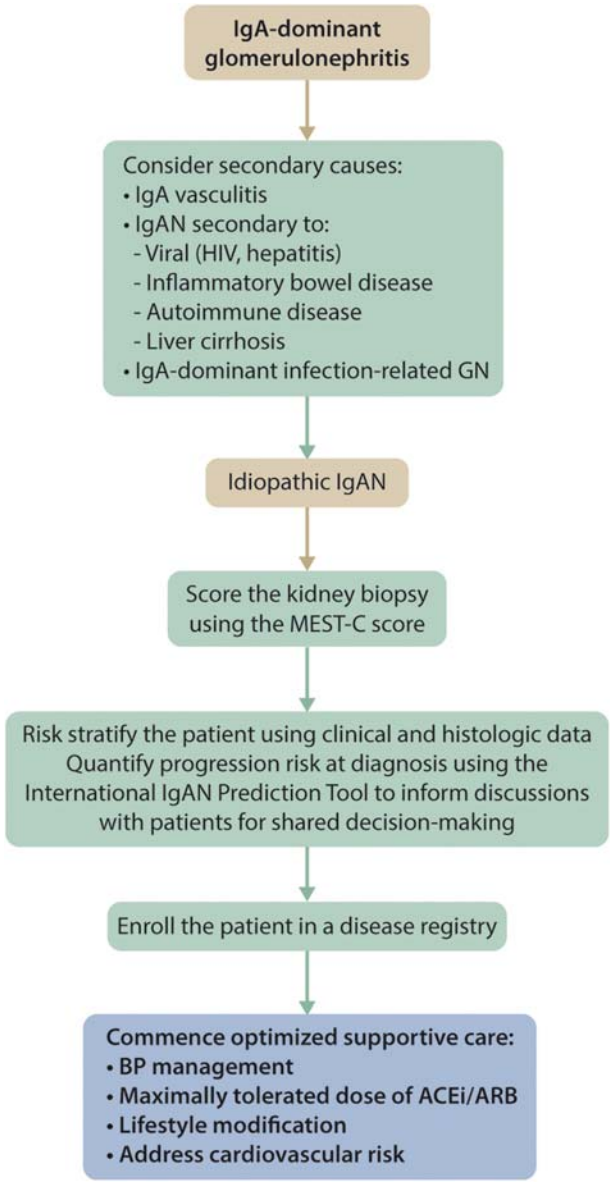

Figure 21 | Initial assessment and management of the patient with IgAN. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; GN, glomerulonephritis; HIV, human immunodeficiency virus; IgAN, immunoglobulin A nephropathy; MEST-C, mesangial (M) and endocapillary (E) hypercellularity, segmental sclerosis (S), interstitial fibrosis/tubular atrophy (T), and crescents (C).

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

This recommendation is based on an extensive body of evidence showing that hypertension and proteinuria are major risk factors for progression of CKD and that treatment of hypertension and reduction of proteinuria reduce the risk of progression to kidney

failure. Data specifically in IgAN, while not extensive, are consistent with these observations. There are no studies to show dual blockade with an ACEi and ARB is superior to single blockade in IgAN. A post hoc *analysis of the STOP-IgAN trial demonstrated no additional benefit with dual blockade.*[89] *In the judgment of the Work Group, a strong recommendation is warranted because of the consistency of the benefits for treatment of hypertension and proteinuria observed across the spectrum of kidney diseases, the generally low risk of harm for hypertension and antiproteinuric treatment, and the lack of rationale for a different recommendation for IgAN specifically.*

Key information

Balance of benefits and harms. Controlling BP and reducing proteinuria slow progression of CKD and reduce CV risk in general CKD populations.[90,91] The benefits of treatment substantially outweigh the potential harms (e.g., orthostatic hypotension and adverse drug reactions). There is no evidence that the benefits and harms are different for patients with CKD due to IgAN, and there is some evidence that they are similar.

Quality of evidence. High-quality data support the benefits of BP control and reduction of proteinuria for slowing of kidney disease progression in all CKD populations.[92] There are limited data specifically in IgAN, but there is no *a priori* reason to suspect that the larger body of evidence is not generalizable to people with IgAN.

The quality of the evidence for the IgAN population is moderate because of the reliance on the indirect evidence from the general CKD studies. Additionally, the small number of RCTs that have examined antihypertensive medication in patients with IgAN have seldom reported critical and important outcomes such as all-cause mortality, kidney failure, or complete remission, and other outcomes are of moderate quality because of study limitations (lack of allocation concealment, or inadequate blinding of participants, and outcome assessors) or imprecision (only one study or few events; Supplementary Table S4[93–95,104] and Supplementary Table S5[93,95–99]).

Values and preferences. The Work Group judged that most patients would place a higher value on the potential benefits of hypertension and antiproteinuric treatment compared to the potential harms associated with treatment.

Resource use and costs. According to the Global Health Observatory data repository (World Health Organization [WHO]), ACEi (and CCB) are widely, but not uniformly, available in high IgAN–prevalence areas. There is much wider variability in the availability of holistic programs to address lifestyle modification, including smoking cessation, weight reduction/dietary modification, and exercise programs for control of hypertension, both across regions and within countries.

Considerations for implementation. Control of BP involves initial lifestyle modification followed by medication in those with persistent hypertension (Chapter 1). Patients should be offered access to weight reduction, dietary modification, and exercise programs, if appropriate, as a part of a holistic approach to control of BP. Targets for BP control in IgAN are no different than those stated in Chapter 1. In particular, there is no evidence to suggest that the BP target should be different between men and women or between people of different races.

Rationale

In comparison to other glomerular diseases, which may be associated with distinct disease relapses, episodes of NS, or AKI, IgAN is typically a slowly progressive disease. In IgAN, strategies to control BP and minimize proteinuria are currently viewed as centrally important in addition to attempts to modify the underlying disease pathogenesis with immunosuppressant medication.[100]

Epidemiologic studies of large IgAN cohorts in North America, Asia, and Europe consistently identify uncontrolled hypertension and proteinuria as independent risk factors for progression in IgAN.[94,101,102] In the study by Le *et al.*, which included outcomes in 1155 patients, there was a statistically significantly improved 10-year kidney survival in patients with sustained proteinuria of 0.5–1 g/d compared to >1 g/d, with 10-year dialysis-free survival of 94% (95% CI: 90%–98%), and 20-year dialysis-free survival of 89% (95% CI: 82%–96%).[101] In an RCT of 49 patients with IgAN, an achieved mean BP of 129/70 mm Hg stabilized GFR over 3 years, whereas patients with an achieved mean BP of 136/76 mm Hg showed an average decline in GFR of 13 ml/min over 3 years.[103] Retrospective data from large registries show that patients with IgAN treated with an ACEi to control BP have a lower rate of annual loss of kidney function than similar patients not treated with ACEi or ARB.[102] An RCT of 44 patients with IgAN demonstrated a benefit of an ACEi (enalapril) on progressive kidney disease (better kidney survival and reduction in proteinuria) compared to equivalent BP control with alternative antihypertensives (nifedipine, amlodipine, atenolol, diuretics, and doxazosin).[96] An RCT of 109 Asian patients with IgAN showed greater proteinuria reduction and slowing of the rate of kidney deterioration with an ARB (valsartan) compared to placebo.[104]

There are no RCT data available on the efficacy or safety of dual blockade with an ACEi and ARB in IgAN. A *post hoc* analysis of the STOP-IgAN trial demonstrated no additional benefit with dual blockade.[89]

Recommendation 2.3.2: We recommend that all patients with proteinuria >0.5 g/d, irrespective of whether they have hypertension, be treated with either an ACEi or ARB *(1B)*.

This recommendation is based on the extensive body of evidence across all types of proteinuric glomerular disease, including IgAN, that higher levels of proteinuria are associated with worse kidney outcomes and that a reduction in proteinuria,

independent of changes in BP control, is associated with improved kidney outcome. There are no studies to show that dual blockade with an ACEi or ARB is superior to single blockade in IgAN. A post hoc *analysis of the STOP-IgAN trial demonstrated no additional benefit with dual blockade.*[89] *In the judgment of the Work Group, a strong recommendation is warranted because of the consistency of the benefit for treatment of proteinuria observed across the spectrum of kidney diseases, the generally low risk of harm of antiproteinuric treatment, and the lack of rationale for a different recommendation for IgAN specifically.*

Key information

Balance of benefits and harms. Reducing proteinuria slows progression of CKD and reduces CV risk.[91,105] For other kidney diseases, the benefits of treatment substantially outweigh the potential harms (e.g., orthostatic hypotension and adverse drug reactions). There is no evidence that the benefits and harms are different for IgAN specifically, and there is some evidence that they are similar. In normotensive individuals, RAS blockade should be initiated cautiously, and we outline a potential approach in the section on *Considerations for implementation*.

Quality of evidence. The evidence for a renoprotective effect of proteinuria reduction in the setting of normotension is of lower quality than the evidence supporting the treatment of hypertension. However, the individual patient-level meta-analysis by Inker *et al.* included studies with a range of BP targets and achieved BP, and across all of these studies, a reduction in proteinuria was associated with improved clinical outcome independent of changes in BP.[106] This analysis has subsequently been updated with results from the TESTING and STOP-IgAN trials and affirmed the initial observations of the Inker *et al.* meta-analysis.[36]

The evidence from the individual patient-level meta-analysis is indirect, as there are a limited number of studies that have compared RASi with usual care in patients with IgAN without hypertension and proteinuria >0.5 g/g. However, 3 studies that include this population reported moderate quality of the evidence for proteinuria and CrCl (study limitations include lack of allocation concealment, or inadequate blinding of participants, and outcome assessors) and low quality of the evidence for doubling SCr (due to very serious imprecision; Supplementary Table S5[93,95–99]).

Values and preferences. The Work Group judged that most patients would place high value on the potential benefits of antiproteinuric treatment compared to the potential harms associated with treatment. However, younger patients with low/normal BP may place a lower value on the potential benefits of RAS blockade due to the risk of orthostatic hypotension.

Resource use and costs. According to the Global Health Observatory data repository (WHO), ACEi are widely, but not uniformly, available in high IgAN–prevalence areas.[107] It is important to note, however, that in some countries, the use of RAS blockade in patients who are normotensive yet proteinuric is widely implemented but not always supported by health insurers.

Considerations for implementation. When commencing RAS blockade in patients who are normotensive, it is imperative that patients are started on low-dose therapy initially, and that dose escalation is controlled with the aim for the patient to be treated with the maximal tolerated dose of either ACEi or ARB to achieve the maximal reduction in proteinuria while minimizing side effects, in particular orthostatic hypotension. The maximal tolerated dose will often be less than the recommended maximal dose for that territory.

Rationale

The severity of proteinuria has been consistently shown in studies from North America, Europe, and Asia to be an independent risk factor for progression in IgAN.[94,101,102] In the study by Le *et al.*, which included outcomes in 1155 patients, there was a statistically significantly improved 10-year kidney survival in patients with sustained proteinuria of 0.5–1 g/d compared to >1 g/d, with 10-year dialysis-free survival of 94% (95% CI: 90%–98%), and 20-year dialysis-free survival of 89% (95% CI: 82%–96%).[101] A meta-analysis of 8 trials involving 866 patients evaluated the antiproteinuric effect of ARB in patients who are normotensive with proteinuria. Compared with a control group, the use of an ARB was associated with a significant reduction in urinary protein excretion in patients with diabetes and moderately increased albuminuria, and nephropathy with overt proteinuria without diabetes. This effect was consistently seen in both Western and Asian populations.[108] Included in this meta-analysis was a small study in IgAN that included 32 patients who were normotensive aged 18–54 years with proteinuria (1–3 g/d) and normal kidney function (CrCl >80 ml/min) who were randomly divided into 4 treatment groups (verapamil 120 mg/d; trandolapril 2 mg/d; candesartan cilexetil 8 mg/d; and placebo).[93] The antiproteinuric response in the trandolapril and candesartan cilexetil groups were similar (–38% vs. –40%) and significantly greater than that of verapamil ($P < 0.01$). In an individual participant-level meta-analysis of data for 830 patients from 11 RCTs, a reduction in proteinuria was associated with a lower risk for doubling of SCr level, ESKD, or death in IgAN, and this was consistent across studies.[106] This effect was independent of the presence or absence of hypertension. There are no RCT data available on the efficacy or safety of dual blockade with an ACEi and ARB in IgAN. A *post hoc* analysis of the STOP-IgAN trial demonstrated no additional benefit with dual blockade.[89]

It is uncertain, however, whether RAS blockade will lead to better outcomes in IgAN with moderately increased albuminuria (30–300 mg/d) and normal BP, given the absence of RCTs addressing this question.

2.3.1 Patients with IgAN who are at high risk of progressive CKD despite maximal supportive care

These patients are defined as those with persistent UPE >1 g/d despite treatment with a maximal tolerated or allowed daily dose of RAS blockade for a minimum of 3 months and having achieved the recommended BP target as described in Chapter

1 for a minimum of 3 months. Variant forms of IgAN may require specific immediate treatment.

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

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

Multiple observational registry studies demonstrate that sustained proteinuria is the most powerful predictor of long-term kidney outcome. Regardless of the nature of the intervention, reduction in proteinuria in observational studies is also independently associated with improved kidney outcome. A recent trial-level analysis of data from RCTs confirms an association between treatment effects on proteinuria and treatment effects on kidney survival (composite of the time to doubling of SCr, ESKD, or death),[36] thereby establishing reduction in proteinuria as a valid surrogate marker of improved outcome in IgAN. Clinical trials included in this analysis typically targeted <1 g/d for proteinuria reduction. Therefore, reduction of proteinuria to <1 g/d is a reasonable target for interventions used in patients with IgAN who remain at high risk of progressive CKD despite maximal supportive care.

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

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

In the absence of a rapidly progressive loss of kidney function, supportive therapy is the mainstay of treatment for adults with IgAN. Following 6 months of optimization of supportive therapy, a substantial proportion of patients with >1 g/d of proteinuria considered for enrollment into clinical trials no longer qualify for randomization due to reduction in proteinuria.[100] Shorter periods of 3 months may be considered in patients already receiving RAS blockade prior to biopsy diagnosis.

The largest available RCT of glucocorticoids is the TESTING study; investigators halted enrollment prematurely due to safety concerns in the glucocorticoid-treated group.[109] Patients in this study had an average level of proteinuria of 2.4 g/d despite intensive conservative therapy; this level is notably higher than that in the patients enrolled in the STOP-IgAN study, in which patients had 1.6–1.8 g of proteinuria per day. Early analysis suggested efficacy of glucocorticoids, and this underlies the recommendation to consider use of this medication in IgAN. However, there were serious adverse events, including 2 deaths related to infectious complications. In discussion with clinicians, patients may choose not to receive glucocorticoids due to risk.

Key information

Balance of benefits and harms. This is a weak recommendation due to the significant risk of toxicity with the therapy. Consideration of glucocorticoid therapy must include a discussion regarding the risk of treatment-emergent toxicity associated with this medication and individualized risk assessment. The efficacy and toxicity of lower doses of glucocorticoids in similar populations are not known and are the subject of an ongoing investigation (NCT01560052).

Quality of evidence. This recommendation is based upon moderate-quality evidence. The quality of the evidence from 4 RCTs that have compared glucocorticoid therapy with supportive therapy was moderate for critical and important outcomes (all-cause mortality, kidney failure, infection, doubling of SCr, and annual GFR loss) because of study limitations or imprecision (few events). However, the quality of the evidence was low for complete remission because of study limitations and inconsistency (I^2 = 60%; Supplementary Table S6[100,109–112]).

Values and preferences. The Work Group judged that most patients would place a high value on preservation of long-term kidney function. However, the tolerance for side effects and adverse events may also be limited in patients with relatively preserved kidney function and asymptomatic proteinuria under 2 g/d. Therefore, clinicians must engage in a thorough discussion of risks and benefits of glucocorticoids and

consider individual patient characteristics that may place them at higher risk of toxicity (Practice Point 2.3.3).

Resource use and costs. Glucocorticoids are included in the WHO Model List of Essential Medicines (2017) and are generally readily accessible and inexpensive.[107] Resources for monitoring for risks of treatment-emergent toxicity (e.g., screening for latent infections, bone mineral density scanning) are, however, not uniformly available.

Considerations for implementation. Practitioners should provide individualized assessment of patient risk of progression and risk of treatment-emergent toxicity. Risks for development of reduction of kidney function and kidney failure can be estimated based using the International IgAN Prediction Tool to guide discussions with patients. Practitioners may consider not offering glucocorticoids in patients with particular clinical characteristics, placing them at higher risk of treatment-emergent toxicity (Practice Point 2.3.2).

Rationale

The Work Group acknowledged the importance of a reduction in proteinuria and short-term loss of eGFR as surrogate markers of long-term prevention of CKD and kidney failure.[36] An initial series of small RCTs supported greater reduction in proteinuria compared to supportive therapy alone, with or without uniform use of RAS blockade.[110,111,113] However, the confidence in estimates of efficacy and toxicity for these studies is low due to small sample size.

The STOP-IgAN RCT included 162 subjects to evaluate the impact of addition of immunosuppressive therapy to supportive care on a hierarchical series of primary outcomes, including proteinuria and GFR targets.[100] At 3 years, patients receiving immunosuppression benefitted from a higher rate of remission of proteinuria (17% vs. 5%, $P < 0.01$). This was not associated with differences in GFR endpoints at 3 years. The proteinuria at randomization was relatively low (1.6 g/d and 1.8 g/d), and over 3 years, patients in the supportive care group experienced only a 4.2 ml/min per 1.73 m^2 decline in kidney function, confirming the impact of rigorous supportive care in IgAN. But this result also means that patients in the immunosuppression arm had low baseline rates of eGFR loss and therefore were unlikely to develop endpoints over a relatively short follow-up period of 3 years. There was one immunosuppression-related death in a patient. Long-term outcome data of the STOP-IgAN cohort after a median follow-up of 7 years showed that 48% of the cohort reached the endpoint of 40% eGFR loss, ESKD, or death, with ESKD developing in 25% of trial participants.[114] The addition of immunosuppression to standard of care did not alter the long-term outcome.

The largest available RCT of patients at high risk of disease progression (TESTING trial) halted enrollment after randomization of 262 of a planned 750 subjects, due to an 11% greater risk of serious adverse events in the glucocorticoid group (95% CI: 4.8%–18.2%).[109] This included 2 deaths related to infectious complications. At the time of analysis, the primary kidney outcome (composite 40% reduction in eGFR, kidney failure, death due to kidney disease) occurred significantly less frequently in the glucocorticoid group (HR: 0.37; 95% CI: 0.17–0.85), suggesting efficacy. There was no difference in the rate of ESKD noted, albeit in the context of premature cessation of the study for safety concerns. There were differences in the patients in the TESTING study compared to the STOP-IgAN trial, and this may account for some differences observed in the toxicity and efficacy of glucocorticoids. Patients were nearly all of Asian descent, had higher median proteinuria excretion (2.5 g/d at baseline), and subjects in the placebo group experienced an annual rate of kidney function decline of –6.95 ml/min per 1.73 m^2.

The TESTING study included patients with eGFR as low as 20 ml/min per 1.73 m^2. However, only 26 randomized patients had an eGFR <30 ml/min per 1.73 m^2, and subgroup analyses were limited by the early termination of the trial. Therefore, evidence of efficacy in patients with very low eGFR is low, and toxicity of immunosuppression may be greater. The TESTING study has continued enrollment with a dose-modified regimen, and the analyses of the originally planned primary outcome is pending. Until these data are available, one can only work with available data suggesting early signs of efficacy of glucocorticoids in patients at high risk of disease progression, with significant risk of toxicity.

Glucocorticoid regimens used in the 3 most recent RCTs are detailed in Figure 22[109–111].

Study	Medication	Start dose	Duration high dose	Taper	Total exposure
TESTING[(1)]	Methylprednisolone	0.6–0.8 mg/kg/d (per investigator), rounded to nearest 4 mg. Max 48 mg/d	2 months	8 mg/month	6–8 months
Manno[(2)]	Prednisone	1 mg/kg/d, max 75 mg/d	2 months	0.2 mg/kg/month	6 months
Lv[(3)]	Prednisone	0.8–1 mg/kg/d	8 weeks	5–10 mg/d every 2 weeks	8 months

Figure 22 | Glucocorticoid regimens used in clinical trials of IgAN where there was uniform use of renin-angiotensin system (RAS) inhibition. [1]Therapeutic Evaluation of Steroids in IgA Nephropathy Global (TESTING)[109]: TESTING Low Dose Study is ongoing [NCT01560052], [2]Manno *et al.*[111], [3]Lv *et al.*[110]

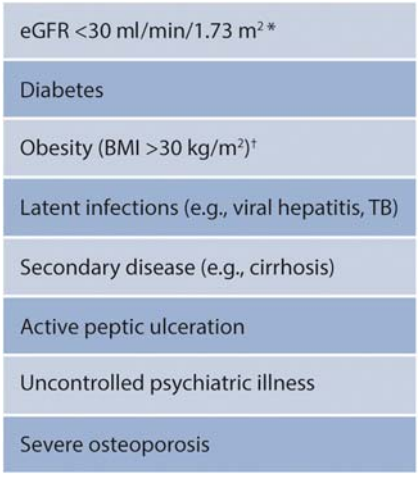

Figure 23 | Situations when glucocorticoids should be avoided, or administered with great caution. *The Therapeutic Evaluation of Steroids in IgA Nephropathy Global (TESTING)[109] study included patients with eGFR 20–30 ml/min per 1.73 m^2, but only 26 patients in total had this range of kidney function. Prespecified subgroup analyses for signals of efficacy and toxicity were underpowered and did not distinguish patients with eGFR <30 ml/min per 1.73 m^2. †High BMI in the TESTING study was not specifically considered an exclusion, but the mean BMI was <24 kg/m^2. BMI, body mass index; eGFR, estimated glomerular filtration rate; TB, tuberculosis.

Practice Point 2.3.1.3: Use of glucocorticoids in IgAN:

- **Clinical benefit of glucocorticoids in IgAN is not established and should be given with extreme caution or avoided entirely in situations listed in Figure 23[109].**
- **There is insufficient evidence to support the use of the Oxford Classification MEST-C score in determining when any glucocorticoid therapy should be commenced.**
- **There are no data to support efficacy or reduced toxicity of alternate-day glucocorticoid regimens, or dose-reduced protocols.**
- **Where appropriate, treatment with glucocorticoid (prednisone equivalent ≥0.5 mg/kg/d) should incorporate prophylaxis against *Pneumocystis* pneumonia along with gastroprotection and bone protection, according to local guidelines.**

Practice Point 2.3.1.4: Management of patients with IgAN who remain at high risk for progression after maximal supportive care (Figure 24[109])

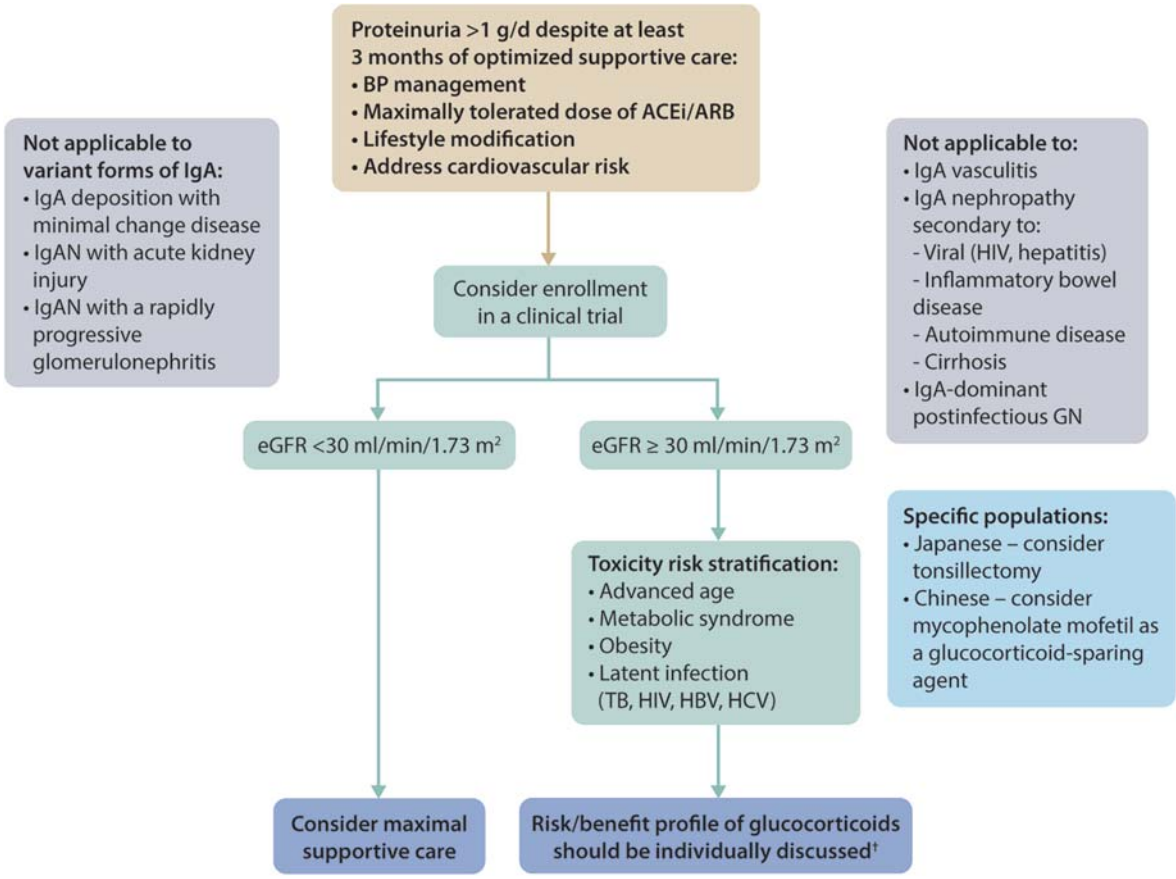

Figure 24 | Management of patients with IgAN who remain at high risk for progression after maximal supportive care. *IgAN with rapidly progressive glomerulonephritis is covered in Practice Point 2.4.3. †The TESTING study[109] shows early evidence of efficacy in patients who had marked proteinuria (2.4 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.

Practice Point 2.3.1.5: Other pharmacologic therapies evaluated in IgAN (Figure 25[115–120])

Agent	Suggested usage	Remarks
Antiplatelet agents	Not recommended	No documented evidence of efficacy
Anticoagulants	Not recommended	No documented evidence of efficacy
Azathioprine	Not recommended	No evidence for efficacy as monotherapy or when combined with glucocorticoids
Cyclophosphamide	Not recommended	Unless in the setting of rapidly progressive IgAN
Calcineurin inhibitors	Not recommended	No documented evidence of efficacy
Rituximab	Not recommended	No documented evidence of efficacy
Fish oil	Not recommended	Patients who wish to take fish oil should be advised of the dose and formulation used in the published clinical trials that reported efficacy.
Mycophenolate mofetil (MMF)	**Chinese patients** In those patients in whom glucocorticoids are being considered MMF may be used as a glucocorticoid-sparing agent	In a single RCT conducted in China, MMF with low-dose glucocorticoids was noninferior to standard-dose glucocorticoids for the treatment of incident IgAN presenting with proliferative histologic lesions (E or C lesions with or without necrosis) on kidney biopsy and proteinuria >1.0 g/d. There were significantly fewer glucocorticoid-related side effects in the combination-therapy arm.[1,5]
	Non-Chinese patients There is insufficient evidence to support the use of MMF	In the RCTs of MMF in non-Chinese patients there was no evidence for efficacy of MMF monotherapy.[2–5]
Hydroxychloroquine	**Chinese patients** In those patients who remain at high risk of progression in spite of optimized supportive care	In a small, short-term RCT conducted in China, hydroxychloroquine introduced to patients with proteinuria of 0.75–3.5 g/d despite optimized ACEi/ARB reduced proteinuria by 48% versus 10% in the placebo group at 6 months.[6]
	Non-Chinese patients There is insufficient evidence to support the use in those patients	Hydroxychloroquine has not been evaluated in non-Chinese patients.

Figure 25 | Other pharmacologic therapies evaluated in IgAN. [1]Hou *et al.*[115], [2]Hogg *et al.*[116], [3]Frisch *et al.*[117], [4]Maes *et al.*[118], [5]Vecchio *et al.*[119], [6]Liu *et al.*[120] ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; IgAN, immunoglobulin A nephropathy; MMF, mycophenolate mofetil; RCT, randomized controlled trial.

	Japanese IgAN	Chinese IgAN	Caucasian IgAN
Clinical practice	Performed routinely (often with pulsed glucocorticoids)	Not routinely performed	Not performed
Remarks	Multiple cohort studies,[1–5] including a large retrospective study with propensity matching,[5] report improved kidney survival following tonsillectomy. A single RCT failed to show a difference in eGFR at 1 year comparing tonsillectomy vs. tonsillectomy and pulsed glucocorticoids, and no longer term data are available from this study.[6]	Inconsistent data from small retrospective cohort studies and a small single-center RCT	Very few data available in this population. Available data do not support the efficacy of tonsillectomy as a treatment for IgAN in Caucasian patients

Figure 26 | Regional use of tonsillectomy as a treatment for IgAN. [1]Yang *et al.*[124], [2]Kawasaki *et al.*[123], [3]Hotta *et al.*[121], [4]Reid *et al.*[95], [5]Hirano *et al.*[125], [6]Kawamura *et al.*[122] eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; RCT, randomized controlled trial.

Practice Point 2.3.1.6: Tonsillectomy in IgAN:

- **Tonsillectomy should not be performed as a treatment for IgAN in Caucasian patients.**
- **Tonsillectomy is suggested in some national guidelines for the treatment of recurrent tonsillitis in patients with IgAN.**
- **Multiple studies from Japan have reported improved kidney survival and partial or complete remission of hematuria and proteinuria following tonsillectomy alone or with pulsed glucocorticoids (Figure 26[95,121–125]; Supplementary Table S7[95,121–124]).**

2.4 Special situations

Practice Point 2.4.1: IgAN with nephrotic syndrome:

- **Rarely, patients with IgAN present with the nephrotic syndrome (including edema and both hypoalbuminemia and nephrotic-range proteinuria >3.5 g/d).**
- **In these cases, mesangial IgA deposition can be associated with light and electron microscopy features otherwise consistent with a podocytopathy resembling MCD.**
- **It is unclear whether this is a specific podocytopathic variant of IgAN or the existence of MCD in a patient with IgAN.**
- **Patients with a kidney biopsy demonstrating mesangial IgA deposition and light and electron microscopy features otherwise consistent with MCD should be treated in accordance with the guidelines for MCD (Chapter 5).**
- **Patients with nephrotic syndrome whose kidney biopsy has coexistent features of a mesangioproliferative glomerulonephritis (MPGN) should be managed in the same way as those patients at high risk of progressive CKD despite maximal supportive care.**
- **Nephrotic-range proteinuria without nephrotic syndrome may also 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.**

Practice Point 2.4.2: IgAN with AKI:

- **AKI can occur in patients with IgAN in the context of severe visible hematuria, commonly in association with an upper respiratory tract infection. 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. Immediate management of AKI with visible hematuria should focus on supportive care for AKI.**
- **IgAN may also present with AKI either *de novo* or during its natural history due to an RPGN with extensive crescent formation, commonly in the absence of visible hematuria. In the absence of visible hematuria and when other causes of an RPGN (e.g., antineutrophil cytoplasmic antibody [ANCA]-associated vasculitis [AAV], anti-glomerular basement membrane [GBM] disease) and reversible causes (e.g., drug toxicity, common pre- and post-kidney causes) have been excluded, a kidney biopsy should be performed as soon as possible.**

Practice Point 2.4.3: IgAN with RPGN:

- **Rapidly progressive IgAN is defined as a ≥50% decline in eGFR over ≤3 months, where other causes of an RPGN (e.g., AAV, anti-GBM disease) and reversible causes (e.g., drug toxicity, common pre- and post-kidney causes) have been excluded.**
- **A kidney biopsy is essential in these cases and will commonly demonstrate mesangial and endocapillary hypercellularity, and a high proportion of glomeruli affected by crescents with areas of focal necrosis.**
- **The presence of crescents in a kidney biopsy in the absence of a concomitant change in serum creatinine (SCr) does not constitute rapidly progressive IgAN; however, these patients require close follow-up to ensure prompt detection of any GFR decline. If this occurs, a second kidney biopsy may be considered.**

- **Patients with rapidly progressive IgAN should be offered treatment with cyclophosphamide and glucocorticoids in accordance with the guidelines for AAV (Chapter 9).**
- **Prophylactic measures that should accompany immunosuppression are discussed in Chapter 1.**
- **There is insufficient evidence to support the use of rituximab for the treatment of rapidly progressive IgAN.**

Practice Point 2.4.4: IgAN and pregnancy planning:
- **IgAN is a disease predominantly of young adults, and all women of childbearing potential should be offered preconception counseling when appropriate.**
- **Preconception counseling should include a discussion on cessation of renin–angiotensin system (RAS) blockade. Blood pressure control should be optimized with alternative antihypertensive medications prior to conception.**
- **In those women at high risk of progressive CKD (Recommendation 2.3.1.1) despite maximal supportive care, a trial of immunosuppression to optimize immunologic activity and reduce proteinuria prior to conception may be preferable to emergent initiation of immunosuppression during pregnancy.**

Practice Point 2.4.5: IgAN in children:
General considerations

- **For the purposes of this practice point, children are defined as those aged <18 years. It is acknowledged that post-pubertal children in some respects may have a similar course and response to treatment as adults with IgAN, but there are insufficient data currently to recommend that they be managed as adults with IgAN.**
- **Visible hematuria is more frequent in children than in adults, and this may account for earlier diagnosis in children.[126]**
- **Children generally have higher eGFR, lower urine protein excretion, and more hematuria than adults at diagnosis.[127]**

Kidney biopsy in children

- **A kidney biopsy is usually performed at presentation of symptoms (hematuria, proteinuria, normal C3) in order to confirm the diagnosis (and rule out other diagnoses) and assess the degree of inflammation/presence of necrosis.**
- **Inflammation, mesangial, and endocapillary hypercellularity tend to be more prevalent in kidney biopsies of IgAN in children than in those of adults.[128–131]**

Treatment

- **There is strong evidence suggesting a benefit of RAS blockade in children.[132] All children with IgAN and proteinuria >200 mg/d or PCR >200 mg/g (>20 mg/mmol) should receive ACEi or ARB blockade, advice on a low-sodium diet, and optimal lifestyle and blood pressure control (systolic blood pressure [SBP] <90th percentile for age, sex, and height).**
- **It is widely acknowledged that treatment of IgAN with immunosuppression differs between adults and children, and that in children, the use of immunosuppressants is more widespread, particularly the use of glucocorticoids. However, RCTs and specific expert consensus-driven indications are lacking.**
- **Evidence derived mostly from retrospective studies suggests that treatment with glucocorticoids (plus second-line immunosuppression) leads to improved kidney survival.[126,133]**
- **In children with proteinuria >1 g/d or PCR >1 g/g (100 mg/mmol) and/or mesangial hypercellularity, most pediatric nephrologists will treat with glucocorticoids in addition to RAS blockade from time of diagnosis. Duration of treatment is not established, but usually 4 weeks of 1–2 mg/kg/d of oral prednisolone (or equivalent) followed by alternate-day tapering over 4–6 months is employed. Regimens including intravenous methylprednisolone are also used.[127,128,130,134]**
- **Evidence for the use of non-glucocorticoid immunosuppressants in addition to glucocorticoids is scarce, but this approach may be considered in more severe cases.**
- **As for adults, IgAN with MCD may be found, and it should be treated as steroid-sensitive nephrotic syndrome (SSNS; Chapter 4).**
- **As in adults, children with rapidly progressive IgAN have a poor outcome, and despite limited evidence, this subgroup should be offered treatment with glucocorticoids (usually as methylprednisolone pulses) and cyclophosphamide.[128,130,135]**

Follow-up

- **Aim for proteinuria ≤200 mg/d (≤400 mg/1.73 m^2/d) or PCR ≤200 mg/g (≤0.2 g/g [≤20mg/mmol]).**
- **Aim for SBP at <90th percentile for age, sex, and height.**
- **Continue to follow patients even after complete remission, as they can relapse even after many years.[136]**

Research recommendations

The following areas are of high priority for future research to improve the treatment and outcomes of patients with IgAN:
- Risk stratification: This is important for both patient evaluation and design of clinical trials.
- The International IgAN Prediction Tool should be:
  - validated in additional racial populations not included in the original cohorts

  - further developed to enable prediction of progression risk after kidney biopsy and serially during follow-up
  - evaluated in relation to specific treatment responses
- Evaluation of therapeutic strategies that minimize or avoid systemic glucocorticoid exposure:
  - Emerging data are required to clarify the role of novel therapies in non-immunosuppressive comprehensive supportive care. The phase 3 PROTECT study (NCT03762850) is evaluating the antiproteinuric and renoprotective effects of sparsentan in IgAN, a novel dual-acting angiotensin II and endothelin type A receptor antagonist. Trials are also underway to evaluate the effect of sodium–glucose cotransporter-2 inhibitors (SGLT2i) on kidney and CV outcomes in nondiabetic kidney disease (NCT03036150, NCT03594110).[137,138] Until all of these studies are completed, the use of SGLT2i in IgAN is not recommended in the absence of diabetes.
  - We need to better understand the value of MMF and hydroxychloroquine in the management of IgAN in different racial groups, and clinical disease severity.
  - A targeted-release formulation (TRF) of budesonide, a glucocorticoid with local release and action in the terminal ileum, has been evaluated in 150 patients with IgAN in a phase 2b study.[139] It has been reported that this approach leads to a significant reduction in proteinuria and offers advantages over systemically acting glucocorticoids with fewer treatment-emergent adverse events. Safety and efficacy of TRF-budesonide is currently being evaluated in a phase 3 study.
  - Other therapeutic strategies being evaluated include inhibition of the complement system (lectin [MASP-2], alternative [Factor B] and final common [C5] pathways, and inhibition of B cell activation and survival (by blocking B cell activation factor [BAFF] of the TNF family and a proliferation-inducing ligand [APRIL] signaling to B cells).
- Identification and validation of serum, plasma, urine, and/or kidney biomarkers to inform:
  - prognostication,
  - treatment selection,
  - monitoring response to treatment,
  - fundamental biology: continued transcontinental collaborative research to identify genetic and environmental factors influencing disease phenotype across races.

IMMUNOGLOBULIN A VASCULITIS

IgA vasculitis (IgAV), formerly Henoch–Schönlein purpura, is a form of vasculitis marked by IgA deposition within the blood vessels of affected tissues. IgAV commonly affects the small blood vessels of the skin, joints, intestines, and kidneys. Rarely, it can affect the lungs and central nervous system. It is the most common form of vasculitis in children. When IgAV occurs in children <16 years old, it is often self-limiting. Adults may have more severe and relapsing disease. Kidney involvement in IgAV is histopathologically indistinguishable from that seen in the kidney-limited disease IgAN. This Chapter outlines management guidance for adults with IgAV-associated nephritis (IgAVN) and provides a practice point for children aged 1–18 years. It must be acknowledged that the evidence base in IgAVN is extremely limited, and so there is a heavy reliance on extrapolating data from IgAN to IgAVN, although we still have no clear understanding of how these 2 diseases are related. We make no specific recommendations on how to treat extrarenal organ involvement, in particular gastrointestinal vasculitis and pulmonary hemorrhage, which can be life-threatening and require immunosuppressive therapy independent of any kidney involvement.

2.5 Diagnosis

Practice Point 2.5.1: Considerations for the diagnosis of immunoglobulin A vasculitis (IgAV):

- **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 based on the criteria described for children.[140,141]**
- **In adults with a vasculitic rash typical of IgAV, a kidney biopsy should be performed in the setting of features consistent with a persistent and/or significant nephritis, RPGN, proteinuria > 1g/d, and/or impaired kidney function.**
- **Assess all adult patients with IgAV for secondary causes.**
- **Assess all adult patients with IgAV for malignancy, with age- and sex-appropriate screening tests.**

2.6 Prognosis

Practice Point 2.6.1: Considerations for the prognostication of IgAV:

- **Retrospective data from a limited number of small registries have identified uncontrolled hypertension and the amount of proteinuria at presentation, and hypertension and mean proteinuria during follow-up, as predictors of a poor kidney outcome in adults with IgAV.[142–144]**
- **The Oxford Classification has not been validated for IgAV.**
- **The International IgAN Prediction Tool[88] is not designed for prognostication in IgAV.**

2.7 Treatment

2.7.1 Prevention of nephritis in IgAV

Recommendation 2.7.1.1: We recommend not using glucocorticoids to prevent nephritis in patients with isolated extrarenal IgAV *(1B)*.

This recommendation puts a high value on the moderate-quality evidence demonstrating the risks of glucocorticoid use with no added benefit for preventing nephritis in IgAV.

Key information

Balance of benefits and harms. The lack of benefit and the well-documented risks associated with glucocorticoids meant the Work Group could not support its use in preventing nephritis in IgAV.

Quality of evidence. This recommendation is based upon moderate-quality evidence derived from RCTs. RCTs that compared prednisone with placebo or supportive therapy in patients with IgAV have not reported on critical and important outcomes, such as all-cause mortality, kidney failure, and complete remission. There was moderate-quality evidence for the development and continuation of kidney disease, but there are concerns due to study limitations (inadequate allocation concealment) and imprecision with very few events (Supplementary Table S8[145–150]).

Values and preferences. The Work Group judged that most patients would place high value on the potential toxicity of this drug and the lack of any clear benefit.

Resource use and costs. None

Considerations for implementation. None

Rationale

There are no RCT data on the effectiveness of strategies to prevent the development of IgAVN in adults with IgAV. There is, however, a significant body of evidence in children that prophylactic use of glucocorticoids in extrarenal IgAV does not reduce the incidence of kidney involvement. In an RCT of 352 children with IgAV, early treatment with prednisolone did not reduce the prevalence of proteinuria 12 months after disease onset.[145] This finding was replicated in 171 children showing that early use of prednisolone did not prevent the development of nephritis.[150] A meta-analysis of 5 RCTs in which 789 children were examined for the effects of short-duration glucocorticoids (2–4 weeks) on preventing persistent nephritis at 6 and 12 months after the presentation concluded that such treatment with glucocorticoid at presentation had no preventive effect on onset of persistent nephritis.[146]

Practice Point 2.7.1.1: Considerations for the treatment of all patients with IgAV-associated nephritis (IgAVN) who do not have an RPGN:

- **Assess cardiovascular risk and commence appropriate interventions as necessary.**
- **Give lifestyle advice, including information on smoking cessation, weight control, and exercise, as appropriate.**
- **No specific dietary intervention has been shown to alter outcomes in IgAVN.**
- **Treat to nationally agreed-upon blood pressure targets. KDIGO suggests treating to an SBP target of <120 mm Hg measured using standardized office blood pressure measurement (Figure 8).**
- **Treat with maximally tolerated dose of ACEi or ARB if proteinuria >0.5 g/d.**
- **Offer participation in a clinical trial if one is available.**

2.7.2 Patients with IgAVN who are at high risk of progressive CKD despite maximal supportive care

These patients are defined as those with persistent UPE >1 g/d despite treatment with a maximal tolerated dose of RAS blockade for a minimum of 3 months and having achieved the recommended BP target as described in Chapter 1 for a minimum of 3 months.

Practice Point 2.7.2.1: Considerations for the treatment of patients with IgAVN who are at high risk of progressive CKD despite maximal supportive care:

- **There is insufficient evidence to support the use of the Oxford Classification MEST-C score in determining whether immunosuppression should be commenced in patients with IgAVN.**
- **The presence of crescents in the kidney biopsy is not in itself an automatic indication for commencement of immunosuppression.**
- **In all patients in whom immunosuppression is being considered, a detailed discussion of the risks and benefits of each drug should be undertaken with the patient with a recognition that adverse treatment effects are more likely in patients with an eGFR <50 ml/min per 1.73 m^2.**
- **In those patients who wish to try immunosuppressive therapy, treatment with glucocorticoids is as described above for IgAN.**

2.8 Special situations

Practice Point 2.8.1: IgAV with RPGN:

- **The potential risks and benefits of immunosuppression should be evaluated at the individual patient level and discussed with the patient.**
- **Patients agreeing to treatment should be treated in accordance with the guidelines for AAV (Chapter 9).**
- **IgAV with RPGN as well as other IgAVN may be associated with significant extrarenal involvement (pulmonary, gastrointestinal, and skin), which may dictate alternative immunosuppressive strategies.**
- **There are insufficient data to determine the efficacy of plasma exchange in IgAVN with RPGN. However, 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.[151] Clinicians are referred to the guidelines of the American Society for Apheresis regarding recommendations regarding plasma exchange for IgAV.[152]**

2.8.1 IgAV-associated nephritis in children

Practice Point 2.8.1.1: For the purposes of this practice point, children are defined as those aged <18 years. It is acknowledged that post-pubertal children in some respects may have a similar course and response to treatment as adults with IgAN, but there are insufficient data currently to recommend that they be managed as adults with IgAN.

Indications for management of IgAVN in children have recently been published as the result of a European consortium initiative.[140] Briefly:

- **There are no data supporting the use of glucocorticoids to prevent nephritis in children with IgAV but mild or absent evidence of kidney involvement.[153,154]**
- **Children >10 years of age more often present with non-nephrotic-range proteinuria and impaired kidney function, and they may suffer more chronic histologic lesions with delay in biopsy and delay in treatment longer than 30 days.[155]**
- **The majority of children who will develop nephritis will do so within 3 months of presentation. Urinary monitoring is necessary for ≥6 months and optimally 12 months from initial presentation of systemic disease.**
- **Children with IgAVN and persistent proteinuria for >3 months should be treated with an ACEi or ARB. A pediatric nephrologist should be consulted.**
- **A kidney biopsy should be performed in children with nephrotic-range proteinuria, impaired GFR, or persistent moderate (>1 g/d) proteinuria.**
- **Oral prednisone/prednisolone or pulsed intravenous methylprednisolone should be used in children with mild or moderate IgAVN.**
- **Children with IgAVN with nephrotic syndrome and/or rapidly deteriorating kidney function are treated in the same way as those with rapidly progressive IgAN.**

Research recommendations

- The Oxford Classification MEST-C score and the International IgAN Prediction Tool should be validated in IgAVN.
- Unlike IgAN, there are currently few clinical trials of novel therapies in IgAVN. The BIOVAS trial (biologic agents in non-ANCA vasculitis) is perhaps the largest and will look at 3 different biologic drugs (infliximab, tocilizumab, and rituximab) in 140 patients (children and adults) with refractory vasculitis (including IgAV) recruited from 15 vasculitis centers in the United Kingdom and Ireland.
- In light of preliminary observational data,[156,157] suggesting a potential benefit with rituximab, we recommend a dedicated prospective RCT of rituximab in IgAV.
- It is recommended that those agents currently being evaluated in IgAN should also be tested for safety and efficacy in IgAVN in adults and children.

Chapter 3: Membranous nephropathy

This chapter makes management recommendations for adults aged >18 years with membranous nephropathy (MN). Data from pediatric populations are extremely limited, but an approach to the management of children with MN is presented in Practice Point 3.4.4.

3.1 Diagnosis

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

Confirming the diagnosis of MN in patients with a compatible clinical presentation is pivotal in guiding management and treatment decisions. A kidney biopsy usually is considered the gold standard for the diagnosis of glomerular disease; however, for MN, antibodies against PLA2R is a biomarker that can establish the diagnosis of MN with high accuracy and without the associated risks of a biopsy, including insufficient tissue for a conclusive diagnosis, pain, and bleeding. Thus, a kidney biopsy should be done for purposes other than establishing a diagnosis of MN in patients who are anti-PLA2R antibody–positive. There are currently insufficient data to support the use of anti-THSD7A antibody as a diagnostic biomarker for MN in lieu of a biopsy.

In a meta-analysis of 9 studies, including 710 patients with MN and 1502 controls, the sensitivity of a positive anti-PLA2R antibody test for the diagnosis of MN was 0.78, and specificity was 0.99.[158] A recent single-center study confirmed the high accuracy, with sensitivity of 64% and specificity of 99%.[159] The 95% confidence interval (CI) for specificity is 0.96 to 1.0, which is comparable to the diagnostic performance of kidney biopsy. The added value of kidney biopsy to diagnose MN was studied in 97 patients who tested positive for anti-PLA2R antibodies, had no evidence of secondary causes of MN, but did undergo a native kidney biopsy.[160] The primary diagnosis in all biopsies was MN. Among 60 patients with a baseline eGFR of >60 ml/min per 1.73 m^2, the biopsy disclosed superimposed diabetic nephropathy or FSGS in only 2 patients, and these findings did not affect patient care or treatment. Among 37 patients with eGFR <60 ml/min per 1.73 m^2, additional findings were reported in 5 patients and included acute interstitial nephritis (n = 1), diabetic nephropathy (n = 1), acute tubular necrosis (n = 1), and FSGS (n = 2) with cellular crescents (n = 1). Although not reported, it is likely that this information affected treatment decisions. A very recent

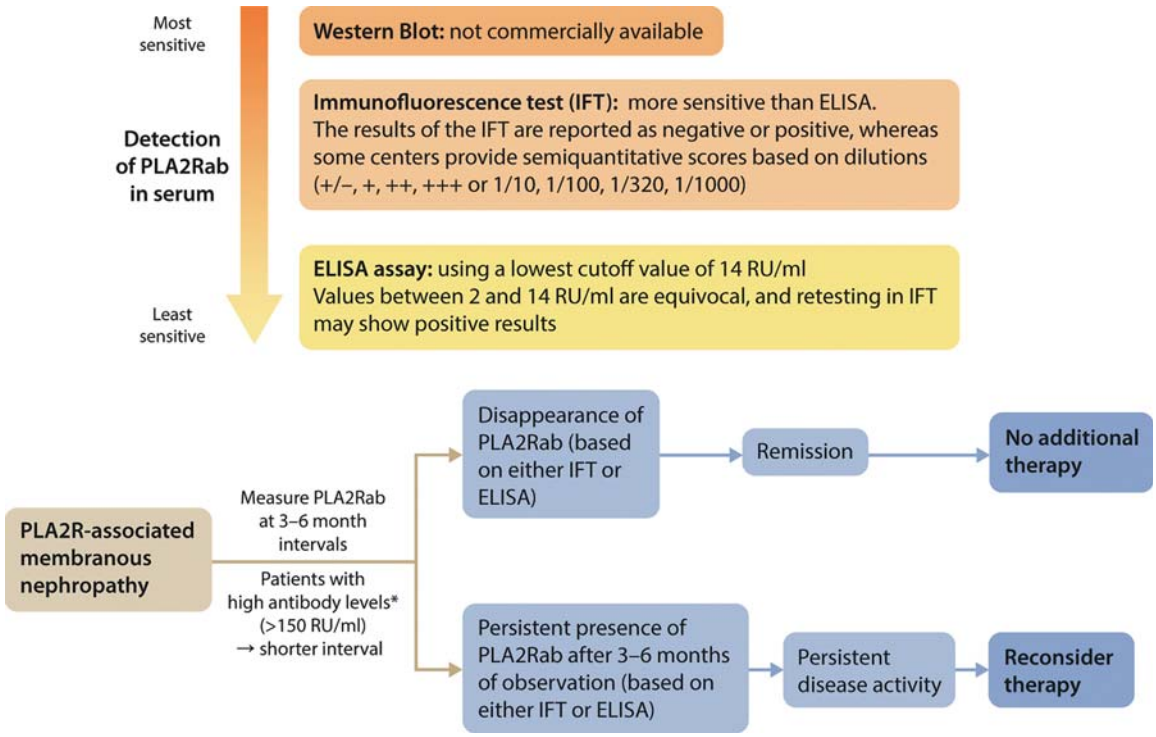

Figure 27 | Guidance for the use and interpretation of the anti-PLA2R antibody assay in patients with known anti-PLA2R-associated MN. *High titers (ELISA) are associated with lower likelihood of spontaneous remission and higher likelihood of nonresponse to low-dose rituximab. ELISA, enzyme-linked immunosorbent assay; PLA2Rab, antibodies against the M-type phospholipase A2 receptor.

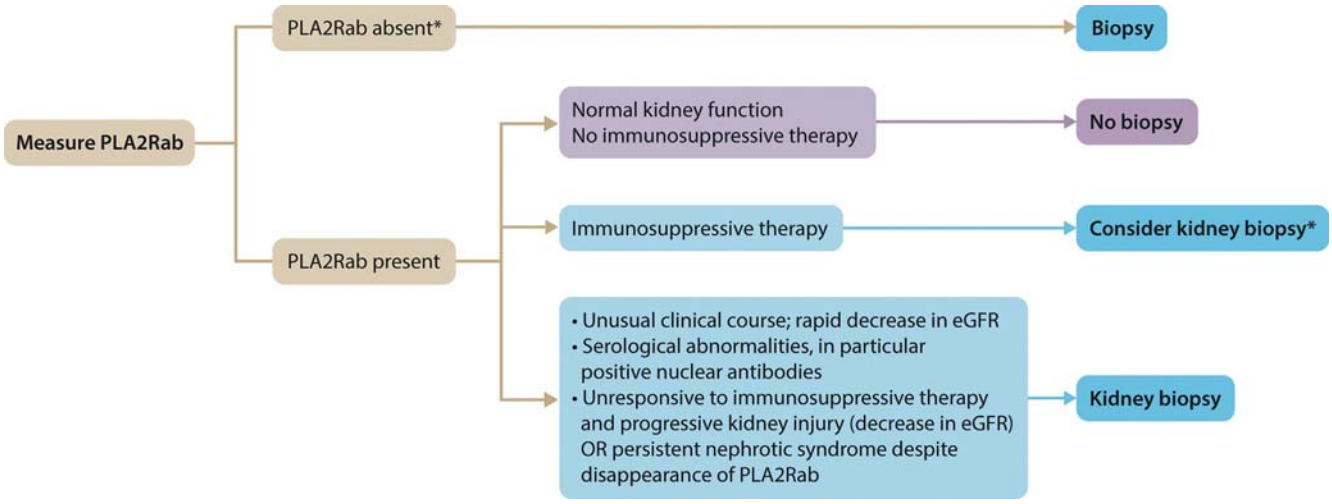

Figure 28 | When to consider a kidney biopsy in a patient who is anti-PLA2R antibody-positive. *In making a decision to perform a kidney biopsy, the risks of a biopsy must be taken into account. The decision is based on patient and physician preferences. This decision to perform a kidney biopsy could be revised in the near future with the development of molecular diagnostics, which could allow for better prediction of outcome for more personalized medicine. eGFR, estimated glomerular filtration rate; PLA2Rab, antibodies against the M-type phospholipase A2 receptor.

study strengthens the conclusion that in anti-PLA2R antibody–positive patients with normal eGFR, a kidney biopsy does not alter the diagnosis of primary MN.[161]

Further details on the anti-PLA2R antibody assay (Figure 27) and when to consider a kidney biopsy in an anti-PLA2R antibody–positive patient (Figure 28) are shown below. In patients who are anti-PLA2R antibody–negative, a kidney biopsy should be performed with staining of the biopsy for the PLA2R antigen, and this may disclose anti-PLA2R antibody–associated MN. This can occur in patients for whom the serum enzyme-linked immunosorbent assay (ELISA) and immunofluorescence test is falsely negative, for example, because of low titers. Moreover, it has been suggested that antibodies may be absent in the early phase of MN, being captured in the kidney, and becoming detectable after prolonged follow-up.

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

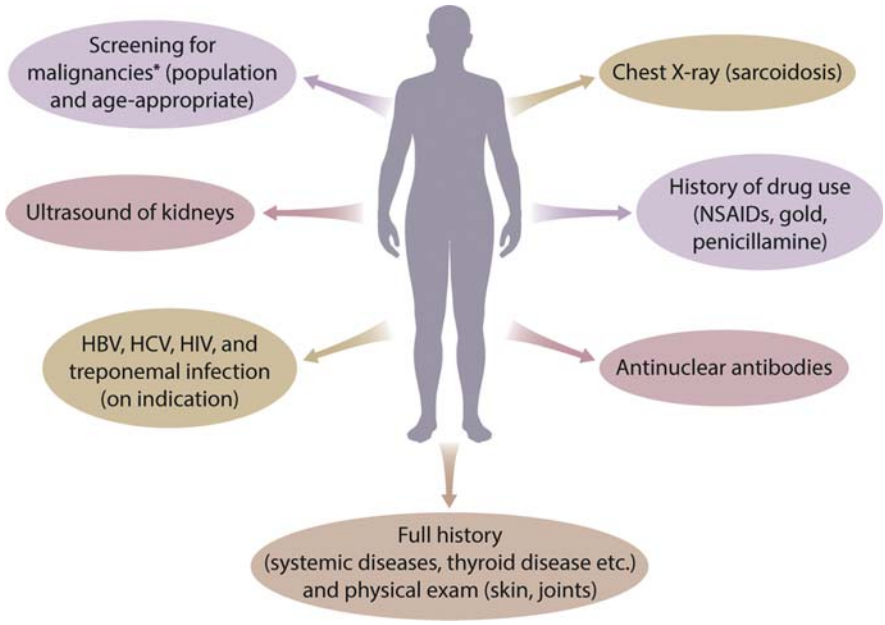

Figure 29 | Evaluation of patients with MN for associated conditions. Patient with MN should be evaluated for associated conditions, independent of the presence or absence of anti-PLA2R antibodies or anti-THSD7A antibodies. *Varies per country; the yield of cancer screening is not very high, especially in younger patients. Many centers will perform chest X-ray or computed tomography (CT) scan, look for iron deficiency, and require the patients to participate in the national screening program for breast and colon cancer; a prostate-specific antigen (PSA) test is done in adult males aged >50–60 years. HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NSAIDs, nonsteroidal anti-inflammatory drugs.

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 30 | 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 creatinine (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-to-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.

3.2 Prognosis

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

Because spontaneous remission is relatively common in MN and because immunosuppressive treatment has adverse effects, it is important to assess the risk of progressive loss of kidney function prior to deciding about whether and when to implement immunosuppressive treatment. Figure 30 shows clinical criteria that may be used to divide patients into categories of low, moderate, high, and very high risk of progressive loss of kidney function.

There are caveats to the evaluation of risk in MN. In most patients, it is reasonable to wait 6 months for spontaneous remission while using maximal antiproteinuria therapy. High levels of proteinuria, anti-PLA2R antibodies, or low–molecular weight proteinuria should lead to re-evaluation earlier than 6 months. Patients with deteriorating kidney function or severe unresponsive NS may be considered for immediate immunosuppressive therapy, as the likelihood of progression is 84% in patients with a documented 20% decrease in eGFR within any time period of fewer than 24 months.[162] A survey of the literature shows that there is a 45% chance of spontaneous remission in patients with proteinuria >4 g/d after 6 months of conservative therapy,[163] a 34% chance of spontaneous remission in patients with proteinuria >8 g/d for more than 6 months,[164] a 25%–30% chance despite high urinary excretion of low–molecular weight proteins,[165] a 17% chance in patients in the upper tertiles of anti-PLA2R antibody levels,[166] and a 20% chance in patients with anti-PLA2R antibody levels >275 RU/ml[167] (A. Rousseau, personal communication, January 15, 2019). There is currently no model that combines all of these clinical considerations, but we suggest that in clinical practice it is useful to think about risk as a combination of factors (e.g., high proteinuria in patients with low antibody titers may be judged differently than high proteinuria in the presence of high antibody titers). Even more important is the disease trajectory; thus, changes in any of the above-mentioned parameters should be taken into account.

3.3 Treatment

Practice Point 3.3.1: Considerations for treatment of patients with primary MN:

- **All patients with primary MN and proteinuria should receive optimal supportive care.**
- **Immunosuppressive therapy should be restricted to patients considered at risk for progressive kidney injury (Figure 31).**

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

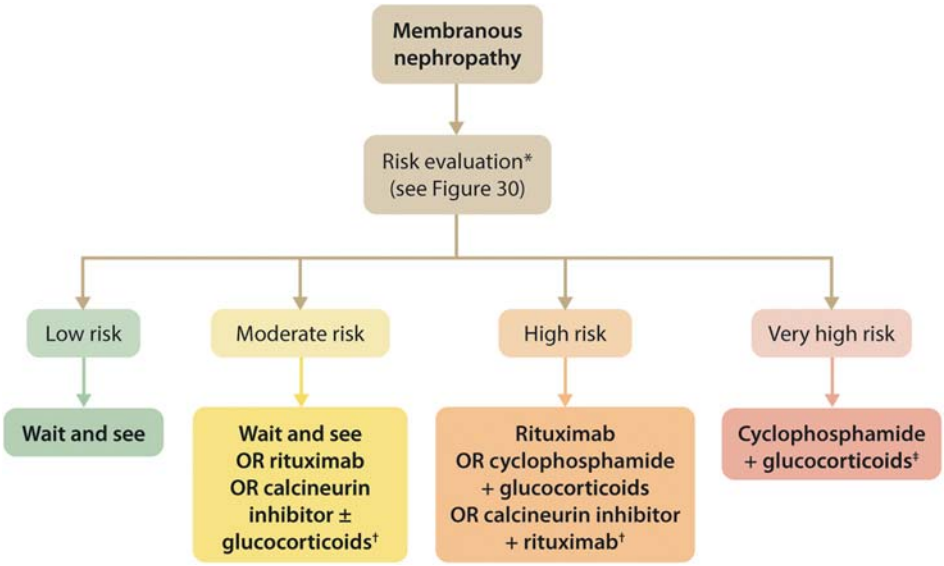

Figure 31 | Risk-based treatment of MN. *See Practice Point 3.2.1 and Figure 30 for a detailed description of risk evaluation. †Calcineurin inhibitor (CNI) monotherapy is considered less efficient. Treatment with CNI for 6–12 months with rapid withdrawal is associated with a high relapse rate. Still, 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.

Patients with MN, normal eGFR, and non-nephrotic proteinuria generally have good outcomes (see below). These patients are also at low risk of thromboembolic complications and have a low burden of symptoms (e.g., edema). They can be managed with conservative therapy (Chapter 1). Patients with MN, normal eGFR, and non-nephrotic proteinuria generally have serum albumin levels >30 g/l. In patients with MN, normal eGFR, non-nephrotic proteinuria, and low serum albumin levels, other causes of hypoalbuminemia should be excluded.

There are no RCTs comparing outcomes in patients with MN and non-nephrotic proteinuria with and without immunosuppressive therapy. However, clinical experience and data from cohort studies show favorable kidney outcomes in patients with MN who are persistently non-nephrotic, despite the absence of immunosuppressive treatment. Immunosuppressive therapy thus adds risks without potential benefits.

Progressive disease can be identified by development of NS or decreasing eGFR, which will be easily notable during follow-up. The presence of a high level of anti-PLA2R antibodies at baseline is associated with a higher risk of developing NS.

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

Many patients with primary MN and NS will develop spontaneous remission. There are no RCTs comparing outcomes in patients with MN and no risk factors for progression with and without immunosuppressive therapy. However, the favorable outcome in such patients is supported by data from RCTs and cohort studies that included patients with MN and even at least one risk factor. These studies show favorable outcomes in many patients with MN, with spontaneous remissions occurring in up to 40% or more of patients. If no risk factor is present, and no complications of NS are evident, the use of immunosuppressive therapy adds risk with little if any benefit. Categorizing patients as low, moderate, high, or very high risk of progressive loss of kidney function (Practice Point 3.2.1) will allow even better selection of the patients who are more likely to develop spontaneous remission.

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

This recommendation places a relatively higher value on preventing progressive kidney failure in higher-risk patients and in reducing the complications and risk of NS, and a relatively lower value on the side effects and inconvenience associated with immunosuppressive treatment. The choice of therapy is dependent on patient characteristics, drug availability, drug efficacy, patient, physician, societal preference, reimbursement policies, and the specific side-effect profile of each drug. The risk-based treatment

Cyclophosphamide (cyclical)	• Methylprednisolone 1 g i.v. for 3 consecutive days at start of month 1, 3, and 5 • Prednisone 0.5 mg/kg/d in months 1, 3, and 5 • Cyclophosphamide 2.5 mg/kg/d in months 2, 4, and 6‡
Cyclophosphamide (continuous)	• Methylprednisolone 1 g i.v. for 3 consecutive days at start of month 1, 3, and 5 • Prednisone 0.5 mg/kg/d every other day in months 1–6, with taper thereafter • Cyclophosphamide 1.5 mg/kg/d in months 1–6‡
Rituximab	• Rituximab 1 g i.v. administered twice within 2 weeks* • Rituximab 375 mg/m^2 given 1–4 times at weekly intervals
Tacrolimus	• Tacrolimus 0.05–0.1 mg/kg/d, target trough level 3–8 ng/ml (3.7–9.9 nmol/l), duration 12 months†
Cyclosporine	• Cyclosporine 3.5 mg/kg/d, target trough level 125–225 ng/ml (104–187 nmol/l)†

Figure 32 | Commonly used treatment regimens for patients with MN. Mycophenolate mofetil is not discussed. The KDIGO 2012 guideline argued against the use of MMF monotherapy in patients with MN. This still holds and is based on the results of 1 RCT.[172] In this study of 36 patients, MMF monotherapy for 12 months did not increase remission rate (37% vs. 41%). MMF in combination with glucocorticoids, is more effective. Small RCTs compared MMF and glucocorticoids with either alkylating agents[173,174] or CNI.[168,175] In these studies, all with relative short follow-up, remission rates were comparable. A study using historical controls and comparing MMF with cyclophosphamide also reported similar remission rates. However, relapse rate within 24 months of follow-up was markedly higher in MMF-treated patients.[176] A more detailed evaluation showed that immunologic remissions were less likely to occur with MMF.[177] The dose of MMF could be the most relevant variable; studies in LN have used higher dosages (3 g vs. 2 g), and in patients with SSNS, relapse rate was lower in patients with higher drug concentrations.[178] Note: Prednisone and prednisolone are equivalent, used in the same dosage, and have both been used in RCTs, depending on the country of origin. All later usages of "prednisone" in this guideline refer to prednisone or prednisolone. All later usages of "glucocorticoids" refer to prednisone or prednisolone, unless specified otherwise. ‡Recent studies have used i.v. cyclophosphamide. These studies included patients with maintained eGFR. There are no RCTs evaluating the efficacy of i.v. cyclophosphamide on kidney endpoints. Older RCTs using i.v. cyclophosphamide that included patients with deteriorating eGFR were negative.[170,171] Intravenous cyclophosphamide might be considered in patients with normal eGFR, in whom the lowest possible cumulative dose of cyclophosphamide should be used (previous use of cyclophosphamide, patients with wishes to bear children) or in countries where p.o. cyclophosphamide is not available. *Consider repeating after 6 months in patients with persistent NS, stable eGFR, especially if anti-PLA2R antibodies remained positive. †Cyclosporine and tacrolimus are often given in combination with prednisone in a dose of 10 mg/d. After 4 months, withdrawal if no response; after 12 months, consider tapering to lower levels. There are few trials that have compared the dose and duration of CNI therapy. Yuan *et al.* compared 6 months versus 24 months of tacrolimus and prednisone.[169] Remission rates after 6 months were comparable (18/20 versus 18/22), however persistent remission after 24 months was observed in only 9/18 patients treated for 6 months versus 18/18 patients treated for 24 months. A meta-analysis confirmed high remission and high relapse rates. These findings can be discussed with the patient while agreeing on the duration of therapy. MN, membranous nephropathy; PLA2R, M-type phospholipase A2 receptor.

algorithm is illustrated in Figure 31. Details of commonly used treatment regimens are shown in Figure 32[168–178].

Key information

Balance of benefits and harms. Many patients with MN and NS will develop spontaneous remission. Any immunosuppressive therapy is associated with risks; thus, immunosuppressive therapy is justifiable only in patients with sufficient complaints and/or risks of NS (such as edema, infections, thrombotic events, progression of kidney failure) and low likelihood of spontaneous remission. RCTs and cohort studies have shown that rituximab and CNIs increase the rate of complete and partial remissions. The beneficial side-effect profile of these drugs favors their use over cyclophosphamide as initial treatment in patients with MN and maintained kidney function. The high relapse rate after treatment with CNIs is a reason for concern, and monotherapy with these agents is justifiable only in patients with a moderate risk of disease progression. Alkylating agents not only increase remission rate but most importantly, they also reduce the risk of kidney failure to a large degree. Alkylating agents are toxic drugs with frequently occurring severe short- and long-term side effects. Although the evidence is of moderate quality, the toxicity profile warrants that cyclophosphamide-based immunosuppressive treatment should be restricted to high-risk patients.[179] Cyclophosphamide is preferred over chlorambucil. The evidence supporting cyclophosphamide over chlorambucil is not strong, but 1 RCT[180] and several cohort studies suggest fewer side effects with cyclophosphamide. Also, in patients with CKD, there is more often a need to adapt the dose and duration of therapy with chlorambucil, which might explain the lower remission rates observed with this drug.[181,182]

Quality of evidence. The ERT has evaluated the quality of the evidence based on RCTs. The quality of the evidence from the RCTs for the use of an oral alkylating agent compared to placebo/no treatment or glucocorticoids is considered moderate because of a serious risk of bias and lack of blinding (Supplementary Table S9[162,183–191]). Alkylating agents were the only agents that were studied in trials that evaluated critical outcomes such as all-cause mortality and kidney failure.

RCTs with rituximab or CNIs were evaluated only for the outcomes of remission and side effects.

For rituximab, the Evaluate Rituximab Treatment for Idiopathic Membranous Nephropathy (GEMRITUX) RCT examined the use of rituximab plus supportive therapy compared with supportive therapy alone (Supplementary Table S10[167,192]). The

Membranous Nephropathy Trial Of Rituximab (MENTOR) trial compared rituximab with cyclosporine. For efficacy outcomes such as complete and/or partial remission, the quality of the evidence is considered low[167] or moderate,[193] respectively, because of serious imprecision. There is low quality in the evidence for outcomes such as infection because of very serious imprecision (wide CIs that indicate less certainty in effect; Supplementary Table S11[192,193]).

The quality of the evidence from RCTs examining the use of CNIs compared with placebo, no treatment, glucocorticoids, or alkylating agents is considered very low, as there is imprecision with wide CIs that indicate appreciable benefit and harm, and insufficient follow-up for clinical outcomes (all-cause mortality, kidney failure; Supplementary Table S12 and Supplementary Table S13[162,168,184,188,192,192a,194–202]). The trials that have sufficient follow-up for complete remission have very serious study limitations and very serious issues regarding the risk of bias, including lack of blinding of participants and investigators, and unclear blinding of outcome assessors, as well as few participants, and inclusion of abstract-only publications.

In rare diseases, and especially disease with serious, objective, clinical outcomes such as mortality or kidney failure, evidence cannot be limited to data from RCTs. Therefore, the Work Group has used information from non-RCTs and cohort studies as part of the evidence base. The Work Group emphasizes the need to use the evaluation of risk factors, which enables identification of high-risk patients with reasonable accuracy (Practice Point 3.2.1). Based on the RCTs and cohort studies, there is strong evidence that alkylating agents reduced the risk of kidney failure. There is moderate-quality evidence that alkylating agents are effective when used according to a restrictive treatment strategy, and in patients with documented kidney function deterioration. There is no evidence that rituximab or CNIs reduce the risk of kidney failure. There is moderate-quality evidence that rituximab or CNIs increase complete and partial remission rate. There is evidence that complete remission (moderate quality) and partial remission (low quality) can be used as surrogate endpoints in studies in patients with NS. There is moderate-quality evidence that alkylating agents have more-frequent and more-severe side effects than rituximab or CNIs. The use of CNIs is associated with a high relapse rate. There is moderate-quality evidence that remissions are more persistent after rituximab in comparison with CNIs.

Values and preferences. Immunosuppressive therapy is associated with side effects. Patients who are likely to have a favorable clinical course (Practice Point 3.2.1) or who are more concerned about adverse effects of immunosuppressive agents will be more likely to decline such treatment. Conversely, patients who experience severe complaints of NS or a complication of NS (e.g., thromboembolic events, infections, AKI) will more likely prefer treatment. Rituximab and CNIs have fewer and less-severe side effects than cyclophosphamide. Therefore, most physicians and patients will prefer initial treatment with rituximab or CNIs over treatment with cyclophosphamide. Development of kidney failure is the most frequent and severe complication of MN. Patients with kidney failure can survive with kidney replacement therapy. However, this therapy is associated with high morbidity and mortality. Moreover, most patients with kidney failure will prefer kidney transplantation, which will lead to lifetime exposure to immunosuppressive drugs. Thus, in the judgment of the Work Group, most well-informed patients with (very high risk of) kidney failure would choose to be treated with cyclophosphamide as compared to conservative treatment only.

The timing of treatment start, the type of drug, and the duration of therapy is dependent on risk estimates, patient characteristics, patient and physician preferences, reimbursement policies, and societal perspective (costs and drug availability).

Resource use and costs. Treatment with immunosuppressive agents is associated with high costs, including therapy, monitoring, and management of the side effects. Kidney replacement therapy is associated with lower quality of life, higher costs, and similar or even more side effects than immunosuppressive agents. To the extent that immunosuppressive treatment prevents progressive loss of kidney function and kidney failure, this recommendation is likely to be cost-effective from the perspective of the healthcare system. Cost-efficacy is less likely in patients with a predicted uneventful disease course. In patients with moderate risk, the side effects of therapy will contribute to the costs to a large degree. Thus, in these patients, drugs with fewer side effects will be more cost-effective. Availability of drugs will vary between countries and regions.

Considerations for implementation. Patients with MN with complaints or complications of NS or risk of developing kidney failure might benefit from immunosuppressive therapy. This holds for all patients, independent of sex and race. Thus, this recommendation holds for patients of all sex and races.

Rationale

This recommendation replaces the KDIGO 2012 recommendation. While acknowledging the proven efficacy of alkylating agents in preventing kidney failure, the current recommendation gives more weight to the severe short- and long-term side effects associated with use of these agents. Physicians and patients are particularly in fear of the long-term malignancy risks.[203] Therefore, effective alternative agents would be preferable. Rituximab- and CNI-based therapy are now introduced as suitable alternatives. Although direct proof that rituximab or CNIs prevent kidney failure is lacking, the Work Group valued the results of studies that showed high remission rates with these agents and appreciated the association of persistent remission with good kidney outcome. In patients with reduced eGFR, only alkylating agents are of proven benefit.

Practice Point 3.3.4: Longitudinal monitoring of anti-PLA2R antibody levels at 6 months after start of therapy may be useful for evaluating treatment response in patients with MN, and can be used to guide adjustments to therapy (Figure 33[193]).

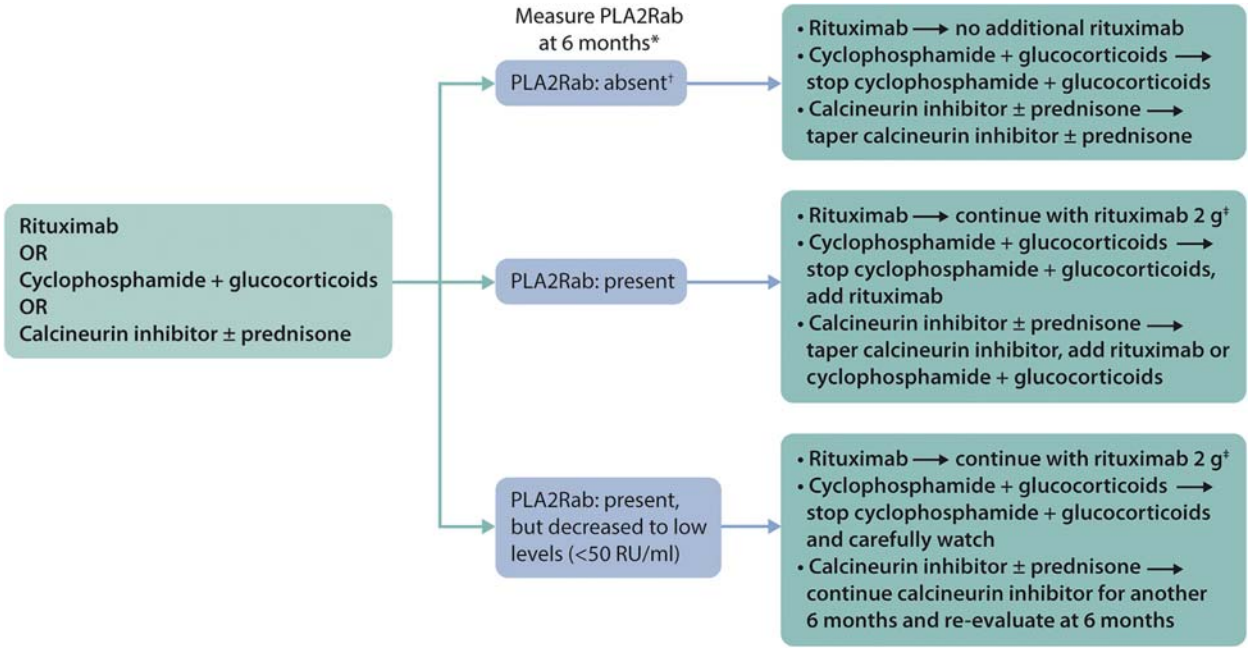

Figure 33 | Immunologic monitoring in MN after start of therapy. See text for current treatment schedules. Note: The cumulative dose of cyclophosphamide should not exceed 36 g in view of the risk of malignancy (Chapter 1). To stay on the safe side, we usually limit the cumulative dose to 25 g (in an 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. CNI 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.[182] CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; MN, membranous nephropathy; PLA2Rab, antibodies against the M-type phospholipase A2 receptor.

3.4 Special situations

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

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

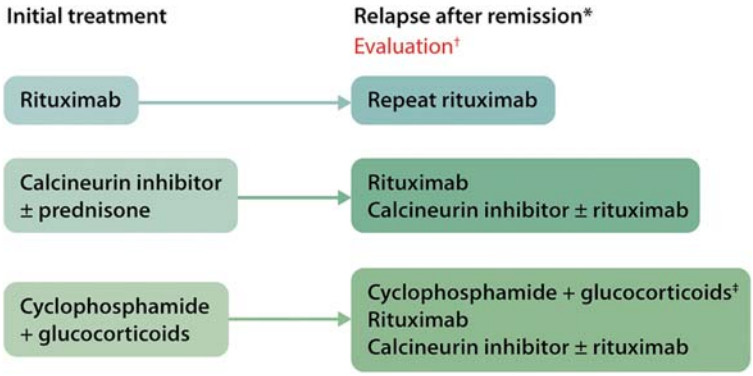

Figure 34 | Management of initial relapse after therapy in MN. Details of commonly used treatment regimens are shown in Figure 32. *The definition of relapse is variable. Some authors define relapse after remission as an increase in proteinuria >3.5 g/d in patients who developed a partial or complete remission. We suggest that the course of serum albumin and PCR should be used in the evaluation. If PCR decreased to values between 2–3.5 g/d without an increase of serum albumin to normal, the subsequent rise in PCR should be considered resistant disease rather than relapse after remission. In patients with a partial remission (characterized by normalization of serum albumin), a relapse should be defined by an increase of proteinuria paralleled by a decrease in serum albumin levels. †Immunologic monitoring is of particularly great value in these situations. If, in the period of "clinical remission," anti-PLA2R antibodies were still positive, this would be evidence for resistant disease. Therefore, in patients with positive anti-PLA2R antibodies, it is advised that anti-PLA2R antibodies be evaluated at the time of remission and relapse. The course of anti-PLA2R antibodies should precede the clinical course. In patients with very early relapse, it is important to consider reasons for the failure of the previous therapy (e.g., compliance, low drug levels, insufficient B cell depletion, presence of anti-rituximab antibodies). ‡Cyclophosphamide can be repeated; however, physicians must 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. MN, membranous nephropathy; PCR, protein-creatinine ratio; PLA2R, M-type phospholipase A2 receptor.

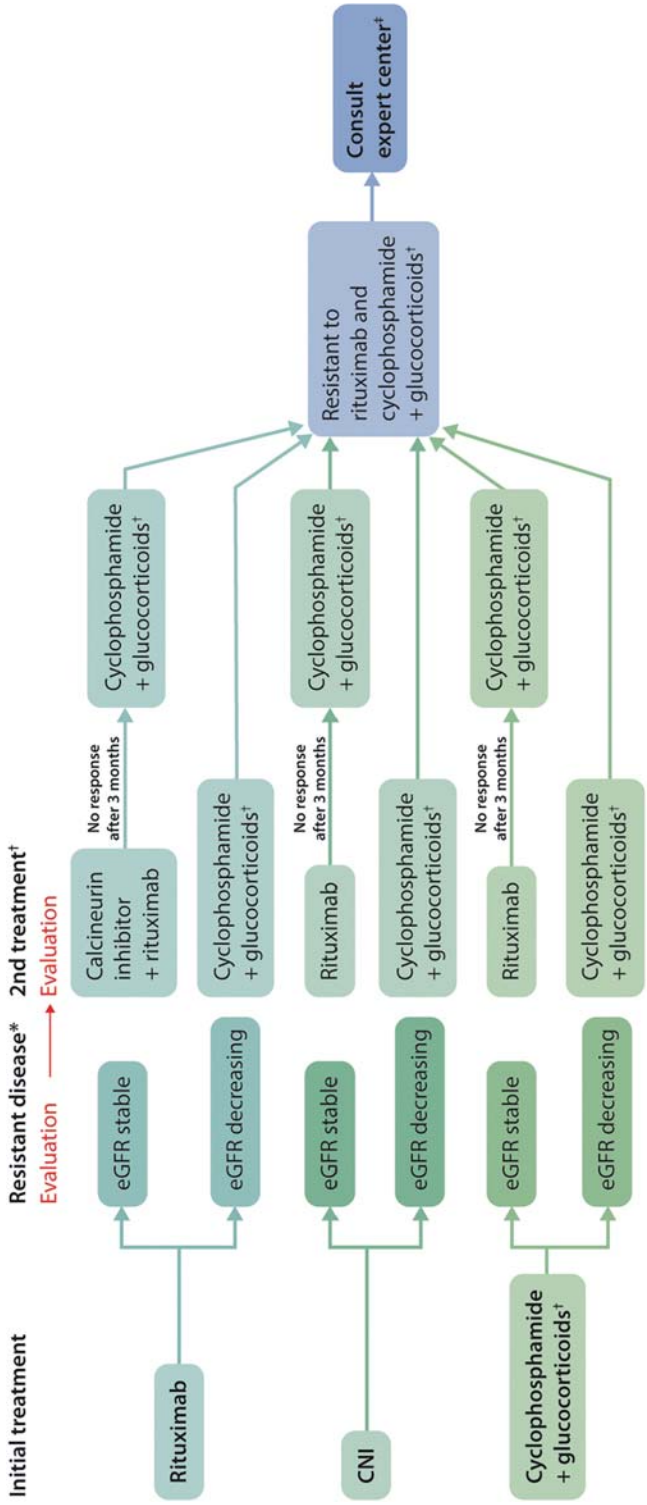

Figure 35 | Management of resistant disease in MN. Details of commonly used treatment regimens are shown in Figure 32. *Evaluation: In patients with resistant disease, compliance should be checked and efficacy monitored (e.g., B cell response, anti-rituximab antibodies, IgG levels, leukocytopenia during cyclophosphamide, CNI levels). Persistent proteinuria is not sufficient to define resistance. If proteinuria persists, while serum albumin has increased, one should consider secondary focal segmental glomerulosclerosis (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.

There is no accepted definition of resistant disease. In patients with MN, with measurable anti-PLA2R antibodies at the start of therapy, resistant disease can be defined by the persistence of anti-PLA2R antibodies at high or unchanged levels after 1 line of immunosuppressive therapy (of sufficient dose and duration). The persistence of moderate proteinuria should not be used to define resistant disease, as proteinuria can persist for 12–24 months after the start of therapy.

Although persistence of anti-PLA2R antibodies suggests therapy resistance, there are patients who develop partial remission of proteinuria with persistent presence of low titers of anti-PLA2R antibodies. These patients should be carefully followed; immunosuppressive therapy often can be withheld.

Obviously, defining resistance is more difficult in patients who are anti-PLA2R antibody–negative. Patients with persistent NS (and thus low serum albumin) can be considered resistant (if duration of follow-up exceeds 6 months). In patients with low-grade proteinuria, and normalized serum albumin, persistent proteinuria likely is explained by secondary FSGS or other factors. In patients with persistent proteinuria and increased but still somewhat reduced serum albumin, it may be difficult to judge. In such cases, a kidney biopsy showing small dense deposits may be used to define persistent disease activity.

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

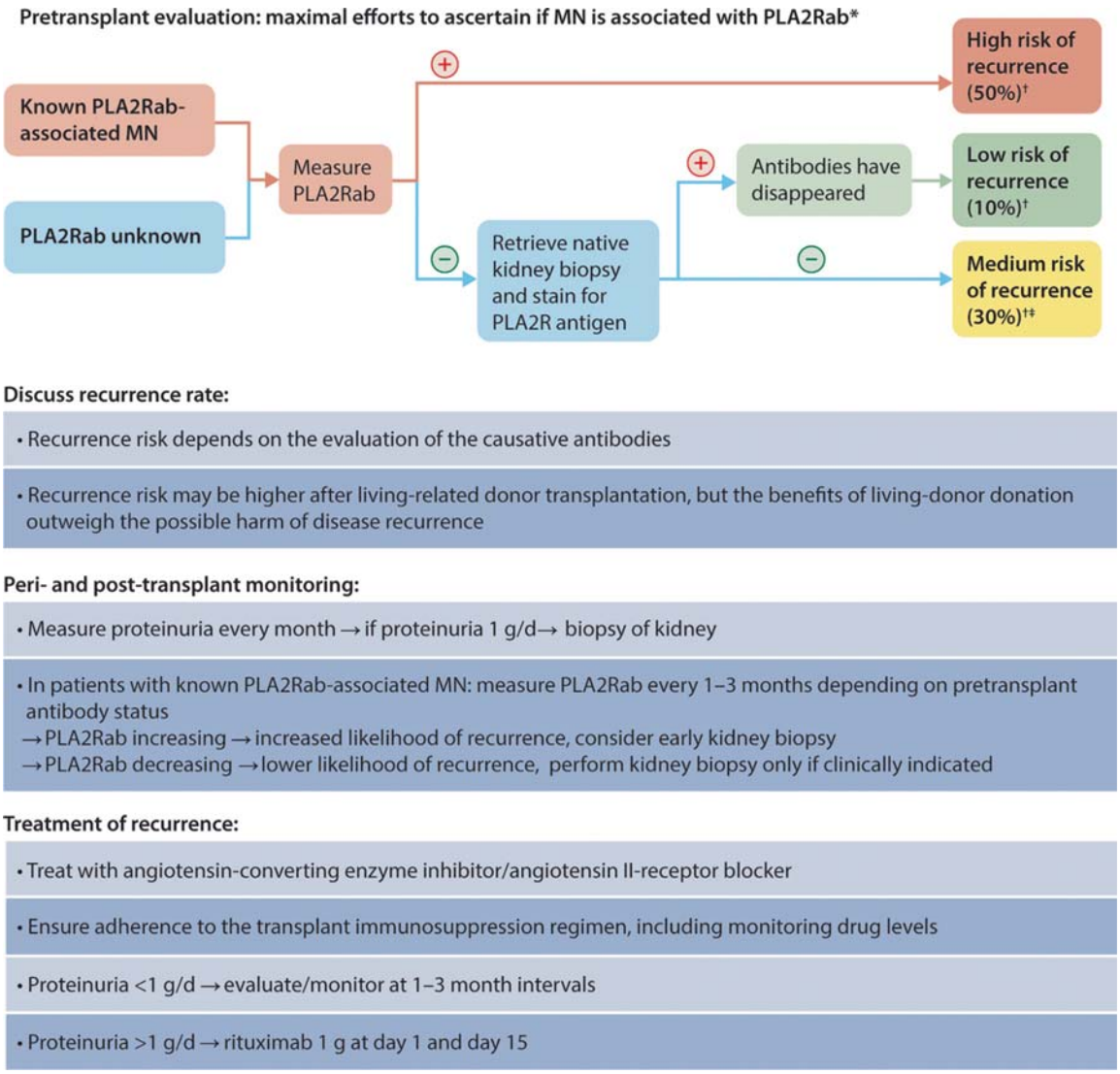

Figure 36 | Evaluation of a kidney transplant recipient with MN. *Limited data available, but the same algorithm likely applies to anti-THSD7A-associated MN. †Clinical recurrence. ‡This is the estimated average recurrence rate for patients with MN and unidentified antigen. We suggest that in these patients the recurrence rate can be better estimated by evaluating the patient for THSD7A antigen/antibodies. MN, membranous nephropathy; PLA2Rab, antibodies against the M-type phospholipase A2 receptor; THSD7A, thrombospondin type-1 domain-containing 7A.

Pre-transplant evaluation

It is important to determine if the patient's MN is related to anti-PLA2R antibodies. The presence of anti-PLA2R antibodies in old or recent serum, or detection of the PLA2R antigen in the native kidney biopsy, confirms a diagnosis of anti-PLA2R-associated MN. The absence of antibodies at the time of transplantation in a patient with anti-PLA2R-associated MN predicts a low risk of recurrence. In contrast, if anti-PLA2R antibodies are present, the risk of recurrence is high(er). Although studies have suggested that higher anti-PLA2R antibody levels (>45 RU/ml) are associated with increased risk, there are insufficient data to define a cutoff value. Although data on anti-THSD7A and kidney transplantation are lacking, it is likely that the same algorithm can be used to evaluate patients with anti-THSD7A-associated MN.

Peri- and post-transplant evaluation

There are insufficient data to support a protocol biopsy or preemptive treatment with rituximab, unless the patient has a history of multiple recurrences and positive antibodies. In patients with MN not associated with anti-PLA2R antibodies, proteinuria should be evaluated monthly for at least 6–12 months after transplantation. A kidney biopsy is needed when proteinuria exceeds 1 g/d. In patients with PLA2R-associated MN, regular measurement of anti-PLA2R antibodies after kidney transplantation is advised in the first 6–12 months after transplantation. The frequency of monitoring may vary from once per month in patients with high titers pretransplant to once per 3 months in patients without measurable anti-PLA2R antibodies pretransplant (antibodies may reappear in these patients, which would suggest reactivation of the disease). A relapse can be anticipated with persistently high or increasing titers of anti-PLA2R antibodies, and in such cases, performing a kidney biopsy in patients with proteinuria 0.3–1.0 g/d can be considered.

Patients with recurrent MN should be treated with maximal conservative, antiproteinuric therapy. If proteinuria >1 g/d, we suggest treatment with rituximab.

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

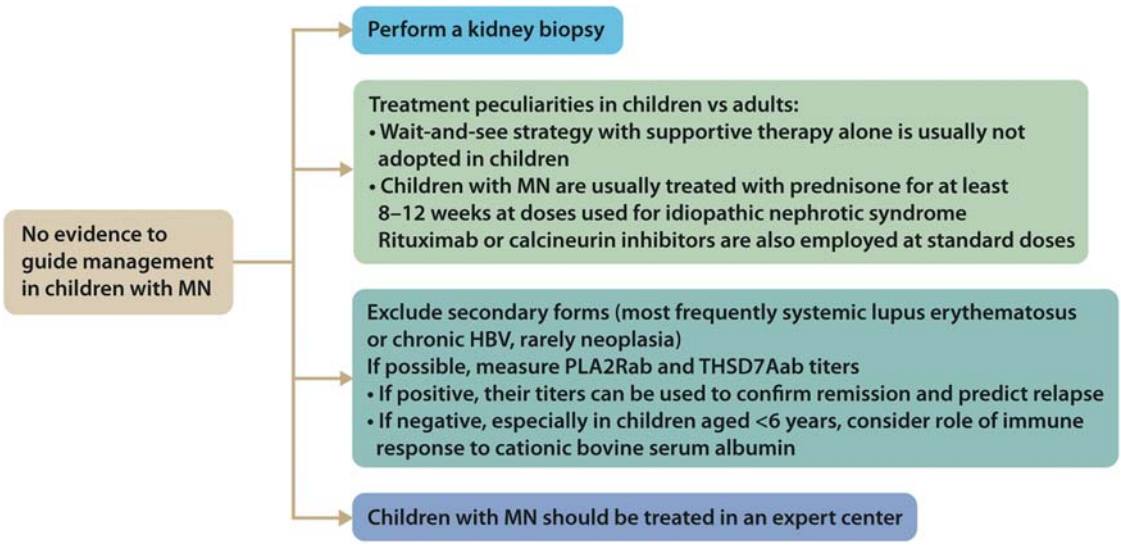

Figure 37 | Management of children with MN. HBV, hepatitis B virus; MN, membranous nephropathy; PLA2Rab, antibodies against the M-type phospholipase A2 receptor; THSD7Aab, antibodies against thrombospondin type-1 domain-containing 7A.

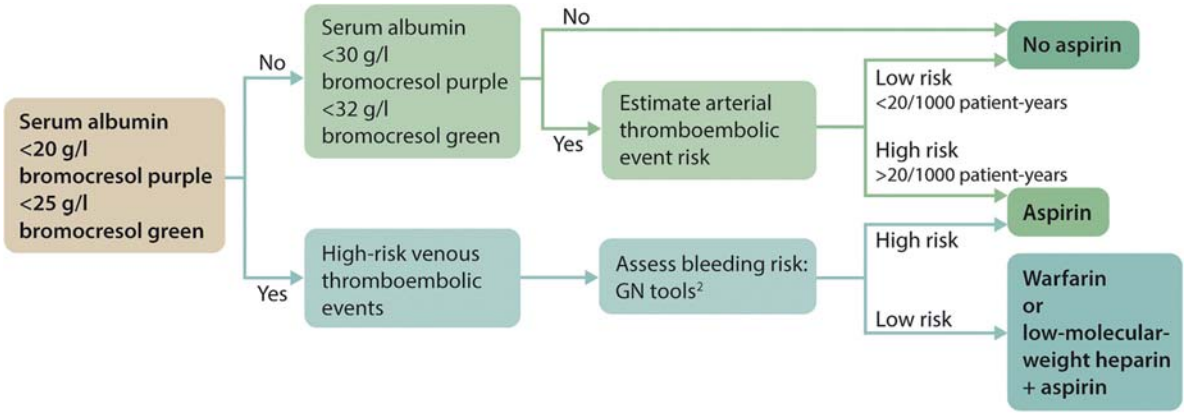

Figure 38 | Anticoagulant therapy in patients with MN. Adapted from *Kidney International*, volume 89, issue 5, Hofstra JM, Wetzels JFM. Should aspirin be used for primary prevention of thrombotic events in patients with membranous nephropathy? Pages 89:981–983, Copyright Copyright 2016, with permission from the International Society of Nephrology.[44] 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.[204] 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 (https://www.med.unc.edu/gntools/bleedrisk.html).
3. Patients with MN and nephrotic syndrome are also at risk of developing arterial thrombotic events. The risk of arterial thromboembolism (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.[44]
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 nephrotic syndrome 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.[205]
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.

Practice Point 3.4.5: Prophylactic anticoagulant therapy in patients with MN and nephrotic syndrome should be based on an estimate of the risk of thrombotic events and the risk of bleeding complications (Figure 38[44,204,205]).

Nephrotic syndrome is associated with an increased risk of VTE and ATE. Patients with MN have the greatest risk. The risk of thrombosis is particularly increased in the first 6–12 months after onset of disease. Thus, it is pivotal to discuss the need of anticoagulant therapy at the time of diagnosis

Research recommendations

Diagnosis.

- Evaluate accuracy of anti-PLA2R antibodies and anti-THSD7A antibodies in diagnosing MN; for how long does positive serology precede the development of the disease with clinical symptoms?
- Compare the different techniques for the evaluation of anti-PLA2R antibody–associated MN, and assess accuracy and optimal cutoff levels for the diagnosis of MN
- New techniques (laser capture microdissection followed by peptide digestion and mass spectrometry) should be used to discover additional antigens in the approximately 20% of patients who are double-negative for PLA2R and THSD7A. Examples of recently discovered antigens exostosin 1/2, NELL-1, and semaphorin 3B

Prognosis.

- Evaluate the accuracy of anti-PLA2R antibody levels in predicting outcome in patients with MN; consider outcome in untreated patients (spontaneous remission) and patients treated with different immunosuppressive therapy. Determine optimal cutoff levels
- Evaluate the predictive value of changes on anti-PLA2R antibody levels over a 3–6-month period in patients with MN, for both those untreated and treated with immunosuppressive therapy. Define cutoff values that provide highest accuracy
- Evaluate the accuracy of anti-THSD7A levels at baseline and changes during follow-up in predicting outcome; consider outcome in untreated patients (spontaneous remission) and in patients treated with different immunosuppressive therapy. Determine optimal cutoff levels
- Develop a calculator that combines risk biomarkers to estimate risk of progressive disease

- Understand the mechanisms of epitope spreading and immunodominance and determine whether analysis of epitope reactivity has a predictive value greater than that of PLA2R-antibody level
- Establish a genetic and clinical risk score for recurrence after transplantation
- Evaluate the role of newly discovered antigens and their association with secondary causes

Treatment.

- Should we aim at complete immunologic remission, or is a substantial reduction of anti-PLA2R–antibody level sufficient?
- Evaluate efficacy of CNIs in reducing the period of NS in patients with MN at low risk for disease progression
- Evaluate efficacy of CNI-based combinations, including combinations with rituximab, in high-risk patients; should we use sequential combinations of immunosuppressive drugs?
- Evaluate the best dosing/protocol for rituximab and the clinical impact of anti-rituximab antibodies
- Compare efficacy of rituximab-based therapy with cyclophosphamide-based therapy in patients with MN and very high risk of disease progression
- Evaluate efficacy of novel B cell (anti-CD20 antibodies, anti-BLyS/BAFF/APRIL antibodies) or plasma cell–directed therapy (proteasome inhibitor or anti-CD38 antibodies) in patients with MN resistant to standard immunosuppressive therapy
- Evaluate the potential and applicability of antigen-targeted therapy

Special situations.

- Evaluate optimal prophylactic anticoagulant therapy
- Evaluate usefulness of measuring B cells, including memory B cells and T-cell phenotypes in patients with MN to predict outcome and response to therapy

Chapter 4: Nephrotic syndrome in children

This chapter makes treatment recommendations for children with nephrotic syndrome (NS), aged 1–18 years. Below the age of 1 year, all children fulfilling the definition of NS should be referred to a specialist in pediatric nephrology. The correct therapeutic approach for such young children is beyond the scope of this work.

4.1 Diagnosis

Practice Point 4.1.1: The definitions relating to nephrotic syndrome in children are based on the clinical characteristics outlined in Figure 39[206].

- **Nephrotic-range proteinuria:** First morning or *24-h PCR ≥2 g/g (or 200 mg/mmol or ≥3+ dipstick)
- **NS:** Nephrotic-range proteinuria and either hypoalbuminemia (serum albumin <30 g/l (3 g/dl)) or edema when albumin level is not available
- **Complete remission:** First morning or *24-h PCR ≤200 mg/g (or 20 mg/mmol or negative or trace dipstick) on three or more consecutive occasions
- **Partial remission:** First morning or *24-h PCR >200 mg/g but <2 g/g (or >20 and <200 mg/mmol) and, if available, serum albumin ≥30 g/l (3 g/dl)
- **Relapse:** Recurrence of nephrotic-range proteinuria. In children, relapse is commonly assessed by urine dipstick and is thus defined as dipstick ≥3+ for 3 consecutive days
- Typical dipstick results are expressed semiquantitatively as follows†, or as stated by manufacturer:
  Negative: 0 to <15 mg/dl
  Trace: 15 to <30 mg/dl
  1+: 30 to <100 mg/dl
  2+: 100 to <300 mg/dl
  3+: 300 to <1000 mg/dl
  4+: ≥1000 mg/dl

- **SSNS:** Complete remission after 4 weeks of prednisone or prednisolone at standard dose
- **Infrequent relapsing NS:** <2 relapses per 6 months within 6 months of disease onset or <4 relapses per 12 months in any subsequent 12-month period
- **Frequent relapsing NS:** ≥2 relapses per 6 months within 6 months of disease onset or ≥4 relapses per 12 months in any subsequent 12-month period
- **Steroid-dependent NS:** Two consecutive relapses during therapy with prednisone or prednisolone (either at full dose or during tapering) or within 15 days of prednisone or prednisolone discontinuation
- **SRNS:** Lack of complete remission at 4 weeks of therapy with daily prednisone or prednisolone at standard dose
- **Late responder:** Complete remission at 6 weeks.
- **Calcineurin inhibitor-responsive SRNS:** Partial remission after 6 months of treatment and/or complete remission after 12 months of treatment with a calcineurin inhibitor at adequate doses and/or levels
- **Calcineurin inhibitor-resistant SRNS:** Absence of partial remission after at least 6 months of treatment with a calcineurin inhibitor at adequate doses and/or levels
- **Multi-drug resistant SRNS:** Absence of complete remission after 12 months of treatment with 2 mechanistically distinct glucocorticoid-sparing agents at standard doses (see below)
- **Secondary SRNS:** A SSNS patient at disease onset who at a subsequent relapse fails to achieve remission after 4 weeks of therapy with daily prednisone or prednisolone at standard dose

Figure 39 | Definitions relating to NS in children aged 1–18 years. *To rule out orthostatic proteinuria, the first morning urine should be collected separately for assessment. †van der Watt *et al.*[206] NS, nephrotic syndrome; PCR, protein-creatinine ratio; SRNS, steroid-resistant nephrotic syndrome; SSNS, steroid-sensitive nephrotic syndrome.

4.2 Prognosis

Practice Point 4.2.1: The prognosis for childhood nephrotic syndrome is best predicted by the patient's response to initial treatment and frequency of relapse during the first year after treatment. Therefore, a kidney biopsy is not usually needed at initial presentation, and instead is reserved for children with resistance to therapy or an atypical clinical course.

Nephrotic syndrome is the most frequent glomerular disease in children, with an incidence of 1.15–16.9 per 100,000 children.[207] Before the availability of antibiotics and glucocorticoids, about 40% of children with NS died of infection, kidney failure, and occasionally thromboembolism.[208] If the children survived, sustained spontaneous remission was observed only after years of disease activity. Antibiotics reduced mortality, but it was the introduction of glucocorticoid use in the 1950s that changed the natural history of the condition.[208] Since the 1970s, following onset of disease, children are treated with a standard dose of glucocorticoids. Response to this standard dosing regimen and the number of relapses in the subsequent year allows classification of the child's NS, and this classification holds more prognostic value than a kidney biopsy, which is therefore not routinely performed at disease onset. In general, it is assumed that children with steroid-sensitive forms of NS, if biopsied, would most frequently be found to have MCD, though mesangial proliferation with IgM and FSGS (the lesion most frequently associated with steroid-resistant forms of NS) has also been described.

In children with steroid-sensitivity receiving timely and appropriate treatment, kidney function is always maintained, and prognosis is correlated with the morbidity of prolonged exposure to glucocorticoids and to second-line glucocorticoid-sparing agents that are prescribed in frequently relapsing and especially in steroid-dependent forms of disease. The disease has a chronic, relapsing–remitting course, which tends to resolve spontaneously following puberty. However, in 15%–25% of cases, it may progress to adulthood, maintaining the peculiar features of the childhood-onset NS with rapid response to glucocorticoids in case of relapse. Moreover, a small percentage of children may, in subsequent relapses, become secondarily steroid-resistant. These children have a high chance of both progressing to kidney failure and relapsing post-transplantation.

A kidney biopsy is therefore performed at onset only in children with atypical features and in all children with steroid-resistance (Figure 43). Subsequently, during the disease course, it may be advisable to perform or repeat a kidney biopsy in children who have had a prolonged (>2–3 years) exposure to CNIs or who have secondary steroid-resistance.

In children with steroid-sensitive (SS) and steroid-resistant (SR) but calcineurin-responsive forms of NS, the optimal treatment strategy is therefore aimed at employing the lowest cumulative doses of glucocorticoids and the safest and most effective glucocorticoid-sparing agents to maintain remission. The use of vitamin D/calcium, gastroprotection, and an appropriate vaccination strategy are also important to minimize morbidity.

In children with resistant forms of NS, prompt genetic testing to allow appropriate management of the kidney disease and, when present, extrarenal features, is mandatory. Optimal conservative therapy to minimize the side effects of prolonged proteinuria and treatment with dialysis and transplantation must be performed in centers that have specific expertise in pediatric nephrology.

4.3 Treatment

A schematic approach to treatment is outlined in Figure 40.

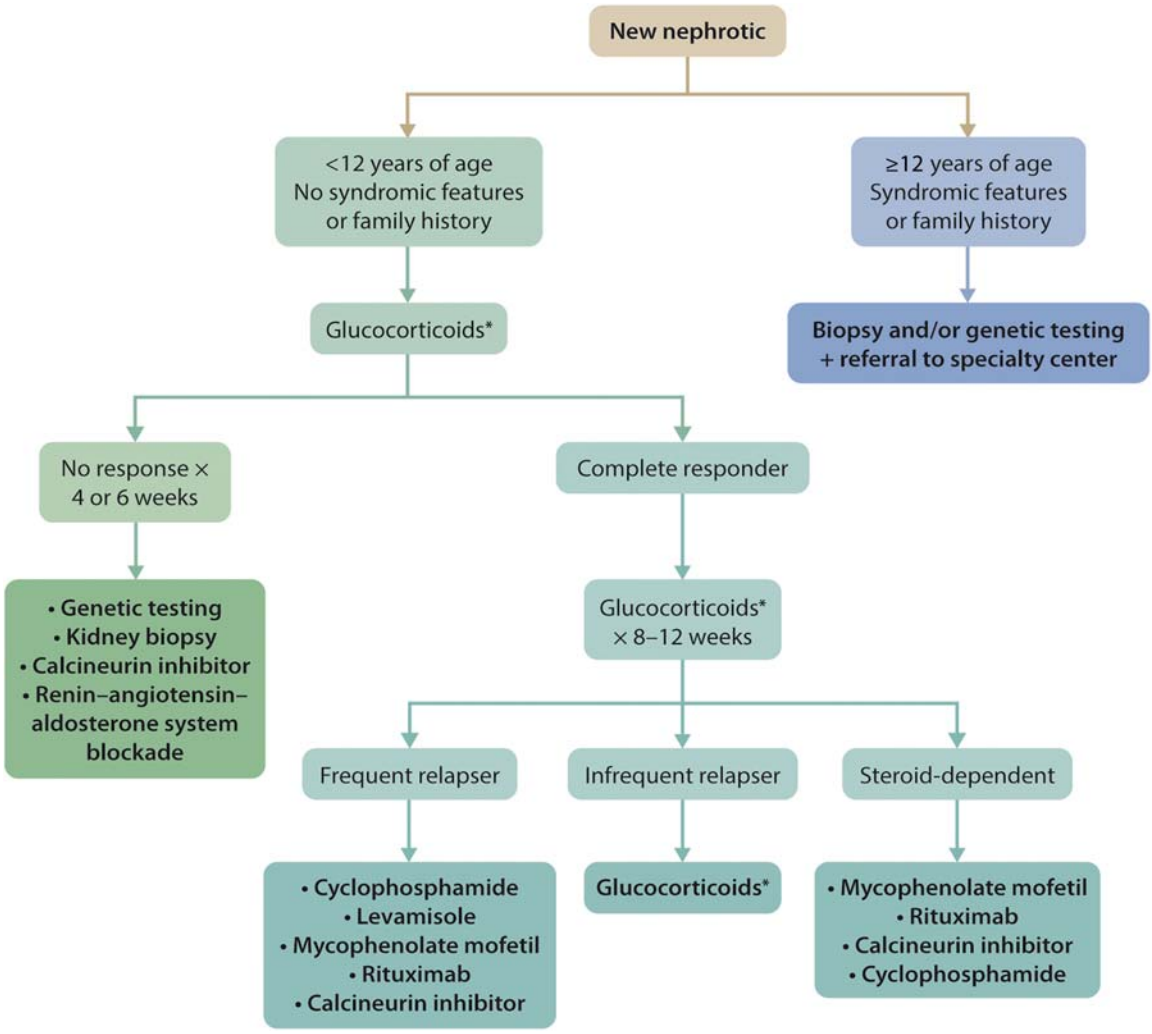

Figure 40 | Treatment algorithm for NS in a newly nephrotic child. Therapeutic approach to NS in children from onset. Refer to clinical trial where appropriate. *Glucocorticoids: p.o. prednisone or prednisolone. NS, nephrotic syndrome.

4.3.1 Initial treatment of NS in children

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

This recommendation places a relatively higher value on the moderate-quality evidence of equivalent clinical outcomes and favorable safety profile associated with shorter-term (8–12 weeks) glucocorticoid treatment, and a relatively higher value on high-quality evidence suggesting prolonged (>12 weeks) glucocorticoid treatment increases the risk of adverse effects without further improving clinical outcomes in terms of relapse rate. The recommendation places a relatively lower value on low-quality evidence suggesting that prolonged glucocorticoid therapy may delay the time to first relapse as compared to 8–12 weeks of treatment.

In terms of oral glucocorticoids, prednisone and prednisolone are equivalent, used in the same dosage, and are both supported by high-quality data. All later usages of "oral glucocorticoids" refer to prednisone or prednisolone.

Recent reports suggest that it may be prudent to dose by body surface area to avoid underdosing, particularly in younger children.[209–212] An RCT comparing single versus divided dose showed that the 2 are equivalent in terms of time to remission and number of subsequent relapses.[213] Therefore, a single daily dose may be preferable to optimize adherence.

Key information

Balance of benefits and harms. Without appropriate treatment, spontaneous remission is very rare for initial episodes of NS, whose morbidity and mortality, if untreated, are considerable.[208] With the introduction of glucocorticoid treatment, prognosis improved dramatically, and from the 1970s, standard protocols were implemented for children at disease onset. The prognosis of children with NS directly

correlates with response to this treatment and subsequently with the number of relapses they experience. The majority of patients who are initially steroid-sensitive remain steroid-sensitive and never progress to kidney failure. Therefore, optimal management is based on minimizing toxicity of treatment, which initially and primarily consists of oral glucocorticoids,[207,214] preserving steroid sensitivity, and prolonging remission.

Since publication of the previous KDIGO 2012 guideline, 4 RCTs have evaluated the optimal glucocorticoid dosage for treatment of the initial episode of SSNS in children: 2 studies comparing 12 weeks to 6 months, 1 study comparing 8 weeks to 6 months, and 1 study comparing 8 weeks to 4 months.[215–217] These studies show that extending initial glucocorticoid treatment from 8–12 weeks to 6 months may delay the first relapse but does not have an impact on the occurrence of frequent relapses, nor on the subsequent disease course.

In an attempt to explain the difference between these more recent findings and earlier evidence, the 2015 Cochrane systematic review examined whether there were systematic differences in the findings of studies at lower versus higher risk of bias.[218] When restricted to studies at lower risk of bias, the pooled findings suggested that prolonged treatment makes little or no difference in the number of children developing frequently relapsing disease. This was true for both studies comparing 12 weeks to 8 weeks of therapy and studies comparing 5–6 months to 8 or 12 weeks of therapy for the initial episode of SSNS. This finding was further confirmed by analysis of the more recently published PREDNOS trial, comparing 8 weeks to 4 months.[219]

In terms of harms, Sinha *et al.* showed that adverse effects related to glucocorticoids (hypertension, Cushingoid appearance, hirsutism, obesity, short stature, and aggressive behavior) and infectious episodes were comparable at randomization, end of intervention, and at 12 months of follow-up in the 2 treatment groups (12 weeks vs. 6 months).[215] Similar findings are reported by Yoshikawa *et al.* (median follow-up 36-38 months),[217] Teeninga *et al.* (median follow-up 47 months),[216] and Webb *et al.* (follow-up 24 months).[219] Although these studies do not demonstrate that the shorter course of treatment has a better safety profile, the totality of evidence from other conditions strongly suggests that the risk of adverse events with glucocorticoid treatment is directly proportional to its duration and cumulative dose. Therefore, as the shorter course does not appear to result in more frequent relapses, its impact in terms of safety appears advantageous, as it entails giving less glucocorticoid at onset.

Quality of evidence. There was moderate-quality evidence from RCTs that compared glucocorticoid therapy for ≥12 weeks duration compared with glucocorticoid therapy of 8 weeks duration (Supplementary Table S14[217–228]). For the important outcome of relapse frequency, the quality of the evidence was low (very serious study limitations). The quality of the evidence was rated as high in a subgroup analysis after removal of studies with a high or unclear risk of bias for allocation concealment. For adverse events (Cushing's syndrome), the evidence was downgraded to moderate because of serious study limitations. However, other adverse events (infection, other glucocorticoid-related adverse events) were downgraded to low- or very-low-quality evidence because of study limitations and serious imprecision (wide CIs—indicating less certainty in effect), or serious inconsistency (substantial heterogeneity). However, there were fewer of these adverse events, so their low quality was not considered critical to the overall quality of the evidence rating. Taking all of these considerations into account, the overall quality in the evidence was rated as moderate.

Values and preferences. The potential benefits of glucocorticoid treatment, including reduction of morbidity from NS and a lower risk of progressive kidney function loss, were judged as critically important to patients and parents. The Work Group also judged that the relatively low risk of clinically important harms, including side effects of glucocorticoids, would be important to many patients. Since preserving steroid sensitivity and maintaining remission is associated with good clinical outcomes, providers and patients must weigh the side effects of glucocorticoids against the risk of undertreating the first episode, which may lead to relapse and a higher cumulative dose of glucocorticoids, along with a higher risk of progressive kidney function loss. Historically, it was thought that intense treatment of the first episode led to fewer relapses and, therefore, to a lower cumulative glucocorticoid dose over >12 months. This attitude, however, may have led to overtreating the first episode. Recent evidence indicates that prolonging glucocorticoid treatment for >12 weeks increases the risk of harm without the benefit of reducing the risk of relapse in the subsequent years. The Work Group judged that all or nearly all well-informed patients and parents would choose to receive 8–12 weeks of glucocorticoids as initial treatment of NS, compared to a longer course of glucocorticoids, another treatment, or no treatment.

There is insufficient evidence to choose between 8 and 12 weeks of glucocorticoid treatment, so usual local practice, available resources, and patient preferences may be used to choose between 8 weeks of treatment as opposed to 12 weeks. Consideration of patient characteristics may also be helpful. For example, 8 weeks, rather than 12 weeks, of treatment may be preferable in children achieving rapid remission (within 7 days from prednisolone initiation) or with comorbidities (obesity, hypertension, type 1 diabetes, etc.).

Resource use and costs. Prednisolone is inexpensive, widely available, and does not require special monitoring (e.g., of drug levels). No published studies have addressed the cost-effectiveness of glucocorticoid treatment among children who are steroid-sensitive, but given its low cost and clinical benefit, this treatment is likely to be cost-effective in most settings.

Considerations for implementation. There are no data evaluating whether the best treatment approach could vary by sex or ethnicity. In children of a particularly young age at disease onset (i.e., 1 to 4–6 years of age) who may be at higher risk of

progressing to a frequently relapsing or steroid-dependent form of NS,[222] prolonging treatment of the initial episode to 16–24 weeks may be beneficial in terms of preventing subsequent relapses with similar side effects.[215] This, however, is true only in children within this age group who experience a delayed response to prednisolone (i.e., remission in 10–15 days from treatment initiation), whereas even in younger patients (1 to 4–6 years old), a standard 8–12-week prednisolone course may be preferable if they respond rapidly to prednisolone (i.e., in <7 days).

Rationale

This recommendation places a relatively higher value on the better clinical outcomes and relatively favorable safety profile associated with shorter-term (8–12 weeks) glucocorticoid treatment compared with no treatment, as well as a relatively higher value on evidence suggesting that prolonged (>12 weeks) glucocorticoid treatment increases the risk of adverse effects without further improving clinical outcomes. The recommendation places a relatively lower value on weaker evidence suggesting that prolonged glucocorticoid therapy may delay the time to first relapse as compared to 8–12 weeks of treatment. Evidence is insufficient to choose between 8 and 12 weeks of treatment.

The recommendation is strong because the Work Group judged that all or nearly all well-informed parents and patients would choose to receive 8 or 12 weeks of glucocorticoids as initial treatment of SSNS, compared to a longer course of glucocorticoids, another treatment, or no treatment.

Practice Point 4.3.1.1: The standard dosing regimen for the initial treatment of nephrotic syndrome is daily oral prednisone/prednisolone 60 mg/m^2/d or 2 mg/kg/d (maximum 60 mg/d) for 4 weeks followed by alternate day prednisone/prednisolone, 40 mg/m^2, or 1.5 mg/kg (maximum of 50 mg) for other 4 weeks, or prednisone/prednisolone 60 mg/m^2/d (maximum 60 mg/d) for 6 weeks followed by alternate day prednisone/prednisolone, 40 mg/m^2, or 1.5 mg/kg (maximum of 50 mg), for other 6 weeks.

4.3.2 Prevention and treatment of relapses of NS in children

Children with SSNS have a good long-term prognosis with expected preservation of GFR into adulthood. Between 80% and 90% of children with SSNS will relapse following an initial response to glucocorticoids. Half of these children will relapse infrequently. The remaining half of these children will experience frequent relapses (FRNS) or become steroid-dependent (SDNS).[229,230] Many children relapse in response to an infectious trigger, but many others will have no identifiable trigger.[231] Prevention of relapse may reduce overall glucocorticoid exposure and decrease the adverse effects of long-term glucocorticoids, which include impaired linear growth, obesity, hypertension, ophthalmologic pathology, behavioral changes, altered bone metabolism, impaired glucose tolerance, acne, and other physical changes related to Cushing's syndrome.[232–235]

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

This recommendation places a relatively higher value on the low-quality evidence that preemptive daily prednisolone reduces the risk of SSNS relapse during infection, and a relatively lower value on low-quality evidence of the potential adverse effects of immunosuppressive risk associated with treatment.

Key information

Balance of benefits and harms. Infections have been long identified as triggers for relapses in children with FRNS. Several trials suggest that relapses might be reduced if glucocorticoids are administered daily for 5–7 days at the onset of upper respiratory tract infection in children with FRNS or SDNS who are either not currently taking glucocorticoids or taking alternate-day glucocorticoids. In the most recent 2017 study by Abeyagunawardena *et al.*, 48 patients with SDNS (but off prednisone for ≥3months) were randomized to receive either 5 days of daily prednisolone at 0.5 mg/kg at the onset of an upper respiratory tract infection, or 5 days of placebo.[236] A minority (34.3%) of the treatment group relapsed, whereas 39.4% of the control group experienced a single relapse, and 18.2% had 2 relapses. These short courses of preemptive glucocorticoid treatment may avert the need for longer courses of glucocorticoids, thereby reducing toxicity.

Although higher doses of glucocorticoids during infection might theoretically cause harmful immunosuppression, available data do not report an increased length or severity of the infections in the children receiving daily versus alternate-day glucocorticoids.

These data are all derived from patients in low-to-middle–income countries, and infection patterns may differ from more-developed nations. Thus, these data need to be confirmed in more diverse populations.

Quality of evidence. There is low quality in the evidence for RCTs examining the use of daily and increased dose prednisolone in patients on maintenance therapy with alternate-day prednisolone during viral infections (Supplementary Table S15[218,236–239]). Relapse and rate of infection-related relapse were the only critical or important outcomes examined in these studies. The quality of the evidence was downgraded because of study limitations and serious imprecision, as there was only 1 RCT that examined each of these outcomes.

Abeyagunawardena *et al.* 2017 is a crossover study that has not reported sufficient data to be included in a paired analysis; therefore, no Supplementary table has been presented.[236] Abeyagunawardena *et al.* 2017[236] was downgraded due to a

31% attrition level for patients not completing both parts of the crossover study, and because of serious imprecision, as it is the only trial that examined prednisone versus placebo in children with SSNS after 3 months off prednisone therapy.

Values and preferences. The Work Group judged that avoiding relapse and the excess morbidity associated with subsequent prolonged high-dose glucocorticoid exposure would be critically important to patients. The Work Group also judged that the adverse effects associated with a short-term increase from alternate-day to daily prednisone dosing, or short-term reinstitution of glucocorticoids if patients were already off treatment, would also be important to patients. Given the moderate reduction in risk of relapse triggered by an infection and the relatively low increase in risk of adverse events with very short-term glucocorticoid treatment, the Work Group judged that all or nearly all well-informed patients with upper respiratory tract or other infections would choose to receive daily prednisone compared to alternate-day prednisone or no treatment.

This preemptive strategy may be preferable in children with FRNS who are more prone to develop untoward side effects from high-dose glucocorticoids—such as severe behavioral changes, sleep disturbance, obesity—or have comorbid conditions such as diabetes.

Resource use and costs. Glucocorticoids are among the most widely available therapies for NS, whereas many other immunosuppressive treatments are either cost-prohibitive or unavailable. This preemptive strategy may further reduce costs by avoiding those associated with the more prolonged treatment courses required when patients relapse.

Considerations for implementation. There are no data to suggest that treatment approach should vary on the basis of sex or ethnicity.

Rationale

The KDIGO 2012 guideline suggested transitioning children with FRNS who were receiving glucocorticoids on alternate days (or not receiving glucocorticoids) to daily prednisone for 5–7 days at the start of an infection. Since that publication, there have been several randomized, but small, clinical trials that have demonstrated up to a 30% reduction in relapses with this treatment approach, warranting this statement to remain as a recommendation.

Practice Point 4.3.2.1: The initial approach to relapse should include oral prednisone/prednisolone as a single daily dose of 60 mg/m^2/d or 2 mg/kg/d (maximum 60 mg/d) until the child remits completely for ≥3 days.

Practice Point 4.3.2.2: After achieving complete remission, reduce oral prednisone/prednisolone to 40 mg/m^2 or 1.5 mg/kg (maximum 50 mg) on alternate days for ≥4 weeks.

Recently, 2 RCTs addressing the treatment of relapses, more specifically the dose and length of alternate day oral prednisone following induction of remission, have been published. One study, the PROPINE trial, compared using 40 mg/m^2 on alternate days for 5 weeks versus using the same cumulative prednisone dose spread out over 10 weeks with a tapering schedule.[240] No benefit in terms of subsequent relapses was found in using the longer treatment schedule. The second study instead attempted to establish the noninferiority of employing a lower oral prednisone dose by comparing 40 mg/m^2 on alternate days for 4 weeks versus 40 mg/m^2 on alternate days for 2 weeks in children with infrequently relapsing nephrotic syndrome.[241] The rate of relapse was similar in the 2 groups of children. However, noninferiority of the short regimen was not established in this study. Taken altogether, these results support the use of oral prednisone/prednisolone at 40 mg/m^2 on alternate days for about 4 weeks following induction of remission for children with SSNS as stated above. Future larger studies may establish that lower doses of oral prednisone/prednisolone can be employed effectively in this setting.

Practice Point 4.3.2.3: For children with frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome without glucocorticoid toxicity, the same glucocorticoid regimen may be employed in subsequent relapses.

Practice Point 4.3.2.4: For children with frequently relapsing nephrotic syndrome without serious glucocorticoid-related adverse effects, low-dose alternate-day oral prednisone/prednisolone (optimally ≤0.5 mg/kg/d) can be prescribed to prevent relapse.

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

This recommendation places a relatively high value on observational data and extensive clinical experience that demonstrate substantial risk of side effects associated with long-term glucocorticoids and efficacy of glucocorticoid-sparing agents in preventing relapse, compared with no treatment.

Key information

Balance of benefits and harms. The complications of NS can be divided into those that are directly disease-associated and those that are treatment-related. There are few studies that have compared glucocorticoids and glucocorticoid-sparing therapies to placebo alone. Historical observational data, however, are clear that the risk of mortality from infections, AKI, and complications from edema and thromboembolism is high in children who are not treated or fail to respond to any treatments.[242]

In a 10-year follow-up study of children with SSNS enrolled in a clinical trial assessing the efficacy of cyclosporine for reducing relapse rate, at least half of the children evaluated experienced severe side effects of glucocorticoids including severe growth failure, obesity, and low-bone density. These findings were attributed to glucocorticoid exposure for frequent relapses following the discontinuation of cyclosporine at 2 years.[233] Additional long-term follow-up of patients into adulthood with childhood-onset NS have demonstrated high prevalence of hypertension, osteoporosis, and cataracts attributable to chronic glucocorticoid exposure.[234,243,244]

To avoid or mitigate glucocorticoid-related adverse effects, children with FRNS or SDNS require other agents, including alkylating agents (cyclophosphamide), levamisole, rituximab, mycophenolate mofetil (MMF), and CNIs (cyclosporine, tacrolimus).

Studies have consistently shown a benefit of second-line therapies in the reduction of relapses for children with FRNS or SDNS compared to either glucocorticoids alone or placebo. In a recent meta-analysis of 26 trials comparing the available immunosuppressive medications to placebo/no treatment, chlorambucil, cyclophosphamide, levamisole, and rituximab were associated with a significantly reduced relapse rate compared to placebo or no treatment at 6- and 12-months follow-up.[245]

Adverse effects of these agents include reduced fertility (alkylating agents), kidney dysfunction, hypertension (CNIs), leukopenia, and an increased risk of serious infections (all second-line treatment options). Despite these challenges, it is the opinion of this Work Group that the overall benefit of these treatments outweighs the almost universal experience of toxicity related to chronic glucocorticoid exposure. Some of the adverse effects, such as leukopenia with levamisole, are uncommon, mild, and reversible. Moreover, strategies to mitigate these potential side effects of some glucocorticoid-sparing agents exist, including limiting the cumulative exposure to cyclophosphamide to <168 mg/kg and monitoring CNI and MMF drug levels.

Quality of evidence. The assessment of the quality of evidence focused on glucocorticoid-sparing agents individually, but overall quality was moderate. RCTs comparing alkylating agents, levamisole, or rituximab to placebo or glucocorticoids had moderate-quality evidence for important outcomes. However, RCTs of CNIs and MMF compared with levamisole in patients with FRNS and SDNS was graded low because of the indirectness of the evidence, and study limitations (see below). Despite the low quality of the evidence for these therapies, the overall quality of the evidence from RCTs was graded as moderate, as the majority of glucocorticoid-sparing agents that have been examined more extensively have a higher quality of evidence. Many of the RCTs do not report long-term clinical outcomes, such as all-cause mortality and kidney failure, given the rarity of these events in this population.

In patients with FRNS, the quality of the evidence for the use of cyclophosphamide or chlorambucil compared to glucocorticoids or placebo was moderate for the outcome relapse at 6–12 months (study limitations) and low at 12–24 months (study limitations, serious imprecision from small numbers of patients and events; Supplementary Table S16[246–253]). Given that there were fewer patients in trials examining relapse at 12–24 months, relapse at 6–12 months was considered the most critical outcome.

The quality of the evidence comparing levamisole with glucocorticoids, placebo, or no treatment in patients with FRNS and SDNS was moderate from RCTs, because there is only 1 RCT in patients with FRNS and 1 trial in patients with SDNS (Supplementary Table S17[213,252–260]).

There was low quality of the evidence from 1 RCT that compared MMF with levamisole (Supplementary Table S18[253,261]). The quality of the evidence was downgraded for important outcomes because of inadequate blinding of participants, study personnel, and outcome assessors, and imprecision (only 1 study).

One RCT compared cyclosporine combined with prednisone to prednisone alone in patients with their first episode of SSNS (Supplementary Table S19[253,262,263]). It is unclear how many patients had FRNS or SDNS in this population, so the quality of the evidence was downgraded. Additionally, the quality of the evidence in this trial was downgraded due to serious imprecision (only 1 study), resulting in a grading of low.

The quality of the evidence for trials comparing rituximab with placebo or standard of care was moderate for the important outcome of relapse at 3 and 6 months because of serious imprecision (few patients) and serious risk of bias, respectively, and this was considered the most critical outcome for rating the quality of the evidence, due to the small number of participants for other outcomes (Supplementary Table S20[209,253,264–269]). For relapse at 12 months, the quality of the evidence was downgraded to moderate, as there were only 2 studies, and substantial heterogeneity was found ($I^2 = 80\%$). The quality of the evidence for infection was very low because the CIs were very wide, indicating appreciable benefit and harm.

There are no RCTs that have examined MMF alone compared with no treatment or glucocorticoids alone in patients with FRNS or SDNS.

Values and preferences. In the judgment of this Work Group, the adverse effects associated with prolonged glucocorticoid exposure would be critically important to patients and their parents. The high morbidity associated with uncontrolled nephrosis, and the high frequency of relapsing disease for many children with FRNS off glucocorticoids, makes the option of nontreatment unfeasible. The Work Group also judged that the potential adverse effects of glucocorticoid-sparing therapies (e.g., risk of infection, reduced fertility, kidney dysfunction, and hypertension) would be less detrimental to patients due to potential risk-mitigation strategies such as drug-level monitoring and dose

limitations. Overall, the Work Group judged that avoiding the adverse effects associated with prolonged glucocorticoid exposure would be more important to patients and their parents than the potential adverse effects of glucocorticoid-sparing therapies.[270,271]

Resource use and costs. CNIs, alkylating agents, MMF, and rituximab are considerably more expensive than glucocorticoids and may require ongoing clinical and/or laboratory monitoring. Some glucocorticoid-sparing agents (or the monitoring that they require) are not available (e.g., levamisole) or affordable in all settings. However, the averted cost associated with preventing glucocorticoid-induced adverse events may offset the increased cost of glucocorticoid-sparing therapies.

Considerations for implementation. Relative efficacies of glucocorticoid-sparing therapies are described in practice points. In addition to expected efficacy, age, ability to tolerate frequent phlebotomy for safety labs, and patient preferences for daily oral therapy versus infrequent hospitalization for i.v. infusions are all factors that should be considered in treatment decision-making.

Rationale

The objective of limiting the long-term adverse effects of glucocorticoids in children with FRNS and SDNS has been consistent across guidelines from multiple bodies in every geographic region. The KDIGO 2012 guideline, a recent 2015 Cochrane review for the treatment of SSNS in children, the British Association of Pediatric Guidelines, and Indian Pediatric Nephrology Group all recommend consideration of glucocorticoid-sparing therapies in children who are steroid-dependent, especially those who have exhibited glucocorticoid toxicity.

Practice Point 4.3.2.5: Patients should ideally be in remission with glucocorticoids prior to the initiation of glucocorticoid-sparing agents such as oral cyclophosphamide, levamisole, mycophenolate mofetil (MMF), rituximab, or calcineurin inhibitors (CNIs). Coadministration of glucocorticoids is recommended for ≥2 weeks following initiation of glucocorticoid-sparing treatment.

Although the goal of glucocorticoid-sparing agents is to let the patients be free of glucocorticoids, low-dose daily or alternate-day glucocorticoids may still be needed to maintain remission in SDNS despite administration of glucocorticoid-sparing agents. In children with SDNS, where alternate-day prednisone is not effective, daily prednisone can be given at the lowest dose to maintain remission without major adverse effects.

Practice Point 4.3.2.6: Choosing the most appropriate glucocorticoid-sparing agent from among oral cyclophosphamide, levamisole, MMF, rituximab, and CNI is a decision that requires careful consideration of specific patient-related issues such as resources, adherence, adverse effects, and patient preferences. Oral cyclophosphamide and levamisole may be preferable glucocorticoid-sparing therapies in frequently relapsing nephrotic syndrome. MMF, rituximab, CNIs, and to a lesser extent, oral cyclophosphamide may be preferable to glucocorticoid-sparing therapies in children with steroid-dependent nephrotic syndrome (Figure 41[178]).

Cyclophosphamide. Patients with frequent relapses might have a superior response to cyclophosphamide and levamisole compared to patients with steroid dependency.[272] In 143 children treated with oral cyclophosphamide for FRNS, SDNS, or evidence of glucocorticoid toxicity, sustained remission was more frequent in children with FRNS versus SDNS (HR: 1.72; 95% CI: 0.99–2.98; $P = 0.05$).[273] Nonetheless, there may be a role for this treatment in some patients with SDNS, especially in areas of the world where other glucocorticoid-sparing agents are not accessible. In 90 children with SDNS who received a single course of oral cyclophosphamide (2 mg/kg/d for 10–12 weeks), a cumulative remission status of 57% at 1 year was achieved.[274] Children with FRNS older than 7.5 years are more likely to experience a long-term remission when treated with cyclophosphamide compared to children who are <4 years of age.[274] Younger age at presentation and having steroid dependence requiring higher doses (>1 mg/kg/d of glucocorticoids) to maintain remission appear to be associated with less-sustained remissions following treatment with oral cyclophosphamide.[275]

Gonadal toxicity appears to affect males more than females, with data supporting a dose-dependent relationship. Azoospermia has been well-documented when cumulative cyclophosphamide exposure exceeds 168 mg/kg. For this reason, second courses of alkylating agents are not recommended.

Levamisole. Adverse effects of levamisole are uncommon and mild, including leukopenia and gastrointestinal disturbance. Data comparing cyclophosphamide and levamisole are quite limited and do not determine efficacy of one therapy over the other in regard to either relapse rates after treatment discontinuation or frequency of infection events.[276] Compared to placebo, levamisole has been shown to delay the time to relapse post-termination of glucocorticoids, and 26% of the patients treated with levamisole were relapse-free for at least 1 year, compared to only 6% of patients in the placebo group.[258] Adverse events in this trial were few and were mostly limited to neutropenia that was easily reversed with discontinuation of therapy. MMF was not superior to levamisole in a trial of 139 children with FRNS and SDNS in regard to sustained remission off glucocorticoids, although it showed a trend toward superiority in children with more severe forms (SDNS).[261]

MMF. Variable outcomes for maintaining remission off glucocorticoids have been reported in children with FRNS or SDNS treated with MMF, and these are mostly limited to retrospective observational data. A recent crossover RCT of 60 children with FRNS compared the efficacy of MMF and cyclosporine directly. Relapses occurred in 36% of patients during MMF therapy versus only 15% during cyclosporine

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 41 | Glucocorticoid-sparing therapies in children with SSNS. *Gellermann *et al.*[178] †The CNI, while often used twice daily, may be dosed once a day, depending on individual formulations. In smaller children (<6 years of age), daily dose of cyclosporine can be divided into 3 doses (every 8 hour) to obtain steady hematic levels. 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.

($P = 0.06$). The time without relapse was significantly longer with cyclosporine than with MMF during the first year ($P < 0.05$), but not during the second year ($P = 0.36$). Notably, adverse events were similar between the treatment arms with the exception of a lower eGFR and more anemia in the cyclosporine arm suggesting more nephrotoxicity.[178]

Post hoc analysis of the Gellermann *et al.* study comparing MMF versus cyclosporine provided data that targeting higher area under the curve (AUC) levels may reduce relapses on therapy.[178] Children with low MPA exposure (AUC <50 μg h/ml) experienced 1.4 relapses per year compared with only 0.27 relapses per year in those with high exposure (AUC >50 μg•h/ml; $P < 0.05$). This study also suggested less nephrotoxicity compared to treatment with CNIs.

Rituximab. Several RCTs and non-RCTs have suggested a favorable response to rituximab in patients with SDNS and FRNS.[265,267,269,277] In an RCT by Iijima *et al.* of 48 children with FRNS or SDNS, a significant difference (267 vs. 101 relapse-free days [HR: 0.27; 95% CI: 0.14–0.53]; $P < 0.0001$) was noted for patients who received rituximab versus placebo.[278] In a randomized noninferiority trial of 30 children with SDNS, all but 1 child in the placebo arm relapsed within 6 months, compared to a median time to relapse of 18 months in the children treated with rituximab (95% CI: 9–32 months).[269] Rituximab was found to decrease the total number of relapses from 88 to 22 and the per-patient median number of relapses from 2.5 (interquartile range [IQR]: 2–4) to 0.5 (IQR: 0–1; $P < 0.001$) during 1 year of follow-up in 44 children and adults with either SDNS or FRNS in the Rituximab in Nephrotic Syndrome of Steroid-Dependent or Frequently Relapsing Minimal Change Disease Or Focal Segmental Glomerulosclerosis (NEMO) trial.[277]

Reported rates of adverse events such as infection have been lower in children with FRNS treated with rituximab versus placebo. In the Ravani *et al.* trial, nausea and skin rash during infusion were common.[269] No such events occurred in the NEMO trial, and in fact, improvement in the growth velocity and reduction of BMI was noted in the participants after 1 year. There are no studies directly comparing adverse event rates in children treated with rituximab compared to cyclophosphamide. One retrospective study in 200 adult patients with MN reported that during a median follow-up of 40 months, patients who received rituximab had significantly fewer adverse events than those who received cyclophosphamide (63 vs. 173, $P < 0.001$), for both serious (11 vs. 46, $P < 0.001$) and nonserious (52 vs. 127, $P < 0.001$) adverse events.[279]

CNIs (cyclosporine and tacrolimus). Relapse following discontinuation of CNI treatment is frequent. Previous trials have reported relapse in up to 70% of children who discontinue their CNI, after 6 and 12 months of treatment. Tubulointerstitial lesions, however, have been reported in 30%–40% of children treated for more than 12 months with cyclosporine, and up to 80% of those treated for more than 4 years. The optimal duration of treatment based on these data for cyclosporine is not clear, and data for tacrolimus are even sparser. To reduce the cost of CNIs, coadministration of ketoconazole has been reported to reduce the dose needed to reach target trough levels by almost 50%, thereby yielding a cost savings of almost 38%, with no reduction in efficacy.

STEROID-RESISTANT NEPHROTIC SYNDROME IN CHILDREN

In a child who does not achieve complete response to glucocorticoids at 4 weeks, SRNS is diagnosed. If partial remission is achieved, SRNS can be strongly suspected, but a small percentage of children will achieve complete response at 6 weeks (defined as late responders). Those who do not will be defined as patients with SRNS at 6 weeks. Between 4 and 6 weeks from the start of glucocorticoid therapy, a RASi should be started, and glucocorticoid administration should be continued. Intravenous methylprednisolone (1 dose daily for 3 days), daily prednisolone, or alternate-day prednisolone can be used. As soon as an established diagnosis of SRNS is made, the first step is to consider the possibility of a genetic cause with which immunosuppression may not be useful. Therefore, if possible, genetic testing performed by experts should be rapidly implemented. Genetic forms of SRNS invariably progress over a variable time course to kidney failure and should be treated conservatively, although a few genetic mutations have been found to have some responsiveness to immunosuppressive therapies, primarily CNIs. Among those children without a genetic cause of SRNS, a substantial proportion will respond to a CNI in a variable amount of time (weeks to months). Children with initial SRNS who are CNI-responders subsequently either remain in stable remission with no or infrequent relapses, or develop steroid-dependent forms of NS. For the latter patients, treat for SDNS as suggested previously and consider conversion to MMF to maintain steroid-free remission. MMF may also be considered in patients presenting with an eGFR <30 ml/min per 1.73 m^2 or used as an alternative to a CNI after remission status has been maintained for >1 year.[280] Rarely, children with an initial diagnosis of SSNS experience a subsequent relapse that does not respond to 4 weeks of glucocorticoid therapy (secondary SRNS). In these cases, often multi-drug resistance develops, leading to kidney failure and a high risk of post-transplant recurrence.

For children with CNI-resistant SRNS, consideration for entry into clinical trials evaluating novel therapies on the horizon should be strongly considered. Sparsentan, a dual endothelin and ARB was found to decrease proteinuria by 45% versus 19% in a phase 2 randomized double-blind trial of those treated only with irbesartan, with no differences in serious adverse events between the groups.[280a] A phase 3 multicenter trial is in progress. Post-approval studies for LDL apheresis are ongoing and provide additional clinical trial options for children with CNI-resistant SRNS. Where clinical trials are not available, there may be a limited role for treatment with rituximab.

For more detailed recommendations on these aspects of care and on management of complications of SRNS in children, refer to the recent International Pediatric Nephrology Association (IPNA) guidelines.[280]

4.4 Treatment

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

This recommendation places a relatively higher value on data suggesting that CNIs are more likely to induce remission than cyclophosphamide, MMF, or rituximab in treatment of children with SRNS. Conversely, it places a relatively lower value on evidence suggesting that prolonged exposure to CNIs may lead to significant nephrotoxicity.

Key information

Balance of benefits and harms. In patients with SRNS, the most commonly used agents include cyclosporine, tacrolimus, high-dose i.v. methylprednisolone, and MMF, although the efficacy of these agents is lower in SRNS compared to FRNS or SDNS. Several RCTs suggested that cyclosporine (with or without glucocorticoids) increases the likelihood of remission among patients as compared to no treatment.[208,281–284] Investigators with the Europe-based PodoNet Registry reported almost 62% of the 1174 children with SRNS followed in a 2015 study received cyclosporine.[285] Complete or partial remission was achieved in at least half of these children. An RCT of 138 children and young adults with steroid-resistant FSGS compared cyclosporine to the combination of MMF and pulse dexamethasone.[286] In this study, no difference in remission rate between the 2 groups was found. This study was designed to randomize 500 patients; however, the low recruitment may have significantly underpowered the ability to measure a moderate effect. A more recent network meta-analysis of 18 clinical trials comprising 790 children diagnosed with SRNS found that tacrolimus and cyclosporine were more efficacious in achieving remission status and were associated with fewer adverse effects compared with i.v. or oral cyclophosphamide, MMF, leflunomide, chlorambucil, azathioprine, and placebo or nontreatment.[287]

No role for cyclophosphamide has been identified for children with SRNS, and data for rituximab suggest that it has a limited role or no role in SRNS.[246,277,288,289] Partial and complete remission occurs significantly more frequently in children with SRNS who receive cyclosporine or tacrolimus compared to those receiving intravenous cyclophosphamide.[290,291] A recent RCT in 60 children who had achieved at least a partial remission with 6 months of tacrolimus treatment revealed that tacrolimus prevented relapses more effectively than MMF (24 relapses over 30.3 person-years in patients receiving tacrolimus compared with 39 relapses during 21.2 person-years in those treated with MMF).[292]

Differences in efficacy between cyclosporine and tacrolimus have not been found, yet the body of literature for cyclosporine is more extensive.[293] The risk of nephrotoxicity is similar for cyclosporine and tacrolimus, but gingival hyperplasia and hypertrichosis are more prevalent with cyclosporine, and glucose intolerance occurs more frequently with tacrolimus. The differing side-effect profiles may guide the choice between cyclosporine and tacrolimus (see *Considerations for implementation*). The large trial of cyclosporine versus MMF plus dexamethasone suggested similar rates of adverse events between the 2 treatment arms.

Quality of evidence. The overall quality of the evidence from RCTs was low. There were only a few small trials that examined the treatment of patients with SRNS. These trials were not of sufficient size to determine differences between therapies; they had various study limitations such as high attrition bias. However, despite 1 comparison (cyclosporine vs. MMF with dexamethasone) having a higher quality of the evidence rating (moderate quality of the evidence), the majority of comparisons had low quality of the evidence; hence, the overall quality of the evidence was rated as low.

In the 3 RCTs that compared cyclosporine with placebo or no treatment, the quality of the evidence was low because of study limitations (attrition bias) and serious imprecision due to a small number of patients (n = 49; Supplementary Table S21[282–284,294]). The effects on adverse events, such as infection, were unclear, because of very low quality in the evidence, and given the low number of participants (n = 17) included in the trial examining this outcome, it was not considered critical in determining the overall quality of the evidence rating for this comparison.

The quality of the evidence was low in 2 RCTs that compared CNIs with i.v. cyclophosphamide (Supplementary Table S22[290,291,294]). The evidence quality was downgraded because of attrition bias and serious imprecision, as there were only a few patients in these RCTs (152 participants).

There is moderate quality of evidence for the RCTs that compared cyclosporine with MMF and dexamethasone (Supplementary Table S23[286,293–295]). The quality of the evidence was downgraded to moderate because trials had insufficient recruitment (few patients) to exclude differences between treatments.

One RCT compared tacrolimus with MMF in ability to maintain disease remission in 60 participants (Supplementary Table S24[292,294]). The quality of the evidence was low because of a lack of blinding in the study and serious imprecision (low number of patients and events).

Values and preferences. The Work Group placed a relatively high value on data suggesting that CNI treatment is superior to no treatment and comparators such as cyclophosphamide and MMF for inducing remission in children with SRNS. The Work Group also placed a relatively high value on the high risk of progressive kidney failure associated with untreated SRNS,[285] and the morbidity associated with untreated NS (e.g., edema, infections, thrombotic complications). The Work Group placed a relatively lower value on the morbidity associated with side effects of CNI treatment, including nephrotoxicity. In the judgment of the Work Group, all or nearly all well-informed patients with SRNS would accept the risk of CNI-associated morbidity in exchange for a lower risk of kidney failure due to SRNS.

Treatment	Dose and duration	Clinical tips
Calcineurin inhibitors	• Oral cyclosporine 5 mg/kg/d (starting dose) in two divided doses. Target 12-h trough level of 60–150 ng/ml [50–125 nmol/l] aiming for lowest levels to maintain remission and avoid toxicity or • Oral tacrolimus 0.1 mg/kg/d (starting dose) given in two divided doses for a minimum of 6 months. Target 12-h trough level of 5–10 ng/ml [6–12 nmol/l] aiming for lowest levels to maintain remission and avoid toxicity	CNIs should be continued for at least 12 months as 70% of those who achieve a complete response or partial response will relapse upon discontinuation. They should be discontinued in those without at least a partial response by 6 months. Tacrolimus may be preferred over cyclosporine in patients for whom the cosmetic side effects of cyclosporine are unacceptable. Cyclosporine may be preferable in patients at risk for diabetic complications. There are no studies that investigate differences in long-term outcomes in SRNS on the basis of treatment duration. Median time to complete response or partial response is variable. Response can be seen as long as 6 months following treatment initiation. Trough levels could be measured to minimize nephrotoxicity
Glucocorticoids	• i.v. methylprednisolone bolus of 500 mg/m^2/d for 3 days prior to starting CNI. Followed by taper: alternate-day oral prednisolone to be tapered gradually over 6 months • Low-dose prednisone (<0.25 mg/kg/d alternate day dosing)	Most clinical trials and observational studies have included low-dose glucocorticoids in combination with CNIs to induce remission. No studies compare the outcomes between children treated with CNIs alone or in combination with low-dose glucocorticoids
Cyclophosphamide	• Not recommended	Two randomized control trials provide moderate-level data demonstrating no benefit using cyclophosphamide to treat children with SRNS. However, in countries with limited resources where CNIs are not available, this approach may be considered
Mycophenolate mofetil	• Starting dose of 1200 mg/m^2/d (given in two divided doses) for 1 year	This approach may be employed in children who have achieved stable remission on a CNI, to maintain remission without accumulating nephrotoxicity
Rituximab	• 375 mg/m^2 i.v.	Giving two infusions (day 1 and day 8) at this dose may be preferable in the presence of nephrotic-range proteinuria to achieve complete B cell depletion. Hepatitis B titers 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

Figure 42 | Treatment of SRNS in children. CNI, calcineurin inhibitor; i.v., intravenous; SRNS, steroid-resistant nephrotic syndrome.

Resource use and costs. The financial burden imposed by both drug costs and need for therapeutic drug monitoring may limit the accessibility of cyclosporine or tacrolimus, especially in low-resource areas. In high-resource areas, payer variability may equally challenge widespread availability. Physicians and patients will need to weigh the cost burden and potential long-term adverse effects of treatment against the high risk of kidney failure and other morbidities associated with nontreatment.

Considerations for implementation. Targeted genetic testing where available may be useful in some patients. Identification of causative podocyte-specific mutations may avoid unnecessary cumulative exposure to immunosuppressive therapies in some cases and help predict possible treatment-responsiveness in others. In Trautmann *et al.*, 11% of the 74 children with an identifiable podocyte mutation achieved at least a partial remission with intensified immunosuppression protocols that included various combinations of glucocorticoids, tacrolimus or cyclosporine, and MMF.[285] Although treatment response rates among patients with podocyte-specific mutations are low, mitigating nephrotic complications in children with at least a partial response may be valuable. A few mutations have been associated with treatment-responsiveness. For example, patients with WT1 and PLCE1 mutations have been found to have variable steroid-responsiveness and responsiveness to low-dose CNIs.[296,297] Proteinuric disease has been mitigated in patients with identified COQ2, COQ6, and ADCK4 mutations with

ubiquinone supplementation.[298–300] The hypertrichosis and gingival hypertrophy associated with CNIs may impede treatment adherence, especially in adolescents. Tacrolimus may need to be avoided in patients with obesity or who may be at risk for diabetes or already have signs of glucose intolerance such as acanthosis. Therapy with CNIs should be discontinued in patients who fail to achieve at least a partial response within 6 months (Figure 42).

Rationale

CNIs appear to increase the likelihood of remission compared to no treatment in children with SRNS and have consistently shown greater efficacy than cyclophosphamide and MMF. The risk for kidney failure is significantly greater for patients who fail to achieve a partial or complete remission with any single or combination therapy. The data comparing the efficacy of cyclosporine versus tacrolimus in children with SRNS are sparse and of low quality, and therefore, a decision to use one versus the other should be based on preferences of the provider, patient, and family, after consideration of the different side effect profiles. Although CNI treatment is associated with adverse effects, the Work Group judged that all or nearly all well-informed patients with SRNS would choose to be treated with a CNI because of the high risk of kidney failure associated with untreated SRNS.

4.5 Special situations

Practice Point 4.5.1: Figure 43[301,302] outlines the general principles in children with nephrotic syndrome.

Research recommendations

RCTs are needed to:

- Compare 8 versus 12 weeks of oral prednisone/prednisolone for initial therapy: explore further shortening of the initial glucocorticoid regimen and assess combination therapy with a glucocorticoid-sparing agent at disease onset
- Optimize subsequent treatment of SSNS after relapse in different forms of disease
- Optimize dosing regimen for glucocorticoid treatment at the start of an infection
- Define the optimal dosing and choice of glucocorticoid-sparing agents in FRNS and SDNS
- Evaluate the optimal duration of glucocorticoid treatment in SRNS, in particular when CNIs are initiated, and stratify patients based on identification of podocytopathy-related genetic mutations
- Determine the mode of action of glucocorticoids and other immunosuppressives in SSNS; determine the potential role of pharmacogenomics in treatment; identify biomarkers or genetic risk haplotypes to stratify disease subgroups
- Include quality-of-life measures as endpoints in clinical trials assessing treatment of children with both SSNS and SRNS

Indication for kidney biopsy*	• Children presenting with nephrotic syndrome ≥ 12 years of age • Steroid-resistant nephrotic syndrome or subsequent failure to respond to glucocorticoids in steroid-sensitive nephrotic syndrome (secondary steroid-sensitive nephrotic syndrome) • A high index of suspicion for a different underlying pathology (macroscopic hematuria, systemic symptoms of vasculitis, hypocomplementemia, etc.) • At onset, kidney failure not related to hypovolemia. Subsequently, decreasing kidney function in children receiving calcineurin inhibitors or prolonged exposure to calcineurin inhibitors (2 to 3 years)
Genetic testing	• Steroid-resistant nephrotic syndrome • Congenital and infantile forms of nephrotic syndrome (<1 year of age) • Nephrotic syndrome associated with syndromic features • Family history of steroid-resistant nephrotic syndrome or focal segmental glomerulosclerosis
Vitamin D/calcium	In patients with steroid-sensitive nephrotic syndrome and normal vitamin D levels, supplementation is not required. However, in frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome in children or in the presence of a known vitamin D deficiency, a reduction in bone mineral content can be prevented by oral supplementation with oral calcium and vitamin D.[1,2]
Gastroprotection	There is insufficient evidence of benefit to recommend prophylactic use of proton-pump inhibitors in children with nephrotic syndrome in the absence of risk factors for gastrotoxicity or of gastric symptoms.

Figure 43 | General principles in children with NS. *If there is an evident extrarenal cause for proteinuria (i.e., lymphoma, monoclonal antibody treatment in ulcerative colitis, human immunodeficiency virus), a kidney biopsy may not be warranted. NS, nephrotic syndrome. [1]Gulati *et al.*[301], [2]Gruppen *et al.*[302]

Chapter 5: Minimal change disease (MCD) in adults

Minimal change disease (MCD) is a podocytopathy more commonly seen in children, but it also accounts for 10%–25% of adult NS.[303] MCD in most patients does not have an underlying cause. The pathogenesis of MCD is unclear, but evidence supports T cell dysregulation driving the podocytopathy.[304] The effectiveness of B cell–depleting therapeutic agents also suggests a role for B cells in disease pathogenesis.[214] Rarely, Hodgkin's disease and drugs such as lithium and nonsteroidal anti-inflammatory agents may underlie MCD.[305] This chapter makes management recommendations for adults (≥18 years of age) who have MCD.

5.1 Diagnosis

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

MCD has a distinctive histology, and its presence cannot be deduced from clinical data alone. Light microscopy shows no glomerular lesions, or only minimal mesangial prominence. Immunofluorescence microscopy is negative or shows low-intensity staining for C3 and/or IgM. Electron microscopy demonstrates extensive foot process effacement but no electron-dense deposits, and in the presence of unremarkable light and immunofluorescence, findings are diagnostic for MCD. One caveat is that early FSGS lesions may be missed if the biopsy sample is small.

5.2 Prognosis

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

Steroid-sensitive MCD rarely, if ever, progresses to kidney disease, although AKI due to high-grade proteinuria is relatively common.[306] Approximately 10%–20% of adult MCD patients are steroid-resistant.[307] On repeat biopsy, lesions of FSGS are seen in a significant number of such patients and are associated with a worse prognosis.[60,306] The treatment of steroid-resistant FSGS is discussed in Chapter 6.

5.3 Treatment

In general, adult MCD is similar to SSNS in children. However, response to glucocorticoid treatment is slower in adults than children. There is a paucity of high-quality RCT evidence evaluating the effectiveness of glucocorticoids over placebo in adult MCD. Treatment recommendations for adult MCD are based on observational studies, small RCTs, and extrapolation from RCTs in children with SSNS.

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

This recommendation places a relatively higher value on low-quality evidence suggesting that high-dose glucocorticoids effectively reduce the significant morbidity associated with prolonged NS compared to no treatment. The recommendation places a relatively lower value on the possibility that MCD will spontaneously remit without treatment and on the risks of adverse events related to glucocorticoid treatment.

Key information

Balance of benefits and harms. Although untreated MCD may undergo spontaneous remission, this is relatively uncommon. Approximately 50%–60% of patients remit over 2–3 years of follow-up, compared to a 30% spontaneous remission rate in MN over 6 months,[308,309] and there is considerable morbidity associated with persistent nephrosis, including infections,[310] thromboembolic events,[311] and hyperlipidemia.[312]

MCD is typically responsive to glucocorticoids, with over 80% of patients achieving remission.[306,313] Observational studies consistently report a high response rate to glucocorticoids as the initial therapy for MCD among adults.[306,307,313–316] In a very early multicenter controlled study of glucocorticoids, compared to no treatment, in 125 nephrotic adults (including 31 patients with MCD defined by light microscopy alone), those treated with ≥20 mg/d prednisone for ≥6 months showed an early and rapid decrease in proteinuria, compared to the control group. However, by 2.5 years, there was no difference in proteinuria or serum albumin in the 2 groups.[308] Similarly, in another RCT of 28 patients with MCD treated with an average of 125 mg prednisone every other day for 2 months, there was no difference in remission rates between the treated group and controls over 77 months of follow-up.[309] This lack of difference is likely a consequence of the significant relapse rates in the treated group despite early remission, plus the fact that a significant number of placebo-treated patients eventually received glucocorticoid treatment.

In addition, numerous high-quality studies demonstrate that glucocorticoids are effective for treatment of SSNS in children (Chapter 4). SSNS in children and adult MCD appear similar in terms of pathogenesis. Therefore, the benefits of glucocorticoid treatment in children are likely to at least partially extend to adults. In children, several RCTs have shown excellent remission rates with glucocorticoids administered for 8–12 weeks.[215–217]

Therefore, in the judgment of the Work Group, the potential benefits of high-dose glucocorticoid treatment substantially outweigh the risk of harms in nearly all patients with MCD.

Quality of evidence. The quality of the evidence from the few RCTs that examine the treatment of the first episode of MCD in adults with NS with glucocorticoids is low (Supplementary Table S25[309,317] and Supplementary Table S26[317–319]). These RCTs include only a small number of participants and have various study limitations that place them at high risk of bias. Additionally, because of the small number of participants, the trials exhibit serious imprecision, with wide CIs indicating less certainty in effect on critical and important outcomes, such as all-cause mortality, doubling of SCr level, and complete remission.

Values and preferences. The Work Group judged that the potential benefits of glucocorticoid treatment, including reduction of morbidity from NS, as well as a lower risk of progressive kidney function loss, are critically important to patients. The Work Group also judged that the relatively low risk of harms of short-term glucocorticoid treatment, including precipitation/worsening of diabetes, psychiatric conditions, and bone loss, would be an important consideration for many patients. Although the quality of the evidence supporting glucocorticoid use is low, the long clinical experience with this regimen, the significant morbidity associated with untreated nephrosis, and the excess morbidity and mortality associated with progressive kidney function loss or kidney failure, together with the low risk of harms, all suggest a highly favorable risk–benefit ratio. The recommendation is strong because, in the judgment of the Work Group, all or nearly all well-informed patients with MCD would want to receive such treatment.

Resource use and costs. Glucocorticoids are inexpensive and require little monitoring (e.g., measurements of drug levels are not required). In low-resource settings, this class of drugs is affordable and may be the only type available.[107]

Considerations for implementation. Adverse effects of glucocorticoids may be higher in certain subgroups of patients (e.g., obese patients and those with poorly controlled diabetes or a serious psychiatric disorder). In such patients, alternate immunosuppressive regimens such as CNI or cyclophosphamide may be considered (Figure 44). There are no known race or sex effects on treatment responses in MCD.

Rationale

Due to the significant reduction in morbidity associated with prolonged NS and progressive kidney failure, the Work Group felt that this should be a strong recommendation. In the opinion of the Work Group, the benefits of high-dose glucocorticoids outweigh the potential harms, and this recommendation would be generalizable to all patients with MCD. Although the evidence has limitations, such as a paucity of large, well-controlled studies in adults, these limitations are offset by the long clinical experience with glucocorticoids and the evidence from large observational studies suggesting that glucocorticoid treatment does induce earlier remission in adult MCD than no treatment. The recommendation is strong because, in the judgment of the Work Group, all or nearly all well-informed patients would choose to receive high-dose glucocorticoids as initial treatment of MCD, as compared to no treatment or other treatments. Also, the treatment is relatively inexpensive and requires minimal monitoring.

Practice Point 5.3.1: Algorithm for the initial treatment of MCD in adults (Figure 44)

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

Despite the lack of RCT evidence, a maximum duration of 16 weeks is recommended to allow the patient to reach remission. This statement is based on observational studies suggesting that a longer course of treatment for MCD may be needed in adults as compared to children. Only 50% of patients will respond after 4 weeks of glucocorticoid, but an additional 10%–25% may respond after a total of 16 weeks of treatment.[306,315]

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

The optimal glucocorticoid taper protocol after remission in adults is not known. Generally, tapering of glucocorticoids is begun after achieving remission. In 2 RCTs in children, 2–3 months of initial prednisolone therapy was not inferior to 6 months of initial therapy in terms of time to

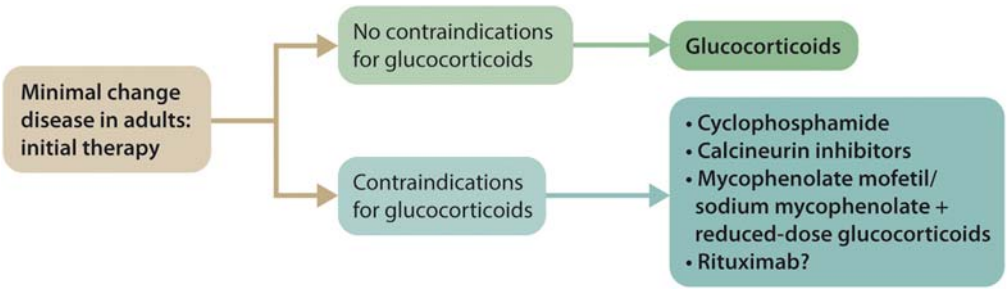

Figure 44 | Initial treatment of MCD in adults. The optimal glucocorticoid regimen is not well-defined; however, suggested doses are outlined in Figure 45. The choice of medication should be based on physician and patient preference. MCD, minimal change disease.

Medication	Regimen	Remission rates (complete and partial)
Initial episode, glucocorticoid treatment		
Prednisone or prednisolone	Dose: 1 mg/kg per day (maximum 80 mg/day) or 2 mg/kg every other day (maximum 120 mg every other day), for a minimum of 4 weeks, and a maximum of 16 weeks (as tolerated). After remission, taper over at least 24 weeks	80%–90%
Initial episode with contraindication to glucocorticoids		
Oral cyclophosphamide	2–2.5 mg/kg per day for 8 weeks	75%
Cyclosporine	3–5 mg/kg per day in divided doses for 1–2 years	75%
Tacrolimus	0.05–0.1 mg/kg per day in divided doses for 1–2 years	90%*
Frequently relapsing/ steroid-dependent patients		
Oral cyclophosphamide	2–2.5 mg/kg/day, adjusted for white blood counts, for 8–12 weeks. 12 weeks may be associated with less relapse in steroid-dependent MCD	75%
Calcineurin inhibitors	**Initial dose:**	
• Cyclosporine	3–5 mg/kg per day in divided doses for 1–2 years	70%–90%
• Tacrolimus	0.05–0.1 mg/kg per day in divided doses for 1–2 years	90%
	• If serum levels are being monitored, suggested initial levels: - Cyclosporine: 150–200 ng/ml (125–166 nmol/l) - Tacrolimus: 4–7 ng/ml (5–8.7 nmol/l) • After withdrawal of glucocorticoids reduce CNI dose if possible Suggested doses: <3mg/kg/day for cyclosporine and <0.05 mg/kg/day for tacrolimus • Attempt gradual taper and discontinuation of CNI after a minimum of one year of therapy if possible • If CNI-dependent reduce dose to lowest possible to maintain remission with monitoring of kidney function (kidney biopsy if kidney dysfunction) Switch to alternate medication if evidence of CNI toxicity	
Rituximab	**Induction regimens:** • 375 mg/m^2 weekly for 4 doses • 375 mg/m^2 × single dose; repeat after one week if CD19 cells >5/mm^3 • 1 g/dose for 2 doses, 2 weeks apart **Relapse after induction:** • 375 mg/m^2 × 1 dose or • 1g i.v. × 1 dose	70% (20% off all immunosuppression, 50% on one other immunosuppressive drug)
Mycophenolic acid analogues	**Initial dose:**	
• Mycophenolate mofetil	1000 mg twice daily	
• Sodium mycophenolate	720 mg twice daily	
	• Attempt gradual taper and discontinuation of mycophenolic acid analogues after a minimum of one year of therapy if possible	

Figure 45 | Treatment of MCD in adults: Initial episode and FR/SD MCD. *Remission rates were not compared in head-to-head studies. CNI, calcineurin inhibitors; MCD, minimal change disease.

onset of FRNS.[215,217] There are no studies comparing a rapid versus a slower glucocorticoid taper in adults. Based on case series, glucocorticoids are usually tapered by 5–10 mg/wk after remission has been achieved for a total period of glucocorticoid exposure of approximately 24 weeks.[306,310,315] It is important to monitor for side effects of glucocorticoids in patients and consider alternate agents if side effects become disabling or if remission has not been achieved.

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

The role of i.v. methylprednisolone followed by lower-dose oral prednisone versus standard-dose oral prednisone alone was compared in 2 RCTs. These approaches were not found to be different in terms of eventual remission and subsequent relapse rates.[318–320]

Observational studies in adults have shown similar remission rates with the 2 regimens.[306,321] For example, in a study comparing prednisone 1 mg/kg/d in 65 patients and 2 mg/kg every other day in 23 patients followed by a taper, there was no significant difference in rate of complete remission, time to remission, rate of relapse, time to first relapse, or adverse events between treatment groups.[306]

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

There are few studies on regimens that are glucocorticoid-sparing or glucocorticoid-free for the initial MCD episode. These treatments are considered in patients who have relative contraindications (severe hyperglycemia, preexisting osteoporosis or osteopenia, or glucocorticoid-induced psychosis) or are unwilling to take glucocorticoids. Cyclophosphamide[307,322–324] and cyclosporine[325] are associated with remission rates of approximately 75% with this limited experience (Figure 45). In an RCT of 116 patients, sodium mycophenolate (SMP) with reduced-dose prednisone (0.5 mg/kg/d, maximum dose 40 mg daily) was similar to conventional high-dose prednisone alone (1 mg/kg/d, maximum dose 80 mg daily) in inducing remission with comparable relapse rates after completing therapy. The frequency of serious adverse effects was also similar between the treatment arms.[326]

In an RCT comparing oral tacrolimus 0.05 mg/kg twice daily with prednisolone 1 mg/kg daily up to 60 mg, complete remission rates and relapse rates were no different between the 2 arms.[327] Rituximab (4 weekly doses of 375 mg/m^2) was used to treat 6 patients with MCD as first-line therapy, with 5 of the 6 patients undergoing complete remission and 1 patient experiencing a 75% decrease in proteinuria.[328] No patient relapsed during the follow-up of 8–36 months despite the recovery of B-cell count.

5.3.1 Treatment of relapses

MCD is a relapsing disease. Most patients will relapse infrequently after remission, but a significant minority will relapse frequently or become steroid-dependent. Up to 33% of patients will become frequent relapsers (11%–29%) or steroid-dependent (14%–30%).[306,307,316,320] Definitions of remission and relapse that are useful in clinically classifying MCD are provided in Figure 46. The optimal duration of glucocorticoid treatment in relapsing MCD is not known. One regimen is to administer oral prednisone at a daily dose of 1 mg/kg

Complete remission
Reduction of proteinuria to <0.3 g/d or PCR <300 mg/g (or <30 mg/mmol), stable serum creatinine and serum albumin >3.5 g/dl (or 35 g/l)
Partial remission
Reduction of proteinuria to 0.3–3.5 g/d or PCR 300–3500 mg/g (or 30–350 mg/mmol) and a decrease >50% from baseline
Relapse
Proteinuria >3.5 g/d or PCR >3500 mg/g (or 350 mg/mmol) after complete remission has been achieved
Steroid-resistant MCD
Persistence of proteinuria >3.5 g/d or PCR >3500 mg/g (or 350 mg/mmol) with <50% reduction from baseline despite prednisone 1 mg/kg/d or 2 mg/kg every other day for >16 weeks
Frequently relapsing MCD
Two or more relapses per 6 months (or four or more relapses per 12 months)
Steroid-dependent MCD
Relapse occurring during, or within 2 weeks of completing glucocorticoid therapy

Figure 46 | Definition of remission, relapse, resistance, and dependence for MCD. MCD, minimal change disease; PCR, protein–creatinine ratio.

(maximum dose of 80 mg/d) for 4 weeks or until remission is achieved, followed by 5-mg decrements every 3–5 days to discontinuation within 1–2 months.

For subsequent relapses, if not frequent (e.g., <3 per year), prolonged glucocorticoid use is associated with side effects including Cushing's syndrome, obesity, glucose intolerance, bone loss, and cataracts.[329] Several drugs are effective in FR/SD MCD and may allow reduced exposure to or elimination of glucocorticoids (Figure 45).

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

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

Infrequent relapses may be treated with glucocorticoids without incurring major side effects if the duration of therapy is limited. The dose and duration of glucocorticoid therapy in patients with infrequent relapses have not been fully investigated. In 1 study, patients were treated with 20–30 mg of prednisolone for a minimum of 7 days or additionally with cyclophosphamide until proteinuria returned to a normal range, suggesting that the high doses of glucocorticoids, as with the initial treatment of MCD, may not be needed.[330] With prolonged and repeated courses, the possibility of cumulative side effects (e.g., hyperglycemia and bone loss) may occur. An RCT of 52 adult patients with MCD in their first relapse of MCD compared cyclosporine (AUC 1700–2000 ng/ml [1414–1664 nmol/l]) combined with prednisolone 0.8 mg/kg/d versus prednisolone 1.0 mg/kg/d and showed lower proteinuria, improved serum albumin, and shorter time to remission in the cyclosporine group over a follow-up period of 6 months.[331]

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

This recommendation places a relatively higher value on avoiding the morbidity associated with prolonged glucocorticoid exposure in FR/SD MCD. It places a relatively lower value on the low-quality evidence supporting the efficacy of cyclophosphamide, rituximab, CNIs, and mycophenolic acid analogs (MPAA), and lower value on the higher cost of these alternative agents compared with prednisone. The choice of therapy for FR/SD MCD may be informed by patient preference, drug side effects, costs, and availability, as there is limited evidence to suggest 1 drug class over the other.

Key information

Balance of benefits and harms. As MCD is a steroid-sensitive disease, other immunosuppressive medications are expected to work in this population. CNIs (cyclosporine, tacrolimus), cyclophosphamide, rituximab, and MPAA (MMF, SMP) have all been reported to be effective therapies for FR/SD MCD.

Clinical benefits. Observational studies and small RCTs showed that all 4 categories of agents reduce relapse rate and induce remission in adult patients with FR/SD MCD (Figure 48[277,306,315,332–338,340]). Efficacy rates range from 70% to 90% in maintaining remission. Generally, these agents are started after inducing remission with glucocorticoids. It may not be possible to withdraw glucocorticoids completely in patients who have been on maintenance glucocorticoids, in view of the possibility of adrenal suppression.

Cyclophosphamide. In patients who are FR/SD experiencing side effects from glucocorticoids, cyclophosphamide has traditionally been the preferred second-line agent. This practice is extrapolated from clinical trials in children, as there is a relative paucity of data in adults that are mainly from observational studies,[306,315,331] and 1 RCT comparing tacrolimus with cyclophosphamide.[332] The risks of infertility, although small, need to be addressed in patients of childbearing age. A single course of oral cyclophosphamide is associated with remission in the majority of patients who are FR/SD. Prolonged therapy (>12 weeks) and repeated courses of cyclophosphamide should be avoided, in view of cumulative toxicities. Cyclophosphamide tends to be associated with more durable remission rates than CNI.[333] Compared to 8 weeks of therapy, 12 weeks of treatment with cyclophosphamide may be associated with more durable remissions in SD MCD.[307]

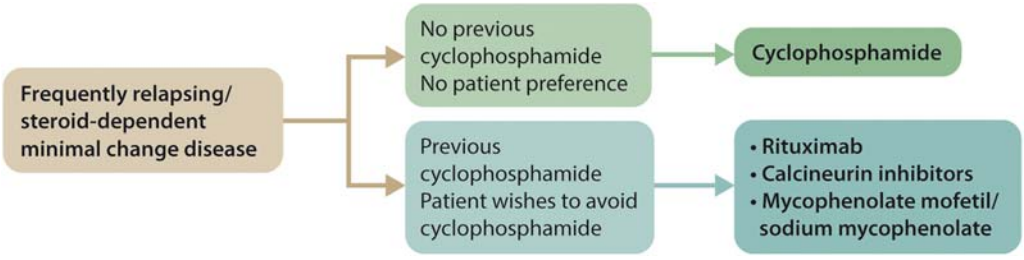

Figure 47 | Treatment of FR/SD MCD in adults. The choice of medication should be based on physician and patient preference. FR/SD, frequently relapsing/steroid-dependent.

Author (ref)	Study design (n with MCD)	Intervention	Outcome
Waldman *et al.*[1]	Observational (39 SD, FR, SR pts)	Cyclosporine trough 150–220 ng/ml (125–183 nmol/l) × 49 ± 14.8 weeks. (12 pts received prednisone 5–10 mg qod)	Remission: 61% Mean time: 5 weeks (2–9)
Meyrier *et al.*[2]	Observational (52/98 SD pts)	Cyclosporine 150–220 ng/ml (125–183 nmol/l) 5 mg/kg/d + prednisone 12–15 mg qod	CR 71% of SD pts at 6 months
Lee *et al.*[3]	Observational (22/27 FR, SD, SR pts)	Cyclosporine 150–220 ng/ml (125–183 nmol/l) 5 mg/kg/d + prednisolone 10 mg/d up to 8 months	CR 84% of SD pts Relapse: 68% at 10 months
Li *et al.*[4]	Prospective cohort study (26 SD pts)	Tacrolimus 4–8 ng/ml (5–10 nmol/l): target trough level 4–8 ng/ml × 24 weeks Cyclophosphamide: intravenous cyclophosphamide (750 mg/m^2, every 4 weeks × 24 weeks)	Tacrolimus: CR 90.9% Cyclophosphamide: CR 76.9% (after 24 weeks therapy) Relapses: tacrolimus: 50%, cyclophosphamide 40%
Ponticelli *et al.*[5]	Randomized, controlled (66 FR, SD MCD pts)	Cyclosporine 150–220 ng/ml (125–183 nmol/l) 5 mg/kg/d × 12 months vs. cyclophosphamide 2.5 mg/kg/d × 8 weeks	Cyclosporine: CR 26/35, PR 5/35 Cyclophosphamide: CR 18/28 Relapse: cyclosporine 75% vs. cyclophosphamide 37%
Mak *et al.*[6]	Observational (22, FR, SD, SR pts)	Cyclophosphamide 2–2.5 mg/kg/d × 8 weeks	CR 86% at 1 year, 74% at 3 years, 63% at 5 years
Waldman *et al.*[1]	Observational (20 SD, FR SD pts)	Cyclophosphamide mean dose 123.6 mg/d for 11.5 + weeks	Remissions: 55% Mean time: 6.4 weeks (5–12)
Munyentwali *et al.*[7]	Observational (17 SD, FR pts)	Rituximab 375 mg/m^2 (1–4 infusions) or 1000 mg × 2 doses, 2 weeks apart	Remission: 65% over mean follow up 26.7 months (5–82)
Iwabuchi *et al.*[8]	Observational (20 SD pts)	Rituximab 375 mg/m^2, 6 monthly × 24 months	CR 100% from 12–24 months Relapses decreased from 108 episodes to 8 (previous 24 months vs. 24 months after rituximab)
Ruggenenti *et al.*[9]	Observational (22 children and adult FR and SD pts)	Rituximab 375 mg/m^2, repeated in 2 weeks if CD20 >5 cells/mm^3	Relapses/patient decreased from 2.5 [IQR 2–4] to 0.5 [IQR 0–1]; P=0.001 during 1 year of follow-up
Guitard *et al.*[10]	Observational (41 SD, FR pts)	Rituximab: 1 g on days 1 and 15 375 mg/m^2 1–4 weekly infusions	CR: 61% PR: 17% NR: 22%
Sandoval *et al.*[11]	Observational (29 FR and SD pts)	MMF: 1500–2000 mg/d or SMP 1440 mg/d. With prednisone tapering to 0–10 mg/d	CR: 86% PR: 7% NR: 7% Mean follow-up of 32.8 months (12–108)
Waldman *et al.*[1]	Observational (10 SD, FR, SD pts)	MMF 1–2 g/d for 36 + 7.9 weeks 10 pts received prednisone 5–10 mg qod	Remissions: 65% Relapses: 35%

Figure 48 | Treatment of FR/SD adult MCD—select clinical studies. [1]Waldman *et al.*[306], [2]Meyrier *et al.*[338], [3]Lee *et al.*[337], [4]Li *et al.*[332], [5]Ponticelli *et al.*[333], [6]Mak *et al.*[315], [7]Munyentwali *et al.*[336], [8]Iwabuchi *et al.*[335], [9]Ruggenenti *et al.*[277], [10]Guitard *et al.*[334], [11]Sandoval *et al.*[340] CR, complete response; FR, frequently relapsing; IQR, interquartile range; MCD, minimal change disease; MMF, mycophenolate mofetil; NR, no response; PR, partial response; qod, every other day; SD, steroid-dependent; SMP, sodium mycophenolate; SR, steroid-resistant.

Rituximab. Rituximab is effective in observational studies of FR/SD MCD in patients needing glucocorticoids with or without other maintenance immunosuppressive therapies.[277,334–336] Overall, the efficacy of rituximab in inducing remission is between 65% and 100%, and notably, it is associated with a reduction in the number of relapses and a reduction in the number of immunosuppressive medications. However, experience with rituximab is limited, and the long-term efficacy/risks in this population are unknown.

Calcineurin inhibitors. In observational studies and 1 RCT, CNIs have been associated with remission in 70%–90% of patient with FR/SD MCD. However, relapse rates are high, and prolonged therapy may be necessary when patients relapse during dose reduction.[60,337,338] In view of relatively long experience with CNIs, these drugs may be favored in patients who relapse after receiving a course of cyclophosphamide or those who would prefer avoiding the alkylating agent because of infertility issues. The value of monitoring drug levels of CNI is uncertain. Older studies used fixed weight–based doses, whereas reports that are more recent used target drug levels.

MPAAs. MMF and SMP were effective in small, uncontrolled studies in patients with FR/SD MCD with remission rates in the 65%–85% range.[306,339,340] In view of this limited experience, the MPAAs may have a role in those patients who have relapsed despite cyclophosphamide and CNIs, and when rituximab is not available.

Adverse events. All 4 categories of agents are associated with an increased risk of infections. CNIs are potentially nephrotoxic, but with lower serum levels used in MCD, this side effect is uncommon.[60] Risk factors for tubulointerstitial lesions in childhood MCD included cyclosporine use for >24 months and presence of heavy proteinuria for >30 days during cyclosporine therapy.[61] The potential side effects of cyclophosphamide, MPAA, and rituximab are discussed in Chapter 1. Cyclophosphamide is generally well-tolerated at the dose used in FR/SD MCD, and when limited to a single course.

Quality of evidence. To date, there have been no RCTs examining the use of cyclophosphamide or rituximab in adults with MCD with FR/SD NS.

Several RCTs examined the use of CNIs compared to glucocorticoids alone in adults with MCD and NS.[331,341,342] The quality of the evidence for these RCTs is low because there are concerns of serious risk of bias because of various study limitations and serious imprecision, as there are only a few studies, with a low number of participants (Supplementary Table S27[317,331,341–343]). These RCTs did not report critical clinical outcomes, all-cause mortality, or kidney failure.

Values and preferences. The Work Group judged that the potential benefit of reduced glucocorticoid exposure is important to patients. However, each of the 4 alternative therapies is associated with potential tradeoffs. These include the increased burden of twice-daily administration with CNIs and MPAAs, and the need for frequent blood tests to monitor dosing and side effects with CNIs. Although cyclophosphamide has a relatively low risk of side effects and is less expensive compared to the other 3 classes, patients of childbearing age may prefer to avoid cyclophosphamide due to the risk of infertility. Rituximab may be preferred by patients, as the medication is given as a single course for induction.

Resource use and costs. The medications discussed in this section, particularly rituximab, are more expensive than glucocorticoids. Serum levels of CNIs need to be continuously monitored, adding to cost. Cyclophosphamide is less expensive than the other 3 classes, is widely available, and does not require any additional laboratory testing apart from monitoring of peripheral blood counts. MPAAs are easy to use and do not require serum-monitoring, but cost may be a limiting factor. Rituximab is the costliest among these drugs, but costs have declined with the advent of biosimilar agents.

Considerations for implementation. There are no known differences in treatment responses of second-line agents based on sex and ethnicity. The use of cyclophosphamide is associated with a risk for infertility. MPAAs, cyclophosphamide, and rituximab are contraindicated in pregnancy. CNIs are classified as US Food and Drug Administration (FDA) category C drugs in pregnancy. Patients being considered for cyclophosphamide or rituximab should be tested for HBV prior to administration of the drug.

Generally, FR patients who are in relapse are retreated with glucocorticoids until remission is achieved before a second-line agent is introduced. After introduction of the second drug, glucocorticoid is slowly tapered off, generally over 2–4 weeks as tolerated. After 3–6 months, if the patient remains dependent on glucocorticoids, then the new drug should be discontinued and other therapies considered.

In the event of a relapse during drug therapy, an increase or resumption of glucocorticoids as in the initial episode of MCD is suggested, followed by a taper over 2–4 weeks, depending on the response. The suggested medication regimens used to treat adult MCD are listed in Figure 45.

Rationale

In the opinion of the Work Group, this recommendation is strong due to the adverse events that occur with glucocorticoids in adult patients with FR/SD MCD, and the low-quality evidence suggesting that the 4 drug classes are effective in reducing relapse rates. The Work Group felt that the benefits of these drugs outweigh the potential adverse events related to the treatments. Most well-informed patients would choose to reduce/discontinue glucocorticoids in an effort to reduce/avoid side effects; however, the optimum second-line agent is not well defined. Factors that need to be addressed with full participation of the patient include the

relative efficacy, adverse effects, duration of therapy, and costs for each drug class before making a decision on the choice of medication.

Research recommendations

- Although glucocorticoid treatment is often effective, a substantial minority of patients do not respond and ultimately require second-line treatment. Studies that identify patients who are likely/unlikely to respond to glucocorticoids, including using biomarkers or a genomics approach, might lead to a more precise, rationale-based therapy.
- Studies to address the morbidity of longer-term glucocorticoids, the optimal length of glucocorticoid treatment (short vs. long duration) and the efficacy of glucocorticoid-sparing/glucocorticoid-free regimens in adult MCD
- RCTs of rituximab, CNI, cyclophosphamide, and MPAA in SD/FR MCD, including optimal dose and duration of therapy
- Exploration of the role of levamisole in adult MCD

Chapter 6: Focal segmental glomerulosclerosis (FSGS) in adults

This chapter makes treatment recommendations for adult patients who present with proteinuria and histologic lesions of focal segmental glomerulosclerosis (FSGS).

Definitions

The nomenclature surrounding the classification of FSGS has been inconsistent and confusing, in part because a histopathologic pattern of injury has also been considered as a distinct disease. Likewise, the traditional classification of FSGS does not reflect practicalities surrounding clinical presentation, and diagnostic and treatment approaches in patients with FSGS lesions on the kidney biopsy. Therefore, the Work Group proposed changes to the nomenclature of FSGS to improve clinical utility and provide clarity about the underlying pathophysiology. Figure 49 provides an overview of the proposed classification of FSGS, and Figure 52 lists the secondary causes of FSGS lesions on the kidney biopsy.

Primary FSGS

The terms "primary" and "idiopathic" FSGS have been used interchangeably, leading to a great deal of confusion around FSGS nomenclature. The Work Group suggests eliminating the use of "idiopathic" to describe any type of FSGS and endorses the following definitions for FSGS going forward.

We define primary FSGS as a clinical–pathologic syndrome in which light microscopy of the kidney biopsy demonstrates FSGS lesions, electron microscopy of the kidney biopsy demonstrates diffuse foot process effacement, and clinically the patients display NS. NS is defined as proteinuria >3.5 g/d plus hypoalbuminemia (<30 g/l), often, but not necessarily accompanied by dyslipidemia and edema. When considering a diagnosis of primary FSGS, there should be no other identifiable causes of FSGS. Although the clinical–pathologic syndrome of primary FSGS has been attributed to a circulating permeability factor, this factor has yet to be identified. Currently, the only form of FSGS that can be reasonably attributed to a circulating permeability factor is FSGS that recurs rapidly after a kidney transplant and can be successfully treated by plasmapheresis to remove the factor.

FSGS can also occur in the absence of a genetic or identifiable secondary cause, in the absence of NS, and without diffuse foot process effacement on electron microscopy of the kidney biopsy. This form of FSGS is distinct from primary FSGS based on its clinical and histologic manifestations. We propose calling this disease FSGS-UC (for undetermined cause). It is conceivable that patients with FSGS-UC have secondary or genetic forms of FSGS that have not yet been elucidated.

Secondary FSGS

When an FSGS lesion, with or without the presence of diffuse podocyte foot process effacement, is found in the setting of an established pathophysiologic process known to cause FSGS, we refer to this as secondary FSGS. The known/presumptive etiologies of secondary FSGS are listed in Figure 52.

Genetic forms of FSGS

FSGS lesions may develop in patients who have mutations in podocyte or glomerular basement membrane proteins. The search for a genetic cause is not routine in adults with FSGS

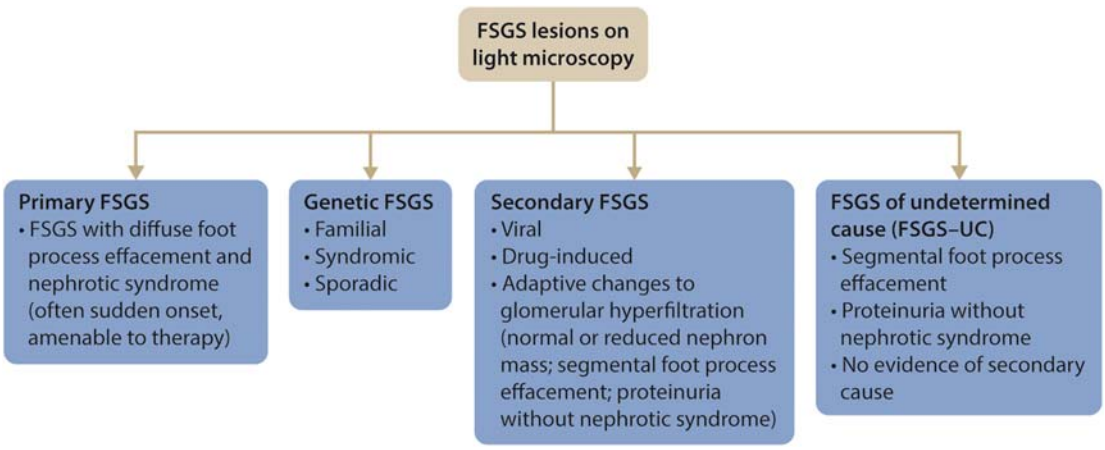

Figure 49 | Proposed classification of FSGS. FSGS, focal segmental glomerulosclerosis.

Complete remission
Reduction of proteinuria to <0.3 g/d or PCR <300 mg/g (or <30 mg/mmol), stable serum creatinine and serum albumin >3.5 g/dl (or 35 g/l)
Partial remission
Reduction of proteinuria to 0.3–3.5 g/d or PCR 300–3500 mg/g (or 30–350 mg/mmol) and a decrease >50% from baseline
Relapse
Proteinuria >3.5 g/d or PCR >3500 mg/g (or 350 mg/mmol) after complete remission has been achieved or an increase in proteinuria by >50% during partial remission
Steroid-resistant FSGS
Persistence of proteinuria >3.5 g/d or PCR >3500 mg/g (or 350 mg/mmol) with <50% reduction from baseline despite prednisone 1 mg/kg/d or 2 mg/kg every other day for at least 16 weeks
Steroid-dependent FSGS
Relapse occurring during or within 2 weeks of completing glucocorticoid therapy
CNI-resistant FSGS
Persistence of proteinuria >3.5 g/d or PCR >3500 mg/g (or 350 mg/mmol) with <50% reduction from baseline despite cyclosporine treatment at trough levels of 100–175 ng/ml (83–146 nmol/l) or tacrolimus treatment at trough levels of 5–10 ng/ml (6–12 nmol/l) for 4–6 months
CNI-dependent FSGS
Relapse occurring during or within 2 weeks of completing cyclosporine or tacrolimus therapy for >12 months

Figure 50 | Definition of remission, relapse, resistance, and dependence for FSGS. CNI, calcineurin inhibitors; FSGS, focal segmental glomerulosclerosis; PCR, protein–creatinine ratio.

(Section 6.1.2. Genetic testing), but should be considered on a case-by-case basis. For example, patients with genetic forms of FSGS are often young, have a family history of kidney disease, may have syndromic features, and are generally resistant to immunosuppressive treatment. If a genetic cause of FSGS is found, we have classified this as genetic FSGS (Figure 52).

Remission, relapse, resistance, and dependence

There is no consensus with regard to the definition of remission, resistance, or relapse in adults with FSGS. It is the judgment of the Work Group that harmonizing these definitions for FSGS and MCD in adults will simplify epidemiologic comparisons and unify treatment approaches for adults with idiopathic NS. Suggested definitions for remission, relapse, treatment resistance, and treatment dependence are listed in Figure 50.

6.1 Diagnosis

6.1.1 Differentiating between primary and secondary FSGS

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

A proposed histopathologic classification of FSGS had suggested a distinction between different variants of FSGS lesions on the kidney biopsy.[344] Although the occurrence of certain variants may suggest a secondary form of FSGS, the predictive value of histopathologic classification in differentiating between primary and secondary FSGS has been inconsistent.[345–347] Moreover, no histopathologic feature is pathognomonic of primary FSGS. Consequently, although diffuse foot process effacement on electron microscopy usually occurs in primary FSGS, variability in the percentage of the glomerular surface affected by foot process effacement in

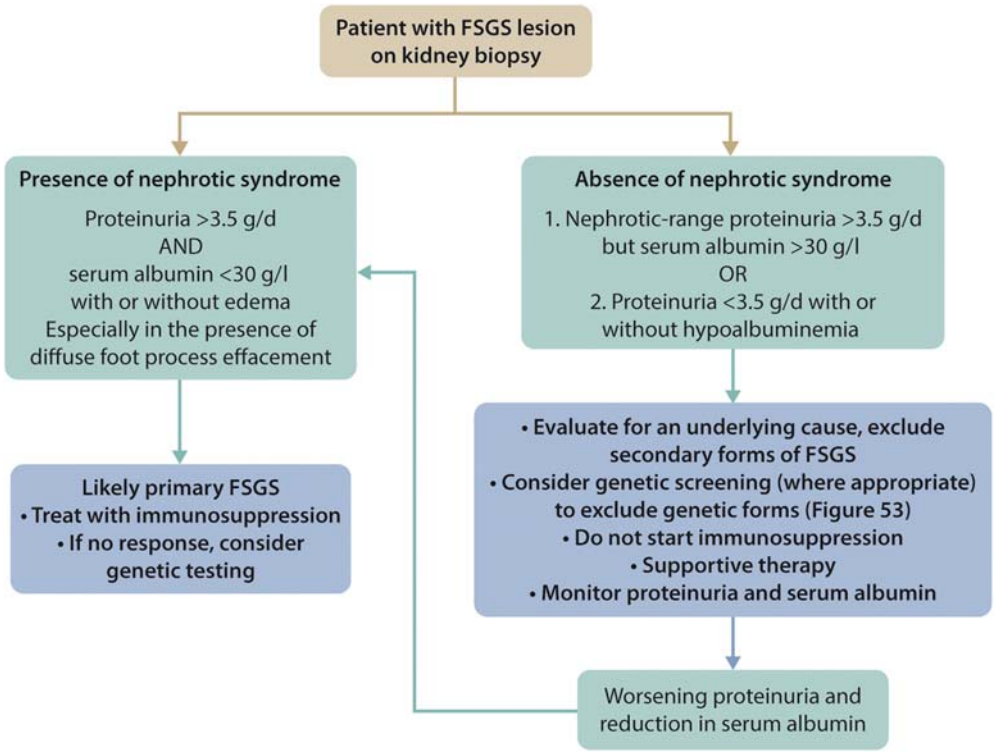

Figure 51 | Evaluation of a patient with FSGS lesion on the kidney biopsy and no evidence of other glomerular pathology. FSGS, focal segmental glomerulosclerosis.

Secondary to alterations of glomerular epithelial cells	
Viral infections	HIV (established) CMV (probably) Parvovirus B19, EBV, HCV (possibly) Hemophagocytic syndrome (possibly) SARS-COV-2 (with *APOL1* risk genotype)
Drug-induced	Direct-acting antiviral therapy mTOR inhibitors, CNIs Anthracyclines Heroin (adulterants) Lithium Interferon Anabolic steroids NSAIDs
Secondary to adaptive changes with glomerular hypertension	
Reduced nephron number	Reflux nephropathy Renal dysplasia Oligomeganephronia Sickle cell disease Age-related FSGS
Normal nephron number	Obesity-related glomerulopathy Primary glomerular diseases Systemic conditions, e.g., diabetic nephropathy, hypertensive nephrosclerosis

Figure 52 | Causes of secondary FSGS. *APOL1*, apolipoprotein L1; CMV, cytomegalovirus; CNI, calcineurin inhibitor; EBV, Epstein-Barr virus; FSGS, focal segmental glomerulosclerosis; HCV, hepatitis C virus; HIV, human immunodeficiency virus; mTOR, mammalian target of rapamycin; NSAID, nonsteroidal anti-inflammatory drug; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Genetic forms of FSGS	
Genetic mutations of podocyte and glomerular basement membrane proteins	• Familial • Sporadic • Syndromic

Considerations for genetic testing in adults with FSGS
• When there is a strong family history and/or clinical features suggestive of a syndromal disease • Aiding in diagnosis, especially if the clinical features are not representative of a particular disease phenotype • Limiting immunosuppression exposure, especially in situations where patients appear to be resistant to treatment • Determining the risk of recurrent disease in kidney transplantation • Allowing for risk assessment in living-related kidney donor candidate, or where there is a high suspicion for *APOL1* risk variants • Aiding in prenatal diagnosis

Figure 53 | Utility of genetic testing in patients with FSGS. *APOL1*, apolipoprotein-L1; FSGS, focal segmental glomerulosclerosis.

secondary forms of FSGS suggests this finding is not completely specific for primary FSGS.[348,349] Similarly, diffuse foot process effacement itself may not be able to differentiate primary FSGS from genetic forms of FSGS. Conversely, the absence of diffuse foot process effacement does not exclude primary FSGS completely, and in one series, the amount of foot process effacement could be as low as 30% in some patients with primary FSGS.[350]

The development of the NS occurs in about 54%–100% of patients with primary FSGS.[347,351–353] The variable incidence of the NS had been attributed to the inclusion of unrecognized secondary FSGS in some studies. Primary FSGS is typically characterized by an abrupt onset of marked proteinuria, and in 1 series, when conditions associated with secondary forms of FSGS were excluded, NS was found in 100% of the study population with primary FSGS.[352] The diagnosis of primary FSGS should, therefore, be revisited in patients who do not have the NS at the time of kidney biopsy, and a search for an underlying condition should be undertaken.

6.1.2 Genetic testing

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

Recent studies have reported on the findings of pathogenic or likely pathogenic genetic variants in patients with familial FSGS, or in patients who are refractory to glucocorticoid therapy.[354] However, the exact role of genetic testing in the management of adult FSGS is uncertain, as this is not readily accessible in many regions, nor is the expertise in interpreting the results of genetic tests widely available. Although genetic testing may yield greater positive results in patients with congenital or infantile-onset disease, where a genetic cause was detected in 100% and 57% of patients, respectively, in 1 study,[355] the genetic likelihood is significantly reduced in patients whose disease starts beyond early childhood.

There are, therefore, no good data to support routine use of genetic testing in all adults with FSGS. Selected patients, such as those with familial kidney disease and/or syndromal features, may be referred to specialized centers for further evaluation when genetic testing could be considered to have potential benefits (Figure 53).[356]

Although the majority of adults with primary FSGS respond to immunosuppression, treatment resistance is a common feature in genetic forms of FSGS, and in particular, resistance to glucocorticoid therapy is a consistent finding in all forms of genetic FSGS.[354] Therefore, a higher genetic diagnostic yield may be obtained when considering genetic testing in individuals who exhibit poor response to immunosuppression agents. Moreover, the discovery of genetic variants in this group should prompt a discussion on discontinuing further immunosuppression treatment.

In addition, primary FSGS had been known to recur commonly after kidney transplantation with poorer allograft outcomes, with 32% having recurrent disease at a median time of 1.5 months after transplantation in 1 particular study.[357] In contrast, it is widely accepted that the recurrence rate of FSGS after transplantation is significantly low in genetic forms of the disease, with some studies reporting no individuals exhibiting recurrent disease after a kidney transplant.[358,359] Therefore, genetic testing in adults with FSGS for whom a kidney transplant is planned may provide prognostic information on transplant outcomes.

Moreover, genetic testing in living related donors is important to advise on the risk of subsequent development of kidney disease after transplantation, especially in individuals who are found to have the genetic risk variants but are asymptomatic at the time of evaluation. In individuals of recent African ancestry, the presence of *APOL1* genetic risk variants have been found to be associated with an increased odds of developing FSGS. Furthermore, it has also been shown that *APOL1* high-risk donor kidneys fail at higher rates than non-risk kidneys, and the recipient *APOL1* genotype has not been demonstrated to

have correlation with allograft survival.[360] Therefore, in donors at high risk for *APOL1* risk variants, genetic testing for *APOL1* mutations may provide information for both the disease risk in the donor and allograft outcomes in the recipient.

6.2 Treatment

6.2.1 Management of FSGS-UC and secondary FSGS

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

Adult patients with FSGS should receive the necessary supportive treatment as advised for all patients with persistent proteinuria (Chapter 1), including the use of RAS blockade, optimal BP control, and dietary salt restriction.

Patients who have secondary FSGS due to an underlying disease process should be managed as required for the primary medical condition. There is no evidence or a *priori* rationale justifying the use of glucocorticoids or other immunosuppressive drugs in this population, and the potential for harm of such treatment is clear.[361]

A management conundrum occurs when a patient presents with nephrotic-range proteinuria without NS and FSGS-UC.[354] The literature is limited in guiding management for this group of patients. The Work Group suggests that these patients receive supportive treatment as outlined above, be monitored for the development of NS, and be considered for a repeat kidney biopsy if there is a change in their clinical status.

The kidney prognosis of FSGS correlates with the magnitude and persistence of proteinuria. Studies have demonstrated that patients with non-nephrotic-range proteinuria had 10-year kidney survival rates >90% without immunosuppressive treatment.[314,362–365] In addition, the reduction of nephrotic-range proteinuria to non-nephrotic levels in patients with primary FSGS was associated with significant improvement in kidney survival (80% vs. 40%), compared to those with persistent NS.[366] These data suggest that the kidney outcomes of patients without NS remain favorable, and do not warrant subjecting the patients to the risks of glucocorticoid treatment.

6.2.2 Initial treatment of primary FSGS

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

This recommendation places a relatively higher value on very low-quality evidence that the use of glucocorticoids may achieve remission of proteinuria in adult patients with primary FSGS, the increased risk of progressive CKD without remission of proteinuria, as well as the high morbidity and mortality associated with kidney failure, and a relatively lower value on the adverse effects of high-dose glucocorticoids.

Key information

Balance of benefits and harms. The true likelihood of spontaneous remission in patients with primary FSGS and the NS is not known, as many such patients are treated with immunosuppression. However, it is generally accepted that spontaneous remission rates are >20%.[367,368] Indeed, patients with the NS have worse kidney prognosis than non-nephrotic patients, with 10-year kidney survival rates of 57% compared to 92% in those with lower degrees of proteinuria.[364] Consequently, many observational studies have demonstrated that remission of proteinuria induced by therapy is associated with favorable kidney survival rates,[364,366,367,369] whereas patients with persistent nephrotic-range proteinuria are more likely to experience loss of kidney function.[364]

Many studies in adults with primary FSGS suggest that glucocorticoid treatment increases the likelihood of achieving remission[366,370–372]; data from children are similar. Therefore, despite the inherent risks of glucocorticoid use, the Work Group judged that the apparent effectiveness of this treatment and the risk of kidney failure that is associated without achieving remission of proteinuria both justify recommending prednisone as the first-line treatment in adult patients with primary FSGS.

Quality of evidence. A search of the Cochrane Kidney and Transplant Registry of studies identified no RCTs that evaluated the use of high-dose glucocorticoids in adult patients with primary FSGS and NS. The quality of the evidence is very low, as the evidence that forms the basis of this recommendation is extracted from observational studies in the adult population. The benefits of glucocorticoid use are also extrapolated from pediatric studies in which RCTs have shown the effectiveness of glucocorticoid treatment in children with NS, some of whom had primary FSGS.

Values and preferences. The potential benefits of glucocorticoid treatment (including the reduction of morbidity from NS as well as a lower risk of progressive kidney function loss) were judged to be critically important to patients. The Work Group also judged that the risk of harms from prolonged high-dose glucocorticoid treatment, including metabolic complications, increased risks for infections, and effects on bone health would be important to patients.

The Work Group judged that most clinically suitable and well-informed patients would choose to receive glucocorticoids as the initial treatment for primary FSGS with the NS, compared to another treatment or to no treatment. Some patients who are at high risk of adverse events from glucocorticoids, or who place a high value on avoiding such adverse events may choose to forgo a trial of glucocorticoid as initial therapy in favor of alternative immunosuppression. In the judgment of the Work Group, few if any well-informed patients would choose to not be treated with immunosuppression for primary FSGS.

Resource use and costs. Glucocorticoids are among the least expensive medications available and do not require therapeutic drug monitoring. In resource-limited settings, this class of drug is affordable and may be the only drug available.

Considerations for implementation. The adverse effects of glucocorticoids may be higher in certain subgroups of patients, including those who are obese and those who have diabetes, osteoporosis, or psychiatric disorders. In such

patients, the adverse effects of prolonged high-dose glucocorticoid therapy should be discussed with the patients, and alternative immunosuppressive therapy with CNI may be explored (Practice Point 6.2.2.4).

Rationale

This recommendation places a high value on very low–quality evidence on the use of glucocorticoids to achieve remission of proteinuria in adult patients with primary FSGS who have NS, with consequent reduction in the morbidity derived from NS and in the risk for kidney failure. The recommendation places a lower value on the adverse effects associated with glucocorticoid use.

The recommendation is strong because, given the significant morbidity from the NS and the increased risks of progressive loss of kidney function with persistent proteinuria, the Work Group judged that the majority of patients would choose glucocorticoids as the initial treatment for primary FSGS. Moreover, due to its low cost, widespread availability, and physician familiarity with glucocorticoids, most physicians would be willing to consider this treatment as the initial therapy in most patients without clinical contraindication to glucocorticoids.

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

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 54 | Initial treatment of primary FSGS. *The CNI, while often used twice daily, may be dosed once a day, depending on individual formulations. Blood levels of CNIs 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. CNI, calcineurin inhibitor; FSGS, focal segmental glomerulosclerosis.

Figure 54 suggests the initial starting dose of glucocorticoids in treating adult patients with primary FSGS. The high starting dose of 1 mg/kg of predniso(lo)ne is extrapolated mainly from RCTs in children and has been used in many observational studies in adults. Because of the potential toxicities of daily high-dose glucocorticoid therapy, 1 observational study evaluated the use of alternate-day glucocorticoid dosing in elderly patients with FSGS (multiple types) and found complete remission rates of about 44% after 3–5 months of treatment,[373] comparable to reported rates in studies using predniso(lo)ne doses at 1 mg/kg/d.[366,371]

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

In the treatment of primary FSGS, glucocorticoids should be used until remission occurs and tapered thereafter. To avoid unduly increasing the risk of relapse after rapid remission, a minimum recommended duration of treatment is required. Conversely, since longer treatment may not further increase the likelihood of remission (or reduce the risk of relapse), a maximum recommended duration of treatment is required to reduce the risk of glucocorticoid exposure without additional benefit.

Earlier studies suggested that primary FSGS is a steroid-resistant disease with dismal outcomes.[314,362,363,374–376] However, subsequent observational studies demonstrated that response to glucocorticoid treatment could be improved with a higher initial dose and longer duration of treatment.[314,364,367,369,377] The optimal duration of high-dose glucocorticoid treatment in adult primary FSGS has not been established, nor has the duration of treatment before considering a diagnosis of steroid-resistant FSGS. Yet, patients are not likely to tolerate indefinite treatment with high-dose prednisone.

Observational studies in adult patients with MCD have demonstrated that extension of high-dose glucocorticoid therapy toward 16 weeks resulted in an increase in remission rate of 10%–25%.[307,315,330,378,379] Primary FSGS is less responsive than MCD; thus, additional therapeutic benefit beyond 16 weeks is unlikely. Defining a maximum duration of high-dose prednisone treatment as 16 weeks avoids the premature labeling of treatment failure and unnecessary treatment with second-line immunosuppressive agents, which are generally more expensive.

Based on available evidence, it is uncertain whether the side effects of 16 weeks of glucocorticoid treatment are significantly worse than those with shorter courses and whether side effects outweigh benefits in primary FSGS, as studies have been inconsistent in the reporting of adverse events.

Therefore, in the judgment of the Work Group, the maximum duration of high-dose glucocorticoid treatment should be 16 weeks because of diminishing benefits and increasing toxicity associated with longer courses of treatment. Of note, patients who are likely to respond to therapy generally demonstrate some degree of proteinuria reduction before 16 weeks, often within 4–8 weeks of initiating treatment.[364,367,377] If proteinuria remains persistent and shows no signs of reduction, especially if the patient experiences glucocorticoid side effects, high-dose prednisone therapy should be stopped before 16 weeks, and alternative treatment should be considered.

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

The optimal duration of glucocorticoid therapy is not known. Treatment schedules have ranged from 4 to 24 months in various studies, with reported complete and partial remission rates of 28%–74% and 0%–50%, respectively.[314,364,367,369] One study found that patients receiving glucocorticoid therapy for >16 weeks had a much higher remission rate of 61% compared to 15% in those with a treatment duration of <16 weeks.[377] Similarly, another study demonstrated that patients who had responded to glucocorticoid therapy had received a significantly longer median treatment duration of 5.7 months.[364] Conversely, another study found that if a patient had not responded to glucocorticoids by 6 months, treatment beyond this duration was not beneficial.[367] Taking into consideration the significant toxicities associated with prolonged glucocorticoid treatment, a total treatment duration of 6 months is proposed. Figure 54 also outlines a suggested approach to tapering glucocorticoids in adults with primary FSGS.

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

Adults may not tolerate prolonged high-dose glucocorticoids well, and with the protracted natural history of primary FSGS, the side effects of glucocorticoids may be unacceptable to some patients.[380] Additionally, patients who are obese, have uncontrolled diabetes, psychiatric conditions, or severe osteoporosis may be deemed to have a relative contraindication to glucocorticoids. Ideally, such patients would be considered for an alternative treatment to glucocorticoids. There are, however, no RCTs that examined alternative immunosuppressive agents as first-line therapy in the treatment of adults with primary FSGS.

Nonetheless, observational studies suggest that CNIs can be used to reduce the overall exposure or even obviate the need for glucocorticoid therapy. A retrospective review of 51 adult patients with primary FSGS used lower doses of prednisolone in combination with either cyclosporine or azathioprine in patients with obesity, borderline diabetes, or bone disease.[270] The combination of low-dose prednisolone and azathioprine or cyclosporine resulted in higher combined complete and partial remission rates of 80% and 85.7%, respectively, compared to high-dose prednisolone alone (62.5%). In addition, a small observational study

demonstrated that tacrolimus monotherapy achieved partial remission in all 6 patients after 6.5 ± 5.9 months, avoiding the use of glucocorticoids completely.[381] Furthermore, the favorable outcomes of using CNIs in the management of steroid-resistant primary FSGS lend additional support to the use of CNIs as an initial treatment option.

Figure 54 outlines a suggested treatment schedule for using CNIs as an alternative first-line therapy for adults with primary FSGS. Other observational studies looking at CNIs as first-line therapy for primary FSGS considered initial doses of cyclosporine at 3 mg/kg/d, with no therapeutic drug monitoring for a mean duration of 25 months,[370] or tacrolimus at 4 mg/d with a target trough level of 4–7 ng/ml (5–9 nmol/l) for a mean duration of 13.6 ± 11.8 months.[381]

6.3 Special situations

6.3.1 Steroid-resistant primary FSGS.

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

This recommendation places a high value on achieving proteinuria remission in reducing the risk of kidney failure and on the excessive risks associated with continued glucocorticoid use in patients unresponsive to prednisone therapy. This recommendation places a lower value on the cost and risks of nephrotoxicity with cyclosporine or tacrolimus treatment, as well as the need for monitoring drug levels in patients treated with these agents.

Key information

Balance of benefits and harms. Many observational studies have shown that reduction of proteinuria and the achievement of remission are associated with improved kidney outcomes,[314,351,366,372] and resistance to glucocorticoids is strongly associated with the risk of kidney failure in adult patients with primary FSGS.[314,372] In patients who do not achieve remission, 5- and 10-year kidney survival was reported to be 60%–90% and 25%–56%, respectively.[314,362,363,382] Notwithstanding the unnecessary side effects associated with continuing high-dose glucocorticoid therapy in patients who are not likely to respond, the poor kidney prognosis with unremitting proteinuria in patients with steroid resistance warrants alternative immunosuppression strategies to attempt to achieve remission. The CNIs, cyclosporine and tacrolimus, are 2 such alternatives.

Cyclosporine has been evaluated in 2 small RCTs for its effectiveness in adult patients with steroid-resistant presumptive primary FSGS. In 1 study, cyclosporine was used as monotherapy for 6 months and compared to supportive therapy in both adult and pediatric patients with SRNS, including MCD and primary FSGS.[284] The second RCT included only adult patients with SR primary FSGS and compared a 26-week treatment with cyclosporine to placebo.[281] All patients received low-dose prednisone. Remission was achieved in 60% and 70% of the study population receiving cyclosporine in the respective 2 studies.

There are no RCTs evaluating tacrolimus in similar settings. However, uncontrolled studies suggest that tacrolimus may be an alternative to cyclosporine.[381,383,384] One uncontrolled study looked at the use of tacrolimus in addition to low-dose glucocorticoids for 6 months in adult patients with primary FSGS and steroid resistance, and either cyclosporine resistance or cyclosporine dependence.[384] Complete and partial remission occurred in 40% and 8%, respectively, with a mean time to remission of about 3 months. Acute reversible decline in GFR occurred in about 40% of patients. Another prospective study evaluated the use of tacrolimus in adult patients with steroid-resistant primary FSGS for 48 weeks and found improved overall remission rates (complete remission: 38.6%; partial remission: 13.6%) with a mean time to remission of 15.2 weeks and acute reversible nephrotoxicity of 15.9%.[383] In the judgment of the Work Group, these limited observational data, as well as the similar mechanism of action for tacrolimus and cyclosporine, suggest that either tacrolimus or cyclosporine may be used in the treatment of steroid-resistant primary FSGS.

Since remissions after the use of cyclosporine may occur slowly and have been reported to take as long as 4–6 months in certain observational studies, we suggest that a minimum treatment duration of 6 months should be attempted before labeling a patient as cyclosporine-resistant. It is the judgment of the Work Group that a minimum duration of 6 months is also appropriate for tacrolimus, as tacrolimus is generally considered to be a more potent immunosuppressive with efficacy in patients with cyclosporine-resistant or cyclosporine-dependent disease, but going beyond 6 months is not likely to improve the rate of treatment response.

Quality of evidence. Systematic reviews were performed by the ERT comparing cyclosporine (with or without glucocorticoids) against supportive therapy or prednisone treatment in adult patients with steroid-resistant primary FSGS (Supplementary Table S28[284,385]; Supplementary Table S29[281,385]; Supplementary Table S30[385,386]).

In a small RCT (n = 22), cyclosporine treatment alone was compared with supportive therapy, and cyclosporine was reported to be superior in terms of effect estimates for the development of ESKD, >50% loss of GFR, doubling of SCr, and infection. However, this is very low–quality evidence because of study limitations and very wide CIs indicating appreciable benefit and harm. There were too few patients who managed to attain complete remission; therefore, conclusions on whether cyclosporine treatment made a difference for complete remission could not be made from this RCT. In addition, the study population was heterogeneous and included both adult and pediatric patients with MCD and FSGS (Supplementary Table S28[284,385]).

When cyclosporine with low-dose prednisone was compared to prednisone treatment alone, treatment with

cyclosporine was associated with greater benefits in achieving partial remission and a lower risk of kidney failure. The quality of evidence from the available RCTs is low because of study limitations and because there was only 1 small RCT (n = 49) for this comparison.[281] The magnitude of the effect between the 2 groups for partial remission was large (342 per 1000 patients with cyclosporine vs. 43 per 1000 patients with prednisone alone). Similar to the previous systematic review, there were too few patients who managed to attain complete remission; therefore, conclusions on whether cyclosporine treatment made a difference for complete remission could not be made from this RCT (Supplementary Table S29[281,385]). Similarly, in 1 small RCT (n = 25), there were too few patients who achieved complete remission to determine if cyclosporine plus prednisolone made a difference compared to treatment with methylprednisolone alone (Supplementary Table S30[385,386]).

Values and preferences. The benefits of achieving disease remission and proteinuria reduction in mitigating the morbidity associated with the NS and risk of progressive loss of kidney function were judged to be critically important to patients. The Work Group also judged that the harmful side effects of prolonged glucocorticoid treatment would be critically important to patients, even if such treatment led to clinical benefits compared to no treatment, which is uncertain. The Work Group also judged that patients would consider the risk of nephrotoxicity with cyclosporine or tacrolimus to be less important than the side effects associated with prolonged glucocorticoid therapy, or the higher risk of kidney failure without CNI treatment, especially if the risk of CNI toxicity was reduced by careful monitoring of drug levels and use of the shortest possible course of CNI treatment.

Resource use and costs. Cyclosporine and tacrolimus treatment entail a much higher financial burden than glucocorticoid treatment or no treatment, as both drugs are significantly more expensive than glucocorticoids, and there are added costs for monitoring drug levels. In addition, cyclosporine and tacrolimus, including generic formulations, may be unavailable and may not be reimbursed by healthcare financing in low-resource settings. Unfortunately, in such situations, treatment options are limited, and physicians will need to weigh the risks of continuing with glucocorticoid treatment against the impact of progression to kidney failure with treatment discontinuation.

Considerations for implementation. There is no head-to-head comparison of cyclosporine and tacrolimus in the treatment of adult patients with steroid-resistant primary FSGS. However, one uncontrolled study suggested that there is a benefit with tacrolimus treatment in patients who do not respond optimally to cyclosporine.[384] Preference for either of the CNIs is discussed in the following section.

Rationale

This recommendation places a high value on achieving proteinuria remission in reducing the risk of kidney failure and on the excessive risks associated with continued glucocorticoid use in patients unresponsive to prednisone therapy, and a lower value on the cost and risks of nephrotoxicity with cyclosporine or tacrolimus treatment.

The recommendation is strong because, despite the absence of proven benefits and the clear potential for harm, the Work Group judged that all or nearly all well-informed patients with primary FSGS would choose to stop glucocorticoid treatment if they are steroid-resistant and would switch to either cyclosporine or tacrolimus.

6.3.2 Dosing schedule for cyclosporine and tacrolimus

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

Figure 55 outlines a proposed treatment schedule for adult patients with steroid-resistant primary FSGS. The initial starting dose for cyclosporine ranged from 3.5 to 6 mg/kg/d[281,387] in various studies, with most starting at 5 mg/kg/d.[60,284,338,388,389] Doses of cyclosporine >5.5 mg/kg/d had been found to be associated with increased risks of nephrotoxicity.[60] There was even greater variability in trough drug-level targets that stretched from 50 to 600 ng/ml (42–500 nmol/l).[281,284,387–389] Considering the cost of cyclosporine, dose-related nephrotoxicity, and the unlikely situation that urgent therapeutic levels are needed, it seems reasonable to start treatment at a lower dose and increase the dose gradually toward target trough levels. Apart from 1 study that targeted cyclosporine trough levels of 250–600 ng/ml (208–500 nmol/l),[284] most demonstrated the ability to induce remission with trough levels of 100–225 ng/ml (83–187 nmol/l), although it was noted that higher trough levels were associated with a greater risk of decline in GFR and nephrotoxicity. It is therefore the judgment of the Work Group that a target trough level of 100–175 ng/ml (83–146 nmol/l) be used to balance the benefits of proteinuria reduction and the risk of GFR decline, and a trough level of 225 ng/ml (187 nmol/l) not be exceeded over a protracted period.

One uncontrolled study considered tacrolimus at an initial dose of 0.15 mg/kg/d, with a target trough level of 5–10 ng/ml (6–12 nmol/l).[384] However, at this dose, the mean trough level exceeded the therapeutic target in the first 4 weeks (10.3–11.8 ng/ml, 12.7–14.6 nmol/l) with levels at the 25th percentile at the higher end of the therapeutic targets (9.2–9.8 ng/ml, 11.4–12.2 nmol/l), suggesting that a lower dose might be more prudent. On the other hand, another prospective study initiated tacrolimus at 0.1 mg/kg/d and managed to achieve mean tacrolimus trough levels of about 7 ng/ml (8.7 nmol/l).[383]

The decision between cyclosporine and tacrolimus is dependent on a variety of factors and takes into consideration issues with drug availability, drug costs, capability of drug level monitoring, clinical factors, physician preference, and familiarity. Drug costs may be less of an issue now that generic forms of both drugs are available. From the transplant literature, it has been suggested that tacrolimus has a more potent immunosuppressive effect than cyclosporine, although

Treatment	Dose and duration
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 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 • Consider discontinuing cyclosporine or tacrolimus if the eGFR continues to decline to <30 ml/min per 1.73 m^2
Inability to tolerate or contraindications to calcineurin inhibitors	• Lack of quality evidence for any specific alternative agents • Mycophenolate mofetil and high-dose dexamethasone, rituximab, and ACTH have been considered • Treatment will need to be personalized and is dependent on availability of drugs and resources, as well as the benefits of further treatment and risks of adverse effects of immunosuppression • Patients should be referred to specialized centers with the appropriate expertise, and should be evaluated on the appropriate use of alternative treatment agents or to discontinue further immunosuppression

Figure 55 | Treatment of glucocorticoid-resistant primary FSGS. *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. ACTH, adrenocorticotropic hormone; CNI, calcineurin inhibitors; eGFR, estimated glomerular filtration rate.

this has not been validated in adult FSGS studies. Cosmetic side effects tend to be less with tacrolimus therapy, and this drug may be more acceptable in young female patients, as patients receiving cyclosporine have a higher risk of hirsutism and gum hypertrophy, with reported incidence of 70% and 30%, respectively, in children treated for >1 year.[390]

6.3.3 Duration of CNI treatment

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

Although CNIs are effective for inducing remission in patients with steroid resistance, relapses are very frequent after their withdrawal. In 1 of the RCTs evaluating the effect of cyclosporine in steroid-resistant disease, relapses occurred in 40% of patients by 1 year, and in 60% by 78 weeks following cyclosporine withdrawal.[281] This outcome was replicated in another RCT, with 69% of patients experiencing a relapse within 12 months of cyclosporine withdrawal.[284] Observational studies of cyclosporine treatment also reported relapse rates ranging of 60%–80%. Similarly, a high incidence of relapse was seen with tacrolimus, with about 76% of patients developing a relapse after drug discontinuation.[384]

With each relapse, the risk of progressive CKD increases, and patients given another course of immunosuppression will have greater exposure to drug side effects and toxicities. It is imperative that all efforts be made to minimize the risk of relapses.

The optimal duration of CNI treatment, especially for the prevention of relapse, has not been established in adult patients with steroid-resistant primary FSGS. An RCT compared cyclosporine and cyclophosphamide in steroid-dependent and frequently relapsing idiopathic NS in both children and adults, with the primary outcome being relapse-free survival. Cyclosporine was prescribed for 9 months and tapered by 25% every month until complete discontinuation by 12 months. In the adult population, the relapse rate at 24 months was similar between those who received cyclosporine (50%) and those who received cyclophosphamide (60%).[333] In addition, prolonged CNI treatment in children with SRNS is a common practice, although the impact of such a

strategy on relapse prevention, risk of nephrotoxicity, or long-term kidney function has not been well-established. These limited data advocate a much more protracted period of CNI treatment to minimize the risk of relapses, particularly in a situation in which the evidence for alternative immunosuppressive therapies is scanty and the risk of relapse is significant.

Figure 55 outlines the treatment schedule for steroid-resistant primary FSGS, suggesting that therapeutic levels of CNIs should be maintained for at least 12 months for patients who respond to treatment. The CNI may be tapered thereafter, with clinical status, drug tolerability, physician comfort, and financial factors informing the tempo and magnitude of dose reduction. Patients in complete remission and with evidence of drug toxicity may need a more rapid reduction in CNI dose.

6.3.4 Patients resistant to or intolerant of CNIs

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

There is a dearth of evidence to inform the treatment of adult patients with steroid-resistant primary FSGS who are intolerant or resistant to CNIs. It is the opinion of the Work Group that these patients require highly specialized care and should be referred to centers with appropriate expertise. Several immunosuppressive drugs have been tried in adult idiopathic FSGS, many of which are listed and referenced in Figure 55. However, most of the studies are poorly designed, observational in nature, underpowered for any valid conclusions, and heterogeneous in their outcomes. Furthermore, additional treatment in this group of patients may be futile, and rather than conferring benefit, it may increase the risks of adverse events from immunosuppressive therapy. Therefore, patients should be evaluated in these specialized centers of the need for further immunosuppression.

MMF and high-dose dexamethasone were given a 2C recommendation in the KDIGO 2012 GN guideline as an alternative for patients who do not tolerate cyclosporine. This recommendation was based on an RCT comparing cyclosporine to the combination of MMF and high-dose dexamethasone in children and young adults with steroid-resistant FSGS that showed no statistically significant difference in remission rates between the 2 arms.[286] However, this trial did not meet the initial recruitment target of 500 patients and was severely underpowered, with only 138 patients eventually randomized to either treatment. Consequently, inferiority of the MMF regimen to cyclosporine cannot be excluded. Moreover, there were significant concerns with the design and inclusion criteria that could have affected the validity of the study results.[391] In considering these issues, the KDIGO 2021 Work Group agreed that it would be more appropriate to remove the use of MMF and high-dose dexamethasone as a clinical recommendation and consider this as an alternative treatment possibility when other therapeutic options have failed.

6.3.5 Management of relapse

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

There is very low–quality evidence to guide the treatment of relapses in primary FSGS. If the relapses occur in patients whose disease was previously sensitive to glucocorticoid therapy, it is suggested that relapses should be approached in the same way as relapsing MCD in adults (Figure 48).

Research recommendations

- Identify and validate biomarkers of steroid-sensitive primary FSGS; this includes identification of the putative permeability factor that has been elusive for decades.
- RCTs are needed:
  - To evaluate the efficacy and adverse effects of glucocorticoid treatment, including daily versus alternate-day glucocorticoids, in adult patients with primary FSGS
  - To determine the optimal duration of glucocorticoid treatment in adult patients with primary FSGS and to compare remission, relapse, and adverse event rates associated with short or prolonged treatment using initial high-dose glucocorticoid therapy
  - To evaluate the effectiveness of CNIs, with or without concomitant glucocorticoids, in the treatment of adult patients with steroid-resistant primary FSGS
  - To examine the optimal duration of CNI treatment in adult patients with steroid-resistant primary FSGS
  - To examine the role of plasmapheresis and LDL apheresis in the treatment of primary FSGS and in the prevention of recurrent FSGS after kidney transplantation

Chapter 7: Infection-related glomerulonephritis

This chapter provides practice guidelines for the diagnosis, prognosis, and treatment of infection-related GN, which may occur in association with bacterial, viral, fungal, protozoal, and helminthic infections. The cost implications for global application of this guideline are addressed in Chapter 1.

7.1 Bacterial infection–related GN

Bacterial infection–related GN can occur after a bacterial infection (postinfectious glomerulonephritis after a latent period, often several weeks after an infection) or in the presence of an ongoing, acute or chronic bacterial infection. Bacterial infection–related GN encompasses several entities[392]:

1. Poststreptococcal GN, which in modern times is a bit of a misnomer as streptococcal infections account for only 28%–47% of this postinfectious acute GN. *Staphylococcus aureus* or *Staphylococcus epidermidis* is isolated in 12%–24% of cases, and gram negative bacteria in up to 22% of cases.[393]
2. Shunt nephritis is an immune complex–mediated GN that rarely develops as a complication of chronic infection on ventriculoatrial, ventriculojugular, or less commonly,

	Postinfectious GN	Shunt nephritis	Endocarditis-related GN	IgA-dominant infection-related GN
Risk and risk features	Children, elderly, immuno-compromised hosts, sub-sanitary 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; immuno-compromised 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 56 | 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.

ventriculoperitoneal shunts inserted for the treatment of hydrocephalus.[394] The infecting organisms are usually *Staphylococcus epidermidis*, *Staphylococcus albus*, or *Staphylococcus aureus*. ANCA titers may be positive.[394]

3. GN related to infective endocarditis, particularly related to *S. aureus*, which has replaced *S. viridans* as the leading cause of infective endocarditis. The incidence of GN associated with *Staphylococcus aureus* endocarditis ranges from 22% to 78%, the highest risk being among intravenous drug users. Patients demonstrate low serum complement C3 (53% of 32 tested) or C4 (only 19% of 32 tested). ANCA and antinuclear antibodies can be present,[395] and pulmonary hemorrhage mimicking anti-GBM disease (due to cryoglobulinemia) has been observed.[396] In some patients, infection-related GN can occur in the absence of demonstrable endocarditis.
4. IgA-dominant infection-related GN (IgADIRGN) is an immune complex–mediated GN described concomitant with methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-sensitive *S. aureus*, *Escherichia coli*, *S. epidermidis*, and *Klebsiella* bacteremia in patients with underlying comorbidities, especially diabetes (Figure 56).[397–399] Bacteremia is often, but not always, found, although presentation may be delayed.[398] IgADIRGN has been reported in patients with skin and joint infections, pneumonia, osteomyelitis, and endocarditis. Hypocomplementemia can be seen in 30%–50% of cases.[399]

7.1.1 Diagnosis

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

The kidney histology shows acute, often exudative, endocapillary GN with mesangial and capillary wall granular immune deposition. In endocarditis-related GN, the most frequent morphologic glomerular change is crescentic GN in >50% of the patients, followed by diffuse endocapillary proliferative GN and mesangial proliferative GN. The intensity of C3 deposition commonly exceeds that of IgG, and C3 predominance without C4 suggests alternate rather than direct complement pathway activation. Subendothelial and subepithelial electron dense deposits, including "humps," can be found on electron microscopy. In shunt nephritis, the histologic findings are typically a mesangial proliferative pattern of injury with granular deposits of IgG, IgM, and C3, and electron-dense mesangial and subendothelial deposits.

In IgADIRGN, the kidney biopsy shows endocapillary proliferation with prominent neutrophil infiltration in 40%–80%, and a minority may have isolated mesangial proliferative or even crescentic GN. On immunofluorescence microscopy, there is mesangial staining in a codominant pattern with IgA and C3, often with κ light chain exceeding λ.[397] Electron microscopy demonstrates electron-dense deposits in the mesangium and capillary walls, the latter often with subepithelial "humps" and less frequently a subendothelial distribution.[400] Differentiation from an exacerbation of classical IgAN can be accomplished taking into account both the characteristic clinical and morphologic features described above, but at times it can be difficult (Chapter 2).

7.1.2 Prognosis and treatment

Practice Point 7.1.2.1: Prognosis and suggested therapy of bacterial infection-related GN are summarized in Figure 57[401–403].

	Postinfectious GN	Shunt nephritis	Endocarditis-related GN	IgA-dominant infection-related GN
Prognosis	Short-term prognosis in children is excellent. In endemic regions, persistent albuminuria may occur and some adults develop low eGFR. In the elderly, kidney prognosis is poor for those who develop persistent albuminuria; mortality may be up to 20%	Outcome is good with early diagnosis and treatment of infection. Most patients recover some kidney function but are left with residual chronic kidney disease	Immediate prognosis is good with prompt infection eradication. Some may require valve replacement	Dialysis is frequently required in the acute setting. Recovery is guarded, with <20% returning to pre-morbid levels of kidney function
Treatment	• No randomized controlled trials guide the treatment in any of these conditions • Antibiotics for underlying infection (although this will not alter GN course in postinfectious GN) per local guidelines. Antibiotics can be given in poststreptococcal GN if streptococci are cultured from any site. This is primarily done to prevent the spread of infection within community sites • Treat edema, hypertension, etc. as well as persistent proteinuria and/or progressive GFR decline as per Chapter 1			
	Value of high dose glucocorticoids remains unproven [1]	Most shunts have been replaced with a shunt with a lesser likelihood of infection. Rarely ventriculocisternostomy has been performed after shunt removal	Utility of glucocorticoids and immunosuppression unproven and carries serious potential risks, even in cases with crescentic GN [2]	For severe kidney functional impairment, weigh risks and benefits of immunosuppression. The risk of infection and glucocorticoid-induced complications in this often elderly population with comorbidities can be substantial. A role for immunosuppression remains unproven and these agents should generally not be used
Course	• Follow kidney function, serum C3 and C4, urinalysis, ACR, and proteinuria at appropriate intervals until complete remission or return to baseline			
	Persistently low C3 beyond 12 weeks may be an indication for kidney biopsy to particularly exclude C3GN.[3] Prevention of epidemic poststreptococcal GN may include socioeconomic interventions and mass antimicrobial use to improve living conditions and limit the spread of infection in populations where Group A streptococcus infection and scabies are highly prevalent	The natural history of the PR3-ANCA seen in some patients is unclear and requires follow-up	If the infection can be identified and promptly eradicated, the prognosis is favorable	The prognosis for recovery is poor, especially in diabetic subjects

Figure 57 | Prognosis and therapy of classic bacterial infection–related GN syndromes. [1]Kapadia *et al.*[401], [2]Okuyama *et al.*[402], [3]Khalighi *et al.*[403] ACR, albumin–creatinine ratio; ANCA, antineutrophil cytoplasmic antibody; C3GN, complement glomerulonephritis; eGFR, estimated glomerular filtration rate; GN, glomerulonephritis; PR3, proteinase 3; RCT, randomized controlled trial.

Research recommendations

Post-streptococcal GN.

- RCT is needed to evaluate the treatment of crescentic poststreptococcal GN with high-dose glucocorticoids with or without immunosuppression
- Research is needed to determine the nature of the streptococcal antigen(s) as a basis for developing immunoprophylactic therapy
- In patients whose kidney lesion transforms, further research is needed to elucidate the distinctions and relationships between immune complex–mediated post-streptococcal GN and C3-dominant, but nonimmune complex–mediated C3 glomerulopathy (C3G)
- Research is needed to confirm the utility of anti-factor B antibodies in the diagnosis of poststreptococcal GN[404]

Shunt nephritis.

- Multicenter observational studies are needed to determine the incidence, prevalence, and long-term prognosis of shunt nephritis, and the outcome of those with PR3-ANCA antibodies

Infective endocarditis-related GN.

- Multicenter studies are needed to determine the incidence, prevalence, long-term prognosis, and mechanism of glomerular injury of infective endocarditis-related GN

IgADIRGN.

- RCTs of IgADIRGN are needed to assess the value, or lack thereof, of glucocorticoid and/or immunosuppressive agents after the infection is controlled

7.2 Viral infection–related GN

7.2.1 Hepatitis C virus (HCV) infection–related GN

The Work Group concurs fully with Recommendations 5.1–5.2.3 of the *KDIGO 2018 Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease*.[405] Please refer to this publication for specific recommendations, selection, and dosing of specific therapeutic agents, and research recommendations.

7.2.2 Hepatitis B virus (HBV) infection–related GN

Approximately 250–350 million people (5% of the world's population) are chronically HBV-infected, making it one of the most common human pathogens,[406–408] and about 3%–5% of patients with chronic HBV infection develop kidney disease as a complication.[409,410]

The most common pattern of glomerular injury seen in HBV infection is MN.[411,412] Lesions of IgAN, membranoproliferative GN (MPGN), FSGS, and crescentic GN are seen less frequently. Rarely, MCD has been observed in HBV infection, with remissions following antiviral therapy.[413] A variable fraction of patients with HBV infection and MN display circulating anti-PLA2R antibodies (Chapter 3).[414,415]

The extrahepatic manifestations of chronic HBV infection also include systemic vasculitis (especially polyarteritis nodosa/Kussmaul-Maier disease),[406,416] Type II (monoclonal IgM κ antipolyclonal IgG), and Type III (polyclonal IgM, IgA, IgG) cryoglobulinemia.[406–408,417]

This section addresses the issues related to treatment of GN in patients with replicative HBV infection. Due to its propensity to integrate into the host genome and the ability to form treatment-resistant, covalently closed circular deoxyribonucleic acid in hepatocytes, HBV infection is very difficult to permanently cure with antiviral agents, unlike HCV infection.[418] Relapses of viral replication are fairly common in HBV infection, and immunosuppressive agents can reactivate dormant or occult infection.[418,419]

7.2.2.1 Diagnosis

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

The diagnosis of HBV-mediated GN requires detection of the serologic manifestations of HBV infection and replicative virus in the blood, detection of HBV-related protein antigens in the glomerular immune deposits, and the exclusion of other causes of glomerular disease. Because HBV infection may be clinically silent, including absence of hepatic enzyme elevations indicative of hepatic inflammation and hepatocyte necrosis, a liver biopsy may be indicated to assess the degree of hepatic damage, especially fibrosis. Serologic identification of HBV exposure and infection is best performed by assessing hepatitis B surface antigen (HBsAg), anti-HBc antibody, and in selected cases, HBV deoxyribonucleic acid (DNA) quantification representing the burden of replicative viral infection.[418,420] Persistently elevated HBe antigen is a sign of replicative infection, and conversion to anti-HBe can be taken as an indication of a remission of viral replication.[418]

HBV infection is particularly common in patients with MN, IgAN, cryoglobulinemia, and polyarteritis nodosa (Kussmaul-Maier disease), and such patients should be routinely assessed for this infection. Whether children and adults with MCD should be routinely screened for HBV infection is uncertain, but this might be wise in countries with a high endemic burden of HBV infection or in patients with high-infection risk behaviors or histories. Because of common coinfection, patients with high-risk behaviors (e.g., i.v. drug abuse, unprotected sexual intercourse) should also be screened for HCV and HIV infection (see HCV and HIV sections). About 10% of HBV-infected subjects are coinfected with HIV, and 10%–30% are coinfected with HCV.[406] Another reason for screening patients with proteinuric glomerular disease for HBV infection is that many such patients may become candidates for immunosuppressive therapy (glucocorticoids and or cytotoxic/immunomodulating agents), which can induce a serious exacerbation of HBV replication (Chapter 1).[419] Occult HBV infection with negative HBs antigen and variable (positive or negative) anti-HBc can best be evaluated by detection and quantification of HBV DNA by polymerase chain reaction.[420] HBs or HBc antigen can occasionally be detected in kidney tissue of patients without serologic evidence of HBV infection.[421] Serum HBV DNA levels have a modest correlation with the severity of clinical findings.[422,423]

7.2.2.2 Prognosis

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

Adult patients with HBV infection and MN have a tendency to progress toward kidney failure, and spontaneous remissions are uncommon.[406,411] Therefore, such patients need careful consideration for treatment beyond attempts to control viral replication with antiviral agents. The choice of adjunctive treatment of HBV infection will depend on the specific manifestations of the kidney (glomerular) disease. Children with HBV-related MN have a high spontaneous remission rate and seldom progress to kidney failure (see section 7.2.2.4 on Special situations below).[406,411] HBV infection may also promote progression in IgAN and FSGS, but this is not well-established.[424–426] Cryoglobulinemia can be associated with severe and rapidly progressive glomerular disease,[417,427] often associated with vasculitis and crescents. Polyarteritis nodosa has a particularly poor prognosis when concomitant HBV infection remains untreated.[416]

7.2.2.3 Treatment

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

Due to the poor prognosis of untreated HBV infection (hepatocellular cancer, cirrhosis of the liver, GN, and/or vasculitis) and the availability of effective (but not curative) antiviral agents, nearly all patients with this condition should be considered candidates for antiviral therapy, unless contraindication exists.

Key information

Balance of benefits and harms. Chronic replicative HBV infection can be recognized by a combination of serologic and viral genome studies.[418] We consider chronic replicative HBV infection to have serious, potentially life-threatening, long-term complications (liver cirrhosis, hepatocellular carcinoma, GN, vasculitis) if left untreated. Because of these risks and the minimally moderate risks of harm from therapy of HBV infection, therapy of replicative HBV infection is worthwhile even though the evidence of (long-term) benefit for a complicating glomerular disease (i.e., MN) is weak due to the lack of high-quality RCTs in this population. Circumstances might exist that would preclude this choice, such as intolerance to all available antiviral agents, but these are expected to be uncommon.

Eradication or control of HBV replicative infection may improve outcomes of GN accompanying HBV infection, at least in observational studies (low-quality evidence). Some agents, notably α-interferon (IFN), may aggravate underlying glomerular disease, and their safety has been questioned. Treatment of HBV-associated GN with nucleos(t)ide analogues is indicated.

Nucleos(t)ide analogues can favorably modify viral replication at an acceptable level of undesirable side effects[418,428]; however, true lasting cure of the infection is evasive due to the biology of the virus (i.e., integration into the host genome and its ability to persist in a dormant fashion in hepatocytes).

CKD, most notably MN, can be a direct consequence of chronic HBV infection in susceptible individuals and can progress to kidney failure in 25%–35% of such subjects if left untreated.[406]

Quality of evidence. A systematic search of the medical literature of RCTs in the management of patients with HBV infection–related GN identified 1 small (n = 40) open-label study in children with HBV-associated MN.[429] This study did not report any of the critical and important outcomes identified for this guideline (all-cause mortality, kidney failure, ≥50% loss of GFR, malignancy, complete remission, annual GFR loss). The quality of the evidence from this RCT was low because of study imprecision (only 1 study) and risk of bias concerns. Additionally, supporting literature for this recommendation has been derived from observational studies that were graded as having low quality of the evidence because of bias by design. The overall quality of the evidence was rated as low.

Values and preferences. This recommendation places a higher value on the avoidance of serious, potentially life-threatening complications of unabated HBV viral replication, and a lower value on the side effects, cost, and inconvenience of treatment with nucleos(t)ide analogues and any associated monitoring that might be required with such treatment. In the judgment of the Work Group, all or nearly all well-informed patients would choose to be treated with nucleos(t)ide analogues rather than to forgo such treatment.

Resource use and costs. This recommendation will entail substantial costs, including out-of-pocket costs, due to the high cost of anti-HBV viral agents and the cost of testing for evaluation of the response to antiviral therapy. There may also be limited availability of these agents in certain regions of the world. These costs may be offset to some degree by avoiding the costs of treatment of long-term complications (such as liver or kidney transplantation, dialysis, or NS). Formal, long-term cost–benefit analyses are required to examine this assumption, especially in subjects with glomerular disease believed to be a complication of HBV infection.

Considerations for implementation. Substantial variation exists in the prevalence of HBV infection in different regions of the world. It is expected that the burden of disease from glomerular complications of chronic HBV infection will be greater in those regions where HBV infection is endemic. Measures to prevent the acquisition of HBV infection, such as vaccination, better hygiene, and elimination of blood-borne infection (e.g., from transfusion or i.v. drug abuse) are crucial. All measures should be considered equally for all sex, races, and ethnicities.

Rationale

To date, evidence-based treatment recommendations for adult patients with replicative viral infection and glomerular disease cannot be made due to lack of appropriate RCTs in this population. Nevertheless, potent nucleos(t)ide analogues with anti-HBV activity and high barriers to development of resistance are now available and widely considered as treatments of choice for HBV infection.[428] Lamivudine has a high association with acquired resistance and is no longer recommended as initial therapy.[418] Pegylated IFN-α is less commonly used due to limited efficacy and tendency to evoke serious side effects, but it may be effective in milder cases with low viral load.[418] Combination therapies using IFN and nucleos(t)ide analogues are not generally recommended, except in special circumstances.[418]

Clinical practice guidelines on the evaluation and management of chronic HBV infection have been recently published, and we have drawn heavily upon these publications for developing current recommendations for HBV infection associated with GN.[407,408,418]

Several drugs are now available for the treatment of chronic HBV infection (entecavir, tenofovir disoproxil, tenofovir alafenamide, adefovir, telbivudine). The efficacy of these drugs for HBV infection has been assessed in RCTs.[418] However, as of 2016, only 1 RCT of treatment of HBV-related GN could be identified.[429] It was an open-label, controlled trial of α-IFN in HBV-related MN in children that showed short-term beneficial effects and a 40% seroconversion rate of HBe and improvement in proteinuria. Side effects were common. This study was judged to be of low quality and potentially biased. However, observational studies in adults have been consistent with these findings.[430] No RCTs using nucleos(t)ide analogues have been reported. Several meta-analyses, including observational studies, have appeared.[431–435] In 1 meta-analysis of 6 trials (1 RCT), α-IFN and lamivudine, with or without accompanying glucocorticoids, were associated with a higher proteinuria remission rate and clearance of HBeAg as a sign of control of replicative viral infection, compared to glucocorticoids or supportive care only. Glucocorticoids alone were judged to be ineffective.[434] The Yang *et al.* analysis was limited to HBV-associated MN and included 3 trials of IFN-α and 2 trials of nucleoside analogues.[432] Antiviral treatment was superior to control in terms of complete or partial remission of proteinuria and clearance of HBeAg. No difference in outcome was observed between nucleoside analogues and IFN, but no head-to-head comparisons of the 2 antiviral regimens were conducted. Serious extrarenal side effects were seen commonly in IFN-treated subjects. The emergence of drug resistance was common in nucleoside analogue (lamivudine) regimens. Sustained viral response was observed in 60% of patients treated with IFN, and in 85% with nucleoside analogues. Spontaneous viral remission was seen in about 6% of controls. Similar favorable responses to antiviral therapy were observed in a small, open-label, uncontrolled trial in HBV-related cryoglobulinemic vasculitis.[417] Very few studies of antiviral therapy of HBV-infection in patients with IgAN or FSGS have been conducted. Observational cohort studies have suggested benefits of combined lamivudine and glucocorticoids in HBV inactive carriers with IgAN.[436] A role for CNIs in the treatment of HBV-associated glomerular disease (MN and FSGS) has been suggested.[437,438] Calcineurin agents can be used safely in patients with glomerular and other autoimmune diseases in the presence of HBV infection, as these agents tend to reduce viral replication by inhibiting HBV entry without interfering with sodium–taurocholate cotransporting polypeptide (NTCP) activity.[439,440] In a pilot study, sulodexide combined with antiviral therapy (entecavir) was shown to have an additive beneficial effect on proteinuria in HBV-related MN, perhaps via a complement-activation-inhibiting mechanism.[441]

Treatment of patients with HBV infection and GN should be conducted according to standard clinical practice guidelines for HBV infection, requiring the identification of replicative viral infection (HBeAg positivity and/or viral DNA levels of >2000 IU/ml).[408,418] Nephrotoxicity of some of the nucleos(t)ide analogues (particularly adefovir and tenofovir) can be of concern. The use of these agents in patients with CKD (due to GN or otherwise) or NS may require dosing modifications.[428]

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

The European Association for Study of the Liver (EASL) clinical practice guidelines suggested that IFN-α–based regimens not be employed in HBV-associated GN, as IFN therapy could aggravate autoimmune phenomena in such patients.[418] In one case, *de novo* MN appeared after starting IFN therapy for HBV infection.[442] The consistency of this effect is uncertain, but since newer antiviral regimens are effective in inducing a viral response with fewer side effects, the utility of use of IFN-based regimens can be questioned.

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

The heterogeneity of patients with HBV infection (e.g., degree of liver function impairment, extent of extrahepatic involvement) creates substantial complexity in establishing treatment guidelines in patients with HBV-mediated kidney disease. Agents that can augment HBV replication (such as glucocorticoids, alkylating agents, rituximab), thus aggravating the hepatic manifestations of disease, constitute a real risk (Chapter 1).[419] Alternative agents, such as CNIs, that have little or no effect (or even a beneficial effect) on HBV replication may be preferred.[437–440] All patients receiving rituximab for any indication should have HBsAg and core antibody (HBcAb) checked. If positive, therapy to treat HBV must be instituted in conjunction with hepatology. Therapy with immunosuppression should be given cautiously, with awareness of its risks and benefits.

7.2.2.4 Special situations

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

The utility of antiviral therapy in patients with simultaneous HBV infection and anti-PLA2R antibody–mediated MN has not been evaluated, but rituximab or cyclophosphamide-based regimens carry a risk of aggravation of HBV replication in such patients and probably should be avoided, at least until a sustained virologic remission has been obtained by nucleos(t)ide analogue therapy (Chapter 3).[443] A CNI regimen might be preferred in such patients, but evidence is lacking to support such use. It is also possible that the association of HBV infection and PLA2R+ MN is coincidental rather than causal, at least in some cases.

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

The role of plasma exchange in treatments of HBV-related cryoglobulinemic vasculitis has been incompletely assessed, but if the plasma level of cryoglobulins is high (CryoCrit >5%, >500 mg/dl) and symptomatic vasculitis is present, it might be tried with 5% albumin or fresh frozen plasma replacement.[417,427]

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

The presence of occult HBV infection and MN (circulating HBs negative with HBs/HBc antigen in the immune deposits) in children may require antiviral therapy, as immune suppression alone is seemingly ineffective.[444]

Research recommendations

- RCTs are needed to establish the most effective antiviral treatment regimen in modifying the progression of HBV-associated GN. Studies will need to account for the extra-renal disease involvement, as well as evaluate varying drug combinations, including timing and duration of therapy
- RCTs in children should be evaluated separately in view of the higher rate of spontaneous remission in HBV-associated GN

7.2.3 Human immunodeficiency virus (HIV)–related GN

This section makes management suggestions for adults aged >18 years with HIV-related glomerular disease.

There are no RCTs for HIV-related kidney disease. For a summary of current issues related to this topic, we refer readers to the publication from the KDIGO HIV Controversies Conference.[445]

According to the United Nations AIDS organization, approximately 36.9 million people were living with HIV in 2017. In 2017, 59% (CI: 44%–73%) of all people living with HIV were accessing treatment.[445] A recent review of HIV-related kidney disease defined by different GFR-estimating formulas (MDRD, CKD-EPI, and Cockcroft–Gault) demonstrated that the presence of kidney disease varied by formula and by region in the world, but it is truly a growing issue in the HIV pandemic (Figure 58).[446,447]

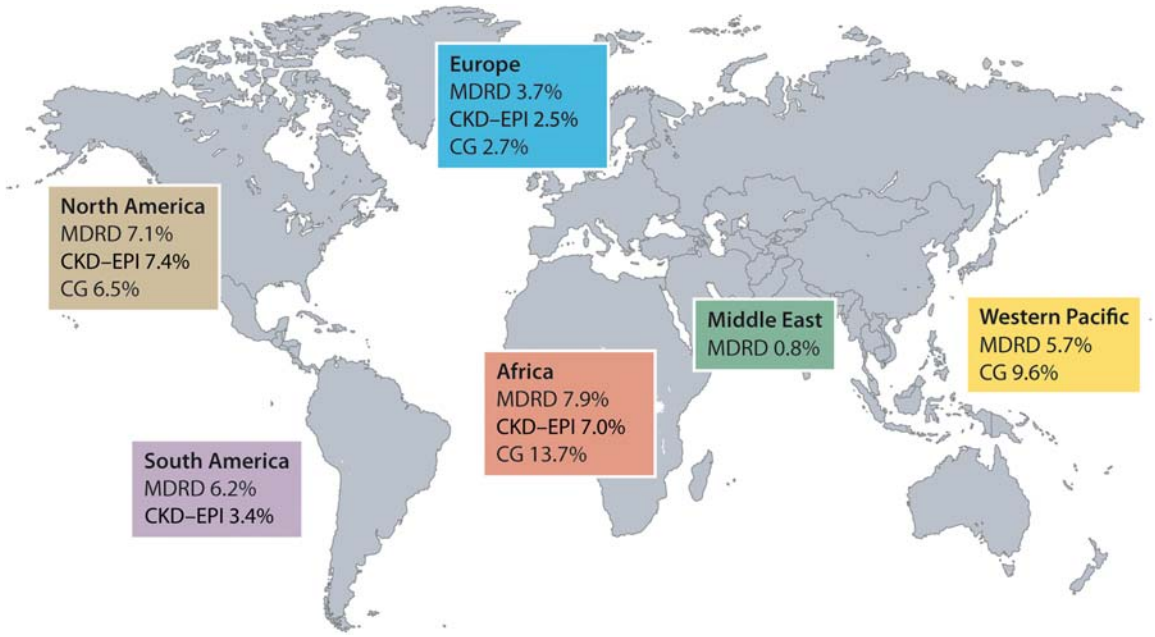

Figure 58 | The global distribution of CKD associated with HIV infection. Reproduced from Ekrikpo UE, Kengne AP, Bello AK, et al. Chronic kidney disease in the global adult HIV-infected population: a systematic review and meta-analysis. *PLoS One*. 2018;13:e0195443.[447] Copyright © 2018 Ekrikpo *et 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-EPI, Chronic Kidney Disease Epidemiology Collaboration; HIV, human immunodeficiency virus; MDRD, Modification of Diet in Renal Disease.

7.2.3.1 Diagnosis

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

The KDIGO Controversies Conference proposed a pathologic classification of HIV-related kidney disease to help highlight the various mechanisms of HIV-related kidney disease.[445]

HIV can have many effects on the kidney. Glomerular, interstitial, and vascular diseases have unique presentations in patients with HIV. Infections, both the actual infection and the treatment, can impact kidney function. Traditional causes of kidney disease in the patients without HIV, such as hypertensive nephropathy or CKD and diabetes, are also in the differential. Finally, medications for the treatment of HIV, for immune prophylaxis and for common ailments, must also be considered when there is a change in kidney function that is of concern to the clinician. In patients with HIV infection, many of these pathologies can mimic HIV-associated nephropathy (HIVAN), but each condition requires a different therapy.[448–450] A kidney biopsy–based approach helps to navigate both the challenges of diagnosis and future knowledge. A recent review highlighted the complexity of diagnosis on biopsy and the need for precision in diagnosis for optimization of management (Figure 59).[451]

Podocytopathy is a common lesion seen in the glomerulus in HIV infection and may take the form of collapsing glomerulopathy (HIVAN), particularly in patients with African genetic background, FSGS without collapsing features (FSGS-UC), or MCD.[1,2,451] Many immune complex–mediated diseases have also been described in the context of HIV, including IgAN, lupus-like GN, MN, and MPGN.[451] Because of the lack of certainty regarding HIV causality in these cases, it has been recommended that the term HIV-associated immune complex kidney disease (HIVICK) not be used. Certain genes, such as *APOL1*, can increase risk of FSGS and HIVAN, but not of immune complex disease in HIV. The pathology of the biopsy is the same, no matter the number of genetic variants.[452] More information on genetic factors is needed (Figure 60[453]).

Tubulointerstitial disease can be present with HIVAN, but it can also be due to medications, or can be a response to infection. Vascular diseases were more prevalent prior to highly active antiretroviral therapy (HAART) therapy.[454,455] More than a third of the patients with HIV who underwent a kidney biopsy had diabetic nephropathy; or MN, MPGN, or IgAN; or another pattern of immune complex GN.[448,456] A

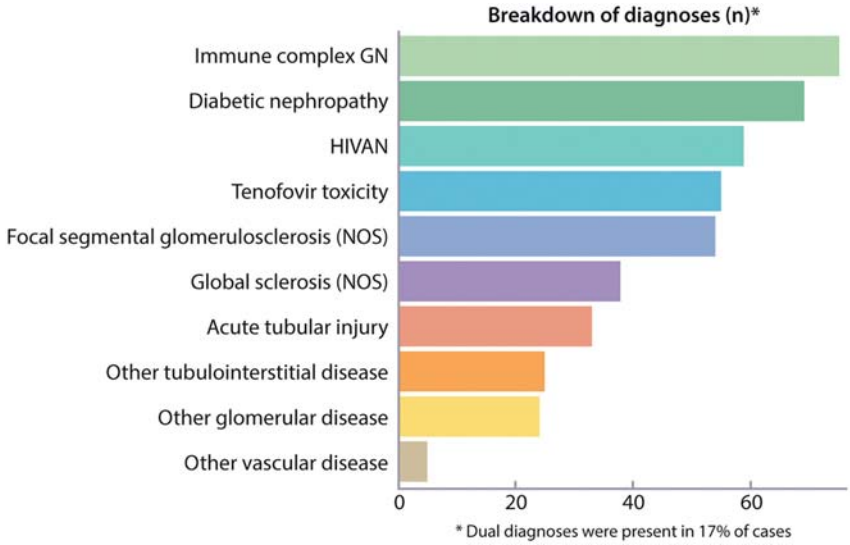

Figure 59 | The spectrum of kidney biopsy findings in patients with HIV in the modern era. Reproduced from *Kidney International*, volume 97, issue 5, Kudose S, Santoriello D, Bomback AS, et al. The spectrum of kidney biopsy findings in HIV-infected patients in the modern era, pages 1006–1016, Copyright © 2020, with permission from the International Society of Nephrology.[451] A total of 26,737 native biopsies from 2010–2018 were retrospectively reviewed; 437 (1.6%) from patients with HIV (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.

	Overall disease frequency	*APOL1* 0 risk alleles	*APOL1* 1 risk allele	*APOL1* 2 risk alleles
		~ 42%	~ 45%	~ 13%
HIVAN (without ART)	10% 1:10	2.5% 1:40	4% 1:25	50% 1:2
HIV– FSGS	0.8% 1:125	0.2% 1:500	0.3% 1:333	4.25% 1:24
HIV+ FSGS	No data	No data	No data	No data

Figure 60 | Lifetime risk of HIVAN or FSGS-UC in the setting of HIV by number of *APOL1* risk alleles. Adapted from *Seminars in Nephrology*, volume 35, issue 3, Dummer PD, Limou S, Rosenberg AZ, et al. APOL1 kidney disease risk variants: an evolving landscape, pages 222–236, 2015, published by Elsevier.[453] *APOL1*, apolipoprotein L1; ART, antiretroviral therapy; FSGS-UC, focal segmental glomerulosclerosis—undetermined cause; HIV, human immunodeficiency virus; HIVAN, HIV-associated nephropathy.

rare disease—diffuse infiltrative lymphocytosis syndrome (DILS)—which is present in patients with HIV, has been reported as a cause of kidney injury in HIV.[457] HIV-related thrombotic microangiopathy has been reported as a first presentation of HIV,[454,455] and it is associated with hematuria and proteinuria. The mechanism of this disease is not clear but seems to be associated with ADAMTS 13 levels.[458]

7.2.3.2 Prognosis

Practice Point 7.2.3.2.1: The factors contributing to the long-term outcome of HIV infection associated with GN are numerous and include persistence of viral replication, response to antiviral treatment, genetic predisposition to glomerular injury (e.g., *APOL1* risk alleles), coinfection with other viruses, and development of immune complex

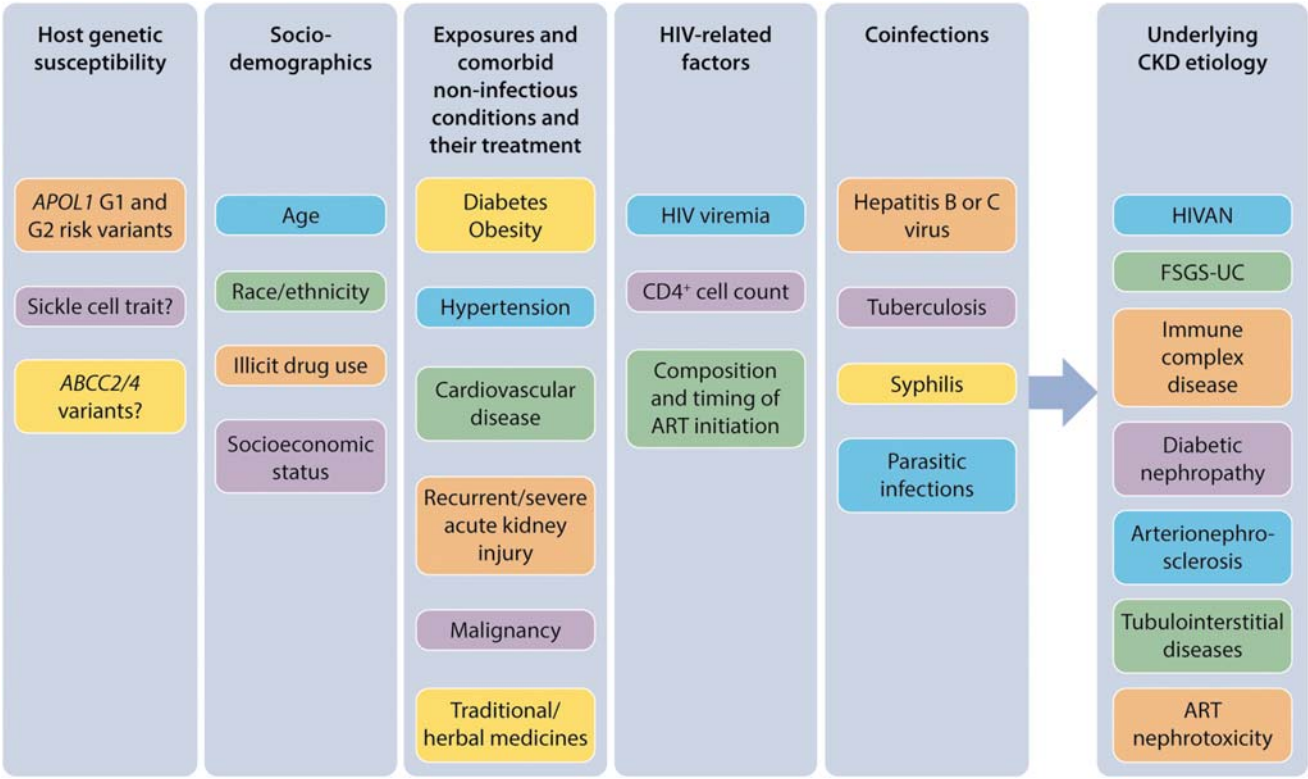

Figure 61 | Risk factors and underlying etiologies of CKD in individuals who are HIV-positive. Reproduced from Swanepoel CR, Atta MG, D'Agati VD, et al. Kidney disease in the setting of HIV infection: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int.* 2018;93:545–559, https://www.kidney-international.org/article/S0085-2538(17)30823-2/fulltext, Copyright © 2017, International Society of Nephrology. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).[445] ABCC, ATP-binding cassette transporter proteins; *APOL1*, apolipoprotein L1; ART, antiretroviral therapy; CKD, chronic kidney disease; FSGS-UC, focal segmental glomerulosclerosis—undetermined cause; HIV, human immunodeficiency virus; HIVAN, HIV-associated nephropathy.

disease or thrombotic microangiopathy. Thus, the estimation of prognosis in individual patients can be very difficult.

No RCTs exist to guide prognosis. A summary of factors to consider is given below (Figure 61[445]). Limited data show that comorbid conditions (HBV, HCV, TB, and syphilis) can impair long-term prognosis.[459–463] AKI is also a risk factor for long-term progression of CKD in HIV to kidney failure.[464] Whether *APOL1* risk alleles should be assessed routinely in patients of west African ancestry with HIVAN remains uncertain.

7.2.3.3 Treatment

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

The presence of CKD is not a contraindication for antiretroviral therapy (ART) of HIV infection. Current consensus data, based on 2 large RCTs on the time to initiate ART, namely 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.[465,466] *This Work Group believes that the benefit outweighs the risk to support this recommendation, and patients with such infections also place a high value on early treatment, when possible.*

Key information

Balance of benefits and harms. These recommendations derive from the benefit of ART in the HIV literature and the low-quality data that the extrapolation to patients with GN seems to support.

Quality of evidence. The quality of the evidence is low, with no RCTs for guidance in patients with HIVAN. The evidence identified to support this recommendation is indirect, as it has been conducted in the general HIV population and in observational studies, which exhibit bias by design.

Values and preferences. The Work Group placed a higher value on minimizing the harmful effects of HIV infection and a lower value on the risk of adverse events, kidney and non-kidney, related to ART and kidney biopsy.

Resource use and costs. Treatment of HIV to prevent kidney side effects is much less costly than kidney transplant and kidney replacement therapy, and many end-stage therapies are not available throughout the world. We have no specific cost data on which to base our recommendations.

Considerations for implementation. At this time, there is not enough information to guide choices based on sex or ethnic background, aside from what is considered in standard treatment for patients who are HIV-positive.

Rationale

At this time, there are no RCTs for HIV-related kidney disease.[467] Supportive data suggest ART therapy is beneficial to HIV-related kidney disease. In patients with HIV, proteinuria, and/or decreased kidney function is associated with increased mortality and worse outcomes.[468] Data from several RCTs suggest that ART is beneficial in both preservation and improvement of kidney function in patients without CKD with HIV.[452,467,469,470] A decrease in HIV viral load during ART is associated with kidney function improvement, and an increase in viral load is associated with worsening kidney function.[453,471,472]

Treatment of HIV-related GN is mostly extrapolated from HIVAN. Observational studies, data from uncontrolled or retrospective studies,[465–467,473–475] and data from an RCT[476] suggest that HAART (defined as combination ART therapy with ≥3 drugs) is beneficial in both preservation and improvement of kidney function in patients with HIVAN. Since the introduction of HAART in the 1990s, there has also been a substantial reduction in the incidence of HIVAN.[477] In multivariate analysis, HIVAN risk was reduced by 60% by use of HAART, and no patient developed HIVAN when HAART had been initiated prior to the development of acquired immune deficiency syndrome (AIDS).[477] The use of HAART has also been associated with improved kidney survival in patients with HIVAN.[478]

Antiviral therapy has been associated with GFR improvements in patients with HIV with both low CD4 lymphocyte counts and impaired baseline kidney function, supporting an independent contribution of HIV-1 replication to CKD in advanced HIV disease.[479] Early observational studies also suggested a benefit for ACEi.[480] Several retrospective observational or uncontrolled studies conducted before or during the initial phases of ART reported variable success with the use of glucocorticoids in patients with HIV-associated kidney diseases.[478,481,482] There is only one study using cyclosporine in 15 children with HIV and NS.[483] These early observational studies suggested a benefit for ACEi and glucocorticoids in HIV-mediated kidney disease, but the studies were done prior to introduction of ART; and in the era of modern HAART therapy, it is not known whether this benefit remains in the context of current management.[480] There is no RCT that evaluates the value of ART therapy in patients with HIVAN.[467] There is very low–quality evidence to suggest that ART may be of benefit in patients with HIV-associated immune complex kidney diseases and thrombotic microangiopathies,[484–487] but other data suggest that antiviral therapy is not specifically beneficial in HIVICK.[448]

With ART, outcomes of patients receiving kidney replacement therapy are the same as those in HIV-negative counterparts.[486] Patients with HIV can now undergo transplantation as a therapeutic option.

Practice Point 7.2.3.3.1: A decision for the use of glucocorticoids as an adjunct therapy for HIVAN must be made

on a case-by-case basis, as the risks and benefits long-term are uncertain.

The potential for harm cannot be ignored. A study in HIVAN compared traditional ART versus ART plus a glucocorticoid regimen (1 mg/kg up to 60 mg) and ACEi or ARB therapy. This study demonstrated a significant increase in GFR, increased adverse events (infections and all-cause mortality), and reduced interstitial inflammation.[488] This finding is consistent with other studies that have demonstrated that glucocorticoids have improved function in HIVAN.[475,480,489] The risk of glucocorticoids versus the benefit must be individually balanced.

Research recommendations

- RCTs are needed to:
  - evaluate the efficacy of ART in HIV-associated glomerular disease, both podocytopathies, and immune-complex diseases
  - evaluate the role of other therapies (e.g., RASi, glucocorticoids, etc.) in combination with ART in the treatment of HIV-associated kidney diseases
  - help determine optimal kidney replacement therapy and transplant regimens for HIV-associated kidney diseases
  - identify the role for assessment of *APOL1* and other genetic risk variants and their clinical application to optimize HIV-related kidney disease treatment.

7.3 Nephropathies due to infections with schistosomiasis, filariasis, and malaria

Chronic parasitic infection is increasingly recognized as a cause of CKD and kidney failure, especially in tropical and subtropical areas of the world, and in areas of socioeconomic depression and inadequate sanitation. This section covers diagnosis, prognosis, and treatment of several parasite infections that may cause glomerulopathy, specifically, schistosomiasis, filariasis, and malaria.

7.3.1 Schistosomal nephropathy

Schistosomiasis (syn. Bilharziasis), a chronic infection by trematodes (blood flukes), is encountered in Asia, Africa, and South America. Schistosomiasis results from an immune response by the host against the schistosome eggs. Schistosomal glomerular disease is postulated to derive from this immune response.

Clinical glomerular disease has been described most frequently in association with hepatosplenic schistosomiasis produced by *Schistosoma mansoni*.[490] Five patterns of schistosomal glomerular pathology have been described by the African Association of Nephrology (AFRAN; Figure 62). A 6th pattern has been proposed to describe the pathology associated with schistosomal GN and HCV coinfection (Figure 62). It should be recognized that in highly endemic areas, the association of GN with schistosomiasis may be coincidental rather than causal.

Many patients may have asymptomatic and self-limited glomerular disease. GN is most commonly seen in young male adults. Histologic studies have documented glomerular lesions in 10%–12% of cases.[491] Hepatic fibrosis from *S. mansoni* is more commonly associated with symptomatic presentation of a schistosomal GN and is an independent risk factor for the development of chronic, progressive glomerulopathy in 10%–15% of patients. The severity of glomerular lesions and proteinuria correlates with liver macrophage dysfunction and decreased immune complex clearance.[492]

AFRAN classification	Etiology
I Mesangial proliferative	*Schistosoma haematobium* *Schistosoma mansoni*
II Proliferative exudative	*Schistosoma haematobium* *Schistosoma mansoni* *Salmonella*
III Membranoproliferative	*Schistosoma haematobium* *Schistosoma mansoni*
IV Focal segmental glomerulosclerosis	*Schistosoma mansoni*
V Amyloidosis	*Schistosoma haematobium* *Schistosoma mansoni*
VI Cryoglobulinemia	*Schistosoma mansoni* Hepatitis C

Figure 62 | Six patterns of schistosomal glomerular pathology. AFRAN, African Association of Nephrology.

7.3.1.1 Diagnosis

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

Coinfections can impact the severity of glomerular disease as well as associated complications. Schistosomiasis with *Salmonella* coinfection is associated with a rapid-onset GN and NS.[493] Treatment of coexistent salmonella infection favorably influences the course of GN.[493–496] Schistosomiasis with HBV or HCV coinfection is associated with a more rapid progression to cirrhosis or liver carcinoma. Schistosomiasis with HIV coinfection is associated with higher HIV viral activity.

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

Kidney biopsy is generally recommended in any patient with overt or progressive kidney disease (proteinuria >1 g/d, hypocomplementemia, hematuria, reduced GFR). A kidney biopsy can reasonably be deferred if the proteinuria is mild (<1 g/d), and the patient lacks hematuria or reduction in GFR, as the directed antiparasitic therapy will also cure mild schistosomal GN. A definitive diagnosis of schistosomal GN requires identification of the parasitic antigens in the glomeruli (specialized laboratories only).

It is important to differentiate MPGN due to schistosomiasis from MPGN caused by HBV or HCV. HIV can also be a common cause of FSGS.

7.3.1.2 Treatment

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

Specific antiparasitic treatment can alter the development or progression of kidney disease when started in the initial phase of infection. Class I and Class II schistosomal GN are likely to spontaneously resolve and/or respond to antiparasitic therapy. The proliferative forms of schistosomal GN (Class III, IV, V, VI) are more likely to progress to kidney failure despite antiparasitic therapy.

Two antiparasitic drugs are available to treat schistosomiasis, and treatment is recommended for all patients that are infected. No dose adjustment is necessary for kidney or hepatic impairment (Figure 63). The drugs should be given with food, separated by at least 4–6 hours. The tablet should not be chewed. Praziquantel dosing is effective in curing 60%–90% of patients with schistosomiasis. Oxamniquine is used for praziquantel-resistant patients or those with refractory schistosomal disease.[497] Successful treatment can prevent development of glomerular disease. However, established schistosomal GN does not respond to either antiparasitic agent.[490] Praziquantel is pregnancy category B, and is excreted in human breast milk, so it should not be used in lactating women. Oxamniquine is contraindicated in pregnancy.

There is no established role for glucocorticoids or immunosuppressant therapy in schistosomal GN. However, immunosuppression may rarely be necessary in severe Class VI schistosomiasis GN, coinfection with HCV, and severe mixed cryoglobulinemia syndrome.[405]

7.3.1.3 Special situations

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

Patients with chronic hepatosplenic schistosomiasis and hepatic fibrosis are at higher risk of developing chronic schistosomal GN and should be monitored for hematuria/proteinuria and SCr changes.[498] In the opinion of the Work Group, annual testing may be reasonable.

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

Infection with *S. haematobium* can lead to genitourinary symptoms due to chronic granulomatous inflammation, leading to ulceration, strictures, and obstructive uropathy. Imaging may be needed to determine if hematuria or kidney disease stems from a chronic obstruction, given that chronic schistosomal disease can also cause acute/chronic GN. Patients are also at an increased risk for bladder cancer. Monitor periodically with urine cytology or cystoscopy (gold standard), especially in the setting of hematuria.[498]

Research recommendation

- Studies are required to evaluate the right sequencing/timing of treatment of antibiotics for salmonella and antiparasitic therapy for schistosomiasis.

7.3.2 Filariasis and glomerular disease

Filarial worms are nematodes that are transmitted to humans through a mosquito vector and dwell in the subcutaneous tissues and lymphatics. Glomerular disease has been reported in association with *Loa loa*, *Onchocerca volvulus*, *Wuchereria*

Dosing	Praziquantel	Oxamniquine
Adult	20 mg/kg, 3 times a day, for 1 day	15 mg/kg, single dose
Pediatric >1 year old	20 mg/kg, 2–3 times a day, for 1 day	20 mg/kg, single dose

Figure 63 | Dosing of antischistosomal agents.

bancrofti, and *Brugia malayi* infections in Africa and some Asian countries. There are limited observational studies and no RCTs in filarial nephropathy.

The incidence, prevalence, and natural history of glomerular involvement in various forms of filariasis are poorly documented. This condition is usually found in areas with poor vector control and inadequate healthcare facilities. Glomerular involvement is infrequent. Light microscopy reveals diffuse proliferative MPGN, MCD, or chronic-sclerosing GN, or the collapsing variant of FSGS.[499] Microfilariae may be found in the arterioles, glomerular and peritubular capillary lumina, tubules, and interstitium.[499]

Immunofluorescence and electron microscopy show immune deposits along with worm antigens and structural components.[500,501] Urinary abnormalities have been reported in 11%–25% and NS is seen in 3%–5% of patients with loiasis and onchocerciasis, especially those with polyarthritis and chorioretinitis.[501,502] Proteinuria and/or hematuria was detected in over 50% of cases with lymphatic filariasis, and 25% showed glomerular proteinuria.[503,504]

7.3.2.1 Treatment

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

A reduction in proteinuria can be observed following antifilarial therapy in patients with non-nephrotic proteinuria and/or hematuria. An increase in proteinuria or decline in kidney function can follow initiation of diethylcarbamazine or ivermectin,[504,505] probably due to an exacerbation of the immune process secondary to antigen release into circulation after death of the parasite.[506] Therapeutic apheresis has been utilized to reduce the microfilarial load and prevent antigen release before starting antifilarial treatment.[507] The renal response to antifilarial therapy is inconsistent in those with NS. Deterioration of GFR may continue despite clearance of microfilariae with treatment.

Potential kidney toxicity of treatment regimens requires careful monitoring of kidney function. Please refer to the WHO treatment guidelines for filariasis.[508]

Diethylcarbamazine is contraindicated in pregnancy (animal studies have shown an adverse effect on the fetus, but no well-controlled studies have been done in humans). However, potential benefits may warrant use of the drug in pregnant women, despite potential risks. Diethylcarbamazine is considered safe during lactation. Ivermectin is in pregnancy category C. Ivermectin is also excreted in breast milk, and its use is not recommended during lactation unless the risk of delayed maternal treatment outweighs potential risk to the nursing infant.

Research recommendations

- Epidemiologic studies of kidney involvement in regions endemic for filaria
- Studies on the effect of population-based treatment with filaricidal agents on the course of filarial kidney disease

7.3.3 Malarial nephropathy

Malaria caused by *Plasmodium* parasites transmitted through the female *Anopheles* mosquito is the most prevalent endemic disease in the world (Figure 64).

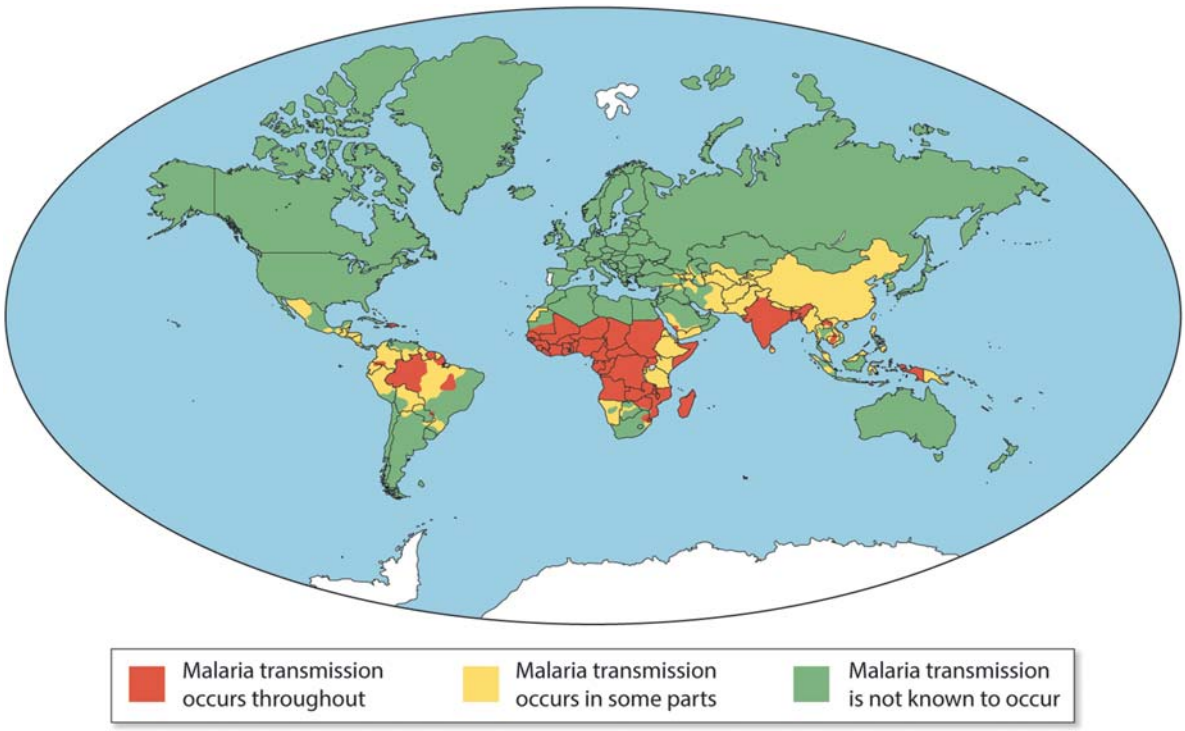

Figure 64 | Global distribution of malaria transmission. Reproduced from Centers for Disease Control and Prevention-CDC. Available at: http://www.cdc.gov/malaria/about/distribution.html. Accessed January 27, 2021.

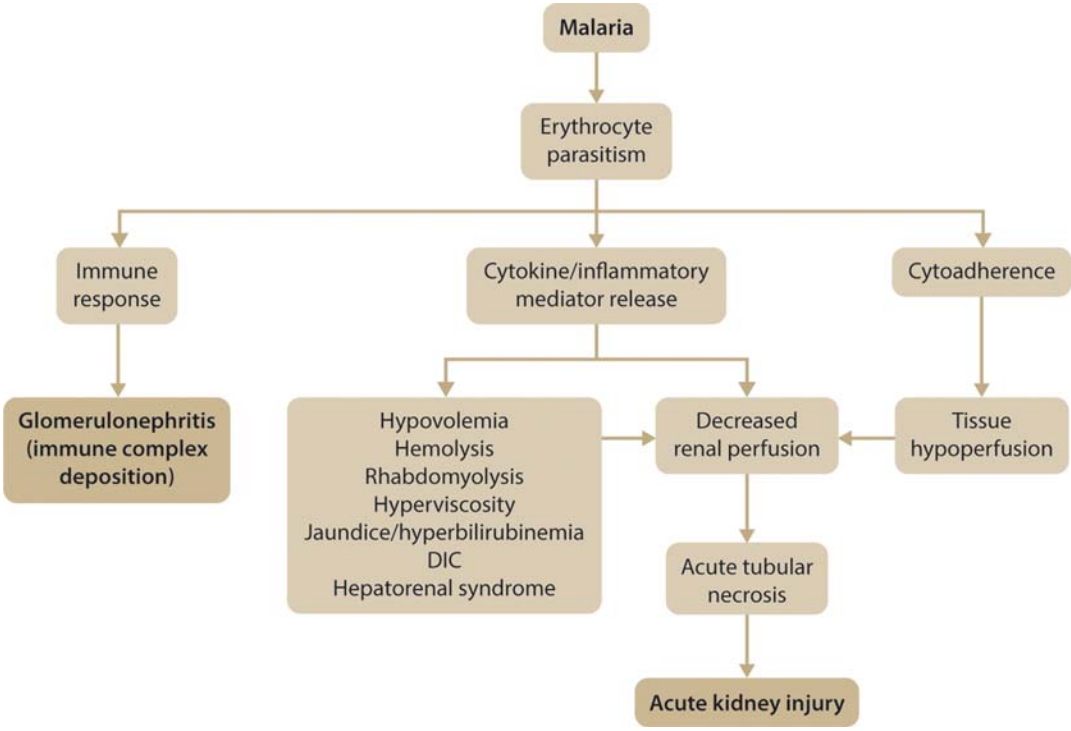

Figure 65 | Pathophysiology of kidney involvement in malaria.[510] DIC, disseminated intravascular coagulation.

Stage 1	Mild focal and segmental
Stage 2	Moderate focal and segmental
Stage 3	Diffuse or segmental lesions with interstitial and tubular changes
Stage 4	Marked sclerosis, and interstitial/tubular atrophy

Figure 66 | Histopathologic staging of quartan malarial nephropathy.

Safe	Unsafe
Chloroquine	Halofantrine
Amodiaquine	Tetracycline/doxycycline
Quinine	Primaquine
Azithromycin	
Sulfadoxine–pyrimethamine	
Mefloquine	
Chlorproguanil–dapsone	
Artemisinin derivatives	
Atovaquone–proguanil	
Lemefantrine	

Figure 67 | Antimalarial drugs and pregnancy.[521]

Malarial infection can cause a diversity of kidney injuries, both acute and chronic. Malarial infection–related GN is believed to be primarily a condition mediated by immune-complex formation.

Malaria-associated AKI can be classified as AKI from acute tubular necrosis (ATN), acute malarial-associated GN (reversible), or chronic and progressive GN (irreversible).[509] Immune-system activation between the malaria antigen and host red blood cells can lead to immune complex complement-mediated GN, acute interstitial nephritis, or acute GN (Figure 65).[510]

The exact incidence of GN in malaria is unknown, but it is estimated to be around 18%.[511] Acute malaria-associated GN can occur with *Plasmodium falciparum* or *Plasmodium vivax* infections, but is more common with *P. falciparum*. These patients will present with NS (transient mild proteinuria, microscopic hematuria, and occasionally low complement levels), and histopathology revealing MPGN or mesangio-proliferative GN.[509]

Chronic infection with *P. malariae* (and to a lesser extent *P. vivax*, *P. ovale*) has been associated with irreversible and progressive GN. In the past, this has been known as tropical nephritis or "quartan malarial nephropathy" (QMN; Figure 66).[512,513] Nephrotic syndrome, sometimes with impaired kidney function, is a common clinical manifestation. QMN is principally encountered in young children.[510] Nowadays, the lesion is much less common, and most children in the tropics with NS have MCD, FSGS, HBV or HIV infection, sickle cell disease, or SLE, rather than QMN.[511,514,515]

7.3.3.1 Treatment

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

The outcome of GN due to malarial infection is difficult to predict, as eradication of the parasitic infection is not always followed by recovery. GN and CKD can develop despite malarial eradication, detectable 3–5 years after primary infection.[516] Complete kidney recovery can be seen in approximately 64%–79% of cases of AKI or acute GN associated with *P. falciparum* and *P. vivax*.[516–519]

There does not appear to be any role for glucocorticoids or immunosuppressant therapy in malarial nephropathy,[512,513] although controlled trials are lacking. Treatment should focus on malarial eradication.

P. falciparum infection: Artemisinin-based combination therapy (ACT) is recommended over monotherapy due to the development of artemisinin resistance. The patient should also receive a single low dose of primaquine to reduce malaria disease transmission. No testing for glucose-6-phosphate dehydrogenase (G6PD) deficiency is required due to low risk of serious toxicity.

P. malariae infection: ACT, or chloroquine in areas without chloroquine-resistance.

P. ovale, P. vivax infections: ACT, or chloroquine in areas without chloroquine-resistance. Primaquine should be added to prevent relapses, adjusted to a patient's G6PD enzyme activity.

Severe malaria requires treatment with i.v. or intramuscular artesunate for at least 24 hours, followed by a complete 3-day course of ACT once the patient is able to tolerate oral medications.

The WHO also provides detailed recommendations for treatment of malaria.[520]

7.3.3.2 Special situations

In cases of severe malaria in children aged <6 years, when injectable medication cannot be given, the child should receive rectal artesunate and then be referred to a healthcare facility where the full level of care can be provided.

Halofantrine is both embryotoxic and cardiotoxic. Tetracycline/minocycline is associated with impairment of bone growth and teeth discoloration in the fetus and during infancy. Both are contraindicated during pregnancy and/or breastfeeding. Primaquine and tafenoquine can cause hemolysis in individuals with G6PD deficiency and are contraindicated in G6PD-deficient individuals, pregnant women (since the G6PD status of the fetus cannot be determined), infants <6 months of age (since G6PD testing can be confounded by fetal hemoglobin in early life), and for women breastfeeding infants <6 months old (Figure 67[521]).

Research recommendations

- Studies on the incidence and prevalence of malarial nephropathy and its response to antimalarial therapy, especially in endemic areas of West Africa
- RCTs to investigate the role of glucocorticoids and immunosuppressive agents when malarial nephropathy progresses, despite eradication of the malarial parasite
- Studies to assess the safety and efficacy of antimalarial treatments in pregnancy, as pregnant women are often excluded from clinical trials[521]

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

This chapter replaces the 2012 guideline chapter for idiopathic MPGN. Given the advances in our understanding of underlying etiology and the recognition that MPGN is not a disease but a pattern of glomerular injury, this updated chapter discusses the evaluation and management of the glomerular disease that often have a membranoproliferative pattern of injury, including C3G.[522]

The treatment of MPGN depends upon identification of an underlying cause. In most cases, the MPGN lesion derives from deposition of immunoglobulins and complement as either immune complexes (secondary to an underlying infection/autoimmune process), or monoclonal immunoglobulins, or is due to dysregulation of the alternative complement pathway.

In a few cases of immune complex–mediated MPGN, an identifiable underlying cause cannot be found despite extensive evaluation. This may be seen in children and young adults, but is rarely seen in adults. These patients are considered to have an "idiopathic" immune complex–mediated MPGN or immune complex–mediated MPGN of unknown etiology.

Because previous controlled trials included patients based on the old and now discarded electron-microscopic classification of MPGN, and not on the current classification that uses immunofluorescence microscopy in combination with presumptive disease pathobiology, there is insufficient high-quality evidence to form recommendations for the management of the various diseases that have MPGN histology. Therefore, practice points will be given to assist in clinical decision-making for these patients.

Nomenclature

The membranoproliferative pattern of GN is a light-microscopic pattern of kidney injury, characterized principally by an increased number of intraglomerular cells and diffuse thickening of the glomerular capillary walls. The clinical presentation is not specific, and patients commonly present with proteinuria (frequently associated with the NS), hypertension, glomerular hematuria, and abnormal kidney function. Hypocomplementemia (C3 and/or C4) is often, but not always, present. An MPGN pattern of injury may be found in many unrelated disorders (Figure 68). Identification of the pathogenic mechanisms specific for a disease is critical for appropriate management.

Membranoproliferative lesions were historically classified based on the location of deposits on electron microscopy examination as:

- *Type I MPGN* (MPGN I)—characterized by *subendothelial* and *mesangial* electron-dense deposits consisting of both immunoglobulin and C3
- *Type II MPGN* (MPGN II—Dense deposit disease [DDD])—characterized by electron-dense *intramembranous* deposits, predominantly consisting of complement
- *Type III MPGN* (characterized by *both subepithelial and subendothelial deposits*)

This historical classification was not based on disease pathogenesis, and as a result, different pathogenic processes fell under the collective designation of MPGN.

Advances in our understanding of underlying disease mechanisms leading to the development of a membranoproliferative pattern of kidney injury have resulted in a new pathobiology-based classification. The new classification relies on immunofluorescence examination; deposits are defined as primarily immunoglobulin (monoclonal), polyclonal immunoglobulin and complement, or predominantly complement (Figure 69).[523,524]

On the basis of the immunofluorescence findings, MPGN can be broadly divided into an immunofluorescence-negative subgroup, a complement-dominant subgroup, and an immunoglobulin subgroup, with or without complement. When MPGN is immunoglobulin-positive, regardless of the presence of complement, evaluation for infection, autoimmune disease, and monoclonal gammopathy should be done. Complement-dominant MPGN is further divided into C3/C4 glomerulopathy. A complement-dominant pattern requires evaluation of the alternative pathway of complement. Absence/trace Ig or C3 suggests a TMA.

It should be understood that the presence of an MPGN lesion implies that the pathogenic process has been present for some time and that other patterns of injury, including endocapillary proliferative GN, mesangioproliferative GN, and crescentic GN, may occur as a result of the same process. Thus, the type of lesion initially seen on light microscopy will depend, in part, on the timing of the kidney biopsy in relation to disease chronicity.[525]

Immune complex–mediated GN (ICGN) with an MPGN pattern

ICGN is characterized by the deposition of immune complexes containing both polyclonal immunoglobulins and

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 68 | 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; 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.

complement (excludes IgAN). This lesion classically results from chronic antigenemia with or without circulating immune complexes. ICGN may manifest with the MPGN pattern of injury or other proliferative glomerular lesions.

ICGN is usually due to:

- **Infections:** Hepatitis C and B viral infections are among the most common underlying causes of ICGN, but bacterial and protozoal infections can also cause ICGN.
- **Autoimmunity:** ICGN can be associated with certain autoimmune disorders, such as SLE, Sjögren's syndrome, and rheumatoid arthritis.

GN with monoclonal immunoglobulin deposits

Proliferative patterns of kidney injury secondary to deposition of monoclonal immunoglobulins are observed in patients with monoclonal gammopathies. These disorders are infrequently found in patients with overt hematologic disease, such as multiple myeloma, Waldenström macroglobulinemia, or B cell lymphoma. They most commonly occur in the setting of an indolent clonal, plasma cell, or lymphocytic disorder, and may be classified as a monoclonal gammopathy of renal significance (MGRS).[526] Kidney injury results from direct glomerular deposition of the monoclonal immunoglobulin. Examples include immunotactoid glomerulopathy, type I and type II cryoglobulinemic GN, and proliferative GN with monoclonal Ig deposits (PGNMID). Of note, in approximately 70% of the cases of PGNMID, a clone cannot be detected.[527] Each type can be differentiated by the distribution and ultrastructural appearance of deposits (i.e., amorphous or organized), by electron microscopy.[528] A complete discussion of these entities is beyond the scope of this guideline.

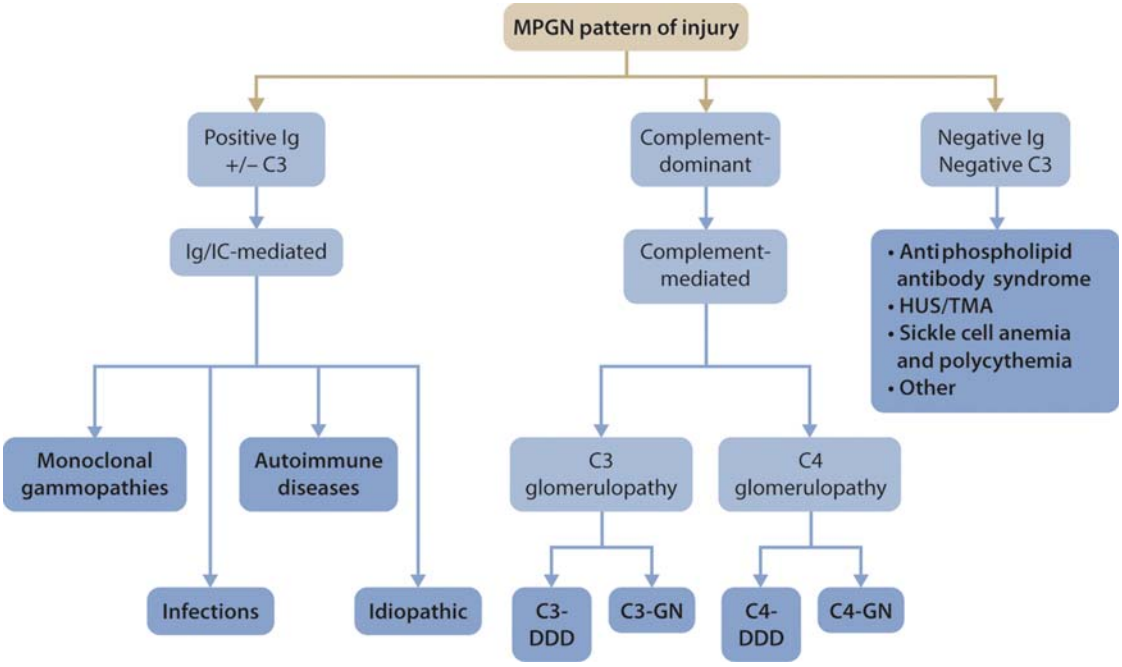

Figure 69 | Pathophysiology of membranoproliferative lesions. DDD, dense deposit disease; GN, glomerulonephritis; HUS, hemolytic–uremic syndrome; IC, immune complex; Ig, immunoglobulin(s); MPGN, membranoproliferative glomerulonephritis; TMA, thrombotic microangiopathy.

Glomerulonephritis with C3- and C4-dominant deposits

C3G is a rare entity that is defined by *C3-dominant glomerulonephritis* (a proliferative histologic lesion with C3 deposition at least 2 orders of magnitude greater than any other immune reactant) on immunofluorescence.[529] This category includes both DDD and the newer designation of C3 glomerulonephritis (C3GN).[530] Although DDD is defined by highly electron-dense osmophilic, predominantly intramembranous deposits, C3GN is characterized by mesangial and capillary wall deposits of lesser intensity. Other C3-dominant glomerular lesions (e.g., infection-related GN) must be excluded. Masked monoclonal immunoglobulin deposits should be considered in patients with a pattern of C3GN when immunofluorescence shows a small amount of immunoglobulin deposition admixed with C3 deposits. Immunofluorescence studies on paraffin-embedded tissue after pronase digestion may unmask glomerular deposits of monoclonal Ig.[531] An MPGN pattern is inconstantly observed in C3G, and hypocomplementemia is present in only about 50% of cases.[532,533] The underlying disease mechanism of C3G is presumed to result from dysregulation of the alternative complement pathway.[534] A similar entity of complement-mediated GN that is characterized by bright C4d staining but with no or minimal C3 or immunoglobulin deposits on immunofluorescence (C4 glomerulopathy [C4G]) has recently been described.[535] Further studies are required to determine its underlying cause.

8.1 Diagnosis

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

First, consider infection such as HBV and HCV infection, chronic bacterial infection (e.g., endocarditis, shunt nephritis, abscesses), fungal, and particularly in the developing world, parasitic infections (e.g., schistosomiasis, echinococcosis, malaria). Streptococcal serology should be performed in patients with recent history of infection. Second, consider autoimmune disorders such as SLE (particularly in the chronic phase of LN) and, less often, Sjögren's syndrome or rheumatoid arthritis. Besides autoimmunity, an underlying immune abnormality may be a trigger for ICGN. ICGN may be associated with malignancy; therefore, age-appropriate cancer screening may be warranted.

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

Patients with PGNMID, as determined by immunofluorescence, should undergo a complete evaluation for a hematologic malignancy or an indolent plasma cell or lymphocytic disorder, regardless of age, that includes: (i) serum and urine protein electrophoresis; (ii) serum and urine immunofixation; (iii) measurement of serum-free light chain levels; and (iv) hematology consultation to further evaluate for the presence of an underlying B cell/plasma cell clone producing the monoclonal immunoglobulin.[526] Working with a hematologist is important not only to further evaluate these patients (i.e., with a bone marrow biopsy, if indicated) but also because a number of the drugs used to treat these patients are not commonly used by practicing nephrologists.

Practice Point 8.1.3: If no underlying etiology is found for ICGN after extensive workup, evaluate for both

Functional assays	CH50, AP50, FH function
Quantification of complement components and regulators	C3, C4, FI, FH, FB, Properdin
Measurement of complement activation	C3d, Bb, sMAC
Autoantibodies	Anti-FH, anti-FB, nephritic factors (C3, C4, C5)
Genetic testing	C3, CFH, CFI, CFB, and CFHR1-5 MLPA
Plasma cell disorders‡	Serum free light chains, serum and urine electrophoresis, and immunofixation†
Immunofluorescence studies on kidney biopsy specimen	IgA, IgG, IgM, C1q, C3, fibrinogen, kappa, lambda, C4d (usually bright C3, negative or minimal Ig, negative C4d)

Figure 70 | Evaluation of abnormalities of the alternative pathway of complement. Adapted from *Kidney International*, volume 89, issue 2, Angioi A, Fervenza FC, Sethi S, et al. Diagnosis of complement alternative pathway disorders, pages 278–288, Copyright © 2016, with permission from the International Society of Nephrology.[539] ‡The presence of a circulating monoclonal gammopathy is less common below the age of 50 years. Ability to detect a monoclonal protein will depend on the sensitivity of the assay used. †Some complement assays may require referral to specialist/research laboratories, and interpretation of complement assays may require expert consultation. AP50, complement alternate pathway activation 50%; Bb, activated factor B; C3d, complement component 3d; C4d, complement component 4d; CFB, complement factor B; CFH, complement factor H; CFHR1-5, complement factor H–related protein 1-5; CFI, complement factor I; CH50, complement hemolytic activity 50%; FB, factor B; FH, factor H; FI, factor I; Ig, immunoglobulin; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; MLPA, multiplex ligation-dependent probe amplification; sMAC, soluble membrane attack complex.

complement dysregulation and drivers of complement dysregulation (Figure 70).

Data support a role for complement dysregulation in ICGN.[536,537] In addition, cohort data demonstrate that classic C3G may masquerade as ICGN (i.e., significant immunoglobulin may be present) when an infectious trigger is present at the time of kidney biopsy.[538] Substantiating a role for excess complement activity may inform a treatment approach, over and above supportive measures, and/or standard immunosuppression for active GN. A complete complement workup includes an assessment of overall complement activity, measurement of serum levels of complement proteins, and in select cases, screening for autoantibodies against complement regulatory proteins and genetic studies (Figure 70[539]).

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

Both infection-related GN (i.e., in the presence of active infection) and postinfectious GN (i.e., in patients with a preceding infection that has resolved) are presumed to be nonrecurrent, acute disease processes requiring only a limited workup. Treatment is best focused on resolving the infection while supporting kidney function. Immunosuppression is unlikely to be required except in extreme cases (i.e., rapidly progressive loss of kidney function and/or crescentic glomerular disease) and only after concurrent infection is controlled.

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

C3G in its classic form is a disease of children and young adults[538,540] related to autoantibody (nephritic factor)-mediated dysregulation of the enzyme complexes of the alternative pathway of complement, or to other key complement pathway proteins, and to a lesser extent to mutations in genes encoding Factor H, Factor I, Complement Factor H–related (CFHR) proteins, or C3.[534] Recently, the association between the production of a monoclonal protein in older adults and the development of C3G has been described.[533,541] In patients over the age of 50 years with C3G, the prevalence of monoclonal gammopathy ranges from 31% to 83% versus approximately 3% in age-matched controls.[533] However, C3G with an associated circulating monoclonal protein has sometimes been reported in patients aged 20–47 years, demonstrating that the disease affects a large age span.[538] The association rests on the epidemiologic findings, as direct evidence demonstrating monoclonal gammopathy as the cause of C3G is lacking in most patients. However, it appears that a number of monoclonal proteins have complement dysregulating features, primarily through direct activation of the complement alternative pathway.[541] The impetus for evaluating a given patient for a clonal B cell disorder stems from the limited data suggesting that a therapeutic strategy that addresses the clone may provide a treatment benefit for a paraprotein-associated C3G.[542] The comprehensive evaluation of a patient suspected of having a monoclonal protein is beyond the scope of this presentation.

8.2 Treatment

8.2.1 ICGN

Prior guidelines supported the use of oral cyclophosphamide or MMF plus low-dose, alternate-day, or daily glucocorticoids

as a therapeutic approach to ICGN, particularly in those with idiopathic disease and NS and/or rapidly progressive diseases. The same advances in our understanding of underlying disease mechanisms that have driven a nomenclature change have also highlighted the confounding heterogeneity of prior disease cohorts. Additionally, idiopathic ICGN is an exceptional condition in adults. Data no longer support the global application of broad-spectrum immunosuppression as in prior recommendations, but rather a more individualized approach. The optimal management of many of the disorders that have an MPGN injury pattern remains to be defined. Unless otherwise indicated, the practice points offered below are based upon very low–quality evidence, clinical experience, and expert opinion. Treatment is often influenced and determined by the severity of proteinuria and kidney dysfunction.

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

After identification of the underlying trigger for ICGN, the most effective therapy is to treat the primary disease process (Figure 68). In addition, all patients with ICGN are likely to benefit from the usual, routine care considered for patients with other active glomerular disease (Chapter 1).

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

Patients with indolent disease may present late when active inflammation has subsided. Such patients may have a bland urine sediment with a variable degree of proteinuria and elevation in SCr. Such patients should be treated with RASi alone, unless the kidney biopsy shows signs of active inflammation. Patients who present with advanced kidney disease and severe tubulointerstitial fibrosis on kidney biopsy are less likely to benefit from immunosuppressive therapy even if there is still some active inflammation in the kidneys, so assessment of the extent of chronicity on the kidney biopsy may help in deciding whether or not to treat with immunosuppression.

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

No evidence exists to support a benefit from immunosuppressive therapy in adults. Given that disease progression can occur, regular monitoring of SCr, proteinuria, and the urinalysis is recommended.

Similarly, there are no data available to inform the threshold for starting immunosuppression for the treatment of ICGN (as defined by the new nomenclature) in children who are not experiencing the NS. The authors recognize that in practice, immunosuppression may be initiated at lower levels of urine protein than may be considered in adults, and MMF is more likely to be utilized as a glucocorticoid-sparing option.

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

Prednisone (or its equivalent) can be initiated at 1 mg/kg/d (maximum dose of 60–80 mg/d) for 12–16 weeks. If the patient responds, prednisone may be gradually tapered to alternate-day therapy over 6–8 months. If there is <30% reduction in proteinuria after 12–16 weeks, we recommend tapering and discontinuation of prednisone.

Patients with a contraindication to glucocorticoids or unwilling to take glucocorticoids can be treated with a CNI. We do not encourage the extended use of glucocorticoids, where a glucocorticoid-sparing option may be available, particularly in children.

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

Prednisone (or its equivalent) can be initiated at 1 mg/kg/d (maximum dose 60–80 mg/d) for 12–16 weeks. Patients who respond with stabilization or improvement in kidney function or ≥30% reduction in proteinuria are considered to have a satisfactory response to initial therapy. In such patients, gradually taper and discontinue prednisone.

Patients that experience worsening kidney function and/or <30% reduction in proteinuria after 12–16 weeks are considered to have had an unsatisfactory response. In such patients, reduce the dose of prednisone to 20 mg/d and add MMF. If, after 6–12 months of combined therapy, there is no improvement in kidney function, hematuria, or proteinuria, discontinue therapy, and consider a repeat kidney biopsy. If the kidney biopsy continues to show active GN, consider using cyclophosphamide or rituximab.

Initiate daily oral cyclophosphamide (2 mg/kg/d; maximum 200 mg/d in adults) with prednisone (10 mg/d) for 3–6 months. The cyclophosphamide dose should be reduced by 25% in older adults (age >60 years) and adjusted appropriately for abnormal kidney function.

Alternatively, in adults, initiate rituximab at 1 g followed 14 days later by a second dose of 1 g and repeat this 2 g regimen at 6 months.

In patients with persistent disease activity despite at least 6 months of MMF plus low-dose prednisone or after 3–6 months of daily oral cyclophosphamide plus prednisone or rituximab, discontinue glucocorticoids and immunosuppression and continue supportive therapy.

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

Initiate treatment with i.v. methylprednisolone (1–3 g) followed by oral glucocorticoids and oral cyclophosphamide using a regimen similar to that used for patients with ANCA-associated vasculitis (AAV; Chapter 9).

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

Unless kidney biopsy shows an active necrotizing crescentic glomerulonephritis (NCGN) or other reason that could support use of immunosuppression (i.e., minimal interstitial fibrosis or concomitant acute tubulointerstitial nephritis), these patients should be treated conservatively with referral for kidney transplant evaluation in due course.

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

8.2.2 C3 glomerulopathy

An optimal treatment strategy for C3G using currently available therapeutics has not been established. Expert opinion has encouraged the usual supportive measures (Chapter 1), as well as the use of immunosuppression in the setting of moderate-to-severe disease, defined as moderate-to-marked proliferation on biopsy and proteinuria (>2 g/d).[543] This opinion is based primarily on 4 retrospective cohorts and on an extrapolation of data from other non-related proliferative glomerulonephritides. Well-controlled data are unavailable.

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

Consider treating patients with C3G who have proteinuria >1 g/d and hematuria or have had declining kidney function for at least 6 months.

The reported effectiveness of immunosuppressive treatment in C3G has been variable. Medjeral-Thomas *et al.* reported 32 patients with C3G who received immunosuppressive treatment (glucocorticoids alone or combined with other drugs). Immunosuppression did not seem to reduce progression to kidney failure as compared to no treatment.[544] Similar results were obtained by Servais *et al.* in a cohort of 85 patients with C3G.[537]

More recent data showed encouraging results with MMF. Rabasco *et al.* reported a relative treatment advantage with MMF in a cohort of 60 patients with C3G.[545] In a mean follow-up of 47 months, the 22 patients who received MMF plus glucocorticoids showed lower rates of ESKD (0% vs. 16.6%) and doubling of SCr (0% vs. 39%) as compared to patients exposed to other immunosuppression. In addition, the rates of remission in the MMF group were significantly higher (19 of 22 patients vs. 9 of 18 patients; $P < 0.05$). The response to immunosuppression seen in this retrospective cohort provided the support for the current expert opinion on treatment approach for C3G.[543]

Similarly, Avasare *et al.* reported the kidney outcomes for 30 patients with C3G after MMF.[546] After a mean follow-up of 3 years, two-thirds had an either stabilized or reduced SCr level and reduced proteinuria. Ravindran *et al.* reported the kidney outcomes on a subcohort of 144 patients with C3G.[533] Of 24 patients given MMF (median follow-up 9.6 months), 3 had improved kidney outcome measures, and 4 had stable disease. Fifteen patients worsened. Finally, Bomback *et al.* reported the results of a subcohort of their 111 patients with C3G.[532] Of the 42 patients exposed to MMF, 19 achieved either a complete or partial remission.

The benefits of terminal complement blockade with the anti-C5 monoclonal antibody eculizumab remain unestablished. A trial involved 3 patients with DDD (including 1 kidney transplant recipient) and 3 patients with C3GN (including 2 kidney transplant recipients), all of whom had proteinuria >1 g/d and/or AKI at enrollment. Complement testing identified pathogenic variants in Complement Factor H (CFH) and CD46 in one patient each and C3 nephritic factors in 3 patients. After 12 months of twice-weekly eculizumab, 3 patients had a renal response (decrease in SCr levels and/or proteinuria), and 1 patient with stable laboratory parameters had histopathologic evidence of improvement. Eculizumab normalized soluble C5b-9 level in all patients with elevated levels of this biomarker of terminal pathway activity at baseline, suggesting it may represent a potentially useful marker of response.

In a recent retrospective study, 26 patients with C3G were treated with eculizumab for a median duration of 14 months. Of these, 6 patients (23%) had a global clinical response, 6 (23%) had a partial clinical response, and 14 (54%) had no response. As compared to those with partial response or no response, responders had lower eGFRs, more rapidly progressive disease, and more extracapillary proliferation on kidney biopsy samples. Age, extent of kidney fibrosis, frequency of NS, and features of alternative pathway activation did not differ. These results are consistent with the fact that eculizumab mainly targets glomerular inflammation and has no effect or limited effect on the complement dysregulation that governs C3G.[547]

In the absence of clear evidence, the use of eculizumab can be considered in patients with progressive disease who fail to respond to other therapies.

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

Research recommendations

- Further define the diagnostic criteria for C3G (utilizing biomarkers and histology characteristics) to allow for the separation of C3G from confounding conditions
- RCTs of immunosuppression in patients with fully characterized idiopathic ICGN and C3G without monoclonal gammopathy
- In-depth study of the role of complement in each of the diseases included in this chapter
- Optimize the evaluation of suspected paraprotein-associated C3G
- RCTs of clone-targeted chemotherapy versus immunosuppression for the treatment of paraprotein-associated glomerular disease

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

9.1 Diagnosis

Small-vessel vasculitis encompasses a group of diseases characterized by necrotizing inflammation of small vessels (i.e., arterioles, capillaries, and venules) and little or no deposition of immune complexes in the vessel wall (pauci-immune). Medium or large vessels may occasionally also be involved. Pauci-immune small-vessel vasculitides include granulomatosis with polyangiitis (GPA), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (eGPA).[548] The kidney lesion associated with these conditions is a pauci-immune focal and segmental NCGN. Active pauci-immune small-vessel vasculitis is typically associated with circulating ANCA, and GPA, microscopic polyangiitis, and eGPA were grouped under the term "ANCA-associated vasculitis" (AAV) in the 2012 Chapel Hill definitions of primary systemic vasculitis.[548] NCGN may occur with or without extrarenal manifestations of disease.

Patients with systemic vasculitis may present with extrarenal manifestations affecting one or several organ systems, with or without kidney involvement. Commonly involved systems are the upper and lower respiratory tract, skin, eyes, and the nervous system. Pulmonary hemorrhage affects 10% of patients with AAV and is associated with an increased risk of death.[549] The need to treat extrarenal vasculitis may influence treatment choices for kidney vasculitis.

The clinical manifestations associated with NCGN include microscopic hematuria with dysmorphic red blood cells and red cell casts, and proteinuria that is usually moderate (1–3 g/d). Pauci-immune NCGN is frequently associated with a rapidly declining GFR over days or weeks. A slowly progressive course has also been described when active vasculitic lesions may be hard to find on histology, and some patients with kidney vasculitis, especially if presenting with extrarenal disease, are diagnosed when the GFR is still normal.

AKI can present together with alveolar hemorrhage and is often referred to as a "pulmonary–renal syndrome." Although several diseases can manifest as a pulmonary–renal syndrome, simultaneous lung and kidney injury should raise concern for vasculitis. In this situation, serologic testing and interpretation are of great diagnostic importance. A positive test for anti-GBM antibodies suggests anti-GBM disease (formerly Goodpasture's syndrome) and a need for urgent plasma exchange without waiting for a positive diagnostic biopsy (Figure 71), whereas a positive test for ANCA is compatible with a diagnosis of AAV. Some patients are positive for both ANCA and anti-GBM antibodies. The diagnosis of AAV relies on the combination of clinical findings and results of imaging studies and laboratory tests (such as C-reactive protein level, complete blood count, kidney parameters, and urine sediment analysis). In addition, myeloperoxidase (MPO)- and proteinase 3 (PR3)-ANCA testing and, when feasible, biopsy of the kidney or other affected organs should be performed.

About 90% of patients with small-vessel vasculitis or NCGN have ANCA, directed primarily to the neutrophil granule proteins MPO or PR3.[550] The 2017 revised

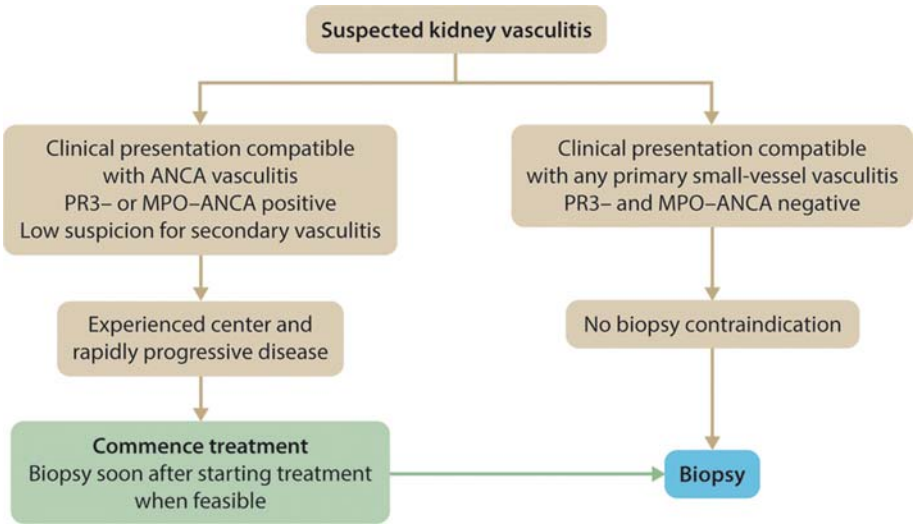

Figure 71 | Biopsy strategy in suspected kidney vasculitis. ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3.

international consensus on testing of ANCA in GPA and microscopic polyangiitis states that high-quality antigen-specific immunoassays are the preferred screening method for MPO- and PR3-ANCA.[551]

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

In AAV, a kidney biopsy is of importance for both the primary diagnosis and recurrent disease. This also relates to recurrent disease after kidney transplantation (Figure 72 and Figure 73). Biopsy remains the gold standard, and in GPA, the diagnostic yield of a kidney biopsy can be as high as 91.5%.[552] The kidney biopsy provides prognostic information through assessment of glomerular, tubulointerstitial, and vascular histopathology.[553] Therefore, a kidney biopsy should always be considered in patients suspected of active kidney involvement, but in the context of positive MPO– or PR3–ANCA serology and a clinical picture compatible with small-vessel vasculitis with low suspicion for secondary vasculitis, an immediate biopsy may not be necessary and should not delay the initiation of treatment.

The treatment recommendations in this guideline derive from studies of patients with AAV and/or NCGN. About 10% of patients presenting with signs and symptoms of microscopic polyangiitis, GPA, or NCGN are persistently ANCA-negative. These patients are treated similarly to patients who are ANCA-positive, although no study has focused specifically on the treatment of patients who are ANCA-negative. Considering patients who are ANCA-negative, it is important to realize that several nonvasculitic diseases may closely mimic small-vessel vasculitis. These include systemic rheumatic diseases, for example, SLE, infections, and malignancies (Figure 74[554]).

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

A center with experience in AAV management is equipped with adequate facilities for rapid diagnosis and management. For diagnosis, adequate serologic and histologic tests should be available. All treatment modalities should be available, including rituximab and plasma exchange. The center should have experience with these treatment modalities and their complications. Finally, a center should have access to an intensive care unit and an acute hemodialysis facility.

9.2 Prognosis

9.2.1 Survival

Factors influencing remission, relapse, kidney and overall survival in AAV have been described.[555–557] Important factors associated with survival are age and kidney function and/or kidney involvement at diagnosis. Without immunosuppressive therapy, AAV is associated with poor outcomes. Consequently, immunosuppressive treatment is pivotal to improve survival of individual patients with active systemic AAV, including older adults (>75 years of age) for whom immunosuppressive treatment has been associated with improved survival.[558]

Disease activity of ANCA-associated vasculitis represents signs or symptoms attributable to active disease in any organ system

Remission is defined as the absence of manifestations of vasculitis and GN. For GN, it is defined as a stable or improved glomerular filtration rate. While hematuria and proteinuria are present at times of active disease and can resolve completely, their persistence does not necessarily imply active disease

Relapse is defined as the occurrence of increased disease activity after a period of partial or complete remission. A return or increase of hematuria with proteinuria may indicate a kidney relapse. Relapse can be divided into major or minor, with major relapses defined as life- or organ-threatening. Examples of major relapse include diffuse alveolar hemorrhage, subglottic stenosis, GN or vasculitis threatening vision

Treatment-resistant disease is defined as the persistence of or appearance of kidney and/or systemic manifestations of vasculitis, while receiving treatment equal in intensity to initial immunosuppressive therapy

Figure 72 | Definition of disease activity, remission, relapse, and treatment-resistant disease in AAV. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; GN, glomerulonephritis.

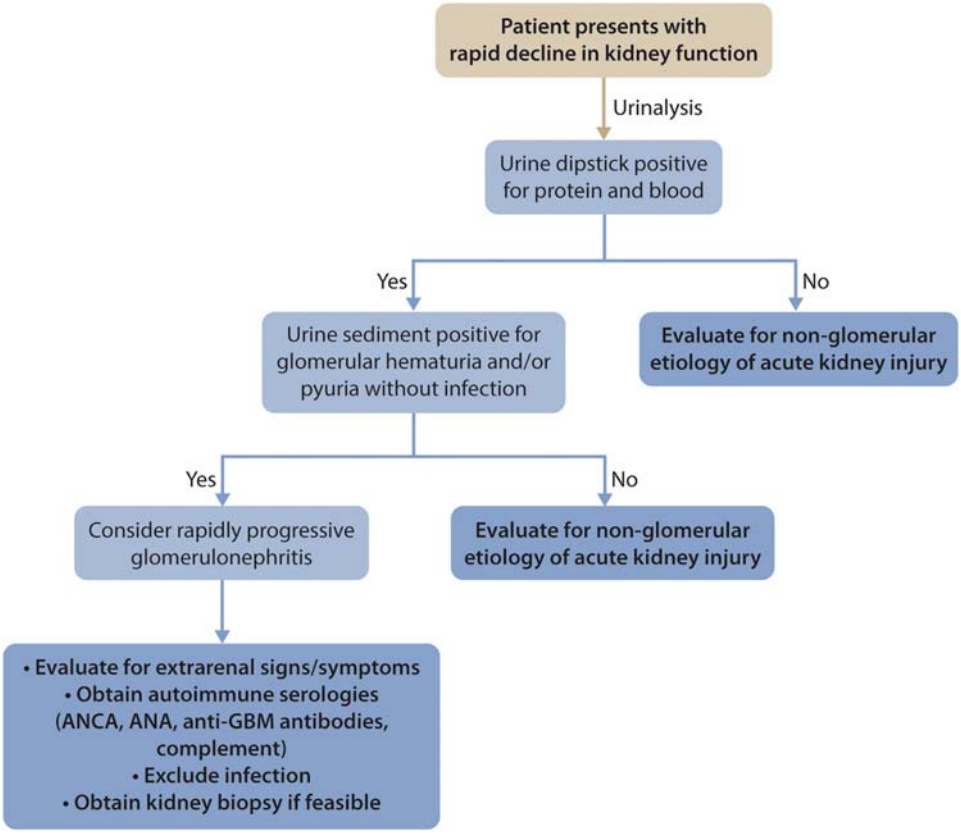

Figure 73 | Diagnostic strategy in rapidly progressive glomerulonephritis. ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane.

Organ system	Microscopic polyangiitis (%)	Granulomatosis with polyangiitis (GPA) (%)	Eosinophilic granulomatosis with polyangiitis (eGPA) (%)
Cutaneous	40	40	60
Kidney	90	80	45
Pulmonary	50	90	70
Ear, nose, and throat	35	90	50
Musculoskeletal	60	60	50
Neurologic	30	50	70
Gastrointestinal	50	50	50

Figure 74 | Frequency of organ involvement in AAV. Reproduced from *The New England Journal of Medicine*, Jennette JC, Falk RJ, Small-Vessel Vasculitis, Volume 337, Pages 1512–1523, Copyright © 1997 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[554] AAV, ANCA-associated vasculitis.

9.2.2 Kidney prognosis and treatment response

Kidney histology is predictive of long-term risk of kidney failure; prognostic histologic scores have been developed (e.g., by Berden *et al.*[553] and Brix *et al.*[559]; Figure 75[553]).

In validation studies of the histopathologic classification by Berden, >50% normal glomeruli in the focal class were associated with a favorable outcome, whereas >50% sclerotic glomeruli were associated with a poor outcome.[560] Also, in the kidney risk score developed by Brix *et al.*, a higher percentage of normal glomeruli (>25%) was associated with favorable kidney outcomes.[559] However, regarding the crescentic class (>50% cellular crescents) and mixed class, discrepancies in outcome have been reported.

Importantly, kidney recovery can be seen in the face of advanced kidney damage, and induction treatment should not be withheld on the basis of unfavorable histologic findings.

Assessing response of kidney vasculitis can be difficult in the presence of persistent hematuria and proteinuria, which are seen in 50% of patients. A stable or falling creatinine level is a guide; control of extrarenal disease and normalization of inflammatory markers (e.g., C-reactive protein) are also helpful but do not exclude ongoing kidney activity. Also, other causes

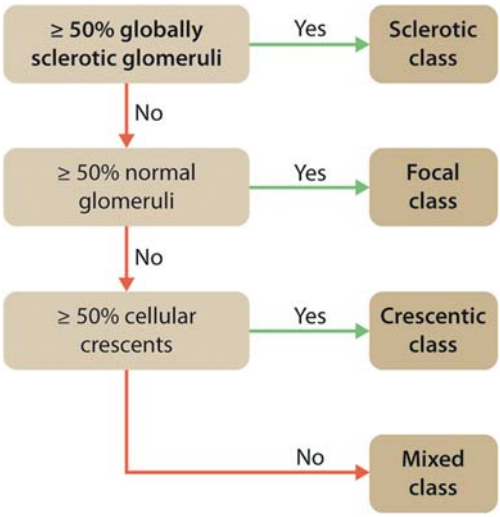

Figure 75 | Histopathologic classification of ANCA-associated glomerulonephritis. Biopsies should be scored for glomerular lesions in the following order: globally sclerotic glomeruli, normal glomeruli, and glomeruli with cellular crescents. Biopsies that do not fit into a category based upon a predominant glomerular phenotype will be included in the mixed category.[553]

of AKI, not related to AAV, should be considered; therefore, a kidney biopsy should be considered at presentation and during follow-up in case of poor treatment response (Figure 71).

Histologic activity is unlikely in the absence of hematuria. Persisting proteinuria can reflect disease activity or chronic parenchymal damage from preceding inflammation. Such chronic damage confers an adverse long-term kidney prognosis. The significance of persisting hematuria is unclear. In a retrospective study, no difference was found in the occurrence of ESKD between patients with and without persisting hematuria, but more patients with hematuria experienced a relapse of kidney disease.[561] More importantly, a return of hematuria after initial resolution may indicate kidney relapse.

9.2.3 Relapses

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

PR3- and MPO-AAV are characterized by the occurrence of relapses. Patients who are PR3-ANCA-positive experience more relapses than those who are MPO-ANCA positive.[562] The achievement of ANCA-negativity after induction treatment is associated with a lower risk of relapse.[563,564] Both a rise or persistence of ANCA are only modestly predictive of future disease relapse.[565] Also, a change in ANCA status from negative to positive has been associated with a higher incidence of relapse, and more frequent clinical assessments should be considered. However, regarding the relapsing phenotype of AAV, ANCA measurements should not guide treatment decisions in individual patients.

9.3 Treatment

Treatment of AAV is generally divided into an initial phase, commonly termed "induction," followed by a "maintenance" phase.

9.3.1 Induction

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

The best evidence is available for patients with new-onset AAV. In patients with severe (SCr >4 mg/dl [>354 μmol/l]) kidney disease, limited data for induction therapy with rituximab are available.

Key information

Balance of benefits and harms. Cyclophosphamide, in combination with glucocorticoids, has been used as induction therapy in several RCTs. In 2 RCTs, rituximab alone or in combination with 2 cyclophosphamide pulses was shown to be equally as effective as cyclophosphamide, with a similar rate of infectious complications (Supplementary Table S31[566–569]). However, *post hoc* analysis of the Rituximab in ANCA-Associated Vasculitis (RAVE) trial found a superior remission rate for the PR3-ANCA subgroup at 6 months treated with rituximab, with an odds ratio (OR) of 2.11 (95% CI: 1.04–4.30) in analyses adjusted for age, sex, and new-onset versus relapsing disease at baseline.[570] In patients with PR3-AAV and relapsing disease, more patients achieved remission at 6 and 12 months with rituximab, with an OR of 3.57 (95% CI: 1.43–8.93) at 6 months and an OR of 4.32 (95% CI: 1.53–12.15) at 12 months.[570] No association between treatment drug and remission was observed in patients with MPO-AAV (RAVE trial; Supplementary Table S32[567,569]).

Regarding the route of cyclophosphamide administration, oral and i.v. cyclophosphamide resulted in similar outcomes. With i.v. cyclophosphamide, a reduction of the total cyclophosphamide dosage is achieved compared to oral cyclophosphamide. In the Pulse Versus Continuous Cyclophosphamide for Induction of Remission in ANCA-Associated Vasculitides (CYCLOPS) study, this resulted in a lower rate of leukopenia (Supplementary Table S33[569,571]). Nevertheless, more patients tended to experience relapses after i.v. cyclophosphamide during long-term follow-up.

In patients with non-life-threatening disease, excluding those with rapidly progressive kidney disease, MMF might be an alternative to cyclophosphamide for the MPO-ANCA subgroup. MMF had a similar remission rate to cyclophosphamide for patients with both PR3- and MPO-ANCA (Supplementary Table S34[569,572–575]), but a much-increased relapse risk in those with PR3-ANCA in the Clinical Trial of Mycophenolate Versus Cyclophosphamide in ANCA Vasculitis (MYCYC) trial.[574]

Methotrexate, with glucocorticoids, has been used for AAV without kidney disease in the absence of irreversible tissue

damage but is associated with a higher relapse rate and higher late accrual of damage compared to cyclophosphamide (Supplementary Table S35[569,576,577]).

Glucocorticoids are major contributors to adverse events. Intravenous methylprednisolone (doses of 1–3 g) is widely used for more severe presentations but has not been tested in an RCT. Oral prednisolone/prednisone starting at 1.0 mg/kg/d has been used in most RCTs, again without direct RCT support. The rate of reduction of glucocorticoids varies between studies, with some aiming for withdrawal by month 5, while others continue 5–10 mg/d after 6 months.[578] The Plasma Exchange and Glucocorticoids for the Treatment of ANCA-Associated Vasculitis (PEXIVAS) trial demonstrated that for patients with GFR <50 ml/min per 1.73 m^2, a more rapid reduction was as effective but safer than a "standard" glucocorticoid tapering regimen.[579] In the RAVE trial, the rituximab group had a lower glucocorticoid exposure, and observational studies have supported early glucocorticoid removal when rituximab is used (Figure 79).

Complement-targeted therapy might be another strategy to reduce glucocorticoid exposure. An oral C5a receptor antagonist, avacopan, has been shown in the A Phase 3 Clinical Trial of CCX168 (Avacopan) in Patients with ANCA-Associated Vasculitis (ADVOCATE) phase 3 trial to be an effective alternative to glucocorticoid treatment in AAV with potential to improve kidney outcomes.[580]

Quality of evidence. The overall quality of evidence is moderate. The RCTs that compared rituximab with cyclophosphamide reported important outcomes of remission and relapse, and the quality of the evidence was rated as moderate for these outcomes because of serious imprecision (Supplementary Table S31[566–569]). The critical outcome, all-cause mortality, was included; however, there were no cases reported for kidney failure in the 2 trials. Only the RAVE trial was blinded for both participants and personnel and is regarded by the panel as the best evidence available. Effects on complete remission at 6 months, relapse rate, and serious adverse events are graded as moderate. In a secondary paper, complete remission in ANCA subgroups was reported; this is graded as low due to imprecision (only 1 study). There were no differences in kidney outcomes, and those with SCr >4 mg/dl (>354 μmol/l) were excluded. Finally, follow-up was short at 18 months.

The studies comparing continuous oral versus i.v. pulse cyclophosphamide were not blinded (participants and study personnel; Supplementary Table S36[569,581–583]). Overall, the quality of evidence on the important endpoints of complete remission and leukopenia is graded as moderate because of study limitations. Other outcomes exhibited low quality of evidence because of serious imprecision due to very few events (relapse, all-cause mortality). The Work Group considers the CYCLOPS study the best available study on this topic because of the addition of azathioprine to both treatment arms; consequently, it was evaluated separately (Supplementary Table S33[569,571]). The quality of the evidence was low for all critical outcomes, due to imprecision, as there was only 1 study.

The RCTs comparing MMF versus cyclophosphamide had few events for many critical and important outcomes (all-cause mortality, ESKD, malignancy, serious adverse events), and hence the quality of the evidence was low (Supplementary Table S34[569,572–575]). However, for the outcomes of infection and relapse, the quality of the evidence was rated as moderate due to study limitations from some studies (unclear blinding of outcome assessors). The MYCYC[574] and Tuin *et al.*[575] studies had an independent, blinded adjudication committee assess the primary endpoint of complete remission at 6 months, but the other studies had concerns regarding blinding and hence the quality of the evidence for this outcome has been rated as moderate.

Values and preferences. This Work Group places a relatively high value on achieving complete remission of disease, which was the primary outcome of most evaluated studies. However, extended immunosuppressive therapy should be associated with a minimum of adverse events. In subgroups of patients for whom fertility is a concern, and in relapsing patients, rituximab may be preferred.

Intravenously pulsed versus oral continuous cyclophosphamide results in a similar outcome. However, the cumulative dosage of cyclophosphamide is lower with i.v. cyclophosphamide. Patients treated with i.v. pulse cyclophosphamide may have an increased risk of relapse, as reported in the CYCLOPS study.

Glucocorticoids are disliked by patients and are major causes of adverse events. Use of rituximab or the combination of rituximab with cyclophosphamide may be associated with a lower glucocorticoid requirement, particularly desirable in those at higher risk of glucocorticoid toxicity.[567,584] C5a receptor inhibition with avacopan is a potential alternative to glucocorticoid treatment, which in addition to its efficacy in controlling disease, has been shown to improve patient quality of life when compared to prednisone in AAV.[580]

Resource use and costs. Rituximab is typically more expensive than cyclophosphamide, although secondary costs for cyclophosphamide (infusions and monitoring) and reduced cost of generic rituximab can make the total costs similar. Ease of administration, simpler monitoring, glucocorticoid sparing, and reduced early toxicity associated with rituximab compared to cyclophosphamide are additional factors that influence cost and resource use.

Regarding i.v. versus oral cyclophosphamide, with intravenous cyclophosphamide, a reduction of the total cyclophosphamide dosage is achieved compared to oral cyclophosphamide. However, oral cyclophosphamide is less

expensive. In patients treated with either i.v. or oral cyclophosphamide, frequent monitoring for treatment toxicity, in particular leukopenia, is important.

Considerations for implementation. The choice of treatment regimen depends on patient comorbidity, age, and preference, as well as local availability and cost.

Rationale

Cyclophosphamide, in combination with glucocorticoids, has been applied as induction therapy in multiple RCTs. In 2 RCTs, rituximab has been shown to be equally effective in inducing remission to cyclophosphamide.[566,567] Rituximab compared to cyclophosphamide probably has little or no difference in relapse rate at 1–6 months (RR: 0.63; 95% CI: 0.35–1.14). Rituximab and cyclophosphamide have similar rates of severe adverse events, including infections. However, risks of long-term comorbidities, such as malignancy, HBV and HCV reactivation, and secondary immunodeficiency, appear to differ between rituximab and cyclophosphamide and may influence choice.[585,586]

In the RAVE study, patients with relapsing disease more often achieved remission at 6 and 12 months in the rituximab group compared to the cyclophosphamide–azathioprine group.[570,587] Analysis of the data according to ANCA status showed that patients with PR3-AAV were significantly more often in complete remission at 6 months than patients treated with cyclophosphamide–azathioprine.[570]

An important consideration when interpreting the RAVE trial is that it excluded patients with severe kidney disease (SCr >4 mg/dl [>354 μmol/l]). A recent single-center retrospective study found that rituximab was comparable to cyclophosphamide in remission induction at 6 months.[588] However, no prospective data on the efficacy of remission induction of rituximab in severe kidney disease are available. In contrast, the Rituximab versus Cyclophosphamide in ANCA-Associated Vasculitis (RITUXVAS) study included such patients and showed that rituximab combined with 2 cyclophosphamide pulses and glucocorticoids was comparable to cyclophosphamide for remission induction and number of adverse events.[566]

Regarding the administration route of cyclophosphamide, 4 RCTs compared induction therapy with i.v. pulse versus continuous oral cyclophosphamide.[569,571,581–583] Intravenous cyclophosphamide and oral cyclophosphamide resulted in a similar rate of complete remission, but less leukopenia was seen in patients given i.v. cyclophosphamide. In the CYCLOPS study, a higher rate of relapse was reported with i.v. pulse cyclophosphamide.[571] This reflects the 50% reduction in cyclophosphamide exposure seen with i.v. regimens; shorter-course oral cyclophosphamide regimens are also associated with higher relapse risk.

In patients with non-severe disease, MMF and methotrexate have been compared to cyclophosphamide. Regarding MMF versus cyclophosphamide, no significant differences were found, but cyclophosphamide tended to show better efficacy and fewer relapses.[569,572–575] Compared to cyclophosphamide, methotrexate was associated with a higher relapse rate (RR: 1.50; 95% CI: 1.03–2.17).[569,576,577,589] Effects on other critical and important outcomes are unclear, as they were not reported or occurred infrequently.

Glucocorticoids are part of induction therapy. In the PEXIVAS study, all patients received oral prednisone/prednisolone at 1 mg/kg/d for the first week, followed by rapid or slow tapering schedules. This led to about a 50% difference in oral glucocorticoid exposure during the first 6 months The lower-dose regimen was noninferior for efficacy and is safer, and therefore is preferred.[579,590] All patients in the PEXIVAS trial received an initial dose of i.v. methylprednisolone of 1–3 g; the optimal dose is yet to be determined.

Cyclophosphamide dose should be reduced for kidney impairment and age, as these patients are at increased risk for infection (Figure 80).

Low-dose sulfamethoxazole/trimethoprim (TMP-SMX), or alternative, is advised for pneumocystis pneumonia prophylaxis for the duration of the cyclophosphamide course or for 6 months following rituximab induction. Longer-term use may be considered in those receiving repeated rituximab infusions, for those with structural lung disease, or those requiring ongoing immunosuppressive or glucocorticoid therapy.

In a retrospective study, the IgG level before rituximab correlated with hypogammaglobulinemia post-rituximab.[591] Therefore, IgG levels should be measured at baseline and every 6 months for patients treated with rituximab. A low level at baseline (defined as IgG <3 g/l; Figure 80) may predict a greater risk of secondary immunodeficiency with rituximab.[591]

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

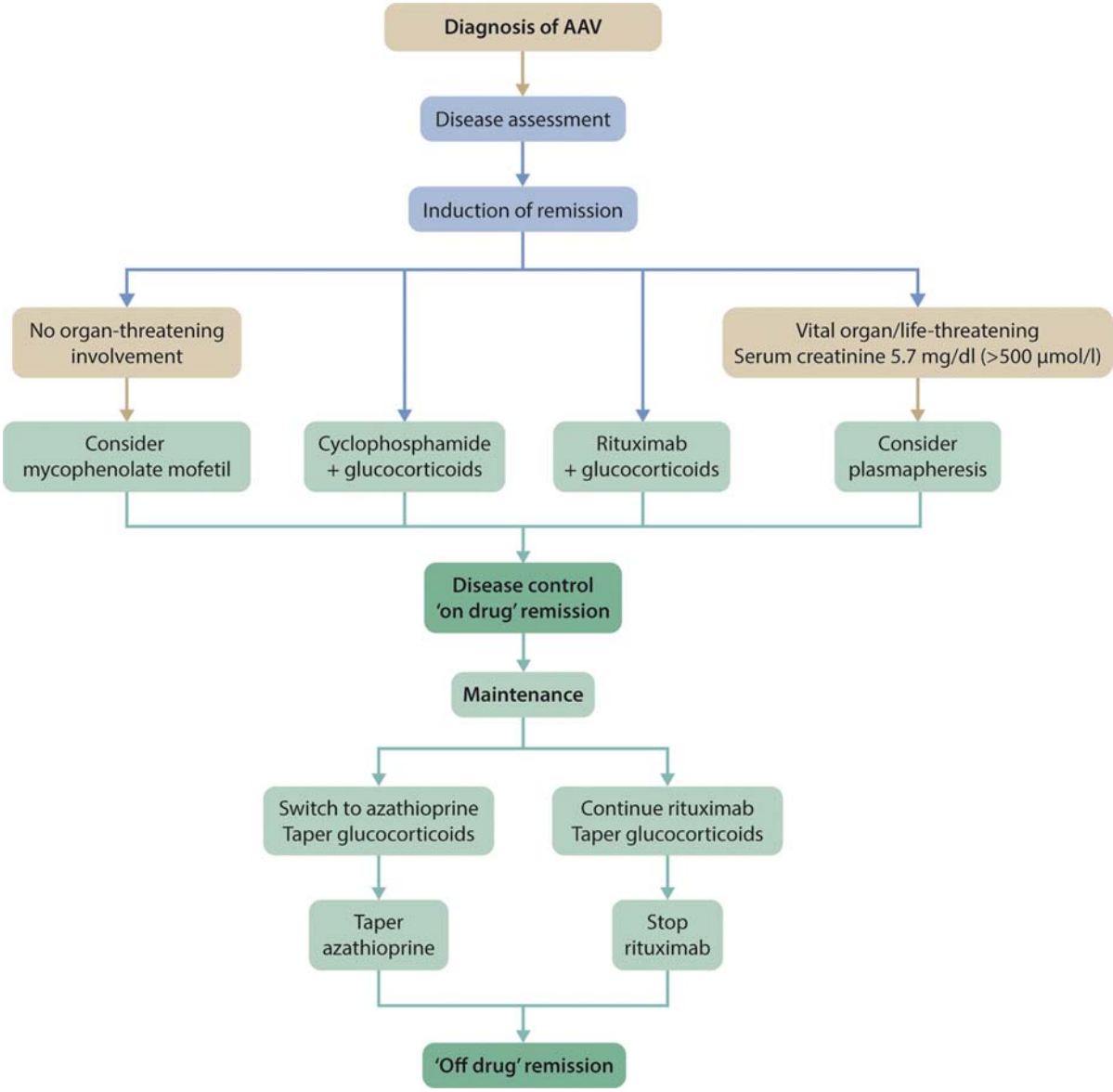

Figure 76 | Recommended treatment regimen for AAV. AAV, ANCA-associated vasculitis.

Practice Point 9.3.1.2: In patients presenting with markedly reduced or rapidly declining GFR (SCr >4 mg/dl [>354 µmol/l]), there are limited data to support rituximab and glucocorticoids. Cyclophosphamide and glucocorticoids are preferred for induction therapy. The combination of rituximab and cyclophosphamide can also be considered in this setting.

No patients with a SCr >4 mg/dl (>354 µmol/l) were included in the RAVE trial, and therefore in severe kidney disease, limited data for induction therapy with rituximab in combination with glucocorticoids are available, and cyclophosphamide is still the preferred agent for induction of remission. In severe kidney disease, combining 4 weekly infusions of rituximab and 2 i.v. cyclophosphamide pulses with glucocorticoids might be an alternative to i.v. cyclophosphamide for 3–6 months. In the RITUXVAS trial, this regimen resulted in a similar rate of remission and adverse events as cyclophosphamide.[566]

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

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 77 | 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.

Intravenous cyclophosphamide	Oral cyclophosphamide
• Patients who already have a moderate cumulative dose of cyclophosphamide • Patients with lower white blood cell counts • Ready access to an infusion center • Adherence may be an issue	• Cost is an important factor • Access to an infusion center difficult • Adherence is not an issue

Figure 78 | Considerations for the route of administration of cyclophosphamide for AAV. AAV, ANCA-associated vasculitis.

Practice Point 9.3.1.4: Considerations for choosing the route of administration of cyclophosphamide are given in Figure 78.

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

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

Following cyclophosphamide induction, oral prednisolone should be reduced to a dose of 5 mg/d by 6 months. Following rituximab induction, prednisolone can be withdrawn by 6 months.

	'Reduced-corticosteroid dose' in PEXIVAS trial		
Week	<50 kg	50–75 kg	>75 kg
1	50	60	75
2	25	30	40
3–4	20	25	30
5–6	15	20	25
7–8	12.5	15	20
9–10	10	12.5	15
11–12	7.5	10	12.5
13–14	6	7.5	10
15–16	5	5	7.5
17–18	5	5	7.5
19–20	5	5	5
21–22	5	5	5
23–52	5	5	5
>52	Investigators' local practice		

Figure 79 | Prednisolone tapering regimen for AAV. AAV, ANCA-associated vasculitis.

The dose of oral prednisolone is 1 mg/kg/d for the first week, and then a programmed reduction is followed (Figure 79). Intravenous methylprednisolone is widely used initially for patients with more severe presentations, at a dose of 1–3 g in total. This approach is not evidence-based and is likely to contribute to glucocorticoid toxicity.

Practice Point 9.3.1.7: Recommendations for immunosuppressive dosing are given in Figure 80.

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

The Methylprednisolone Versus Plasma Exchange for Renal Vasculitis (MEPEX) trial showed improved kidney outcomes in patients with severe kidney disease (SCr >5.7 mg/dl [>500 μmol/l]) who were treated with plasma exchange.[592] Also, a meta-analysis that looked at the addition of plasma exchange showed a reduction in the occurrence of ESKD at 3 and 12 months after diagnosis (Supplementary Table S37[566,569,592–598]). The PEXIVAS trial failed to demonstrate that plasma exchange delayed the time to ESKD or death for patients with AAV presenting with GFR <50 ml/min per 1.73 m^2 or alveolar hemorrhage over a median follow-up of 2.9 years.[579] *Post hoc* studies of the PEXIVAS dataset and meta-analysis may generate results relevant to future recommendations. However, no meta-analysis on the effect of plasma exchange in patients with severe kidney disease (SCr >5.7 mg/dl [>500 μmol/l]), including the PEXIVAS study, is yet available. For now, the routine use of plasma exchange is not recommended for

Oral cyclophosphamide	Intravenous cyclophosphamide	Rituximab	Rituximab and i.v. cyclophosphamide	MMF
2 mg/kg/d for 3 months, continue for ongoing activity to a maximum of 6 months	15 mg/kg at weeks 0, 2, 4, 7, 10, 13 (16, 19, 21, 24 if required)	375 mg/m^2/week × 4 weeks OR 1 g at weeks 0 and 2	Rituximab 375 mg/m^2/week × 4 weeks, with i.v. cyclophosphamide 15 mg/kg at weeks 0 and 2 OR Rituximab 1 g at 0 and 2 weeks with cyclophosphamide 500 mg/2 weeks × 6	2000 mg/d (divided doses), may be increased to 3000 mg/d for poor treatment response
Reduction for age: • 60 yr, 1.5 mg/kg/d • 70 yr, 1.0 mg/kg/d Reduce by 0.5 mg/kg/day for GFR <30 ml/min/1.73 m^2	Reduction for age: • 60 yr 12.5 mg/kg • 70 yr, 10 mg/kg Reduce by 2.5 mg/kg for GFR <30 ml/min/1.73 m^2			

Figure 80 | Immunosuppressive drug dosing for AAV. AAV, ANCA-associated vasculitis; GFR, glomerular filtration rate; i.v., intravenous; MMF, mycophenolate mofetil.

patients presenting with a GFR <50 ml/min per 1.73 m^2, but plasma exchange can be considered in those with more severe presentations (SCr >5.7 mg/dl [>500 μmol/l], especially if oliguric) or in those with alveolar hemorrhage and hypoxemia in whom early mortality is high.

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

In a single-center study, 5% of patients who were ANCA-positive were also positive for anti-GBM antibodies, and 32% of patients who were anti-GBM-positive patients had detectable ANCA.[599] Thus, double-positivity for both ANCA and anti-GBM antibodies is common. These patients behave more like those with anti-GBM disease than like those with AAV, supporting the initiation of plasma exchange (Figure 81). However, unlike those with pure anti-GBM disease, these patients have a tendency to relapse and should receive maintenance therapy.

9.3.2 Maintenance therapy

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

This recommendation places a higher value on prevention of relapses and a relatively lower value on adverse events related to immunosuppressive drugs.

Key information

Balance of benefits and harms. To date, most maintenance studies have been done after induction of remission with

ANCA vasculitis with severe kidney disease	Vasculitis with diffuse pulmonary hemorrhage	Vasculitis in association with anti-GBM antibodies
Seven treatments over a maximum of 14 days, 60 ml/kg volume replacement, albumin substitution	Daily until bleeding stops, replace albumin with fresh, frozen plasma	Daily for 14 days or until anti-GBM antibodies are undetectable

Figure 81 | Plasma exchange dosing and frequency for AAV. If a patient is at risk of bleeding, volume replacement should be with fresh, frozen plasma. ANCA, antineutrophil cytoplasmic antibody.

cyclophosphamide plus glucocorticoids. Maintenance regimens have evolved over time, and several immunosuppressive medications have been evaluated. Azathioprine, given after ≥3 months of cyclophosphamide induction, was found to be equally effective for relapse prevention with less leukopenia than extending cyclophosphamide for 12 months (Supplementary Table S38[569,600]). Compared to azathioprine, MMF maintenance was less effective in relapse prevention and did not have a superior infection profile (Supplementary Table S39[569,601]). In contrast, methotrexate and azathioprine were found to be equally effective in relapse prevention with similar toxicity and long-term outcomes (Supplementary Table S40[569,602]). Overall, azathioprine has been the standard immunosuppressive used for maintenance of remission in AAV over the past several years.

The duration of azathioprine maintenance has been examined. Compared to tapering maintenance azathioprine after 12 months of treatment, tapering after 4 years of therapy decreased relapse rate and the incidence of kidney failure.[577,603] The benefits of longer-duration azathioprine maintenance therapy did not differ between PR3- or MPO-ANCA, or in patients who remained ANCA-positive or became ANCA-negative after 12 months. In these studies, there were no differences in all-cause mortality, infection, or serious adverse events between treatment arms, but the quality of the evidence was very low (Supplementary Table S41[569,577,603]).

After rituximab was found to be effective for induction of remission in AAV, it was tested as a maintenance medication. In new-onset disease, after cyclophosphamide induction, maintenance with rituximab decreased major, but not minor, relapses compared to azathioprine (MAINtenance of Remission Using RITuximab in Systemic ANCA-associated Vasculitis [MAINRITSAN]; Supplementary Table S42[569,604]). However, after rituximab induction for relapsing AAV, rituximab maintenance decreased major and minor disease relapses compared to azathioprine (Rituximab versus azathioprine as therapy for maintenance of remission for anti-neutrophil cytoplasm antibody-associated vasculitis [RITAZAREM]).[605] No difference in infection rate was found between azathioprine and rituximab (Supplementary Table S43[569,606]).

As a maintenance drug, rituximab can be dosed on a fixed schedule or upon reappearance of CD19+ B cells and/or ANCA. Although both regimens prevented relapse equally well, dosing based on reappearance of B cells required fewer rituximab infusions. No differences in adverse events were reported (MAINRITSAN2; Supplementary Table S42[569,604]).

Addition of TMP-SMX (160/800 mg) compared with placebo in maintenance therapy may have little or no difference on complete remission at 1 or 2 years (Supplementary Table S44[569,607,608]).

Quality of evidence. The overall quality of the evidence was rated as low due to the lower quality of the evidence for rituximab as maintenance therapy, which is based on fewer RCTs compared with that for azathioprine. All comparisons, apart from azathioprine duration, included data from single studies with relatively low numbers of patients and limited follow-up, resulting in wide CIs and serious imprecision, in particular for the critical outcomes of all-cause mortality and kidney failure. The quality of the evidence for azathioprine as maintenance therapy was moderate for relapse in RCTs that compared azathioprine with cyclophosphamide (Supplementary Table S38[569,600]), methotrexate (Supplementary Table S40[569,602]), MMF (Supplementary Table S39[569,601]), and RCTs that compared extended with standard azathioprine therapy (Supplementary Table S41[569,577,603]).The quality of the evidence was downgraded because of imprecision, as there was only 1 study for each comparison. However, the comparison of MMF with azathioprine exhibited low quality of evidence for infection because of very wide CIs that indicated less certainty in the effect.

There is currently limited evidence available for maintenance therapy after induction therapy with rituximab and glucocorticoids. There was low-quality evidence from RCTs that compared rituximab with azathioprine for major relapse because of a lack of blinding of outcome assessors, and serious imprecision, as there are 2 RCTs that examined this comparison (Supplementary Table S42[569,604] and Supplementary Table S43[569,606]). The RCT, which compared tailored rituximab therapy based on the reappearance of $CD19^+$ B cells and ANCA-levels, exhibited low quality of evidence for major relapse and adverse events, including all-cause mortality, infection, and malignancy (Supplementary Table S42[569,604]). The quality of the evidence was downgraded from this RCT because of very serious imprecision, as there was only 1 study, and outcomes exhibited very wide CIs, indicating less certainty regarding the treatment effect.

Data are also limited regarding the continuation of glucocorticoids during maintenance. In most RCTs, glucocorticoids were withdrawn within or shortly after the induction window. However, in the Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis (REMAIN) trial, low-dose glucocorticoids were combined with azathioprine maintenance.[577] In a meta-analysis of observational studies and RCTs, a longer course of glucocorticoids in AAV was associated with fewer relapses.[609]

Values and preferences. This Work Group places a relatively high value on the prevention of relapses of disease, which are associated with morbidity, and advises that maintenance therapy be given to all patients after induction of remission. However, extended immunosuppressive therapy should be associated with a minimum of adverse events, and relapse risk may influence maintenance initiation, choice of medication, and duration.

Several AAV relapse risk factors have been identified, including a prior history of relapse and having a PR3-ANCA rather than an MPO-ANCA.[562,610] In the RAVE study, patients did not receive maintenance therapy after induction with rituximab, and a high relapse rate was seen in both the rituximab and cyclophosphamide–azathioprine groups, but glucocorticoids were withdrawn before 6 months.[570] Current

practice, and therefore expert opinion, varies on whether maintenance therapy can be avoided in patients with MPO-AAV after induction of remission with rituximab. It also varies on the use and duration of glucocorticoids in maintenance regimens. In the REMAIN trial, which studied patients with a history of renal vasculitis, no difference in relapse risk with ANCA serotype was seen. If maintenance therapy is not used, such patients should be considered at higher risk of relapse, and monitored accordingly.[577]

In the subgroup of patients with MPO-AAV presenting with kidney failure without extrarenal disease manifestations, the risk of relapses is low, so the risk of adverse infectious events from immunosuppression might outweigh the benefits of relapse prevention.[611] Therefore, in patients with MPO-ANCA who are treated with dialysis and have no extrarenal manifestations of disease, despite thorough review including chest computed tomography (CT) scanning, the risks of maintenance therapy could outweigh the benefit. Further, when a complete clinical remission is achieved in the subgroup of patients with MPO-ANCA disease and abnormal kidney function, these patients may not need maintenance immunosuppression, but instead could be closely monitored with regular ANCA serologies.

In summary, the best evidence for effective relapse prevention is available for rituximab maintenance or prolonged azathioprine in combination with low-dose glucocorticoids. However, there may be an advantage in favor of rituximab. In the MAINRITSAN study, health-related quality of life was compared between patients treated with rituximab and azathioprine. Mean improvements of Health Assessment Questionnaire (HAQ) scores from baseline to 24 months were significantly better for the rituximab group as compared to the azathioprine group.[612]

Therefore, this Work Group prefers rituximab for maintenance therapy, particularly for patients with known relapsing disease, PR3-AAV, and azathioprine allergy, and after rituximab induction (RITAZAREM). However, some caution should be exercised, as there is a paucity of data on the long-term effects of rituximab maintenance treatment. Although significant falls in IgG were not seen after rituximab in the RCTs, longer-term observational data suggest an increasing risk of secondary immunodeficiency in this population.

Resource use and costs. Rituximab is relatively expensive and is not available worldwide; however, biosimilars will potentially generate global access to this drug. Additionally, prevention of relapses reduces the costs of hospitalization, and induction therapy with its frequent hospital visits. Rituximab also permits the withdrawal of glucocorticoids.

Rationale

This Work Group advises maintenance therapy be given to all patients with AAV after induction of remission with either cyclophosphamide or rituximab. The aim of this maintenance therapy is to prevent relapse of disease after induction of remission. Remission is defined as the absence of manifestations of vasculitis. To score the absence of clinical features of active disease, a validated scoring system such as the Birmingham Vasculitis Activity Score (BVAS) can be used.[613] During follow-up, a structured clinical assessment in combination with inflammatory markers and kidney function should be conducted in all patients.

Rituximab maintenance after cyclophosphamide induction has been shown to be superior to azathioprine for preventing relapses in 1 RCT. It probably decreases major relapses; no difference in adverse events was reported (MAINRITSAN).[604] Azathioprine maintenance up to 18 months after induction of remission with cyclophosphamide has been shown to be equally effective as continuing cyclophosphamide (Cyclophosphamide versus Azathioprine for Early Remission Phase of Vasculitis [CYCAZAREM]) for 1 year and then switching to azathioprine.[600] MMF has not been shown to be more effective than azathioprine.[601]

The evidence for the minimum duration of maintenance is weak; longer maintenance reduces relapse rate but could be associated with more adverse events. Azathioprine prolongation (REMAIN trial; Extended versus standard azathioprine maintenance therapy in newly diagnosed proteinase 3 anti-neutrophil cytoplasmic antibody-associated vasculitis patients who remain cytoplasmic anti-neutrophil cytoplasmic antibody-positive after induction of remission: a randomized clinical trial [AZA-ANCA]) limits relapse rate after 4 versus 2 years.[577,603]

As the aim of maintenance therapy is the prevention of relapses, the risk of relapse should be considered for both the choice of the immunosuppressive agent and the duration of maintenance therapy.

Reported risk factors for relapse are PR3-ANCA versus MPO-ANCA, and CV or lung involvement.[562,610] Persistent ANCA-positivity after induction of remission has also been reported.[577,614] The RCT that tested extended azathioprine for 4 years versus azathioprine for 2 years in patients with PR3-AAV who remained ANCA-positive showed a nonsignificant difference (at 4 years, 48% standard vs. 24% extended relapses) but was underpowered.[603]

Comparison with other guidelines. Considering other guidelines, the European League Against Rheumatism/ European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) prefers azathioprine and glucocorticoids over rituximab for remission maintenance.[578] According to the evidence reviewed by the ERT, rituximab was found to be superior to azathioprine, due to lower rates of major relapse. Therefore, this panel prefers rituximab over azathioprine for maintenance therapy in AAV. The EULAR/ERA-EDTA guideline advises maintenance therapy for at least 24 months following induction. This panel has not advised a fixed duration of maintenance but an interval of 18 months to 4 years following induction of remission, tailored according to an individual's risk of relapse and the drug used for maintenance. Additionally, in MPO-AAV after induction of remission with rituximab, maintenance therapy may sometimes be avoided if the patient can be monitored intensively. However, this point is based on expert opinion; little evidence is available, and no consensus was reached, even among experts.

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

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

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

The preference of this Work Group, based upon observational reports and unpublished data from the RITAZAREM study, is for rituximab maintenance. The RITAZAREM study showed that also after rituximab induction for relapsing AAV, rituximab maintenance decreased major and minor disease relapses compared to azathioprine maintenance (RITAZAREM).[615] However, azathioprine combined with glucocorticoids can be considered as an alternative.

In the RAVE study, no maintenance was given following induction of remission in AAV. The relapse rate was lower in MPO-AAV compared to PR3-AAV. This finding led some experts to opine that patients with MPO-AAV in complete clinical remission after induction therapy with rituximab with a low relapse risk may not need maintenance therapy, but instead could be closely monitored with regular ANCA serologies and home urine checks. Consensus regarding no maintenance was, however, not reached within the KDIGO Work Group.

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

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

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

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

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

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 83 | 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.

Rituximab	Azathioprine	MMF
Scheduled dosing protocol: **1.** 500 mg × 2 at complete remission, and 500 mg at months 6, 12 and 18 thereafter (MAINRITSAN scheme) OR **2.** 1000 mg infusion after induction of remission, and at months 4, 8, 12, and 16 after the first infusion (RITAZAREM* scheme)	1.5–2 mg/kg/d at complete remission until one yr after diagnosis then decrease by 25 mg every 3 mo	2000 mg/d (divided doses) at complete remission for 2 yrs
	Extend azathioprine at complete remission until 4 yrs after diagnosis; start at 1.5–2 mg/kg/d for 18–24 mo, then decrease to a dose of 1 mg/kg/d until 4 yrs after diagnosis, then taper by 25 mg every 3 mo. Glucocorticoids should also be continued at 5–7.5 mg/d for 2 yrs and then slowly reduced by 1 mg every 2 mo	

Figure 84 | Immunosuppressive dosing and duration of AAV maintenance therapy. *RITAZAREM was in relapsing AAV. MAINRITSAN, MAINtenance of Remission Using RITuximab in Systemic ANCA-associated Vasculitis; MMF, mycophenolate mofetil; RITAZAREM, Rituximab versus azathioprine as therapy for maintenance of remission for antineutrophil cytoplasm antibody-associated vasculitis (AAV).

Practice Point 9.3.2.8: Recommendations for dosing and duration of maintenance therapy are given in Figure 84.

9.3.3 Relapsing disease

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

Relapses respond to immunosuppression with a similar response rate as the initial presentation, and severe relapses should be treated by reintroducing induction therapy. When deciding whether to use cyclophosphamide again, the cumulative dose of cyclophosphamide already given should be taken into account. Cumulative dosages above 36 g have been associated with the occurrence of malignancies.[616] In a *post hoc* analysis of the RAVE trial, higher remission rates were seen in relapsing patients treated with rituximab compared to cyclophosphamide, especially for patients with PR3-AAV.[570] Rituximab is therefore preferred for relapsing AAV. The RITAZAREM trial studied the effect of rituximab induction in 187 patients with relapsing GPA/microscopic polyangiitis—there was a high rate of remission, >90% by 4 months.[605]

In patients with non-severe relapses, immunosuppression should be increased while avoiding cyclophosphamide. Apart from MMF, which has been tested in combination with glucocorticoids in RCTs for induction therapy in relapsing patients, there is no strong evidence to support other regimens.[574,575] However, if non-severe relapses are treated with MMF, there is an increased rate of future relapse, and glucocorticoid exposure will be increased accordingly; therefore, in the current guideline, rituximab is preferred.

9.4 Special situations

9.4.1 Refractory disease

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

The causes of refractory disease include drug intolerance, nonadherence, concomitant morbidities complicating treatment, a secondary drive for vasculitis such as malignancy, drugs or infection, and true treatment failure. Progression of kidney failure can reflect chronic damage and does not necessarily imply active disease; a kidney biopsy can be considered to assess ongoing kidney disease activity. Several small series suggest a role for rituximab in resistant ANCA vasculitis.

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

In the absence of hypoxemia, diffuse alveolar hemorrhage has a benign prognosis and responds as extrapulmonary disease is controlled. Alveolar hemorrhage with hypoxemia has a high early mortality risk, and plasma exchange should be considered in addition to glucocorticoids with either cyclophosphamide or rituximab. Patients in the intensive care unit, such as those receiving assisted ventilation, have a particularly high risk of infection and death. Leukopenia should be avoided, with glucocorticoid use minimized. Plasma exchange and high-dose i.v. immunoglobulins can be considered in this setting.

9.4.2 Transplantation

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

AAV can recur after kidney transplantation. The frequency of disease recurrence in AAV has been assessed in several retrospective studies and is about 0.02–0.03 per patient-year.[617,618] This relapse rate was not influenced by remission duration or ANCA status before transplantation.[617]

Research recommendations

- RCTs to incorporate patient-reported outcomes, to assess long-term outcomes, to define the use of rituximab in severe AAV, and to assess therapies in ethnically diverse populations
- Biomarker studies to identify early markers of disease relapse, markers to guide the choice of therapy, including plasma exchange, markers to predict optimal dosing and dosing interval for rituximab, and surrogate markers of response

Chapter 10: Lupus nephritis

The reported lifetime incidence of lupus nephritis (LN) in patients with SLE is 20%–60%, depending on the demographics of the population studied.[619–622] Kidney involvement in SLE has been associated with higher mortality, especially for patients progressing to kidney failure.[623–625] The ultimate goal of treating LN is to preserve kidney function and reduce the morbidity and mortality associated with CKD and kidney failure, while minimizing medication-associated toxicities.

This chapter makes management recommendations for adults who have SLE with kidney involvement. The focus is on immune complex–mediated GN in the setting of SLE, commonly referred to as LN, but other types of kidney injury in patients with SLE are also discussed. Information for pediatric populations is limited, but an approach to the management of children with LN is outlined in Practice Point 10.3.3.

10.1 Diagnosis

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

Patients with SLE should be actively and regularly monitored, as the clinical presentation of kidney involvement can remain silent or asymptomatic for a significant period of time. As the incidence of LN varies by race/ethnicity and age, a high index of suspicion should be maintained for patients of Asian, African/Caribbean, and Hispanic descent.[619–622] There is a higher incidence of LN and more-severe disease in childhood-onset SLE compared to adult-onset SLE.[626] Although a proteinuria level of 500 mg/d is suggested as a threshold for further investigations, taking into consideration physiological causes of low-level proteinuria and to avoid unnecessary kidney biopsies, it is important to note that the severity of proteinuria varies considerably in severe active nephritis and can appear relatively "insignificant" at times. A holistic assessment including clinical, urinary, and laboratory parameters, and also repeated investigations to note the progression of abnormal findings over time, are important in informing clinical management decisions. Because clinical findings do not always correlate with the extent or severity of kidney involvement,[627,628] a kidney biopsy is useful to confirm the diagnosis and for the assessment of activity and chronicity features that inform treatment decisions and prognosis.[627–637] Kidney biopsies should be read by an experienced kidney pathologist and classified according to the ISN/RPS scheme.[638–640] Electron microscopy, where available, is helpful in ascertaining ultrastructural details of histopathology such as the extent and severity of podocyte injury and the loci of immune deposits. Clinicians should pay attention to the detailed description of both active and chronic histopathologic features affecting different elements of the kidney parenchyma, especially regarding potentially reversible active lesions versus chronic damage not reversible by immunosuppressive medications (Figure 86).

10.2 Treatment

10.2.1 General management of patients with lupus nephritis

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

This recommendation places a relatively higher value on the various benefits associated with hydroxychloroquine use reported in observational studies (including lower rates of disease flares, progressive kidney damage, and vascular complications) and on the generally favorable safety profile of hydroxychloroquine treatment. It places a relatively lower value on the lack of large-scale prospective RCT data.

Key information

Balance of benefits and harms. The reported benefits of antimalarial use in SLE include lower flare (including kidney) rates,[641,642] higher response rates to therapy,[641–644] lower incidence of CV and thrombotic events in patients with antiphospholipid antibodies,[645–648] less organ damage,[649–654] improved lipid profile,[655,656] and better preservation of bone mass.[657]

Hydroxychloroquine use in pregnancy has been associated with a decrease in lupus activity and a satisfactory safety profile in both the mother and the fetus.[658–660] Significant side effects are uncommon but include skin rash, increase in skin pigmentation, muscle weakness, and visual change or loss of vision. Hydroxychloroquine may accumulate in lysosomes and cause a form of phospholipidosis with accumulation of multilamellar zebra bodies in podocytes that can mimic the appearance of Fabry disease.[661,662]

Quality of evidence. Moderate-quality data support the benefit of hydroxychloroquine use in patients with SLE, but in LN, the available evidence is predominantly from observational studies and *post hoc* analyses. In a 24-week RCT that included 47 patients, the Canadian Hydroxychloroquine Study Group reported a higher incidence of SLE flares in patients who stopped hydroxychloroquine compared to those who continued treatment, with a hazard ratio (HR) of 2.50 (95%

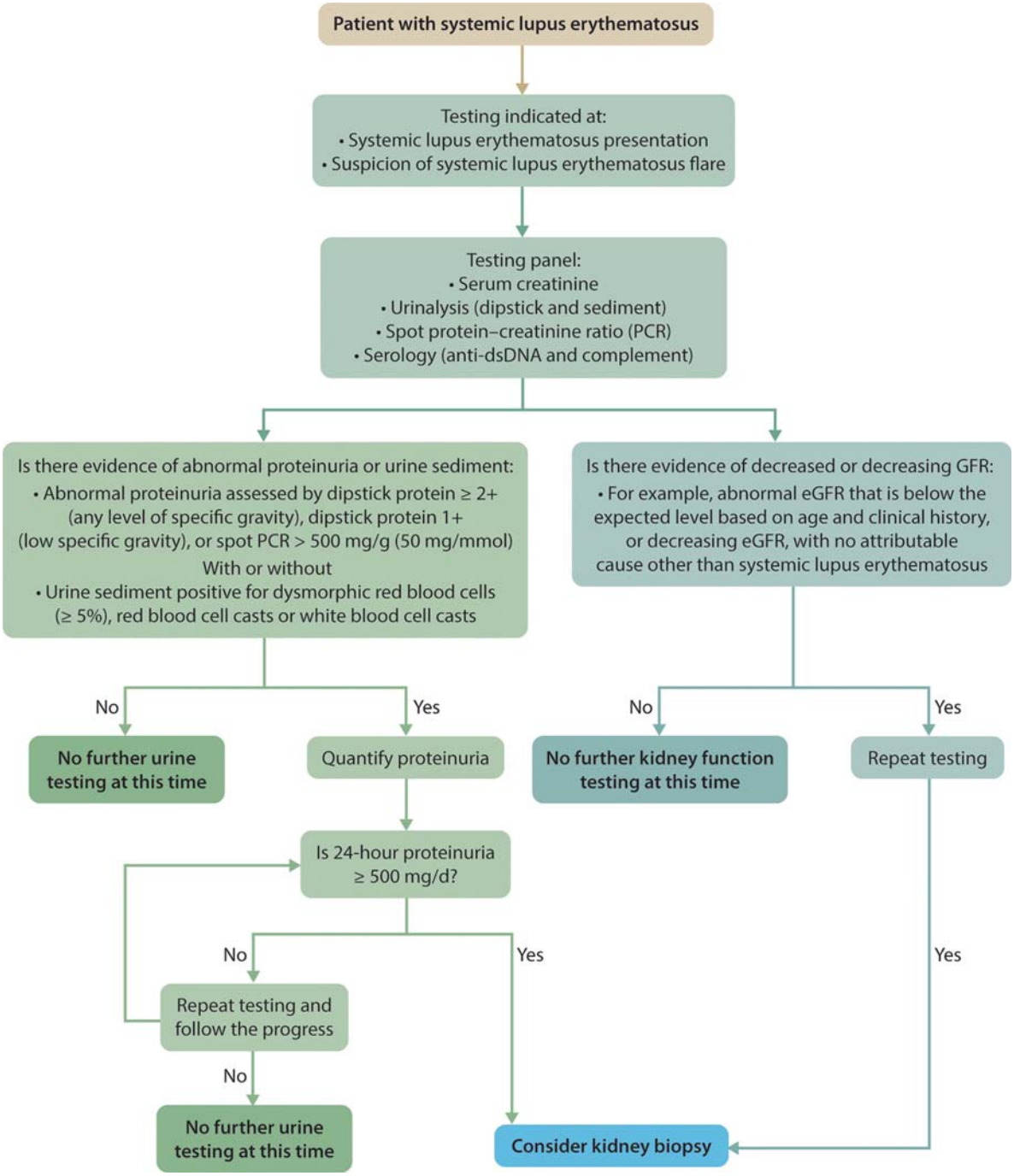

Figure 85 | Diagnosis of kidney involvement in SLE. eGFR, estimated glomerular filtration rate.

CI: 1.08–5.58). The frequency of severe LN flares was also increased but did not reach statistical significance.[663] A systematic review that included 95 reports published between 1982 and 2007, 5 of which were RCTs, concluded that hydroxychloroquine use could prevent SLE flares and increase long-term patient survival, while toxicity was infrequent, mild, and usually reversible; and hydroxychloroquine use in pregnancy was associated with a decrease in lupus activity without harm to the fetus.[664] Low-quality observational studies have indicated that hydroxychloroquine may have kidney benefits, protective effects against infection, and may increase complete remission rate in patients with LN. The quality of the evidence is low because of study limitations, indirectness, or imprecision, but it has been upgraded because of the large reported effect sizes (Supplementary Table S45[643,644,651–666]). Two observational studies reported an association between hydroxychloroquine treatment and reduced mortality in patients with LN, but the quality of evidence for this outcome is very low (Supplementary Table S45[654,666]).

Components of the activity index	Score	Calculating the activity score Extent of lesion	Points
• Endocapillary hypercellularity	0–3	Not present	0
• Neutrophils and/or karyorrhexis	0–3	Present in <25%	1
• Fibrinoid necrosis	(0–3) × 2	Present in 25%–50%	2
• Hyaline deposits (wire loop and/or hyaline thrombi)	0–3	Present in >50%	3
• Cellular/fibrocellular crescents	(0–3) × 2		
• Interstitial inflammation (interstitial leukocytes)	0–3		
	Total: 0–24		
Items included into the NIH chronicity score	**Score**	**Calculating the chronicity score Extent of lesion**	**Points**
• Total glomerulosclerosis (global + segmental)	0–3	Present in <10%	0
• Fibrous crescents	0–3	Present in 10%–25%	1
• Interstitial fibrosis	0–3	Present in 25%–50%	2
• Tubular atrophy	0–3	Present in >50%	3
	Total: 0–12		
Other histologic findings not included in the activity or chronicity score			
• Foot process effacement (lupus podocytopathy) • Collapsing lupus glomerulopathy • Vascular lesions (arteriosclerosis, non-inflammatory vascular immune complex deposits, thrombotic microangiopathy, non-inflammatory necrotizing vasculitis, true renal vasculitis)			

Figure 86 | Activity and chronicity items included in LN kidney biopsy report. NIH, National Institutes of Health, USA.

Values and preferences. The potential benefits of preventing organ damage and vascular complications were judged as being important to patients. The Work Group also judged that the relatively low risk of adverse events associated with hydroxychloroquine would also be important to patients. Therefore, the Work Group felt that nearly all well-informed patients in the target population would choose to receive hydroxychloroquine treatment in comparison to no treatment.

Resource use and costs. Hydroxychloroquine can be an expensive drug in some countries. Therefore, in low-resource settings, it may be acceptable to substitute structurally similar drugs such as chloroquine that have a similar mechanism of action but are less expensive.

Considerations for implementation. Because of the risk of hemolysis in patients who have glucose-6-phosphate dehydrogenase (G6PD) deficiency, measurement of G6PD levels is preferred in men, especially those of African, Asian, or Middle Eastern origin, before starting hydroxychloroquine. However, this risk appeared low, according to the findings of a recent report.[667] All patients should have a baseline retinal examination and then annual eye testing, especially after 5 years of use. Clinicians should be aware that antimalarials may be cardiotoxic (e.g., congestive heart failure, conduction abnormalities) after long-duration therapy or high cumulative exposure. The dosing of hydroxychloroquine is 6.5 mg/kg ideal weight/d or 400 mg/d, and during the maintenance phase, this should be lowered to 4 to 5 mg/kg/d. In patients with eGFR <30 ml/min per 1.73 m^2, the dose of hydroxychloroquine should be reduced by ≥25%.

Rationale

Data from multiple observational cohort studies show various benefits of hydroxychloroquine treatment in SLE, notably a reduced incidence of flare and organ damage accrual, and a relatively low rate of drug-related adverse effects, including ocular toxicity. Despite the relatively low-quality evidence, the overall balance between benefits and potential risks provides the basis for recommending its use as part of general management in patients with SLE.

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

Although many of the above recommendations also apply to patients with proteinuric kidney diseases treated with immunosuppression in general (Chapter 1), some risks are especially relevant to patients with SLE and LN. Patients with SLE show increased mortality rates when compared to age- and sex-matched controls in the general population.[668,669] Infections, CV complications, and CKD, especially kidney failure, are major causes of death.[623–625,670] Early deaths are related to infections or lupus activity, while CV and malignant complications and deaths related to kidney failure account for late mortalities.[671]

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 87 | 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.

Cardiovascular complications in patients with LN. Patients with SLE have both traditional (dyslipidemia, smoking, obesity, etc.) and non-traditional (proteinuria, inflammation, etc.) CV risk factors. A patient often has multiple risk factors, which can be secondary to disease-related organ damage (especially CKD, hypertension, proteinuria) or treatment (such as glucocorticoids and CNIs). Regular evaluation of various risk factors and timely treatment are essential to prevent premature CV complications.[672]

Infections in patients with LN. Infection is a leading cause of death in patients with LN, and infection-related deaths are more common during the initial phase of management following exposure to intensive immunosuppressive therapy.[665,668,673] There are data to suggest a higher incidence of adverse outcomes related to infections in Asia, which may be related to delayed presentation and the access to care.[673] Avoidance of overimmunosuppression is an important measure to reduce the risk of infections and adverse outcomes. Prophylaxis for *Pneumocystis* is standard practice in organ transplant recipients, but its role in patients on high-dose glucocorticoid therapy without HIV infection remains controversial, and there are few data from patients with SLE.[618,619] Antibiotic-related adverse drug reactions are not infrequent in patients with lupus, and in an early survey, 31% reported allergy to sulfonamide, with one-fifth of these patients also reporting worsening of SLE with the drug intolerance.[674] In a retrospective study from Thailand that included 132 patients with various connective tissue diseases, TMP-SMX was effective in preventing pneumocystis pneumonia, and adverse drug reaction occurred in only 9.4% of patients with SLE given prophylaxis.[675] However, a recent retrospective study from Japan reported a drug allergy rate of 41.9% in patients with lupus given TMP-SMX prophylaxis with conventional dosing, but only 10.7% in those with gradual introduction of the drug over a 9-day period.[676] Pneumocystis pneumonia is a severe complication in patient who are immunosuppressed and can result in fatality. Prophylaxis should be actively considered, taking into consideration a patient's allergic diathesis. The rate of *Herpes zoster* is 2–10 times higher in patients with SLE than in healthy controls, but the role of antiviral prophylaxis is uncertain. Available zoster vaccine preparations include the live-attenuated vaccine Zostavax® and the adjuvanted recombinant vaccine Shingrix. In general, live vaccines should be avoided in immunosuppressed subjects. There are no data on the

efficacy of the recombinant zoster vaccine in patients with lupus, and there is concern about whether the adjuvant might affect disease activity. There is also concern that the polio vaccination has been associated with lupus flares, whereas the data on influenza vaccination are conflicting. Response to vaccination is reduced following exposure to high-dose immunosuppression.[677]

Contraception and pregnancy. Pregnancy in patients with LN is associated with increased maternal complications and inferior fetal outcomes compared with the occurrence in healthy individuals, and the risks are higher when LN is active. Some of the frequently used medications in patients with lupus are contraindicated during pregnancy, such as MMF, cyclophosphamide, and warfarin. Counseling with regard to contraception and pregnancy should be done early in patients of childbearing age. Patients should be seen by a gynecologist to discuss the choice of methods for contraception. For patients who prefer oral hormonal contraception, estrogen–progestin contraceptives with ethinyl estradiol dose at not higher than 30 μg may be used in patients who are negative for antiphospholipid antibodies and with stable low disease activity, whereas progestin-only contraceptives are preferable in patients with a moderate or high level of disease activity. Estrogen-containing contraceptives should be avoided in patients with antiphospholipid antibodies or a history of thrombosis, in view of the risk of thromboembolism.[678] Data from women exposed to chemotherapy showed efficacy of gonadotrophin-releasing hormone (GnRH) analogues in reducing the rate of premature ovarian failure, whereas the putative gonadal protective effect of oral contraceptive pills appeared variable.[679] Fertility protection with GnRH agonists, or sperm and oocyte cryopreservation, should be considered in patients treated with cyclophosphamide, especially in patients with high cumulative exposure.

Bone health. Glucocorticoid therapy, especially when high doses are used for long durations, increases bone loss.[680,681] In children, glucocorticoid cumulative dose affects peak bone mass and growth.[682] Individual evaluation of fracture risk can be estimated using patient demographics and clinical history, glucocorticoid dose, and the Fracture Risk Assessment Tool (FRAX) score.[683] Calcium (optimal intake 1000–1200 mg/d) and vitamin D supplementation are recommended for patients with LN, as well as consideration for oral bisphosphonates according to individual risk assessment.[684,685]

Malignancies in patients with LN. Patients with SLE have increased risk of malignant tumors, including non-Hodgkin's lymphoma, lung, liver, vulvar/vaginal, thyroid, nonmelanoma skin cancer, and the risk (especially with bladder cancer) is increased in patients with a history of exposure to cyclophosphamide.[686,687] In general, the surveillance for malignancies in patients with LN follows the cancer-screening policies for the general population in the local community, and specific malignancy screening guidelines for patients with SLE are either lacking or largely opinion-based.[688] Although there is preliminary evidence showing efficacy and safety of human papillomavirus vaccines in patients with SLE, there is also controversy about whether the vaccine may cause predisposition to the development of SLE or lupus-like disease.[689,690]

10.2.2 Class I or Class II lupus nephritis

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

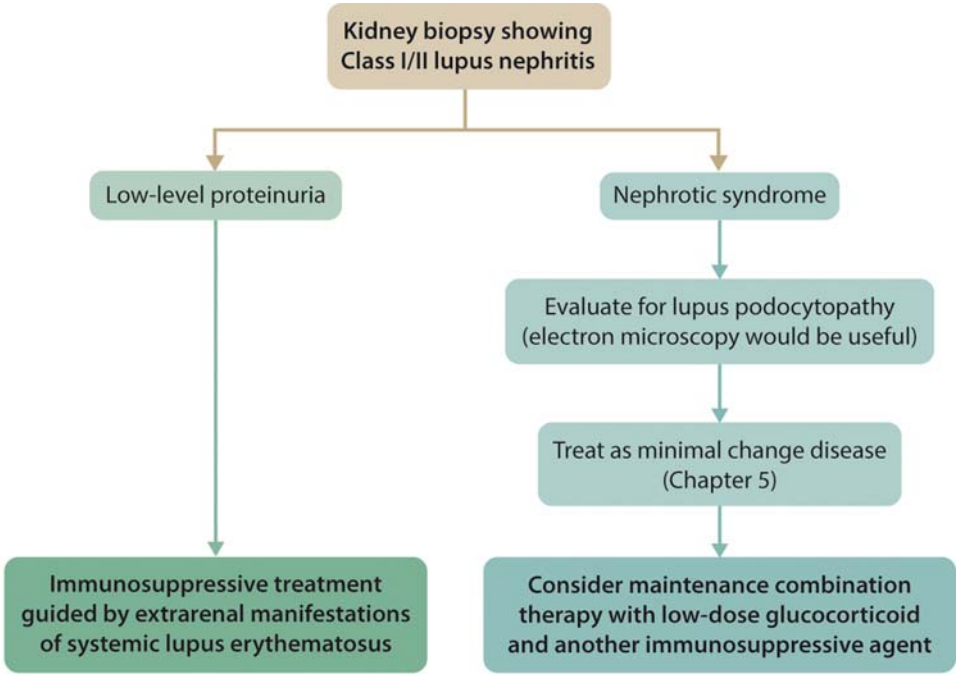

Figure 88 | Immunosuppressive treatment for patients with Class I or Class II LN. LN, lupus nephritis.

Patients with Class I or Class II LN generally have normal kidney function, or at most, low-grade proteinuria that is well below the nephrotic-range, and sometimes microscopic hematuria. For these patients, no specific immunosuppressive therapy beyond what is being given for nonrenal lupus is needed.[691]

Patients with Class I or II histology but with nephrotic-range proteinuria or NS are considered to have lupus podocytopathy. This diagnosis may be confirmed by demonstrating diffuse podocyte effacement on electron microscopy. Clinically and histologically, these patients are similar to those with MCD or FSGS, often showing a good response to glucocorticoid treatment.[692–694] Although there have been no RCTs, observational data showed that over 90% of patients given glucocorticoid monotherapy achieved remission within a median time of 4 weeks.[692,695–699] Data on relapse are even more limited, but there appears to be a significant risk of relapse after glucocorticoids are tapered.[700] Although optimal duration is not known, maintenance with low-dose glucocorticoid plus an additional agent such as an MPAA, azathioprine, or a CNI is suggested, especially in patients with a history of relapse.

10.2.3 Class III or Class IV lupus nephritis

10.2.3.1 Initial therapy of active Class III/IV lupus nephritis

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

This recommendation places a high value on the data demonstrating that glucocorticoids, in combination with MPAA or standard-dose cyclophosphamide, will improve kidney outcomes in active severe LN. It also places a high value on the data demonstrating comparable efficacy between MMF and cyclophosphamide in active severe LN. The Work Group recognizes that 2 new therapies have been approved for LN by the US FDA recently. The data leading to the approvals have recently been published.[701,702] This evidence has not yet been systematically reviewed in the context of current therapies, and it has not been graded for quality. Nevertheless, these therapies are promising and are discussed in subsequent practice points. All potential approaches to initial treatment of proliferative LN are shown in Figure 89.

Key information

Balance of benefits and harms. The short-term prognosis of patients with proliferative LN improved dramatically when treatment with high-dose glucocorticoids was started in the 1960s.[703] However, the long-term kidney prognosis continued to be poor as many patients progressed to kidney failure despite treatment. In landmark studies during the 1980s, the addition of cyclophosphamide to glucocorticoids was shown to be superior to treatment with glucocorticoids alone in preserving long-term kidney survival in active severe LN.[630,704–707]

For decades, the accepted standard of care for proliferative LN was high-dose glucocorticoids plus cyclophosphamide, but the risk of severe side effects prompted investigation of alternative induction regimens. This led to several trials comparing other agents to cyclophosphamide for initial treatment of LN, including azathioprine and MPAA.

MPAAs received considerable attention and were shown to have efficacy similar to that of cyclophosphamide for initial treatment of LN.[708,709] Although some studies suggested that MPAAs were associated with fewer adverse effects than cyclophosphamide, several investigations demonstrated a similar prevalence but different profile of adverse events.

However, all studies used concomitant high-dose glucocorticoids, and these likely accounted for many treatment-associated adverse events.[629,631,708–710] The dose of MPAA also differed between the studies. Nonetheless, based on relatively favorable "real-world" clinical experience, MPAA-based regimens have mostly replaced cyclophosphamide-based regimens for the initial treatment of proliferative LN. The dose of MMF is typically 2–3 g/d. Figure 91 shows the details of cyclophosphamide-dosing regimens.

Based on the hypothesis that the risk–benefit ratio of initial LN treatment could be improved further, a reduced-dose cyclophosphamide regimen was compared to standard high-dose cyclophosphamide in a study of 90 patients of European descent with active nephritis. The results showed no statistically significant difference in efficacy both short- and long-term and an improved side-effect profile.[634,711] This regimen was also tested in a short-term trial that included 100 Indian patients and showed similar remission rates compared to MPAA.[709] In view of the scarcity of data on reduced-dose cyclophosphamide in patients of African or Hispanic descent, there is concern as to whether this regimen is effective in these patient groups.

It is important to note that of all these treatment options, only initial treatment with cyclophosphamide has long-term data from controlled trials showing its higher efficacy in preserving kidney function compared to treatment with glucocorticoids alone.[705,706] All the other regimens have shown comparable or superior short-term efficacy, but trials have not been carried out to compare long-term efficacy on kidney survival. There is increasing evidence, based on data from observational studies,[632,711–715] that effective induction of renal response after initial therapy, especially a complete renal response, is associated with more-favorable long-term kidney outcomes.

In summary, Class III and Class IV LN are often very severe, and without treatment, they are associated with significant patient morbidity and mortality and a very high risk of kidney loss. Four distinct approaches have evolved to achieve renal response and prevent loss of kidney function. The attempt to reduce medication side effects

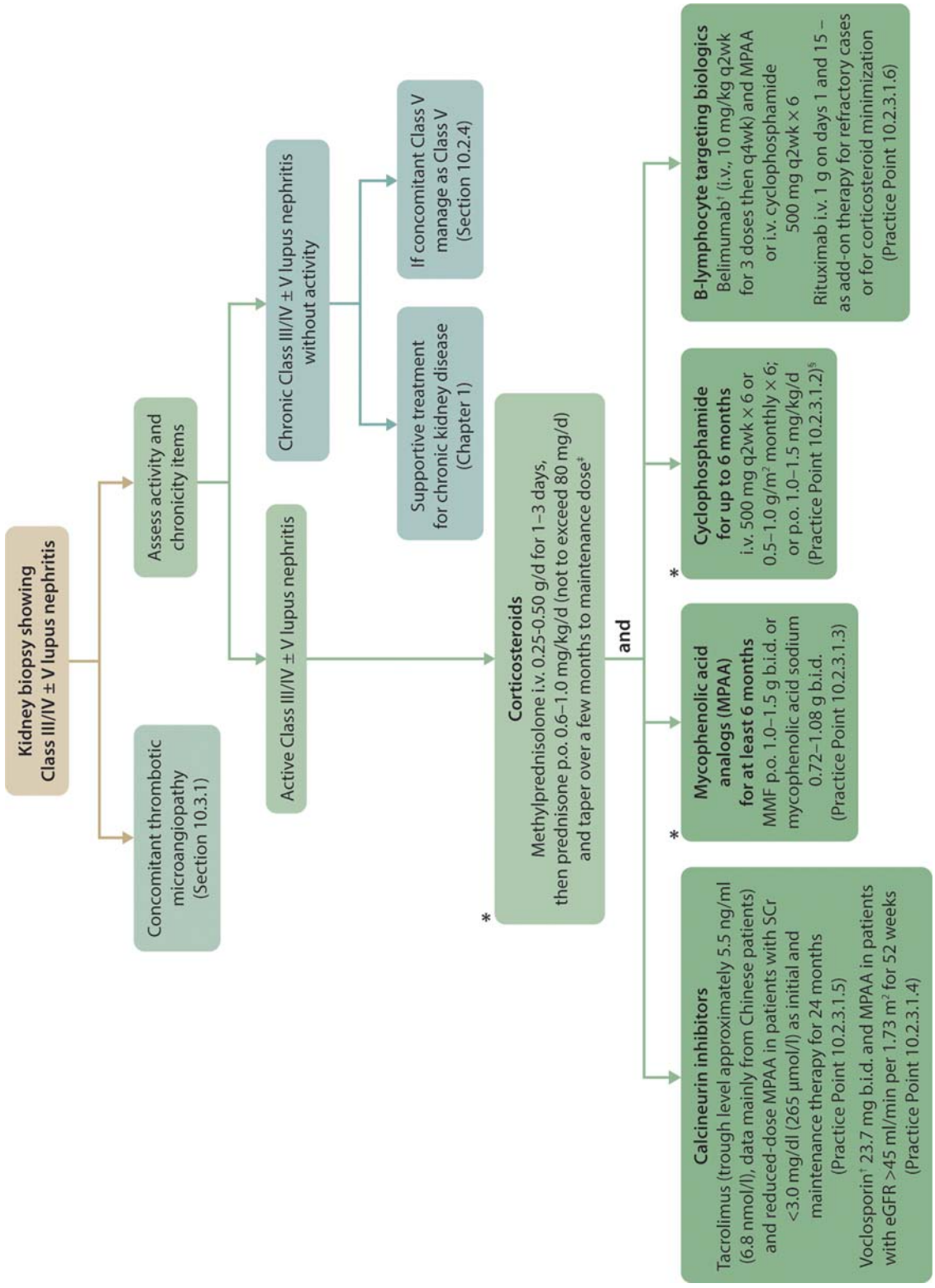

Figure 89 | Recommended approach for initial therapy of active Class III/IV LN. *Treatments in Recommendation 10.2.3.1.1. ‡Refer to Figure 90 for examples of corticosteroid treatment regimen. §Refer to Figure 91 for comments on cyclophosphamide regimens. †Denotes treatments approved by the U.S. Food and Drug Administration. b.i.d., twice daily; eGFR, estimated glomerular filtration rate; i.v., intravenous; MMF, mycophenolate mofetil; MPAA, mycophenolate acid analogs; p.o., oral; q2wk, every 2 weeks; q4wk, every 4 weeks; s.c., subcutaneous; SCr, serum creatinine.

has been modestly successful, shifting side-effect profiles away from the leukopenia, infertility, and future cancers associated with high cyclophosphamide exposure. Despite the potential of important treatment-associated toxicities, the benefits of treating proliferative LN outweigh the harms.

Quality of evidence. In the 6 RCTs that compared i.v. cyclophosphamide with glucocorticoids, there was moderate quality of evidence for a kidney benefit and decrease in kidney relapse. The quality of the evidence from these RCTs was downgraded to moderate because of study limitations (unclear blinding of participants and personnel, unclear allocation concealment; Supplementary Table S46[630,704,705,707,716–718]).

High-dose versus low-dose cyclophosphamide has been compared in a few RCTs (Supplementary Table S47[634,718–721]). The results from these trials indicate that low-dose cyclophosphamide is associated with fewer adverse events (such as infection, malignancy, leukopenia, and bone toxicity[718]; although in some studies, the efficacy also appeared lower than that of the high-dose regimen), with moderate quality of the evidence because of serious imprecision (only a few events, resulting in wide CIs indicating appreciable benefit and harm).

From the RCTs, there is moderate quality in the evidence that MMF exhibits a similar efficacy, and a different side-effect profile compared with i.v. cyclophosphamide. The quality of the evidence was downgraded to moderate because of unclear reporting of allocation concealment in trials (Supplementary Table S48[629,708–710,718,722–725]).

Values and preferences. Without treatment, the prognosis for kidney survival in patients with proliferative LN is poor, so the Work Group judged that most well-informed patients with Class III and IV LN would choose to be treated with one of the immunosuppression regimens outlined previously. Given the risks of infertility associated with cyclophosphamide and the spectra of future malignancy, most patients of childbearing age who anticipate conceiving in the future, and most patients, in general, will likely opt for initial treatment with MPAA over standard-dose cyclophosphamide. Low-dose i.v. cyclophosphamide has less risk than standard-dose and is a reasonable alternative to MPAA, but because the data favoring low-dose cyclophosphamide have largely come from White patients with mild to moderately severe LN, this alternative may not be appropriate for the treatment of severe LN in patients of African or Hispanic ancestry.

Resource use and costs. Management of active LN with immunosuppression is resource and labor intensive because the medications and the surveillance for potential complications are costly. Intravenous administration requires an infusion center with supervision, and patients must be monitored frequently for treatment- or disease-related complications, and require frequent clinical laboratory testing. However, it is likely that these costs are less over time than those associated with managing CKD and kidney failure resulting from no treatment, although a direct economic analysis has not been done. Furthermore, there have been no comparisons of quality of life between patients with CKD, patients with kidney failure receiving kidney replacement therapy, and patients receiving immunosuppression, especially with high-dose or prolonged administration of glucocorticoids. MPAA regimens were associated with higher medication costs but lower facility costs and a superior quality of life compared to i.v. cyclophosphamide regimens.[726–728]

Considerations for implementation. In view of the significant treatment costs,[728–730] the choice of therapy is often region-specific and depends on drug availability, reimbursement policies, and the financial means of individual patients. Other considerations when choosing initial therapy for LN include likelihood of adherence, age, prior immunosuppressive exposure, disease tempo and severity, and race and ethnicity.

Physicians may choose an i.v. regimen if suboptimal adherence is anticipated. Age is an important factor with respect to preservation of fertility, as susceptibility to gonadal failure after cyclophosphamide use increases with age. Susceptibility to future malignancies increases with higher lifetime cyclophosphamide exposure, so a detailed knowledge of prior therapies is important. Despite these considerations for cyclophosphamide, many physicians would initially choose standard-dose cyclophosphamide for patients in whom kidney function is rapidly deteriorating and whose biopsy shows severe activity (e.g., capillary necrosis, an abundance of crescents). It should be noted that there are sparse data on this group of patients who present with aggressive disease, as their clinical characteristics precluded them from inclusion in clinical trials. Physicians caring for patients of mixed ethnic background or Hispanic ethnicity may choose MPAA over cyclophosphamide as there are some *post hoc* analysis data suggesting it has higher efficacy,[731,732] whereas physicians caring for Chinese patients may want to choose MPAA and glucocorticoids, or triple immunosuppression with glucocorticoids plus low-dose MPAA plus low-dose CNI, as opposed to a cyclophosphamide-based regimen.[636,733]

Rationale

Class III or IV LN is an aggressive disease that requires prompt and effective therapy to abate ongoing injury and destruction of normal nephrons. Immunosuppressive treatment targets the active inflammatory lesions in kidney histopathology, in contrast to the chronic lesions, the extent of which portend CKD and long-term kidney prognosis.

The choice of initial treatment for Class III or IV LN entails personalized consideration of the balance between benefit and risk and is informed by data on short-term response and long-term efficacy and safety, potential adverse effects including infections and cumulative toxicities, quality of life, and factors relevant to patient experience and adherence.

Patient and kidney survival rates in Class III or Class IV LN have improved since the 1970s, first with the use of glucocorticoids, and subsequently following the adoption of

combined immunosuppressive regimens with cyclophosphamide or MPAA as standard therapy.

Glucocorticoids remain an integral component in initial therapy for Class III or IV LN based on their anti-inflammatory and immunosuppressive actions. The addition of cyclophosphamide or MPAA was associated with lower relapse rates and improved long-term kidney survival compared with glucocorticoid treatment alone. Combined immunosuppressive regimens also facilitate glucocorticoid minimization, thereby reducing their adverse effects (Figure 90).

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

Glucocorticoids are used in all current treatment regimens of LN. These drugs have both immunosuppressive and anti-inflammatory effects and provide immediate treatment for the often extensive intrarenal inflammation that is seen in patients with Class III and Class IV LN. This regimen is necessary because there is a lag before the immunosuppressive effects of cyclophosphamide, MPAA, CNIs, or B cell–directed therapies are seen. The dose, tapering regimen, and duration of glucocorticoid schemes vary considerably among clinicians and are largely opinion-based. Examples are given in Figure 90.

The role of i.v. methylprednisolone pulses at the start of treatment is not well-studied but is commonly given as up to 3 daily doses of 500 mg each (range 250–1000 mg/d), especially in patients who present with a clinical syndrome of RPGN—acute and severe deterioration of kidney function often accompanied by a high proportion of crescents or vascular lesions in the kidney biopsy, or when there are severe extrarenal manifestations, such as central nervous system or lung involvement.

To minimize the side effects due to high cumulative exposure to glucocorticoids, there is increasing use of initial i.v. glucocorticoid pulses followed by a lower starting dose and/or more-rapid taper of oral glucocorticoid in recent clinical trials.[734] Results from a retrospective propensity analysis of data from 63 patients enrolled in the Aspreva Lupus Management Study (ALMS) and the phase 2 Aurinia Urinary Protein Reduction Active-Lupus with Voclosporin (AURA-LV) trial suggested that doses of glucocorticoids and MPAA lower than those adopted in ALMS may result in better long-term safety, including a reduction in lymphoproliferative disorders, skin cancers, and glucocorticoid-related side effects.[735] In children, the avoidance of excessive glucocorticoid exposure also has implications for growth, psychosocial issues, and drug adherence.[736] With accumulating data on the efficacy and glucocorticoid-sparing role of immunosuppressive medications such as cyclophosphamide and MMF, there is a move toward reducing exposure to glucocorticoids (Supplementary Table S49[718,737]). Examples of dosing and tapering regimens in initial treatment of LN, based on published literature and recent clinical trials that investigate the efficacy and safety of new therapeutic agents, are shown in Figure 90. They serve to illustrate variations in exposure to glucocorticoids, but it is premature to recommend one over the other, as the regimens have not been formally compared to one another in prospective clinical trials.

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

Cyclophosphamide may be given orally or intravenously, and in a standard-dose (also known as the modified National

	Standard-dose scheme	Moderate-dose scheme	Reduced-dose scheme
Methylprednisolone intravenous pulses	Nil or 0.25–0.5 g/day up to 3 days as initial treatment	0.25–0.5 g/day up to 3 days often included as initial treatment	0.25–0.5 g/day up to 3 days usually included as initial treatment
Oral prednisone equivalent (/day)			
Week 0–2	0.8–1.0 mg/kg (max 80 mg)	0.6–0.7 mg/kg (max 50 mg)	0.5–0.6 mg/kg (max 40 mg)
Week 3–4	0.6–0.7 mg/kg	0.5–0.6 mg/kg	0.3–0.4 mg/kg
Week 5–6	30 mg	20 mg	15 mg
Week 7–8	25 mg	15 mg	10 mg
Week 9–10	20 mg	12.5 mg	7.5 mg
Week 11–12	15 mg	10 mg	5 mg
Week 13–14	12.5 mg	7.5 mg	2.5 mg
Week 15–16	10 mg	7.5 mg	2.5 mg
Week 17–18	7.5 mg	5 mg	2.5 mg
Week 19–20	7.5 mg	5 mg	2.5 mg
Week 21–24	5 mg	<5 mg	2.5 mg
Week >25	<5 mg	<5 mg	<2.5 mg

Figure 90 | Example of glucocorticoid regimens for LN. LN, lupus nephritis.

	Intravenous cyclophosphamide – modified (NIH regimen)	Intravenous cyclophosphamide (Euro-Lupus regimen)	Oral cyclophosphamide
Cyclophosphamide	i.v. 0.5–1 g/m^2 monthly for 6 months	i.v. 500 mg every 2 weeks for 3 months	p.o. 1.0–1.5 mg/kg/d (max 150 mg/d) for 2–6 months
Comments	Efficacy data included patients of different races/ethnicities	Efficacy data mainly in Caucasian patients, with some data from patients of Afro/Caribbean descent, Hispanic descent, Indian patients, and other Asian countries	Efficacy data included patients of different races/ethnicities

Figure 91 | Cyclophosphamide dosing regimens, combined with glucocorticoids, in initial treatment for active Class III/IV LN. i.v., intravenous; LN, lupus nephritis; max, maximum; NIH, National Institutes of Health, USA.; p.o., oral.

Institutes of Health (NIH) regimen or high-dose regimen) or low-dose (also known as the Euro-Lupus regimen). The dosing and duration for these regimens are given in Figure 91.

The choice of which regimen to use depends on several factors and can be individualized:

- *Efficacy:* Oral and standard-dose i.v. cyclophosphamide regimens have been used in diverse ethnic populations and for all levels of disease severity, and show equivalent efficacy.[635,738–741] Reduced-dose cyclophosphamide (Euro-Lupus regimen) shows equivalent efficacy to standard-dose cyclophosphamide but was tested mainly in White patients.[634,711] Emerging data suggest low-dose cyclophosphamide is effective in Asians, Hispanics, and Black patients, but these studies did not make direct comparisons to standard-dose i.v. cyclophosphamide (Supplementary Table S47[634,718–721,742]).
- *Cost:* Intravenous cyclophosphamide is more expensive than oral and requires the availability of an infusion suite and experienced staff.
- *Convenience:* Oral cyclophosphamide does not require patients to stop work or family activities.
- *Toxicity:* The toxicities of cyclophosphamide may be considered immediate (e.g., gastrointestinal, susceptibility to infection) or delayed (e.g., loss of fertility, future malignancies).
- Standard-dose i.v. cyclophosphamide was shown to be less toxic than oral cyclophosphamide, but the dose and duration of oral treatment in these reports were substantially higher and longer than those currently recommended (Supplementary Table S50[630,718,741]). The incidence of bladder toxicity is also felt to be lower with i.v. cyclophosphamide. Reduced-dose i.v. cyclophosphamide has the most favorable immediate toxicity profile among the 3 cyclophosphamide regimens.
  - The risk of future hematologic malignancy is related to total lifetime exposure (>36 g), as is myelofibrosis (>80 g). Total lifetime exposure plus age constitutes a significant risk factor for premature ovarian failure (>7.5–15 g/m^2 for young to older pediatric patients, respectively; 300 mg/kg for adults).

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

Trials of MMF for initial treatment of proliferative LN have targeted dosing of 2–3 g/d. Several studies have shown that MMF has comparable short-term efficacy to oral or i.v. cyclophosphamide for induction of complete and partial renal responses (Supplementary Table S48[629,631,632,710,718,722–725]). MMF has significant gastrointestinal toxicity, and at moderate-to-high doses, some patients may not tolerate it. In patients with gastrointestinal intolerance, a trial of enteric-coated MPA in a dose range of 1440–2160 mg is warranted, in view of its greater gastrointestinal tolerance.[737]

Although MPAA does not predispose patients to gonadal failure or hematologic malignancies as does cyclophosphamide, the ALMS trial (target dose 3 g/d) showed a similar incidence of side effects between patients treated with MMF plus glucocorticoids and patients treated with cyclophosphamide plus glucocorticoids.[629] In this trial, 9 deaths occurred in the MMF group, and 5 in the cyclophosphamide group. Seven of the 9 deaths in the MMF group were due to infections, and 7 of the 9 deaths in MMF-treated patients occurred in Asia. Concomitant high-dose glucocorticoids and the relatively high MPA exposure have been proposed as contributory factors to the higher-than-expected infection-related adverse outcomes in this trial. In this regard, data from kidney transplant clinical trials showed that, compared with an MMF dose of 2 g/d, an increased MMF dose of 3 g/d did not result in a higher efficacy in the non-Black patient population, but was associated with more adverse events.[743] Therefore, consideration of the race or ethnicity of a patient, or the geographic locality, may also be relevant when deciding on the dose of MPAA to be used, in view of the potential differences in risk profiles among patients.

MPA pharmacokinetics varies considerably among patients, especially in the context of hypoalbuminemia and impaired kidney function. Data from small-scale studies

suggested that an MPA area under the concentration-versus-time curve of 35–45 mg/hr/l or a trough level of 3.0–4.5 mg/l may serve to ensure adequate exposure during initial therapy, but the role of therapeutic drug-level monitoring remains to be established.[744–748]

MMF has been tested successfully in diverse ethnic groups. A more granular look at the efficacy of MMF in specific ethnic groups was done through a *post hoc* analysis of data from the ALMS study, the largest trial comparing MMF to i.v. cyclophosphamide to date.[629,731] The analysis showed higher treatment response rates for MMF compared to cyclophosphamide in Hispanic patients (60.9% vs. 38.8%, $P = 0.011$) and patients from Latin America (60.7% vs. 32%, $P = 0.003$), whereas the response to MMF was numerically higher but not statistically different than that to cyclophosphamide in Black patients (53.9% vs. 40.0%, $P = 0.39$). A higher response rate to MMF than to cyclophosphamide in Hispanic patients was also reported in cohort studies.[732] In contrast, the response rate to cyclophosphamide was numerically higher but not statistically different than that to MMF in Asian patients (63.9% vs. 53.2%, $P = 0.24$).[629,731]

Cyclophosphamide has historically been the first-choice treatment for very severe proliferative LN. An analysis of pooled data from various clinical trials of patients with Class III/IV LN, crescents in >15% of glomeruli, and abnormal SCr level at presentation showed a comparable early response to glucocorticoids plus either cyclophosphamide or MMF.[749] However, the analysis also suggested that initial treatment with cyclophosphamide might be associated with a more sustained response and more favorable long-term kidney outcome than initial treatment with MMF. In the maintenance phase of ALMS,[633] although not statistically different, patients initially treated with cyclophosphamide had numerically lower rates of disease flare compared with those initially treated with MMF.

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

Calcineurin inhibitors (CNI) are potent immunosuppressive medications due to their inhibition of T lymphocyte activation and release of interleukin-2. They also modulate the podocyte cytoskeleton, leading to reduction of proteinuria in various glomerular diseases. The use of a CNI in the treatment of LN may therefore lead to more effective or more rapid reduction of proteinuria.

Data from short-term studies with follow-up of 6–12 months suggest that a regimen of glucocorticoids combined with cyclosporine or tacrolimus, with or without reduced-dose MPAA, as initial LN therapy has comparable efficacy to glucocorticoids combined with cyclophosphamide.[636,750,751] Until recently, most of these trials had been done in Asia (see Practice Point 10.2.3.1.5). The largest trial, conducted in China, combined a fixed, relatively low-dose of tacrolimus (4 mg/d, achieved trough levels of 5.2–5.5 ng/ml [6.4–6.8 nmol/l]) with low-dose MMF (1 g/d) in patients with a baseline serum creatinine level ≤3.0 mg/dl (265 μmol/l), and reported earlier attainment of renal response than in controls treated with NIH-cyclophosphamide regimen with a higher complete renal response rate (46% vs. 26%) after 24 weeks of treatment.[636] Extended follow-up, however, showed comparable renal response rates in both groups during the second year of treatment.[733] Similarly, a study from Japan reported a complete response rate of 80% after 6 months of treatment with a triple immunosuppressive regimen that included glucocorticoids, reduced-dose cyclophosphamide, and tacrolimus.[750]

The evidence from the few RCTs that compared triple-therapy to cyclophosphamide is judged as low quality because of study limitations and indirectness (Supplementary Table S51[636,718,752]). As these early trials mainly included patients of Asian ethnicity, and some excluded patients with severe disease, the generalizability of this therapy to the broader LN population is unclear (see also Practice Point 10.2.3.1.5).

Of importance, in the large Chinese study, the number of infections was higher in patients who received triple therapy than in those who were treated with cyclophosphamide, although this difference did not reach statistical significance. More data are also required on the incidence of acute and chronic CNI nephrotoxicity, the metabolic side effects of CNIs and their effect on blood pressure control, as well as the optimal duration of treatment and whether there may be a rebound of proteinuria after stopping CNI.[751]

Practice Point 10.2.3.1.5: In patients with baseline eGFR of at least 45 ml/min per 1.73 m^2, voclosporin can be added to MPAA and glucocorticoids as initial therapy for 1 year.

Voclosporin is an analogue of cyclosporine that exhibits enhanced potency in calcineurin inhibition. Voclosporin was noninferior to tacrolimus in the prevention of biopsy-proven acute rejection in a 6-month multicenter open-label phase 2b trial that involved 334 low-risk kidney transplant recipients.[753] Voclosporin for the treatment of active biopsy-proven Class III, IV, or V lupus nephritis was investigated in Aurinia Urinary Protein Reduction Active - Lupus With Voclosporin (AURA-LV),[734] a phase 2 RCT of 265 subjects and Aurinia Renal Response in Active Lupus With Voclosporin (AURORA),[702,754] a phase 3 RCT of 357 subjects. Both trials included patients of diverse ancestry. Voclosporin was compared to placebo, and all patients received glucocorticoids and MMF (target dose: 2 g/d) as background therapy. The rapidly tapered corticosteroid regimen used was novel. All patients received 2 doses of intravenous methylprednisolone (500 mg/dose) followed by 20–25 mg prednisone that was rapidly tapered to 2.5 mg/d by 16 weeks. The primary endpoint of these trials was renal response (RR), defined as urine PCR ≤0.5 mg/mg, eGFR ≥60 ml/min per 1.73m^2, or no decline of >20% from baseline, and prednisone dose of <10 mg/d for the 8 weeks prior to endpoint measurement.

In AURA-LV, 33% of patients treated with voclosporin 23.7 mg twice per day reached an RR at 24 weeks compared to 19% of placebo-treated patients (OR 2.03, $P < 0.05$).[734] Similarly, in AURORA, 41% of voclosporin-treated patients achieved RR at 52 weeks, compared to 23% of placebo-treated patients (OR 2.65, $P < 0.001$).[702,754] A pooled analysis of the 2 trials showed that patients treated with voclosporin added to standard therapy had an RR rate of 44% at 1 year, compared to 23% in placebo patients ($P < 0.0001$).[755] Adverse events were similar between the placebo and voclosporin arms.

Compared to other CNIs, such as cyclosporine and tacrolimus, voclosporin has a more consistent pharmacokinetic–pharmacodynamic relationship due to enhanced binding of the voclosporin–cyclophilin complex to calcineurin and reduced drug and metabolite load. Preliminary evidence, based on data from the AURA-LV and AURORA trials, suggests that therapeutic drug monitoring may not be necessary in patients.[756]

Results from these 2 pivotal trials led to the US FDA approval of voclosporin to treat adult patients with LN in January 2021. Of note, voclosporin is not recommended for patients with a baseline eGFR ≤45 ml/min per 1.73 m^2, as these patients were excluded from the trials. Also, voclosporin has not been studied with cyclophosphamide.

The positive results of AURA-LN and AURORA coupled with the Asian studies of tacrolimus and cyclosporine suggest triple immunosuppressive therapy incorporating a CNI can be an effective treatment regimen for LN. An advantage of a CNI-based regimen is the more rapid reduction of proteinuria. However, more data on long-term efficacy and safety of CNI use in LN are required.

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

Results from phase 2 and phase 3 clinical trials did not demonstrate superiority in efficacy when B cell–targeting therapies (rituximab, ocrelizumab), costimulatory blockade (abatacept), or anti-interleukin-6 monoclonal antibody were added to standard initial therapy of glucocorticoids and either MMF or cyclophosphamide.[757–762] The negative outcomes contrast with reports of case series that suggested efficacy when patients with suboptimal response to standard therapy were treated with rituximab.[763–766] Interestingly, patients treated with rituximab and abatacept in the RCTs showed more effective suppression of anti-double-stranded deoxyribonucleic acid (dsDNA) levels and complement activation, but this biological efficacy did not translate to conventional clinical indicators of treatment response.[757,759] Reasons for the apparent discrepancy between biological efficacy versus clinical observations, and between the case series versus RCT results, include the different populations of patients studied, the outcome parameters used in the trials, and the relatively short duration of observation in the trials. Some trials using biologics have yielded encouraging results. For example, in a prospective single-center pilot study to investigate whether rituximab could facilitate corticosteroid avoidance, 50 patients with active LN (22 Class V, 28 Class III/IV ± V) were treated with rituximab 1 g and methylprednisolone 500 mg i.v. on day 1 and day 15 and were maintained on MMF (maximum dose 1.5 g twice per day, target trough blood level of mycophenolic acid 1.2–2.4 μg/ml [3.7–7.5 μmol/l]) without glucocorticoids, and by 52 weeks, 52% of patients achieved complete remission and 34% achieved partial remission.[767]

The negative outcomes in previous clinical trials do not preclude a therapeutic role for some of these novel agents in selected patients, including those who have not responded well to or who do not tolerate standard therapy, or when steroid-sparing is attempted (Supplementary Tables S56–S59[718,742,757–759,764]).[767]

Ongoing clinical trials continue to investigate the role of biologics for the treatment of LN. A recent phase 2 study showed that in adult patients with active proliferative LN treated with MPAA and glucocorticoids, the addition of obinutuzumab resulted in higher complete renal response rates at week 76 (40% vs. 18%, $P = 0.007$), and at week 104 compared to placebo (54% vs. 29%, $P = 0.005$). The rate of serious adverse events and serious infections did not differ between the 2 groups.[760]

A phase 3 RCT of belimumab (10 mg/kg i.v. on days 1, 15, and 29, then every 28 days to week 100) added to standard-of-care therapy resulted in approval of belimumab for LN by the U.S. FDA in December 2020.[701] This trial, Efficacy and Safety of Belimumab in Patients with Active Lupus Nephritis (BLISS-LN), examined the 2-year primary efficacy renal response (PERR) after belimumab or placebo was added to standard-of-care therapy, which was either MMF or the Euro-Lupus reduced-dose cyclophosphamide regimen chosen by the site investigator. PERR was defined as a ratio of PCR of <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 use of rescue therapy for treatment failure. At week 104, significantly more patients who received belimumab achieved a PERR compared to the number of those who received placebo (43% vs. 32%; OR 1.60; $P = 0.03$; Supplementary Table S60[701]). Key secondary endpoints included complete renal response and the risk of renal event or death. These also favored belimumab. Subgroup analysis showed that the overall PERR response was driven by the results in the larger subgroup (73.5%) of patients who received MMF as background therapy. Belimumab treatment was not associated with excess adverse events.

In summary, there are accumulating data on the biological and clinical efficacy of various biologics. Although long-term results are awaited, results on these biologics have expanded the armamentarium of therapeutic options and potential combinations of treatments. The favorable safety profile associated with some of the new biologics presents a distinct advantage. Further investigations are necessary to define the profiles and characteristics of

patients who would benefit most from each of the various novel therapies.

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

Azathioprine combined with methylprednisolone pulses showed a comparable short-term renal response rate to that for prednisolone combined with standard-dose i.v. cyclophosphamide in a study that included 87 patients in the Netherlands, but the azathioprine and pulse methylprednisolone group had more infections, and their extended follow-up data showed a higher relapse rate and greater progression of CKD (Supplementary Table S52[630,718,768,769]). Nonetheless, some patients may not tolerate MPAA, cyclophosphamide, or CNIs, or these drugs may be unavailable, too costly in some regions of the world, or contraindicated, as in pregnant patients.

Short-term studies in Chinese patients compared leflunomide against i.v. cyclophosphamide, in both cases combined with glucocorticoids, and reported comparable renal response rates of approximately 70% after 6 months.[770,771]

Other therapies that have not shown significant benefit when added to standard therapy include plasmapheresis (Supplementary Table S53[618,635,772–774]), and the anti-interleukin-6 antibody sirukumab (Supplementary Table S54[618,775]). In a phase 2a trial, laquinimod was associated with a higher renal response rate (62.5% compared with 33.3% in the placebo group) when added to standard-of-care treatment with glucocorticoids and MMF in patients with active LN (Supplementary Table S55[618,776]).

10.2.3.2 Maintenance therapy for Class III and Class IV lupus nephritis

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

This recommendation places a high value on the data demonstrating that long-term, reduced-dose MPAA decrease the risk of LN relapse compared to azathioprine or no treatment and that MPAA have effectiveness comparable to that of cyclophosphamide but with a lower risk of adverse events. The recommendation places a lower value on the risk of adverse events associated with long-term MPAA treatment as compared to no treatment (Figure 92).

Key information

Balance of benefits and harms. High-intensity immunosuppression for the initial treatment of LN is given for 3–6 months, depending on the regimen (Section 10.2.3.1). At the end of initial therapy, only about 10% to 40% of patients achieve complete response as defined by clinical parameters,[2,628,634,636] and approximately 20% achieve complete histologic remission, defined as an activity index of zero on repeat kidney biopsy.[627] Also, LN relapses frequently, and relapses predispose to additional kidney damage and progression to kidney failure. Ongoing treatment is therefore needed to consolidate initial responses into more complete and sustained responses, and to prevent disease flares. After initial therapy, ongoing immunosuppression is designated as maintenance therapy.

The evolution of current maintenance therapy for proliferative LN is an example of how investigators have tried to balance preservation of kidney function against the toxicities of long-term immunosuppressive therapy. After it became

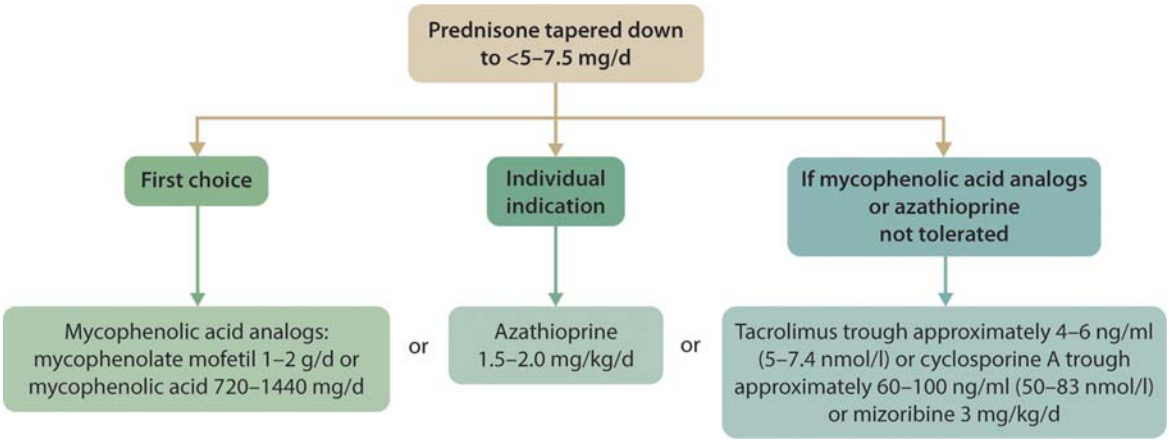

Figure 92 | Maintenance therapy for Class III and Class IV LN. The target ranges for CNIs have been based on the transplant literature. The KDIGO Work Group acknowledges that targets for glomerular diseases are not known. Most clinicians check these levels to verify adherence and avoid CNI toxicity. 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 level, reducing the dose if serum creatinine level 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.

clear that the addition of a cytotoxic agent to glucocorticoids during the initial treatment of LN improved long-term kidney survival, patients were kept on oral, or in later studies i.v., cyclophosphamide for months or years.[716] This led to considerable lifetime cyclophosphamide exposure and toxicity.[777,778] A study reported in 2004 compared quarterly i.v. cyclophosphamide against oral MMF or azathioprine for LN maintenance, and the results showed not only a significant reduction in side effects in those treated with MMF or azathioprine but also improved kidney and patient outcomes compared to the cyclophosphamide group.[779] This led to a decrease in the use of quarterly cyclophosphamide as maintenance treatment. Favorable long-term results with sequential immunosuppressive regimen have been published by others,[712,713] and together, they ushered in the current era of intense, high-dose immunosuppression for the initial treatment of proliferative LN, followed by prolonged immunosuppression with a less intense regimen to reduce adverse events while ensuring the continued suppression of immune-mediated pathogenic processes so that the response following initial therapy is consolidated, the disease remains quiescent, flares are prevented, and further damage to the kidney or other organs is avoided.

MMF and azathioprine were directly compared as maintenance agents in 2 major clinical trials (Supplementary Table S61[629,718,779–781]).[633,711] In an LN cohort of 227 ethnically diverse patients, the maintenance phase of ALMS showed that over 3 years of follow-up, the composite treatment failure endpoint of death, ESKD, LN flare, sustained doubling of SCr, or requirement for rescue therapy was observed in 16% of MMF-treated patients and in 32% of azathioprine-treated patients ($P = 0.003$).[633] LN flares occurred in 12.9% of MMF-treated patients and 23.4% of azathioprine-treated patients. In contrast, the Mycophenolate Mofetil Versus Azathioprine for Maintenance Therapy of Lupus Nephritis (MAINTAIN) trial randomized 105 predominantly White patients to MMF or azathioprine and glucocorticoid maintenance therapy after initial therapy with the low-dose cyclophosphamide regimen and showed no difference in time to kidney flare between the 2 groups, with a cumulative kidney flare rate of around 20% in both groups after 36 months.[711] A higher proportion of patients in the azathioprine group had adverse events leading to withdrawal of therapy in the ALMS maintenance trial (39.6% vs. 25.2%), and there was a higher incidence of cytopenia in the azathioprine group in the MAINTAIN trial. Thus, in most LN populations, MMF (MPAA) is the maintenance drug of choice.

An RCT compared maintenance treatment with triple immunosuppression that included low-dose MPAA, low-dose tacrolimus, and low-dose glucocorticoids ("multitarget" regimen) against azathioprine in responders following "multitarget" regimen or NIH i.v. cyclophosphamide as initial treatment for 6 months in the 2 groups respectively, and the results showed similar efficacy in preventing flares in the 2 groups and a higher incidence of adverse events due to transaminitis in the azathioprine group.[733] However, the follow-up duration of 18 months was relatively short, and the generalizability of data needs further investigation. Also, although the response rate was significantly higher in the "multitarget" group after 6 months of initial treatment, the cumulative response rate was similar between the 2 groups during the second year of therapy, increasing to approximately 90% by the end of 24 months. Other investigators have reported relatively favorable results with various "multitarget" triple immunosuppressive maintenance treatment regimens that comprised glucocorticoids with MPAA and either cyclosporine[782,783] or tacrolimus.[784]

Based on these considerations collectively, the Work Group concluded that the benefits of maintenance immunosuppression far outweigh its potential harms, and MPAA is the preferred drug based on the data to date (Practice Point 10.2.3.2.1).

Quality of evidence. Only 1 RCT compared long duration (18 months) of cyclophosphamide therapy encompassing both the initial treatment period and the maintenance phase with short duration (6 months) of cyclophosphamide therapy as initial treatment followed by maintenance treatment with variable immunosuppressive regimens. Due to study limitations and very serious imprecision (only 1 study, and very wide CIs, indicating appreciable benefit and harm), the quality of the evidence for this trial is very low (Supplementary Table S62[716]).

Similarly, only 1 RCT (n = 39) compared azathioprine with quarterly pulse cyclophosphamide as maintenance treatment, indicating very low quality of the evidence because of study limitations and very serious imprecision (only 1 study, wide CIs) (Supplementary Table S63[779]).

The ALMS trial compared azathioprine with MMF as maintenance therapy in patients with proliferative LN and showed an increased rate of composite "treatment failure" endpoint and adverse effects (e.g., leukopenia) in patients who received azathioprine.[633] Despite the large sample size and the fact that this was an RCT, the quality of the evidence was downgraded to moderate because of imprecision (few events) or study limitations (unclear allocation concealment).

Data on the use of CNIs or mizoribine as maintenance treatment are generally of low quality (Practice Point 10.2.3.2.4[785–788]).

Values and preferences. In the judgment of the Work Group, most well-informed patients who have undergone aggressive immunosuppression to control their LN would choose maintenance therapy to try to attain complete remission if it had not yet been achieved, and in all cases to avoid disease relapses needing reinstitution of high-dose immunosuppression. In the judgment of the Work Group, the better efficacy of MPAA with its generally favorable tolerability profile, compared to azathioprine, attests that most well-informed patients would choose MPAA as the first-line treatment.

However, patients who have had severe adverse effects while on MPAA, or who place a high value on becoming pregnant, may choose azathioprine (or a CNI) over MPAA, as

may patients for whom MPAAs are unavailable or unaffordable.

Resource use and costs. In general, it is reasonable to assume that the personal and societal cost of not using maintenance therapy and risking disease relapse after investing in initial therapy would be higher than the cost of maintenance medications. Compared with initial therapy, facility costs are often lower, as maintenance regimens are oral, and outside of medication expense, with major resource implications arising from laboratory monitoring of lupus activity and immunosuppression and managing complications of treatment. Although the drug cost of MPAA is considerably higher than that of azathioprine, there are few cost-effectiveness analyses of maintenance treatment for LN.[789] Also, some drugs may have limited accessibility in certain regions, and this may influence choices. Drug-level monitoring is required in patients treated with CNIs, but not when azathioprine or MPAA is used, and this also has implications for affordability and accessibility.

Considerations for implementation. Apart from availability and cost of MPAA, the major consideration for implementation of maintenance therapy is safety during pregnancy. Although it is not advisable to attempt pregnancy until LN and SLE have been well-controlled for some time, which would give ample opportunity to switch patients over to a "pregnancy-friendly" regimen, pregnancy decisions are complex, and maintenance therapy often needs to be individualized on this basis (Section 10.3.2.). MPAA is contraindicated during pregnancy and should be discontinued well in advance of trying to conceive. In contrast, low-dose azathioprine and CNIs can be used during pregnancy.

Rationale

The use of maintenance combined immunosuppressive therapy in Class III/IV LN to consolidate response to initial immunosuppressive treatment and prevent disease flares is supported by evidence of at least moderate quality. There are more robust data supporting the superiority of MPAA over azathioprine as maintenance therapy, from clinical trials that included patients of different races and ethnicities.

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

As discussed under Recommendation 10.2.3.2.1, the direct comparison between MPAA and azathioprine as maintenance treatment in LN, both combined with low-dose glucocorticoids, is mainly based on data from ALMS and the MAINTAIN trial.[633,780] Although the results from the latter showed no statistically significant difference in time to disease flare or long-term clinical outcomes in Caucasian patients, data from ALMS based on a large sample size from different countries with different ancestry demonstrated superior efficacy of MPAA compared with azathioprine, and in both trials, azathioprine was associated with more adverse effects, such as leukopenia and abnormal liver-enzyme levels. However, azathioprine is much cheaper than MPAA, and financial barriers may limit access to MPAA in many countries. Under such circumstances, or in patients who do not tolerate MPAA because of side effects, low-dose glucocorticoids combined with azathioprine are an effective maintenance immunosuppressive treatment. Observational cohort data from Chinese patients showed that in patients who received MPAA as initial therapy, the disease flare rate was increased when the total duration of MPAA was <2 years,[632,715] and that long-term maintenance treatment with MPAA was associated with a low disease flare rate.[790] Overall, although the efficacy and safety data to date favor MPAA as maintenance treatment, azathioprine is an acceptable alternative, especially in the later phase of long-term management.

Practice Point 10.2.3.2.2: Glucocorticoids should be tapered to the lowest possible dose during maintenance, except when glucocorticoids are required for extrarenal lupus manifestations; discontinuation of glucocorticoids can be considered after patients have maintained a complete clinical renal response for ≥12 months.

Prolonged glucocorticoid exposure is associated with continued and significant organ damage accrual and morbidity.[737,791] At the end of the initial phase of treatment, the goal is to have reduced most patients to a daily dose of prednisone (or equivalent) that is ≤7.5 mg, and preferably as low as possible. The tapering regimen and duration of glucocorticoid maintenance therapy vary considerably among clinicians and are largely opinion-based, informed by individualized considerations of a patient's risk of developing disease flare, and the risk–benefit balance of the prevailing dose of immunosuppressive medications. A recent open-label controlled trial (Evaluation of the Discontinuation of Maintenance Corticosteroid Treatment in Quiescent Systemic Lupus [CORTICOLUP] trial) compared continuation of prednisone 5 mg daily against discontinuation in 124 multiethnic patients in Paris with stable and quiescent SLE (history of LN in 34% and 41%, respectively).[792] The results showed a significantly increased flare rate over 52 weeks of follow-up in patients who discontinued prednisone (HR: 0.2 in those who continued prednisone 5 mg daily, $P = 0.002$), and 45 of 63 patients in the discontinuation group remained glucocorticoid-free. Glucocorticoid discontinuation in patients with stable quiescent disease can be considered, but it should be undertaken with caution and careful monitoring for disease flare. Glucocorticoid avoidance in maintenance therapy has been attempted with the use of rituximab, but the evidence to support this approach remains limited to one cohort.[767]

Practice Point 10.2.3.2.3: The dose of MMF in the early maintenance phase is approximately 750–1000 mg twice daily, and for MPA, approximately 540–720 mg twice daily.

The suggested dosages are largely based on data from the ALMS and MAINTAIN trial.[633,780] As mentioned before, the

Work Group recommends maintenance of these doses until achievement of complete response and then tapering (Figure 93). Due to pharmacogenetic differences, the level of MPA exposure varies considerably among patients receiving the same dose of MPAA. Although there are insufficient data to date to provide recommendations on therapeutic drug monitoring, measurement of MPA exposure may be helpful in patients with unsatisfactory treatment response or who manifest drug toxicities. There are preliminary data associating disease flares with low MPA exposure, but optimal drug level at different phases of clinical management remains to be determined.[793]

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

Experience in Japanese patients suggested that low-dose tacrolimus at 3 mg/d was safe and effective when given as long-term maintenance therapy together with low-dose glucocorticoids.[785,794] In a study of 70 Chinese patients who achieved remission after initial therapy with glucocorticoids and either i.v. cyclophosphamide or tacrolimus, maintenance therapy with tacrolimus (trough blood level target of 4–6 ng/ml [5–7.4 nmol/l]) was compared with azathioprine 2 mg/kg/d, both in combination with prednisone 10 mg/d. Over 6 months of follow-up, kidney relapse occurred in 2 azathioprine-treated patients and in none in the tacrolimus group (Figure 93).[795]

Adding tacrolimus or cyclosporine to maintenance therapy was reported in case series as effective in reducing proteinuria in patients with unsatisfactory suppression of proteinuria following initial therapy with glucocorticoids and MMF, especially in patients who showed features of MN in their baseline kidney biopsies.[783,786,796–798] Caution is required when considering adding CNI for the purpose of decreasing proteinuria. It is desirable that there be histologic evidence of podocyte injury so that the CNI is likely to be effective. Also, it is prudent to avoid over-immunosuppression and chronic CNI nephrotoxicity, especially in patients with CKD.

Although most studies were done in patients of Asian origin, it is reasonable to consider a CNI for maintenance therapy in any patients who cannot take MPAA or azathioprine. CNIs can also be used safely during pregnancy (Figure 93).

The experience with mizoribine as maintenance therapy in LN is largely limited to Japanese patients.[787,799] Results from a post-marketing surveillance study that included 559 mizoribine-treated patients showed that nearly all were receiving glucocorticoids, and 43.8% were receiving tacrolimus as concomitant treatment. Overall, 63.3% of patients achieved complete or partial remission, and only 3.6% of patients experienced serious adverse drug reactions within 2 years of mizoribine treatment, and the authors concluded that mizoribine was safe and effective (Figure 93).[800]

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

The optimal duration of maintenance immunosuppression in patients with proliferative LN is not known. If withdrawn too early, patients may relapse even after having had a good response to treatment. Prolonged maintenance increases exposure to immunosuppression and may not provide sufficient continued benefits to outweigh toxicity risk. The Work Group recommends that the total duration of immunosuppression (initial therapy plus maintenance) for patients with proliferative LN who have achieved a complete renal response and have no ongoing extrarenal manifestations be ≥36 months, based on considering the following evidence collectively:

- In Chinese patients who received MMF as initial therapy, discontinuation of MMF before 2 years was associated with an increased risk of disease flare.[632,715]
- During the third to fourth year of MMF maintenance therapy, kidney flare was associated with low 12-hour trough MPA blood levels, whereas patients with trough levels of approximately 2 mg/l remained in remission.[801]

Maintenance immuno-suppressive regimens	Low-dose glucocorticoid AND				
	Mycophenolic acid analogs	AZA	CNI	Mizoribine	Mycophenolic acid analogs and CNI
Comments	Preferred treatment based on high-quality evidence Lower flare rate than alternative regimens such as AZA	Safe in pregnancy Low medication cost	Tacrolimus or cyclosporine Safe in pregnancy	Data mostly from Japanese patients	Data predominantly from Chinese and Japanese patients Long-term safety data of triple immunosuppression required

Figure 93 | Maintenance immunosuppressive regimens in patients with LN. AZA, azathioprine; CNI, calcineurin inhibitor; LN, lupus nephritis.

- The ALMS maintenance phase data reported a relatively high incidence of treatment failure (16%–32%) and kidney flares (13%–23%) despite 36 months of immunosuppression and maintenance with low-dose glucocorticoids and either MMF or azathioprine.[633]
- In an Italian cohort, immunosuppression was tapered in patients who were in complete remission for >12 months, and 27% relapsed. One of the predictors of successful treatment discontinuation was a longer duration (median of 4 years) of prior immunosuppressive therapy.[802]
- Despite ≥36 months of immunosuppression and ≥12 months of sustained complete clinical renal response, 28%–50% of patients continue to show inflammatory histologic activity on repeat kidney biopsy.[803–805] Patients with persistent histologic activity have an increased risk of LN flare after maintenance immunosuppression is discontinued, compared to patients who have no residual inflammatory activity in their kidneys.[804,805]
- Patients who have achieved a partial remission tend to be left on maintenance immunosuppression indefinitely. Kidney biopsy studies of such patients have shown that many have resolution of histologic activity[803–805] but are clinically only in partial remission due to residual proteinuria. In such patients, proteinuria may reflect CKD as opposed to active disease, and immunosuppression may be able to be discontinued in the absence of ongoing kidney inflammation.

In summary, despite not knowing the optimal duration of maintenance immunosuppression for proliferative LN, most patients will require ≥3 years of therapy. Clinical response findings do not correlate completely with ongoing kidney inflammation. A repeat kidney biopsy could be considered to inform the decision to continue or withdraw maintenance immunosuppression.

10.2.4 Class V lupus nephritis

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

Class V LN accounts for 5%–10% of all LN cases. Data on clinical management are based on very few RCTs with small sample sizes, analyses of pooled data, and observational studies. Because 10%–30% of patients with Class V LN and nephrotic proteinuria progress to kidney failure during long-term follow-up, heavy proteinuria does not usually spontaneously remit, as it may in primary MN, and as heavy proteinuria increases CV morbidity and predisposes patients to thrombosis, treatment of Class V patients who have nephrotic-range proteinuria or NS is warranted.[806–809]

A small RCT demonstrated that remission was significantly more likely with prednisone plus cyclophosphamide (60%) or prednisone plus cyclosporine (84%) than prednisone alone (27%), but cyclophosphamide maintained remission longer (no relapses within a year) than CNI treatment (40% relapsed within a year of discontinuing the CNI).[738] Pooled data from 2 studies showed that prednisone plus either cyclophosphamide or MMF had similar efficacy in lowering proteinuria after 6 months of treatment.[810] Other studies with relatively

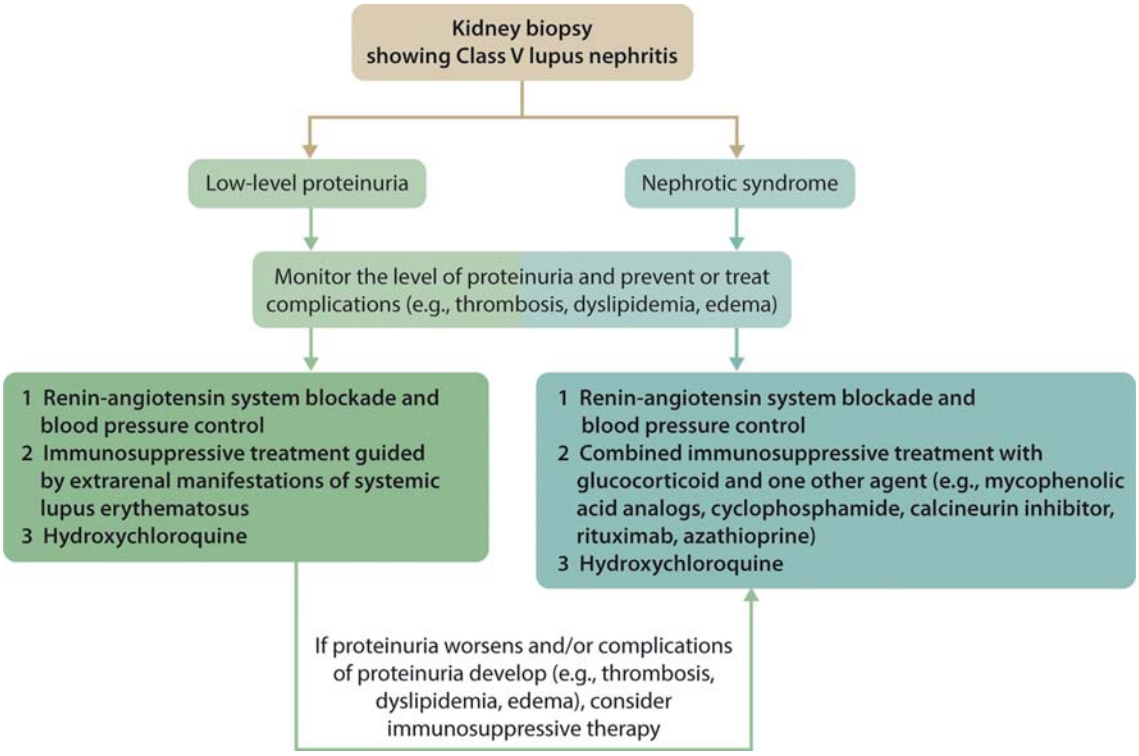

Figure 94 | Management of patients with pure Class V LN. LN, lupus nephritis.

small sample sizes reported the efficacy of glucocorticoids combined with azathioprine,[644,809] oral cyclophosphamide,[811] i.v. cyclophosphamide,[738,812] MMF,[643,644,812–815] CNIs,[738,797,814,816–818] and rituximab,[767,819] with response rates of 40%–60%. Tacrolimus was reported as effective when given together with glucocorticoids as initial therapy to patients with Class V LN who presented with NS, or when given as add-on therapy to patients with mixed Class V and Class III/IV LN whose proteinuria response was judged suboptimal after initial treatment with prednisolone and MMF.[786] In the phase 3 voclosporin trial (AURORA; see Practice Point 10.2.3.1.5), 14% of the patients had pure Class V LN.[754] Although adding voclosporin to background therapy was more effective than background immunosuppression alone in achieving renal response, the details on the patients with Class V have not been presented. There is a lack of robust data in the management of Class V LN, especially in patients who present with NS. The data to date are more in favor of combining glucocorticoids with MPAA, a CNI, or short-term cyclophosphamide than with other options.

In addition to general methods to reduce urine protein, such as RASi and meticulous BP control, MMF is a reasonable first choice for treating patients with Class V and nephrotic-range proteinuria. If ineffective, we suggest cyclophosphamide for ≤6 months next in an effort to induce long-term remission, but long-term CNI or rituximab may also be tried if the patient has had prior significant exposure to cyclophosphamide or is reluctant to take the medication in view of the associated toxicities. Appropriate measures to prevent venous thrombosis should be considered in patients whose proteinuria persists despite treatments (Chapter 1).

10.2.4.1 Assessing treatment response in LN.

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

All response criteria currently used in clinical trials of LN require improvement in proteinuria and stabilization or improvement in kidney function. Several observational studies suggest that long-term kidney health is considerably more favorable in patients who respond to treatment.[712,820–822] However, there are no universally accepted criteria for the level of improvement required, which makes direct comparisons of different clinical trials more difficult.

The definitions in Figure 95 are commonly used with "baseline" kidney function referring to the level before disease flare, which is not known in patients with no previous medical record. Long-term data from 2 large European LN trials showed that favorable kidney outcomes were predicted by achieving a proteinuria level of 0.7–0.8 g/d after 12 months of therapy, a conclusion supported by other reports.[714,823–825] In this regard, renal response at week 104 or week 52 have been used as study endpoints in recent clinical trials such as the phase 3 BLISS-LN study.[701]

Another caveat is the lack of consensus on the appropriate time when response should be assessed. For logistic and economic reasons, large clinical trials often evaluate response at 6–12 months, but improvement of proteinuria and eGFR is continuous over time, and the rate of improvement varies considerably among patients. Also, there are marked differences in baseline kidney abnormalities at disease presentation. Therefore, the time to reach prespecified proteinuria and eGFR cutoffs, either absolute or relative to baseline, varies considerably among patients.[629,631,632,739,797,826,827]

Outside of a formal clinical trial setting, the Work Group suggests that if patients are improving, allowing 18–24 months to achieve a complete response is reasonable in patients who show continuous improvement. A potential tool to predict kidney outcomes was derived from a *post hoc* analysis of the large ALMS trial. This analysis suggested favorable kidney outcomes are predicted by normalization of complement levels and ≥25% reduction of proteinuria after 8 weeks of treatment.[828]

SLE is a systemic disease, and the kidney should not be examined in isolation from other clinical manifestations. Several other clinical parameters have not been evaluated in detail in clinical studies but are relevant at individual levels such as systemic activity of SLE (e.g., SLEDAI score), BP control, edema resolution, urine sediment, hemoglobin and albumin improvements, and serologic parameters, including dsDNA antibodies and serum complements. If

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 95 | 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-h urine specimen. LN, lupus nephritis; PCR, protein–creatinine ratio.

lupus serologies are abnormal, it is reasonable to expect improvement with therapy for LN, although many patients remain positive for anti-dsDNA and/or have low complement levels despite resolution of proteinuria. Extrarenal lupus activity requiring continuation or a change in therapy could remain even if the kidney improves. Finally, response is currently only assessed clinically. Considerable data suggest that persistent intrarenal lupus activity may remain, despite resolution of proteinuria and eGFR.[803–805] A repeat kidney biopsy may, therefore, be useful in confirming renal response, especially before important major treatment decisions such as discontinuation of immunosuppression.[627]

10.2.4.2 Management of unsatisfactory response to treatment

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

Judging the response to therapy as unsatisfactory is difficult because there are no robust data with which to compare an individual's response trajectory, and there needs to be a balance between giving a patient sufficient time to respond and the likelihood of ongoing nephron loss. Nonetheless, patients are expected to show improvement over time after treatment. So, no improvement or worsening despite treatment for 3–4 weeks is clearly unsatisfactory and warrants early appraisal of potential causes for nonresponse and early intervention, whereas patients who show response to treatment can be closely observed, and investigated when the level of improvement after 3–4 months of therapy is suboptimal or below expectation. A 2-month time frame to see improvement was suggested based on *post hoc* analysis of data from the ALMS trial,[828] but deterioration needs to be evaluated on an individual basis in terms of rapidity and severity.

The role of nonadherence in unsatisfactory treatment response cannot be over-emphasized. The prevalence of nonadherence in patients with SLE could be >60%.[829–832] Switching from oral immunosuppression to i.v. cyclophosphamide should be considered when nonadherence is suspected or proven.

The quality of evidence on the management of LN "refractory" to standard initial therapy is marred by variable definitions of treatment response or refractoriness, the disparity between kidney histology and clinical outcome parameters, the legacy effect of prior therapy, and the impact of factors other than disease activity on outcome parameters such as proteinuria and kidney function. Available data on the management of refractory disease are largely from uncontrolled observational cohort studies, with varied inclusion criteria and based on relatively small sample size.

The role of switching between therapeutic regimens has not been formally investigated. In a US study that compared mycophenolate with i.v. cyclophosphamide, patients who did not show response, defined as improvement by ≥30%, after 12 weeks of treatment were switched to the other treatment arm.[710] Another study reported efficacy of MMF in patients refractory to or who had relapsed after cyclophosphamide treatment.[833] However, a legacy effect of prior therapy could not be excluded. Unequivocal evidence on the efficacy of switching therapies is lacking.

Evidence supporting the use of rituximab for refractory LN is from open-label observational studies that have reported response rates of 50%–80%[762,790,834–845] and a meta-analysis of 31 studies with 1112 patients that showed complete and partial response rates of 46% and 32%, respectively, after rituximab was added.[846] The role of other biologics with demonstrated efficacy in recent clinical trials, such as obinutuzumab or belimumab, warrants further investigation.

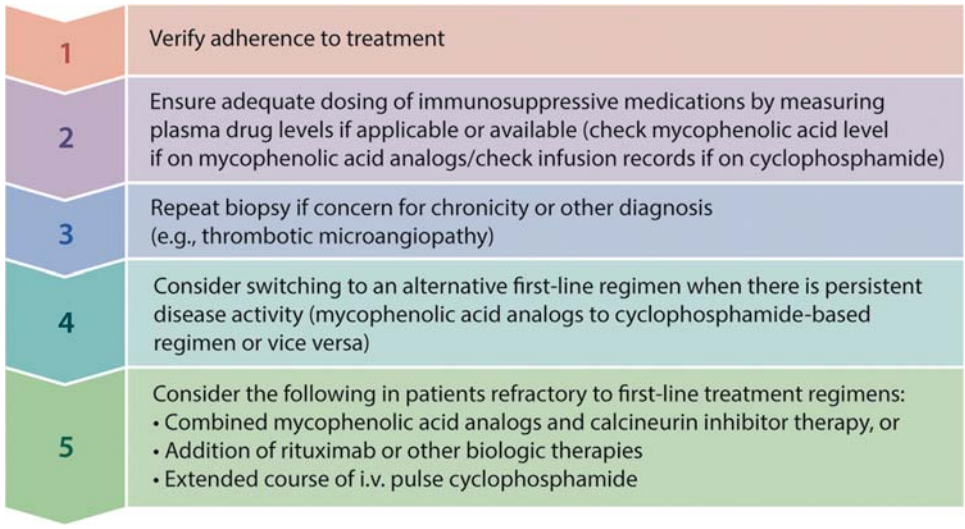

Figure 96 | Management of patients who show unsatisfactory response to initial therapy for active LN. i.v., intravenous; LN, lupus nephritis.

Similarly, data from observational cohorts suggested efficacy of CNIs, combined with either glucocorticoids and/or MMF, in patients with refractory or relapsing LN.[783,784,847–851]

10.2.4.3 Treatment of LN relapse

Relapses of LN are common, and LN flare is an important predictor of poor long-term kidney survival.[852–855] LN flare rates of 10%–50% have been reported, and relapses occur over time.[856] Failure to achieve complete remission increases the risk of subsequent relapse.[706,712,857] Relapse rates of 39% and 64% were found in patients who achieved complete remission or partial remission, respectively, and time-to-relapse after complete response was 36 months, compared to 18 months after partial response.[706] Similarly, an HR of 6.2 for relapse was reported in Chinese patients who did not achieve complete remission after initial therapy.[712]

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

There are no data that focus on the treatment of LN flares alone. However, it is generally agreed that there is no major difference between management of an LN flare and that of *de novo* active LN, and initial therapies are the same as outlined above. Although not yet ready for clinical management, emerging data from a recent transcriptomic study of paired serial kidney biopsies showed slight differences in intrarenal inflammatory gene expression between the initial presentation and LN relapse.[858] All LN clinical trials testing initial, induction therapies for LN include both types of patients. Although these considerations form the basis for Practice Point 10.2.4.3.1, there are several caveats in choosing an approach:

1. If patients had been treated with cyclophosphamide in the past, it is important to calculate lifetime exposure. Ovarian failure has been associated with age (and oocyte reserve) and cumulative dose, with sustained amenorrhea occurring in up to 50% of patients aged >32 years with a cumulative exposure of 8 g/m^2.[859,860] The chance of future malignancy increases after a total exposure of 36 g, so if a patient is approaching this level, cyclophosphamide is better avoided.
2. If patients relapse during pregnancy, treatment choices are more limited. These are discussed in Section 10.3.2.
3. Patient preference and/or tolerance of the initial regimen should be considered. Also, patient adherence should be considered in the choice of treatment.
4. Disease activity should be verified, as proteinuria may be secondary to CKD.

The last point is critical but complex. The same clinical criteria used to diagnose *de novo* LN are used to diagnose LN flares absent a kidney biopsy. That is, flares are generally considered when proteinuria increases beyond a certain threshold, with or without an active urinary sediment or deterioration of kidney function. Without histology, it is sometimes difficult to determine whether changes in proteinuria are due to active inflammatory kidney injury or reflect progression of chronic damage incurred during preceding episodes of active LN, because there is often discordance between clinical findings and histologic findings.[627,628] The tempo and magnitude of change in proteinuria may help with rapid increases, and large changes often reflect active disease. SLE serologies (e.g., complement, anti-dsDNA) may support a flare diagnosis but need to be evaluated in the context of prior serologic trends. A change from normal to abnormal is more useful than serologic studies that are always normal or always abnormal. Given the risks of immunosuppression, if the diagnosis of flare remains uncertain, a repeat kidney biopsy to assess disease activity versus chronic damage is important to inform treatment decisions.[861]

In lieu of waiting until LN flares before treating it, some investigators have examined preemptive treatment to prevent flare. A trial in the Netherlands compared "early treatment" of 16 patients to conventional management of 23 patients who increased their anti-dsDNA levels by 25%.[862] Prednisone was increased by 30 mg/d in the early treatment group and was tapered back to baseline over 18 weeks. After a mean follow-up of <2 years, 2 major relapses (12.5%, both with LN relapse) occurred in the early treatment group, compared to 20 relapses (87%), 7 of which were major (1 kidney relapse), in the conventionally managed patients. A prospective trial in the US randomized 41 patients who showed an increase in both anti-dsDNA and C3a to prednisone (30 mg/d tapered >4 weeks) or placebo. During a short follow-up (90 days), no patients given prednisone had a severe flare, but 6 placebo patients did, and 3 of the flares were kidney-related.[863] A recently published retrospective study of Chinese patients with LN suggested that a moderate increase in immunosuppressive treatment dose was effective in preventing kidney and nonrenal flares without excessive treatment-related adverse effects.[793] Taken together, all of these data suggest that impending LN flares may be preventable, at least for some patients, but larger RCTs of sufficient duration are needed before this approach can be endorsed.

10.3 Special situations

10.3.1 Lupus nephritis and thrombotic microangiopathy

Practice Point 10.3.1.1: Patients with LN and thrombotic microangiopathy (TMA) should be managed according to the underlying etiology of TMA, as shown in Figure 97[864].

TMA is a pathologic description of vascular endothelial injury secondary to various etiologies.[865] The causes of TMA most relevant to patients with LN are thrombotic thrombocytopenic purpura (TTP), antiphospholipid syndrome (APS), and complement-mediated TMA. However, patients with lupus can also develop TMA due to Shiga-toxin-hemolytic uremic syndrome, infections, drugs, or malignancies.[454,866] The key to a good outcome for TMA in LN is rapid diagnosis and prompt treatment. When appropriate expertise is available, it is preferable that patients with LN and TMA be comanaged with an experienced hematologist. However,

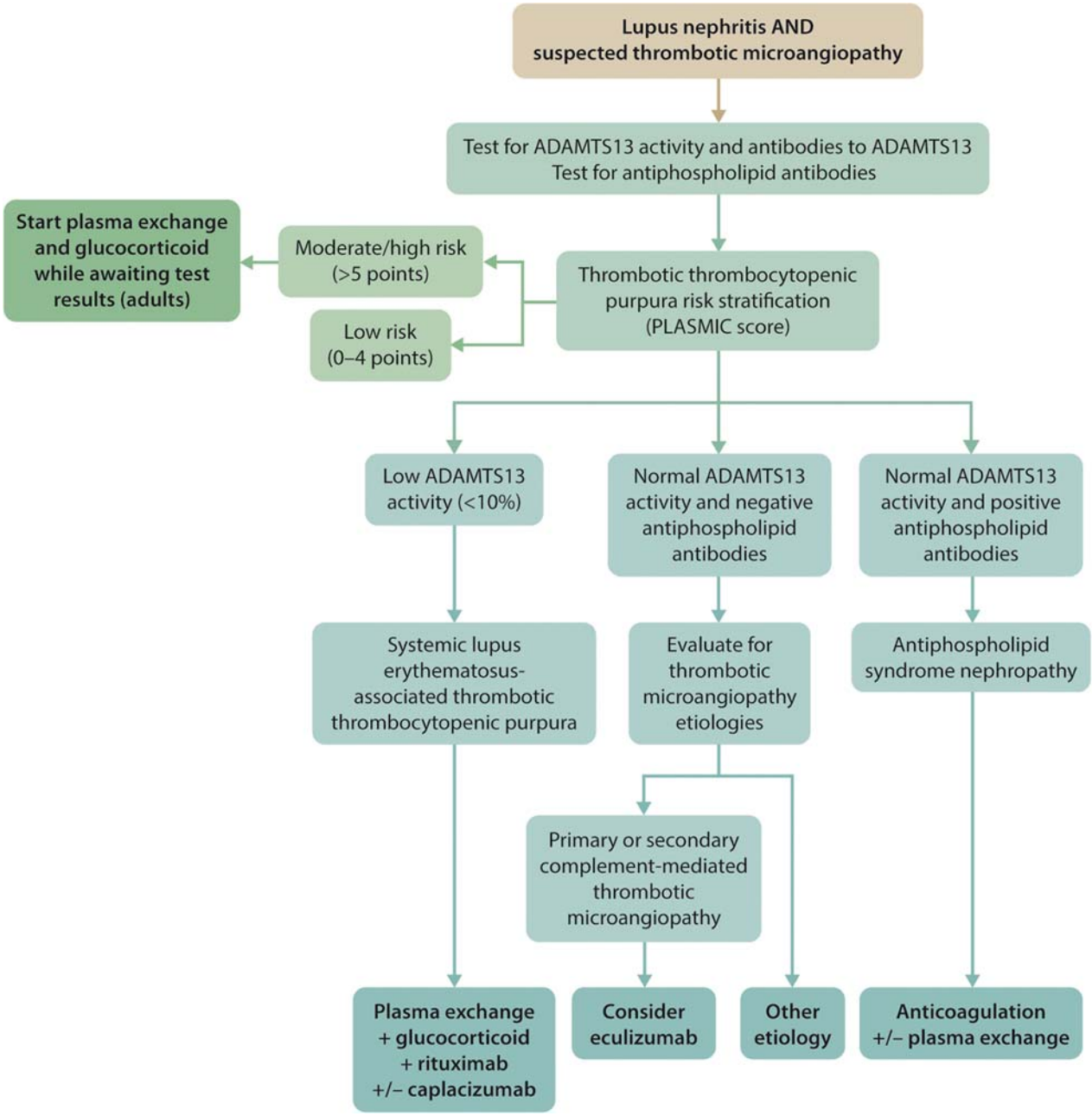

Figure 97 | Management of patients with LN and TMA. Bendapudi PK, Hurwitz S, Fry A, et al. Derivation and external validation of the PLASMIC score for rapid assessment of adults with thrombotic microangiopathies: a cohort study. *Lancet Haematol.* 2017;4:e157–e164.[864] ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; PLASMIC, Platelet count, combined hemoLysis variable, absence of Active cancer, absence of Stem-cell or solid-organ transplant, MCV, INR, Creatinine.

some of the serologic and genetic testing needed for a specific diagnosis, such as ADAMTS13 activity or the presence of anti-ADAMTS13 antibodies in the case of TTP, antiphospholipid antibodies, and complement studies may not be available, and even when they are available, they often take considerable time to complete (Figure 97). If TTP is suspected, one may consider using the PLASMIC score,[864] and if the score defines an intermediate-to-high risk of TTP, adults should be started on plasma exchange and glucocorticoids while waiting for the investigation results. In children, TTP is less common, and plasma exchange has been associated with considerable morbidity,[867] so it is acceptable to defer plasma exchange for 24–48 hours until the ADAMTS13 result is available to confirm that the procedure is indicated.[868]

TMA due to lupus-associated TTP. The diagnosis of TTP is mainly reserved for patients with TMA and low ADAMST13 activity (≤10%).[865,869] The treatment of confirmed TTP in LN is extrapolated from that of acquired TTP and includes plasma exchange,[870,871] high-dose glucocorticoids,[872,873] rituximab,[874–877] and/or caplacizumab (von Willebrand factor inhibitor; Figure 97).[878,879]

TMA due to APS. Antiphospholipid antibodies (aPLA) are found in about 30% of patients with SLE and may be associated with venous and/or arterial macro- or microvascular thrombosis, thrombocytopenia, adverse pregnancy outcomes, and neurologic abnormalities. Kidney damage is a well-recognized complication of APS, presenting as renal artery thrombosis or stenosis, RVT, or injury to the kidney microvasculature, also known as APS nephropathy.[880] There are few data on the management of APS nephropathy. In a retrospective study of 97 patients with kidney TMA, 62.9% tested positive for aPLA, 38.1% for lupus anticoagulant, and 13.4% had APS.[881] Complete and partial response rates were 38.1% and 22.6%, respectively, after 12 months of immunosuppressive treatment. Thirty-seven of 61 patients who were aPLA-positive also received anticoagulation therapy, and anticoagulated patients showed a higher complete response rate (59.5% vs. 30.8%), and the partial response rate was 18.9% and 26.9% in patients who had or had not received anticoagulant therapy, respectively. Therefore, it is reasonable to treat APS nephropathy with long-term anticoagulation with warfarin. Direct oral anticoagulants are not recommended, as they were inferior to warfarin in preventing thromboembolic events in this setting.[882,883]

Catastrophic APS is characterized by thrombosis, often of rapid onset, affecting multiple organs, and it is associated with high mortality. Treatment includes both total anticoagulation and high-dose glucocorticoids.[884] Plasma exchange is often used in catastrophic APS[152] and has been associated with improved patient survival in retrospective studies.[885] There are recent anecdotal reports on the potential efficacy of rituximab in catastrophic APS.[886,887] It has been shown that complement activation is involved in the pathogenesis of tissue injury induced by aPLA, and there is emerging evidence on the efficacy of eculizumab in the treatment of catastrophic APS.[888–890]

Complement-mediated TMA and atypical hemolytic uremic syndrome (aHUS). Many cases of kidney TMA with ADAMTS13 activity >10% and negative aPLA correspond to complement-mediated TMA, and these patients ideally should be evaluated with complement studies when they are available.[539,543] aHUS is a rare and severe form of TMA caused by dysregulation of the alternative complement pathway due to genetic or acquired functional defects in complement regulatory proteins, resulting in excessive production of the terminal complement complex C5b-C9, triggering endothelial cell injury that predominantly affects the kidney vasculature in the arterioles and interlobular arteries.

Complement-mediated TMA in LN does not respond well to plasma exchange or immunosuppression with glucocorticoids and cyclophosphamide, and it may be best treated with a complement inhibitor such as eculizumab, although the optimal dose and duration remain controversial.[891–893] The limited data to date show a high response rate, with resolution of TMA in 68% of patients with secondary aHUS.[894] Data from 31 adult patients (26 treated with plasma therapy and 5 plasma-resistant patients treated with eculizumab) showed complete kidney recovery in 4 of 5 eculizumab-treated patients.[895] Efficacy of eculizumab treatment was also reported in a patients with lupus and heterozygous deletion in complement factor H CFHR1-CFHR3 gene presenting with TMA, and a review of 20 patients showed a kidney recovery rate of 85% in patients with SLE and/or APS after treatment with eculizumab.[896] A recent report on 9 patients with TMA associated with SLE and/or APS showed that kidney function improved by 25% in half of the patients after 4 weeks of eculizumab treatment, and 2 of 3 patients were able to discontinue dialysis.[897]

Another recent report on 11 patients with TMA and LN showed complement regulatory protein mutations in 6 patients, and response to eculizumab treatment in 10 patients.[889]

Prior to the advent of eculizumab, plasma exchange and/or plasma infusion was the only treatment for aHUS, with efficacy in less than half of patients and little benefit in patients with membrane cofactor protein mutations.[873,898,899] As complement studies often take some time to return, initiation of plasma exchange is warranted during the waiting period, or if access to eculizumab is limited. The rationale and objectives of plasma infusion and plasma exchange include the replacement of absent or mutated circulating complement regulators such as CFH and the removal of antibodies directed to complement regulatory proteins or mutated factors that play a permissive role in aberrant complement activation. In the absence of eculizumab, the efficacy of plasma exchange and plasma infusion varies, and the duration of therapy is dependent on the treatment response.[900–903] Data from 31 adult patients (26 treated with plasma therapy and 5 plasma-resistant patients treated with eculizumab) showed recovery of kidney function in approximately 40% of patients given plasma therapy.[895]

10.3.2 Pregnancy in patients with lupus nephritis

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

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

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

Adverse pregnancy outcomes, such as preeclampsia, preterm birth, and fetal loss, are higher in patients with active LN.[904,905] Commonly used medications for LN induction and maintenance therapy, particularly cyclophosphamide and MMF formulations, are toxic to the fetus or teratogenic, respectively. A discussion of acceptable methods of contraception should, therefore, take place as part of initiating treatment for LN. Because of the increased risk of clotting in patients with SLE and antiphospholipid antibodies, use of estrogen-containing birth control should be avoided or minimized. A risk-factor checklist has been proposed by some organizations to stratify, plan, and counsel pregnancy in patients with lupus.[906]

Hydroxychloroquine is considered safe in pregnancy and may decrease the rate of preterm birth and intrauterine growth retardation, whereas withdrawal of hydroxychloroquine has been associated with LN flare, so it should be continued when an LN patient becomes pregnant.[659,664,907] Low-dose aspirin (≤100 mg/d) may also reduce the risk of preeclampsia and intrauterine growth retardation and can be started at conception or as soon as pregnancy is recognized.[908,909] The incidence of LN flare in pregnancy has been reported to be 11%–28% and is higher if patients have low serum complement levels or high anti-dsDNA antibody titers.[904] Active LN during pregnancy can be treated with glucocorticoids plus azathioprine and/or a CNI, although in the first trimester, the use of glucocorticoids is associated with an increased risk of gestational diabetes and cleft palate. For patients on maintenance therapy, if they are on azathioprine, this can be continued, but if they are on MPAA, this must be discontinued or changed to azathioprine.

10.3.3 Treatment of lupus nephritis in children

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

Approximately 20% of SLE is diagnosed before the age of 18 years, and genetic components are more common in childhood-onset SLE.[910–912] There is suggestive evidence that disease is often more severe in the pediatric population. In adolescent patients with SLE and isolated proteinuria, orthostatic or postural proteinuria should be excluded, as this phenomenon has been observed frequently in this population.[913,914]

There are few large-scale RCTs to guide treatment of children with LN, and much of the current literature reports the results of adult regimens applied to this population. The data are insufficient to confirm superiority of efficacy for any particular treatment regimen. Several issues must be addressed when treating pediatric lupus, including adherence concerns, which may favor i.v. medications; growth concerns, which may favor limiting glucocorticoid exposure; fertility concerns, especially as patients approach adolescence, which may favor limiting cyclophosphamide exposure; and psychosocial concerns relating to school and socialization with peers. Special considerations regarding glucocorticoid dosing in children are included under Practice Point 10.2.3.1.1. Children with LN should be comanaged by pediatric nephrologists and rheumatologists with expertise in lupus, and the expertise of other professionals, such as clinical psychologists, psychiatrists, or social workers, can be helpful.

10.3.4 Management of lupus patients with kidney failure

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

There are no data to favor one form of dialysis over another in kidney failure due to LN. Patients with lupus receiving hemodialysis display similar 3-year survival rates and mortality due to CV or infectious complications to those of patients receiving peritoneal dialysis.[915–917] Therefore, kidney replacement therapy should be individualized, taking into account patient characteristics and preferences.

Kidney transplantation is preferred to dialysis. Kidney transplant outcomes are similar to those in patients who developed kidney failure due to other types of kidney disease,[918,919] and transplanted patients have lower mortality than patients with lupus who remain on dialysis.[920] As clinical outcomes are better in patients with shorter durations of dialysis,[921,922] transplantation may be carried out as soon as disease is quiescent. Although lupus activity tends to decrease after kidney failure develops, patients can still flare,[923] so periodic monitoring is required. LN can recur in kidney allografts, but the risk is low, and flares do not generally result in allograft loss.[924–926] One important consideration is that patients who have antiphospholipid antibodies may experience dialysis vascular access clotting or allograft thrombosis and may require prophylactic anticoagulation.[927–929]

Research recommendations

- Identify and validate biomarkers of kidney histology that can be used to follow the tissue response to treatment in real-time to help in managing immunosuppression.
- Identify and validate biomarkers of impending LN flare that can be used to decide if preemptive immunosuppressive therapy is indicated.
- Classify LN on the basis of molecular pathogenesis and histology as opposed to histology alone. This classification ideally could be used in conjunction with novel, targeted

therapies for LN to select the most appropriate treatment, including biologic medications targeting specific pathogenic pathways.
- Establish renal response criteria that reflect resolution of disease activity at the tissue level and are also predictive of long-term kidney survival and patient survival without need of kidney replacement therapy.
- Establish criteria for duration of maintenance immunosuppression and the safe withdrawal of therapy.
- RCTs are needed to test the following questions:
  - What is the optimal therapy for patients with severe Class III/IV LN (i.e., patients presenting with severe AKI and/or markedly abnormal SCr level or eGFR) who have been excluded from the majority of clinical trials to date?
  - What is the optimal therapy for pure Class V LN?
  - Do antimalarials improve the responsiveness of LN to treatment and/or help maintain disease quiescence and prevent flares?
  - Is there a role for complement inhibition in the management of LN?
  - What are the optimal or prioritized therapies for childhood LN?
  - What are the efficacy and safety profiles of CNIs, including the optimal drug exposure when used as initial or maintenance treatment of LN? What are the long-term implications of such treatment?
  - What are the optimal glucocorticoid-reduction protocols for LN management?

Chapter 11: Anti-glomerular basement membrane (Anti-GBM) antibody glomerulonephritis

Anti-glomerular basement membrane (GBM) antibody GN is a rare glomerular disease with an incidence of 0.5–1 per million population. It is caused by autoantibodies against the noncollagenous domain of the α3 chain of type IV collagen. Anti-GBM GN may present either as an isolated kidney disease or as a pulmonary–renal syndrome (Goodpasture's syndrome). Anti-GBM is usually a rapidly progressive crescentic GN, and about 80% of patients have crescents in half or more of their glomeruli.[930] Goodpasture's syndrome occurs in 40%–60% of patients, and kidney disease is accompanied by sometimes massive and fatal pulmonary hemorrhage.[931] Anti-GBM disease with pulmonary involvement is more frequent in men (about 80%) and typically occurs during the second decade.[932] Isolated anti-GBM nephritis does not have clear male preponderance and may also occur in older persons.[933] If untreated, anti-GBM disease has very high morbidity, with almost all patients going on to kidney failure, and it can have significant mortality. In patients with Goodpasture's syndrome, the mortality rate was 96% before the introduction of immunosuppression, and 47% despite treatment with immunosuppression.[934] Most patients died of respiratory failure.[932] The cornerstone of the treatment is rapid removal of the pathogenic autoantibodies and suppression of their production to prevent further kidney and pulmonary injury. This chapter makes management recommendations for adults (≥18 years of age) who have anti-GBM GN with or without pulmonary involvement.

11.1 Diagnosis

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

In patients who present with a suspected RPGN, serologic testing for the presence of anti-GBM antibodies should be done urgently using commercially available enzyme-linked immunoassays. The immunoassays for anti-GBM antibodies may be negative in up to 10% of patients, and in these individuals, diagnosis may be established only by kidney biopsy demonstrating linear IgG deposition along the GBM.[935,936]

Diagnosis of diffuse alveolar hemorrhage is usually done clinically and confirmed by high-resolution CT scan. Bronchoscopy and pulmonary functional testing may be useful, but they are often unnecessary and may be difficult to perform in critically ill and unstable patients. Diagnosis should be made without delay, and kidney biopsy findings should be reported to the clinician by the pathologist on the day of the biopsy (Figure 98).

11.2 Treatment

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

This recommendation places a relatively higher value on preventing mortality and further loss of kidney function and a relatively lower value on the potential adverse events that may occur with the intense immunosuppression regimen recommended. Given the uniformly poor prognosis of untreated disease, almost every patient and physician would be expected to choose this treatment regimen.

Key information

Balance of benefits and harms. Untreated anti-GBM disease is associated with considerable morbidity and mortality. Observational studies have shown that early mortality of anti-GBM decreased from 47%[932] to 8.5% with plasma exchange and immunosuppression,[933] and 5-year patient survival is currently >90% with treatment.[937] In contrast, although kidney survival has improved with plasma exchange and immunosuppressive treatment, it still remains relatively poor, in part because of delayed diagnosis and initiation of treatment. Since 2007, the 5-year kidney survival rate of treated patients has improved from about 25% to 50%, probably because of both earlier diagnosis and a higher proportion of patients being treated with plasma exchange.[937,938]

Plasma exchange, in combination with immunosuppression is, undoubtedly, life-saving and helps prevent kidney failure in patients with independent kidney function at presentation.

Potential harms include infections associated with immunosuppression and bleeding after plasma exchange. Administration of fresh frozen plasma after plasma exchange may be indicated, especially in patients with alveolar hemorrhage and after kidney biopsy.

Quality of evidence. The evidence is based mostly on the comparison of treated patients with historical controls; there has been only one RCT, which is of very low quality. No systematic review of observational studies was undertaken by the ERT. However, the observational studies that were

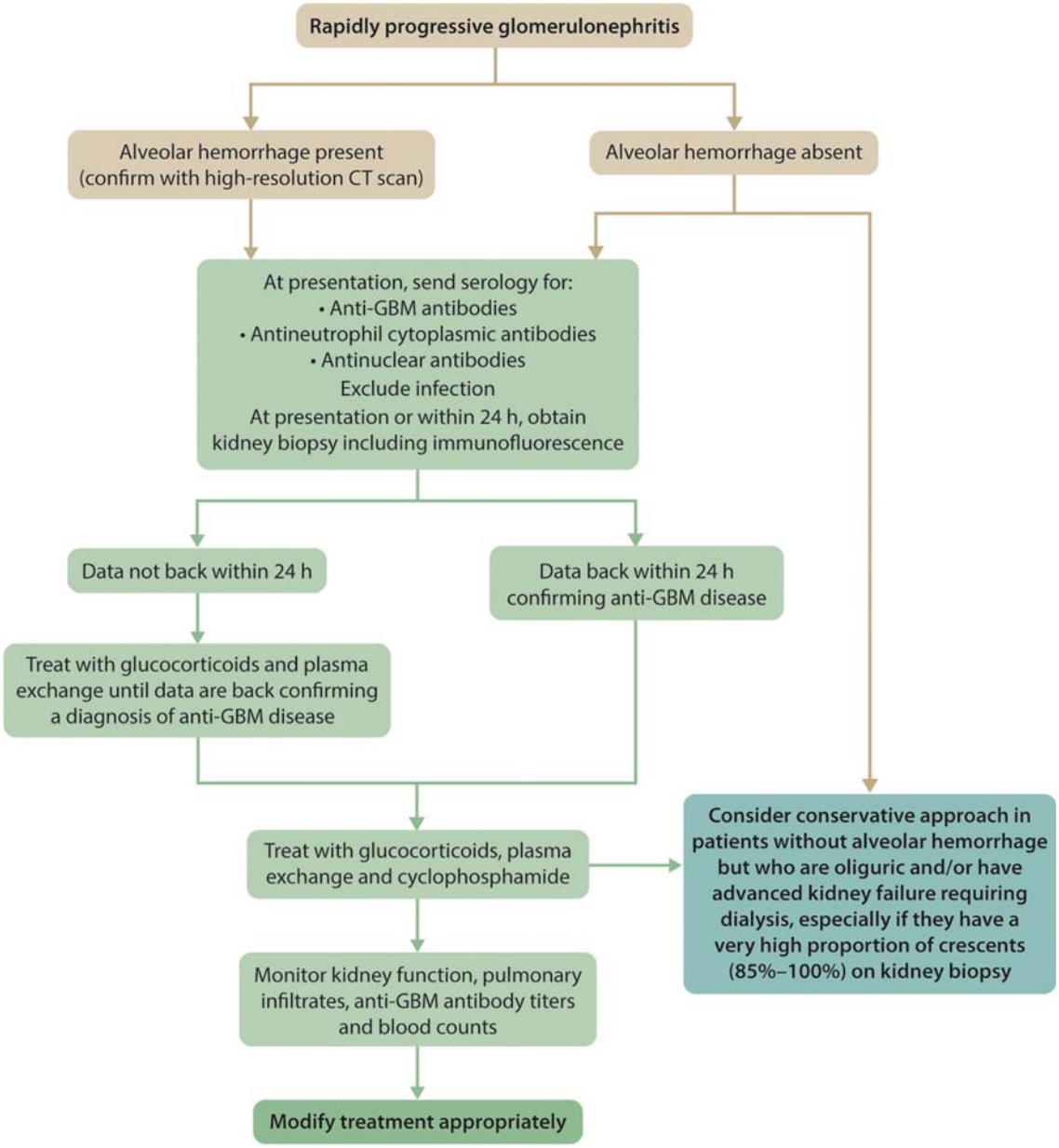

Figure 98 | Diagnosis and therapy in anti-GBM disease. CT, computed tomography; GBM, glomerular basement membrane.

identified by the Work Group exhibit strong mortality and kidney benefit for patients treated with immunosuppression and plasma exchange, compared with those receiving incomplete treatment or no treatment. Therefore, the overall quality of evidence was rated as low.

One small (n = 17) RCT compared plasma exchange with standard of care in patients with anti-GBM disease (Supplementary Table S64[939]). The quality of the evidence for critical outcomes (all-cause mortality, kidney failure, and infection) was very low because of study limitations (unclear randomization and allocation concealment methods used) and very serious imprecision (only 1 study, with few patients and very wide CIs indicating less certainty in effect). Other outcomes, such as anti-GBM antibodies, were not considered to be critical and important outcomes for the guideline.

Values and preferences. Because untreated anti-GBM GN and Goodpasture's syndrome carry a high risk of mortality and morbidity (kidney failure), it is likely all patients and physicians would opt for treatment with aggressive immunosuppressive therapy.

Resource use and costs. The management of anti-GBM disease and Goodpasture's syndrome is expensive and resource-intensive. Patients with suspected anti-GBM disease optimally require a specialized center with available intensive care, plasma exchange, nephropathology, and acute hemodialysis capabilities, some or all of which may not be available in some regions. Costs are offset to some extent if treatment results in preservation of independent kidney function, and patients do not require long-term kidney replacement therapy.

Considerations for implementation. Treatment for anti-GBM disease should be started as soon as possible for most patients. However, the chance for recovery and preservation of independent kidney function is low in patients presenting with certain clinical and pathologic conditions. Recovery of kidney function is only about 5% in patients who have a high proportion of crescents (85%–100%) on kidney biopsy, oliguria, and/or advanced kidney failure requiring initiation of dialysis.[940] In such patients, the decision to initiate therapy should take into account this low chance of kidney recovery and the ability of the patients to withstand intense immunosuppression based on their other clinical characteristics. However, treatment is necessary in these patients if they have pulmonary hemorrhage.

Anti-GBM disease is more common in Caucasian patients. In Chinese patients, the disease occurs more frequently in older people.[941] Pulmonary disease is more frequent in smokers,[942] and presence of pulmonary disease may be associated with better kidney outcomes,[943] probably because of earlier diagnosis. Pulmonary–renal syndrome occurs more frequently in young men; isolated anti-GBM nephritis may occur in older persons and with less male preponderance.

Rationale

The aim of treatment is to suppress kidney inflammation, remove circulating pathogenic autoantibodies (with plasma exchange), and suppress the formation of the autoantibodies (with immunosuppression). This treatment is able to prevent ongoing kidney damage, but it is unable to reverse already established chronic kidney damage. Treatment usually results in recovery from alveolar hemorrhage.

Formation of anti-GBM antibodies ceases spontaneously after several months and within weeks in patients treated with plasma exchange and immunosuppression. Relapses are rare (mostly in smokers), and long-term maintenance immunosuppression is not necessary. When anti-GBM antibodies are persistently negative, kidney transplantation is associated with a very low recurrence rate.

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

As anti-GBM antibodies are pathogenic, they should be removed completely from the circulation as quickly as possible. Antibodies are cleared in most patients treated with plasma exchange combined with immunosuppression within 8 weeks.[933] Acceleration of the anti-GBM removal could improve the recovery of kidney function in anti-GBM disease. If there is a high index of suspicion of anti-GBM disease, treatment should start without delay (within 24 hours), even before the diagnosis is confirmed with a kidney biopsy.

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

Plasma exchange gradually and relatively slowly (within several weeks) eliminates anti-GBM antibodies from the circulation and usually needs to be performed for 2–3 weeks before anti-GBM antibodies disappear completely.[933,935,944] In patients with alveolar hemorrhage, or immediately after kidney biopsy, plasma exchange should be done with fresh frozen plasma. If albumin is used, administration of fresh frozen plasma at the end of plasma exchange is warranted.

Practice Point 11.2.3: Cyclophosphamide should be administered for 2–3 months and glucocorticoids for about 6 months (Figure 99[931,945,946]).

Formation of anti-GBM antibody ceases spontaneously after 6–9 months.[947] However, based on available clinical experience, oral cyclophosphamide daily for 3 months and gradually tapered glucocorticoids completely withdrawn within 6 months seem to be appropriate in most patients to prevent new antibody production.[933,948] In patients with persistent anti-GBM antibody after 3 months of cyclophosphamide, continuation of treatment with either azathioprine or mycophenolate (in combination with glucocorticoids) is suggested.[945]

As the risk of infection in patients with kidney failure treated with cyclophosphamide is high,[949] prophylaxis of *Pneumocystis* pneumonia with cotrimoxazole can be considered.[945] In patients with serious infection during treatment with plasma exchange, adding i.v. immunoglobulin therapy to antibiotics can be considered. Intravenous immunoglobulin should be given immediately after plasma exchange to limit its removal, but the real impact of this approach is uncertain.[950]

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

Relapses of anti-GBM disease are uncommon (0%–6% of cases). None of 41 patients with anti-GBM disease had recurrent antibodies or relapsed beyond 6 months.[935] Individual patients with relapses many years after the first presentation of the disease were, however, reported,[951–954] and repeated relapses may occur in patients who do not stop smoking or who are exposed to lung irritants.[955,956] Treatment of patients who do not have detectable anti-GBM antibodies beyond 6 months is not recommended. Smoking should be strongly discouraged.

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

Double positivity of anti-GBM and ANCA is frequent. About 5% of patients with AAV will also have anti-GBM antibodies, and up to one-third of patients with anti-GBM GN may be ANCA-positive.[599]

Double-positive patients also may have severe kidney disease and often have lung hemorrhage at presentation, but they have a greater chance of kidney recovery from dialysis-dependence than patients with only anti-GBM antibodies. In contrast to patients with only anti-GBM antibodies, double-positive patients have a similar relapse rate as that of patients with AAV and require aggressive early treatment as for anti-GBM disease followed by maintenance immunosuppression as for AAV (Chapter 9).[935]

Intervention	Dosing	Duration of treatment
Plasma exchange	• 40–50 ml/kg ideal body weight exchange daily against 5% albumin • Add fresh frozen plasma at the end of plasma exchange in patients with alveolar hemorrhage and/or after kidney biopsy	Until circulating anti-GBM antibodies can no longer be detected; usually 14 days
Cyclophosphamide	• 2–3 mg/kg orally (reduce to 2 mg/kg in patients >55 years); experience with pulse intravenous cyclophosphamide is limited and efficacy is uncertain • Cyclophosphamide dosing should be reduced (or treatment interrupted) in cases of leukopenia • In patients not tolerating (or not responding to) cyclophosphamide, rituximab or mycophenolate mofetil may be tried but experience is limited and efficacy uncertain	3 months
Glucocorticoids	• Pulse methylprednisolone may be given initially up to 1000 mg/d on 3 consecutive days • Prednisone 1 mg/kg orally • Reduce to 20 mg/d by 6 weeks	6 months

Figure 99 | Treatment of anti-GBM disease. Adapted from *Journal of the American Society of Nephrology*, volume 10, issue 11, Kluth DC, Rees AJ. Anti-glomerular basement membrane disease, pages 2446–2453, Copyright © 1999, with permission from the American Society of Nephrology.[946] Adapted from *Clinical Journal of the American Society of Nephrology*, volume 12, issue 7, McAdoo SP, Pusey CD. Anti-glomerular basement membrane disease, pages 1162–1172, Copyright © 2017, with permission from the American Society of Nephrology.[931] Adapted from Kaplan AA, Appel GB, Pusey CE, et al. Anti-GBM (Goodpasture) disease: treatment and prognosis. UpToDate: Evidence-based Clinical Decision Support. Available at: www.uptodate.com. Accessed September 7, 2021.[945]

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

Refractory anti-GBM disease is rare (<10%).[952] Experience with rituximab in anti-GBM disease is limited to case reports, along with 2 small case series of 8 patients who incompletely responded to standard treatment and were successfully rescued with rituximab,[957] and 4 patients treated with dialysis primarily treated with rituximab instead of cyclophosphamide as first-line therapy for pulmonary remission with no effect on the kidney.[958]

There are several case reports of patients with anti-GBM disease who were successfully treated with mycophenolate or MPA instead of cyclophosphamide.[959–962] Mycophenolate could be used instead of cyclophosphamide in patients who refuse cyclophosphamide or are intolerant of cyclophosphamide because of its toxicity.

Imlifidase is an IgG-degrading endopeptidase from *Streptococcus pyogenes* (IdeS) that cleaves human IgG into F(ab')2 and Fc fragments, and inhibits antibody- and complement-dependent cytotoxicity. IdeS treatment immediately cleared anti-GBM antibodies from the circulation of 3 patients with anti-GBM disease who were treated with dialysis, but none of these patients recovered independent kidney function.[963] A clinical trial testing the utility and safety of IdeS in anti-GBM disease is currently underway (NCT03157037).

Immune adsorption removes anti-GBM antibody effectively. Among 10 patients with anti-GBM disease treated with immunoadsorption, dialysis dependency was successfully reversed in 3 out of 6 patients.[964]

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

Survival of patients with anti-GBM disease after kidney transplantation is comparable to that in patients with other causes of kidney failure.[965] Recurrence of anti-GBM disease may be as high as 50% after transplantation in patients who have detectable anti-GBM antibodies at the time of transplantation,[966] but it is very rare (<3%) in patients who have no antibodies.[948]

Anti-GBM antibodies form in 5%–10% of patients with Alport syndrome after kidney transplantation, but overt anti-GBM disease is less frequent. If clinical anti-GBM GN occurs, it often does so early and results in graft loss.[967]

Research recommendations

- Compare:
  - Rituximab to cyclophosphamide plus glucocorticoids and plasma exchange for induction of remission in anti-GBM disease
  - MMF to cyclophosphamide plus glucocorticoids and plasma exchange for induction of remission in anti-GBM disease
  - Immune adsorption to plasma exchange plus background immunosuppression for induction of remission in anti-GBM disease

Methods for guideline development

Aim

This is an update of the KDIGO Clinical Practice Guideline for Glomerulonephritis published in 2012.[968] In November 2017, KDIGO held a Controversies Conference to determine whether there was sufficient new evidence to support updating any of the guideline recommendations. It was decided that a guideline update was required.[1,2]

The objective of this project was to update the evidence-based clinical practice guideline for the management of glomerular diseases. The guideline development methods are described below.

Overview of the process

This guideline adhered to international best practices for guideline development (Appendix B: Supplementary Tables S2 and S3).[969] This guideline has been developed and reported in accordance with the AGREE II reporting checklist.[970] The processes undertaken for the development of the KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases are described below.

- Appointing Work Group members and the ERT
- Finalizing guideline development methodology
- Defining scope and topics of the guideline
- Formulating clinical questions—identifying the Population, Intervention, Comparator, Outcome, Methods (PICOM)
- Selecting topics for systematic evidence review and linking to existing Cochrane Kidney and Transplant systematic reviews
- Developing and implementing literature search strategies
- Selecting studies according to predefined inclusion criteria
- Data extraction and critical appraisal of the literature
- Evidence synthesis and meta-analysis
- Grading the quality of the evidence for each outcome across studies
- Grading the strength of the recommendation, based on the quality of the evidence and other considerations
- Convening a public review in June 2020
- Updating the guideline
- Finalizing and publishing the guideline

Commissioning of Work Group and ERT. The KDIGO Co-Chairs appointed the Work Group Co-Chairs, who then assembled the Work Group, to include content experts in adult and pediatric nephrology, pathology, epidemiology, and public health. Cochrane Kidney and Transplant was contracted to conduct systematic evidence review and provide expertise in guideline development methodology. The ERT consisted of adult and pediatric nephrologists, and methodologists with expertise in evidence synthesis and guideline development. The ERT coordinated the methodological and analytical processes of guideline development, including literature searching, data extraction, critical appraisal, evidence synthesis and meta-analysis, grading the quality of the evidence per outcome, and grading the quality of the evidence for recommendations. The Work Group was responsible for writing the recommendations and practice points and underlying rationale, as well as grading the strength of each recommendation.

The KDIGO Co-Chairs, KDIGO Methods Chair, Work Group Co-Chairs, and the ERT had a 1-day meeting in Houston, Texas, USA in February 2018 to discuss the previous guideline and the findings from the KDIGO Controversies Conference on Glomerulonephritis,[1,2] and finalize the guideline development process. Guideline topics from the previous guideline and new guideline topics were linked with appropriate clinical questions to underpin the systematic evidence review. The draft guideline topics and review topics were finalized with feedback from the Work Group.

Defining scope and topics and formulating key clinical questions. The guideline Work Group, with assistance from the ERT, determined the overall scope of the guideline. A preliminary list of topics and key clinical questions was informed by the previous KDIGO guideline[968] and the KDIGO Controversies Conference on Glomerular Diseases.[1,2] Analytical frameworks were developed to present a visual representation of the clinical question and facilitate discussion about the scope of the guideline. The majority of clinical questions for this guideline were based upon RCTs to avoid bias by design. Clinical questions adhered to the PICOM format (a list of critical and important outcomes was compiled after voting from the Work Group [Table 1]). The Work Group and the ERT further refined the clinical questions to finalize the inclusion and exclusion criteria to guide literature searching and data extraction. Clinical questions were mapped to existing Cochrane Kidney and Transplant systematic reviews. These systematic reviews were updated accordingly. For clinical questions that did not map to any Cochrane Kidney and Transplant systematic reviews, *de novo* systematic reviews were undertaken. The previous guideline was reviewed to ensure all identified studies were included in the evidence review.[968] Details of the PICOM questions and associated Cochrane Kidney and Transplant systematic reviews are provided in Table 2[95,112,146,192,218,253,294,317,385,475,569,718]. All evidence reviews were conducted in accordance with the Cochrane Handbook,[971] and guideline development adhered to the standards of GRADE (Grading of Recommendations, Assessment, Development, and Evaluation).[972]

Table 1 | Hierarchy of outcomes

Hierarchy	Outcomes
Critical outcomes	• All-cause mortality • Kidney failure (formerly known as ESKD) • ≥50% loss of GFR • Infection • Glucocorticoid-related adverse events • Malignancy
Important outcomes	• Complete remission/relapse • Annual GFR loss (minimum 3 years follow-up)

ESKD, end-stage kidney disease; GFR, glomerular filtration rate.
The critical and important outcomes were voted on by the Work Group using an adapted Delphi process (1–9 Likert scale). Critical outcomes were rated 7–9, and important outcomes were rated 4–6 on the 9-point scale.

Table 2 | Clinical questions and systematic review topics in PICOM format

Guideline Chapter 1	General principles in the management of glomerular diseases
Clinical question	**In patients with glomerular diseases, what are patient preferences and values for immunosuppressive and non-immunosuppressive therapy?**
Population	Patients with glomerular disease
Factor of interest	Values and preferences for immunosuppressive or non-immunosuppressive therapy
Outcomes	Values and preferences
Study design	All study types
SoF tables	Supplementary Tables S65–S67
Guideline Chapter 2	**IgAN/IgAV**
Clinical question	**In patients with biopsy-proven IgAN, what non-immunosuppressive agents, compared to no treatment or placebo, improve efficacy outcomes and reduce adverse effects?**
Population	Patients with IgAN
Intervention	Fish oil, anticoagulants or antiplatelets, antioxidants, tonsillectomy, statins, traditional Chinese medicine, vitamin D, vitamin E, allopurinol, etc.
Comparator	No treatment or placebo
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic review	Reid SM, *et al.* Non-immunosuppressive agents for treating IgA nephropathy (Review). *Cochrane Database of Systematic Reviews.* 2011:3;CD003962[95]
SoF tables	Supplementary Tables S4, S5, S7, and S87–S104
Clinical question	**In patients with biopsy-proven IgAN, what immunosuppressive agents, compared to no treatment or placebo, improve efficacy outcomes and reduce adverse effects?**
Population	Patients with IgAN
Intervention	Immunosuppressive therapy
Comparator	No treatment or placebo
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic review	Natale P, *et al.* Immunosuppressive agents for treating IgA nephropathy (Review). *Cochrane Database of Systematic Reviews.* 2020:3;CD003965[112]
SoF tables	Supplementary Tables S6 and S68–S86
Clinical question	**In patients with biopsy-proven IgAV (Henoch-Schönlein purpura nephritis), what immunosuppressive agents, compared to no treatment, placebo, or standard of care, improve efficacy outcomes and reduce adverse effects?**
Population	Patients with IgAV (Henoch-Schönlein purpura nephritis)
Intervention	Immunosuppressive therapy
Comparator	No treatment, placebo, or standard of care
Outcomes	Outcomes listed in Table 1 Additional outcomes—BMI
Study design	RCTs
Cochrane systematic review	Hahn D, *et al.* Interventions for preventing and treating kidney disease in Henoch-Schönlein purpura (HSP) (Review). *Cochrane Database of Systematic Reviews.* 2015:8;CD005128[146]
SoF tables	Supplementary Tables S8 and S105–S109
Guideline Chapter 3	**MN**
Clinical question	**In adults with biopsy-proven MN and NS, what immunosuppressive agents, compared to no treatment, placebo, or other immunosuppressive therapies, improve efficacy outcomes and reduce adverse effects?**
Population	Adults with primary MN and NS
Intervention	Immunosuppressive therapy
Comparator	No treatment, placebo, or other immunosuppressive therapies
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic review	Chen Y, *et al.* Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome (Review). *Cochrane Database of Systematic Reviews.* 2014:10;CD004293[192]
SoF tables	Supplementary Tables S9–S13 and S110–S131
Guideline Chapter 4	**NS in children**
Clinical question	**In children (3–18 years of age) with SSNS, what glucocorticoid therapy regimens, compared with no treatment, placebo, or standard of care, improve efficacy outcomes and reduce adverse effects?**
Population	Children (3–18 years of age) with SSNS
Intervention	Glucocorticoid therapy
Comparator	No treatment, placebo, or standard of care
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic review	Hahn D, *et al.* Corticosteroid therapy for nephrotic syndrome in children (Review). *Cochrane Database of Systematic Reviews.* 2020:8;CD001533[218]
SoF tables	Supplementary Tables S14–S15 and S132–S147

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Table 2 | (Continued) **Clinical questions and systematic review topics in PICOM format**

Guideline Chapter 4	NS in children
Clinical question	**In children (3–18 years of age) with SSNS, what non-glucocorticoid immunosuppressive regimens, compared to no treatment, placebo, or standard of care, improve efficacy outcomes and reduce adverse effects?**
Population	Children (3–18 years of age) with SSNS
Intervention	Non-glucocorticoid immunosuppressive therapy
Comparator	No treatment, placebo, or standard of care
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic review	Larkins NG, *et al.* Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children (Review). *Cochrane Database of Systematic Reviews.* 2020:4;CD002290[253]
SoF tables	Supplementary Tables S16–S20 and S148–S163
Clinical question	**In children (3–18 years of age) with SRNS, what immunosuppressive therapy, compared to no treatment, placebo, or other immunosuppressive medication, improves efficacy outcomes and reduces adverse effects?**
Population	Children (3–18 years of age) with SRNS
Intervention	Immunosuppressive therapy
Comparator	No treatment, placebo, or other immunosuppressive therapies (including glucocorticoids)
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic review	Liu ID, *et al.* Interventions for idiopathic steroid-resistant nephrotic syndrome in children (Review). *Cochrane Database of Systematic Reviews.* 2019:11; CD003594[294]
SoF tables	Supplementary Tables S21–S24 and S164–S173
Guideline Chapter 5	**MCD in adults**
Clinical question	**In adults with biopsy-proven MCD and NS, what immunosuppressive agents, compared to no treatment, placebo, or other immunosuppressive therapy, improve efficacy outcomes and reduce adverse effects?**
Population	Adults with biopsy-proven MCD and NS
Intervention	Immunosuppressive therapy
Comparator	No treatment, placebo, or other immunosuppressive therapies
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic review	Palmer SC, *et al.* Interventions for minimal change disease in adults with nephrotic syndrome (Review). *Cochrane Database of Systematic Reviews.* 2008:1;CD001537[317]
SoF tables	Supplementary Tables S25–S27 and S174
Guideline Chapter 6	**FSGS in adults**
Clinical question	**In adults with biopsy-proven FSGS, what immunosuppressive agents, compared to no treatment, placebo, or other immunosuppressive therapy, improve efficacy outcomes and reduce adverse effects?**
Population	Adults with biopsy-proven FSGS
Intervention	Immunosuppressive therapy
Comparator	No treatment, placebo, or other immunosuppressive therapies
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic reviews	Braun N, *et al.* Immunosuppressive treatment of focal segmental glomerulosclerosis in adults. *Cochrane Database of Systematic Reviews.* 2008:3;CD003233[385]
SoF tables	Supplementary Tables S28–S30 and S175–S181
Guideline Chapter 7	**Infection-related glomerulonephritis**
Clinical question	**In adult patients with HBV- or HCV-related GN, what antiviral treatment therapy, compared to no treatment, placebo, or standard of care, improves efficacy outcomes and reduces adverse effects?**
Population	Adults with HBV- or HCV-related GN
Intervention	Antiviral treatment therapy
Comparator	No treatment, placebo, or standard of care
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic reviews	None relevant
SoF tables	Supplementary Tables S182–S184
Clinical question	**In patients with HIV-associated nephropathy, what antiretroviral treatment, compared to no treatment, placebo, or standard of care, improves efficacy outcomes and reduces adverse effects?**
Population	HIV-associated nephropathy
Intervention	Highly active antiretroviral therapy (HAART; alone or combined with antihypertensive agents, glucocorticoids, and immunosuppressive therapies)
Comparator	No treatment, placebo, or standard of care

(*Continued on following page*)

Table 2 | (Continued) **Clinical questions and systematic review topics in PICOM format**

Guideline Chapter 7	Infection-related glomerulonephritis
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic reviews	Yahaya I, *et al.* Interventions for HIV-associated nephropathy (Review). *Cochrane Database of Systematic Reviews.* 2013:1;CD007183[475]
SoF tables	Supplementary Table S185
Guideline Chapter 8	**Immunoglobulin- and complement-mediated glomerular diseases with an MPGN pattern of injury**
Clinical question	**In patients with complement-mediated disease, what immunosuppressive agents, compared to no treatment, placebo, or standard of care, improve efficacy outcomes and reduce adverse effects?**
Population	Patients with C3-mediated GN, C3 DDD, CFHR5 nephropathy, C4-mediated GN, idiopathic MPGN
Intervention	Immunosuppressive therapy
Comparator	No treatment, placebo, or standard of care
Outcomes	Outcomes listed in Table 1
Study design	RCTs and observational studies
Cochrane systematic reviews	None relevant
SoF tables	Supplementary Table S186 and S187
Clinical question	**In adults with proliferative GN (monoclonal immunoglobulin deposits [monoclonal immunoglobulin deposition disease], immunotactoid GN, fibrillary GN, cryoglobulinemia-related kidney disease), compared to no treatment, placebo, or standard of care, does immunosuppressive therapy improve clinically relevant outcomes and decrease harms?**
Population	Adults with proliferative GN kidney with monoclonal immunoglobulin deposits (monoclonal immunoglobulin deposition disease), immunotactoid GN, fibrillary GN, cryoglobulinemia-related kidney disease,
Intervention	Immunosuppressive therapy
Comparator	No treatment, placebo, or standard of care
Outcomes	Mortality, kidney failure, complete kidney remission, hematologic response, adverse events
Study design	RCTs and observational studies
Cochrane systematic reviews	None relevant
SoF tables	Supplementary Tables S188 and S189
Guideline Chapter 9	**ANCA-associated vasculitis**
Clinical question	**In adults with AAV, what immunosuppressive agents compared to no treatment, placebo, or other immunosuppressive therapies improve clinical efficacy outcomes and reduce adverse effects?**
Population	Adults with AAV
Intervention	Immunosuppressive therapy
Comparator	No treatment, placebo, or other immunosuppressive therapies
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic reviews	Walters *et al.* Interventions for renal vasculitis in adults (Review). *Cochrane Database of Systematic Reviews.* 2020:1;CD003232[569]
SoF tables	Supplementary Tables S31–S44 and S190–S200
Guideline Chapter 10	**Lupus nephritis**
Clinical question	**In patients with biopsy-proven LN, compared to no treatment, placebo, or standard of care, does antimalarial therapy improve clinical efficacy outcomes and reduce adverse effects?**
Population	Patients with biopsy-proven LN
Intervention	Antimalarial therapy
Comparator	No treatment, placebo, or standard of care
Outcomes	Outcomes listed in Table 1
Study design	RCTs and observational studies
Cochrane systematic reviews	None relevant
SoF tables	Supplementary Table S45
Clinical question	**In patients with nonproliferative (Class I, II, V, or VI) LN, what immunosuppressive agents, compared to no treatment, placebo, or other immunosuppressive therapies, improve efficacy outcomes and reduce adverse effects?**
Population	Patients with biopsy-proven nonproliferative (Class I, II, V, or VI) LN
Intervention	Immunosuppressive therapy
Comparator	No treatment, placebo, or other immunosuppressive therapies
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic reviews	None relevant
SoF tables	Supplementary Tables S203, S204, and S205

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Table 2 | (Continued) **Clinical questions and systematic review topics in PICOM format**

Guideline Chapter 10	Lupus nephritis
Clinical question	**In patients with biopsy-proven proliferative (Class III, IV, III/V, or IV/V) LN, what immunosuppressive agents, compared to no treatment, placebo, or other immunosuppressive therapies, improve efficacy outcomes and reduce adverse effects?**
Population	Patients with biopsy-proven proliferative (Class III, IV, III/V, or IV/V) LN
Intervention	Immunosuppressive therapy
Comparator	No treatment, placebo, or other immunosuppressive therapies
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic reviews	Tunnicliffe DJ, *et al.* Immunosuppressive treatment for proliferative lupus nephritis. *Cochrane Database of Systematic Reviews*. 2018:6;CD002922[718]
SoF tables	Supplementary Tables S46–S63, S201–S204, and S207–S218
Guideline Chapter 11	**Anti-GBM antibody GN**
Clinical question	**In patients with biopsy-proven anti-GBM, what immunosuppressive agents, compared to no treatment, placebo, or other immunosuppressive therapies, improve efficacy outcomes and reduce adverse effects?**
Population	Patients with biopsy-proven anti-GBM
Intervention	Immunosuppressive therapy
Comparator	No treatment, placebo, or other immunosuppressive therapies
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic reviews	None relevant
SoF tables	Supplementary Table S64

AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; BMI, body mass index; CFHR5, Complement factor-H–related protein 5; DDD, dense deposit disease; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; GN, glomerulonephritis; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IgAN, immunoglobin A nephropathy; IgAV, immunoglobin A vasculitis; LN, lupus nephritis; MCD, minimal change disease; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis; NS, nephrotic syndrome; PICOM, Population, Intervention, Comparator, Outcomes, Methods; RCT, randomized controlled trial; SoF, summary of findings; SRNS, steroid-resistant nephrotic syndrome; SSNS, steroid-sensitive nephrotic syndrome.

Literature searches and article selection. Searches for RCTs utilized the Cochrane Kidney and Transplant Registry of studies in October 2018 and supplemented until September 2019. An updated search was undertaken in June 2020. The Cochrane Kidney and Transplant Registry of studies is a database of RCTs in kidney disease that is maintained by information specialists. The database is populated by monthly searches of the Cochrane Central Register of Controlled Trials, weekly searches of MEDLINE OVID, yearly searches of Embase OVID, hand-searching of major kidney and transplant conference proceedings, searches of trial registries, including clinicaltrials.gov and the International Clinical Trials Register search portal.

For review topics that matched existing Cochrane Kidney and Transplant systematic reviews, an updated search for the review using the Cochrane Kidney and Transplant Registry of studies was conducted. The Cochrane Kidney and Transplant Registry of studies was searched for clinical questions that included only RCTs and were not linked to any existing Cochrane systematic review. For clinical questions that included other study types, for example, observational studies, the medical literature databases MEDLINE and Embase were searched. The search strategies are provided in Supplementary Appendix A: Supplementary Table S1.

The titles and abstracts resulting from the searches were screened by 2 members of the ERT who independently assessed retrieved abstracts, and if necessary, the full text, to determine which studies satisfied the inclusion criteria. Disagreement about inclusion was resolved by discussion with a third member of the ERT.

A total of 25,925 citations were screened. Of these, 479 RCTs and 102 observational studies were included in the evidence review (Figure 100).

Data extraction. Data extraction was performed independently by 2 members of the ERT. Unclear data were clarified by contacting the author of the study report, and any relevant data obtained in this manner were included. The ERT designed data extraction forms to capture data on study design, study participant characteristics, intervention and comparator characteristics, and critical and important outcomes. Any differences in extraction between members of the ERT were resolved through discussion. A third reviewer was included if consensus could not be achieved.

Critical appraisal of studies. The majority of reviews undertaken were intervention reviews that included RCTs. For these reviews, the Cochrane Risk of Bias tool was used to assess individual study limitations based on the following items[973]:

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at risk of bias?

All critical appraisal was conducted independently by 2 members of the ERT, with disagreements regarding the risk of bias adjudications resolved by consultation with a third review author.

Evidence synthesis and meta-analysis. *Measures of treatment effect.* Dichotomous outcome (all-cause mortality, kidney failure, ≥50% loss of GFR, infection, malignancy, complete remission/relapse) results were expressed as RR with 95% CI. When continuous scales of measurement were used to assess the effects of treatment, such as annual GFR loss, the mean difference (MD) with 95% CI was used. Data synthesis. Data were pooled using the

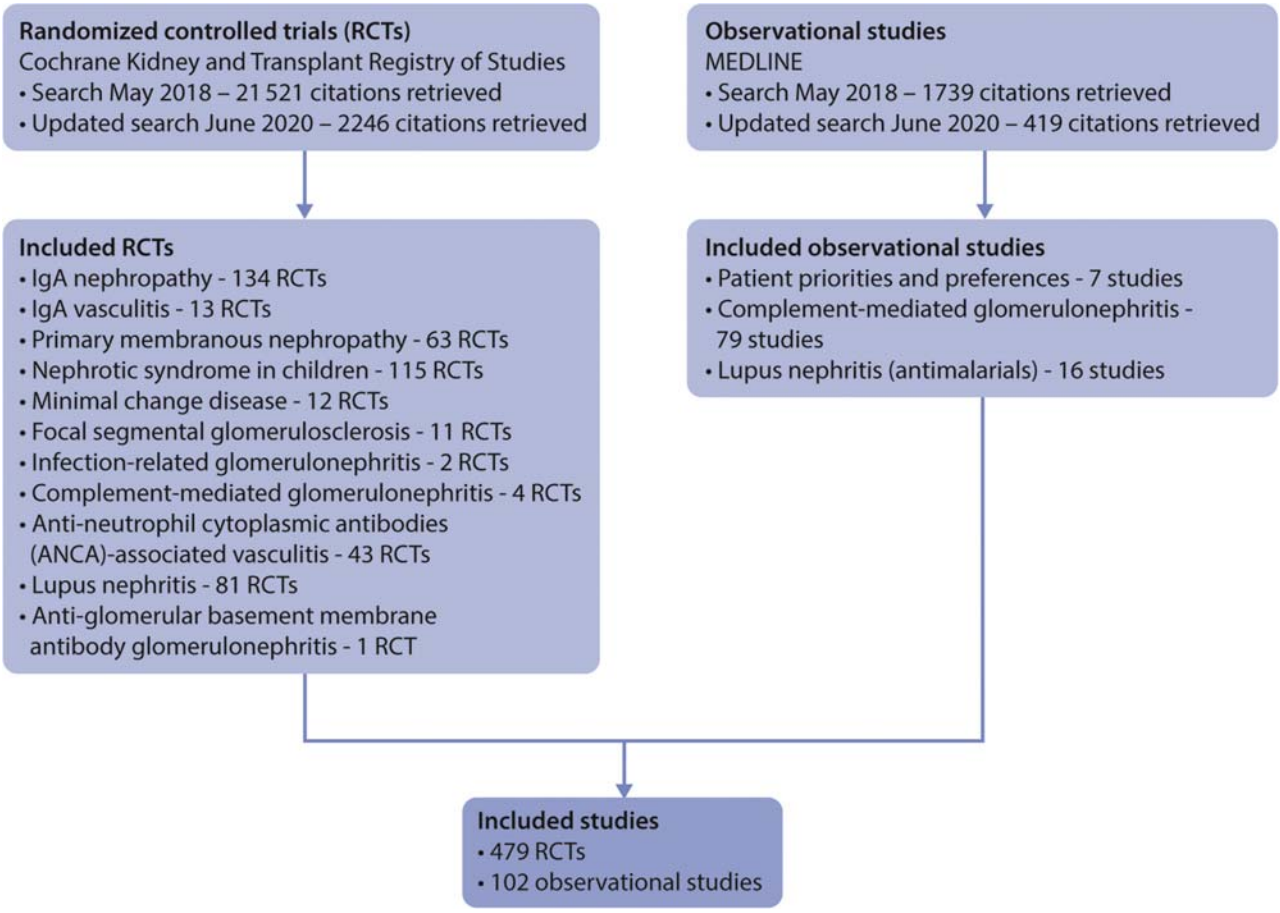

Figure 100| Search yield and study flow diagram.

Mantel-Haenszel random-effects model for dichotomous outcomes and the inverse variance random-effects model for continuous outcomes. The random-effects model was chosen because it provides a conservative estimate of effect in the presence of known and unknown heterogeneity.[971]

Assessment of heterogeneity. Heterogeneity was assessed by visual inspection of forest plots of standardized mean effect sizes, and of risk ratios, and by χ^2 tests. A P value of <0.1 was used to denote statistical heterogeneity, and an I^2 was calculated to measure the proportion of total variation in the estimates of treatment effect that was due to heterogeneity beyond chance.[971] We used conventions of interpretation as defined by Higgins *et al.*[974]

Assessment of publication bias. We made every attempt to minimize publication bias by including unpublished studies (for example, by searching online trial registries). To assess publication bias, we used funnel plots of the log odds ratio (effect vs. standard error of the effect size) when a sufficient number of studies were available (i.e., >10 studies).[971] Other reasons for the asymmetry of funnel plots were considered.

Subgroup analysis and investigation of heterogeneity. Subgroup analysis was undertaken to explore whether there were clinical differences among the studies that may have systematically influenced the differences that were observed in the critical and important outcomes. However, subgroup analyses are hypothesis-forming rather than hypothesis-testing and should be interpreted with caution. The following subgroups were considered: baseline kidney function (GFR, proteinuria, presence of albuminuria, presence of macroscopic hematuria), histopathologic class of disease, primary versus secondary forms of disease, sex, and adult versus pediatric. The test of subgroup differences used the I^2 statistic and a P value of 0.10 (noting that this is a weak test).[971]

Sensitivity analysis. The following sensitivity analyses were considered:

- Repeating the analysis excluding unpublished studies
- Repeating the analysis, taking account of the risk of bias, as specified
- Repeating the analysis excluding any very long or large studies, to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: language of publication, source of funding (industry vs. other), and country in which the study was conducted.

However, the available data were insufficient to determine the influence of these factors on the effect size of critical and important outcomes.

Grading the quality of the evidence and the strength of a guideline recommendation. *Grading the quality of the evidence for each outcome across studies.* The overall quality of the evidence related to each critical and important outcome was assessed using the GRADE approach,[972,975] which assesses the quality of the evidence for each outcome. For outcomes that are based on data from RCTs, the initial grade for the quality of the evidence is considered to be high. For observational studies, the initial quality of

Table 3 | Classification for quality and certainty of the evidence

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

the evidence is low. The quality of the evidence is lowered in the event of study limitations; important inconsistencies in results across studies; indirectness of the results, including uncertainty about the population, intervention, and outcomes measured in trials and their applicability to the clinical question of interest; imprecision in the evidence review results; and concerns about publication bias. For imprecision, data were benchmarked against optimal information size, low event rates in either arm, CIs that indicate appreciable benefit and harm (25% decrease and 25% increase in the outcome of interest), and sparse data (only 1 study), all indicating concerns about the precision of the results.[972] The final grade for the quality of the evidence for an outcome could be high, moderate, low, or very low (Table 3). For observational studies and other study types, it is possible for the quality of the evidence to be upgraded from a rating of low quality, according to the specified criteria. For further details on the GRADE approach for rating quality of the evidence, see Table 4.

Summary of findings (SoF) tables. The SoF tables were developed to include a description of the population, intervention, and comparator. In addition, the SoF tables included results from the data synthesis as relative and absolute effect estimates. The grading of the quality of evidence for each critical and important outcome is also provided in the SoF tables. The SoF tables were generated using MAGICapp, an online software application designed to support guideline development, and they are available in the Data Supplement: Appendix C and Appendix D (https://kdigo.org/guidelines/gd/).

Developing the recommendations. The recommendations were drafted by the Work Group Co-Chairs and Work Group members. Recommendations were revised in a multistep process during face-to-face meetings (Amsterdam, The Netherlands, August 2018 and Budapest, Hungary, June 2019) and by email communication. The final draft was sent for external public review, and reviewers provided open-ended responses. Based on the external stakeholder feedback, the draft was further revised by the Work Group. All Work Group members provided feedback on initial and final drafts of the guideline statements and text and approved the final version of the guideline. The ERT also provided a descriptive summary of the evidence quality in support of the recommendations.

Grading the strength of the recommendations. The strength of a recommendation is graded as strong or weak (Table 5). The strength of a recommendation was determined by the balance of benefits and harms across all critical and important outcomes, the grading of the overall quality of the evidence, patient values and preferences, resource use and costs, and considerations for implementation (Table 6).

Balance of benefits and harms. The Work Group and ERT determined the anticipated net health benefit on the basis of expected benefits and harms across all critical and important outcomes from the underlying evidence review.

Quality of evidence. The overall quality of the evidence was based on the certainty of the evidence for all critical and important outcomes, taking into account the relative importance of each outcome to the population of interest. The overall quality of the evidence was graded (A, B, C, or D—Table 3).

Patient values and preferences. No patients or caregivers were involved in the Work Group. The Work Group, from their experience in managing patients with glomerular disease and their understanding of the best available scientific literature, made judgments

Table 4 | GRADE system for grading quality of evidence

Study design	Starting grade for the quality of evidence	Step 2—Lower grade	Step 3—Raise grade for observational evidence
RCT	High	Study limitations: −1, serious −2, very serious	Strength of association +1, large effect size (e.g., <0.5 or >2) +2, very large effect size (e.g., <0.2 or >5)
	Moderate	Inconsistency: −1, serious −2, very serious	Evidence of a dose–response gradient
Observational	Low	Indirectness: −1, serious −2, very serious	All plausible confounding would reduce the demonstrated effect
	Very low	Imprecision: −1, serious −2, very serious	
		Publication bias: −1, serious −2, very serious	

RCT, randomized controlled trial; GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

Table 5 | KDIGO nomenclature and description for grading of recommendations

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

Table 6 | Determinants of the strength of recommendation

Factors	Comment
Balance of benefits and harms	The larger the difference between the desirable and undesirable effects, the more likely a strong recommendation is provided. The narrower the gradient, the more likely a weak recommendation is warranted.
Quality of evidence	The higher the quality of evidence, the more likely a strong recommendation is warranted. However, there are exceptions for which low or very low quality of the evidence will warrant a strong recommendation.
Values and preferences	The more variability in values and preferences, or the more uncertainty in values and preferences, the more likely a weak recommendation is warranted. Values and preferences were obtained from the literature, when possible, or were assessed by the judgment of the Work Group when robust evidence was not identified.
Resource use and costs	The higher the costs of an intervention—that is, the more resources consumed—the less likely a strong recommendation is warranted.

on the values and preferences of patients. Formal qualitative evidence synthesis on patient priorities and preferences was undertaken, but there was limited evidence available to inform the formulation of guideline recommendations (Appendix D).

Resource use and costs. Healthcare and non-healthcare resources, including all inputs in the treatment management pathway,[976] were considered in grading the strength of a recommendation. The following resources were considered: direct healthcare costs; non-healthcare resources, such as transportation and social services; informal caregiver resources (e.g., time of family and caregivers); and changes in productivity. Economic evaluations, including cost-effectiveness analysis, were not conducted for any of the guideline topics.

Practice points

In addition to graded recommendations, KDIGO guidelines now include "practice points" to help clinicians better evaluate and implement the guidance from the expert Work Group. Practice points are consensus statements about a specific aspect of care, and they supplement recommendations for which a larger quantity of evidence was identified. These were used when no formal systematic evidence review was undertaken, or there was insufficient evidence to provide a graded recommendation. Practice points represent the expert judgment of the guideline Work Group, but they also may be based on limited evidence. For example, practice points were provided on monitoring, frequency of testing, dosing adjustments for the stage of CKD, and use of therapies in specific subgroup populations. Practice points were sometimes formatted as a table, a figure, or an algorithm to make them easier to use in clinical practice.

Format for guideline recommendations

Each guideline recommendation provides an assessment of the strength of the recommendation (strong, level 1; or weak, level 2) and the quality of the evidence (A, B, C, D). The recommendation statements are followed by Key information (Balance of benefits and harms, Quality of evidence, Values and preferences, Resource use and costs, Considerations for implementation), and Rationale. Each recommendation is linked to relevant SoF tables. An underlying rationale also may support a practice point.

Limitations of the guideline development process

The evidence review prioritized RCTs as the primary source of evidence. For a select number of clinical questions in this guideline, the ERT undertook a comprehensive evidence review beyond RCTs. However, these reviews were not exhaustive, as specialty or regional databases were not searched, and manual searching of journals was not performed for these reviews. In the development of these guidelines, no scoping exercise with patients, limited searches of the qualitative literature, or formal qualitative evidence synthesis examining patient experiences and priorities were undertaken. As noted, although resource implications were considered in the formulation of recommendations, formal economic evaluations were not undertaken for all topics.

Biographic and disclosure information

Jürgen Floege, MD (Work Group Co-Chair), received his training at the Hannover Medical School, Hannover, Germany; the Albert Einstein College of Medicine, New York, NY, USA; and the University of Washington, Seattle, WA, USA. He was appointed as head of the Division of Nephrology and Immunology at the University of Aachen, Aachen, Germany in 1999.

Professor Floege is a former executive council member of the International Society of Nephrology (ISN), European Renal Association-European Dialysis and Transplant Association (ERA-EDTA), and KDIGO. He is a Distinguished Fellow of the ERA-EDTA and recipient of the 2018 ERA-EDTA Award for Outstanding Clinical Contributions to Nephrology, past-president of the German Society of Nephrology, as well as an honorary member of the Japanese, Polish, Portuguese, Serbian, and Slovakian Societies of Nephrology. Together with Professors Richard Johnson, Marcello Tonelli, and John Feehally, he edits the best-selling textbook *Comprehensive Clinical Nephrology*. He is associate editor of *Kidney International* and a member of the editorial board of *Journal of the American Society of Nephrology*, *Journal of Nephrology*, and other journals. Until 2017, he served as associate editor of *Nephrology Dialysis Transplantation*.

His research interests encompass progression of kidney disease, in particular kidney fibrosis, immune-mediated renal disease, in particular IgA nephropathy, as well as bone and mineral disorders (CKD-MBD) and cardiovascular disease in uremic patients.

His scientific work encompasses about 600 original papers, reviews, editorials, and 40 book chapters.

JF reports consultancy for Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Calliditas, MorphoSys, Novo Nordisk, Omeros, and Travere (formerly Retrophin); and speaker bureau for Amgen and Fresenius-Vifor.

Brad H. Rovin, MD, FACP, FASN (Work Group Co-Chair), is the Lee A. Hebert Professor of Nephrology at The Ohio State University Wexner Medical Center, Columbus, OH, USA. He is the division director of nephrology and medical director of The Ohio State University Clinical Research Management Organization, Columbus, OH, USA. Dr. Rovin conducts translational research on autoimmune glomerular diseases and applies these studies to clinical trial development and design for investigator-initiated and industry-sponsored trials of novel therapeutics.

BHR reports consultancy for AstraZeneca/MedImmune, Aurinia, Biogen Idec, Bristol Myers Squibb, Calliditas, ChemoCentryx, EMD Serono, Genentech/Hoffmann-La Roche, Omeros, Janssen, Lupus Foundation of America, MorphoSys, Novartis, Pfizer, RILITE Foundation, and Travere (formerly Retrophin); grant/research support from Lupus Clinical Investigators Network* and the National Institutes of Health**
**Monies paid to institution.*

Sharon G. Adler, MD, is Chief of Nephrology and Hypertension at Harbor-University of California Los Angeles (UCLA) Medical Center, Los Angeles, CA, USA, and a Professor of Medicine at the Geffen School of Medicine at UCLA, Los Angeles, CA, USA. Dr. Adler has made many contributions to our understanding of clinical and experimental diabetic kidney and glomerular diseases. She is a member of several active clinical consortia, including the Nephrotic Syndrome Study Network (NEPTUNE), Cure Glomerulonephropathy (CureGN), and the Kidney Research Network. With Karger Publishers, she founded a new journal to focus on the glomerulus, aptly called *Glomerular Diseases*, which is expected to launch in the first half of 2021. She has authored more than 100 publications in peer-reviewed journals and over 50 chapters, reviews, and editorials.

SGA reports consultancy for Bayer and MorphoSys; and grants/research support from Bayer, Bristol Myers Squibb*, Omeros*, NIDDK (REBOOT), and Travere (formerly Retrophin).*
**Monies paid to institution.*

Jonathan Barratt, MBChB, PhD, is the Mayer Professor of Renal Medicine, Department of Cardiovascular Sciences at the University of Leicester, Leicesiter, UK. He leads the Renal Research Group within the College of Life Sciences, University of Leicester. His research is focused on a bench-to-bedside approach to improving our understanding of the pathogenesis of IgA nephropathy, a common global cause of kidney failure. Dr. Barratt is the IgA Nephropathy Rare

Disease Group lead for the United Kingdom (UK) National Registry of Rare Kidney Diseases (RaDaR), and a member of the steering committee for the International IgA Nephropathy Network. He works closely with pharmaceutical companies interested in new treatments for IgA nephropathy and is the chief investigator for several international randomized controlled Phase 2 and 3 clinical trials in IgA nephropathy. He was a Work Group member of the Food and Drug Administration (FDA) and American Society of Nephrology (ASN) Kidney Health Initiative "Identifying Surrogate Endpoints for Clinical Trials in IgA Nephropathy."

JB reports serving on Study Steering Committees for Alnylam, Calliditas, Chinook, Novartis, Omeros, and Travere (formerly Retrophin); consultancy for Alnylam, Argenx, Astellas, BioCryst, Calliditas, Chinook, Dimerix, Galápagos, Novartis, Omeros, Syncona, Takeda, Travere (formerly Retrophin), UCB, Vera Therapeutics, and Visterra; grant/research support for basic science work for 6 companies under confidentiality agreements; and he is named in a patent to be submitted by Calliditas, based on analysis of exploratory data generated from the NEFECON® trial, conducted at the University of Leicester.*

**Monies paid to institution.*

Frank Bridoux, MD, PhD, is professor of nephrology and head of the Nephrology, Dialysis and Renal Transplantation Department at Poitiers University Hospital, Poitiers, France. After completing his nephrology residency at Lille University, Lille, France in 1999, he was a clinical assistant and senior consultant at the Poitiers University Hospital. He completed his PhD thesis in immunology at the French National Centre for Scientific Research (CNRS) Unit 7276 in Limoges, France, in 2003.

Dr. Bridoux's main area of work is clinical nephrology. His research interests are mostly focused on the pathophysiology and treatment of monoclonal immunoglobulin-associated kidney disorders, covering basic research on experimental animal models and clinical studies, including randomized controlled trials. Dr. Bridoux has co-authored more than 170 peer-reviewed publications and several book chapters. He is one of the co-founders and a past president of the International Kidney and Monoclonal Gammopathy Research Group, and the current associate coordinator of amyloid light-chain (AL) amyloidosis and other disorders associated with monoclonal immunoglobulin deposits at the CNRS.

FB reports consultancy for AstraZeneca, Baxter, and Prothena; grants/research support from Amgen; and speaker bureaus for Amgen, AstraZeneca, Celgene, and Janssen.

Kelly A. Burdge, MD, received her BA in Art History and Chemistry from Northwestern University, Evanston, IL, USA. She completed her medical degree in 1999 at the Wright State University Boonshoft School of Medicine, Dayton, OH, USA. She trained in internal medicine and pediatrics and completed a fellowship in adult nephrology at The Ohio State University, Columbus, OH, USA.

Dr. Burdge has held clinical associate professorships at the University of South Dakota, Vermillion, SD, USA and Tufts University School of Medicine, Boston, MA, USA. She currently practices general nephrology in Boston, MA, USA in private practice as part of the Mass General Brigham-Salem Hospital. She is passionate about patient care, efficiency, and reducing waste in medicine. In addition to her interest in clinical nephrology and patient management, Dr. Burdge is a participant in the Chronic Kidney Disease Outcomes and Practice Patterns (CKDopps) Trial. She is a fellow of the ASN, a member of the National Kidney Foundation (NKF), and a member of Women in Nephrology.

KAB declared no competing interests.

Tak Mao Chan, MBBS, MD, DSc, FHKCP, FHKAM, MD, FRCP, FASN, obtained his MBBS, MD, and DSc from the University of Hong Kong (HKU), Hong Kong, China. He became Personal Chair Professor at HKU in 2005, Yu Professor in Nephrology in 2008, and Yu Chiu Kwong Professor in Medicine in 2011. Dr. Chan has been chief of nephrology since 2010. He has served as associate dean, senate member, and University Selection & Promotion Committee member at HKU, president of the Asian Pacific Society of Nephrology (APSN), and council member of the ISN. Since 2016, he has served as vice-president and chairman of the Education and Accreditation Committee of the Hong Kong College of Physicians, Hong Kong, China.

Dr. Chan's research focuses on lupus nephritis and viral hepatitis in patients with kidney diseases. His work has helped establish mycophenolate as the standard-of-care for lupus nephritis and preventive antiviral therapy for hepatitis B in kidney transplant recipients, contributing to significant improvements in clinical management and patient outcomes. Translational studies from his laboratory have increased the understanding of pathogenic mechanisms in kidney inflammation and fibrosis. Dr. Chan's publications have appeared in the *New England Journal of Medicine*, *Kidney International*, *Journal of the American Society of Nephrology*, *Arthritis & Rheumatology*, *Nature Reviews of Nephrology*, *Hepatology*, and *UpToDate*. He received the Asian-Pacific Society of

Nephrology (APSN) Kenzo Oshima Award in 2014. He is also the author of the chapter on "The Far East" in *Brenner and Rector's The Kidney*, 11th Edition.

TMC reports consultancy for Novartis; and grant/research support from Astellas, AstraZeneca, and Baxter.

H. Terence Cook, MBBS, MRCP, MRCPath, FRCPath, FMedSci, is a professor of renal pathology at Imperial College, London, UK, and a consultant renal pathologist at Hammersmith Hospital, London, UK. He qualified at St Mary's Hospital Medical School, London, UK in 1980 and became a lecturer in Experimental Pathology in 1983. Since then, he has pursued research in experimental glomerulonephritis and human glomerular disease at Imperial College, London, UK. He has major interests in the role of complement activation in glomerular disease and in how histologic features in human kidney biopsies can be used to predict outcomes and responses to treatment. He has organized international collaborative studies to develop consensus classifications of lupus glomerulonephritis, IgA nephropathy, and C3 glomerulopathy. He is a past president of the Renal Pathology Society. He has over 370 peer-reviewed publications.

HTC reports consultancy for Alexion, Apellis, Aurinia, and Novartis; grant/research support from Achillion and Ra Pharmaceuticals*; and speaker bureau for Alexion.*
**Monies paid to institution.*

Fernando C. Fervenza, MD, PhD, is a professor of medicine at the Mayo Graduate School of Medicine, Rochester, MN, USA. He received his medical degree at the Pontificia Universidade Catolica do Rio Grande do Sul, Porto Alegre, Brazil. Dr. Fervenza underwent his clinical nephrology and research training at Oxford University, Oxford, UK, and the Oxford Renal Unit from 1985 to 1991. Subsequent training included a postdoctoral fellowship at Stanford University, Stanford, CA, USA (1993–1997). Dr. Fervenza is a fellow of the ASN and the American College of Physicians, a past member of the American Board of Internal Medicine nephrology section, and an *UpToDate* section editor for glomerular disease. His area of interest is pursuing patient-oriented research projects aiming to bring new bench research discoveries to the bedside treatment of patients with glomerular diseases.

FCF reports serving as a board member of UpToDate—Associate Editor; consultancy for Alexion, Alnylam, BioCryst, and Takeda; grant/research support from Achillion, Genentech, Janssen, MorphoSys, and Travere (formerly Retrophin).

Keisha L. Gibson, MD, MPH, received her medical degree and Master of Public Health degree in epidemiology from the University of North Carolina (UNC) Chapel Hill, NC, USA. She completed a residency in general pediatrics at the Medical University of South Carolina, Charleston, SC, USA and a clinical fellowship in pediatric nephrology from UNC Chapel Hill. She is currently an associate professor of medicine and pediatrics, the chief of pediatric nephrology in the Division of Nephrology and Hypertension, and the Vice-Chair of Diversity and Inclusion for the Department of Medicine at UNC Chapel Hill.

Dr. Gibson's research and clinical interests focus on lupus nephritis and other glomerular diseases. In the area of epidemiology, she is interested in ethnic and socioeconomic disparities and their effect on patient outcomes. She has been involved as a co-investigator with large consortium studies such as the Nephrotic Syndrome Network Study (NEPTUNE Study) and the Cure Glomerulonephropathy Network (CureGN Study).

KLG reports serving as an advisory board member for Reata and Travere (formerly Retrophin); and consultancy for Aurinia.

Richard J. Glassock, MD, MACP, graduated from the UCLA School of Medicine, Los Angeles, CA, USA, in 1960 and received post-graduate training at UCLA, Los Angeles, CA, USA; Harvard University, Cambridge, MA, USA; and the Scripps Research Institute, La Jolla, CA, USA. His main interests are in glomerular disease and clinical nephrology. He has published over 750 original papers, books, book chapters, and reviews. He is the past-president of the ASN and the NKF (USA), and past-chairman of the American Board of Internal Medicine. He is the former chair of the Department of Medicine at the University of Kentucky, Lexington, KY, USA (1992–1999) and Harbor-UCLA Medical Center, Los Angeles, CA, USA (1980–1992). He is a Master of The American College of Physicians, Philadelphia, PA, USA and a fellow of The Royal College of Physicians, London, UK.

Dr. Glassock was the founding editor-in-chief of the *Nephrology Self-Assessment Program (NephSAP) Journal of the American Society of Nephrology* (2002). He is an editor of the nephrology section of *UpToDate*, an associate editor of the *American Journal of Nephrology*, and a founding moderator of the ASN Communities website. He received the David Hume Memorial Award of the NKF, the Robert Narins Award of the ASN, and Distinguished Achievement Awards from UCLA and the Association of Professors of Medicine. He is currently Professor Emeritus at the David Geffen School of Medicine at UCLA, Los Angeles, CA, USA and an independent medical consultant.

RJG reports consultancy for Apellis, Aurinia, BioCryst, Bristol Myers Squibb, Calliditas, ChemoCentryx, Equillium Bio, Horizon, Ionis, Natera (Renasight), Novartis, Omeros, Travere (formerly Retrophin), and Walden Biosciences; providing expert testimony for legal firms in the USA; speaker bureau for Aurinia; providing manuscript preparation for Neph-SAP—Associate Editor, Karger, and Wolters Kluwer (UpToDate); owning stock/stock options in Reata; and receiving travel expenses from various academic centers in the USA, Europe, China, and South America.

David R.W. Jayne, MD, FMedSci, is a professor of clinical autoimmunity at the University of Cambridge, Cambridge, UK, and director of the Vasculitis and Lupus Service at Addenbrooke's Hospital, Cambridge, UK. He trained at the Universities of Cambridge and London, Cambridge and London, UK, and in nephrology at Harvard Medical School, Boston, MA, USA. Dr. Jayne was a research fellow at Imperial College, London, UK and the University of Cambridge and was appointed as a senior lecturer in Nephrology at St George's Hospital, London, UK. He is a co-founder and the current president of the European Vasculitis Society, and his research focus has been ANCA vasculitis, having led a sequence of international randomized controlled trials over the past 25 years. His research group conducted the first studies on disease trials of newer immunosuppressives and biologics in vasculitis and lupus. He has published over 400 peer-reviewed papers and has contributed to numerous guideline statements. The clinical service in Cambridge cares for over 2000 patients with complex multisystem autoimmunity and receives tertiary referrals from throughout the UK and beyond.

DRWJ reports consultancy for AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, ChemoCentryx, Chugai, CSL Behring, GlaxoSmithKline (GSK), InflaRx, Janssen, Novartis, Roche/Genentech, Takeda and Vifor; serving in the speaker bureau for Vifor; and grant/research support from GSK, Medical Research Council*, National Institute for Health Research*, and Roche/Genentech*.*
**Monies paid to institution.*

Vivekanand Jha, MD, DM, FRCP, FAMS, is the executive director at the George Institute for Global Health, New Delhi, India, chair of Global Kidney Health at Imperial College, London, UK, and the current president of the ISN. Dr. Jha's research is focused on finding locally appropriate treatment and implementation strategies for patients with kidney diseases in low-resource settings through observational, intervention, and health systems research using innovative methodologies. He also has a translational program focused on finding markers of kidney disease assessment, risk stratification, progression, and complications. He has led a number of clinical trials in membranous nephropathy, FSGS, and IgA nephropathy. He has served as a Work Group member on prior KDIGO guidelines, including the Glomerulonephritis; Care of Kidney Transplant Recipients; and Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in CKD. He has also participated in several KDIGO Controversies Conferences. Dr. Jha is an expert in the effect of tropical ecology on kidney diseases and the impact of infections on patients with kidney diseases. He has published over 300 papers and about 50 textbook chapters.

VJ reports consultancy for NephroPlus; grants/research support from Baxter Healthcare*, Biocon*, and GSK*; and speaker bureaus for AstraZeneca* and Baxter Healthcare*.*
**Monies paid to institution.*

Adrian Liew, MD, MBBS, MRCP, FAMS, FASN, FRCP, MClinEpid, is a senior consultant nephrologist and director of The Kidney & Transplant Practice at Mount Elizabeth Novena Hospital in Singapore. He received his medical degree from the National University of Singapore, Singapore. Dr. Liew is an elected member of the executive committee and council of the ISN and an elected executive and honorary secretary of the International Society for Peritoneal Dialysis (ISPD). He chairs the ISN Oceania-Southeast Asia Regional Board, the ISN End-Stage Kidney Disease Strategy Dialysis Subgroup, and the ISN Renal Disaster Preparedness Working Group. He is a member of the ISN Dialysis Working Group, the ISN Continuing Medical Education (CME) Committee, and the Asia-Pacific Society of Nephrology CME Committee. He received the John Maher Award from the ISPD in 2020 for his contribution to peritoneal dialysis research. Dr. Liew is also an associate editor for the journal *Nephrology* and serves on the editorial board for *Kidney International*. His research interests include glomerular diseases, peritoneal dialysis, and diabetic kidney disease. He sits on the steering committees and is the national leader for several multicenter clinical trials. Dr. Liew chairs the Southeast Asia Glomerulonephritis Network and the Southeast Asia Peritoneal Dialysis Network. He is the co-principal investigator for the PROMiSE study, a clinical registry for peritoneal dialysis across 8 countries in Southeast Asia.

AL reports consultancy for Alnylam, AstraZeneca, DaVita, and George Clinical; and speaker bureau for AstraZeneca and Baxter Healthcare.

Zhi-Hong Liu, MD, is a professor of medicine and academician at the Chinese Academy of Engineering, Beijing, China, a director at the National Clinical Research Center of Kidney Disease, Jinling Hospital, Nanjing, China, and dean of the Zhejiang University School of Medicine, Hangzhou, China. Dr. Liu is the past-president of the Chinese Society of Nephrology. She was an executive committee member of the ISN and KDIGO. She is the editor-in-chief of *Kidney Diseases*, *Chinese Journal of Nephrology*, and *Dialysis & Transplantation*.

Dr. Liu has devoted herself to patient care, research, and medical education. Her primary interest is in the field of kidney disease, with a special interest in glomerulonephritis, diabetic nephropathy, and kidney replacement therapy. She has published 650 articles, edited 5 books on kidney disease, and contributed chapters to textbooks on nephrology. She is the chief scientist of the National Basic Research Program of China (973 Program) and was honored with the National Science and Technology Progress Award of China.

Z-HL declared no competing interests.

Juan Manuel Mejía-Vilet, MD, PhD, is a consultant nephrologist at Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, a clinical researcher for the Mexican National Research System, Mexico City, Mexico, and a professor of medicine for the National University of Mexico, Mexico City, Mexico, Panamerican University, Mexico City, Mexico, and the Monterrey Institute of Technology and Higher Education, Monterrey, Mexico.

Dr. Mejia-Vilet received his medical degree from the University of San Luis Potosi, San Luis Potosi, Mexico. He was trained in internal medicine and nephrology at the National University of Mexico and completed an ISN Glomerular Diseases fellowship at The Ohio State University, Columbus, OH, USA. He received a Master of Medical Science and a PhD degree from the National University of Mexico for his study of lupus nephritis pathophysiology and biomarker development.

His primary research area is centered on non-invasive biomarkers and prognosis of glomerular diseases, especially lupus nephritis and ANCA vasculitis. He currently follows a local lupus nephritis cohort comprising more than 700 subjects, the local glomerular diseases registry, and actively participates in clinical trials in these areas.

JMMV declared no competing interests.

Carla M. Nester, MD, MSA, FASN, is the Jean Robillard Professor of Pediatric Nephrology and the Division Director of Pediatric Nephrology, Dialysis and Transplantation at the Stead Family Children's Hospital, University of Iowa, Iowa City, IA, USA. She is the associate director of the Molecular Otolaryngology and Renal Research Laboratory (MORL), the largest combined clinical and research laboratory in North America with a focus on complement biology.

Dr. Nester is a National Institutes of Health–funded, tenured faculty member with a translational research program focusing on rare, complement-mediated kidney diseases. She is the primary clinical investigator for the C3 Glomerulopathy Natural History Study, the largest cohort of rare C3G patients in North America. As a result of the latter, she is an advisor to KidNeeds, a global C3G family community. Finally, Dr. Nester is a clinical trialist; her clinical practice has become a hub for bringing a new generation of anti-complement therapeutics to a rare disease population.

Dr. Nester's background in complement biology, combined with her unique training as an adult and pediatric glomerular disease clinician, facilitates her role as a highly sought-after speaker and educator in the area of complement biology and kidney disease.

CMN reports being on advisory boards for Achillion, Alexion, BioCryst, Novartis, and Pfizer; grant/research support from Achillion, Alexion, BioCryst, Novartis, and Travere (formerly Retrophin); and receiving author royalties from UpToDate.

Jai Radhakrishnan, MD, MS, MRCP, FACC, FASN, is a professor of medicine at Columbia University Medical Center, New York, NY, USA, and the clinical director of the nephrology division at New York-Presbyterian Hospital, New York, NY, USA. After completing his initial medical training in India and the United Kingdom, he completed his nephrology training at the Massachusetts General Hospital in Boston, MA, USA and Columbia University Medical Center in New York, NY, USA. He completed his master's degree in biostatistics from the Mailman School of Public Health, Columbia University, New York, NY, USA.

His clinical and research interests are in glomerular diseases. He is an associate editor of *Kidney International* and founding editor/editor-in-chief of *Kidney International Reports*. As a clinician–educator, Dr. Radhakrishnan has served on educational committees with the ASN and the ISN, and is a global education ambassador for the ISN. He has lectured extensively both nationally and internationally.

JR reports being an advisory board member for Reata; consultancy for Aurinia, Equillium Bio, Novartis, Reata, and Travere; and grant/research support from Travere.

Elizabeth M. Rave, MD, completed her undergraduate degree in chemical engineering at the University of Toledo, Toledo, OH, USA, and worked in industry for several years before going to medical school. Dr. Rave attended medical school at the University of Toledo Medical School (formerly Medical College of Ohio, MCO) and completed both her internal medicine residency and nephrology fellowship training at The Ohio State University, Columbus, OH, USA.

Dr. Rave has been busy as a private practice nephrologist since graduation from fellowship but also enjoys teaching students and residents who are in community-based training at several local hospitals in Columbus, Ohio. In addition to clinical responsibilities, she is heavily involved with patient care improvement through several hospital committees, including the OhioHealth Clinical Guidance Council, and serves as the Section Chair of Nephrology at Riverside Methodist Hospital. She has been a co-investigator in the Simplicity III and Reduce Hypertension trials (with OhioHealth), as well as the Reata Bardoxolone Study. She is on the Information Technology board for DaVita. She has been a board member for the Columbus chapter of the NKF since 2015 and was recently honored as the NKF Medical Advisor Board member of the year for 2019. She is currently serving as the president of Ohio Kidney Consultants.

EMR reports being a board member for Davita.

Heather N. Reich, MD, CM, PhD, FRCPC, is a graduate of McGill University Faculty of Medicine, Montreal, Quebec, Canada. She completed her post-graduate clinical training and PhD at the University of Toronto, Toronto, Ontario, Canada, where she is an associate professor and holds the Gabor Zellerman Chair in Nephrology Research. She works as a nephrologist-scientist at the University Health Network (UHN) and is passionate about improving the clinical care and outcomes of patients with glomerulonephritis.

Dr. Reich directs the glomerulonephritis program at Toronto General Hospital, Toronto, Ontario, Canada. This rich program spans clinical care of patients with glomerulonephritis, contribution to clinical trials, and translational research. Her research program objective is to identify clinical and molecular markers of progressive glomerular diseases and to identify and evaluate novel therapeutic targets to improve outcomes of patients with glomerulonephritis. She has contributed to over 95 publications, and her work has been consistently supported by peer-reviewed awards from agencies including the Kidney Foundation of Canada and the Canadian Institutes of Health Research. She enjoys training future leaders in glomerulonephritis care and research, and she was the co-director of the annual educational pre-course in glomerulonephritis for the ASN.

HNR reports consultancy for Calliditas, Omeros, Pfizer, Retrophin; and the UHN GN Fellowship is supported by the Louise Fast Foundation; conducting clinical trials for Alnylam, Calliditas, ChemoCentryx, Omeros, and Pfizer; and speaker fees from Gilead Pharmaceuticals and Omeros.

Pierre Ronco, MD, PhD, is an Emeritus Professor of Nephrology at Sorbonne Université, Paris, France. He received his PhD in immunology from University Paris 7, Paris, France, and his MD from the Medical Faculty Saint-Antoine, Sorbonne Université, Paris, France. He has devoted most of his career to the care of patients with glomerular disease and identification of relevant mechanisms as head of the renal division (1995–2018) and director of the INSERM Kidney Research Unit (1998–2018) at the Tenon Hospital in Paris, France.

Dr. Ronco's major contributions to clinical science, renal immunopathology, and rare kidney diseases resulted in over 500 research publications, including in the *New England Journal of Medicine*, *Lancet*, *Science*, *Journal of Experimental Medicine*, *Journal of Cell Biology*, and other major journals of nephrology, as well as 30 textbook chapters.

He served as president of the Francophone Society of Nephrology and the 49th ERA-EDTA Congress in Paris (2012). He chaired or co-chaired the Scientific Programme Committee of 4 World Congresses of Nephrology (Madrid, Milan, Cape Town, Mexico City). He is currently serving as the editor-in-chief of *Kidney International*, a position he has held since January 1, 2018.

He has been awarded international prizes and honors, including the Jean Hamburger Award (ISN) and the prize for outstanding basic research (ERA-EDTA). He is Doctor Honoris Causa of the Louvain Catholic University and a member of the Academia Europeae, the French Academy of Medicine, the Royal Academy of Medicine (Belgium), and the Institut Universitaire de France.

PR reports consultancy for Alexion, Amicus, Idorsia, and MorphoSys; grant/research support from Alexion and*

Amgen; providing manuscript preparation for UpToDate; receiving travel expenses from the ASN, the French Society of Nephrology, and Sanofi-Genzyme.*
**Monies paid to institution.*

Jan-Stephan F. Sanders, MD, PhD, is a nephrologist and the program director of the Kidney and Pancreas Transplantation Program at the University Medical Center Groningen (UMCG), Groningen, The Netherlands. Dr. Sanders received his MD degree in 2002 at the University of Groningen. He did a research fellowship at Hammersmith Hospital, Imperial College London, UK. Thereafter, Dr. Sanders trained in internal medicine and nephrology at Medical Center Leeuwarden, Leeuwarden, The Netherlands, and at University Medical Center Groningen (UMCG). He combined this with a PhD trajectory, which he completed in 2009 with his thesis "Disease-activity in ANCA-associated Vasculitis." Since September 2010, he has been a staff member at the division of nephrology at UMCG, focusing on kidney transplantation and ANCA-vasculitis. Since October 2019, he has served as the program director of the Kidney and Pancreas Transplantation Program at UMCG. His primary research interests are ANCA vasculitis and kidney transplantation. He has received research grants from the Dutch Kidney Society and the Netherlands Organisation for Health Research and Development.

J-SFS reports grant/research support from Chiesi, Dutch Kidney Society, The Netherlands Organisation for Health Research and Development, and Novartis.

Sanjeev Sethi, MD, PhD, graduated from Assam Medical College, Dibrugarh, India. He pursued graduate studies thereafter at Albany Medical College, Albany, NY, USA, and received his PhD in experimental pathology in 1995. Subsequently, Dr. Sethi completed his pathology residency at Yale University, New Haven, CT, USA (1995–1999) and his fellowship in renal pathology at Brigham and Women's Hospital, Harvard University, Boston, MA, USA (1999–2001). He is currently a professor at the Mayo Clinic, Rochester, MN, USA. His primary interests and research are in glomerulonephritis, with a focus on the management approach to glomerulonephritis, the role of monoclonal gammopathy in glomerulonephritis, and the role of alternative pathways of complement in glomerulonephritis, as well as the application of proteomics in renal pathology. New diseases have been identified using this novel approach. These studies have resulted in over 225 peer-reviewed publications.

SS reports consultancy for Novartis.

Yusuke Suzuki, MD, PhD, is currently a professor of nephrology at the Juntendo University Faculty of Medicine and Graduate School of Juntendo University, Tokyo, Japan. His academic positions include director of Japanese Society of Nephrology (JSN), councilor of the Japanese Society of Internal Medicine, Japanese Society of Dialysis Therapy, Japanese Society of Hypertension, and the ISN council, deputy chair of the ISN North and East Asia Regional Board, sub-chief (2011–2016) and chief (2017–present) researcher of the Special Research Group of IgA Nephropathy in Progressive Renal Diseases Research from the Ministry of Health, Labor and Welfare of Japan. Dr. Suzuki is also the chief researcher of a biomarker project on IgA nephropathy from Research on Intractable Disease from the Japan Agency for Medical Research and Development. His research mainly focused on the pathogenesis of IgA nephropathy. He has more than 160 English publications in peer-reviewed journals, including *Kidney International*, *Journal of the American Society of Nephrology*, *Journal of Clinical Investigation*, *JAMA Internal Medicine*, *JAMA Network*, and *Natural Medicine Journal*. He is now an editorial board member for *Kidney International*, *Nephrology*, and the *American Journal of Kidney Diseases*.

YS reports consultancy for Bayer, Chinook, Chugai, Daiichi Sankyo, Kyowa Kirin, Mitsubishi Tanabe Pharma, MorphoSys, Novartis Pharma, Travere (formerly Retrophin), and Visterra; grant/research support from Astellas, Bayer*, Chinook, Chugai*, Daiichi Sankyo*, Japan Agency for Medical Research and Development*, Japan Society for the Promotion of Science*, Kyowa Kirin*, 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; speaker bureau 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 providing 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.*
*Monies paid to institution.

Sydney C.W. Tang, MD, PhD, FRCP, FACP, FHKCP, FHKAM, is Chair of Renal Medicine and Yu Professor in Nephrology at the University of Hong Kong, Hong Kong, China and an honorary consultant physician at Queen Mary Hospital, Hong Kong. He trained in internal medicine and nephrology and has been a research fellow at King's College London, London, UK, and the University of Washington, Seattle, WA, USA. As a clinician–scientist, his research interests are in the pathogenesis of diabetic and chronic kidney disease and the treatment of IgA nephropathy. He has published over 270 scientific papers and contributed over 30 book chapters, including one on diabetic kidney disease (DKD) in *Comprehensive Clinical Nephrology*. He is currently editor-in-chief of *Nephrology (Carlton)*, theme editor (DKD) of *Nephrology Dialysis Transplantation*, associate editor of *Glomerular Diseases*, and on the editorial boards of *Kidney International, Clinical Journal of the American Society of Nephrology, Seminars in Nephrology*, *American Journal of Nephrology,* and *Kidney Diseases*. He is president-elect (2019–2022) of the Asian Pacific Society of Nephrology, a member of the KDIGO Executive Committee (from 2020), deputy chair (from 2018) of the CME Advisory Committee of the ISN, an International Honorary Member of the Japanese Society of Nephrology, and past-chairman (2016–2018) of the Hong Kong Society of Nephrology.

SCWT reports consultancy for Novartis and Travere (formerly Retrophin); grants/research support from Sanofi; and speaker bureau for AstraZeneca.

Vladimír Tesar, MD, PhD, FERA, FASN, is head of the Department of Nephrology, 1st Faculty of Medicine and General University Hospital, Charles University, Prague, Czech Republic. He is a member of the Executive Committee of the ISN, former chair of the Immunonephrology Working Group of ERA-EDTA, and the former member of the council of ERA-EDTA. He is a member of the editorial board of the *Clinical Journal of the American Society of Nephrology*; *Nephrology Dialysis Transplantation*; and *Journal of Nephrology*, and former editor-in-chief of *Kidney and Blood Pressure Research*. His main interests are glomerular disease, inherited diseases of the kidney, and cardiovascular complications of chronic kidney disease. He participated in many genetic and biomarker studies in glomerular diseases and on the steering committees of many randomized, controlled (including investigator-initiated) clinical trials. He has co-authored more than 400 papers in international journals, mostly dedicated to glomerular disease.

VT reports consultancy for Abbvie, Amgen, Baxter, Bayer, Boehringer Ingelheim, Calliditas, ChemoCentryx, and Fresenius Medical Care, Omeros, and Travere; speaker bureaus for Bayer and Boehringer Ingelheim; and receiving travel expenses for AbbVie.

Marina Vivarelli, MD, trained in pediatrics at the University of Pavia, Pavia, Italy, is working in pediatric rheumatology in Dr. Fabrizio De Benedetti's lab, on the pathogenesis of juvenile idiopathic arthritis. She completed a 2-year research fellowship at Children's Hospital, Boston, MA, USA with Professor Raif Geha, studying a mouse deficient in RIP, a protein that is pivotal in B cell response to toll-like receptor 4.

Since 2006, in the Division of Nephrology of the Bambino Gesù Pediatric Hospital in Rome, Italy, she has worked to establish a new front of translational research in pediatric immune-mediated kidney diseases. Her focus has been on nephrotic syndrome, and her expertise in B cell biology has led her to address the question of why B cell–depleting therapy is effective in some forms of this disease.

She has designed and conducted a phase 1 trial on the use of mesenchymal stem cells in difficult forms of nephrotic syndrome and has also contributed to the design and conduct of trials evaluating the use of belimumab and comparing rituximab and mycophenolate mofetil in pediatric nephrotic syndrome.

She treated the first patient with dense deposit disease (DDD) with eculizumab and has participated in trials evaluating complement inhibitors for children with aHUS and C3 glomerulopathy.

MV reports consultancy for Apellis, Novartis, Roche, and Travere (formerly Retrophin).

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appointed professor of nephrology in the Department of Nephrology at Radboud University Nijmegen. His chair is committed to teaching and research with an emphasis on the diagnosis and treatment of patients with glomerular diseases. Dr. Wetzels is a member of the steering committee of the European Reference Network for Rare Kidney Diseases (ERKnet) and co-chair of the Immune-glomerulopathies Working Group within ERKnet.

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 bureau for Novartis.**
**Monies paid to institution.*

KDIGO Chairs

Michel Jadoul, MD, received his medical degree in 1983 at the Université Catholique de Louvain (UCLouvain) in Brussels, Belgium. Dr. Jadoul trained in internal medicine and nephrology under the mentorship of Professor Charles van Ypersele de Strihou. He has served as chair at the Department of Nephrology of the Cliniques Universitaires Saint-Luc, Brussels, Belgium since 2003 and is currently a full clinical professor at UCLouvain. Dr. Jadoul's clinical activities focus on the follow-up of hemodialysis and CKD patients, and his main research interests include β2-microglobulin amyloidosis, hepatitis C, and other complications (e.g., falls, bone fractures, sudden death) in hemodialysis patients, as well as cardiovascular complications after kidney transplantation and various causes of kidney disease (e.g., drug-induced).

Dr. Jadoul has co-authored over 260 scientific papers, most of them published in major nephrology journals. He is currently serving as a theme editor of *Nephrology Dialysis Transplantation*, and he is also a country co-investigator for the Dialysis Outcomes and Practice Patterns Study (DOPPS; 2001–present). In 2008, he received the international distinguished medal from the US NKF. He was previously a member of the KDIGO Executive Committee (2010–2015) and the ERA-EDTA Council (2013–2016). Presently, Dr. Jadoul is a KDIGO Co-Chair.

MJ reports consultancy for Astellas, AstraZeneca*, Merck Sharp & Dohme*, Mundipharma*, and Vifor Fresenius Medical Care Renal Pharma*; providing expert testimony for Vifor Fresenius Medical Care Renal Pharma*; grants/research support from Amgen*, Janssen-Cilag*, Otsuka*, and Roche*; speaker bureau for Amgen*, Menarini*, Merck Sharp & Dohme*, Mundipharma, and Vifor Fresenius Medical Care Renal Pharma*; and travel fees paid by Amgen* and Sanofi**
**Monies paid to institution.*

Wolfgang C. Winkelmayer, MD, MPH, ScD, is the Gordon A. Cain Chair of Nephrology and professor of medicine at Baylor College of Medicine in Houston, TX, USA. Dr. Winkelmayer received his medical degree (1990) from the University of Vienna, Vienna, Austria, and later earned a Master of Public Health in healthcare management (1999) and a Doctor of Science in health policy (2001) from Harvard University, Cambridge, MA, USA. He then spent 8 years on the faculty of Brigham and Women's Hospital and Harvard Medical School, Boston, MA, where he established himself as a prolific investigator and leader in the discipline of comparative-effectiveness research as it pertains to patients with kidney disease. From 2009 to 2014, he was the director of clinical research in the Division of Nephrology at Stanford University School of Medicine, Palo Alto, CA, USA. He assumed his current position as chief of nephrology at Baylor College of Medicine in September 2014. His main areas of research interest include comparative effectiveness and safety research of treatment strategies for anemia, as well as of various interventions for cardiovascular disease in patients with kidney disease. Dr. Winkelmayer is a member of the American Society of Clinical Investigation. His clinical passion lies in providing quality kidney care to the predominantly disadvantaged and un(der)insured population in the public safety net health system of Harris County, Texas. Dr. Winkelmayer has authored over 300 peer-reviewed publications, and he has a particular interest in medical publishing. He currently serves as an associate editor for the *Journal of the American Medical Association*, was a co-editor of the *American Journal of Kidney Disease* from 2007 to 2016, and has been appointed to several other editorial boards of leading nephrology and epidemiology journals. He also volunteers his time toward important initiatives of the ASN (e.g., Public Policy Board). He joined the KDIGO Executive Committee in 2015 and has served as KDIGO Co-Chair since 2016.

WCW reports consultancy for Akebia, Amgen, AstraZeneca, Bayer, Daiichi Sankyo, Relypsa, and Vifor Fresenius Medical Care Renal Pharma.

METHODS Chair

Marcello A. Tonelli, MD, SM, MSc, FRCPC, is senior associate dean (clinical research) at the Cumming School of Medicine in Calgary, Alberta, Canada. He is associate vice president (health research) at the University of Calgary, Calgary, Alberta, Canada. He received a medical degree from the University of Western Ontario, Ontario, Canada, a Master of Science in

epidemiology from Harvard University, Cambridge, MA, USA, and a Master of Science in health policy from Imperial College London, UK. He is a nephrologist and professor at the University of Calgary.

Dr. Tonelli has served in the past as president of the Canadian Society of Nephrology, councilor of the ISN, and a member of the KDIGO Executive Committee. Dr. Tonelli is chair emeritus of the Canadian Task Force for Preventive Health Care, a national panel of experts that makes recommendations about preventive health services to Canada's 36,000 family physicians.

A unique aspect of Dr. Tonelli's research program includes partnering with regional, provincial, and national decision makers to ensure that the findings will be used to produce rational health policy.

*MT has received honoraria from AstraZeneca and Travere (formerly Retrophin).**

**Monies donated to charity*

Evidence Review Team

Jonathan C. Craig, MBChB, DipCH, FRACP, M Med (Clin Epi), PhD, Evidence Review Team Director, is an internationally recognized clinician and scientist and holds the position of vice president and executive dean of the College of Medicine & Public Health at Flinders University, Adelaide, South Australia, Australia. Professor Craig has made a significant contribution to the clinical research landscape in the prevention, identification, management, and treatment of CKD, particularly in relation to children and in indigenous communities.

He has led the formation of state, national, and international networks to conduct high-quality, relevant trials in children. He has been instrumental in the development and implementation of best-practice methods and guidelines relating to CKD in Australia and globally. Professor Craig's many current advisory roles include member of the National Health and Medical Research Council's (NHMRC) Health Translation Advisory Committee, the Pharmaceutical Benefits Advisory Committee, Medical Services Advisory Committee, and Commonwealth Department of Health Life Savings Drug Program.

He is a past member of the World Health Organization expert review panel for global strategy and plan of action on public health, innovation and intellectual property, a past chairman of the Steering Group of the Cochrane Collaboration, and a past member of the Expert Advisory Group for the Structural Review of NHMRC's Grant Program.

JCC declared no competing interests.

Suetonia C. Palmer, MBChB, FRACP, PhD, Evidence Review Team Co-Director, is an academic nephrologist at the University of Otago at Christchurch in New Zealand. She studied medicine at the University of Otago, graduating in 1995. She became a fellow of the Royal Australasian College of Physicians in Nephrology in 2005. She later completed a PhD in 2010 on the link between kidney function and heart health, and a 2-year postdoctoral fellowship in Boston, MA, USA, at the Brigham and Women's Hospital.

Dr. Palmer began as an author with the Cochrane Kidney and Transplant Group in 2004 during her training to become a nephrologist. Through systematic reviews, she discovered a passion for understanding more about the amount and quality of evidence that are required to make good clinical decisions in nephrology. She is actively engaged in the conduct of systematic reviews of interventions (the treatments we use), prognosis (whether risk factors for disease link to important outcomes), and trial quality (how good is the evidence on which to base our decisions).

Dr. Palmer enjoys training others in systematic review and meta-analysis using an evidence-based approach to research. She has strong collaborative links with researchers in Italy, Australia, Europe, and North America with an increasing research output, including recent publications in key internal medicine and nephrology journals.

SCP declared no competing interests.

Giovanni F.M. Strippoli, MD, MPH, M Med (Clin Epi), PhD, Evidence Review Team Co-Director, has made significant contributions to clinical research in CKD, with particular focus on prevention of kidney disease and management of kidney failure, including hemodialysis, peritoneal dialysis, and kidney transplantation. He has contributed strongly to the development of policy in the area of kidney disease management through an international network designing and conducting epidemiologic studies in the field, including systematic reviews, randomized trials, and cohort studies, among others. Professor Strippoli has been an active contributor in his positions as chairman, deputy chairman, and council in nephrology societies, including the ISN and the Italian Society of Nephrology, as well as editorial positions in nephrology and general medicine scientific journals.

GFMS declared no competing interests.

Martin Howell, PhD, Assistant Project Director, is a senior research fellow in health economics in the Sydney School of Public Health (University of Sydney), Sydney, New South Wales, Australia. Since 2009, Martin has been responsible for evidence review and synthesis and the development of over 20 clinical practice guidelines for the Kidney Health Australia—Caring for Australasians with Renal Impairment (KHA-CARI) guidelines group. His research focuses on applied health economics, predominantly in the areas of assessment of

preferences using discrete choice methods and economic evaluations. His PhD project involved the application of a type of choice experiment known as a Best Worst Scaling survey to elicit preferences of recipients of kidney transplants for outcomes after transplantation. This methodology has since been applied to address a diverse range of health-related issues. He is currently leading the economic evaluations of 9 active clinical trials. He is an author of 57 publications (first author on 10). These publications show the broad application of his research from clinical trials to translation of clinical evidence to clinical practice guidelines and patient-centered care.

MH declared no competing interests.

David J. Tunnicliffe, PhD, Evidence Review Project Team Leader and Project Manager, is a research fellow at the University of Sydney, School of Public Health, Sydney, and the Centre for Kidney Research at the Children's Hospital at Westmead, New South Wales, Australia. He was awarded his PhD in 2018 at the University of Sydney and was awarded a National Health and Medical Research Council (NHMRC) Emerging Leadership 1 Investigator Grant (APP1197337) to examine the implementation and evaluation of living evidence in kidney disease. David has a research interest in meta-research of CKD and teaching epidemiology, which he performs through the Masters (Medicine) Clinical Epidemiology program, as a unit coordinator of introductions to systematic reviews.

As part of Cochrane Kidney and Transplant, David has served as the evidence review project team leader and project manager for the 2020 KDIGO update of the KDIGO Clinical Practice Guideline on the Management of Blood Pressure in CKD, providing methodological expertise on evidence synthesis and guideline development. His role was key in coordinating the formation of key clinical questions to guide literature searching and leading data extraction, critical appraisal, meta-analysis, and evidence grading.

DJT declared no competing interests.

Fiona Russell, PhD, *Cochrane Kidney and Transplant*, Managing Editor, has more than 20 years' experience at media organizations such as News Corp and Fairfax Media, Sydney, Australia in a variety of editorial positions, including reporter, sub-editor, deputy editor, and production editor. Two years as an information technology supervisor led to an ongoing technological change management role at both companies, developing new system procedures and workflows, and providing training solutions for new and existing staff.

During her editorial career, Dr. Russell also gained a bachelor's degree in journalism, international relations, and literary studies, a graduate degree in cognitive science, and a PhD in comparative cognition research. She has been the managing editor of *Cochrane Kidney and Transplant* since October 2015.

FR has grants/grants pending from the National Health and Medical Research Council of Australia.

Gail Y. Higgins, BA, Grad Ed, Grad Dip LibSc, Information Specialist, completed a bachelor's degree in arts, a graduate diploma in education from the University of Sydney, Sydney, New South Wales, Australia, and a graduate diploma in Library Science from Kuring-gai College of Advanced Education, Sydney, New South Wales, Australia. Following a number of years as a teacher–librarian, she changed tack and spent 3 years with the New South Wales Technical and Further Education (NSW TAFE) Information Systems Division. After that, she joined the University of Sydney Library and worked as a pharmacy librarian and then as an internet training librarian. She has worked as an information specialist for the Cochrane Haematological Malignancies Group in Cologne, Germany, and the Cochrane Cancer Network in Oxford, UK. In 2007 and 2008, she completed a secondment with the World Health Organization in Geneva, Switzerland, on the International Clinical Trials Registry Platform (ICTRP) project.

GYH declared no competing interests.

Brydee Cashmore, MPH, Research Associate, has a Master of Public Health from the University of Sydney, Sydney, New South Wales, Australia, as well as a bachelor's degree in science, a double major in physiology and human nutrition, a graduate diploma in science in psychology, and a postgraduate diploma in science in human nutrition from Massey University, Palmerston North, New Zealand. She is a researcher at the Centre for Kidney Research at the University of Sydney, where she undertakes evidence review and synthesis for *Cochrane Kidney and Transplant* and the KHA-CARI Guideline group. She was involved across all of the KDIGO Clinical Practice Guideline for the Management of Glomerular Diseases subtopics and undertook key aspects of the evidence review, including data extraction, evidence synthesis, and the writing and preparation of evidence summaries in MAGICapp.

BC declared no competing interests.

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