KDIGO CLINICAL PRACTICE GUIDELINE ON GLOMERULAR DISEASES

PUBLIC REVIEW DRAFT

JUNE 2020

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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**.

Grade	Implications		
	Patients	**Clinicians**	**Policy**
Level 1 "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 "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 lies 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 effect is very uncertain, and often will be far from the truth.

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CKD is <u>defined</u> as abnormalities of kidney structure or function, present for > 3 months, with implications for health. CKD is <u>classified</u> based on <u>C</u>ause, <u>G</u>FR category (G1-G5), and <u>A</u>lbuminuria category (A1-A3), abbreviated as CGA.

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012				**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
GFR categories (ml/min/ 1.73 m²) Description and range	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.

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
PCR	mg/g	0.1	mg/mmol

Note: Conventional unit x conversion factor = SI unit

ALBUMINURIA CATEGORIES IN CKD

Category	AER (mg/24 hours)	ACR (approximate equivalent) (mg/mmol)	(mg/g)	Terms
A1	< 30	< 3	< 30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased*
A3	> 300	> 30	> 300	Severely increased**

ACR, albumin-creatinine ratio; AER, albumin excretion rate; CKD, chronic kidney disease
*Relative to young adult level
**Including nephrotic syndrome

ABBREVIATIONS AND ACRONYMS

ACEi	Angiotensin-converting enzyme inhibitor(s)
ACR	Albumin-creatinine ratio
AKI	Acute kidney injury
ANCA	Anti-neutrophil cytoplasmic antibody
ARB	Angiotensin II-receptor blocker
BP	Blood pressure
CI	Confidence interval
CKD	Chronic kidney disease
CNI	Calcineurin inhibitor
CP	Cyclophosphamide
CrCl	Creatinine clearance
CVD	Cardiovascular disease
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EM	Electron microscopy
ERT	Evidence Review Team
ESKD	End-stage kidney disease
FSGS	Focal segmental glomerulosclerosis
GBM	Glomerular basement membrane
GFR	Glomerular filtration rate
GN	Glomerulonephritis
GI	Gastrointestinal
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HBV	Hepatitis B virus
HCV	Hepatitis V virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
IgAN	Immunoglobulin A nephropathy
IgAV	Immunoglobulin A vasculitis
IgG	Immunoglobulin G
IgM	Immunoglobulin M
i.v.	Intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
MCD	Minimal change disease
MPAA	Mycophenolic acid analogs
MMF	Mycophenolate mofetil
MN	Membranous nephropathy
NS	Nephrotic syndrome
NSAIDS	Nonsteroidal anti-inflammatory drugs
OR	Odds ratio
PCR	Protein-creatinine ratio
PLA2R	M-type phospholipase-A2-receptor
PLA2Rab	Antibodies against the M-type phospholipase-A2-receptor
p.o.	Oral
RAS(i)	Renin-angiotensin system (inhibitor)
RCT	Randomized controlled trial
RR	Relative risk
SCr	Serum creatinine
SLE	Systemic lupus erythematosus
SRNS	Steroid-resistant nephrotic syndrome
SSNS	Steroid-sensitive nephrotic syndrome
THSD7Aab	Antibodies against thrombospondin type-1 domain-containing 7A
UK	United Kingdom
US	United States

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, and updated in March 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. Health-care professionals using these recommendations should decide how to apply them to their own clinical practice.

SECTION II: DISCLOSURE

Kidney Disease: Improving Global Outcomes (KDIGO) makes every effort to avoid any actual or reasonably perceived conflicts of interest that may arise from an outside relationship or a personal, professional, or business interest of a member of the Work Group. All members of the Work Group are required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived as or are actual conflicts of interest. This document is updated annually, and information is adjusted accordingly. All reported information is published in its entirety at the end of this document in the Work Group members' Disclosure section and is kept on file at KDIGO.

FOREWORD

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 its 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. Currently, KDIGO is updating two existing guidelines on Blood Pressure Management in CKD and Glomerular Diseases, respectively. In addition, KDIGO has convened a group of experts to develop guideline recommendations related to Diabetes Management in CKD. All three 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, its frequent manifestation in younger patients, it is critical that they are 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 twelve distinct diseases based on evidence available through November 2011. Since this 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 expertise to identify key issues relevant to the optimal management of primary and secondary glomerular diseases. The goal was to determine best practice treatment and areas of uncertainties in the treatment of glomerular diseases, review key relevant literature published since the 2012 KDIGO 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 draft is now made available for public review, too, and the Work

Group will critically review the public input and revise 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 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 Craig, MBChB, DipCH, FRACP, M Med (Clin Epi), PhD; Martin Howell, PhD; and David Tunnicliffe, PhD, who made this guideline possible.

KDIGO recently appointed Marcello Tonelli, MD, SM, 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. In addition, he introduced the new format called Practice Points, which is a new form of guidance produced in addition to formal recommendations. Where 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 this guideline update on Glomerular Diseases develop into a highly useful document, rich in guidance and helpful implementation tools for the user, while still 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.

In summary, we are confident that this guideline will prove useful to clinicians treating people with glomerular diseases throughout the world, and 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
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KDIGO Co-Chairs

Updates to the KDIGO Guideline Format

KDIGO guidelines continue to use the GRADE methodology, but we have strengthened the link between evidence and the recommendations themselves.

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 simultaneously posted online in MAGICapp; the online format will facilitate rapid updates as new evidence emerges.

Below is an FAQ outlining the rationale for this shift, along with an example recommendation in the new format.

Practice Points are used when

- No systematic review was conducted

- There is insufficient evidence

- Evidence was inconclusive (less evidence than required)

- The alternative option is illogical

- The guidance does not imply action for the physician

- Consensus statements providing guidance and guidance in the absence of evidence may consider benefits and harms but will not be explicitly discussed

- Guidance does not require an explicit discussion of values and preferences or of resource considerations, although is implied that these were considered

- The guidance may be more useful as a table/figure/algorithm

Recommendations will be provided when

- Systematic review was conducted

- Ample evidence is available

- Evidence shows a clear preference for one action over the alternatives

- Guidance is always actionable

- Consensus statements are supported with evidence and explicit discussion of the balance of benefits and harms, values and preferences will be necessary

- Application of guidance requires explicit discussion of values and preferences or on resource

- The guidance is more useful displayed as or requires additional explanation in text

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 will systematically review and analyze the evidence.
- The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach is used to analyze certainty in the evidence and strength of guideline recommendations.

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 observed) 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 should be 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 is comprised 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
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?

- Practice Points are consensus statements about a specific aspect of care, and supplement recommendations for which a larger quality of evidence was identified.
- 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.

New guideline disseminated → Start with recommendations → Consider relevant practice points

What happened to the old "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 link 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. We recommend treating patients with type 2 diabetes, CKD and GFR $\geq$30 ml/min/1.73 m^2 with metformin (1B).

Why was this formatted as a recommendation?
- Balance of benefits and harms (all based on published, scientific studies):
  - Benefits: HbA1c reduction, greater weight reduction compared to other drugs, protective against cardiovascular events in general population, etc.
  - Harms: potential for lactic acid accumulation
- Quality of evidence: to form this recommendation was based on clinical recommendations extracted from RCTs, systematic reviews performed in the general population, and outcomes from observational studies were considered.
- Resources and other costs: drug is least expensive, widely available, and affordable.
- Considerations for implementation: dose adjustments are required, no safety data for patients with eGFR <30 ml/min/1.73 m^2, and must be switched off when this level is reached.

Practice Point 1. Treat kidney transplant recipients with type 2 diabetes and eGFR $\geq$30 ml/min/1.73 m^2 with metformin according to recommendations for patients with type 2 diabetes and CKD

Why was this formatted as a Practice Point?
- Less robust data than recommendation; no systematic review was done.
- Little evidence was found, most data from registry and pharmacy claims. This evidence cannot be considered conclusive.
- Based on the limited evidence available, the Work Group decided to base their guidance to use metformin in the transplant population should be based on the eGFR, same approach as for CKD group.

Practice Points may also have accompanying algorithms to aid in implementation

For example:

Practice Point 2. Monitor eGFR in patients treated with metformin. Increase the frequency of monitoring when eGFR is <60 ml/min/1.73 m^2

```
                                    Yes
                    eGFR < 30  ─────────►  Stop metformin; not to initiate metformin

                        No

        eGFR ≥ 60            eGFR 45–59              eGFR 30–44

Dose         Immediate Release:
initiation   • Initial 500 mg or 850 mg once daily
             • Titrate upwards by 500 mg or 850 mg/day      Initiate at half the dose
               every 7 days till maximum dose               and titrate upwards to
                                                            half of maximum
             OR                                             recommended dose

             Extended Release:
             • If GI side effects from immediate release
             • Initial 500 mg daily
             • Titrate upwards by 500 mg/day every 7 days
               until maximum dose

Monitor      Annually if on metformin for more than 4 years or at risk of vitamin B12 deficiency
vitamin B12

Monitor
kidney           At least annually              At least 3–6 monthly
function

        eGFR ≥ 60            eGFR 45–59              eGFR 30–44

Subsequent   Continue        Continue same dose.      Half the dose
dose         same dose       Consider dose reduction in
adjustment                   certain conditions (see text)
```

Why was this formatted as a practice point?
- Limited evidence to support the guidance but monitoring eGFR in these patients is necessary.
- No systematic review was done.
- An algorithm was a clear visual presentation of the approach to monitoring; one can imagine trying to describe this algorithm in a series of statements, but the graphic is more useful to the reader.

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ABSTRACT

The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Glomerular Diseases is an update to the 2012 KDIGO guideline on the topic. The aim is to assist clinicians caring for individuals with glomerulonephritis (GN), both adults and children. The scope includes various glomerular diseases, including IgA nephropathy and IgA vasculitis, membranous nephropathy, idiopathic nephrotic syndrome, minimal change disease, focal segmental glomerulosclerosis, infection-related GN, anti-neutrophil cytoplasmic antibody (ANCA) vasculitis, lupus nephritis, and anti-glomerular basement membrane antibody GN. In addition, this guideline will be the first to address the subtype of Complement-mediated diseases. Each chapter follows the same template 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 useful infographics based on a rigorous formal literature systematic 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 GN while being mindful of implications for policy and payment. Development of this guideline update followed an explicit process of evidence review and appraisal. Treatment approaches and guideline recommendations are based on systematic reviews of relevant studies, and appraisal of the quality of the evidence and the strength of recommendations followed the 'Grading of Recommendations Assessment, Development and Evaluation' (GRADE) approach. Limitations of the evidence are discussed, with areas of future research also presented.

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

INTRODUCTION FROM THE GUIDELINE CO-CHAIRS

Glomerulonephritis (GN), be it primary or secondary, occurring in the setting of systemic autoimmune diseases, infections, drugs, or malignancy, affects individuals of all ages. In most end-stage kidney disease registries, glomerular diseases account for about 20% to 25% of the prevalent cases. However, in children, teenagers, and young adults, GNs are one of the most common causes of irreversible kidney damage and, as such, are 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 eight years that have passed, several major discoveries have been made that relate to our understanding of the pathogenesis, diagnosis, and therapy of GN. 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 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 more appropriate and 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., IgA nephropathy, membranous nephropathy, nephrotic syndrome including minimal change disease and focal segmental glomerulosclerosis, and infection-related GN), as well as systemic immunological 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 Glomerulonephritis* that discusses supportive therapies appropriate for all GNs 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 with a new chapter entitled *Immunoglobulin and Complement-Mediated Glomerular Diseases with an MPGN Pattern of Injury*. The chapter on *Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis* compares and contrasts B-cell targeted therapies with traditional cytotoxic drugs. The chapter on *Focal Segmental Glomerulosclerosis* 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.

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's 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 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 on 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 GNs 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-one 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 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 outcome of patients with immune-mediated glomerular diseases.

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SUMMARY OF RECOMMENDATION STATEMENTS AND PRACTICE POINTS

CHAPTER 1. GENERAL PRINCIPLES FOR THE MANAGEMENT OF GLOMERULAR DISEASES

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.

Practice Point 1.1.2. The evaluation of kidney tissue should meet standards of biopsy adequacy.

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 GN patients for whom initiation or intensification of immunosuppression is necessary, or who have a change in clinical status.

Practice Point 1.2.2. Quantify proteinuria in GN, as it has disease-specific relevance for prognosis and treatment decision-making. Qualitative assessment of proteinuria may be useful in selected instances.

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 GN.

Practice Point 1.3.2. Monitoring of hematuria (magnitude and persistence) may have prognostic value in many forms of GN.

1.4. Management of complications of glomerular disease

Table GP3. Edema management in the nephrotic syndrome

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 may be acceptable for reduced GFR • Increase dose to cause clinically significant diuresis or until maximally effective dose has been reached • Change from furosemide to torsemide/torasemide or bumetanide if treatment failure 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 thiazide-like diuretics and/or mineralocorticoid antagonists in combination with loop diuretics and sodium restriction for synergistic treatment of resistant edema in the nephrotic syndrome	• Metolazone may be more effective than hydrochlorothiazide or chlorthalidone in patients with reduced GFR <30 ml/min
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
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

GFR, glomerular filtration rate; i.v., intravenous

1.5. Management of hypertension and proteinuria reduction in GN

Table GP4. Management of hypertension and proteinuria in GN

Practice Point 1.5.1.	Use an ACEi or ARB to maximally tolerated or allowed dose as first-line in treating patients with both hypertension and proteinuria	• Do not stop ACEi or ARB with modest and stable increase in serum creatinine (up to 20%) • Stop ACEi or ARB if kidney function continues to worsen, and/or refractory hyperkalemia 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.	Goal systolic blood pressure is <120 mm Hg using standardized office BP measurement (adults). Goal mean arterial pressure is ≤50% age/sex (children)	• Refer to KDIGO BP Guideline (https://kdigo.org/guidelines/blood-pressure-in-ckd/)
Practice Point 1.5.3.	Uptitrate an ACEi or ARB to maximally tolerated or allowed daily dose as first-line 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.	Goal proteinuria 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
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
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 • Thiazides 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 of 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 (see also Practice Point 1.5.7 above)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; MCD, minimal change disease; NS, nephrotic syndrome; RAS, renin-angiotensin system; SSNS, steroid-sensitive nephrotic syndrome

1.6. Management of hyperlipidemia in GN

Table GP5. Management of hyperlipidemia in GN

Practice Point 1.6.1.	Treatment of hyperlipidemia may be considered in patients with the nephrotic syndrome, particularly for treatment-unresponsive 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 the 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
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 atherosclerotic cardiovascular disease risk • Statins can be initiated in children > 8 years with concerning family history, extremely elevated low density lipoprotein cholesterol or Lp(a), in 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 μg/mg) are independently associated with an elevated risk of atherosclerotic cardiovascular disease • Atherosclerotic cardiovascular disease risk enhancers include chronic inflammatory conditions such as systemic lupus erythematosus, rheumatoid arthritis, history of pre-eclampsia, early menopause, South Asian ancestry, chronic kidney disease and human immunodeficiency virus/AIDS (accuracy of atherosclerotic cardiovascular disease 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 low density lipoprotein cholesterol 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 atherosclerotic cardiovascular disease risk and fail to achieve low density lipoprotein cholesterol or triglyceride goals despite maximally tolerated statin dose: • Bile acid sequestrants • Fibrates • Nicotinic acid • Ezetimibe • PCSK9 inhibitor	• 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 the 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

AIDS, acquired immunodeficiency syndrome

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 GP5).

Figure GP5. Anticoagulation in nephrotic syndrome

For thromboembolic events, full-dose anticoagulation is required for 6–12 months and/or for the duration of the nephrotic syndrome	Prophylactic full-dose anticoagulation should be considered if:*	Contraindications to prophylactic anticoagulation
Venous thrombosis Arterial thrombosis Pulmonary embolus Nonvalvular atrial fibrillation	Serum albumin <2.0–2.5 g/dl and any of the following: • Proteinuria >10 g/d • Body mass index >35 kg/m^2 • Genetic disposition for thromboembolism • Heart failure New York Heart Association class III or IV • Recent orthopedic or abdominal surgery • Prolonged immobilization	• Patient preference/ability to adhere • Bleeding diathesis • Central nervous system lesion prone to hemorrhage • Genetic mutations influencing warfarin metabolism/efficacy • Frailty (falls) • Prior gastrointestinal bleed

*Membranous GN carries a particularly high risk of thromboembolic events

Practice Point 1.7.2. Anticoagulant dosing considerations in patients with nephrotic syndrome (Figures GP6 and GP7).

Figure GP6. Anticoagulant dosing considerations in patients with nephrotic syndrome

Prophylactic anticoagulation during transient high risk events

- Low dose anticoagulation (e.g., 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

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 Cockroft–Gault equation), age, and weight. The urinary clearance of the Xai 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%
  - 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 GP7. Glomerulonephritis/nephrotic syndrome algorithm for prophylactic anticoagulation[*†]

*Hofstra, JM. et al. Kidney International. 2016; 89 (5): 981 - 983
†Note: This algorithm was developed for patients with membranous GN. Its value is unknown for patients with nephrotic syndrome due to other underlying diseases
‡ Albumin value of 2.5 g/dl is measured using bromocresol green (BCG)

1.8. Risks of infection

Practice Point 1.8.1. Use pneumococcal vaccine in patients with GN and nephrotic syndrome, as well as in patients with CKD.

Practice Point 1.8.2. Screen for TB, HBV, HCV, HIV, and syphilis in clinically appropriate patients (see 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 IgE levels.

Practice Point 1.8.4. Prophylactic trimethoprim-sulfamethoxazole should be considered in patients receiving high-dose prednisone or other immunosuppressive agents (rituximab, cyclophosphamide). Dapsone may be substituted for the sulfa-allergic.

1.9. Outcome measures

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

Practice Point 1.9.2. A reduction in the slope of decline in GFR or avoidance of a >40% decline in GFR from baseline over two years or more can be taken as a favorable surrogate outcome of treatment.

1.13. Therapeutic drug monitoring

Table GP7. Minimization of immunosuppression-related adverse effects

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
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

1.14. Dietary management in GN

Table GP8. Dietary suggestions in GN

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 and level of kidney function	• Nephrotic range proteinuria • 0.8–1 g/kg/d protein intake* • Additional 1 g per gram of protein losses (up to 5 g/d)
Practice Point 1.14.3.	Replace nephrotic protein losses	• Estimated glomerular filtration rate <60 ml/min/1.73 m² with non-nephrotic range proteinuria • 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	• Nephrotic range proteinuria • 35 kcal/kg/d • Estimated glomerular filtration rate < 60 ml/min/1.73 m² • 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 • Saturated fat 7–10% of total calories

*Ideal body weight

1.15. Pregnancy and reproductive health in women with GN

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

1.16. Treatment costs and related issues

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

CHAPTER 2. IMMUNOGLOBULIN A NEPHROPATHY/IMMUNOGLOBULIN A VASCULITIS

IMMUNOGLOBULIN A NEPHROPATHY

2.1. Diagnosis
Practice Point 2.1.1. Considerations for the diagnosis of IgAN:
- **IgAN can only be diagnosed with a kidney biopsy.**
- **Score the kidney biopsy using the revised Oxford MEST-C Classification.[3]**
- **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 assess the patient using the International IgAN Prediction Tool.**
    - **Available at: Calculate by QxMD**
- **The International IgAN Prediction Tool 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 may require specific immediate treatment.**

Practice Point 2.3.2. Algorithm for the initial assessment and management of the patient with IgAN (Figure IgAN1).

Figure IgAN1. 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

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/24h, we recommend that initial therapy be with either an ACEi or ARB, but not both *(1B)*.

Recommendation 2.3.2. We recommend that all patients with proteinuria >0.5 g/24h, irrespective of whether they have hypertension, are treated with either an ACEi or ARB (1B).

Practice Point 2.3.3. 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 >1g/24h despite at least 90 days of optimized supportive care.**
- **Immunosuppressive drugs should only be considered in patients with IgAN who remain at high risk of progressive CKD despite maximal supportive care.**
- **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 with a recognition that adverse treatment effects are more likely in patients with an eGFR below 50 ml/min/1.73 m². **
- **There is insufficient evidence to support the use of the Oxford 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 2.3.4. Proteinuria reduction to under 1 g/d is a surrogate marker of improved kidney outcome in IgAN.

Recommendation 2.3.3. We suggest that patients who remain at high risk of progressive CKD despite maximal supportive care are considered for a six-month course of corticosteroid therapy. The important risk of treatment-emergent toxicity must be discussed with patients, particularly those who have an eGFR below 50 ml/min/1.73 m² (2B).

Practice Point 2.3.5. Use of corticosteroids in IgAN:

- **Clinical benefit of corticosteroids in IgAN is not established and should be given with extreme caution or avoided entirely in the following situations:**

eGFR <30 mL/min/1.73m^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

BMI, body mass index; eGFR, estimated glomerular filtration rate; TB, tuberculosis
*The TESTING study included patients with eGFR 20-30 ml/min/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/1.73m^2.
†High BMI in the TESTING study was not specifically considered an exclusion, but the mean BMI was <24 kg/m^2.

- **Corticosteroid therapy is also relatively contraindicated in patients with controlled psychiatric illness and severe osteoporosis.**
- **There is insufficient evidence to support the use of the Oxford MEST-C score in determining when corticosteroids should be commenced.**
- **There are no data to support efficacy or reduced toxicity of alternate-day corticosteroid regimens, or dose-reduced protocols.**
- **Where appropriate, high-dose treatment with corticosteroid should incorporate prophylaxis against *Pneumocystis* pneumonia along with gastroprotection and bone protection according to national guidelines.**

Practice Point 2.3.6. Management of the patients with IgAN who remain at high risk for progression after maximal supportive care (Figure IgAN2).

Figure IgAN2. Management of the patient with IgAN who remains at high risk for progression after maximal supportive care[*]*

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure, eGFR, estimated glomerular filtration rate; GN, glomerulonephritis; HIV, human immunodeficiency virus; IgAN, immunoglobulin A nephropathy; TB, tuberculosis
*IgAN with rapidly progressive glomerulonephritis is covered in Practice Point 2.4.3.

Practice Point 2.3.7. Other pharmacologic therapies evaluated in IgAN (Table IgAN3)

Table IgAN3. Other pharmacological therapies in IgAN

Agent	Suggested usage	Remarks
Anti-platelet 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 corticosteroids
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 corticosteroids are being considered MMF may be used as a steroid-sparing agent	In a single RCT conducted in China, MMF with low dose corticosteroids was non-inferior to standard dose corticosteroids 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/day. There were significantly fewer corticosteroid related side effects in the combination therapy arm. (PICO 18.16)[1,6]
	Non-Chinese patients There is insufficient evidence to support the use of mycophenolate mofetil	In the RCTs of MMF in non-Chinese patients there was no evidence for efficacy of MMF monotherapy. (PICO 18.15)[2,3,4,5,6]

[1]Hou JH, Le WB, Chen N, *et al*. Mycophenolate Mofetil Combined With Prednisone Versus Full-Dose Prednisone in IgA Nephropathy With Active Proliferative Lesions: A Randomized Controlled Trial. American Journal of Kidney Disease. 2017;(6):788-795

[2]Hogg RJ, Bay RC, Jennette JC *et al*. Randomized controlled trial of mycophenolate mofetil in children, adolescents, and adults with IgA nephropathy. American Journal of Kidney Disease. 2015;66(5):783-791

[3]Frisch G, Lin J, Rosenstock J, *et al*. Mycophenolate mofetil (MMF) vs placebo in patients with moderately advanced IgA nephropathy: a double-blind randomized controlled trial. Nephrology Dialysis Transplantation. 2005;20(10):2139-2145

[4]Maes BD, Oyen R, Claes K, *et al*. Mycophenolate mofetil in IgA nephropathy: results of a 3-year prospective placebo-controlled randomized study. Kidney International. 2004;65(5):1842-1849

[5]Tang S, Leung JC, Chan LY *et al*. Mycophenolate mofetil alleviates persistent proteinuria in IgA nephropathy. Kidney International. 2005;68(2):802-812

[6]Vecchio M, Bonerba B, Palmer SC *et al*. Immunosuppressive agents for treating IgA nephropathy. The Cochrane database of systematic reviews 2015;(8):CD003965

IgAN, immunoglobulin A nephropathy; MMF, mycophenolate mofetil; RCT, randomized controlled trial

Practice Point 2.3.8. Tonsillectomy in IgAN:
- **Tonsillectomy should not be performed as a treatment for IgAN in Caucasian patients.**
- **Tonsillectomy may be indicated 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**

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or complete remission of hematuria and proteinuria following tonsillectomy alone or with pulsed corticosteroids (Table S6[4-8]).

2.4. Special situations

Practice Point 2.4.1. IgAN with the 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 EM features consistent otherwise 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 LM and EM features consistent otherwise with MCD should be treated in accordance with the guidelines for MCD (Chapter 5).**
- **Patients with the nephrotic syndrome whose kidney biopsy has coexistent features of a mesangioproliferative glomerulonephritis 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 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 two 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 a rapidly progressive glomerulonephritis (RPGN) with extensive crescent formation, commonly in the absence of visible hematuria. In the absence of visible hematuria and when reversible causes have been excluded (e.g., drug toxicity, common pre- and post-kidney causes), a kidney biopsy should be performed as soon as possible.**

Practice Point 2.4.3. IgAN with a rapidly progressive glomerulonephritis:

- **Rapidly progressive IgAN is defined as a ≥50% decline in eGFR over three months or less, where reversible causes have been excluded (e.g., drug toxicity, common pre- and post-kidney causes).**

- **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 SCr does not constitute rapidly progressive IgAN.**
- **We suggest patients with rapidly progressive IgAN are treated with cyclophosphamide and corticosteroids in accordance with the guidelines for ANCA-associated vasculitis (Chapter 9).**
- **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 child-bearing potential should be offered pre-conception counseling where appropriate.**
- **Pre-conception counseling should include a discussion on cessation of RAS blockade before conception. BP control should be optimized with alternative antihypertensive medications prior to conception.**
- **In those women at high risk of progressive CKD (see Recommendation 2.3.3.) 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
- **Visible hematuria is more frequent in children than in adults, and this may account for earlier diagnosis in children.[9]**
- **Children generally have higher eGFR, lower urine protein excretion, and more erythrocyturia than adults at diagnosis.[10]**
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 adults.[11-14]**
Treatment
- **There is strong evidence suggesting a benefit of RAS blockade in children.[15] All IgAN children with proteinuria >200 mg/d should receive ACEi or ARB blockade, advice on a low sodium diet, and optimal lifestyle and BP control (≤50th percentile for age and height).**

- **Evidence derived mostly from retrospective studies suggests that treatment with corticosteroids (+ second-line immunosuppression) leads to improved kidney survival.[9, 16]**
- **In children with proteinuria >1 g/d and mesangial hypercellularity (Oxford M1) most pediatric nephrologists will treat with corticosteroids in addition to RAS blockade from time of diagnosis.[10, 11, 13, 17]**
- **As in adults, children with rapidly progressive IgAN have a poor outcome and, despite limited evidence, this subgroup should be offered treatment with corticosteroids (usually as methylprednisolone pulses) and oral cyclophosphamide.[11, 13, 18]**

Follow-up
- **Aim for proteinuria <200 mg/24h.**
- **Aim for BP at ≤50th percentile for age and height.**
- **Continue to follow patients even after complete remission as they can relapse even after many years.[19]**

IMMUNOGLOBULIN A VASCULITIS

2.5. Diagnosis
Practice Point 2.5.1. Considerations for the diagnosis of IgAV:
- **In adults, unlike children, there are no internationally agreed-upon criteria for the diagnosis of IgAV, although a clinical diagnosis of IgAV is often made in adults based on the criteria described for children.[20, 21]**
- **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 patients with IgAV for secondary causes.**
- **Assess all 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.[22-24]**
- **The Oxford classification has not been validated for IgAV.**

- **The International IgAN Prediction Tool[25] is not derived for prognostication in IgAV.**

2.7. Treatment

2.7.1. Prevention of nephritis in IgAV

Recommendation 2.7.1.1. We recommend not using corticosteroids 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 a rapidly progressive glomerulonephritis:
- **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 KDIGO-agreed BP targets.**
- **Treat with maximally tolerated dose of RASi if proteinuria >0.5 g/24h.**
- **Offer participation in a clinical trial if one is available.**

2.7.2. Patients with IgAV with associated nephritis who are at high risk of progressive CKD

Practice Point 2.7.2.1. Considerations for the treatment of patients with IgAV with associated nephritis who are at high risk of progressive CKD despite maximal supportive care:
- **There is insufficient evidence to support the use of the Oxford 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 below 50 ml/min/1.73 m^2.**
- **In those patients who wish to try immunosuppressive therapy, treatment with corticosteroids is as described above for IgAN.**

2.8. Special situations

Practice Point 2.8.1. IgAVN 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 with cyclophosphamide and corticosteroids in accordance with the guidelines for ANCA-associated vasculitis (Chapter 9).**
- **IgAVN with RPGN may also 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 corticosteroid therapy to accelerate recovery in patients with life, or organ-threatening extrarenal complications of IgAV.[26] Clinicians are referred to the guidelines of the American Society for Apheresis regarding recommendations regarding plasma exchange for IgAV.[27]**

2.8.1. IgAV-associated nephritis in children

Practice Point 2.8.1.1. Indications for management of IgAVN in children have recently been published as the result of a European consortium initiative.[20] Briefly:
- **There are no data supporting the use of corticosteroids to prevent nephritis in children with IgAV but mild or absent evidence of kidney involvement.[28, 29]**
- **Children above 10 years of age more often present with non-nephrotic range proteinuria, impaired kidney function, and may suffer more chronic histological lesions with delay in biopsy and treatment longer than 30 days.[30]**
- **The majority of children who will develop nephritis will do so within three months of presentation. Urinary monitoring is necessary for at least six and optimally 12 months from initial presentation systemic disease.**
- **Children with IgAVN and persistent proteinuria for greater than three months, should be treated with ACEi or ARB blockade. 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 rapidly progressive IgAN.**

CHAPTER 3. MEMBRANOUS NEPHROPATHY

3.1. Diagnosis

Practice Point 3.1.1. A kidney biopsy may not be required to confirm the diagnosis of MN in patients with a compatible clinical and serological presentation.

Practice Point 3.1.2. Patients with MN should be evaluated for associated conditions, regardless of whether PLA2Rab and/or TSHD7Aab are present or absent (Figure MN3).

Figure MN3. Evaluation of patients with MN for associated conditions*

HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NSAIDs, nonsteroidal anti-inflammatory drugs

*Patient with MN should be evaluated for associated conditions, independent of the presence or absence of PLA2Rab or TSHD7Aab

†Varies per country; the yield of cancer screening is not very high especially in younger patients. Many centers will perform chest X-ray or CT scan, look for iron deficiency, and require the patients to have to participate in the national screening program for breast and colon cancer; a PSA test is done in adult males >50-60 years.

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 (Table MN1).

Table MN1. Clinical criteria for assessing risk of progressive loss of kidney function[‡]

Low risk	Moderate risk	High risk	Very high risk
• Normal eGFR, proteinuria <3.5 g/d and/or serum albumin >30 g/L	• Normal eGFR, proteinuria >4 g/d and no decrease >50% after 6 months of conservative therapy with ACEi/ARB • PLA2Rab <50 RU/ml† • Mild low molecular weight proteinuria • Selectivity index <0.15 • U IgG <250 mg/d	• eGFR <60 ml/min/1.73m^{2*} • Proteinuria >8 g/d for >6 months • PLA2Rab >150 RU/ml† • High low molecular weight proteinuria • U IgG >250 mg/d • Selectivity index >0.20	• Life-threatening nephrotic syndrome • Rapid deterioration of kidney function not otherwise explained • High low molecular weight proteinuria in two urine samples collected with interval of 6–12 months

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; IgG, immunoglobulin G; PLA2Rab, antibodies against the M-type phospholipase-A2-receptor

*Most studies have used SCr values to guide management, and SCr values >1.5 mg/dl are often used to define kidney insufficiency. An eGFR value of 60 ml/min/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 reflects an eGFR of 50 ml/min/1.73 m^2 in a 60-year-old male patient and 37 ml/min/1.73 m^2 in a 60-year-old female patient. Thus, when using eGFR in risk estimation, age should be taken into account.

†Cut-off values are not validated. PLA2Rab should be measured at 3- to 6-month intervals, the shorter interval being performed in patients with high PLA2Rab levels at baseline. Changes in PLA2Rab levels during follow-up likely add to risk estimation. Disappearance of PLA2Rab precedes clinical remission and should lead to refraining from additional therapy. Detailed data are lacking.

‡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.

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 MN4).**

Figure MN4. Risk-based treatment of MN
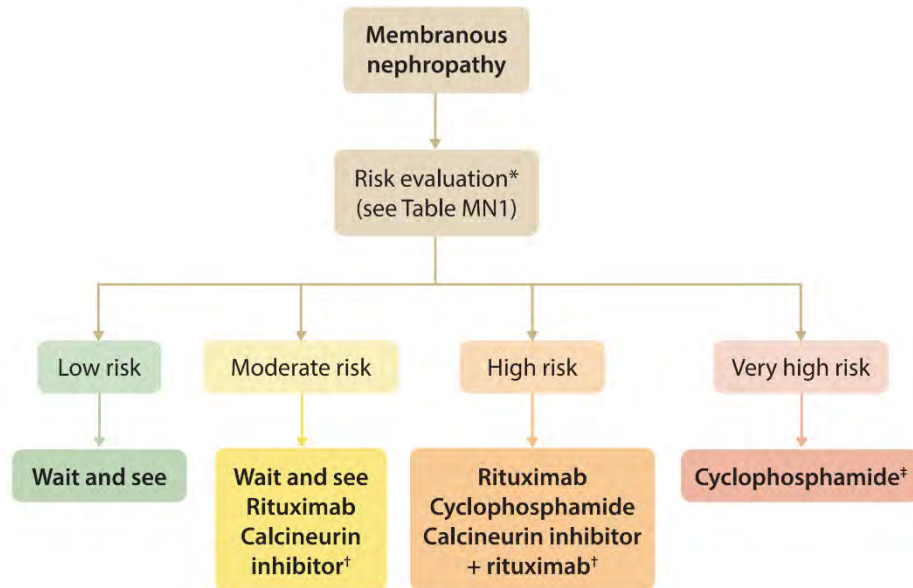
*See Practice Point 3.2.1 and Table MN1 for a detailed description of risk evaluation.

†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 estimated glomerular filtration rate (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 six months of treatment with CNI is advised, with the possible exception of patients with documented disappearance of PLA2Rab after CNI treatment.

‡There is insufficient evidence that rituximab used in standard doses prevents development of kidney failure. In patients who do not tolerate or can no longer use cyclophosphamide, consultation with an expert center is advised.

Practice Point 3.3.2. Immunosuppressive therapy is not required in patients with MN, proteinuria <3.5 g/d, and eGFR >60 ml/min/1.73 m².

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 unless 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 steroids for six months, or tacrolimus-based therapy for at least six months, with the choice of treatment depending on the risk estimate (Table MN1 and Figure MN4) *(1B)*.

Practice Point 3.3.4. Longitudinal monitoring of PLA2Rab levels at three and six 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 (Figure MN5).

Figure MN5. Immunological monitoring in MN after start of therapy

PLA2Rab, antibodies against the M-type phospholipase-A2-receptor

*A large decrease in PLA2Rab levels may indicate a good clinical response. Although there are no defined cut-off values, many experts consider reductions of 50-90% to represent a large decrease in PLA2Rab levels.

†This algorithm is simplified to allow easy decision-making. The course may be less well-defined or more difficult to interpret in many patients. However, if it is impossible to classify a patient as a good responder or resistant to disease, we suggest consulting an expert center.

‡See text for current treatment schedules. NB: the cumulative dose of cyclophosphamide should not exceed 25 g (approximately six months of therapy at a dose of 1.5 mg/kg/day). Lower doses (maximum 10g) must be used in patients who wish to conceive. CNI are unlikely to induce late immunological remission; in patients with persistent PLA2Rab, 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.

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3.4. Special situations

Practice Point 3.4.1. Algorithm for the treatment of patients with MN and initial relapse after therapy (Figure MN6).

Figure MN6. Management of initial relapse after therapy

*The definition of relapse is variable. Some authors define relapse after remission as an increase in proteinuria >3.5 g/day 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 and 3.5 g/day without an increase of serum albumin to normal, the subsequent rise in PCR should be considered a 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.

†Immunological monitoring is of particularly great value in these situations. If, in the period of "clinical remission," PLA2Rab were still positive, this would be evidence for resistant disease. Therefore, in patients with positive PLA2Rab, it is advised to evaluate PLA2Rab at the time of remission and relapse. The course of PLA2Rab 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 25 g to limit risk of malignancies.

Details of commonly used treatment regimens are shown in Table MN2.

Practice Point 3.4.2. Algorithm for management of patients with treatment-resistant membranous nephropathy (Figure MN7).

Figure MN7. Management of resistant disease[§]

CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate

*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 FSGS. This would be further supported by the disappearance of PLA2Rab. In patients with persistent proteinuria with normal or near normal serum albumin levels or patients with persistent proteinuria despite loss of PLA2Rab, a kidney biopsy should be considered to document active membranous nephropathy.

†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 PLA2Rab should be evaluated after three months. Cyclophosphamide treatment should take into account the maximal tolerable dose: the cumulative dose should not exceed 10 g if preservation if fertility is required. The cumulative dose should not exceed 25 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 be consulted with an expert center. These centers may choose experimental therapies (bortezomib, daratumumab, antibody to CD38 antibody, and belimumab) or a higher dose of conventional immunosuppressive therapy.

§Details of commonly used treatment regimens are shown in Table MN2.

Practice Point 3.4.3. Evaluation of a kidney transplant recipient with MN (Figure MN8).

Figure MN8. Evaluation of a kidney transplant recipient with MN

Discuss recurrence rate:

- Recurrence risk depends on the evaluation of the causative antibodies

- Recurrence risk may be higher after living related donor transplantation, but the benefits of living donor donation outweigh the possible harm of disease recurrence

Peri- and post-transplant monitoring:

- Measure proteinuria every month → if proteinuria 1 g/d→ biopsy of kidney

- In patients with known PLA2Rab-associated MN: measure PLA2Rab every 1–3 months depending on pretransplant antibody status
→ PLA2Rab increasing → increased likelihood of recurrence, consider early kidney biopsy
→ PLA2Rab decreasing → lower likelihood of recurrence, perform kidney biopsy only if clinically indicated

Treatment of recurrence:

- Treat with angiotensin-converting enzyme inhibitor/angiotensin II-receptor blocker

- Optimize immunosuppressive therapy, therapeutic drug monitoring of mycophenolate mofetil aiming at AUC > 50 mg*hr/L

- Proteinuria <1 g/d → evaluate/monitor at 1–3 month intervals

- Proteinuria >1 g/d → rituximab 1 g at day 1 and day 15

MN, membranous nephropathy; PLA2Rab, antibodies against the M-type phospholipase-A2-receptor
*Limited data available, but the same algorithm likely applies to THSD7A-associated MN.

Practice Point 3.4.4. Algorithm for management of children with MN (Figure MN9)

Figure MN9. Management of children with MN
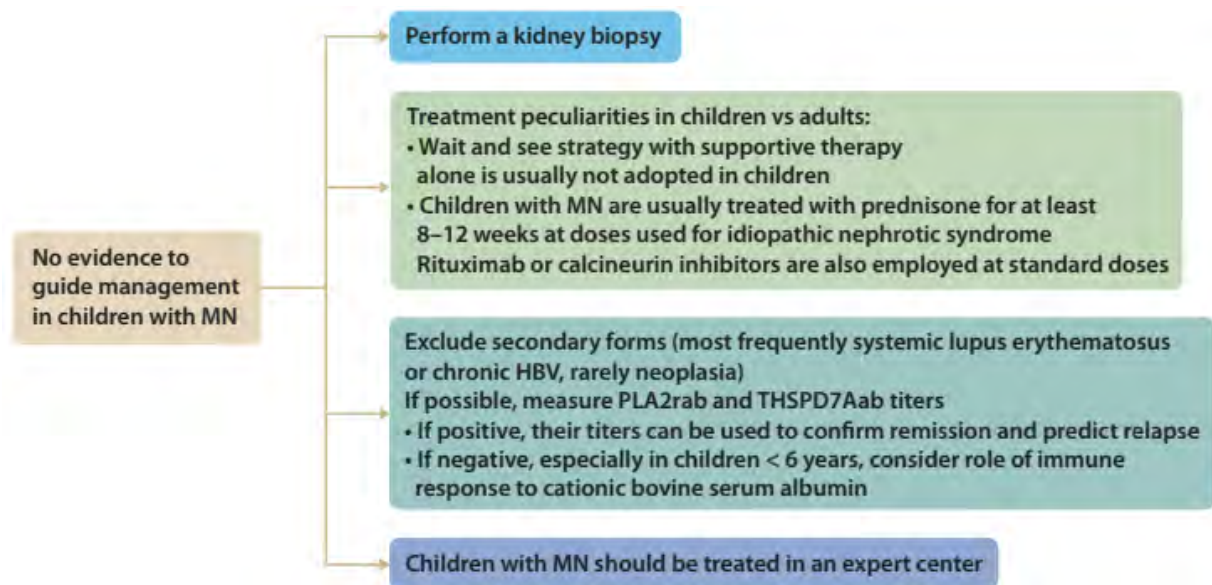
HBV, hepatitis B virus; MN, membranous nephropathy; THSPD7Aab, antibodies against thrombospondin type-1 domain-containing 7A

Practice Point 3.4.5. Prophylactic anticoagulant therapy in patients with membranous nephropathy and nephrotic syndrome should be based on an estimate of the risk of thrombotic events and the risk of bleeding complications (Figure MN10).

Figure MN10. Anticoagulant therapy in patients with MN
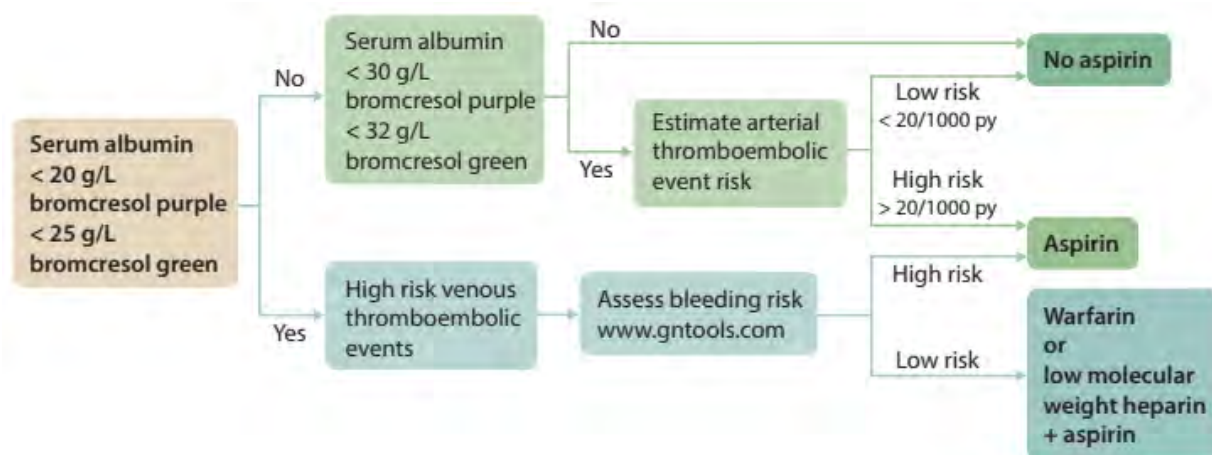
Adapted from Hofstra, JM. *et al*. Kidney International. 2016; 89 (5): 981 - 983
Proposed algorithm for anticoagulant therapy in patients with membranous nephropathy
This algorithm provides guidance for clinicians. The proposed cut-off values are based on expert opinion. When considering anticoagulant 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 realize that there is a large bias between the serum albumin assays (van de Logt KI 2019). Serum albumin of 25 g/l with bromocresol green (BCG), ~20

g/l with bromocresol purple (BCP), or immunonephelometry. It is likely that most studies have used BCG assay. Consider using 25 g/l as threshold when using BCG and 20 g/l when using BCP or immunonephelometry.

2. Assess risk of venous thrombosis and risk of bleeding (www.gntools.com).
3. Patients with membranous nephropathy and nephrotic syndrome are also at risk of developing arterial thrombotic events. The risk of an arterial thrombotic event is dependent on age, history of previous events, diabetes, eGFR, smoking, and severity of nephrotic syndrome. Risk assessment can be done using the Framingham risk score, and including previous events and proteinuria. (Hofstra KI 2016).
4. Use of aspirin is insufficient to prevent VTE; use of warfarin is sufficient to prevent ATE.
5. Treatment with warfarin: There is more INR variability in nephrotic syndrome and low eGFR; increased risk of thrombosis immediately after starting high-dose warfarin. Consider starting anticoagulation therapy with low-dose molecular weight heparin and then folding-in warfarin, and when therapeutic, stop the heparin. A good alternative is to use low-dose LMW heparin + aspirin for a period of three months before switching to warfarin, allowing to judge the course of proteinuria (Medjeral-Thomas CJASN 2014).
6. Steroids increase the risk of thrombosis; thus, anticoagulant therapy should not be omitted in patients who start prednisone therapy.

CHAPTER 4. NEPHROTIC SYNDROME IN CHILDREN

4.1. Diagnosis

Practice Point 4.1.1. The definitions relating to the nephrotic syndrome in children are based on the clinical characteristics outlined in Table NS1.

Table NS1. Definitions relating to NS in children aged 1 to 18 years

- **Nephrotic-range proteinuria:** first morning or *24 hr urine PCR ≥2 mg/mg (or 200 mg/mmol or 3+ dipstick)

- **NS:** nephrotic-range proteinuria and either hypoalbuminemia (serum albumin <3 g/dL) or edema when albumin level is not available

- **Complete remission:** first morning or *24 hr urine PCR ≤0.2 mg/mg (or 20 mg/mmol or negative or trace dipstick) on three or more consecutive occasions

- **Partial remission:** first morning or *24 hr urine PCR >0.2 but <2 mg/mg (or >20 and <200 mg/mmol) and, if available, serum albumin ≥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 or ≥1+ for 7 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 or <4 relapses per 12 months

- **Frequent relapsing NS:** ≥2 relapses per 6 months or ≥4 relapses per 12 months

- **Steroid-dependent NS:** 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 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 steroid-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

NS, nephrotic syndrome; PCR, protein-creatinine ratio; SRNS, steroid resistant nephrotic syndrome; SSNS, steroid sensitive nephrotic syndrome
*To rule out orthostatic proteinuria, the first-morning urine should be collected separately for assessment
†van der Watt, Ped Nephrol 7th ed. 2016)

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, but 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 corticosteroids be given for eight weeks (four weeks of daily corticosteroids followed by four weeks of alternate-day corticosteroids) or 12 weeks (six weeks of daily corticosteroids followed by six weeks of alternate-day corticosteroids) *(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 four or six weeks. After four to six weeks, give alternate-day prednisone/prednisolone, 40 mg/m^2 or 1.5 mg/kg/d, for another four to six weeks.

Practice Point 4.3.1.2. In children who may be at higher risk of progressing to a frequently-relapsing or steroid-dependent form of nephrotic syndrome due to their young age at onset (1 to 4-6 years), prolonging treatment of the initial episode to 16 to 24 weeks may be beneficial in terms of preventing subsequent relapses with similar side effects.

Practice Point 4.3.1.3. Prolonging treatment of the initial episode to 16 to 24 weeks may be particularly helpful in younger children with a delayed response to prednisolone (i.e., remission in 10-15 days from treatment initiation), while even in younger patients (1-4 years old), a standard eight to 12-week prednisolone course may be preferable for patients who respond rapidly to prednisolone (i.e., in <7 days).

4.3.2. Treatment of relapses of NS in children

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

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

Practice Point 4.3.2.2. After achieving complete remission, reduce prednisone to 40 mg/m^2, or 1.5 mg/kg on alternate days for at least four weeks.

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

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

Practice Point 4.3.2.4. Patients should ideally be in remission with corticosteroids prior to the initiation of steroid-sparing agents such as cyclophosphamide, levamisole, MMF, rituximab, or CNIs. Coadministration of steroids is recommended for at least two weeks following initiation of steroid-sparing treatment.

Practice Point 4.3.2.5. Cyclophosphamide and levamisole may be preferable steroid-sparing therapies in frequently-relapsing nephrotic syndrome.

Practice Point 4.3.2.6. MMF, rituximab, cyclophosphamide, and CNIs may be preferable steroid-sparing therapies in children with steroid-dependent nephrotic syndrome.

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. Table NS4 outlines the general principles in children with nephrotic syndrome.

Table NS4. General principles in children with NS

Indication for kidney biopsy	• Children presenting with nephrotic syndrome ≥ 12 years of age • Steroid-resistant nephrotic syndrome or subsequent failure to respond to corticosteroids in steroid-sensitive nephrotic syndrome (secondary steroid-resistant nephrotic syndrome) • A high index of suspicion for a different underlying pathology (macroscopic hematuria, extra-kidney symptoms, 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 frequent relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome 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
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

[1] Gulati S. Nephrol Dial Transplant. 2005; 20(8): 1598-603
[2] Gruppen MP. Nephrol Dial Transplant. 2013; 28(8):2099-106

CHAPTER 5. MINIMAL CHANGE DISEASE IN ADULTS

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

5.2. Prognosis
Practice Point 5.2.1. Long-term kidney survival is excellent in MCD patients who respond to corticosteroids but less certain for patients who do not respond.

5.3. Treatment
Recommendation 5.3.1. We recommend high-dose oral corticosteroids for initial treatment of MCD *(1C)*.

Practice Point 5.3.1. Algorithm for the initial treatment of MCD in adults (Figure MCD1)

Figure MCD1. Initial treatment of MCD in adults[*]
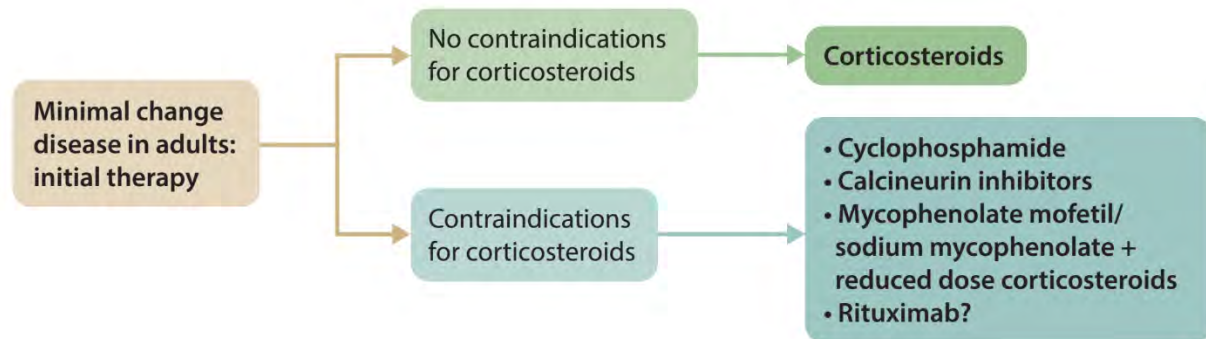
*The optimal corticosteroid regimen is not well-defined; however, suggested doses are outlined in Table MCD1

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

Practice Point 5.3.3. Begin tapering of corticosteroids two weeks after remission.

Practice Point 5.3.4. Although daily oral corticosteroids 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 corticosteroids may be relatively contraindicated, consider initial therapy with cyclophosphamide, a CNI, or MMF.

5.3.1. Treatment of relapses

Table MCD2. Definition of remission, relapse, resistance and dependence for MCD

Complete remission
Reduction of proteinuria to <0.3 g/day or urine protein:creatinine ratio <300 mg/g (or <30 mg/mmol), stable serum creatinine and serum albumin >3.5 g/dl (or 35 g/L)
Partial remissions
Reduction of proteinuria to 0.3–<3.5 g/day or urine PCR 300–<3500 mg/g (or 30–<350 mg/mmol) and a decrease >50% from baseline
Relapse
Proteinuria >3.5 g/day or urine PCR >3500 mg/g (or 350 mg/mmol) after complete remission has been achieved
Corticosteroid-resistant MCD
Persistence of proteinuria >3.5 g/day or urine PCR >3500 mg/g (or 350 mg/mmol) with <50% reduction from baseline despite prednisone 1 mg/kg/day 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)
Corticosteroid-dependent MCD
Relapse occurring during, or within 2 weeks of completing corticosteroid therapy

MCD, minimal change disease

Practice Point 5.3.1.1. Algorithm for treatment of frequently-relapsing/steroid-dependent MCD in adults (Figure MCD2)

Figure MCD2. Treatment of FR/SD MCD in adults
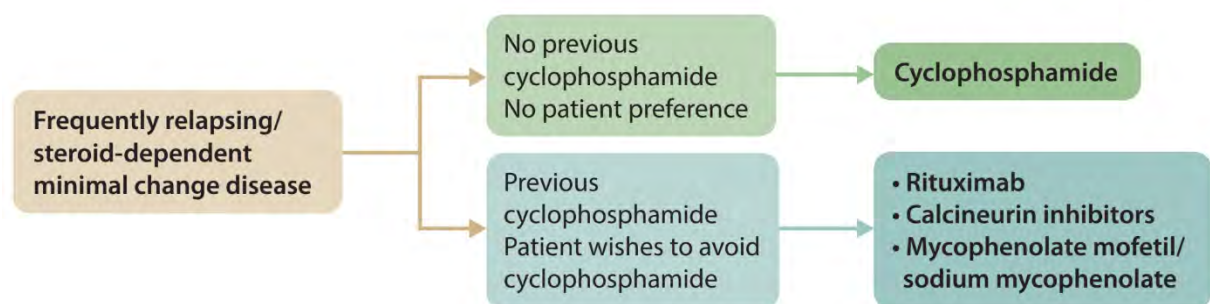
Practice Point 5.3.1.2. Treat infrequent relapses with corticosteroids (Table MCD2).

Recommendation 5.3.1.1. We recommend cyclophosphamide, rituximab, calcineurin inhibitors, or mycophenolic acid analogs (MPAA) for the treatment of frequently-relapsing/corticosteroid-dependent MCD as compared to prednisone alone or no treatment *(1C)*.

CHAPTER 6. FOCAL SEGMENTAL GLOMERULOSCLEROSIS 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 FSGS2, Table FSGS2).

Figure FSGS2. Evaluation of a patient with FSGS lesion on the kidney biopsy and no evidence of other glomerular pathology

FSGS, focal segmental glomerulosclerosis

Table FSGS2. Causes of secondary FSGS

Secondary to alterations of glomerular epithelial cells	
Viral infections	HIV (established) CMV (probably) Parvovirus B19, EBV, HCV (possibly) Hemophagocytic syndrome (possibly)
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

CMV, cytomegalovirus; EBV, Epstein-Barr virus; FSGS, focal segmental glomerulosclerosis; HCV, hepatitis C virus; HIV, human immunodeficiency virus; mTOR, mammalian target of the rapamycin; NSAID, nonsteroidal anti-inflammatory drugs

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 (Table FSGS3).

Table FSGS3. Utility of genetic testing in patients with FSGS

Genetic forms of focal segmental glomerulosclerosis	
Genetic mutations of podocyte and glomerular basement membrane proteins	Familial Sporadic Syndromic Hereditary nephropathies (e.g. Alport's syndrome, other collagenopathies)

Potential benefits of genetic testing in patients with FSGS
• Aiding in diagnosis, especially if the clinical features are not compelling of a particular disease phenotype • Limiting immunosuppression exposure, especially in situations where patients appear to be resistant to treatment • Determining risk of recurrent disease in kidney transplantation • Allowing for risk assessment in candidate living-related kidney donors • Aiding in pre-natal diagnosis • Screening in other members of a family when there is a strong family history and/or clinical features suggestive of a syndromal disease

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 corticosteroids be used as the first-line immunosuppressive treatment for primary FSGS *(1D)*.

Practice Point 6.2.2.1. Suggested dosing schedule for corticosteroids in the initial treatment of primary FSGS (Table FSGS4 – see below)

Practice Point 6.2.2.2. Initial high-dose corticosteroids 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 corticosteroid treatment should receive corticosteroids for at least six months.

Practice Point 6.2.2.4. In adults with relative contraindications or intolerance to corticosteroids, alternative immunosuppression with calcineurin-inhibitors should be considered as the initial therapy in patients with primary FSGS (Table FSGS4).

Table FSGS4. Initial treatment of primary FSGS

Treatment	Dose and duration
Corticosteroids	**Starting dose:** • High dose corticosteroid 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 corticosteroid treatment duration:** • Continue high dose corticosteroid 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 corticosteroid therapy until 16 weeks if the proteinuria is persistent and unremitting, especially in patients who are experiencing side-effects **Corticosteroid tapering:** • If complete remission is achieved rapidly, continue high dose corticosteroid treatment for at least 4 weeks or for 2 weeks 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 corticosteroid 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 corticosteroid-resistant or develops significant toxicities, corticosteroids 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/day in 2 divided doses OR tacrolimus 0.05–0.1 mg/kg/day in 2 divided doses • Target trough levels could be measured to minimize nephrotoxicity • Cyclosporine target trough level: 100–175 ng/ml • Tacrolimus target trough level: 5–10 ng/ml **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

CNI, calcineurin inhibitors

6.3. Special situations

6.3.1. Corticosteroid-resistant primary FSGS

> **Recommendation 6.3.1.1. For adults with corticosteroid-resistant primary FSGS, we recommend that cyclosporine or tacrolimus be given for at least six months rather than continuing with corticosteroid monotherapy or not treating *(1C)*.**

6.3.2. Dosing schedule for cyclosporine and tacrolimus

Practice Point 6.3.2.1. Treatment of corticosteroid-resistant primary FSGS: suggested dosing schedule for cyclosporine and tacrolimus (Table FSGS5)

Table FSGS5. Treatment of corticosteroid-resistant primary FSGS

Treatment	Dose and duration
Calcineurin inhibitors	**Starting dose:** • Cyclosporine 3–5 mg/kg/day in 2 divided doses OR tacrolimus 0.05–0.1 mg/kg/day in 2 divided doses • Target trough levels could be measured to minimize nephrotoxicity • Cyclosporine target trough level: 100–175 ng/ml • Tacrolimus target trough level: 5–10 ng/ml **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
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

ACTH, adrenocorticotropic hormone; CNI, calcineurin inhibitors

6.3.3. Duration of CNI treatment

Practice Point 6.3.3.1. Adults with corticosteroid-resistant primary FSGS who respond to CNI treatment should receive CNIs for a minimum of 12 months to minimize the risk of relapses (Table FSGS5).

6.3.4. Patients resistant or intolerant to CNIs

Practice Point 6.3.4.1. Adults who have corticosteroid-resistant primary FSGS with resistance to or intolerance of CNIs should be referred to specialized centers for consideration of re-biopsy, alternative treatment, or the subsequent need for further immunosuppression (Table FSGS5).

6.3.5. Management of relapse

Practice Point 6.3.5.1. Adults with previous corticosteroid-sensitive primary FSGS who experience a relapse should be treated by the same approach as adults with relapsing minimal change disease (Figure MCD2).

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 GN, particularly when culture evidence of infection is elusive, the diagnosis is in doubt, to assess prognosis, and/or for potential therapeutic reasons. In some cases, biopsy may be critical at arriving at the correct diagnosis, as comorbidities may contribute to confounding effects.

7.1.2. Prognosis and treatment
Practice Points 7.1.2.1. Suggested evaluation, prognosis, and therapy of bacterial infection-related GN (Table IGN1)

Table IGN1. Evaluation, prognosis and therapy of classic bacterial infection-related GN syndromes

	Post-infectious 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
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

	Post-infectious GN	Shunt nephritis	Endocarditis-related GN	IgA-dominant infection-related GN
Prognosis	Short-term prognosis in children 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 post-infectious GN) per local guidelines. Antibiotics can be given in post-streptococcal GN if streptococci are cultures from any site. This is primarily done to prevent the spread of infection within communal sites • Treat edema, hypertension, etc. as well as persistent proteinuria and/or progressive GFR decline as per Chapter 2			
	Value of high-dose steroids remains unproven [11]	Most shunts have been replaced with a shunt with a lesser likelihood of infection. Rarely ventriculocisternostomy has been performed after shunt removal	Utility of steroids and immunosuppression unproven and carries serious potential risks, even in cases with crescentic GN [12]	For severe kidney functional impairment, weigh risks and benefits of immunosuppression. The risk of infection and steroid-induced complications in this often elderly population with substantial 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 [13]. Prevention of epidemic post-streptococcal GN may include socioeconomic interventions and mass antimicrobial use to improve living conditions and 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

ACR, albumin-creatinine ratio; ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibodies; C3GN, complement glomerulonephritis; CKD, chronic kidney disease; CSF, cerebrospinal fluid; eGFR, estimated glomerular filtration rate; GBM, glomerular basement membrane; GN, glomerulonephritis; HIV, human immunodeficiency virus; PCR, protein-creatinine ratio; PR3, proteinase 3; RCT, randomized controlled trial; UA, urine analysis

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 through 5.2.3 of the *KDIGO 2018 Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease*.[357] Please refer to this publication for specific recommendations, selection and dosing of specific therapeutic agents, and research recommendations. (https://kdigo.org/wp-content/uploads/2017/02/KDIGO-2018-Hep-C-GL.pdf).

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 antiPLA2R 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 Pont 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 anti-viral treatment, and genetic predisposition to glomerular injury (e.g., *APOL1* risk alleles), coinfection with other viruses, 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 should be initiated in all patients with HIV and CKD, especially biopsy-proven HIV-associated nephropathy (HIVAN), regardless of CD4 count, adjusted to the degree of kidney function (*1C*).

Practice Point 7.2.3.3.1. A decision for the use of steroids 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.

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 serum creatinine 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.

CHAPTER 8. IMMUNOGLOBULIN AND COMPLEMENT-MEDIATED GLOMERULAR DISEASES WITH AN MPGN PATTERN OF INJURY

8.1. Diagnosis

Practice Point 8.1.1. Evaluate patients with ICGN for underlying disease (Table ICGM1).

Table ICMG1. Causes of a membranoproliferative pattern of injury

Immunoglobulin/ immune-complex-mediated	• Deposition of antigen–antibody immune complexes as a result of an infection • Deposition of immune-complexes as a result of an autoimmune disease • Deposition of monoclonal Ig as a result of a monoclonal gammopathy due to a plasma cell or B cell disorder • Fibrillary glomerulonephritis
Complement-mediated	• C3 glomerulonephritis and C3 DDD • C4 glomerulonephritis and C4 DDD
MPGN without immune complexes or complement	• Occurs due to various diseases (see text for detail)
"Idiopathic" forms of MPGN	• None of the conditions above are present

DDD, dense deposit disease; MPGN, membranoproliferative glomerulonephritis

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

Practice Point 8.1.3. If no underlying etiology is found for immunoglobulin/ICGN after extensive workup, evaluate for complement dysregulation (Table ICMG2).

Table ICMG2. Evaluation of abnormalities of the alternative pathway of complement[*]

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, CFHR-5
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)

AP50, complement alternate pathway; Bb, activated factor B; C3d, complement component 3d; C4d, complement component 4d; CFB, complement factor B; CFH, complement factor H; CFHRI-5, complement factor H-related protein-5; CFI, complement factor I; CH50, total hemolytic complement; FB, factor B; FH, factor H; FI, factor I; Ig, immunoglobulin; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; sMAC, soluble membrane attack complex
*Modified from Angioi *et al.*[31]
[†]Some complement assays may require referral to specialist/research laboratories and interpretation of complement assays may require expert consultation
[‡]The presence of a circulating monoclonal gammopathy is less common below the age of 50. Ability to detect a monoclonal protein will depend on the sensitivity of the assay used.

Practice Point 8.1.4. Rule out infection-related GN or post-infectious GN prior to assigning the diagnosis of 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 ICMD1).

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 only carefully considered use of immunosuppression.

Practice Point 8.2.1.3. For patients with idiopathic ICGN and proteinuria <3.5 g/day, 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 nephrotic syndrome and normal or near-normal serum creatinine, try a limited treatment course of corticosteroids.

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 corticosteroids 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 corticosteroids and cyclophosphamide.

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

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, and if this fails, eculizumab.

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. ANTI-NEUTROPHIL CYTOPLASMIC ANTIBODIES (ANCA)-ASSOCIATED VASCULITIS (AAV)

9.1. Diagnosis

Practice Point 9.1.1. In case of a clinical presentation compatible with small-vessel vasculitis in combination with positive MPO- or 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 ANCA1).

Figure ANCA1. Biopsy strategy in suspected kidney vasculitis
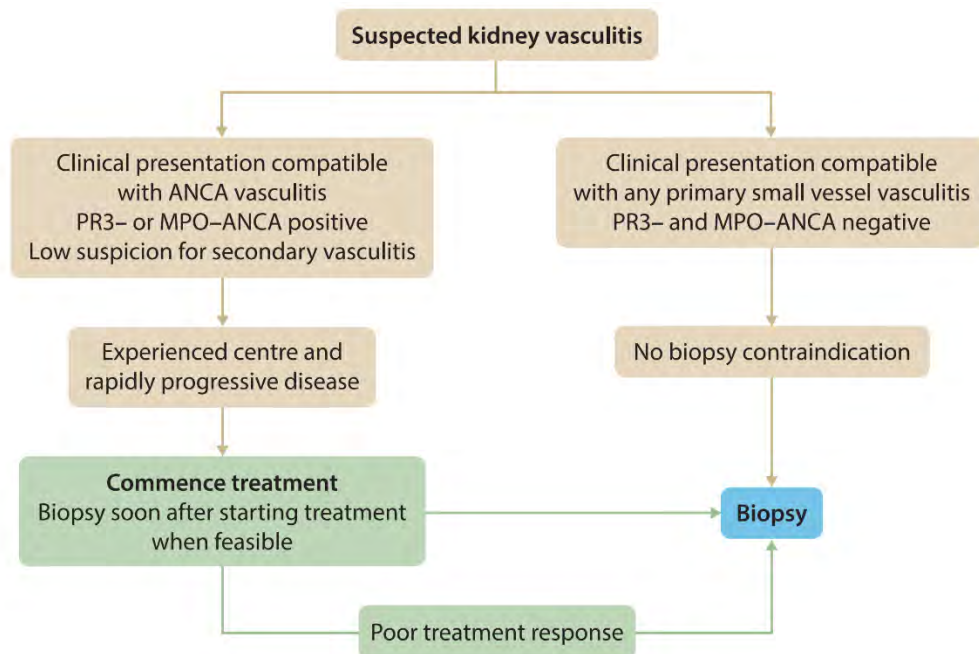
ANCA, anti-neutrophil cytoplasmic antibodies; MPO, myeloperoxidase; PR3, proteinase-3

Practice Point 9.1.2. Patients with AAV should be treated at centers with experience in AAV management.

9.2. Prognosis

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 corticosteroids 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 is given in Figure ANCA4.

Figure ANCA4. Recommended treatment regimen for AAV
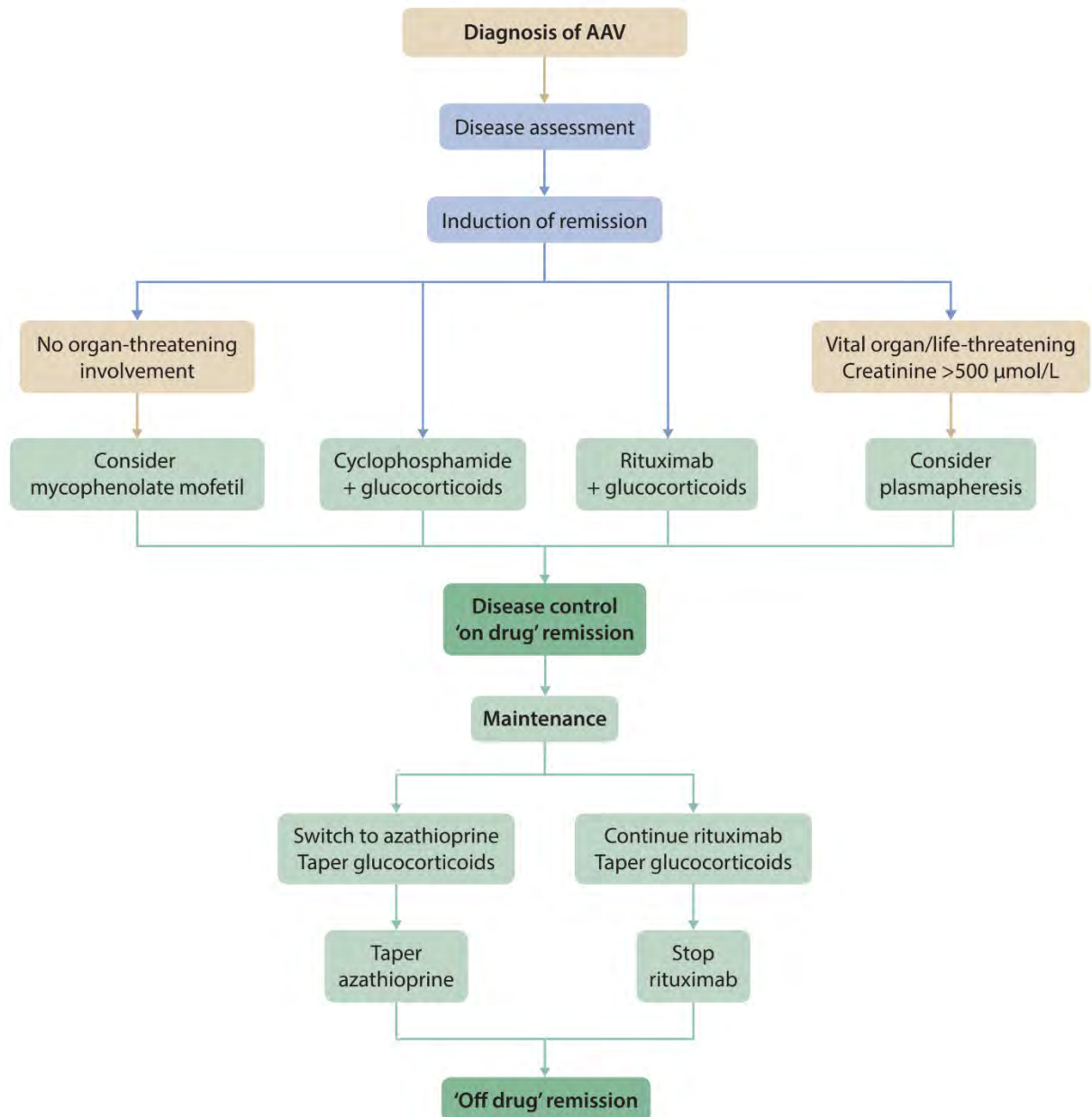
AAV, ANCA-associated vasculitis

Practice Point 9.3.1.2. In patients presenting with markedly reduced or rapidly declining GFR (SCr >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 Table ANCA3.

Table ANCA3. Factors for consideration when choosing between rituximab and cyclophosphamide for induction therapy of AAV

Rituximab preferred	Cyclophosphamide preferred
Children and adolescents	Rituximab difficult to access
Pre-menopausal women and men concerned about their fertility	Severe GN (SCr >350 µmol/l at diagnosis), combination of two intravenous pulses of cyclophosphamide with rituximab can be considered
Frail older adults	
Glucocorticoid-sparing especially important	
Relapsing disease	
PR3–ANCA disease	

ANCA, anti-neutrophil cytoplasmic antibodies; 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 Table ANCA4.

Table ANCA4. Considerations for the route of administration of cyclophosphamide for AAV

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

Practice Point 9.3.1.5. Discontinue immunosuppressive therapy after three months in patients who remain dialysis-dependent and who do not have any extrarenal manifestations of disease.

Practice Point 9.3.1.6. Recommendations for oral corticosteroid tapering are given in Table ANCA5.

Table ANCA5. Prednisolone tapering regimen for AAV

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		

Practice Point 9.3.1.7. Recommendations for immunosuppressive dosing are given in Table ANCA6.

Table ANCA6. Immunosuppressive drug dosing for AAV

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			

GFR, glomerular filtration rate; i.v., intravenous; MMF, mycophenolate mofetil

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Practice Point 9.3.1.8. Consider plasma exchange for patients requiring dialysis or with rapidly increasing serum creatinine, 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 four 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 corticosteroid 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 (Table ANCA8).

Table ANCA8. Factors that increase relapse risk for AAV

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

ANCA, anti-neutrophil cytoplasmic antibodies; PR3, proteinase-3

Practice Point 9.3.2.6. Consider methotrexate for maintenance therapy in patients induced with methotrexate or who are intolerant of azathioprine and MMF, but not if GFR is <60 ml/min/1.73 m².

Practice Point 9.3.2.7. Considerations for choosing rituximab or azathioprine for maintenance therapy are presented in Table ANCA9.

Table ANCA9. Considerations for using rituximab or azathioprine for AAV maintenance therapy

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

ANCA, anti-neutrophil cytoplasmic antibodies; 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 Table ANCA10.

Table ANCA10. Immunosuppressive dosing and duration of AAV maintenance therapy

Rituximab	Azathioprine	MMF
Scheduled dosing protocol: 1. 500 mg infusion at complete remission, and at months 6, 12, and 18 thereafter 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 year after diagnosis then decrease by 25 mg every 3 months	2000 mg/d (divided doses) at complete remission for 2 years
	Extended azathioprine at complete remission until four years after diagnosis; started at 1.5–2 mg/kg/d for 18–24 months, then decrease to a dose of 1 mg/kg/d until four years after diagnosis, then taper by 25 mg every 3 months. Corticosteroids should also be continued at 5–7.5 mg/d for two years and then slowly reduced by 1 mg every 2 months	

MMF, mycophenolate mofetil

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 at least six 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 SLE (Figure LN1)

Figure LN1. Diagnosis of kidney involvement in SLE
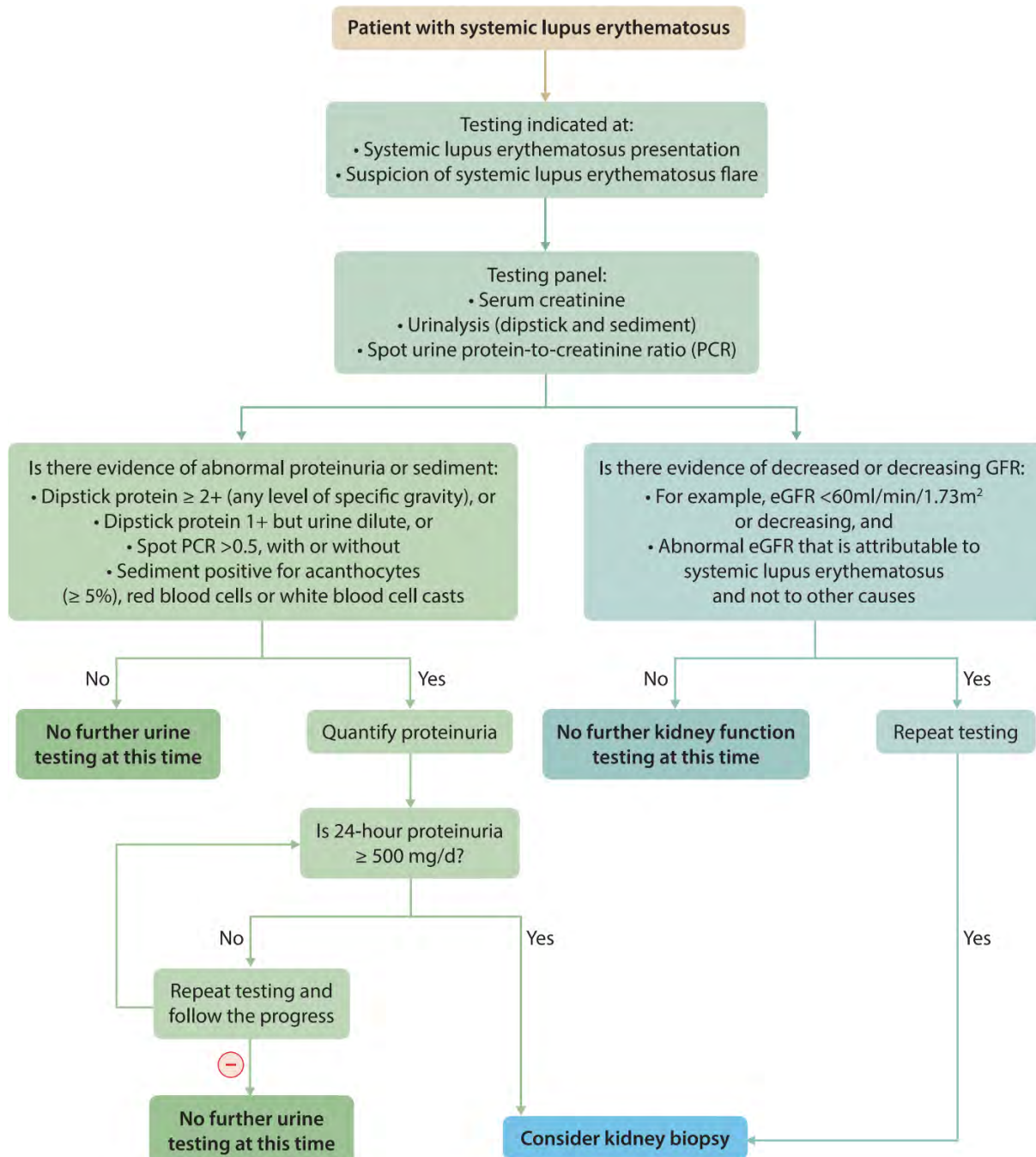
eGFR, estimated glomerular filtration rate

10.2. Treatment

10.2.1. General management of patients with lupus nephritis

> **Recommendation 10.2.1.1. We recommend that patients with LN be treated with hydroxychloroquine or an equivalent antimalarial unless contraindicated *(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 Table LN2.

Table LN2. Measures to minimize the risk of complications related to LN or its treatment

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 • RAAS 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
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

HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; RAAS, renin-angiotensin-aldosterone-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 LN2)

Figure LN2. Immunosuppressive treatment for patients with Class I or Class II LN
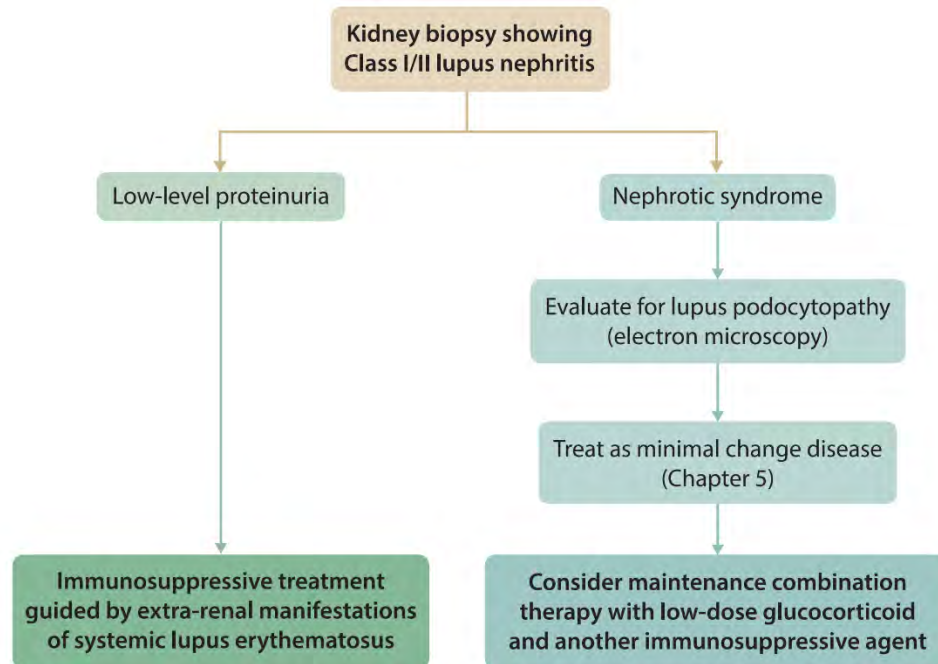
10.2.3. Class III or Class IV lupus nephritis
10.2.3.1. Initial therapy of active Class III/IV lupus nephritis

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 corticosteroids plus either low-dose intravenous cyclophosphamide or MPAA *(1B)*.

Practice Point 10.2.3.1.1. A regimen of reduced-dose corticosteroids may be considered during the initial treatment of active LN (Table LN3).

Table LN3. Example of corticosteroid regimens for LN

	Standard-dose scheme	Reduced-dose scheme
Methylprednisolone pulses	0.25–0.5 g/day × 3	0.25–0.5 g/day × 2–3
Oral prednisone equivalent		
Week 0–2	0.6–1.0 mg/kg (max 80 mg/day)	20–25 mg
Week 3–4	0.3–0.5 mg/kg	20 mg
Week 5–6	20 mg	15 mg
Week 7–8	15 mg	10 mg
Week 9–10	12.5 mg	7.5 mg
Week 11–12	10 mg	5 mg
Week > 12	5.0–7.5 mg	2.5 mg

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 should be used as 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 triple immunosuppressive regimen that includes a calcineurin inhibitor, reduced-dose MPAA, and corticosteroids should be reserved for patients who cannot tolerate standard-dose MPAA and are unfit for or will not use cyclophosphamide-based regimens.

Practice Point 10.2.3.1.5. Other therapies, such as azathioprine or leflunomide combined with corticosteroids, 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.

Practice Point 10.2.3.1.6. The place of biologics for the initial treatment of proliferative LN is evolving, and while not yet ready to be recommended as first-line, may be considered for individual patients.

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, who do not have access to MPAA, or who consider pregnancy.

Practice Point 10.2.3.2.2. Corticosteroids should be tapered to the lowest possible dose during maintenance, except when corticosteroids are required for extrarenal lupus manifestations, and discontinuation of corticosteroids should be considered after patients have maintained a complete clinical kidney response for approximately 12 months.

Practice Point 10.2.3.2.3. The dose of MMF in the early maintenance phase is approximately 750 to 1000 mg twice daily, and for MPA, approximately 540 to 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 less than 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 LN5.

Figure LN5. Management of patients with pure Class V LN

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 Table LN6.

Table LN6. Commonly used definitions of response to therapy in LN

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

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 LN6.

Figure LN6. Algorithm for the management of patients who show unsatisfactory response to initial therapy for active LN

1	Verify adherence to treatment
2	Ensure adequate dosing of immunosuppressive medications by measuring plasma drug levels if applicable or available (check mycophenolic acid level if on mycophenolic acid analogs/check infusion records if on cyclophosphamide)
3	Repeat biopsy if concern for chronicity or other diagnosis (e.g. thrombotic microangiopathy)
4	Consider switching to an alternative first-line regimen when there is persistent disease activity (mycophenolic acid analogs to cyclophosphamide-based regimen or vice versa)
5	Consider the following in patients refractory to first-line treatment regimens: • Combined mycophenolic acid analogs and calcineurin inhibitor therapy, or • Addition of rituximab, or • Extended course of i.v. pulse cyclophosphamide

i.v., intravenous

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 that was used to achieve the original response or an alternative recommended first-line therapy.

10.3. Special situations
10.3.1. LN and thrombotic microangiopathy (TMA)
Practice Point 10.3.1.1. Patients with LN and TMA should be managed according to the underlying etiology of TMA, as shown in Figure LN7.

Figure LN7. Management of patients with LN and TMA[*]
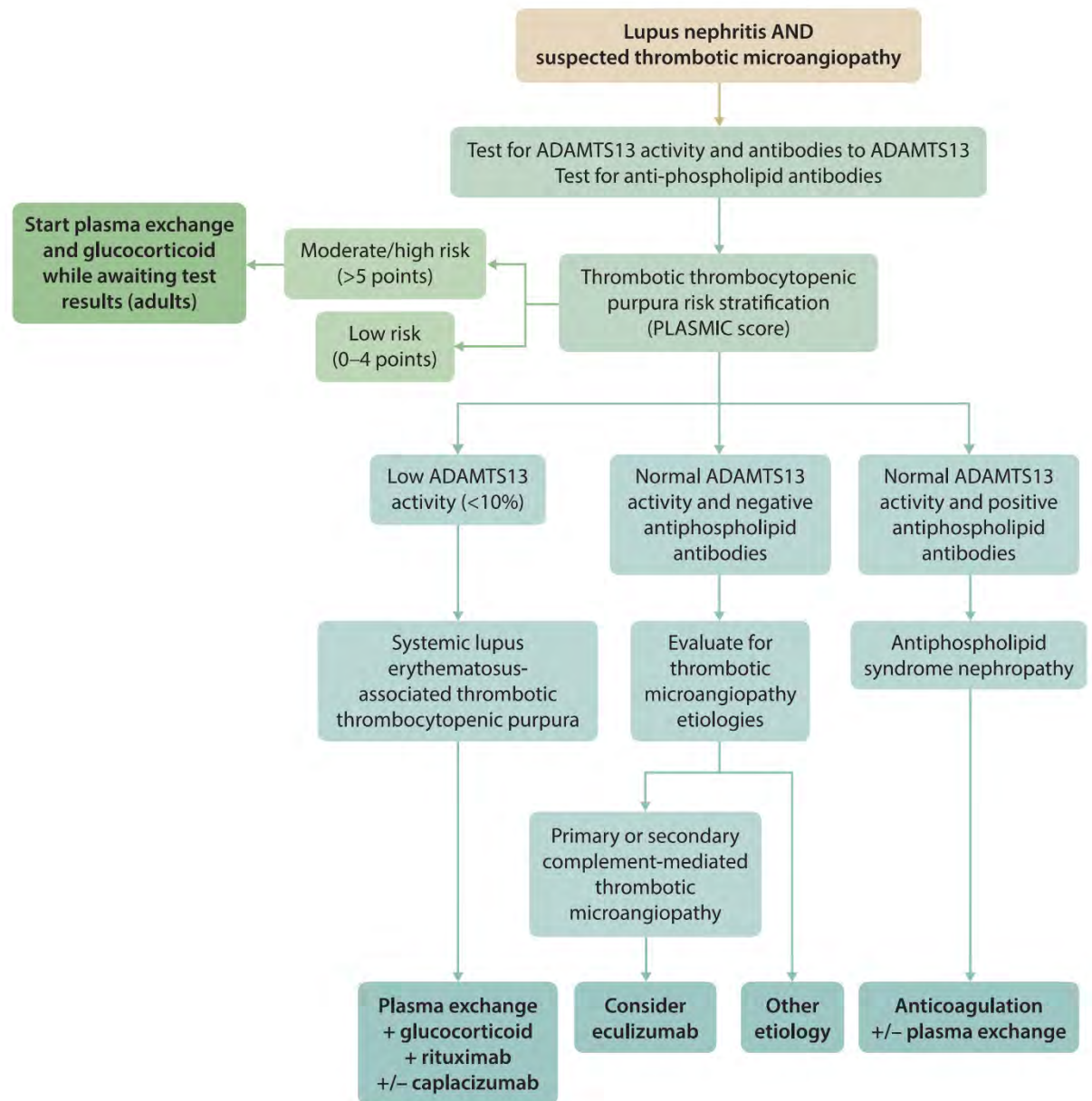
*Bendpudi PK. Lancet Haematol 2017; 4: e57

10.3.2. Pregnancy in patients with LN
Practice Point 10.3.2.1. Patients with active LN should be counseled to avoid pregnancy while the disease is active or when treatment with potentially teratogenic drugs is ongoing, and for at least six 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 corticosteroids, hydroxychloroquine, azathioprine, and CNIs are considered safe immunosuppressive treatments during pregnancy.

10.3.3. Treatment of LN in children

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

10.3.4. Management of lupus patients with kidney failure

Practice Point 10.3.4.1. LN patients 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 ANTIBODY GLOMERULONEPHRITIS

11.1. Diagnosis

Practice Point 11.1.1. Diagnosis of anti-GBM disease should be made urgently in all patients with suspected rapidly progressive glomerulonephritis.

11.2. Treatment

Recommendation 11.2.1. We recommend initiating immunosuppression with cyclophosphamide and corticosteroids plus plasmapheresis in all patients with anti-GBM GN except those who are dialysis-dependent at presentation, have 100% crescents 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 prolonged to two to three months and corticosteroids to about six months.

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

Practice Point 11.2.5. Patients with glomerulonephritis 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 at least six months.

CHAPTER 1. GENERAL PRINCIPLES FOR THE MANAGEMENT OF GLOMERULAR DISEASES

The general management principles covered in this chapter apply to most or all of the histologic forms of glomerulonephritis (GN). 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 made in each disease-specific chapter. The evidence underlying these general principles is varied and often of low or moderate quality since relevant randomized clinical trials (RCTs) are infrequent or have only been conducted 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 will not usually be 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) (see Chapter 4), and in post-streptococcal GN (see Chapter 7), clinical presentations are usually sufficiently characteristic to direct initial treatment without a biopsy. In adults, the wider spectrum of possible underlying glomerular diseases had often necessitated a kidney biopsy in most non-diabetic patients prior to treatment. In recent years, advances in serological 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 (see Chapter 3).[32] Although this approach has not been formally analyzed for all conditions, in the presence of a contraindication or a patient objection to biopsy, it may be reasonable to waive knowledge of a morphological diagnosis prior to treatment.

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 GP1. Considerations for a kidney biopsy in patients with proteinuria and/or glomerular hematuria
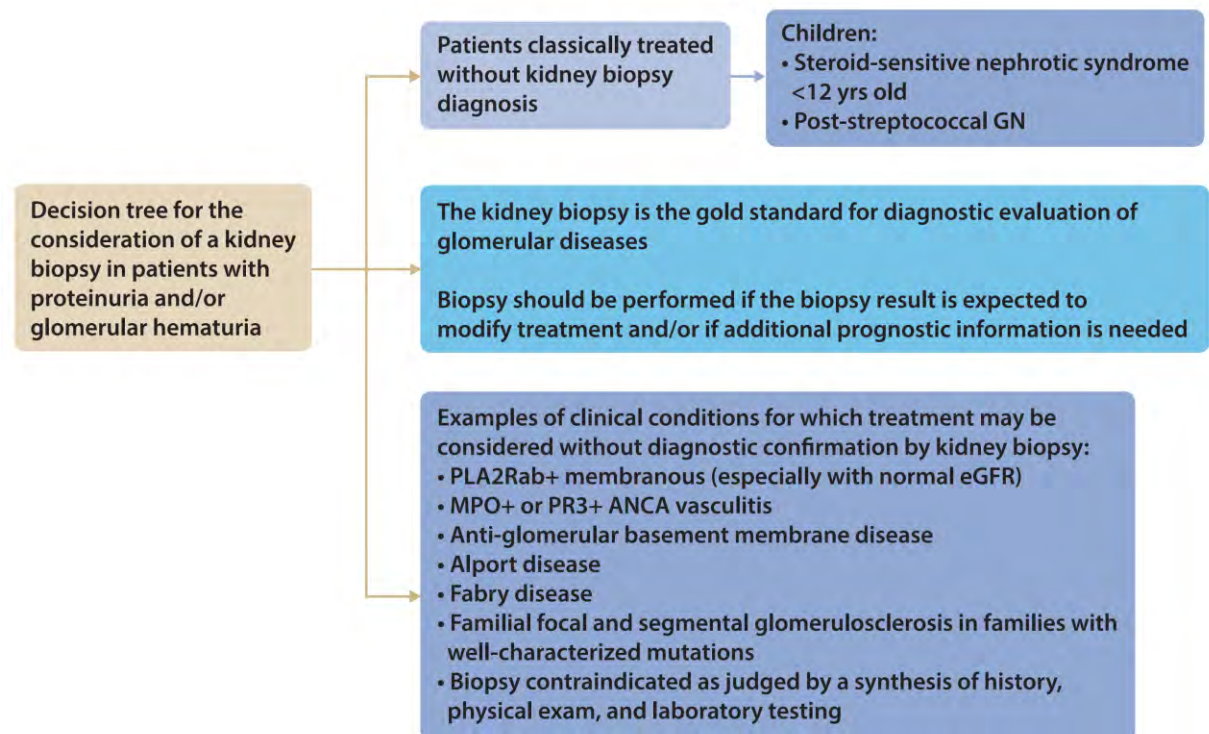
ANCA, anti-neutrophil cytoplasmic antibodies; eGFR, estimated glomerular filtration rate; GN, glomerulonephritis; MPO, myeloperoxidase; PLA2Rab+, phospholipase-A2-receptor antibody positive, PR3, proteinase 3

Treating without morphological analysis foregoes 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 GP2. Evaluation of kidney tissue
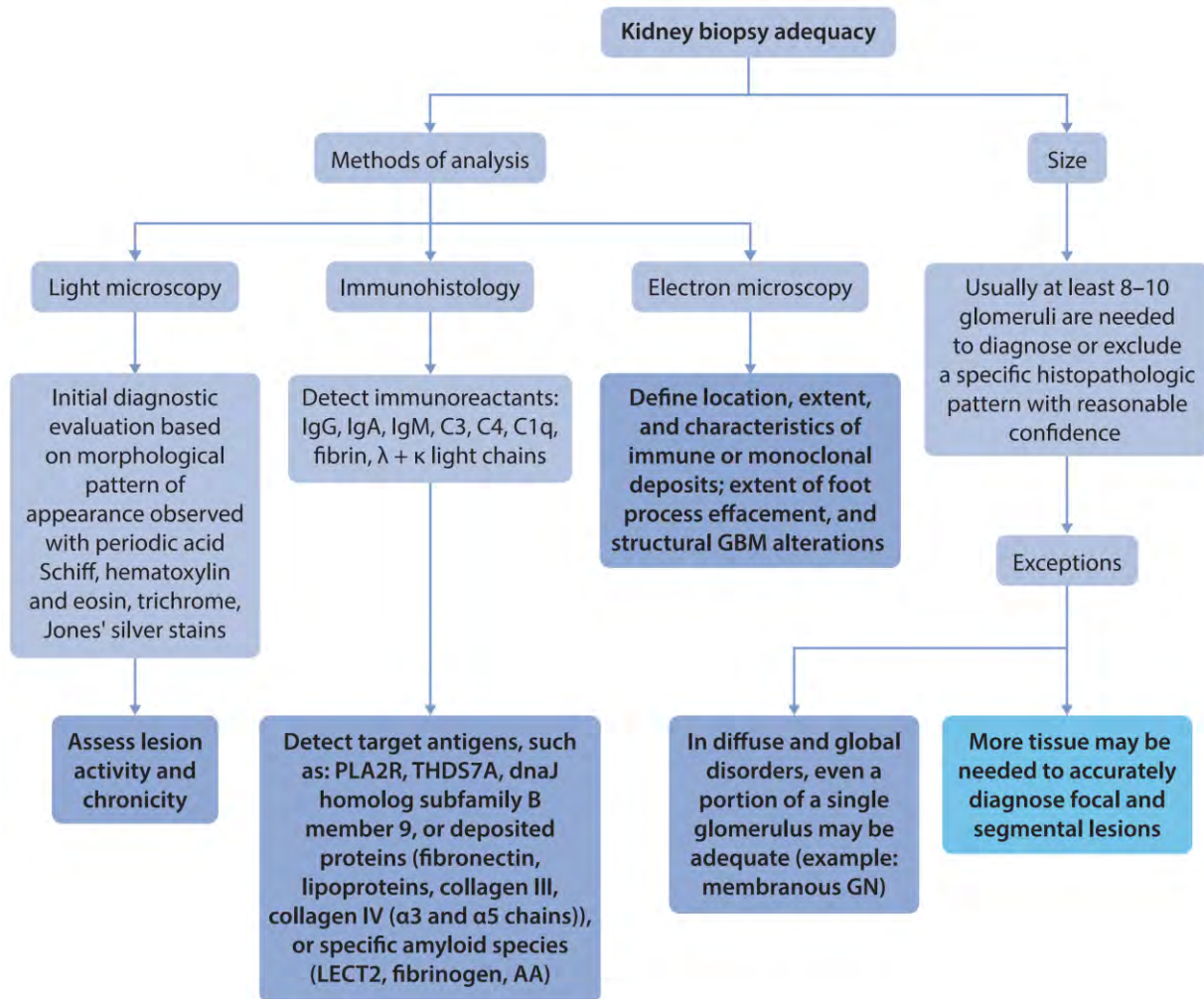
AA, amyloid A; GBM, glomerular basement membrane; GN, glomerulonephritis; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; LECT2, leukocyte cell-derived chemotaxin-2; PLA2R, phospholipase-A2-receptor; THDS7A, thrombospondin type I domain-containing 7A

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 requires at least eight to10 glomeruli.[33, 34] In some diseases, for example, focal segmental glomerulosclerosis (FSGS) and necrotizing GN associated with anti-neutrophil cytoplasmic antibodies (ANCA), lesions are only seen in some segments of some glomeruli. In these cases, it is important that the biopsy is examined by light microscopy (LM) at several levels if lesions are not to be missed. Fewer glomeruli may be acceptable for diffuse and global disorders, like membranous GN, where even a portion of a single glomerulus may be adequate.

Optimally, samples should be studied by light, immunofluorescence (IF), and electron microscopy (EM) and evaluated by an experienced nephropathologist. LM examination should minimally provide an initial diagnostic evaluation based on the morphological 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 (IP) analyses are required to detect immune-reactants immunoglobulin G (IgG), immunoglobulin A (IgA), immunoglobulin M (IgM), C3, C4, C1q, fibrin, and lambda and kappa 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 (THDS7A), DnaJ Homolog Subfamily B Member 9 (fibrillary GN), fibronectin, lipoproteins, collagen III, collagen IV α3 and α5 chains, or 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 LM, immune-histology, and EM. Due to cost and equipment limitations, it is recognized that EM may not be available everywhere. EM defines the location, extent, and specific characteristics, including organized substructure, of the immune or monoclonal deposits, the extent of foot process effacement, structural GBM alterations, and glycoprotein or lipid deposition. Some diagnoses, including minimal change disease (MCD) and immunotactoid deposition disease, are dependent on EM. In others, EM contributes significant descriptive and semi-quantitative information about podocytes and glomerular basement membrane (GBM), adding to diagnostic certainty. In centers where EM is not available, consideration should be made for the development of consultative relationships to obtain EM 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 GN; when of particular relevance, this 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 scoring in IgA nephropathy (IgAN), ISN/RPS scores 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 histopathological 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. (see also Chapters 5 & 6) A repeat kidney biopsy might be considered (even when the original biopsy was adequate for diagnosis) in the following circumstances:

- Evaluate a cause for an unexpected deterioration in kidney function not compatible with the known natural history;
- When the response to treatment is unsatisfactory, especially when a change of therapy is considered
- Evaluate 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[35]);
- Re-affirm the morphological diagnosis and re-evaluate the relative contributions of disease activity and chronicity, to determine whether to intensify, maintain, reduce, or otherwise modify therapy; or
- Define 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 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 RECOMMENDATIONS
- Determine whether proteomics, mass spectroscopy, and/or RNA sequencing analyses on kidney biopsy material can supplement or replace therapeutic decision-making based on morphological characterizations alone.

1.2. Assessment of kidney function

Key measures for the diagnosis, evaluation of prognosis, and management decision in patients with glomerular diseases 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 GN, particularly when marked proteinuria is present on qualitative testing.[36] 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 over-collection or under-collection. Simultaneous measurement of urine creatinine and protein in an aliquot of an intended 12 to 24-hour urine collection is a good compromise 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 use of albumin excretion rate (AER) or albumin-creatinine ratio (ACR) is not commonly used in non-diabetic forms of glomerular disease, even though these measurements are recommended for the categorization of CKD and for estimation of prognosis by Kidney Failure Risk Equations.[37]

Prediction of AER or ACR from PER or PCR values can be made using prediction formulas, but these are rather unreliable at low PER values (less than 500 mg/d), perhaps because of the presence of tubular proteinuria where PER can consist of non-albumin low molecular weight proteins.[38] 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). Gender, dietary, racial, 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 on 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. "Nephrotic syndrome" can be present in some patients whose urine protein quantification doesn't quite meet the traditional definition of nephrotic-range proteinuria, but in whom clinical symptoms match a classic presentation. (Table GP1)

Table GP1. Definition of "nephrotic syndrome", "nephrotic range proteinuria," and "non-nephrotic range proteinuria"

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 (<300 mg/mmol)
Proteinuria (children)* • ≥40 mg/m²/h • ≥300 mg/dl • 3+ on urine dipstick	Proteinuria (children) • ≥40 mg/m²/h • ≥300 mg/dl • 3+ on urine dipstick	• 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	

*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. (see Clase *et al.*[39]) The values of serum albumin measured by BCG are about 5.5g/l higher than those measured by BCP, CE, or iMN methods, so that the definition of the degree of hypoalbuminemia required to meet a definition of nephrotic syndrome varies according to the method used for quantifying serum albumin concentration.
‡Variable

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

Quantifying 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 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- to 24-hour urine collection at first presentation or a PCR on a first-morning void. Random "spot" PCR are discouraged for evaluation of patients with GN, unless 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. Quantify proteinuria in GN, 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 GN 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 GN and even within individual GN 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 macroglobulin, but in specific diseases (such as 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, non-radioisotopic iothalamate, Tc99 DPTA, or Cr51EDTA techniques. Other techniques include adjustment of SCr for age, weight, and sex using the 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.[40-46] The details of GFR assessment can be found in other *KDIGO Clinical Practice Guideline for the Evaluation and Management of CKD*. (https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf)

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/1.73 m². 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.[45, 47] GFR estimations are also unreliable during episodes of acute kidney injury (AKI) and may possibly be influenced by altered creatinine generation in patients with chronic corticosteroid-related myopathy.

In children, there are alternative validated formulas for eGFR, notably the Schwartz or Full-age spectrum (FAS) formulas.

Table GP2. Assessment of kidney function in GN

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

• Measured GFR*
  - Inulin clearance (Gold standard)
  - Radioisotopic plasma clearance[1]
    • I[125]iothalamate; TC[99]DTPA; Cr[51]EDTA
  - Non-radioisotopic plasma clearance
    • Iohexol[2]
	Adults
	• Cockcroft–Gault[3] (140-age)(wt, kg (0.85 if female)/72 (serum creatinine)
	• Modification of diet in renal disease (MDRD) equations[4] (not valid for eGFR >60 ml/min)
	  - CKD-Epi creatinine equation (preferred)
	    • Valid with eGFR >60ml/min
	  - CKD-Epi-cystatin C equations[5] (valid for eGFR >60 ml/min)
	  - FAS equation[7]
	    • Valid even in eGFR >60 ml/min
	
	Children
	• Schwartz equation and its modifications[6]
	• Full-age spectrum (FAS) formulae[7]
		• 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

AKI, acute kidney injury; eGFR, estimated GFR in ml/min/1.73 m^2

* in ml/min/1.73 m^2

1. Perrone RD, Steinman TI, Beck GJ, Skibinski CI, Royal HD, Lawlor M, *et al*. Utility of radioisotopic filtration markers in chronic kidney insufficiency: simultaneous comparison of 125I-iothalamate, 169Yb-DTPA, 99mTc-DTPA, and inulin. The Modification of Diet in Renal Disease Study. AJKD. 1990; 16(3): 224-235

2. Gaspari F, Perico N, Ruggenenti P, Mosconi L, Amuchastegui CS, Guerini E, *et al*. Plasma clearance of nonradioactive iohexol as a measure of glomerular filtration rate. J Am Soc Nephrol. 1995; 6:257-263

3. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976; 16: 31-41

4. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function - measured and estimated glomerular filtration rate. N Engl J Med. 2006; 354: 2473-2483.

5. Stevens LA, Coresh J, Schmid CH, Feldman HI, Froissart M, Kusek J, *et al*. Estimating GFR Using Serum Cystatin C Alone and in Combination With Serum Creatinine: A Pooled Analysis of 3,418 Individuals With CKD. AJKD. 2006; 51:395-406

6. Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, *et al*. New Equations to Estimate GFR in Children with CKD. JASN. 2009; 20 (3): 629-637

7. Pottel H, Delanaye P, Schaeffner E, Dubourg L, Eriksen BO, Melsom T, *et al*. Estimating glomerular filtration rate for the full age spectrum from serum creatinine and cystatin C. Nephrology Dialysis Transplantation. 2018; 32(3): 497-507

8. Branten AJW, Vervoort G, Wetzels JFM. Serum creatinine is a poor marker of GFR in nephrotic syndrome. Nephrology Dialysis Transplantation. 2005; 20(4): 707-711

9. Zhai JL, Ge N, Zhen Y, Zhao Q, Liu C. Corticosteroids Significantly Increase Serum Cystatin C Concentration without Affecting Renal Function in Symptomatic Heart Failure. Clin Lab. 2016; 62(1-2): 203-207

10. Levey AS, Perrone RD, Madias NE. Serum creatinine and renal function. Annual Review of Medicine. 1988; 39: 465-490

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
- Can validated GFR-estimating equations in patients with marked proteinuria 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. Dipsticks 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 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 a fresh centrifuged urine sediment by phase-contrast microscopy or brightfield optics under low and high-power magnification. Staining of the urine sediment (Sterrnheimer-Malbin) can aid in the recognition of cells and formed elements. Flow assisted cell sorting (FACS) 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 (RBCs) or the presence of acanthocytes (>5% of all RBCs) 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. As such, 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,[48] 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 GN.

Practice Point 1.3.2. Monitoring of hematuria (magnitude and persistence) may have prognostic value in many forms of GN.

RESEARCH RECOMMENDATIONS
- Further prospective studies of the impact of persistent hematuria on prognosis of specific forms of GNs 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 positively impact 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 address other metabolic and thrombophilic consequences of the NS. These relatively non-toxic therapies may prevent, or at least modulate, the need for immunosuppressive drugs with their 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).

Figure GP3. Summary of supportive management of GN
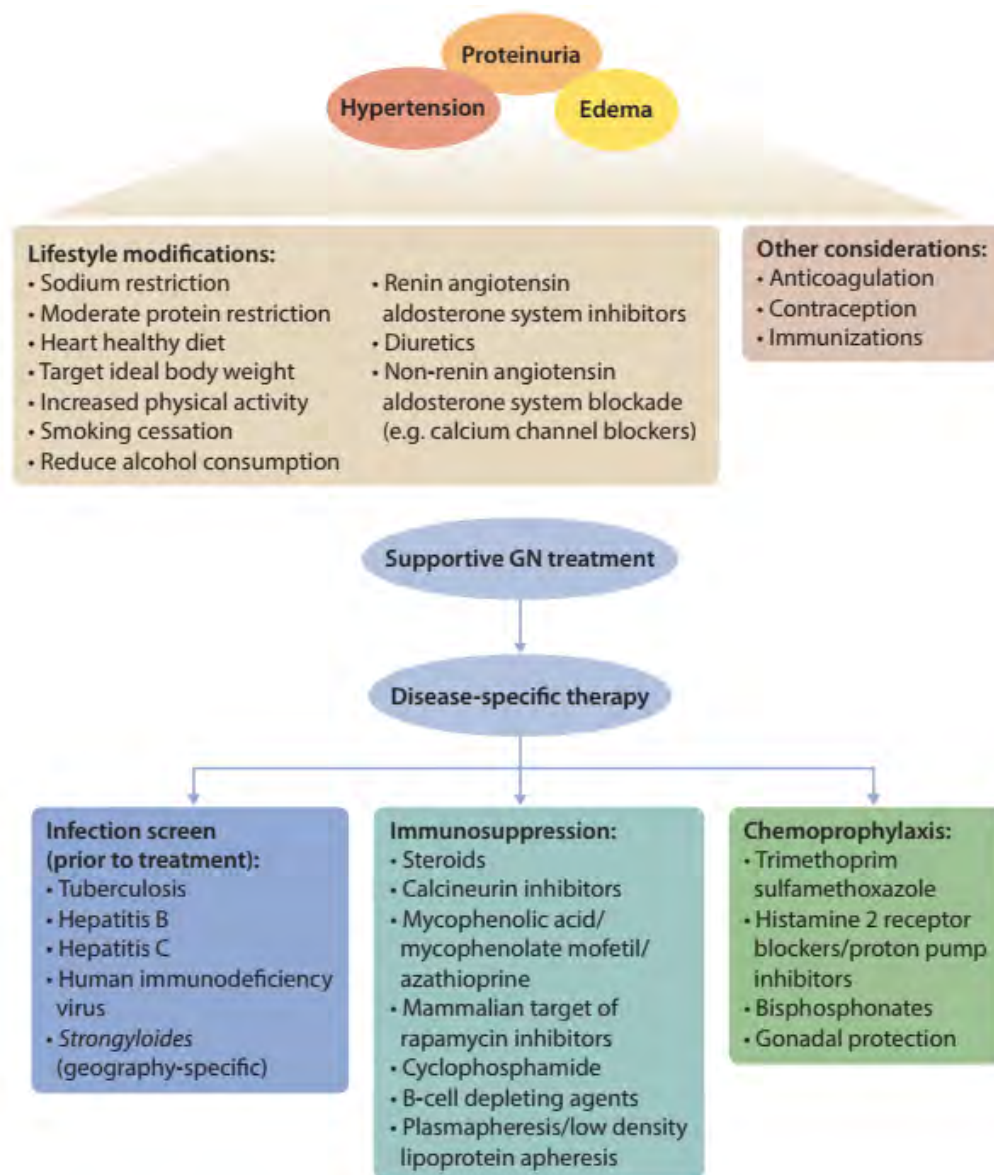
GN, glomerulonephritis

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.[49] The mainstay of treatment are diuretics accompanied by moderate dietary sodium restriction (1.5–2 g or 60-90 mmol sodium per 24 hours).

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 loops diuretics are typically required, due to decreased delivery of the drugs to the loop of Henle (larger volume of distribution with hypoalbuminemia), or due 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. Growing evidence demonstrates more favorable pharmacokinetic profiles and more consistent orally bioavailable with longer-acting torsemide and bumetanide, as compared with furosemide (at least in heart failure studies).[50]

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 a recent small randomized trial of patients with diuretic-resistant nephrotic edema, diuresis was more effective when furosemide was preceded by one week of acetazolamide (250 mg) plus hydrochlorothiazide (50 mg) as compared to furosemide (40 mg) plus hydrochlorothiazide (50 mg).[51]

Plasmin in nephrotic urine can activate the epithelial sodium channel, potentially contributing to diuretic resistance. Amiloride blocks the epithelial sodium channel (ENaC) and may be a potentially useful add-on therapy for edema/hypertension management in the NS.[52] The use of amiloride has not been validated in randomized clinical trials.

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 diuresis may be due to decreased intravascular volume with associated activation of 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. It may be reasonable to consider intravenous albumin in the diuretic-resistant patient that fails to respond to maximal dosing of intravenous diuretic alone or in diuretic combinations. 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 is 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.[53]

Table GP3. Edema management in the nephrotic syndrome

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 may be acceptable for reduced GFR • Increase dose to cause clinically significant diuresis or until maximally effective dose has been reached • Change from furosemide to torsemide/torasemide or bumetanide if treatment failure 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 thiazide-like diuretics and/or mineralocorticoid antagonists in combination with loop diuretics and sodium restriction for synergistic treatment of resistant edema in the nephrotic syndrome	• Metolazone may be more effective than hydrochlorothiazide or chlorthalidone in patients with reduced GFR <30 ml/min
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
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

GFR, glomerular filtration rate; i.v., intravenous

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
- RCT testing the efficacy of amiloride versus other diuretic classes for nephrotic edema

1.5. Management of hypertension and proteinuria reduction in GN

As in all chronic kidney disease (CKD), the aim of BP control is both to protect against the cardiovascular risks of hypertension (stroke, heart failure, coronary artery disease) and to 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. Anti-hypertensive therapy may not be necessary in all patients with GN (i.e., steroid-sensitive MCD).

Reduction in proteinuria is important, as it reflects control of the primary disease, reduction of glomerular hypertension, and also reduction of podocyte damage (a likely major factor in glomerular scarring). Most studies suggest that the loss of kidney function in the progressive

histologic patterns discussed in this guideline can largely be prevented if proteinuria can be reduced to levels below 0.5 g/d, and progression slowed if reduced to levels below 1 to 1.5 g/d. The exceptions are MCD and SSNS, where 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 to normal of serum proteins (particularly albumin). This elevation in serum albumin reduces thromboembolic and infection risk and often alleviates many of the patient's symptoms, the metabolic complications of the NS, and thereby improves quality of life.

The anti-proteinuric agents of choice are angiotensin-converting enzyme inhibitors (ACEi) or angiotensin-receptor blockers (ARB), 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. While concomitant use of ACEi and ARBs may result in additive anti-proteinuric activity, the combination has been associated with an increase in AKI and hyperkalemia events in RCTs involving diabetic subjects.[54, 55]

Although this has not been demonstrated directly in large RCTs involving patients with non-diabetic glomerular disease, 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, the use of ACEi or ARB may further contribute to kidney insufficiency and should not be used. If anti-proteinuric 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 (safety/efficacy has not been tested in RCTs). 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 receptor antagonist (MRA) can be used.[56] Similar to ACEi/ARB, hyperkalemia and reduction in GFR are side effects of these medications and routine laboratory monitoring is recommended. However, the use of combination ACEi or ARB with DRI is not recommended due to an increased risk of hyperkalemia,[57] at least as described in trial involving diabetic subjects.

Some patients are unable to tolerate even low-dose ACEi, ARB, MRA, or DRI. In this circumstance, alternative anti-hypertensive agents are recommended for both control of BP and for improvement in urine protein excretion. Non-dihydropyridine calcium channel blockers (CCB), such as diltiazem and verapamil, modestly reduce proteinuria. Beta blockers, diuretics,

and alpha-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 non-pharmacologic means of reducing proteinuria.

Meta-analyses have suggested that a sustained decline of 30% from baseline for urinary albumin or total protein excretion rate may be an acceptable surrogate outcome for eventual doubling of SCr or ESKD as hard outcome criteria for a favorable impact on CKD progression.[58-60]

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

Table GP4. Management of hypertension and proteinuria in GN

Practice Point 1.5.1.	Use an ACEi or ARB to maximally tolerated or allowed dose as first-line in treating patients with both hypertension and proteinuria	• Do not stop ACEi or ARB with modest and stable increase in serum creatinine (up to 20%) • Stop ACEi or ARB if kidney function continues to worsen, and/or refractory hyperkalemia 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.	Goal systolic blood pressure is <120 mm Hg using standardized office BP measurement (adults). Goal mean arterial pressure is ≤50% age/sex (children)	• Refer to KDIGO BP Guideline (https://kdigo.org/guidelines/blood-pressure-in-ckd/)
Practice Point 1.5.3.	Uptitrate an ACEi or ARB to maximally tolerated or allowed daily dose as first-line 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.	Goal proteinuria 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
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
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 • Thiazides 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 of 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 (see also Practice Point 1.5.7 above)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; MCD, minimal change disease; NS, nephrotic syndrome; RAS, renin-angiotensin system; SSNS, steroid-sensitive nephrotic syndrome

Figure GP4. Management of hypertension in GN

Management of hypertension in glomerular disease

Target blood pressure
• Adults: SBP <120 mmHg if proteinuria
• Children: <50th percentile for age and sex or local standards

General recommendations
• Salt restriction
• Weight normalization
• Regular exercise
• Smoking cessation

Medications

First line: angiotensin-converting enzyme inhibitors and/or angiotensin II-receptor blockers

Use combination with caution due to possible hyperkalemia and/or acute kidney injury

Caveats:
• Educate regarding discontinuation if volume depletion (vomiting, diarrhea, sweating from high fever/strenuous exercise)
• Monitor serum creatinine and potassium frequently: discontinue if serum creatinine rises >20%; lower increment may be acceptable hemodynamic change
• Potassium-lowering medications may be considered to optimize tolerablity of angiotensin-converting enzyme inhibitor/angiotensin II-receptor blocker treatment

Second line: mineralocorticoid receptor antagonists
• May be useful for antihypertensive and anti-proteinuric effects, particularly in patients who are intolerant to angiotensin-converting enzyme inhibitors/angiotensin II-receptor blockers
• May require discontinuation for hyperkalemia, although salvage therapy with potassium binders may be feasible

Additional strategies
• Use of antihypertensive agents without angiotensin blocking activity to achieve the goal blood pressure also contributes to proteinuria control
• Loop and thiazide diuretics aid in blood pressure control and the management of hyperkalemia, and enhance renin-angiotensin-aldosterone system inhibitor antiproteinuric effects

RESEARCH RECOMMENDATIONS

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

1.6. Management of hyperlipidemia in GN

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, mTOR inhibitors (sirolimus and everolimus), and calcineurin inhibitors (CNI) (cyclosporine A more often than tacrolimus).[61, 62] 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 cardiovascular event reduction or quality of life improvement is lacking in patients with hyperlipidemia from

glomerular disease or its treatment.[63] Risk factors include family history, obesity, 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 these 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 combinations with other drugs, notably an increased risk of myalgia/myositis when combined with CNI. Extremely limited data are available regarding the efficacy of ezetimibe or fibrates for lowering LDL in NS. A recent meta-analysis concluded that the limited information available does not support the use of these agents as monotherapy.[63]

Lipid apheresis, approved to treat familial hyperlipidemia, has also been used to treat hyperlipidemia in patients with steroid-resistant NS. 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,[62, 64] but to date, only a few case reports support the use of these agents. More data is needed concerning the utility of PSCK9 inhibitors in nephrotic hyperlipidemia before they can be broadly recommended.

Table GP5. Management of hyperlipidemia in GN

Practice Point 1.6.1.	Treatment of hyperlipidemia may be considered in patients with the nephrotic syndrome, particularly for treatment-unresponsive 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 the 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
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 atherosclerotic cardiovascular disease risk • Statins can be initiated in children > 8 years with concerning family history, extremely elevated low density lipoprotein cholesterol or Lp(a), in 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 µg/mg) are independently associated with an elevated risk of atherosclerotic cardiovascular disease • Atherosclerotic cardiovascular disease risk enhancers include chronic inflammatory conditions such as systemic lupus erythematosus, rheumatoid arthritis, history of pre-eclampsia, early menopause, South Asian ancestry, chronic kidney disease and human immunodeficiency virus/AIDS (accuracy of atherosclerotic cardiovascular disease 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 low density lipoprotein cholesterol 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 atherosclerotic cardiovascular disease risk and fail to achieve low density lipoprotein cholesterol or triglyceride goals despite maximally tolerated statin dose: • Bile acid sequestrants • Fibrates • Nicotinic acid • Ezetimibe • PCSK9 inhibitor	• 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 the 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

ACR, albumin-creatinine ratio; AIDS, acquired immunodeficiency syndrome; ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; Lp, lipoprotein; PCSK9, proprotein convertase subtilisin/kexin type 9.

RESEARCH RECOMMENDATIONS

- Randomized, prospective clinical trials are needed to assess the safety and efficacy of pharmacological treatment for the hyperlipidemia accompanying nephrotic and non-nephrotic glomerular diseases.
- Studies of the impact of lifestyle modifications for reduction of hyperlipidemia in the NS
- Impact of statin drugs on reduction of cardiovascular events in patients with the NS; many RCTs show reduction in cardiovascular 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

1.7. Hypercoagulability and thrombosis

The risk of arterial or venous thrombotic events in the NS for both children and adults is higher than the general population, especially within the first six months of diagnosis. 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 – see Table GP1) remain the best predictors for thrombotic risk. Independently, a low serum albumin (regardless of degree of proteinuria) can increase the thrombotic event risk.

Additional risk factors include prior thrombosis, genetic predisposition to thrombosis, anti-phospholipid antibodies, immobility, obesity, malignancy, pregnancy, or surgery (1,2). An online tool to help calculate bleeding risk versus benefits of anticoagulation in NS is available at http://www.med.unc.edu/gntools/. 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

Direct-acting oral factor Xa inhibitors (DOAC) have not been systematically studied in nephrotic patients for prophylaxis or treatment of thrombosis. In August 2018, the literature consisted only of four case reports and three conference proceedings.[65, 66] An open-label pharmacokinetic study of apixaban is underway in non-diabetic nephrotic patients, 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) and arterial thromboembolism (ATE) and PE in NS requires additional study. DOAC use in atrial fibrillation was associated with lower bleeding and all-cause mortality when compared to warfarin (all stages of CKD, including dialysis).[66, 67]

The efficacy and safety of DOACs in pediatric patients is not established. Pediatric VTE is uncommon; however, its incidence has been increasing over the past two decades. Heparin and warfarin have been traditionally used in this population, mostly by 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 GP5).

Figure GP5. Anticoagulation in nephrotic syndrome

For thromboembolic events, full-dose anticoagulation is required for 6–12 months and/or for the duration of the nephrotic syndrome	Prophylactic full-dose anticoagulation should be considered if:*	Contraindications to prophylactic anticoagulation
Venous thrombosis Arterial thrombosis Pulmonary embolus Nonvalvular atrial fibrillation	Serum albumin <2.0–2.5 g/dl and any of the following: • Proteinuria >10 g/d • Body mass index >35 kg/m² • Genetic disposition for thromboembolism • Heart failure New York Heart Association class III or IV • Recent orthopedic or abdominal surgery • Prolonged immobilization	• Patient preference/ability to adhere • Bleeding diathesis • Central nervous system lesion prone to hemorrhage • Genetic mutations influencing warfarin metabolism/efficacy • Frailty (falls) • Prior gastrointestinal bleed

*Membranous GN carries a particularly high risk of thromboembolic events

Practice Point 1.7.2. Anticoagulant dosing considerations in patients with nephrotic syndrome (Figures GP6 and GP7).

Figure GP6. Anticoagulant dosing considerations in patients with nephrotic syndrome

Prophylactic anticoagulation during transient high risk events

- Low dose anticoagulation (e.g., 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

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 Cockroft–Gault equation), age, and weight. The urinary clearance of the Xai 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%
  - 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 GP7. Glomerulonephritis/nephrotic syndrome algorithm for prophylactic anticoagulation[*][†]

*Hofstra *et al*. Kidney International. 2016; 89 (5): 981 - 983)
†Note: This algorithm was developed for patients with membranous GN. Its value is unknown for patients with nephrotic syndrome due to other underlying diseases
‡ Albumin value of 2.5 g/dl is measured using bromocresol green (BCG)

RESEARCH RECOMMENDATIONS

- RCTs of prophylactic anticoagulation in the nephrotic patient with GN
- Robust estimates of absolute thrombosis risk-adjusted for GN type, serum albumin, PCR, ACR, eGFR, age, comorbidities (e.g., obesity, genetic thrombophilia, immobilization, prior DVT/PE)
- Prospective randomized studies 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

1.8. Risks of infection

Epidemiology

A high order of clinical vigilance for bacterial infection is vital in patients with GN, 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 may be informative.

Parenteral antibiotics should be started once cultures are taken, and the regimen should include benzylpenicillin (to treat pneumococcal infection). If repeated infections occur, serum immunoglobulins should be measured. If serum IgG is less than 600 mg/dl (6 g/l), there is limited evidence that infection risk is reduced by monthly administration of intravenous immunoglobulin 400mg/kg to keep serum IgG >600 mg/dl (>6 g/l). Patients with GN 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.

- Serological tests for syphilis, HIV, hepatitis B (HBV), and hepatitis C (HCV) are commonly sought as potential underlying causes for glomerular disease. (see 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 (steroids and or cytotoxic/immunomodulating agents, rituximab) can induce a serious exacerbation of HBV replication and thus aggravate the hepatic manifestations of disease constitute a real risk (see Chapter 7.)

- Latent tuberculosis (TB), common in many populations, should be screened for if appropriate by quantiferon testing and/or purified protein derivative (PPD) skin testing and treated concomitant with immunosuppression. A recent study demonstrated that four months of rifampin is noninferior to nine months of isoniazid and pyridoxine for treatment of latent tuberculosis.[68] Some caution should be exercised in prescribing

rifampin in patients receiving corticosteroids, as rifampin may decrease the bioavailability of steroids.

- Infection with the helminth *Strongyloides stercoralis* should be screened for and treated in at-risk individuals prior to the initiation of immunosuppression, especially corticosteroids. The diagnosis, treatment, and prevention of hyperinfection from *Strongyloides* has recently been reviewed.[69] 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 corticosteroid therapy. In patients at risk of harboring asymptomatic *Strongyloides* in whom corticosteroid therapy is contemplated, screening is advised. The least expensive 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 not available.

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 corticosteroid 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 one to three months. Following treatment of the first episode of SSNS, non-immunized 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). Since 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 immunosuppressed and

immunodeficient patients. 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 three to six weeks after vaccination.

As noted below, prophylactic trimethoprim sulfamethoxazole 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 GN and nephrotic syndrome, as well as in patients with CKD.

Practice Point 1.8.2. Screen for TB, HBV, HCV, HIV, and syphilis in clinically appropriate patients (see 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 IgE levels.

Practice Point 1.8.4. Prophylactic trimethoprim-sulfamethoxazole should be considered in patients receiving high-dose prednisone or other immunosuppressive agents (rituximab, cyclophosphamide). Dapsone may be substituted for the sulfa-allergic.

<div align="center">

RESEARCH RECOMMENDATIONS
</div>

- Further studies concerning prevention and treatment of infections developing in patients with GN receiving immunosuppressive agents

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 SONG initiative is focusing on these issues from both the patient and provider perspectives.[70] Safety is also an important component of evaluation of treatment effects. Very few studies in GN 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 GN 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 per 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 at least 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.[59, 71]

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 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% or greater decline in eGFR from baseline over a two-to-three-year period has been suggested as a surrogate outcome measure for kidney failure. In the absence of kidney failure as a defined adverse outcome, 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.[72, 73]

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 compared to another group with similar clinical and histologic characterizations and in the setting of an RCT. Where available, these will be 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/1.73 m²) 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 may have masked any therapeutic benefit. Even among patients who have reached a point where 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 are often an underappreciated and/or unmeasured parameter in the evaluation of many of the clinical trials reviewed in this guideline. This is particularly relevant when considering the risk-benefit ratio analysis of interventions, which may include the short- and long-term risks of immunosuppressive treatments, but often does 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 females treated with corticosteroids could impact adherence to therapy). The recent introduction of patient-related outcomes (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 the SONG-GN initiative[70])

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

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

Practice Point 1.9.2. A reduction in the slope of decline in GFR or avoidance of a >40% decline in GFR from baseline over two years or more can be taken as a favorable surrogate outcome of treatment.

- Further analysis of disease-specific surrogate outcome measures in the specific forms of GN
- Additional data on impact of treatments of quality of life in GN.

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 the effectiveness of regimens for LN proven in Caucasians can be 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 is suggestive 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 GN.

RESEARCH RECOMMENDATIONS
- 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 diseases. 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 lesion of FSGS, targeted whole genome or whole exon sequencing is likely to have value in the assessment of the phenotype of steroid-resistant forms of FSGS.[74] Transcriptomic patterns of what appears to the phenotype of glomerular pathology

may yet reveal new promising targets for novel therapeutics.[75] The proteomic and metabolomic patterns of serum or urine may also provide important insights to 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.[76, 77]

RESEARCH RECOMMENDATIONS

- Continued research into the genetic origins of specific glomerular lesions (especially 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 corticosteroids 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 GN 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.[78] 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 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 female than in an older male). 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. Specific recommendations are beyond the scope of this guideline and are without an evidence base specific to the treatment of GN. It is reasonable to consider potential complications of long-term immunosuppression in GN 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 example, during cyclophosphamide therapy, women may be offered prophylaxis with gonadotropin-releasing hormone analog (leuprolide) treatment and men testosterone treatment during cyclophosphamide therapy.[79] Screening for latent infections prior to initiation of some forms of immunosuppression is discussed above.

Corticosteroids
Chronic steroid 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 steroid 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 in unexplained CKD, as well as case reports linking PPI use to AKI and interstitial nephritis, PPI use as first-line for peptic ulcer prophylaxis may need to be reconsidered.[78, 80, 81] Bisphosphonates (except in the presence of kidney failure) are used to minimize loss of bone density during prolonged treatment with corticosteroids. Please refer to *KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder* (https://kdigo.org/wp-content/uploads/2017/02/KDIGO-2009-CKD-MBD-Guideline-English.pdf).

Calcineurin inhibitors

CNIs are potentially nephrotoxic, but with lower serum trough levels used in MCD and other GNs, this side effect is uncommon.[82] 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.[83] 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% or more) in patients with eGFR below 30 ml/min/1.73 m², 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 six months, and in patients treated with oral cyclophosphamide, the drug should be taken in the morning, and patients instructed to have copious fluid intake. Sodium-2-mercaptoethane (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 500mg/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 pre-existing hypogammaglobulinemia. Hypogammaglobulinemia, when severe (<200-400 mg/dl), can promote risk of bacterial infections. 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-CSAF) may be indicated in patients at high risk of infection.

Table GP6. Screening/prophylaxis for all patients with GN on immunosuppression

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)

*Not recommended while being treated with moderate to high immunosuppression (e.g., prednisone 10 mg/d) because of reduced antibody response (Salemi *et al*. Int Rev Immunol. 2010)

1.13. Therapeutic drug monitoring

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 GN 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.

While 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 repeated flares or who develop drug-related complications despite being treated with conventional mycophenolate dosage.

Table GP7. Minimization of immunosuppression-related adverse effects

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
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

RESEARCH RECOMMENDATIONS

- Specific target drug levels best suited for achieving remission in GN
- Guidelines for bone loss screening/prophylaxis for short-term use of high-dose steroids in a GN patient
- RCT of prophylactic IVIG in hypogammaglobulinemic subjects treated with rituximab

1.14. Dietary management in GN

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

Ensure adequate dietary protein intake in the proteinuric patient (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/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 cardiovascular and kidney complications (i.e., faster rate of progression of CKD and kidney failure). Patients with GFR <60 ml/min/1.73 m^2 should consume 30 to 35 kcal/kg/d. Patients with elevated serum cholesterol who are at risk for cardiovascular complications should follow a heart-healthy diet. In addition, fats should be restricted to <30% of total calories, with saturated fats <10%.

Table GP8. Dietary suggestions in GN

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 and level of kidney function	• Nephrotic range proteinuria • 0.8–1 g/kg/d protein intake* • Additional 1 g per gram of protein losses (up to 5 g/d)
Practice Point 1.14.3.	Replace nephrotic protein losses	• Estimated glomerular filtration rate <60 ml/min/1.73 m² with non-nephrotic range proteinuria • 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	• Nephrotic range proteinuria • 35 kcal/kg/d • Estimated glomerular filtration rate < 60 ml/min/1.73 m² • 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 • Saturated fat 7–10% of total calories

*Ideal body weight

RESEARCH RECOMMENDATIONS

- Further studies on the beneficial effects of diet on progression of disease in GN and upon quality of life

1.15. Pregnancy and reproductive health in women with GN

In women of child-bearing 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 obstetrician-gynecologist (OB-GYN) and maternal fetal medicine, as detailed in the figure below (Figure GP8).[84, 85] A review of women diagnosed with GN showed that many patients presented during pregnancy with complications, and this may be an opportunity for health care providers to act early in the disease process.[86]

Figure GP8. Coordinated care of pregnant patients with GN[*]

| Prepregnancy | • Discuss timing of contraception
• Contraception advice if needed
• Fertility assessment if needed | • Assess disease activity with repeat biopsy confirmation if necessary
• Optimize blood pressure control | • Change to non-teratogenic medications and provide reassurance about continuation of safe medications in pregnancy | • Explain risk of pregnancy complications and need for heightened surveillance |

| Antenatal | • Target BP <140/90 mmHg | • Start low dose aspirin
• Consider vitamin D and calcium supplements | • Baseline and serial renal function, proteinuria (albumin:creatinine or protein:creatinine ratios or 24 h collections) and markers of disease activity
• Monitoring of calcineurin levels if required |
| | • Oral glucose tolerance test (especially important in women taking steroids or calcineurin inhibitors) | • Frequent fetal monitoring if concerns about fetal wellbeing
• Up to twice weekly BPPs
• Up to weekly placental Dopplers
• q2 weekly growth scans | • Consider venous thromboembolic event prophylaxis if risk factors, e.g. nephrotic syndrome, previous venous thromboembolic events, high body mass index |

| Delivery | • Delivery if presence of fetal or maternal decompensation
• NOT at pre-specified gestation
• Corticosteroid administration for fetal lung maturation at least 24 h and up to 7 d prior to anticipated delivery if <34 weeks' gestation | • Aim for vaginal delivery if possible
• Hydrocortisone stress dosing if required |

| Postnatal | • Encourage breast-feeding | • Careful surveillance for active glomerulonephritis
• Calcineurin inhibitor level if dose changed in pregnancy | • Continue venous thromboembolic event prophylaxis for at least 6 weeks if necessary | • Emotional support |

BP, blood pressure; BPP, biophysical profile; q2, every 2
*Reproduced from CJASN. 2017;12: 1862-1872

Contraception is also an important consideration as well. RASi and many GN therapies are known to be Category X (potentially teratogenic or embryotoxic) medications. Additionally, immunosuppression, such as cyclophosphamide, can have impact on long-term fertility. Birth control should continue for a minimum of six weeks after stopping mycophenolate. In men treated with mycophenolate, it is recommended to wear a condom when having sex with a woman who might become pregnant and to continue this practice for a minimum of 90 days after stopping mycophenolate. These issues and the psychological impact of these treatments on the patient has to be considered. A summary is provided below on GN considerations with contraception subtypes.

Table GP9. Contraception in women with glomerular disease[*]

Contraceptive method	Unintended pregnancy rate within 1st year of use (37%)		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		

*Kidney Int Rep. 2018 Mar; 3(2): 258–270.

The frequency of GN present during pregnancy varies by specific diseases. IgAN was the most commonly reported GN, and smaller numbers for FSGS, MCD, and MN. The number of patients in many of these review studies is small.[85] Control of GN is recommended prior to planning pregnancy. A major predictor of pregnancy outcome is the GFR at time of conception[87-89] and during mid-pregnancy.[90]

Because of the suggested high risk of preeclampsia in patients with GN, low-dose aspirin (60-150 mg) should be considered after the first trimester to reduce risk and important adverse perinatal health outcomes, but no large trials have been conducted.[91]

Risk to mother and fetus in pregnancy may vary by GN 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 anti-phospholipid syndrome, but exact risk is not known.[92] 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.[93] Anti-phospholipid antibodies were associated with hypertension, premature birth, and an increased rate of induced abortion. Stable disease seemed to predict the best outcomes.[94, 95] The take-home message from all of these studies is that women with active disease should be strongly discouraged from conceiving until their lupus is controlled.[96-99]

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

<div align="center">RESEARCH RECOMMENDATIONS</div>

- Further studies on the specific effects of each GN on maternal and fetal outcomes are needed

1.16. Treatment costs and related issues

These guidelines have been developed with the goal of providing evidence-based treatment recommendations for GN 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 not only to the high cost and limited availability of replacement fluids (including human albumin and fresh frozen plasma) but also to the 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. This is another indication of the urgent need for developing trials that will provide robust evidence of their efficacy. 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, but unfortunately, none exist. Research has started in this topic area but the data are still sparse.

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

RESEARCH RECOMMENDATIONS
- Further analyses of cost-effectiveness of therapeutic agents, including biosimilars, in GN

1.17. 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 GN 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 GN. Where there are specific recommendations in particular variants of GN that relate to management before transplantation, they will be discussed in each relevant chapter.

CHAPTER 2. IMMUNOGLOBULIN A NEPHROPATHY/IMMUNOGLOBULIN A VASCULITIS

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% to 30% of any cohort developing kidney failure within 20 to 25 years of presentation. Unlike the majority of glomerular diseases included in this guideline, management of IgAN is focused on non-immunosuppressive 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 (see Chapter 1).

While IgAN is characterized by a single histopathological 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 to 18 years. Where possible, we have highlighted where there may be racial differences in response to particular treatment regimens.

IgA vasculitis (Henoch Schoenlein Purpura) is dealt with later in this chapter.

2.1. Diagnosis
Practice Point 2.1.1. Considerations for the diagnosis of IgAN:
- **IgAN can only be diagnosed with a kidney biopsy.**
- **Score the kidney biopsy using the revised Oxford MEST-C Classification.[3]**
- **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.[3, 100-104] More recently, the standardized MEST score has been incorporated into development of prognostic scoring systems[105] and machine-learning used to select predictive variables.[106] 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.[25] The five-year risk of halving of 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 remote 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 Table IgAN1.

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 assess the patient using the International IgAN Prediction Tool.**
    - ○ **Available at: Calculate by QxMD**
- **The International IgAN Prediction Tool 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.**

Table IgAN1. The data elements included in the International IgAN Prediction Tool[*]

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

Systolic blood pressure at biopsy...mmHg

Diastolic blood pressure at biopsy..mmHg

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

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; GFR, glomerular filtration rate; MEST, mesangial (M) and endocapillary (E) hypercellularity, segmental sclerosis (S) and interstitial fibrosis/tubular atrophy (T)
[*]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.

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 may require specific immediate treatment.**

Practice Point 2.3.2. Algorithm for the initial assessment and management of the patient with IgAN (Figure IgAN1)

Figure IgAN1. 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/24h, we recommend that initial therapy be with either an ACEi or ARB, but not both *(1B)*.

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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, is consistent with these observations. 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 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 cardiovascular risk.[107, 108] 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 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.[109] There is 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 IgA nephropathy population is moderate because of 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, ESKD, 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) (Table S3,[7, 15, 110] Table S2[7, 110-114]).

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 Organisation), 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 (see 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. Age-related targets for BP control in IgAN are no different to those stated in Chapter 1. In particular, there is no evidence to suggest 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 frequent relapses, episodes of NS, or AKI; IgAN is typically a slowly progressive disease resulting in kidney failure in a minority of patients over time. In IgAN, strategies to control BP and minimize proteinuria are currently as important as attempts to modify the underlying disease pathogenesis with immunosuppressant medication.[115]

Epidemiological 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.[116-118] 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 g/d to 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%).[117] In an RCT of 49 patients with IgAN, an achieved mean BP of 129/70 mm Hg stabilized GFR over three years, whereas patients with an achieved mean BP of 136/76 mm Hg showed an average decline in GFR of 13 ml/min over three years.[119] 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.[118] An RCT of 44 IgAN patients 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).[112] 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.[120]

> **Recommendation 2.3.2. We recommend that all patients with proteinuria >0.5 g/24h, irrespective of whether they have hypertension, are 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. 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 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 cardiovascular risk.[108, 121] 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 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 kidney-protective 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.[122] 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.[60]

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, two 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 complete remission of proteinuria, ESKD, and doubling SCr (due to very serious imprecision) (Table S3[7, 15, 110]).

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 (World Health Organisation), ACEi are widely, but not uniformly, available in high IgAN prevalence areas. It is important to note, however, that in some countries (e.g., Japan and South Korea), the use of RAS blockade in normotensive yet proteinuric patients is not supported by health insurers.

Considerations for implementation

When commencing RAS blockade in normotensive patients, it is imperative that patients are started on low-dose therapy initially, and 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.[116-118] 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 g/d to 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% (82%, 96%).[117] A meta-analysis of eight trials involving 866 patients evaluated the antiproteinuric effect of ARB in normotensive patients with proteinuria. Compared with a control group, the use of an ARB was associated with a significant reduction in urinary protein excretion in diabetic patients with moderately increased albuminuria and nondiabetic nephropathy with overt proteinuria. This effect was consistently seen in both Western and Asian populations.[123] Included in this meta-analysis was a small study in IgAN that included 32 normotensive patients aged 18 to 54 years with proteinuria (1-3 g/d) and normal kidney function (CrCl >80 ml/min) who were randomly divided into four treatment groups (verapamil 120 mg/d; trandolapril 2 mg/d; candesartan cilexetil 8 mg/d; and placebo).[110] 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.[122] This effect was independent of the presence or absence of hypertension.

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

<u>Patients with IgAN who are at high risk of progressive CKD despite maximal supportive care</u>
These patients are defined as those with persistent urine protein excretion >1 g/24h despite treatment with a maximal tolerated or allowed daily\ dose of RAS blockade for a minimum of three months and having achieved the recommended BP target as described in Chapter 1 for a minimum of three months. Variant forms of IgAN may require specific immediate treatment.

Practice Point 2.3.3. 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 >1g/24h despite at least 90 days of optimized supportive care.**
- **Immunosuppressive drugs should only be considered in patients with IgAN who remain at high risk of progressive CKD despite maximal supportive care.**
- **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 with a recognition that adverse treatment effects are more likely in patients with an eGFR below 50 ml/min/1.73 m².**
- **There is insufficient evidence to support the use of the Oxford 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),[60] 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 this target 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 2.3.4. Proteinuria reduction to under 1 g/d is a surrogate marker of improved kidney outcome in IgAN.

> **Recommendation 2.3.3. We suggest that patients who remain at high risk of progressive CKD despite maximal supportive care are considered for a six-month course of corticosteroid therapy. The important risk of treatment-emergent toxicity must be discussed with patients, particularly those who have an eGFR below 50 ml/min/1.73 m² (2B).**

In the absence of a rapidly progressive loss of kidney function, supportive therapy is the mainstay of treatment for adults with IgAN. Following six months 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.[115] Shorter periods of three months may be considered in patients already receiving RAS blockade prior to biopsy diagnosis.

The largest available RCT of corticosteroids halted enrollment after randomization prematurely due to safety concerns in the corticosteroid-treated group.[124] Early analysis suggested efficacy, however, there were serious adverse events, including two deaths related to infectious complications. In discussion with clinicians, patients may choose not to receive corticosteroids 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 corticosteroid 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 corticosteroids in similar populations is 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 four RCTs that have compared corticosteroid therapy with supportive therapy was moderate for critical and important outcomes (all-cause mortality, ESKD, infection,

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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=68%) (Table S5[60, 115, 124-126]).

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

Resource use and costs

Corticosteroids are included in the WHO Model List of Essential Medicines (2017) and are generally readily accessible and inexpensive. The availability of resources for monitoring for risks of treatment-emergent toxicity (e.g., screening for latent infections, bone mineral density scanning) is, 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 corticosteroids in patients with particular clinical characteristics, placing them at higher risk of treatment-emergent toxicity (see 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.[60] An initial series of small randomized placebo-controlled trials supported greater reduction in proteinuria compared to supportive therapy alone, with or without uniform use of RAS blockade.[125-127] However, the confidence in estimates of efficacy and toxicity for these studies is low due to small sample size.

The randomized STOP-IgAN study 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.[115] At three 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 three years. The proteinuria at randomization was relatively low (1.6 g/d and 1.8 g/d), and over three years,

patients in the supportive care group experienced only a 4.2 ml/min/1.73 m^2 decline in kidney function confirming the impact of rigorous supportive care in IgAN, but also meaning patients in the immunosuppression arm had low baseline rates of eGFR loss; therefore, were unlikely to develop endpoints over a relatively short follow-up period of three 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 seven 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.[115] 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 steroid group (95% CI 4.8%, 18.2%).[124] This included two 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 steroid 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 corticosteroids. 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/1.73 m^2.

The TESTING study included patients with eGFR as low as 20 ml/min/1.73 m^2. However, only 26 randomized patients had an eGFR under 30 ml/min/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.

Corticosteroid regimens used in the three most recent RCTs are detailed in Table IgAN2.

Table IgAN2. Corticosteroid regimens used in clinical trials where there was uniform use of RAS inhibition

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

[1]TESTING: Lv J, Zhang H, Wong MG, *et al*. Effect of Oral Methylprednisolone on Clinical Outcome in Patients with IgA Nephropathy: The TESTING Randomized Clinical Trial. JAMA. 2017; 318(5): 432-442
[2]Manno: Manno C, Torres DD, Rossini M, Pesce F, Schena FP. Randomized controlled clinical trial of corticosteroids plus ACE-inhibitors with long-term follow-up in proteinuric IgA nephropathy. Nephrol Dial Transplant. 2009; 24(12):3694-3701
[3]Lv: Lv J, Zhang H, Chen Y, *et al*. Combination therapy of prednisone and ACE inhibitor versus ACE-inhibitor therapy alone in patients with IgA nephropathy: a randomized controlled trial. *Am J Kidney Dis.* 2009;53(1):26-32

Practice Point 2.3.5. Use of corticosteroids in IgAN:

- **Clinical benefit of corticosteroids in IgAN is not established and should be given with extreme caution or avoided entirely in the following situations:**

eGFR <30 mL/min/1.73m^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

BMI, body mass index; eGFR, estimated glomerular filtration rate; TB, tuberculosis
*The TESTING study included patients with eGFR 20-30 ml/min/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/1.73m^2.
† High BMI in the TESTING study was not specifically considered an exclusion, but the mean BMI was <24 kg/m^2.

- **Corticosteroid therapy is also relatively contraindicated in patients with controlled psychiatric illness and severe osteoporosis.**

- **There is insufficient evidence to support the use of the Oxford MEST-C score in determining when corticosteroids should be commenced.**
- **There are no data to support efficacy or reduced toxicity of alternate-day corticosteroid regimens, or dose-reduced protocols.**
- **Where appropriate, high-dose treatment with corticosteroid should incorporate prophylaxis against *Pneumocystis* pneumonia along with gastroprotection and bone protection according to national guidelines.**

Practice Point 2.3.6. Management of the patients with IgAN who remain at high risk for progression after maximal supportive care (Figure IgAN2)

Figure IgAN2. Management of the patient with IgAN who remains at high risk for progression after maximal supportive care[*]

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure, eGFR, estimated glomerular filtration rate; GN, glomerulonephritis; HIV, human immunodeficiency virus; IgAN, immunoglobulin A nephropathy; TB, tuberculosis
*IgAN with rapidly progressive glomerulonephritis is covered in Practice Point 2.4.3.

Practice Point 2.3.7. Other pharmacologic therapies evaluated in IgAN (Table IgAN3)

Table IgAN3. Other pharmacological therapies in IgAN

Agent	Suggested usage	Remarks
Anti-platelet 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 corticosteroids
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 corticosteroids are being considered MMF may be used as a steroid-sparing agent	In a single RCT conducted in China, MMF with low dose corticosteroids was non-inferior to standard dose corticosteroids 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/day. There were significantly fewer corticosteroid related side effects in the combination therapy arm. (PICO 18.16)[1,6]
	Non-Chinese patients There is insufficient evidence to support the use of mycophenolate mofetil	In the RCTs of MMF in non-Chinese patients there was no evidence for efficacy of MMF monotherapy. (PICO 18.15)[2,3,4,5,6]

IgAN, immunoglobulin A nephropathy; MMF, mycophenolate mofetil; RCT, randomized controlled trial

[1]Hou JH, Le WB, Chen N, *et al*. Mycophenolate Mofetil Combined With Prednisone Versus Full-Dose Prednisone in IgA Nephropathy With Active Proliferative Lesions: A Randomized Controlled Trial. American Journal Kidney Disease. 2017;(6):788-795

[2]Hogg RJ, Bay RC, Jennette JC, *et al*. Randomized controlled trial of mycophenolate mofetil in children, adolescents, and adults with IgA nephropathy. American Journal of Kidney Disease. 2015;66(5):783-791

[3]Frisch G, Lin J, Rosenstock J, *et al*. Mycophenolate mofetil (MMF) vs placebo in patients with moderately advanced IgA nephropathy: a double-blind randomized controlled trial. Nephrology Dialysis Transplantation. 2005;20(10):2139-2145

[4]Maes BD, Oyen R, Claes K, *et al*. Mycophenolate mofetil in IgA nephropathy: results of a 3-year prospective placebo-controlled randomized study. Kidney International. 2004;65(5):1842-1849

[5]Tang S, Leung JC, Chan LY, *et al*. Mycophenolate mofetil alleviates persistent proteinuria in IgA nephropathy. Kidney International. 2005;68(2):802-812

[6]Vecchio M, Bonerba B, Palmer SC, *et al*. Immunosuppressive agents for treating IgA nephropathy. The Cochrane database of systematic reviews 2015;(8):CD003965

Practice Point 2.3.8. Tonsillectomy in IgAN:

- **Tonsillectomy should not be performed as a treatment for IgAN in Caucasian patients.**
- **Tonsillectomy may be indicated 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 corticosteroids (Table S6[4-8]).**

Table IgAN4. Regional use of tonsillectomy as a treatment for IgAN

	Japanese IgAN	Chinese IgAN	Caucasian IgAN
Clinical practice	Performed routinely (often with pulsed corticosteroids)	Not routinely performed	Not performed
Remarks	Multiple cohort studies including a large retrospective study with propensity matching 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 corticosteroids, no longer-term data is available from this study	Inconsistent data from small retrospective cohort studies and a small single center RCT	Very few data available in this population. Available data does not support the efficacy of tonsillectomy as a treatment for IgAN in Caucasian patients

[1] Kawamura T, Yoshimura M, Miyazaki Y, *et al*. A multicenter randomized controlled trial of tonsillectomy combined with steroid pulse therapy in patients with immunoglobulin A nephropathy. Nephrology Dialysis Transplantation 2014;29(8):1546-1553

[2] Yang D, He L, Peng X, *et al*. The efficacy of tonsillectomy on clinical remission and relapse in patients with IgA nephropathy: a randomized controlled trial. Renal Failure 2016;38(2):242-248

[3] Kawasaki Y, Takano K, Suyama K, *et al*. Efficacy of tonsillectomy pulse therapy versus multiple-drug therapy for IgA nephropathy. Pediatric Nephrology 2006;21(11):1701-1706

[4] Hotta O, Taguma Y, Kurosawa K, *et al*. Early intensive therapy for clinical remission of active IgA nephropathy: a three-year follow-up study. Japanese Journal of Nephrology 1993;35(8):967-973

[5] Reid S, Cawthon PM, Craig JC, *et al*. Non-immunosuppressive treatment for IgA nephropathy. The Cochrane database of systematic reviews 2011;(3):CD003962- PubMed Journal

[6] Hirano K, Matsuzaki K, Yasuda T, *et al*. Association Between Tonsillectomy and Outcomes in Patients With Immunoglobulin A Nephropathy. JAMA Network Open 2019;2(5):e194772- Pubmed Journal

eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; RCT, randomized controlled trial

2.4. Special situations

Practice Point 2.4.1. IgAN with the 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 EM features consistent otherwise 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 LM and EM features consistent otherwise 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 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 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 two 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 a rapidly progressive glomerulonephritis (RPGN) with extensive crescent formation, commonly in the absence of visible hematuria. In the absence of visible hematuria and when reversible causes have been excluded (e.g., drug toxicity, common pre- and post-kidney causes), a kidney biopsy should be performed as soon as possible.**

Practice Point 2.4.3. IgAN with a rapidly progressive glomerulonephritis:
- **Rapidly progressive IgAN is defined as a ≥50% decline in eGFR over three months or less, where reversible causes have been excluded (e.g., drug toxicity, common pre- and post-kidney causes).**
- **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 SCr does not constitute rapidly progressive IgAN.**
- **We suggest patients with rapidly progressive IgAN are treated with cyclophosphamide and corticosteroids in accordance with the guidelines for ANCA-associated vasculitis (Chapter 9).**
- **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 child-bearing potential should be offered pre-conception counseling where appropriate.**
- **Pre-conception counseling should include a discussion on cessation of RAS blockade before conception. BP control should be optimized with alternative antihypertensive medications prior to conception.**
- **In those women at high risk of progressive CKD (see Recommendation 2.3.3.) 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

- **Visible hematuria is more frequent in children than in adults, and this may account for earlier diagnosis in children.[9]**
- **Children generally have higher eGFR, lower urine protein excretion, and more erythrocyturia than adults at diagnosis.[10]**

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 adults.[11-14]**

Treatment

- **There is strong evidence suggesting a benefit of RAS blockade in children.[15] All IgAN children with proteinuria >200 mg/d should receive ACEi or ARB blockade, advice on a low sodium diet, and optimal lifestyle and BP control (≤50th percentile for age and height).**
- **Evidence derived mostly from retrospective studies suggests that treatment with corticosteroids (+ second-line immunosuppression) leads to improved kidney survival.[9, 16]**
- **In children with proteinuria >1 g/d and mesangial hypercellularity (Oxford M1) most pediatric nephrologists will treat with corticosteroids in addition to RAS blockade from time of diagnosis.[10, 11, 13, 17]**
- **As in adults, children with rapidly progressive IgAN have a poor outcome and, despite limited evidence, this subgroup should be offered treatment with corticosteroids (usually as methylprednisolone pulses) and oral cyclophosphamide.[11, 13, 18]**

Follow-up

- **Aim for proteinuria <200 mg/24h.**

- **Aim for BP at ≤50th percentile for age and height.**
- **Continue to follow patients even after complete remission as they can relapse even after many years.[19]**

RESEARCH RECOMMENDATIONS

- Develop the International IgAN Prediction Tool to predict risk of progression after kidney biopsy and serially during follow-up.
- Identify prognostic biomarkers to improve the accuracy of the International IgAN Prediction Tool.
- There are more clinical trials of new therapies in IgAN recruiting than ever before: drugs targeting the lectin (MASP-2), alternative (Factor B) and final common (C5) complement pathways, combined angiotensin and endothelin receptor blockade, BAFF and APRIL signaling to B cells and enteric IgA synthesis. If all of these agents prove efficacious and safe, there will be a need to identify biomarkers capable of predicting which patients should receive which new therapy or combination of therapies to allow personalization of treatment of IgAN.
- Identify biomarkers capable of predicting early response to therapy to help guide therapeutic decision-making.
- Continue transcontinental research to identify genetic and environmental factors influencing disease phenotype across races.

IMMUNOGLOBULIN A VASCULITIS

IgA vasculitis (IgAV), formerly Henoch-Schoenlein 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 younger than 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 makes management recommendations for adults with IgAV-associated nephritis (IgAVN) and provides a practice point on how to apply these recommendations to children aged 1 to 18 years. 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. IgAN is dealt with above.

2.5. Diagnosis

Practice Point 2.5.1. Considerations for the diagnosis of IgAV:

- **In adults, unlike children, there are no internationally agreed-upon criteria for the diagnosis of IgAV, although a clinical diagnosis of IgAV is often made in adults based on the criteria described for children.[20, 21]**
- **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 patients with IgAV for secondary causes.**
- **Assess all 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.[22-24]**
- **The Oxford classification has not been validated for IgAV.**
- **The International IgAN Prediction Tool[25] is not derived for prognostication in IgAV.**

2.7. Treatment

2.7.1. Prevention of nephritis in IgAV

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

Key information

Balance of benefits and harms

The lack of benefit and the well-documented risks associated with corticosteroids 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, ESKD, and complete remission (Table S7[128-133]). There was moderate-quality evidence for the development of and continued kidney disease due to study limitations (inadequate allocation concealment) and concerns about imprecision with very few events.

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 corticosteroids 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.[128] This finding was replicated in 171 children showing early use of prednisolone did not prevent the development of nephritis.[133] A meta-analysis of five RCTs in which 789 children were examined for the effects of short-duration corticosteroids (2-4 weeks) on preventing persistent nephritis at six and 12 months after the presentation concluded that such treatment with corticosteroid at presentation had no preventive effect on onset of persistent nephritis.[129]

Practice Point 2.7.1.1. Considerations for the treatment of all patients with IgAV-associated nephritis who do not have a rapidly progressive glomerulonephritis:
- **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 BP targets.**
- **Treat with maximally tolerated dose of RASi if proteinuria >0.5 g/24h.**
- **Offer participation in a clinical trial if one is available.**

2.7.2. Patients with IgAV with associated nephritis who are at high risk of progressive CKD despite maximal supportive care

These patients are defined as those with persistent urine protein excretion >1 g/24h despite treatment with a maximal tolerated dose of RAS blockade for a minimum of three months and having achieved the recommended BP target as described in Chapter 1 for a minimum of three months.

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

- **There is insufficient evidence to support the use of the Oxford 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 below 50 ml/min/1.73 m².**
- **In those patients who wish to try immunosuppressive therapy, treatment with corticosteroids is as described above for IgAN.**

2.8. Special situations

Practice Point 2.8.1. IgAVN 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 with cyclophosphamide and corticosteroids in accordance with the guidelines for ANCA-associated vasculitis (Chapter 9).**
- **IgAVN with RPGN may also 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 corticosteroid therapy to accelerate recovery in patients with life, or organ-threatening extrarenal complications of IgAV.[26] Clinicians are referred to the guidelines of the American Society for Apheresis regarding recommendations regarding plasma exchange for IgAV.[27]**

2.8.1. IgAV-associated nephritis in children

Practice Point 2.8.1.1. Indications for management of IgAVN in children have recently been published as the result of a European consortium initiative.[20] Briefly:

- **There are no data supporting the use of corticosteroids to prevent nephritis in children with IgAV but mild or absent evidence of kidney involvement.[28, 29]**

- **Children above 10 years of age more often present with non-nephrotic range proteinuria, impaired kidney function, and may suffer more chronic histological lesions with delay in biopsy and treatment longer than 30 days.[30]**
- **The majority of children who will develop nephritis will do so within three months of presentation. Urinary monitoring is necessary for at least six and optimally 12 months from initial presentation systemic disease.**
- **Children with IgAVN and persistent proteinuria for greater than three months should be treated with ACEi or ARB blockade. 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 rapidly progressive IgAN.**

RESEARCH RECOMMENDATIONS

- The Oxford MEST-C score and the International IgAN Prediction Tool should be validated in IgAV.
- 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 three different biologic drugs (infliximab, tocilizumab, and rituximab) in 140 patients (children & adults) with refractory vasculitis (including IgAV) recruited from 15 vasculitis centers in the United Kingdom and Ireland.
- In light of preliminary observational data,[134, 135] 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 may not be required to confirm the diagnosis of MN in patients with a compatible clinical and serological presentation.

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 diseases; however, for MN, the antibodies against PLA2R (PLA2Rab) 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 PLA2Rab-positive patients. There are currently insufficient data to support the use of THSD7Aab as a diagnostic biomarker for MN in lieu of a biopsy.

In a meta-analysis of nine studies, including 710 patients with MN and 1502 controls, the sensitivity of a positive PLA2Rab test for the diagnosis of MN was 0.78 and specificity 0.99.[136] A more recent study confirmed the high accuracy, with sensitivity of 64% and specificity of 99%.[137] The 95% confidence interval 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 PLA2R antibodies, had no evidence of secondary causes of MN, but did undergo a native kidney biopsy.[138] The primary diagnosis in all biopsies was MN. Among 60 patients with a baseline eGFR of >60 ml/min/1.73 m^2, the biopsy disclosed superimposed diabetic nephropathy or FSGS in only two patients, and these findings did not affect patient care or treatment. Among 37 patients with eGFR <60 ml/min/1.73 m^2, additional findings were reported in five 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 study strengthens the conclusion that in PLA2Rab-positive patients with normal eGFR a kidney biopsy does not alter the diagnosis of primary MN.[139]

Further details on the PLA2Rab assay (Figure MN1) and when to consider a kidney biopsy in a PLA2Rab-positive patient (Figure MN2) are shown below. In patients who are

PLA2Rab-negative, a kidney biopsy should be performed with staining of the biopsy for the PLA2R antigen, and this may disclose PLA2Rab-associated MN. This can occur in patients where the serum ELISA and IFT 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.

Figure MN1. Guidance for the use and interpretation of the PLA2Rab assay in patients with known PLA2R-associated MN
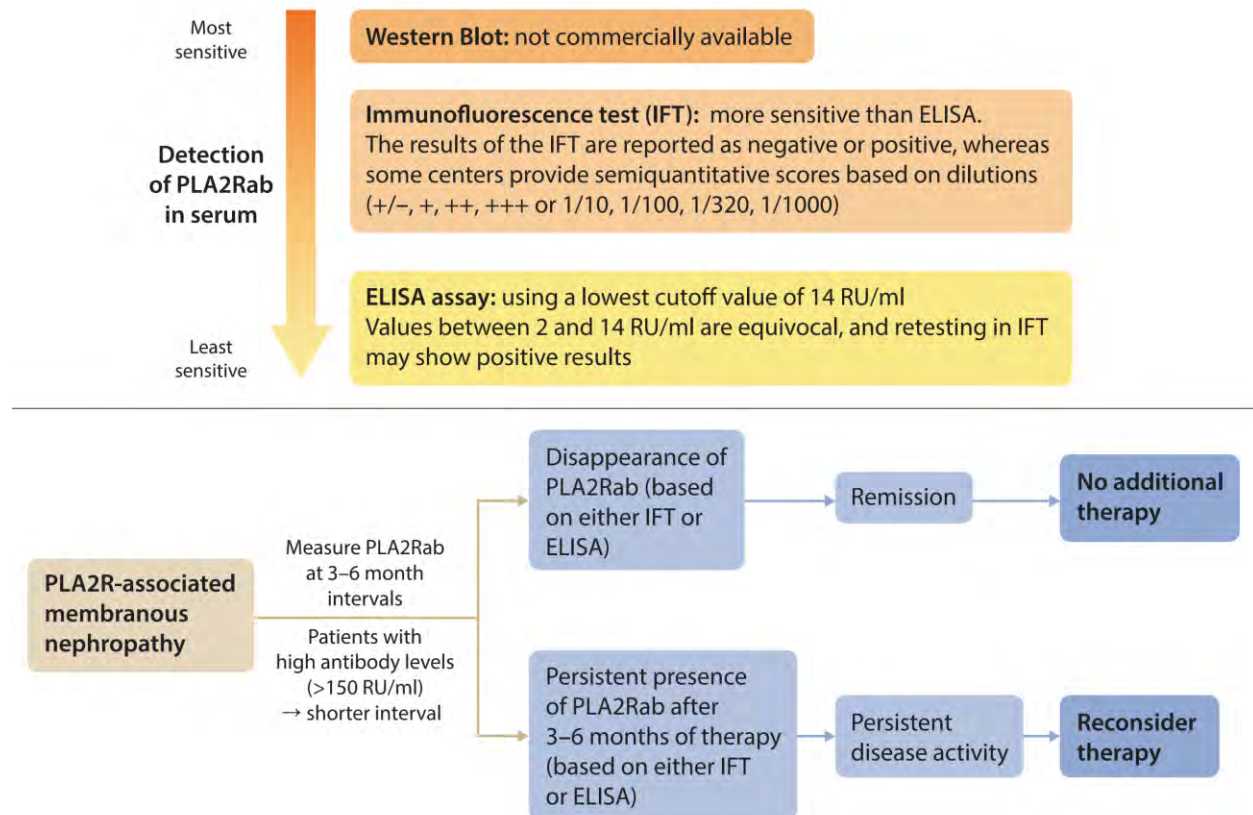
ELISA, enzyme-linked immunosorbent assay; PLA2Rab, antibodies against the M-type phospholipase-A2-receptor
*High titers (ELISA) are associated with lower likelihood of spontaneous remission and higher likelihood of non-response to low-dose rituximab

Figure MN2. When to consider a kidney biopsy in a PLA2Rab-positive patient[*]
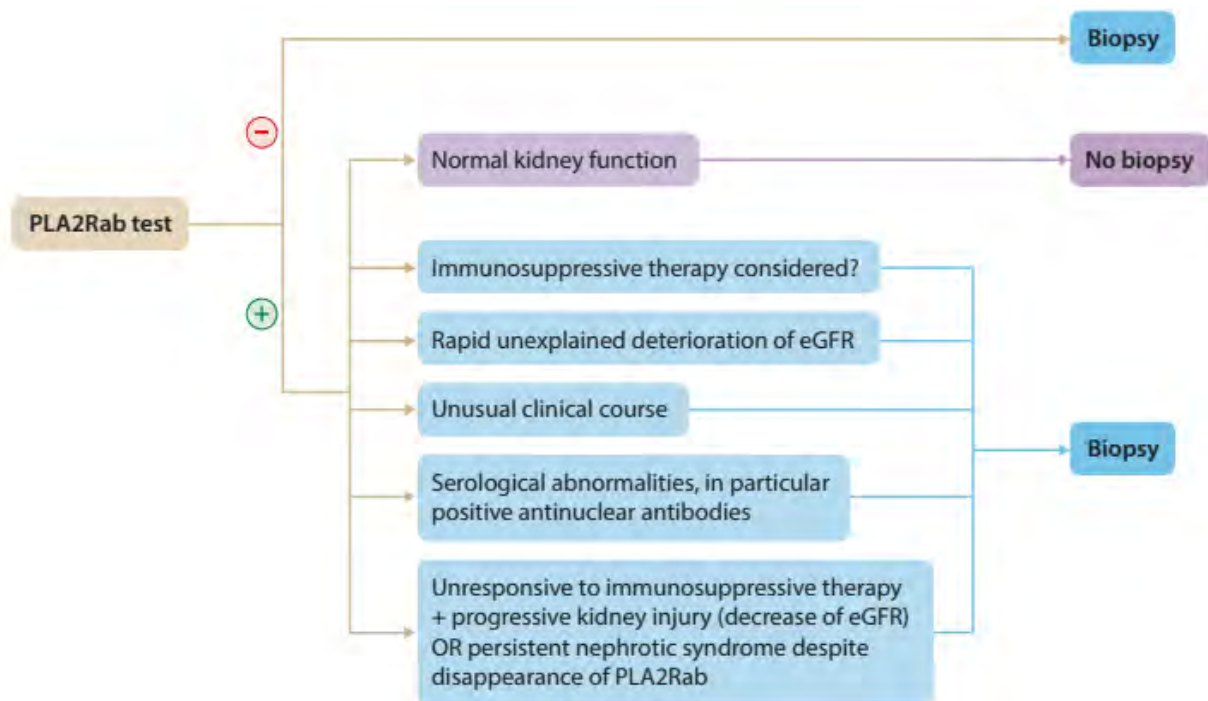
eGFR, estimated glomerular filtration rate; PLA2Rab, antibodies against the M-type phospholipase-A2-receptor
*In making a decision to perform a kidney biopsy, the risks of a biopsy must be taken into account. The decision is based on patient and physician preferences. This decision to perform a kidney 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.

Practice Point 3.1.2. Patients with MN should be evaluated for associated conditions, regardless of whether PLA2Rab and/or TSHD7Aab are present or absent. (Figure MN3)

Figure MN3. Evaluation of patients with MN for associated conditions*

HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NSAIDs, nonsteroidal anti-inflammatory drugs

*Patient with MN should be evaluated for associated conditions, independent of the presence or absence of PLA2Rab or TSHD7Aab

†Varies per country; the yield of cancer screening is not very high especially in younger patients. Many centers will perform chest X-ray or CT scan, look for iron deficiency, and require the patients to have to participate in the national screening program for breast and colon cancer; a PSA test is done in adult males >50-60 years.

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 (Table MN1).

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. Table MN1 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.

Table MN1. Clinical criteria for assessing risk of progressive loss of kidney function[‡]

Low risk	Moderate risk	High risk	Very high risk
• Normal eGFR, proteinuria <3.5 g/d and/or serum albumin >30 g/L	• Normal eGFR, proteinuria >4 g/d and no decrease >50% after 6 months of conservative therapy with ACEi/ARB • PLA2Rab <50 RU/ml[†] • Mild low molecular weight proteinuria • Selectivity index <0.15 • U IgG <250 mg/d	• eGFR <60 ml/min/1.73m²[2*] • Proteinuria >8 g/d for >6 months • PLA2Rab >150 RU/ml[†] • High low molecular weight proteinuria • U IgG >250 mg/d • Selectivity index >0.20	• Life-threatening nephrotic syndrome • Rapid deterioration of kidney function not otherwise explained • High low molecular weight proteinuria in two urine samples collected with interval of 6–12 months

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; IgG, immunoglobulin G; PLA2Rab, antibodies against the M-type phospholipase-A2-receptor

*Most studies have used SCr values to guide management, and SCr values >1.5 mg/dl are often used to define kidney insufficiency. An eGFR value of 60 ml/min/1.73 m² 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 reflects an eGFR of 50 ml/min/1.73 m² in a 60-year-old male patient and 37 ml/min/1.73 m² in a 60-year-old female patient. Thus, when using eGFR in risk estimation, age should be taken into account.

†Cut-off values are not validated. PLA2Rab should be measured at 3- to 6-month intervals, the shorter interval being performed in patients with high PLA2Rab levels at baseline. Changes in PLA2Rab levels during follow-up likely add to risk estimation. Disappearance of PLA2Rab precedes clinical remission and should lead to refraining from additional therapy. Detailed data are lacking.

‡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.

There are caveats to the evaluation of risk in MN. In most patients, it is reasonable to wait six months for spontaneous remission while using maximal antiproteinuria therapy. High levels of proteinuria, PLA2Rab, or low molecular weight (LMW) proteinuria should lead to re-evaluation earlier than six months. Patients with deteriorating kidney function, 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.[140] A survey of the literature shows that there is a 45% chance of spontaneous remission in patients with proteinuria >4 g/d after six months of conservative therapy,[141] a 34% chance of spontaneous remission in patients with proteinuria >8 g/d for more than six months,[142] a 25% to 30% chance despite high urinary excretion of LMW proteins,[143] a 17% chance in patients in the upper tertiles of PLA2Rab levels,[144] and a 20% chance in patients with PLA2Rab levels > 275 RU/ml.[145] 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).

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 MN4).**

Figure MN4. Risk-based treatment of MN
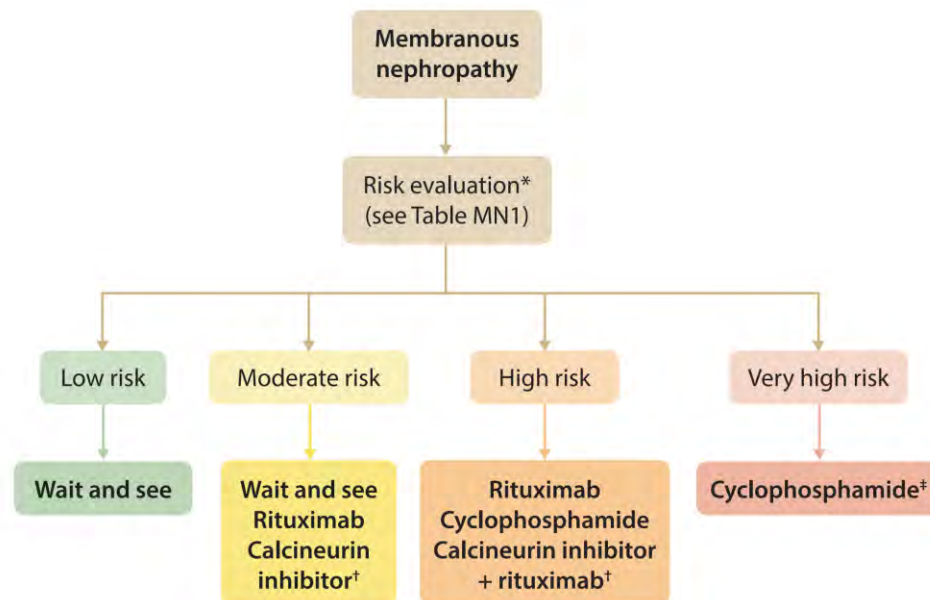
*See Practice Point 3.2.1 and Table MN1 for a detailed description of risk evaluation.
†CNI monotherapy is considered less efficient. Treatment with CNI for 6-12 months with rapid withdrawal is associated with a high relapse rate. Still, its use may be considered in patients with normal eGFR and moderate 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 six months of treatment with CNI is advised, with the possible exception of patients with documented disappearance of PLA2Rab after CNI treatment.
‡There is insufficient evidence that rituximab used in standard doses prevents development of kidney failure. In patients who do not tolerate or can no longer use cyclophosphamide, consultation with an expert center is advised.

Practice Point 3.3.2. Immunosuppressive therapy is not required in patients with MN, proteinuria <3.5 g/d, and eGFR >60 ml/min/1.73 m².

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).

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 high level of antiPLA2Rab 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 unless 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, and very high risk of progressive loss of kidney function (see 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 steroids for six months, or tacrolimus-based therapy for at least six months, with the choice of treatment depending on the risk estimate (Table MN1 and Figure MN4)** *(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 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 algorithm is illustrated in figure MN4. Details of commonly used treatment regimens are shown in Table MN2.

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 CNI 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 CNI 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 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 low quality, the toxicity profile warrants that cyclophosphamide-based immunosuppressive treatment should be restricted to high-risk patients.[146] Cyclophosphamide is preferred over chlorambucil. The evidence supporting cyclophosphamide over chlorambucil is not strong, but one RCT[147] 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.[148, 149]

Quality of evidence

The ERT has evaluated the quality of the evidence based on RCTs. The quality of the evidence for the use of oral alkylating agent compared to placebo/no treatment or steroids from the RCTs is considered moderate because of a serious risk of bias and lack of blinding. (Table S8[140, 150-159]) Alkylating agents were the only agents that were studied in trials that evaluated critical outcomes such as all-cause mortality and ESKD.

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

For rituximab, the GEMRITUX RCT examined the use of rituximab plus supportive therapy compared with supportive therapy alone (Table S9[160, 161]). The MENTOR trial compared rituximab with cyclosporine. For efficacy outcomes such as complete remission, the quality of the evidence is considered low[161] or moderate,[162] because of serious imprecision. There is low quality in the evidence for outcomes such as infection because of very serious imprecision (wide confidence intervals that indicating less certainty in effect) (Table S10[160, 162]).

The quality of the evidence from RCTs examining the use of CNI compared with placebo, no treatment, steroids, or alkylating agents is considered low, as there is imprecision with wide confidence intervals that indicate appreciable benefit and harms, and insufficient follow-up for clinical outcomes (all-cause mortality, ESKD) (Table S11 and Table S12[140, 151, 155, 160, 163-170]). The trials that have sufficient follow-up for complete remission have very

serious study limitations and very serious concerns about 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 ESKD, evidence cannot be limited to data from RCTs. Therefore, the Work Group has used information from non-RCTs and cohort studies to adjust the evidence. The Work Group emphasizes the need to use the evaluation of risk factors, which enable identification of high-risk patients with reasonable accuracy (see Practice Point 3.2.1). Based on the RCTs and cohort studies, there is strong evidence that alkylating agents reduced the risk of ESKD. There is moderate-quality evidence that alkylating agents are effective when used according a restrictive treatment strategy, and in patients with documented kidney function deterioration. There is no evidence that rituximab or CNI reduce the risk of kidney failure. There is moderate-quality evidence that rituximab or CNI increase complete and partial remission rate. There is evidence that complete remission (moderate quality) and partial remission (low quality) can be used as surrogate end-point 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 CNI. The use of CNI is associated with a high relapse rate. There is moderate-quality evidence that remissions are more persistent after rituximab in comparison with CNI.

Values and preferences

Immunosuppressive therapy is associated with side effects. Patients who are likely to have a favorable clinical course (see 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 CNI have fewer and less severe side effects than cyclophosphamide. Therefore, most physicians and patients will prefer initial treatment with rituximab or CNI 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 is associated with high morbidity and mortality. Moreover, most patients with kidney failure will prefer kidney transplantation, which will lead to life-time 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).

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Resources and other 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 health care 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 gender and race. Thus, this recommendation holds for patients of all gender and race.

Rationale

This recommendation replaces the 2012 KDIGO 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.[146] 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.

Table MN2. Commonly used treatment regimens for patients with MN§

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/m² given 1–4 times at weekly intervals
Tacrolimus	• Tacrolimus 0.05–0.1 mg/kg/d, target trough level 3–8 µg/ml, duration 12 months[†]
Cyclosporine	• Cyclosporine 3.5 mg/kg/d, target trough level 125–225 µg/ml[†]

*Consider repeating after six months in patients with persistent nephrotic syndrome, stable eGFR, especially if PLA2Rab remained positive.

†Cyclosporine and tacrolimus are often given in combination with prednisone in a dose of 10 mg/day. After four 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 six months versus 24 months of tacrolimus and prednisone.[171] Remission rates after six months were comparable (18/20 versus 18/22), however persistent remission after 24 months was observed in only 9/18 patients treated for six 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.

‡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 end-points. Older RCTs using i.v. cyclophosphamide that included patients with deteriorating eGFR were negative.[172, 173] 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 childhood wish).

§Mycophenolate mofetil is not discussed. The 2012 KDIGO guideline argued against the use of MMF monotherapy in patients with MN. This still holds and is based on the results of one RCT.[174] In this study in 36 patients, MMF monotherapy for 12 months did not increase remission rate (37% vs. 41%). MMF in combination with corticosteroids, is more effective. Small RCTs compared MMF and steroids with either alkylating agents[175, 176] or calcineurin inhibitors[177, 178]. 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.[179] A more detailed evaluation showed that immunological remissions were less likely to occur with MMF.[180] The dose of MMF could be the most relevant variable; studies in lupus nephritis have used higher dosages (3 g versus 2 g), and in patients with SSNS relapse rate was lower in patients with higher drug concentrations.[181]

Practice Point 3.3.4. Longitudinal monitoring of PLA2Rab levels at three and six 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 (Figure MN5).

Figure MN5. Immunological monitoring in MN after start of therapy

PLA2Rab, antibodies against the M-type phospholipase-A2-receptor

*A large decrease in PLA2Rab levels may indicate a good clinical response. Although there are no defined cut-off values, many experts consider reductions of 50-90% to represent a large decrease in PLA2Rab levels.

†This algorithm is simplified to allow easy decision-making. The course may be less well-defined or more difficult to interpret in many patients. However, if it is impossible to classify a patient as a good responder or resistant to disease, we suggest consulting an expert center.

‡See text for current treatment schedules. NB: the cumulative dose of cyclophosphamide should not exceed 25 g (approximately six months of therapy at a dose of 1.5 mg/kg/day). Lower doses (maximum 10g) must be used in patients who wish to conceive. CNI are unlikely to induce late immunological remission; in patients with persistent PLA2Rab, 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.

3.4. Special situations

Practice Point 3.4.1. Algorithm for the treatment of patients with MN and initial relapse after therapy (Figure MN6)

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Figure MN6. Management of initial relapse after therapy

*The definition of relapse is variable. Some authors define relapse after remission as an increase in proteinuria >3.5 g/day 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 and 3.5 g/day 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.

†Immunological monitoring is of particularly great value in these situations. If, in the period of "clinical remission", PLA2Rab were still positive, this would be evidence for resistant disease. Therefore, in patients with positive PLA2Rab, it is advised to evaluate PLA2Rab at the time of remission and relapse. The course of PLA2Rab 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 25 g to limit risk of malignancies.

Details of commonly used treatment regimens are shown in Table MN2.

Practice Point 3.4.2. Algorithm for management of patients with treatment-resistant membranous nephropathy (Figure MN7)

Resistant disease is defined as persistent NS after immunosuppressive therapy. It is important to perform a proper evaluation of these patients, i.e., measure PLA2Rab in PLA2Rab-associated MN. Disappearance of the antibodies most commonly precedes clinical remission. It is advised to wait at least six to 12 months after antibody disappearance before evaluation of treatment response. Alternatively, persistent proteinuria in parallel with persistent or increasing antibody levels, defines resistance.

Figure MN7. Management of resistant disease[§]

CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate

*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 FSGS. This would be further supported by the disappearance of PLA2Rab. In patients with persistent proteinuria with normal or near-normal serum albumin levels or patients with persistent proteinuria despite loss of PLA2Rab, a kidney biopsy should be considered to document active membranous nephropathy.

†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 PLA2Rab should be evaluated after three months. Cyclophosphamide treatment should take into account the maximal tolerable dose: the cumulative dose should not exceed 10 g if preservation if fertility is required. The cumulative dose should not exceed 25 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 be consulted with an expert center. These centers may choose experimental therapies (bortezomib, daratumumab, antibody to CD38 antibody, and belimumab) or a higher dose of conventional immunosuppressive therapy.

§Details of commonly used treatment regimens are shown in Table MN2.

Practice Point 3.4.3. Evaluation of a kidney transplant recipient with MN (Figure MN8)

Figure MN8. Evaluation of a kidney transplant recipient with MN

AUC, area under the curve; MN, membranous nephropathy; PLA2Rab, antibodies against the M-type phospholipase-A2-receptor; THSPD7A, thrombospondin type-1 domain-containing 7A

*Limited data available, but the same algorithm likely applies to THSD7A-associated MN.

Pre-transplant evaluation

It is important to determine if the patient's MN is related to PLA2Rab. The presence of antiPLA2Rab in old or recent serum or detection of the PLA2R antigen in the native kidney biopsy confirms a diagnosis of PLA2R-associated MN. The absence of antibodies at the time of transplantation in a patient with PLA2R-associated MN predicts a low risk of recurrence. In contrast, if antiPLA2Rab are present, the risk of recurrence is high(er). Although studies have suggested that higher PLA2Rab levels (>45 RU/ml) are associated with increased risk, there

are insufficient data to define a cutoff value. Although data on THSD7A and kidney transplantation are lacking, it is likely that the same algorithm can be used to evaluate patients with THSD7A-associated MN.

Peri- and posttransplant evaluation

There is 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 PLA2Rab, proteinuria should be evaluated monthly for at least six to 12 months after transplantation. A kidney biopsy is needed when proteinuria exceeds 1g/d. In patients with PLA2R-associated MN, regular measurement of antiPLA2Rab after kidney transplantation is advised in the first six to 12 months after transplantation. The frequency of monitoring may vary from once per month in patients with high titers pretransplant to once per three months in patients without measurable antiPLA2Rab 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 antiPLA2Rab, and in such cases performing a kidney biopsy in patients with proteinuria 0.3 to 1.0 g/d can be considered.

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

Practice Point 3.4.4. Algorithm for management of children with MN (Figure MN9)

Figure MN9. Management of children with MN

Perform a kidney biopsy

Treatment peculiarities in children vs adults:
• Wait and see strategy with supportive therapy alone is usually not adopted in children
• Children with MN are usually treated with prednisone for at least 8–12 weeks at doses used for idiopathic nephrotic syndrome Rituximab or calcineurin inhibitors are also employed at standard doses

No evidence to guide management in children with MN

Exclude secondary forms (most frequently systemic lupus erythematosus or chronic HBV, rarely neoplasia)
If possible, measure PLA2rab and THSPD7Aab titers
• If positive, their titers can be used to confirm remission and predict relapse
• If negative, especially in children < 6 years, consider role of immune response to cationic bovine serum albumin

Children with MN should be treated in an expert center

HBV, hepatitis B virus; MN, membranous nephropathy; THSPD7Aab, Antibodies against thrombospondin type-1 domain-containing 7A

Practice Point 3.4.5. Prophylactic anticoagulant therapy in patients with membranous nephropathy and nephrotic syndrome should be based on an estimate of the risk of thrombotic events and the risk of bleeding complications (Figure MN10).

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 six-to-twelve months after onset of disease. Thus, it is pivotal to discuss the need of anticoagulant therapy at the time of diagnosis

Figure MN10. Anticoagulant therapy in patients with MN
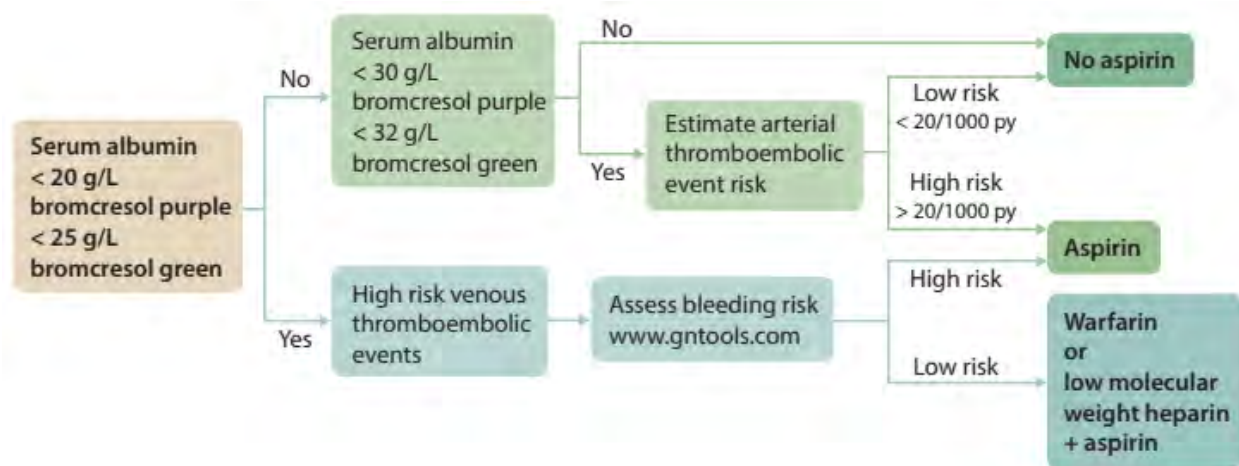
Adapted from Hofstra, Julia M. *et al*. Kidney International; 89 (5): 981 - 983)
Proposed algorithm for anticoagulant therapy in patients with membranous nephropathy
This algorithm provides guidance for the clinicians. The proposed cut-off values are based on expert opinion. When considering anticoagulant 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 realize that there is large bias between the serum albumin assays (van de Logt KI 2019). Serum albumin of 25 g/l with bromocresol green (BCG), ~20 g/l with bromocresol purple (BCP), or immunonephelometry. It is likely that most studies have used BCG assay. Consider using 25 g/l as threshold when using BCG and 20 g/l when using BCP or immunonephelometry.
2. Assess risk of venous thrombosis and risk of bleeding (www.gntools.com).
3. Patients with membranous nephropathy and nephrotic syndrome are also at risk of developing arterial thrombotic events. The risk of arterial thrombotic event is dependent on age, history of previous events, diabetes, eGFR, smoking, and severity of nephrotic syndrome. Risk assessment can be done using the Framingham risk score, and including previous events and proteinuria. (Hofstra KI 2016).
4. Use of aspirin is insufficient to prevent VTE; use of warfarin is sufficient to prevent ATE.
5. Treatment with warfarin: There is more INR variability in nephrotic syndrome and low eGFR; increased risk of thrombosis immediately after starting high-dose warfarin. Consider starting anticoagulation therapy with low-dose molecular weight heparin and then folding-in warfarin and, when therapeutic, stop the heparin. A good alternative is to use low-dose LMW heparin + aspirin for a period of three months before switching to warfarin, allowing to judge the course of proteinuria (Medjeral-Thomas CJASN 2014).
6. Steroids increase the risk of thrombosis; thus, anticoagulant therapy should not be omitted in patients who start prednisone therapy.

RESEARCH RECOMMENDATIONS

Diagnosis

- Evaluate accuracy of PLA2Rab and THSD7Aab in diagnosing MN; for how long, positive serology precedes the development of the disease with clinical symptoms?
- Compare the different techniques for the evaluation of PLA2Rab-associated MN, and assess accuracy, optimal cut-off levels for the diagnosis of MN.
- Identify additional antigens in the about 20% of patients double-negative for PLA2R and THSD7A.

Prognosis

- Evaluate the accuracy of PLA2Rab levels in prediction outcome in patients with MN; consider outcome in untreated patients (spontaneous remission) and in patients treated with different immunosuppressive therapy. Determine optimal cut-off levels.
- Evaluate the predictive value of changes on PLA2Rab levels over a three- to six-month period in patients with MN both untreated and treated with immunosuppressive therapy. Define cut-off values that provide highest accuracy.
- Evaluate the accuracy of 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 cut-off 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 PLA2Rab level.
- Establish a genetic and clinical risk score for recurrence after transplantation.

Treatment

- Should we aim at complete immunological remission, or is a substantial reduction of PLA2Rab level sufficient?
- Evaluate efficacy of CNI 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 very high risk of disease progression.

- Evaluate efficacy of plasma cell-directed therapy in patients with MN resistant to standard immunosuppressive therapy.
- Evaluate the potential and applicability of antigen targeted therapy.

<u>Specific situations</u>
- 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 NS, aged 1 to 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 to such young children is beyond the scope of this work.

4.1. Diagnosis

Practice Point 4.1.1. The definitions relating to the nephrotic syndrome in children are based on the clinical characteristics outlined in Table NS1.

Table NS1. Definitions relating to NS in children aged 1 to 18 years

- **Nephrotic-range proteinuria:** first morning or *24 hr urine PCR ≥2 mg/mg (or 200 mg/mmol or 3+ dipstick)

- **NS:** nephrotic-range proteinuria and either hypoalbuminemia (serum albumin <3 g/dL) or edema when albumin level is not available

- **Complete remission:** first morning or *24 hr urine PCR ≤0.2 mg/mg (or 20 mg/mmol or negative or trace dipstick) on three or more consecutive occasions

- **Partial remission:** first morning or *24 hr urine PCR >0.2 but <2 mg/mg (or >20 and <200 mg/mmol) and, if available, serum albumin ≥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 or ≥1+ for 7 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 or <4 relapses per 12 months

- **Frequent relapsing NS:** ≥2 relapses per 6 months or ≥4 relapses per 12 months

- **Steroid-dependent NS:** 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 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 steroid-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

*To rule out orthostatic proteinuria, the first-morning urine should be collected separately for assessment
†van der Watt, Ped Nephrol 7th ed. 2016)

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, but is reserved for children with resistance to therapy or an atypical clinical course.

NS is the most frequent glomerular disease in children, with an incidence of 1.15 to 16.9 per 100.000 children.[182] Before the availability of antibiotics and corticosteroids, about 40% of children with NS died of infection, kidney failure, and occasionally thromboembolism.[183] If the children survived, sustained spontaneous remission was observed only after years of disease activity. Antibiotics reduced mortality, but it was the introduction of corticosteroid use in the 1950s that changed the natural history of the condition.[183] Since the 1970s, following onset of disease, children are treated with a standard dose of corticosteroids. 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) have 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 corticosteroids and to second-line steroid-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% to 25% of cases, it may progress to adulthood, maintaining the peculiar features of the childhood-onset NS with rapid response to corticosteroids in case of relapse. Moreover, a small percentage of children may, in subsequent relapses, become secondarily steroid-resistant. These have a high chance both of progressing to kidney failure and to relapse post-transplantation.

A kidney biopsy is therefore performed at onset only in children with atypical features (see Table NS4) and in all children with steroid-resistance. Subsequently, during the disease course, it may be advisable to perform or repeat a kidney biopsy in children who have had a prolonged (>2 to 3 years) exposure to CNIs or in children with 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 corticosteroids and the safest and most effective steroid-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 of the side effects of prolonged proteinuria and treatment with dialysis and transplantation must be performed in centers with specific expertise in pediatric nephrology.

4.3. Treatment
A schematic approach to treatment is outlined in Figure NS1.

Figure NS1. Treatment algorithm for NS in newly nephrotic child[†]*
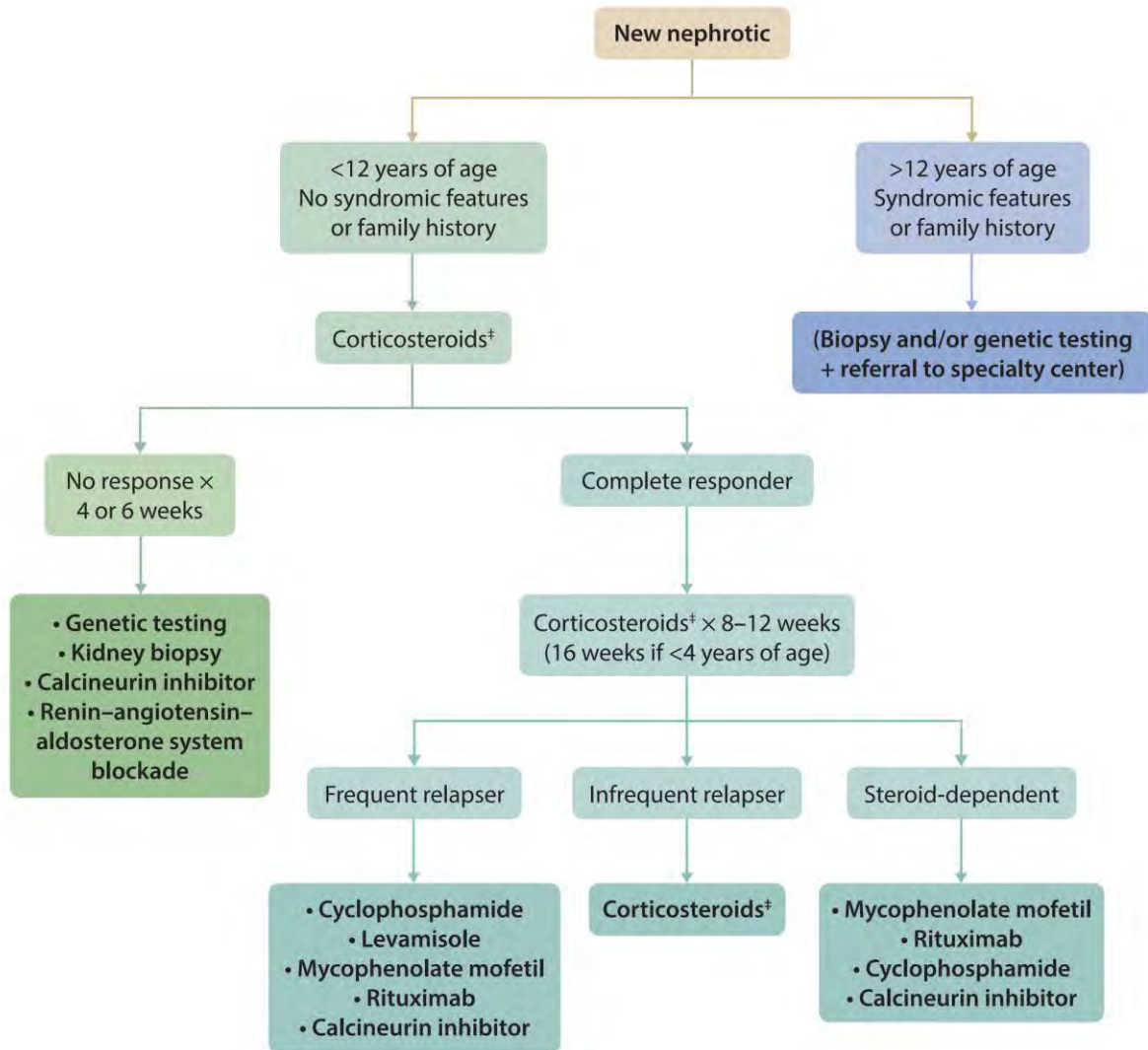
*Therapeutic approach to nephrotic syndrome in children from onset

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4.3.1. Initial treatment of NS in children

> **Recommendation 4.3.1.1. We recommend that oral corticosteroids be given for eight weeks (four weeks of daily corticosteroids followed by four weeks of alternate-day corticosteroids) or 12 weeks (six weeks of daily corticosteroids followed by six weeks of alternate-day corticosteroids)** *(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 to 12 weeks) corticosteroid treatment, and a relatively higher value on high-quality evidence suggesting prolonged (>12 weeks) corticosteroid 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 corticosteroid therapy may delay the time to first relapse as compared to eight to 12 weeks of treatment.

In terms of oral corticosteroids, prednisone and prednisolone are equivalent, used in the same dosage, and are both supported by high-quality data. All later references to oral corticosteroids 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.[184, 185] An RCT comparing single versus divided dose showed that both are equivalent in terms of time to remission and of number of subsequent relapses.[186] 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.[183] With the introduction of corticosteroid 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 that they experience. The majority of initially steroid-sensitive patients 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 corticosteroids,[182, 187] preserving steroid sensitivity, and prolonging remission.

Since publication of the previous 2012 KDIGO guidelines, four RCTs have evaluated the optimal corticosteroid dosage for treatment of the initial episode of SSNS in children: two studies comparing 12 weeks to six months, one study comparing eight weeks to six months and one comparing eight weeks to four months.[188-190] These studies show that extending initial corticosteroid treatment from eight to 12 weeks to six 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.[191] 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 both for studies comparing 12 weeks to eight weeks of therapy and also for studies comparing five to six months to eight 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 eight weeks to four months.[192]

In terms of harms, Sinha *et al.* showed that adverse effects related to corticosteroids (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 two treatment groups (12 weeks vs. six months).[188] Similar findings are reported by Yoshikawa *et al.* (median follow-up 36 to 38 months),[190] Teeninga *et al.* (median follow-up 47 months),[189] and Webb *et al.* (follow-up 24 months).[192] 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 corticosteroid 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 corticosteroid at onset.

Quality of evidence
There was moderate quality in the evidence from RCTs that compared corticosteroid therapy for 12 weeks or more duration compared with corticosteroid therapy of eight weeks duration (Table S13[190-201]). 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 sub-group 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 corticosteroid-related adverse events) were downgraded to low quality evidence because of study limitations and serious imprecision (wide CIs – indicating less

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certainty in effect), or serious inconsistency (substantial heterogeneity). However, there were fewer of these adverse events, hence, 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 corticosteroid 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 corticosteroids, 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 corticosteroids against the risk of under-treating the first episode, which may lead to relapse and a higher cumulative dose of corticosteroids, 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 corticosteroid dose over >12 months. This attitude, however, may have led to over-treating the first episode. Recent evidence indicates that prolonging corticosteroid treatment for more than 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 eight to 12 weeks of corticosteroids as initial treatment of NS, compared to a longer course of corticosteroids, another treatment, or to no treatment.

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

None identified. There is no data evaluating whether the best treatment approach could vary by sex or ethnicity.

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) corticosteroid treatment compared with no treatment, as well as a relatively higher value on evidence suggesting that prolonged (>12 weeks) corticosteroid 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 corticosteroid therapy may delay the time to first relapse as compared to eight to 12 weeks of treatment. Evidence is insufficient to choose between eight 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 eight to 12 weeks of corticosteroids as initial treatment of SSNS, compared to a longer course of corticosteroids, 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 four or six weeks. After four to six weeks, give alternate-day prednisone/prednisolone, 40 mg/m^2, or 1.5 mg/kg/d, for another four to six weeks.

Practice Point 4.3.1.2. In children who may be at higher risk of progressing to a frequently-relapsing or steroid-dependent form of nephrotic syndrome due to their young age at onset (1 to 4-6 years), prolonging treatment of the initial episode to 16 to 24 weeks may be beneficial in terms of preventing subsequent relapses with similar side effects.

Practice Point 4.3.1.3. Prolonging treatment of the initial episode to 16 to 24 weeks may be particularly helpful in younger children with a delayed response to prednisolone (i.e., remission in 10-15 days from treatment initiation), while even in younger patients (1-4 years old), a standard eight to 12-week prednisolone course may be preferable for patients who respond rapidly to prednisolone (i.e., in <7 days).

4.3.2. 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 corticosteroids. Half of these children will relapse infrequently. The remaining half of these children will experience frequent relapses (FRNS) or become steroid-dependent (SDNS).[202, 203] Many children relapse in response to an infectious trigger, but many others will have no identifiable trigger.[204] Prevention of relapse may reduce overall corticosteroid exposure and decrease the adverse effects of long-term corticosteroids 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.[205-208]

> **Recommendation 4.3.2.1. For children with frequently-relapsing and steroid-dependent SSNS who are currently taking alternate-day corticosteroids or are off corticosteroids, we recommend that daily corticosteroids 0.5 mg/kg be given during episodes of upper respiratory tract and other infections for five to seven days to reduce the risk for relapse (1C).**

This recommendation places a relatively higher value on the low-quality evidence that preemptive daily prednisolone reduces the risk of an 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 corticosteroids are administered daily for five to seven days at the onset of upper respiratory tract infection in children with FRNS or SDNS who are either not currently taking corticosteroids or taking alternate-day corticosteroids. In the most recent 2017 study by Abeyagunawardena *et al.*, 48 patients with SDNS (but off prednisone for at least three months) were randomized to receive either five days of daily prednisolone at 0.5 mg/kg at the onset of an upper respiratory tract infection or five days of placebo[209] A minority (34.4%) of the treatment group relapsed, whereas 40.6% of the control group experienced a single relapse, and 18.8% had two relapses. These short courses of preemptive corticosteroid treatment may avert the need for longer courses of corticosteroids, therefore reducing toxicity.

Although higher doses of corticosteroids 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 those receiving alternate-day corticosteroids.

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 (Table S14[191, 209-212]). Relapse and rate of infection-related relapse were the

only critical and important outcomes examined in these studies. The quality of the evidence was downgraded because of study limitations and serious imprecision, as there was only one RCT that examined each of these outcomes.

Abeyagunawardena 2017 is a cross-over study that has not reported sufficient data to be included in a paired analysis; therefore, no PICO table has been presented.[209] Abeyagunawardena 2017 was downgraded due to a 31% attrition for patients not completing both parts of the cross-over study, and serious imprecision as it is the only trial that examined prednisone versus placebo in children with SSNS after three months off prednisone therapy.

Values and preferences
The Work Group judged that avoiding relapse and the excess morbidity associated with subsequent prolonged high-dose steroid exposure would be critically important to patients. The Work Group also judged that the adverse effects associated with short-term increase from alternate-day to daily prednisone dosing or short-term reinstitution of steroids 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 corticosteroid 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 corticosteroids such as severe behavioral changes, sleep disturbance, obesity, or have comorbid conditions such as diabetes.

Resource use and costs
Corticosteroids are amongst the most widely available therapies for NS, while many other immunosuppressive treatments are either cost-prohibitive or not available. 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 2012 KDIGO guidelines suggested transitioning children with FRNS who were receiving corticosteroids on alternate days (or not receiving corticosteroids) to daily prednisone for five to seven days at the start of an infection. Since that publication, there have been several

clinical trials that have demonstrated up to a 30% reduction in relapses with this treatment approach, warranting an increase in the strength of this recommendation from weak to strong.

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

Practice Point 4.3.2.2. After achieving complete remission, reduce prednisone to 40 mg/m^2 or 1.5 mg/kg on alternate days for at least four weeks.

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

> **Recommendation 4.3.2.2. For children with frequently-relapsing nephrotic who develop serious corticosteroid-related adverse effects and for all children with steroid-dependent nephrotic syndrome, we recommend that corticosteroid-sparing agents be prescribed, rather than no treatment or continuation with corticosteroid 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 corticosteroids and efficacy of steroid-sparing agents in preventing relapse over 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 which are treatment-related. There are few studies that have compared steroids and steroid-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 are high in children who are not treated or fail to respond to any treatments.[213]

In a ten-year follow-up study of children with SSNS enrolled in clinical trial assessing the efficacy of cyclosporine for reducing relapse rate, at least half of the children evaluated experienced severe side effects of steroids including severe growth failure, obesity, and low bone density. These findings were attributed to corticosteroid exposure for frequent relapses following the discontinuation of cyclosporine at two years.[206] 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 corticosteroid exposure.[207, 214, 215]

To avoid or mitigate corticosteroid-related adverse effects, children with FRNS or SDNS require other agents, including alkylating agents (cyclophosphamide), levamisole, rituximab, mycophenolate mofetil (MMF), and CNI (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 corticosteroids 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 six and 12 months follow-up.[216]

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 steroid 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 steroid-sparing agents exist, including limiting the cumulative exposure of cyclophosphamide to <200 mg/kg and monitoring CNI and MMF drug levels.

Quality of evidence
The assessment of the quality of evidence focused on steroid-sparing agents individually, but overall quality was moderate. RCTs comparing alkylating agents, levamisole, or rituximab to placebo or corticosteroids 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. 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 steroid-sparing agents that have been examined more extensively have a higher quality of evidence. Many of the RCTs do no report long-term clinical outcomes, such as all-cause mortality and ESKD 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 steroids or placebo was moderate for the outcome relapse at six to12 months (study limitations) and low at 12 to 24 months (study limitations, serious imprecision from small numbers of patients and events) (Table S15[217-224]). Given, fewer patients in trials that examined relapse at 12 to 24 months, relapse at six to 12 months was considered the most critical outcome.

The quality of the evidence comparing levamisole with steroids or placebo or no treatment in patients with FRNS and SDNS was moderate from RCTs because there is only one RCT in patients with FRNS and one trial in patients with SDNS (Table S16[186, 223-231]).

There was low quality of the evidence from one RCT that compared MMF with levamisole (Table S17[223, 232]). The quality of the evidence was downgraded for important outcomes because of inadequate blinding of participants, study personnel, and outcome assessors, and imprecision (only one study).

One RCT compared cyclosporine combined with prednisone to prednisone alone in patients with SSNS (Table S18[223, 233, 234]). It is unclear how many patients had FRNS or SDNS in this population. The quality of the evidence in this trial was downgraded to low because of serious imprecision (only one study) and the indirectness of the study population.

The quality of the evidence for trials comparing rituximab with placebo or standard of care was moderate for the important outcome of relapse at three and six months because of serious imprecision (few patients), 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 (Table S19[223, 235-240]). For relapse at 12 months, the quality of the evidence was downgraded to low as there were only two studies and substantial heterogeneity was found (I^2=80%). The quality of the evidence for infection was very low because the confidence intervals were very wide, indicating appreciable benefit and harm.

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

Values and preferences
In the judgment of this Work Group, the adverse effects associated with prolonged corticosteroid exposure would be critically important to patients and their parents. The high morbidity associated with uncontrolled nephrosis and high frequency of relapsing disease for many children with FRNS off corticosteroids makes the option of non-treatment unfeasible. The Work Group also judged that the potential adverse effects of steroid-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 like drug-level monitoring and dose limitations. Overall, the Work Group judged that avoiding the adverse effects associated with prolonged corticosteroid exposure would be more important to patients and their parents than the potential adverse effects of steroid-sparing therapies.[241, 242]

Resource use and costs

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CNIs, alkylating agents, MMF, and rituximab are considerably more expensive than corticosteroids and may require ongoing clinical and/or laboratory monitoring. Some steroid-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 steroid-induced adverse events may offset the increased cost of steroid-sparing therapies.

Considerations for implementation

Relative efficacies of steroid-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 intravenous infusions are all factors that should be considered in treatment decision-making.

Rationale

The objective of limiting the long-term adverse effects of corticosteroids in children with FRNS and SDNS has been consistent across guidelines from multiple bodies in every geographic region. The 2012 KDIGO guidelines, 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 steroid-sparing therapies in children who are steroid-dependent and especially in those that have exhibited steroid toxicity.

Practice Point 4.3.2.4. Patients should ideally be in remission with corticosteroids prior to the initiation of steroid-sparing agents such as cyclophosphamide, levamisole, MMF, rituximab, or CNIs. Coadministration of steroids is recommended for at least two weeks following initiation of steroid-sparing treatment.

Although the goal of steroid-sparing agents is to let the patients be free of corticosteroids, low-dose daily or alternate-day corticosteroids may still be needed to maintain remission in SDNS despite receiving corticosteroid-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 4.3.2.5. Cyclophosphamide and levamisole may be preferable steroid-sparing therapies in frequently-relapsing nephrotic syndrome.

Patients with frequent relapses might have a superior response to cyclophosphamide and levamisole compared to patients with steroid dependency.[243] Children with FRNS older than seven and a half years are more likely to experience a long-term remission treated with cyclophosphamide compared to children that are less than four years of age.[244] 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 200 mg/kg. For this reason, second courses of alkylating agents are not recommended. Adverse effects of levamisole are uncommon and mild, including leukopenia and GI disturbance. Data comparing cyclophosphamide and levamisole is quite limited and unable to determine efficacy of one therapy over the other in regard to relapse rates after treatment discontinuation or frequency of infection events.[245] Compared to placebo, levamisole has been shown to delay the time to relapse post-termination of corticosteroids and allowed 26% of the patients treated with levamisole to be relapse-free for at least a year compared to only 6% of patients in the placebo group. [229] Adverse events in this trial were few and mostly limited to neutropenia that easily reversed with discontinuation of therapy. MMF was not superior to levamisole in a trial of 139 children with FRNS and SDNS in regards to sustained remission off corticosteroids, although it showed a trend towards superiority in children with more severe forms (SDNS).[232]

Practice Point 4.3.2.6. MMF, rituximab, cyclophosphamide, and CNIs may be preferable steroid-sparing therapies in children with steroid-dependent nephrotic syndrome.

MMF

Variable outcomes for maintaining remission off steroids have been reported in children with FRNS or SDNS treated with MMF, and these are mostly limited to retrospective observational data. A recent randomized controlled crossover trial 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 (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.[181]

Post hoc analysis of the Gellerman *et al*. study comparing MMF versus cyclosporine provided data that targeting higher area under the curve (AUC) levels may reduce relapses on therapy. 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-randomized studies have suggested a favorable response to rituximab in patients with SDNS and FRNS.[236, 238, 240, 246] 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.[247] In a randomized non-inferiority trial of 30 children with SDNS, all but one child in the placebo arm relapsed within six months compared to a median time to relapse of 18 months in the children treated with rituximab (95% CI 9, 32 months).[240] 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 (IQR 2, 4) to 0.5 (IQR 0, 1; p<0.001) during one year of follow-up in 44 children and adults with either SDNS or FRNS in the NEMO trial.[246]

Reported rates of adverse events such as infection have been lower in children with FRNS treated with rituximab versus placebo. In the Ravani trial, nausea and skin rash during infusion were common.[240] 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 one 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 non-serious (52 vs. 127, p<0.001) adverse events.[248]

Cyclophosphamide

In 143 children treated with oral cyclophosphamide for FRNS, SDNS, or evidence of steroid toxicity, sustained remission was more frequent in children with FRNS versus SDNS [HR 1.72 (95% CI 0.99, 2.98), p=0.05].[249] Nonetheless, there may be a role for this treatment in some patients with SDNS, especially in areas of the world where other steroid-sparing agents are not accessible. In 90 children with SDNS who received a single course of oral cyclophosphamide (2 mg/kg/d for 10 to 12 weeks), a cumulative remission status of 57% at one year was achieved.[244] Younger age at presentation and patients with steroid dependence requiring higher doses (>1 mg/kg/d of corticosteroids) to maintain remission appear to associate with less sustained remissions following treatment with cyclophosphamide.[250]

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 six and 12 months of treatment. Tubulointerstitial lesions, however, have been reported in 30% to 40% of children treated more than 12 months with cyclosporine, and up to 80% of those treated more than four years. The optimal duration of treatment based on these data for cyclosporine is not clear, and

data for tacrolimus is even more sparse. 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.

Table NS2. Steroid-sparing therapies in children with SSNS

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 corticosteroids. 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 corticosteroid 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/m²/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
• Rituximab	375 mg/m² 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 corticosteroid-sparing oral agents, and/or who have serious adverse effects of therapy. Current trials report 1 to 4 doses of rituximab. There is insufficient data to make a recommendation for specific number of needed doses. Where available, CD20 levels should be monitored. 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
• 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

ANCA, Anti-neutrophil cytoplasmic antibodies; CBC, complete blood count; CNI, calcineurin inhibitor
*Gellerman et al.

In a child who does not achieve complete response to corticosteroids at four 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 six weeks (defined as late responders). Those who do not will be defined as SRNS patients at six weeks. Between four and six weeks from the start of corticosteroid therapy, a RASi should be started and corticosteroid administration should be continued. Intravenous methylprednisolone (one dose daily for three 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 where 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. Among those children without a genetic cause of SRNS, a substantial proportion will respond to 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. Rarely children with an initial diagnosis of SSNS experience a subsequent relapse that does not respond to four weeks of corticosteroid therapy (secondary SRNS). In these cases, often multi-drug resistance develops, leading to kidney failure and to a high risk of post-transplant recurrence.

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 intravenous 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 corticosteroids) increases the likelihood of remission among patients as compared to no treatment.[183, 251-254] Investigators with the European based PodoNet Registry reported almost 62% of the 1174 children with SRNS followed in a 2015 study received cyclosporine.[255] 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.[256] In this study, no difference in remission rate between the two 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 associated with fewer adverse effects over intravenous or oral cyclophosphamide, MMF, leflunomide, chlorambucil, azathioprine, and placebo or nontreatment.[257]

No role for cyclophosphamide or rituximab has been identified in children with SRNS.[217, 246, 258] Partial and complete remission occurs significantly more frequently in children with SRNS who receive cyclosporine or tacrolimus compared to those receiving intravenous cyclophosphamide.[259, 260] A recent RCT in 60 children who had achieved at least a partial remission with six 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).[261]

Differences in efficacy between cyclosporine and tacrolimus have not been found, yet the body of literature for cyclosporine is more extensive.[262] 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 two 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 one comparison (cyclosporine vs. MMF with dexamethasone) having a higher quality of the evidence rating (moderate quality of the evidence), the majority of comparisons were of low quality of the evidence; hence, the overall quality of the evidence was rated as low.

In the three 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) (Table S20[252-254, 263]). The effects on adverse events, such as infection, were unclear because of very low quality in the evidence and given the few number of participants (n=17) that were 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 two RCTs that compared CNIs with intravenous cyclophosphamide (Table S21[259, 260, 263]). 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 (Table S22[256, 262-264]). 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 to maintain disease remission in 60 participants (Table S23[261, 263]). The quality of the evidence was low because of a lack of blinding in the study and serious imprecision (few 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,[255] 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.

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 non-treatment.

Considerations for implementation
Targeted genetic testing where available may be useful in some patients (see Table MN3). Identification of causative podocyte-specific mutations may avoid unnecessary cumulative exposure to immunosuppressive therapies. 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 steroids, tacrolimus or cyclosporine, and MMF.[255] While treatment response rates among patients with podocyte-specific mutations are low, the benefit of mitigating nephrotic complications in children with at least a partial response may be valuable. 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 six months (Table NS3).

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 is sparse and of low quality, and, therefore, decision of one over 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 that is associated with untreated SRNS.

Table NS3. Treatment of SRNS in children

Treatment	Dose and duration	Clinical tips
Calcineurin inhibitors	• Oral cyclosporine 5 mg/kg/d (starting dose) in two divided doses. Target 12 hour 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 hour 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
Steroids	• i.v. Methylprednisolone bolus of 500 mg/m²/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 corticosteroids in combination with CNIs to induce remission. No studies compare the outcomes between children treated with CNIs alone or in combination with low dose corticosteroids
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/m²/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/m² 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

CNI, calcineurin inhibitor; i.v., intravenous; SRNS, steroid-resistant nephrotic syndrome

4.5. Special situations

Practice Point 4.5.1. Table NS4 outlines the general principles in children with nephrotic syndrome.

Table NS4. General principles in children with NS

Indication for kidney biopsy	• Children presenting with nephrotic syndrome ≥ 12 years of age • Steroid-resistant nephrotic syndrome or subsequent failure to respond to corticosteroids in steroid-sensitive nephrotic syndrome (secondary steroid-resistant nephrotic syndrome) • A high index of suspicion for a different underlying pathology (macroscopic hematuria, extra-kidney symptoms, 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 frequent relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome 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
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

[1] Gulati S. Nephrol Dial Transplant. 2005; 20(8): 1598-603
[2] Gruppen MP. Nephrol Dial Transplant. 2013; 28(8):2099-106

RESEARCH RECOMMENDATIONS

RCTs are needed to:

- Compare eight versus 12 weeks of prednisone for initial therapy: explore further shortening of the initial corticosteroid regimen and assess combination therapy with a steroid-sparing agent at disease onset.
- Optimize subsequent treatment of SSNS after relapse in different forms of disease
- Optimize dosing regimen for corticosteroid treatment at the start of an infection.
- Define the optimal dosing and choice of corticosteroid-sparing agents in FRNS and SDNS.
- Evaluate the optimal duration of corticosteroid 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 corticosteroids and other immunosuppressives in SSNS; determine the potential role of pharmacogenomics in treatment; identify biomarkers or genetic risk haplotypes to stratify disease subgroups.

CHAPTER 5. MINIMAL CHANGE DISEASE IN ADULTS

Minimal change disease (MCD) is a podocytopathy more commonly seen in children, but it also accounts for 10% to 25% of adult NS.[265] Most patients with MCD do not have an underlying cause. The pathogenesis of MCD is unclear, but evidence supports T-cell dysregulation driving the podocytopathy.[266] The effectiveness of B-cell depleting therapeutic agents also suggests a role for B cells in disease pathogenesis.[187] Rarely, Hodgkin's disease, and drugs such as lithium and non-steroidal anti-inflammatory agents may underlie MCD.[267] 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 only be diagnosed with a kidney biopsy.

MCD has a distinctive histology, and its presence cannot be deduced from clinical data alone. LM shows no glomerular lesions or only minimal mesangial prominence. Immunofluorescence microscopy is negative or shows low-intensity staining for C3 and/or IgM. EM demonstrates extensive foot process effacement but no electron-dense deposits, and in the presence of unremarkable light and IF 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 MCD patients who respond to corticosteroids, but less certain for patients who do not respond.

Corticosteroid-sensitive MCD rarely, if ever, progresses to kidney disease, although AKI due to high-grade proteinuria is relatively common.[268] Approximately 10% to 20% of adult MCD patients are corticosteroid-resistant.[269] On repeat biopsy, lesions of FSGS are seen in a significant number of such patients and are associated with a worse prognosis.[82, 268] The treatment of corticosteroid-resistant FSGS is discussed in Chapter 6.

5.3. Treatment
In general, adult MCD is similar to SSNS in children. However, response to corticosteroid treatment is slower than in children. There is a paucity of high-quality RCT evidence evaluating the effectiveness of corticosteroids 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 corticosteroids for initial treatment of MCD *(1C)*.**

This recommendation places a relatively higher value on low-quality evidence suggesting that high-dose corticosteroids 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 corticosteroid treatment.

Key information

Balance of benefits and harms

Although untreated MCD may undergo spontaneous remission, this is relatively uncommon. Approximately 50% to 60% of patients remit over two to three years of follow-up compared to a 30% spontaneous remission rate in MN over six months,[270, 271] and there is considerable morbidity associated with persistent nephrosis including infections,[272] thromboembolic events,[273] and hyperlipidemia.[274]

MCD is typically responsive to corticosteroids, with over 80% of patients achieving remission.[268, 275] Observational studies consistently report a high response rate to corticosteroids as the initial therapy for MCD among adults.[268, 269, 275-278] In a very early multicenter controlled study of corticosteroids compared to no treatment in 125 nephrotic adults (including 31 MCD patients defined by LM alone), those treated with at least 20 mg/d prednisone for at least six months showed an early and rapid decrease in proteinuria compared to the control group. However, by two and a half years, there was no difference in proteinuria or serum albumin in the two groups.[270] Similarly, in another RCT of 28 patients with MCD treated with an average of 125 mg prednisone every other day for two months, there was no difference in remission rates between the treated group and controls over 77 months of follow-up.[271] This 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 corticosteroid treatment.

In addition, numerous high-quality studies demonstrate that corticosteroids are effective for treatment of SSNS in children (discussed in Chapter 4). SSNS in children and adult MCD appear similar in terms of pathogenesis. Therefore, the benefits of corticosteroid treatment in children are likely to at least partially extend to adults. In children, several RCTs have shown excellent remission rates with corticosteroids administered for eight to 12 weeks.[188-190]

Therefore, in the judgment of the Work Group, the potential benefits of high-dose corticosteroid 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 corticosteroids is low (Table S24 and Table S25[271, 279-281]). These RCTs only include a small number of participants and have various study limitations that place them at a high risk of bias. Additionally, because of the small number of participants, the trials exhibit serious imprecision with wide confidence intervals indicating less certainty in effect on critical and important outcomes, such as all-cause mortality, doubling SCr, and complete remission.

Values and preferences

The Work Group judged that the potential benefits of corticosteroid 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 corticosteroid treatment, including precipitation/worsening of diabetes, psychiatric conditions, or bone loss, would be an important consideration for many patients. Although the quality of the evidence supporting corticosteroid 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.

Resources and other costs

Corticosteroids 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 drug available.[282]

Considerations for implementation

Adverse effects of corticosteroids 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 MCD1). There are no known race or gender 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 this should be a strong recommendation. In the opinion of the Work Group, the benefits of high-dose corticosteroids 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 corticosteroids and the evidence from large observational studies suggesting that corticosteroid 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 corticosteroids 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 MCD1)

Figure MCD1. Initial treatment of MCD in adults[*]
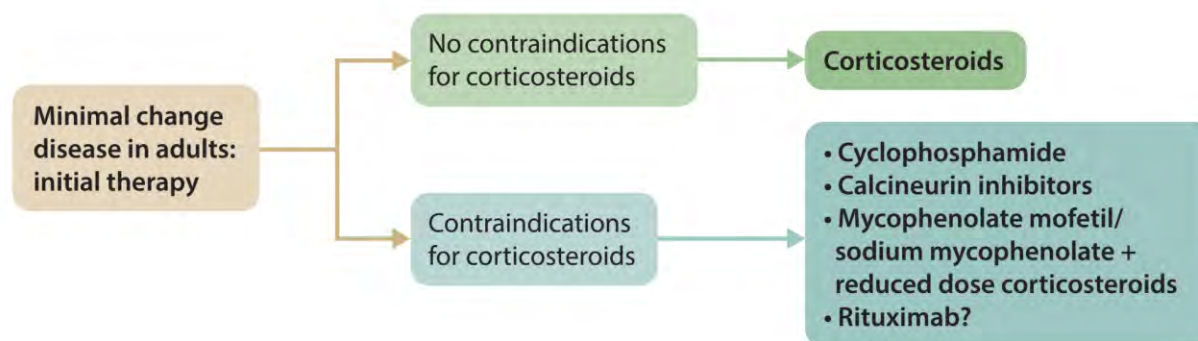
*The optimal corticosteroid regimen is not well-defined; however, suggested doses are outlined in Table MCD1

Table MCD1. Treatment of MCD in adults: Initial episode and frequently-relapsing (FR)/steroid-dependent (SD) MCD

Medication	Regimen	Remission rates (complete and partial)
Initial episode, corticosteroid 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 corticosteroids Oral cyclophosphamide Cyclosporine Tacrolimus	2–2.5 mg/kg per day for 8 weeks 3–5 mg/kg per day in divided doses for 1–2 years 0.05–0.1 mg/kg per day in divided doses for 1–2 years	75% 75% 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 • Cyclosporine • Tacrolimus	**Initial dose:** 3–5 mg/kg per day in divided doses for 1–2 years 0.05–0.1 mg/kg per day in divided doses for 1–2 years • If serum levels are being monitored, suggested initial levels: - Cyclosporine: 150–200 ng/ml - Tacrolimus: 4–7 ng/ml • After withdrawal of corticosteroids 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	70–90% 90%
Rituximab	**Induction regimens:** • 375 mg/m² weekly for 4 doses • 375 mg/m² × single dose; repeat after one week if CD19 cells >5/mm³ • 1 g/dose for 2 doses, 2 weeks apart **Relapse after induction:** • 375mg/m² × 1 dose or • 1g i.v. × 1 dose	70% (20% off all immunosuppression, 50% on one other immunosuppressive drug)
Mycophenolic acid analogues • Mycophenolate mofetil • Sodium mycophenolate	**Initial dose:** 1000 mg twice daily 720 mg twice daily • Attempt gradual taper and discontinuation of mycophenolic acid analogues after a minimum of one year of therapy if possible	

CNI, calcineurin inhibitors; MCD, minimal change disease
* Remission rates were not compared in head-to-head studies.

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Practice Point 5.3.2. High-dose corticosteroid 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 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 four weeks of corticosteroid, but an additional 10% to 25% may respond after a total of 16 weeks of treatment.[268, 277]

Practice Point 5.3.3. Begin tapering of corticosteroids two weeks after remission.

The optimal corticosteroid taper protocol after remission in adults is not known. Generally, tapering of corticosteroids is begun after achieving remission. In two RCTs in children, two to three months of initial prednisolone therapy was not inferior to six months of initial therapy in terms of time to onset of FRNS.[188, 190] There are no studies comparing rapid versus a slower corticosteroid steroid taper in adults. Based on case series, steroids are usually tapered by 5 to 10 mg/week after remission has been achieved for a total period of corticosteroid exposure of approximately 24 weeks.[268, 272, 277] It is important to monitor for side effects of corticosteroids 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 corticosteroids are used most often to treat MCD, the route and frequency of administration can be individualized to patient needs.

The role of intravenous methylprednisolone followed by lower-dose oral prednisone versus standard-dose oral prednisone alone was compared in two RCTs. These approaches were not found to be different in terms of eventual remission and subsequent relapse rates.[279, 281, 283]

Observational studies in adults have shown similar remission rates with the two regimens.[268, 284] 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.[268]

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

There are few studies on regimens that are corticosteroid-sparing or corticosteroid-free for the initial MCD episode. These treatments are considered in patients who have relative contraindications (severe hyperglycemia, pre-existing osteoporosis or osteopenia, or steroid-induced psychosis) or are unwilling to take steroids. Cyclophosphamide[269, 285-287] and cyclosporine[288] are associated with remission rates of approximately 75% with this limited experience (Table MCD1). More recently, in an RCT of 116 patients, sodium mycophenolate 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.[289]

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 corticosteroid-dependent. Up to 33% of patients will become frequent relapsers (11%–29%) or steroid-dependent (14%–30%).[268, 269, 278, 283] Definitions of remission and relapse that are useful in clinically classifying MCD are provided in Table MCD2. The optimal duration of corticosteroid treatment in relapsing MCD is not known. One regimen is to administer oral prednisone at a daily dose of 1 mg/kg (maximum dose of 80 mg/d) for four weeks or until remission is achieved, followed by 5 mg decrements every three to five days to discontinuation within one to two months.

For subsequent relapses, if not frequent (e.g., less than three per year), prolonged corticosteroid use is associated with side effects including Cushing's syndrome, obesity, glucose intolerance, bone loss, and cataracts.[290] Several drugs are effective in FR/SD MCD and may allow reduced exposure to or elimination of corticosteroids (Table MCD1).

Table MCD2. Definition of remission, relapse, resistance, and dependence for MCD

Complete remission
Reduction of proteinuria to <0.3 g/day or urine protein:creatinine ratio <300 mg/g (or <30 mg/mmol), stable serum creatinine and serum albumin >3.5 g/dl (or 35 g/L)
Partial remissions
Reduction of proteinuria to 0.3–<3.5 g/day or urine PCR 300–<3500 mg/g (or 30–<350 mg/mmol) and a decrease >50% from baseline
Relapse
Proteinuria >3.5 g/day or urine PCR >3500 mg/g (or 350 mg/mmol) after complete remission has been achieved
Corticosteroid-resistant MCD
Persistence of proteinuria >3.5 g/day or urine PCR >3500 mg/g (or 350 mg/mmol) with <50% reduction from baseline despite prednisone 1 mg/kg/day 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)
Corticosteroid-dependent MCD
Relapse occurring during, or within 2 weeks of completing corticosteroid therapy

MCD, minimal change disease; PCR, protein-creatinine ratio

Practice Point 5.3.1.1. Algorithm for treatment of frequently-relapsing/steroid-dependent MCD in adults (Figure MCD2)

Figure MCD2. Treatment of FR/SD MCD in adults
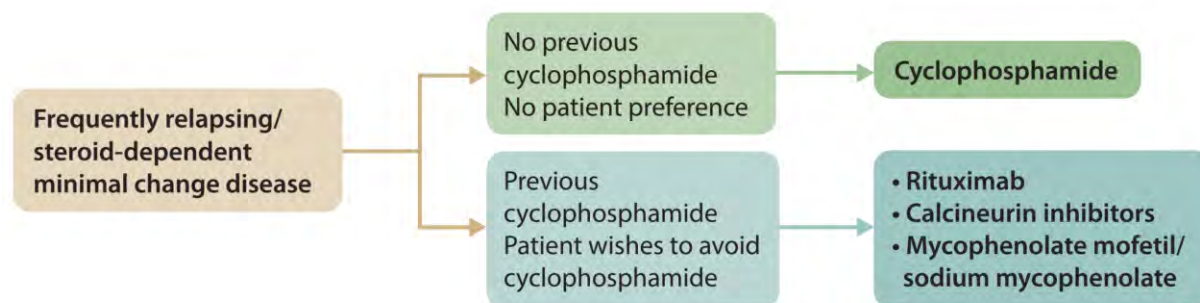
Practice Point 5.3.1.2. Treat infrequent relapses with corticosteroids (Table MCD2).

Infrequent relapses may be treated with corticosteroids without incurring major side effects if the duration of therapy is limited. The dose and duration of corticosteroid therapy in patients with infrequent relapses have not been fully investigated. In one study, patients were treated with 20 to 30 mg of prednisolone for a minimum of seven days or additionally with cyclophosphamide until proteinuria returned to a normal range, suggesting that the high doses of corticosteroids, as with the initial treatment of MCD, may not be needed. [291] With prolonged and repeated courses, the possibility of cumulative side effects (e.g., hyperglycemia and bone loss) may occur. An RCT of 52 adult MCD patients in their first relapse of MCD compared cyclosporine (AUC 1700-200 ng/ml) 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 six months.[292]

> **Recommendation 5.3.1.1. We recommend cyclophosphamide, rituximab, calcineurin inhibitors, or mycophenolic acid analogs (MPAA) for the treatment of frequently-relapsing/corticosteroid-dependent MCD as compared to prednisone alone or no treatment** *(1C)*.

This recommendation places a relatively higher value on avoiding the morbidity associated with prolonged corticosteroid exposure in FR/SD MCD. It places a relatively lower value on the low-quality evidence supporting the efficacy of CYC, RTX, CNI, and 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 since there is limited evidence to suggest one drug class over the other.

Key information
Balance of benefits and harms

As MCD is a corticosteroid-sensitive disease, other immunosuppressive medications are expected to work in this population. CNI (cyclosporine, tacrolimus), cyclophosphamide, rituximab, and MPAA (MMF, sodium mycophenolate (SMP)) have all been reported to be effective therapies for FR/SD MCD.

Clinical benefits

Observational studies and small RCTs showed that all four categories of agents reduce relapse rate and induce remission in FR/SD adult MCD patients (Table MCD3). Efficacy rates range from 70% to 90% in maintaining remission (Table MCD3). Generally, these agents are started after inducing remission with corticosteroids. It may not be able to withdraw corticosteroids completely in patients who have been on maintenance corticosteroids in view of the possibility of adrenal suppression.

Cyclophosphamide

In FR/SD patients who are experiencing side effects from corticosteroids, 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,[268, 277, 292] and one RCT comparing tacrolimus with cyclophosphamide.[293] The risks of infertility, although small, need to be addressed in patients of child-bearing age. A single course of oral cyclophosphamide is associated with remission in the majority of FR/SD patients. 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.[294] Compared to eight weeks of therapy, 12 weeks of treatment with cyclophosphamide may be associated with more durable remissions in SD MCD.[269]

Rituximab

Rituximab is effective in observational studies of FR/SD MCD in patients needing corticosteroids with or without other maintenance immunosuppressive therapies.[246, 295-297] Overall, the efficacy of rituximab in inducing remission is between 65% and 100% and, notably, 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 one RCT, CNIs have been associated with remission in 70% to 90% of FR/SD MCD patients. However, relapse rates are high and prolonged therapy may be necessary when patients relapse during dose reduction.[82, 298, 299] In view of relatively long experience with CNIs, these drugs may be favored in patients who relapse after receiving a course of cyclophosphamide or in those patients 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 FR/SD MCD patients with remission rates in the 65% to 85% range.[268, 300, 301] 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.

Table MCD3. Treatment of FR/SD adult MCD-selected clinical studies

Author (ref)	Study design (n with MCD)	Intervention	Outcome
Waldman et al. (Waldman, Crew et al. 2007)	Observational (39 SD, FR, SR pts)	Cyclosporine trough 150–220 ng/ml × 49 ± 14.8 weeks. (12 pts received prednisone 5–10 mg QOD)	Remission: 61% Mean time: 5 weeks (2–9)
Meyrier et al. (Meyrier, Condamin et al. 1991)	Observational (52/98 SD pts)	Cyclosporine 5 mg/kg/d + prednisone 12–15 mg QOD	CR 71% of SD pts at 6 months
Lee (Lee, Kim et al. 1995)	Observational (22/27 FR, SD, SR pts)	Cyclosporine 5 mg/kg/d + prednisolone 10 mg/d up to 8 months	CR 84% of SD pts Relapse: 68% at 10 months
Li (Li, Li et al. 2008)	Prospective cohort study (26 SD pts)	Tacrolimus: target trough level 4–8 ng/ml × 24 weeks Cyclophosphamide: intravenous cyclophosphamide (750 mg/m², every 4 weeks × 24 weeks)	Tacrolimus: CR 90.9% Cyclophosphamide: 76.9% (after 24 weeks therapy) Relapses: tacrolimus: 50%, cyclophosphamide 40%
Ponticelli et al. (Ponticelli, Edefonti et al. 1993)	Randomized, controlled (66 FR, SD MCD pts)	Cyclosporine 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 (Mak, Short et al. 1996)	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 (Waldman, Crew et al. 2007)	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 (Munyentwali, Bouachi et al. 2013)	Observational (17 SD, FR pts)	Rituximab 375 mg/m² (1–4 infusions) or 1000 mg × 2 doses, 2 weeks apart	Remission: 65% over mean follow up 26.7 months (5–82)
Iwabuchi (Iwabuchi, Takei et al. 2014)	Observational (20 SD pts)	Rituximab 375 mg/m², 6 monthly × 24 months	CR 100% from 12–24 months Relapses decreased from 108 to 8 (previous 24 months vs. 24 months after rituximab)
Ruggenti (Ruggenenti, Ruggiero et al. 2014)	Observational (22 children and adult FR and SD pts)	Rituximab 375 mg/m², repeated in 2 weeks if CD 20 >5 cells/mm³	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 (Guitard, Hebral et al. 2014)	Observational (41 SD, FR pts)	Rituximab: 1 g on days 1 and 15 375 mg/m² 1–4 weekly infusions	CR: 61% PR: 17% NR: 22%
Sandoval (Sandoval, Poveda et al. 2017)	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 (Waldman, Crew et al. 2007)	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%

<u>Adverse events</u>

All four 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.[82] 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.[83] 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 steroids alone in adults with MCD and NS.[292, 302, 303] 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 (Table S26[280]). These RCTs did not report critical clinical outcomes, all-cause mortality, or ESKD.

Values and preferences

The Work Group judged that the potential benefit of reduced corticosteroid exposure is important to patients. However, each of the four 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 three classes, patients of child-bearing 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.

Resources and other costs

The medications discussed in this section, particularly rituximab, are more expensive than corticosteroids. Serum levels of CNIs need to be continuously monitored, adding to cost. Cyclophosphamide is less expensive than the other three 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 gender 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 FDA category C drugs in pregnancy. Patients being considered for rituximab should be tested for HBV prior to administration of the drug.

Generally, FR patients who are in relapse are retreated with corticosteroids until remission is achieved before a second-line agent is introduced. After introduction of the second drug, corticosteroid is slowly tapered off, generally over two to four weeks as tolerated. After three to six months, if the patient remains dependent on corticosteroids, 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 corticosteroids as in the initial episode of MCD is suggested, followed by a taper over two to four weeks, depending on the response. The suggested medication regimens used to treat adult MCD are listed in Table MCD1.

Rationale

In the opinion of the Work Group, this recommendation is strong due to the adverse events of corticosteroids in adult patients with FR/SD MCD, and on the low-quality evidence suggesting that the four 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 corticosteroids 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 corticosteroid 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 corticosteroids, including using biomarkers or a genomics approach, might lead to a more precise, rationale-based therapy.
- Studies are needed to address the morbidity of longer-term corticosteroids, the optimal length of corticosteroid treatment (short vs, long duration) and the efficacy of corticosteroid-sparing/corticosteroid-free regimens in adult MCD.

- RCTs of rituximab, CNI, cyclophosphamide, and MPAA in SD/FR MCD, including optimal dose and duration of therapy are needed.
- Role of levamisole in adult MCD should be explored

CHAPTER 6. FOCAL SEGMENTAL GLOMERULOSCLEROSIS IN ADULTS

This chapter makes treatment recommendations for adult patients who present with proteinuria and histologic lesions of focal segmental glomerulosclerosis (FSGS).

<u>Definitions</u>

The nomenclature surrounding the classification of FSGS has been inconsistent and confusing, in part because a histopathological pattern of injury has generally been considered as a distinct disease. Likewise, the traditional classification of FSGS does not reflect practicalities surrounding clinical presentation, 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 1 provides an overview of the proposed classification of FSGS, and Table FSGS2 lists the secondary causes of FSGS lesions on the kidney biopsy.

Figure FSGS1. Proposed classification of FSGS
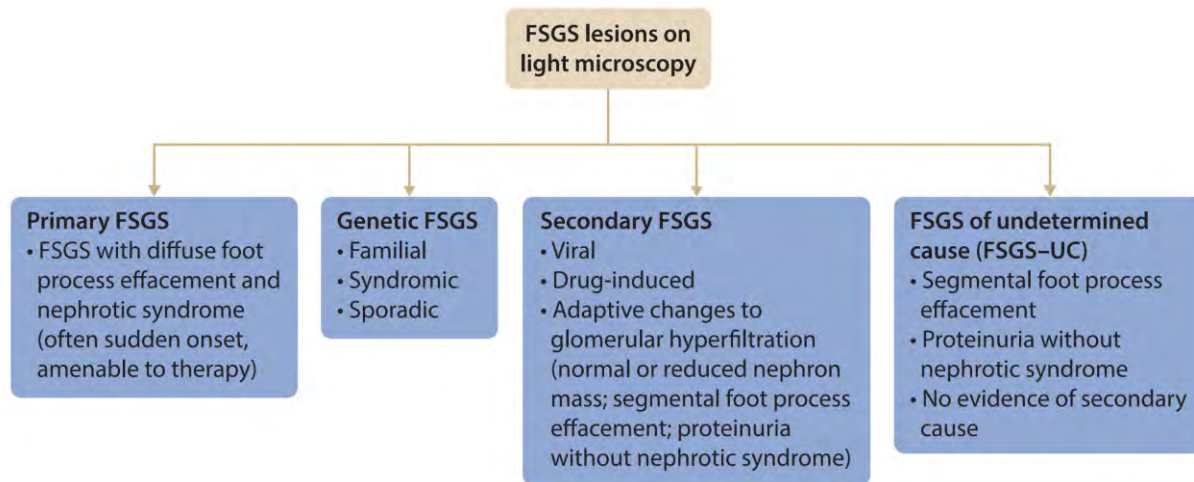
FSGS, focal segmental glomerulosclerosis

<u>Primary FSGS</u>

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 LM of the kidney biopsy demonstrates FSGS lesions, EM 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. While 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 reasonably be attributed to a circulating permeability factor is FSGS that recurs rapidly after a kidney transplant, and that 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 nephrotic syndrome, and without diffuse foot process effacement on EM 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 Table FSGS2.

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 (see 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 (Table FSGS2).

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 epidemiological comparisons and unify treatment approaches for adults with idiopathic NS. Suggested definitions for remission, relapse, treatment resistance, and treatment dependence are listed in Table FSGS1.

Table FSGS1. Definition of remission, relapse, resistance, and dependence for FSGS

Complete remission

Reduction of proteinuria to <0.3 g/d or urine 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 urine PCR 300–3500 mg/g (or 30–350 mg/mmol) and a decrease >50% from baseline

Relapse

Proteinuria >3.5 g/d or urine PCR >3500 mg/g (or 350 mg/mmol) after complete remission has been achieved or an increase in proteinuria by >50% during partial remission

Corticosteroid-resistant FSGS

Persistence of proteinuria >3.5 g/d or urine 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

Corticosteroid-dependent FSGS

Relapse occurring during or within 2 weeks of completing corticosteroid therapy

CNI-resistant FSGS

Persistence of proteinuria >3.5 g/d or urine PCR >3500 mg/g (or 350 mg/mmol) with <50% reduction from baseline despite cyclosporine treatment at trough levels of 100–175 ng/ml or tacrolimus treatment at trough levels of 5–10 ng/ml for >6 months

CNI-dependent FSGS

Relapse occurring during or within 2 weeks of completing cyclosporine or tacrolimus therapy for >12 months

CNI, calcineurin inhibitors; FSGS, focal segmental glomerulosclerosis; PCR, protein-creatinine ratio

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 FSGS2, Table FSGS2).

Figure FSGS2. Evaluation of a patient with FSGS lesion on the kidney biopsy and no evidence of other glomerular pathology

FSGS, focal segmental glomerulosclerosis

Table FSGS2. Causes of secondary FSGS

Secondary to alterations of glomerular epithelial cells	
Viral infections	HIV (established) CMV (probably) Parvovirus B19, EBV, HCV (possibly) Hemophagocytic syndrome (possibly)
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

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 the rapamycin; NSAID, nonsteroidal anti-inflammatory drugs

A proposed histopathological classification of FSGS had suggested a distinction between different variants of FSGS lesions on the kidney biopsy.[304] While the occurrence of certain variants may suggest a secondary form of FSGS, the predictive value of histopathological classification in differentiating between primary and secondary FSGS has been inconsistent.[305-307] Moreover, no histopathological feature is pathognomonic of primary FSGS. Consequently, while diffuse foot process effacement on EM usually occurs in primary FSGS, variability in the percentage of the glomerular surface affected by foot process effacement in secondary forms of FSGS suggests this finding is not completely specific for primary FSGS.[308, 309] 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.[310]

The development of the NS occurs in about 54% to 100% of patients with primary FSGS.[307, 311-313] 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 one series, when conditions associated with secondary forms of FSGS were excluded, NS was found in 100% of the study population with primary FSGS.[312] 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 (Table FSGS3).

Table FSGS3. Utility of genetic testing in patients with FSGS

Genetic forms of focal segmental glomerulosclerosis	
Genetic mutations of podocyte and glomerular basement membrane proteins	Familial Sporadic Syndromic Hereditary nephropathies (e.g. Alport's syndrome, other collagenopathies)

Potential benefits of genetic testing in patients with FSGS
• Aiding in diagnosis, especially if the clinical features are not compelling of a particular disease phenotype • Limiting immunosuppression exposure, especially in situations where patients appear to be resistant to treatment • Determining risk of recurrent disease in kidney transplantation • Allowing for risk assessment in candidate living-related kidney donors • Aiding in pre-natal diagnosis • Screening in other members of a family when there is a strong family history and/or clinical features suggestive of a syndromal disease

FSGS, focal segmental glomerulosclerosis

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 corticosteroid therapy.[314] 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. While 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 one study,[315] 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 (Table FSGS3).[316]

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 (see 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 corticosteroids or other immunosuppressive drugs in this population, and the potential for harm of such treatment is clear.[317]

A management conundrum occurs when a patient presents with nephrotic range proteinuria without NS and FSGS-UC.[314] 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 ten-year kidney survival rates greater than 90% without immunosuppressive treatment.[276, 318-321] 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% versus 40%) when compared to those with persistent NS.[322] These data suggest that the kidney outcomes of patients without NS remain favorable, and do not warrant subjecting the patients to the risks of corticosteroid treatment.

Recommendation 6.2.2.1. We recommend that high-dose oral corticosteroids 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 corticosteroids 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 corticosteroids.

Key information
Balance of benefits and harms

The true likelihood of spontaneous remission in primary FSGS patients with the NS is not known, as many such patients are treated with immunosuppression. However, it is generally accepted that spontaneous remission rates are less than 20%.[323, 324] Indeed, patients with the NS have worse kidney prognosis than non-nephrotic patients, with ten-year kidney survival rates of 57%, compared to 92% in those with lower degrees of proteinuria.[320] Consequently, many observational studies have demonstrated that remission of proteinuria induced by therapy is associated with favorable kidney survival rates,[320, 322, 323, 325] while patients with persistent nephrotic-range proteinuria are more likely to experience loss of kidney function.[320]

Many studies in adults with primary FSGS suggest that corticosteroid treatment increases the likelihood of achieving remission;[322, 326-328] data from children are similar. Therefore, despite the inherent risks of corticosteroid 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 corticosteroids in adult patients with primary FSGS and NS. The quality of the evidence is low, as the evidence that forms the basis of this recommendation is extracted from observational studies in the adult population. The benefits of corticosteroid use are also extrapolated from pediatric studies, where RCTs have shown the effectiveness of corticosteroids treatment in children with NS, some of whom had primary FSGS.

Values and preferences

The potential benefits of corticosteroid 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 corticosteroid 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 corticosteroids 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 corticosteroids, or who place a high value on avoiding such adverse events may choose to forgo a trial of corticosteroid as initial therapy in favor of alternative immunosuppression. In the judgment of the Work Group, few if any well-informed patients would choose not to be treated with immunosuppression for primary FSGS.

Resources and other costs

Corticosteroids 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 corticosteroids may be higher in certain subgroups of patients, including those who are obese or who have diabetes, osteoporosis, or psychiatric disorders. In such patients, the adverse effects of prolonged high-dose corticosteroid therapy should be discussed with the patients, and alternative immunosuppressive therapy with CNI may be explored. (see below)

Rationale

This recommendation places a high value on very low quality evidence on the use of corticosteroids to achieve remission of proteinuria in adult patients with primary FSGS and having NS, with consequent reduction in the morbidity derived from NS and in the risk for kidney failure, and a lower value on the adverse effects associated with corticosteroid 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 majority of patients would be willing to choose corticosteroids as the initial treatment for primary FSGS. Moreover, due to its low cost, widespread availability, and familiarity with corticosteroids, most physicians would be willing to consider this treatment as the initial therapy in most patients without clinical contraindication to corticosteroids.

Practice Point 6.2.2.1. Suggested dosing schedule for corticosteroids in the initial treatment of primary FSGS (Table FSGS4 – see below).

Table FSGS4 suggests the initial starting dose of corticosteroids in treating adult patients with primary FSGS. The high starting dose of 1 mg/kg of prednisone 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 corticosteroid therapy, one observational study evaluated the use of alternate-day corticosteroid dosing in elderly patients with FSGS (multiple types) and found complete remission rates of about 44% after three to five months of treatment,[329] comparable to reported rates in studies using corticosteroids doses at 1 mg/kg/d.[322, 327]

Practice Point 6.2.2.2. Initial high-dose corticosteroids 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, corticosteroids 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 corticosteroid exposure without additional benefit.

Earlier studies suggested that primary FSGS is a corticosteroid-resistant disease with dismal outcomes.[276, 318, 319, 330-332] However, subsequent observational studies demonstrated that response to corticosteroid treatment could be improved with a higher initial dose and longer duration of treatment.[276, 320, 323, 325, 333] The optimal duration of high-dose corticosteroid treatment in adult primary FSGS has not been established, nor has the duration of treatment before considering a diagnosis of corticosteroid-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 corticosteroid therapy towards 16 weeks resulted in an increase in remission rate of 10% to 25%.[269, 277, 291, 334, 335] Primary FSGS is less responsive than MCD; thus, additional therapeutic benefit beyond 16 weeks is unlikely. Defining a maximum high-dose prednisone treatment duration of 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 corticosteroid treatment are significantly worse than 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 corticosteroid 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 four to eight weeks of initiating treatment.[320, 323, 333] If proteinuria remains persistent and shows no signs of reduction, especially if the patient experiences corticosteroid 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 corticosteroid treatment should receive corticosteroids for at least six months.

The optimal duration of corticosteroid therapy is not known. Treatment schedules have ranged from four to 24 months in various studies, with reported complete and partial remission rates of 28% to 74% and 0% to 50%, respectively.[276, 320, 323, 325] One study found that patients receiving corticosteroid therapy for more than 16 weeks had a much higher remission rate of 61% compared to 15% in those with treatment duration of less than 16 weeks.[333] Similarly, another study demonstrated that patients who had responded to corticosteroid therapy had received a significantly longer median treatment duration of 5.7 months.[320] Conversely, another study found that if a patient had not responded to corticosteroids by six months, treatment beyond this duration was not beneficial.[323] Taking into consideration the significant toxicities associated with prolonged corticosteroid treatment, a suggested total treatment duration of six months is proposed. Table FSGS4 also outlines a suggested approach to tapering corticosteroids in adults with primary FSGS.

Practice Point 6.2.2.4. In adults with relative contraindications or intolerance to corticosteroids, alternative immunosuppression with calcineurin-inhibitors should be considered as the initial therapy in patients with primary FSGS (Table FSGS4).

Adults may not tolerate prolonged high-dose corticosteroids well, and with the protracted natural history of primary FSGS, the side effects of corticosteroids may be unacceptable to some patients.[336] Additionally, patients who are obese, have uncontrolled diabetes, psychiatric conditions, or severe osteoporosis may be deemed to have a relative contraindication to corticosteroids. Ideally, such patients would be considered for an alternative

treatment to corticosteroids. 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 corticosteroid 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.[326] 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 six patients after 6.5 ± 5.9 months, avoiding the use of corticosteroids completely.[337] Furthermore, the favorable outcomes of using CNIs in the management of corticosteroid-resistant primary FSGS lends additional support to the use of CNIs as an initial treatment option.

Table FSGS4 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 [326] or tacrolimus at 4 mg/day with target trough level of 4 to 7 ng/ml for a mean duration of 13.6 ± 11.8 months.[337]

Table FSGS4. Initial treatment of primary FSGS

Treatment	Dose and duration
Corticosteroids	**Starting dose:** • High dose corticosteroid 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 corticosteroid treatment duration: • Continue high dose corticosteroid 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 corticosteroid therapy until 16 weeks if the proteinuria is persistent and unremitting, especially in patients who are experiencing side-effects
	Corticosteroid tapering: • If complete remission is achieved rapidly, continue high dose corticosteroid treatment for at least 4 weeks or for 2 weeks 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 corticosteroid 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 corticosteroid-resistant or develops significant toxicities, corticosteroids 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/day in 2 divided doses OR tacrolimus 0.05–0.1 mg/kg/day in 2 divided doses • Target trough levels could be measured to minimize nephrotoxicity • Cyclosporine target trough level: 100–175 ng/ml • Tacrolimus target trough level: 5–10 ng/ml
	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

CNI, calcineurin inhibitors

6.3. Special situations

6.3.1. Corticosteroid-resistant primary FSGS

Recommendation 6.3.1.1. For adults with corticosteroid-resistant primary FSGS, we recommend that cyclosporine or tacrolimus be given for at least six months rather than continuing with corticosteroid 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 corticosteroid 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,[276, 311, 322, 328] and resistance to corticosteroids is strongly associated with the risk of kidney failure in adult patients with primary FSGS.[276, 328] In patients who do not achieve remission, five-year and 10-year kidney survival was reported to be 60% to 90% and 25% to 56%, respectively.[276, 318, 319, 338] Notwithstanding the unnecessary side-effects associated with continuing high-dose corticosteroid therapy in patients who are not likely to respond, the poor kidney prognosis with unremitting proteinuria in patients with corticosteroid resistance warrants alternative immunosuppression strategies to attempt to achieve remission. The CNIs, cyclosporine and tacrolimus, are two such alternative strategies.

Cyclosporine has been evaluated in two small RCTs for its effectiveness in adult patients with corticosteroid-resistant presumptive primary FSGS. In one study, cyclosporine was used as monotherapy for six months and compared to supportive therapy in both adult and pediatric patients with corticosteroid-resistant NS, including MCD and primary FSGS.[254] The second RCT included only adult patients with corticosteroid-resistant primary FSGS and compared a 26-week treatment with cyclosporine to placebo.[251] All patients received low-dose prednisone. Remission was achieved in 60% and 70% of the study population receiving cyclosporine in the respective two studies.

There are no RCTs evaluating tacrolimus in similar settings. However, uncontrolled studies suggest that tacrolimus may be an alternative to cyclosporine.[337, 339, 340] One uncontrolled study looked at the use of tacrolimus in addition to low-dose corticosteroids for six months in adult primary FSGS patients with corticosteroid resistance and either cyclosporine resistance or cyclosporine dependence.[340] Complete and partial remission occurred in 40% and 8%, respectively, with a mean time to remission of about three months. Acute reversible decline in GFR occurred in about 40% of patients. Another prospective study evaluated the use of tacrolimus in adult patients with corticosteroid-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%.[339] 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 corticosteroid-resistant primary FSGS.

Since remissions after the use of cyclosporine may occur slowly and have been reported to take as long as four to six months in certain observational studies, we suggest that a minimum treatment duration of six months should be attempted before labeling a patient as cyclosporine-resistant. It is the judgment of the Work Group that a minimum duration of six 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 six 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 corticosteroids) against supportive therapy or prednisone treatment in adult patients with corticosteroid-resistant primary FSGS (Table S27[254, 341]; Table S28[251, 341]; Table S29[341, 342]).

In a small RCT (n=22), cyclosporine treatment alone was compared with supportive therapy, and cyclosporine was found 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 confidence intervals 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 (Table S27[254, 341]).

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 one small RCT (n=49) for this comparison.[251] The magnitude of the effect between the two groups for partial remission was large (342 per 1000 patients with cyclosporine versus 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 (Table S27[251, 341]). Similarly, in one 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 (Table S29[341, 342]).

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 corticosteroid 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 as less important than the side-effects associated with prolonged corticosteroid 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 using the shortest possible course of CNI treatment.

Resources and other costs

Cyclosporine or tacrolimus treatment entails a much higher financial burden than corticosteroid treatment or no treatment, as both drugs are significantly more expensive than corticosteroids, and there are added costs for monitoring drug levels. In addition, cyclosporine and tacrolimus, including generic formulations, may not be available nor 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 corticosteroid 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 corticosteroid-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.[340] The preference towards either of the CNIs will be 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 corticosteroid 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, given 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 corticosteroid treatment if they are corticosteroid-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 corticosteroid-resistant primary FSGS: suggested dosing schedule for cyclosporine and tacrolimus (Table FSGS5).

Table FSGS5. Treatment of corticosteroid-resistant primary FSGS

Treatment	Dose and duration
Calcineurin inhibitors	**Starting dose:** • Cyclosporine 3–5 mg/kg/day in 2 divided doses OR tacrolimus 0.05–0.1 mg/kg/day in 2 divided doses • Target trough levels could be measured to minimize nephrotoxicity • Cyclosporine target trough level: 100–175 ng/ml • Tacrolimus target trough level: 5–10 ng/ml **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
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

ACTH, adrenocorticotropic hormone; CNI, calcineurin inhibitors

Table FSGS5 outlines a proposed treatment schedule for adult patients with corticosteroid-resistant primary FSGS. The initial starting dose for cyclosporine ranged from 3.5 to 6 mg/kg/day[251, 343] in various studies with most starting at 5 mg/kg/day.[82, 254, 299, 344, 345] Doses of cyclosporine greater than 5.5 mg/kg/day had been found to be associated with increased risks of nephrotoxicity.[82] There was even greater variability in trough drug level targets that stretched from 50 to 600 ng/ml.[251, 254, 343-345] 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 towards target trough levels. Apart from one study that targeted cyclosporine trough levels of 250-600 ng/ml,[254] most demonstrated the ability to induce remission with trough levels of 100-225 ng/ml, though 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 preferable target trough level of 100 to 175 ng/ml be used to balance the benefits proteinuria

reduction and the risk of GFR decline, and not to exceed a trough level of 225 ng/ml over a protracted period.

One uncontrolled study considered tacrolimus at an initial dose of 0.15 mg/kg/day with a target trough level of 5 to 10 ng/ml.[340] However, at this dose, the mean trough level exceeded the therapeutic target in the first four weeks (10.3-11.8 ng/ml) with levels at the 25th percentile at the higher end of the therapeutic targets (9.2-9.8 ng/ml), suggesting that a lower dose might be more prudent. On the other hand, another prospective study initiated tacrolimus at 0.1 mg/kg/day and managed to achieve mean tacrolimus trough levels of about 7 ng/ml.[339]

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, physicians' 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 though 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 more than one year.[346]

6.3.3. Duration of CNI treatment
Practice Point 6.3.3.1. Adults with corticosteroid-resistant primary FSGS who respond to CNI treatment should receive CNIs for a minimum of 12 months to minimize the risk of relapses (Table FSGS5).

While CNIs are effective for inducing remission in patients with corticosteroid resistance, relapses are very frequent after their withdrawal. In one of the RCTs evaluating the effect of cyclosporine in corticosteroid-resistant disease, relapses occurred in 40% of patients by one year and 60% by 78 weeks following cyclosporine withdrawal.[251] This outcome was replicated in another RCT, with 69% of patients experiencing a relapse within 12 months of cyclosporine withdrawal.[254] Observational studies of cyclosporine treatment also reported relapse rates ranging from 60% to 80%. Similarly, a high incidence of relapse was seen with tacrolimus with about 76% of patients developing a relapse after drug discontinuation.[340]

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 corticosteroid-resistant primary FSGS. An RCT compared cyclosporine and cyclophosphamide in corticosteroid-dependent and FR idiopathic NS in both children and adults, with the primary outcome being relapse-free survival. Cyclosporine was prescribed for nine 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%) or cyclophosphamide (60%).[294] In addition, prolonged CNI treatment in children with corticosteroid-resistant NS is a common practice, though 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 where the evidence for alternative immunosuppressive therapies is scanty, and the risk of relapse is significant.

Table FSGS5 outlines the treatment schedule for corticosteroid-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 or intolerant to CNIs
Practice Point 6.3.4.1. Adults who have corticosteroid-resistant primary FSGS with resistance to or intolerance of CNIs should be referred to specialized centers for consideration of re-biopsy, alternative treatment, or the subsequent need for further immunosuppression (Table FSGS5).

There is a dearth of evidence to inform the treatment of adult patients with corticosteroid-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 Table FSGS5. 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 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 2012 KDIGO iteration of these guidelines as an alternative for patients who do not tolerate

cyclosporine. This was based on an RCT comparing cyclosporine to the combination of MMF and high-dose dexamethasone in children and young adults with corticosteroid-resistant FSGS that showed no statistically significant difference in remission rates between the two arms.[256] 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.[347] In considering these issues, the 2019 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 corticosteroid-sensitive primary FSGS who experience a relapse should be treated by the same approach as adults with relapsing minimal change disease (Figure MCD2).

There is very low quality of evidence to guide the treatment of relapses in primary FSGS. If the relapses occur in patients whose disease was previously sensitive to corticosteroid therapy, it is suggested that relapses should be approached in the same way as relapsing MCD in adults (Table MCD3).

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 corticosteroid treatment, including daily versus alternate-day corticosteroids, in adult patients with primary FSGS.
    - To determine the optimal duration of corticosteroid treatment in adult patients with primary FSGS and to compare remission, relapse, and adverse events rates associated with short or prolonged treatment using initial high-dose corticosteroid therapy.
    - To evaluate the effectiveness of CNIs, with or without concomitant corticosteroids, in the treatment of adult patients with corticosteroid-resistant primary FSGS.
    - To examine the optimal duration of CNI treatment in adult patients with corticosteroid-resistant primary FSGS.

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 (post-infectious glomerulonephritis (PIGN) 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:[348]

1. Post-streptococcal GN which in modern times is a bit of a misnomer as streptococcal infections account for only 28% to 47% of this post-infectious acute GN. *Staphylococcus aureus* or *Staphylococcus epidermidis* is isolated in 12% to 24% of cases and gram-negative bacteria in up to 22% of cases.[349]

2. Shunt-nephritis is an immune complex–mediated GN that rarely develops as a complication of chronic infection on ventriculo-atrial, ventriculo-jugular, or less commonly, ventriculo-peritoneal shunts inserted for the treatment of hydrocephalus.[350] The infecting organisms are usually *Staphylococcus epidermidis*, *Staphylococcus albus*, or *Staphylococcus aureus*. ANCA titers may be positive.[350]

3. GN related to infective endocarditis particularly related to *Staphylococcus aureus*, which has replaced *Streptococcus 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 anti-nuclear antibodies can be present,[351] and pulmonary hemorrhage mimicking anti-GBM disease (due to cryoglobulinemia) has been observed.[352] 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 *Staphylococcus aureus*, *Escherichia coli*, *Staphylococcus epidermidis*, and *Klebsiella* bacteremia in patients with underlying comorbidities, especially diabetes (Table IGN1).[353-355]Bacteremia is often, but not always, found although presentation may be delayed.[354]

IgADIRGN has been reported in patients with skin and joint infections, pneumonia, osteomyelitis, and endocarditis. Hypocomplementemia can be seen in 30% to 50% of cases.[355]

7.1.1. Diagnosis

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

The kidney histology shows acute, often exudative, endocapillary GN with mesangial and capillary wall granular immune deposition. In endocarditis-related GN, the most frequent morphological glomerular change is crescentic GN in >50% of the patients, followed by diffuse 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. Sub-endothelial and sub-epithelial electron dense deposits, including "humps", can be found on EM. In shunt nephritis, the histologic findings are typically a mesangioproliferative 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% to 80%, while a minority may have isolated mesangioproliferative or even crescentic GN. On IF microscopy, there is mesangial staining in a co-dominant pattern with IgA and C3, often with kappa light chain exceeding lambda.[353] EM demonstrates electron dense deposits in the mesangium and capillary walls, the latter often with sub-epithelial "humps" and less frequently a subendothelial distribution.[356] Differentiation from an exacerbation of classical IgAN is accomplished taking into account both the characteristic clinical and morphological features described above, but at times can be difficult (Chapter 2).

7.1.2. Prognosis and treatment

Practice Points 7.1.2.1. Suggested evaluation, prognosis, and therapy of bacterial infection-related GN (Table IGN1)

Table IGN1. Evaluation, prognosis and therapy of classic bacterial infection-related GN syndromes

	Post-infectious 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
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

	Post-infectious GN	Shunt nephritis	Endocarditis-related GN	IgA-dominant infection-related GN
Prognosis	Short-term prognosis in children 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 post-infectious GN) per local guidelines. Antibiotics can be given in post-streptococcal GN if streptococci are cultures from any site. This is primarily done to prevent the spread of infection within communal sites • Treat edema, hypertension, etc. as well as persistent proteinuria and/or progressive GFR decline as per Chapter 2			
	Value of high-dose steroids remains unproven [11]	Most shunts have been replaced with a shunt with a lesser likelihood of infection. Rarely ventriculocisternostomy has been performed after shunt removal	Utility of steroids and immunosuppression unproven and carries serious potential risks, even in cases with crescentic GN [12]	For severe kidney functional impairment, weigh risks and benefits of immunosuppression. The risk of infection and steroid-induced complications in this often elderly population with substantial 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 [13]. Prevention of epidemic post-streptococcal GN may include socioeconomic interventions and mass antimicrobial use to improve living conditions and 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

ACR, albumin-creatinine ratio; ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibodies; C3GN, complement glomerulonephritis; CKD, chronic kidney disease; CSF, cerebrospinal fluid; eGFR, estimated glomerular filtration rate; GBM, glomerular basement membrane; GN, glomerulonephritis; HIV, human immunodeficiency virus; PCR, protein-creatinine ratio; PR3, proteinase-3; RCT, randomized controlled trial; UA, urine analysis

RESEARCH RECOMMENDATIONS

Post-streptococcal GN

- RCT is needed to evaluate the treatment of crescentic post-streptococcal GN with high-dose corticosteroids with or without immunosuppression.
- Research is needed to determine the nature of the streptococcal antigen(s) as a basis for developing immuno-prophylactic therapy.
- In patients whose kidney lesion transforms, further research is needed to elucidate the distinctions and relationships between immune-complex mediated PSGN and C3-dominant, but non-immune complex mediated, C3 glomerulopathy.

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 for steroid 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 through 5.2.3 of the *KDIGO 2018 Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease*.[357] Please refer to this publication for specific recommendations, selection and dosing of specific therapeutic agents, and research recommendations. (https://kdigo.org/wp-content/uploads/2017/02/KDIGO-2018-Hep-C-GL.pdf).

7.2.2. Hepatitis B virus (HBV) infection-related GN

Approximately 250 to 350 million people (5% of the world's population) are chronically HBV-infected making it one of the most common human pathogens,[358-360] and about 3% to 5% of patients with chronic HBV infection develop kidney disease as a complication.[361, 362]

The most common pattern of glomerular injury seen in HBV infection is MN.[363, 364] 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 anti-

viral therapy.[365] A variable fraction of patients with HBV infection and MN display circulating antiPLA2Rab (Chapter 3).[366, 367]

The extra-hepatic manifestations of chronic HBV infection also include systemic vasculitis (especially polyarteritis nodosa/Kussmaul-Meier disease),[359, 368] Type II (monoclonal IgM kappa anti polyclonal IgG), and Type III (polyclonal IgM, IgA, IgG) cryoglobulinemia.[358-360, 369]

This section will address 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 DNA (cccDNA) in hepatocytes, HBV infection is very difficult to permanently cure with anti-viral agents, unlike HCV infection.[370] Relapses of viral replication are fairly common in HBV infection and immunosuppressive agents can reactivate dormant or occult infection.[370, 371]

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 serological 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. Serological identification of HBV exposure and infection is best performed by assessing HBs antigen, anti-HBc antibody, and in selected cases, HBV DNA quantification representing the burden of replicative viral infection.[370, 372] 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.[370]

HBV infection is particularly common in patients with MN, IgAN, cryoglobulinemia, and polyarteritis nodosa (Kussmaul-Meier 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., intravenous 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% to 30% are coinfected with HCV.[359] Another reason for screening patients with proteinuric glomerular diseases for HBV infection is that many such patients may become candidates for immunosuppressive therapy (steroids and or cytotoxic/immunomodulating agents) which can induce a serious exacerbation of HBV replication (Chapter 1).[371] 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.[372] HBs or HBc antigen can occasionally be detected in kidney tissue of patients without serological evidence of HBV infection.[373] Serum HBV DNA levels have a modest correlation with the severity of clinical findings.[374, 375]

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 towards kidney failure and spontaneous remissions are uncommon.[359, 363] Therefore, such patients need careful consideration for treatment beyond attempts to control viral replication with anti-viral 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 on Special situations below).[359, 363] HBV infection may also promote progression in IgAN and FSGS, but this is not well-established.[376-378] Cryoglobulinemia can be associated with severe and rapidly progressive glomerular disease,[369, 379] often associated with vasculitis and crescents. Polyarteritis nodosa has a particularly poor prognosis when concomitant HBV infection remains untreated.[368]

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) anti-viral agents, nearly all patients with this condition should be considered candidates for anti-viral therapy, unless contraindication exist

Key information

Balance of benefits and harms

Chronic replicative HBV infection can be recognized by a combination of serologic and viral genome studies.[370] 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 anti-viral 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 alpha interferon, 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;[370, 380] however, true lasting cure of the infection is evasive to the biology of the virus (particularly its integration into the 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% to 35% of such subjects if left untreated.[359]

Quality of evidence

A systematic search of the medical literature of RCTs in the management of patients with HBV infection-related GN identified one small (n=40), open-label study in children with HBV-associated MN.[381] This study did not report any of the critical and important outcomes identified for this guideline (all-cause mortality, ESKD, ≥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 one study) and risk of bias concerns. Additionally, supporting literature for this recommendation has been derived from observational studies that were graded as 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 forego 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 anti-viral 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 (transfusion, intravenous drug abuse) will be crucial. All measures should be considered equally for all genders, 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 barrier to development of resistance are now available and widely considered as treatments of choice for HBV infection.[380] Lamivudine has a high association with acquired resistance and no longer recommended as initial therapy.[370] Pegylated interferon alfa is less commonly used due to limited efficacy and tendency to evoke serious side effects, but may be effective in milder cases with low viral load.[370] Combination therapies using interferon and nucleos(t)ide analogues are not generally recommended, except in special circumstances.[370]

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.[358, 360, 370]

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 have been assessed in RCTs.[370] However, as of 2016, only one RCT of treatment of HBV-related GN could be identified.[381] It was an open label, controlled trial of alpha interferon 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 low quality and potentially biased. However observational studies in adults have been consistent with these findings.[382] No RCTs using nucleo(t)side analogues have been reported. Several meta-analyses, including observational studies have appeared.[383-387] In one meta-analysis of six trials (one RCT), alpha interferon or lamivudine with or without accompanying steroids were associated with a higher proteinuria remission rate and clearance of HBeAg as a sign of control of replicative viral infection, compared to steroids or supportive care only. Steroids alone were judged to be ineffective.[386] The Yang *et al.* analysis was limited to HBV-associated MN and included three trials of interferon alpha and two trials of nucleoside analogues.[384] Anti-viral 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 interferon, but no head-to-head comparison of the two anti-viral regimens were conducted. Serious extrarenal side effects were seen commonly in interferon-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 interferon and 85% with nucleoside analogues. Spontaneous viral remission was seen in about 6% of controls. Similar favorable responses to anti-viral therapy were observed in a small, open-label, uncontrolled trial in HBV-related cryoglobulinemic vasculitis.[369] Very few studies of anti-viral therapy of HBV-infection in patients with IgAN or FSGS have been conducted. Observational cohort studies have suggested benefits of combined lamivudine and steroids in HBV inactive carriers with IgAN.[388] A role for CNI in the treatment of HBV-associated glomerular disease (MN and FSGS) has been suggested.[389, 390] Calcineurin agents can be safely used in patients with glomerular and other auto-immune 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.[391, 392] In a pilot study, sulodexide combined with anti-viral therapy (entecavir) was shown to have an additive beneficial effect on proteinuria in HBV-related MN, perhaps via a complement-activation-inhibiting mechanism.[393]

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).[370, 380, 392] 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.[380]

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 interferon alpha-based regimens not be employed in HBV-associated GN as interferon therapy could aggravate auto-immune phenomena in such patients.[370] In one case, *de novo* MN appeared after starting IFN therapy for HBV infection.[394] The consistency of this effect is uncertain, but since newer anti-viral 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 steroids, alkylating agents, rituximab) thus aggravating the hepatic manifestations of disease, constitute a real risk (Chapter 1).[371] Alternative agents, such as CNI, having little or no effect (or even a beneficial effect) on HBV replication may be preferred.[389-392]

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 antiPLA2R antibody-mediated MN until a sustained virologic remission has been obtained by nucleos(t)ide analogue therapy.

The utility of anti-viral therapy in patients with simultaneous HBV infection and antiPLA2Rab-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).[395] 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.[369, 379]

Practice Pont 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 anti-viral therapy as immune suppression alone is seemingly ineffective.[396]

<center>RESEARCH RECOMMENDATIONS</center>

- 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 extrarenal 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 to the publication from the KDIGO HIV Controversies Conference.[397]

According to the United Nations AIDS organization, approximately 36.9 million people were living with HIV in 2017. In 2017, 59% (44% to 73%) of all people living with HIV were accessing treatment.[397] 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 is truly a growing issue in the HIV pandemic.[398]

Figure IGN1. The global distribution of CKD associated with HIV infection[*]

Europe
MDRD 3.7%
CKD–Epi 2.5%
CG 2.7%

North America
MDRD 7.1%
CKD–Epi 7.4%
CG 6.5%

Middle East
MDRD 0.8%

Western Pacific
MDRD 5.7%
CG 9.6%

Africa
MDRD 7.9%
CKD–Epi 7.0%
CG 13.7%

South America
MDRD 6.2%
CKD–Epi 3.4%
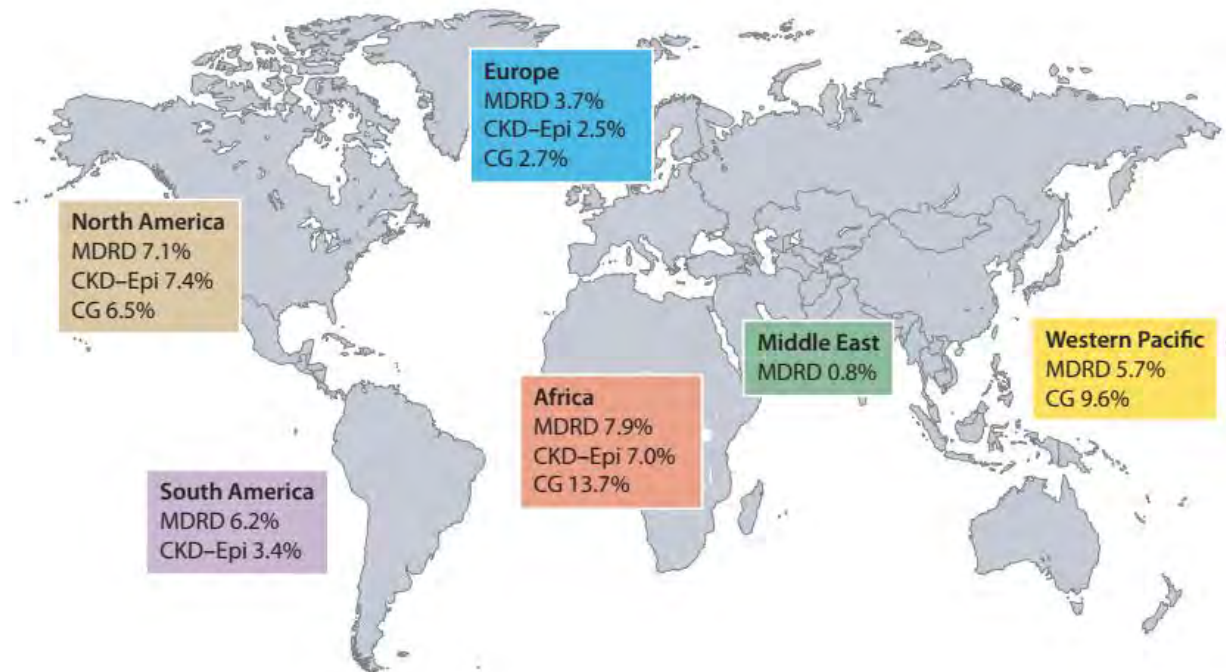
***From Ekrikpo UE, Kengne AP, Bello AK, *et al*. Chronic Kidney Disease in-the global HIV infected patient: a systematic review and meta-analysis. PLoS One 2018; 13:e019443

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.[397]

HIV can have many effects on the kidney. Glomerular, interstitial, and vascular diseases have unique presentations in HIV patients. Infections, both the actual infection and the treatment, can impact kidney function. Traditional causes of kidney disease in the non-HIV patient, 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 HIVAN, but each condition requires a different therapy.[399-401] 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 highlighted the need for precision in diagnosis for optimization of management.[402]

Figure IGN2. The spectrum of kidney biopsy findings in HIV-infected patients in the modern era[*]

Breakdown of diagnoses (n)*

* Dual diagnoses were present in 17% of cases
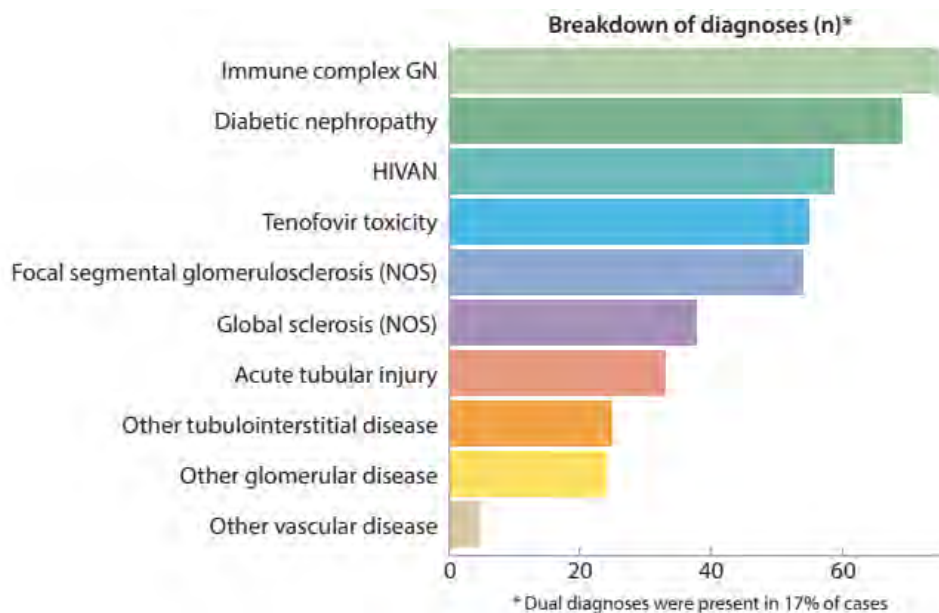
*26,737 native biopsies from 2010-2018 were retrospectively reviewed; 437 (1.6%) from HIV-infected patients (mean age 53 years, 66% male, 58% black, 25% white, 17% Hispanic, <1% Asian, 80% on antiretroviral therapy (ART), comorbidities included: 57% hypertension, 31% diabetes, 27% hepatitis C coinfection); Conclusion: AART has changed the landscape of HIV-associated kidney disease toward diverse immune complex GN, diabetic nephropathy, and non-collapsing glomerulosclerosis, but has not eradicated HIV-associated nephropathy

HIVAN is a lesion of focal and segmental glomerulosclerosis. HIV-associated collapsing glomerulopathy is generally included under the heading of HIVAN. Other podocytopathies can also be present such as MCD. HIV-associated immune complex kidney disease (HIVICK) can manifest like other primary immune complex GNs, such as IgAN, SLE, MN, and MPGN, but the outcome may not be the same.[403] Some have suggested using HIVICK may have been too broad a term for the complicated nature of the immune complex deposition in the glomerulus.[404] Certain genes, such as APOL1, can increase risk of FSGS and HIVAN, but not of HIVICK. The pathology of the biopsy is the same, no matter the number of genetic variants.[405] More information on genetic factors is needed.

Table IGN2. Lifetime risk of HIVAN or FSGS (NOS) in the setting of HIV by number of APOL1 risk alleles

	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

APOL1, apolipoprotein L1; ART, antiretroviral therapy; FSGS (NOS), focal segmental glomerulosclerosis, not otherwise specified; HIV, human immunodeficiency virus; HIVAN, HIV-associated nephropathy
Modified from Dummer PD.[406]

Tubulointerstitial disease can be present with HIVAN, but also can be due to medications, or as a response to infection. Vascular diseases were more prevalent prior to highly active antiretroviral therapy (HAART) therapy.[407, 408] More than a third of the patients with HIV who underwent a kidney biopsy had diabetic nephropathy; or MN, MPGN, IgAN; or another pattern of immune-complex GN.[399, 409] A rare disease, diffuse infiltrative lymphocytosis syndrome (DILS), which is present in HIV patients, has been reported as a cause of kidney injury in HIV.[410] HIV-related thrombotic microangiopathy has been reported as a first presentation of HIV,[407, 408] and associated with hematuria and proteinuria. The mechanism of this disease is not clear but seems to be associated with ADAMTS 13 levels.[411]

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 anti-viral treatment, and genetic predisposition to glomerular injury (e.g., *APOL1* risk alleles), coinfection with other viruses, development of immune complex 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. Limited data show that comorbid conditions (HBV, HCV, TB, and syphilis) can impair long-term prognosis.[412-416] AKI is also a risk factor for long-term progression of CKD in HIV to kidney failure.[417] Whether APOL1 risk alleles should be assessed routinely in patients of west African ancestry with HIVAN remains uncertain.

Figure IGN3. Risk factors and underlying etiologies of CKD in HIV-positive individuals[*]
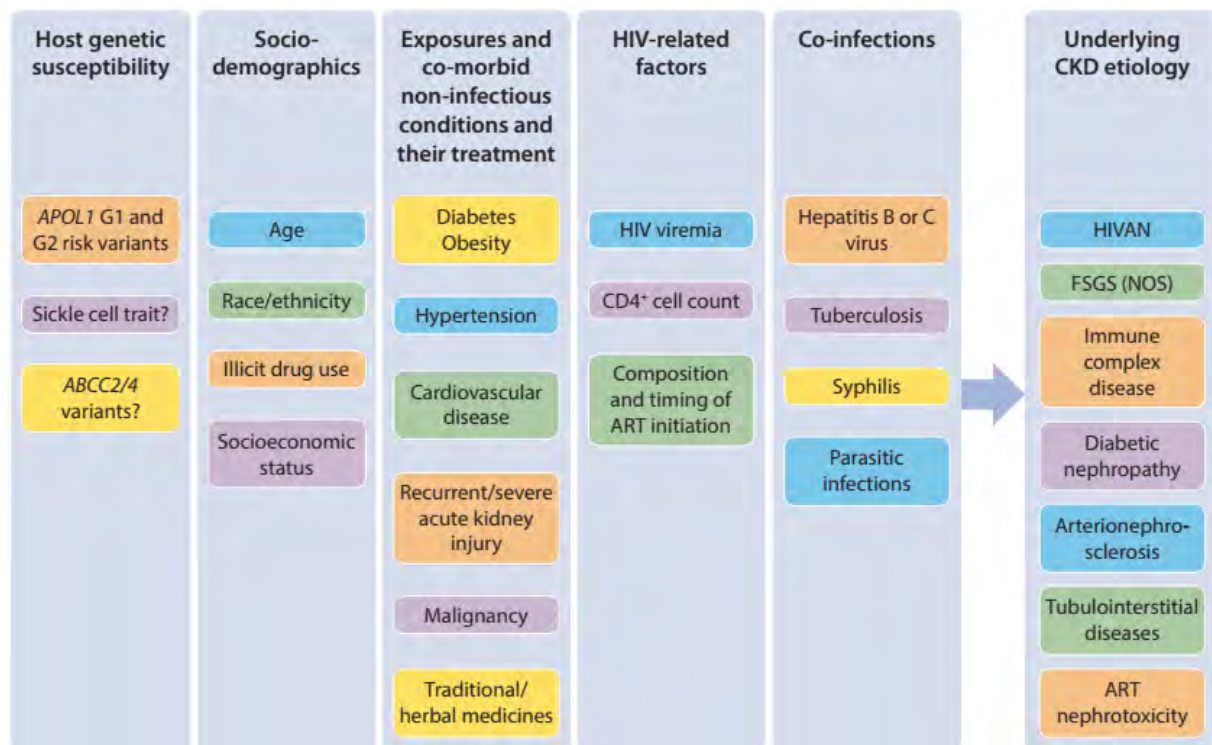
APOL1, apolipoprotein L1; ART, antiretroviral therapy; CKD, chronic kidney disease; FSGS (NOS), focal segmental glomerulosclerosis, not otherwise specified; HIV, human immunodeficiency virus; HIVAN, HIV-associated nephropathy
*From Swanepoel *et al.* Kidney disease in the setting of HIV infection: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference Kidney International (2018) 93, 545–559

7.2.3.3. Treatment

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

The presence of CKD is not a contraindication for antiretroviral therapy (ART) of HIV infection. Current consensus data, based on two large RCTs on the time to initiate ART, START, and TEMPRANO, demonstrate benefit of early initiation of ART at the time of diagnosis, regardless of CD4 count.[405, 418] This Work Group believes that the benefit outweighs the risk to support this recommendation,[419] 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 weak data that the extrapolation to patients with GN seems to support this data.

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 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 with which to base our recommendations.

Considerations for implementation

At this time, there is not enough information to guide choices based on gender or ethnic background, aside from what is considered in standard treatment for HIV-positive patients.

Rationale

At this time, there are no RCTs for HIV-related kidney disease.[420] 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.[421] Data from several RCTs suggest that ART is beneficial in both preservation and improvement of kidney function in patients without CKD with HIV.[405, 420, 422, 423] A decrease in HIV viral load during ART is associated with kidney function improvement, while an increase in viral load is associated with worsening kidney function.[406, 424, 425]

Treatment of HIV-related GN is mostly extrapolated from HIVAN. Observational studies, data from uncontrolled or retrospective studies,[420, 426-430] and from an RCT[431] suggest that HAART (defined as combination ART therapy with three or more 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.[432] 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).[432] The use of HAART has also been associated with improved kidney survival in patients with HIVAN.[433]

Antiviral therapy has been associated with GFR improvements in HIV patients with both low CD4 lymphocyte counts and impaired baseline kidney function, supporting an independent contribution of HIV-1 replication to chronic kidney disease in advanced HIV disease.[434] Early observational studies suggested a benefit for ACEi.[435] Several retrospective observational or uncontrolled studies conducted before or during the initial phases of ART reported variable success with the use of corticosteroids in patients with HIV-associated kidney diseases.[433, 436, 437] There is only one study using cyclosporine in 15 children with HIV and NS.[438] These early observational studies suggested a benefit for ACEi and corticosteroids in HIV-mediated kidney disease, but the studies were 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.[435] There is no RCT that evaluates the value of ART therapy in patients with HIVAN.[420] 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,[439-441] but other data to suggest that antiviral therapy is not specifically beneficial in HIVICK.[399]

With ART, outcomes of patients receiving kidney replacement therapy are the same as in HIV-negative counterparts.[442] HIV patients can now undergo transplantation as a therapeutic option

Practice Point 7.2.3.3.1. A decision for the use of steroids 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 steroid 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.[443] This is consistent with other studies that have demonstrated steroids have improved function in HIVAN.[404, 430, 435] The risk of steroids versus the benefit must be individually balanced.

<div align="center">

RESEARCH RECOMMENDATIONS

</div>

- RCTs are needed to evaluate the efficacy of ART in HIV-associated glomerular diseases, both podocytopathies, and immune-complex diseases.
- RCT is needed to evaluate the role of other therapies (e.g., RAS inhibition, steroids, etc.) in combination with ART in the treatment of HIV-associated kidney diseases.
- RCTs are needed to help determine optimal kidney replacement therapy and transplant regimens for HIV-associated kidney diseases.

- RCTs are needed to 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, with areas of socioeconomic depression and inadequate sanitation. This section will cover 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 *S. mansoni*.[444] Five patterns of schistosomal glomerular pathology have been described by the African Association of Nephrology (AFRAN). (Table IGN3) A sixth pattern has been proposed to describe the pathology associated with schistosomal GN and HCV coinfection. It should be recognized that in highly endemic areas, the association of GN with schistosomiasis may be coincidental rather than causal.

Table IGN3. Five patterns of schistosomal glomerular pathology

AFRAN classification	Etiology
I Mesangial proliferative	*Schistosoma hematobium* *Schistosoma mansoni*
II Proliferative exudative	*Schistosoma hematobium* *Schistosoma mansoni* *Salmonella*
III Membranoproliferative	*Schistosoma hematobium* *Schistosoma mansoni*
IV Focal segmental glomerulosclerosis	*Schistosoma mansoni*
V Amyloidosis	*Schistosoma hematobium* *Schistosoma mansoni*
VI Cryoglobulinemia	*Schistosoma mansoni* Hepatitis C

Many patients may have asymptomatic and self-limited glomerular disease. GN is most commonly seen in young male adults. Histological studies have documented glomerular lesions in 10% to 12% of cases.[445] 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% to 15% of patients. The severity of glomerular lesions and proteinuria correlates with liver macrophage dysfunction and decreased immune complex clearance.[446]

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.[447] Treatment of coexistent salmonella infection favorably influences the course of GN.[447-450] 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 membranoproliferative GN 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.

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. The drugs should be given with food, separated by at least four to six hours. The tablet should not be chewed. Praziquantel dosing is effective in curing 60% to 90% patients with schistosomiasis. Oxamiquine is used for praziquantel-resistant patients or those with refractory schistosomal disease.[451] Successful treatment can prevent development of glomerular disease. However, established schistosomal GN does not respond to either antiparasitic agent.[444] 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.

Table IGN4. Dosing of antischistosomal agents

Dosing	Praziquantel	Oxamiquine
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

There is no established role for steroids 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.[357] (https://kdigo.org/wp-content/uploads/2017/02/KDIGO-2018-Hep-C-GL.pdf)

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.[452] 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 serum creatinine 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.[452]

RESEARCH RECOMMENDATIONS
- 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 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 health-care facilities. Glomerular involvement is infrequent. LM reveals diffuse proliferative MPGN, MCD, or chronic-sclerosing GN, or the collapsing variant of FSGS.[453] Microfilariae may be found in the arterioles, glomerular and peritubular capillary lumina, tubules, and interstitium.[453]

IF and EM show immune deposits along with worm antigens and structural components.[454, 455] Urinary abnormalities have been reported in 11% to 25% and NS is seen in 3% to 5% of patients with loiasis and onchocerciasis, especially those with polyarthritis and chorioretinitis.[455, 456] Proteinuria and/or hematuria was detected in over 50% of cases with lymphatic filariasis, 25% showed glomerular proteinuria.[457, 458]

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 anti-filarial therapy in patients with non-nephrotic proteinuria and/or hematuria. An increase in proteinuria or decline in kidney function can follow initiation of diethylcarbamazepine or ivermectin,[458, 459] probably due to an exacerbation of the immune process secondary to antigen release into circulation after death of the parasite.[460] Therapeutic apheresis has been utilized to reduce the microfilarial load and prevent antigen release before starting anti-filarial treatment.[461] The kidney response to anti-filarial 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 World Health Organization treatment guidelines for filariasis.[462]

Diethylcarbamazine is contraindicated in pregnancy (animal studies have shown adverse effect on the fetus but no well-controlled studies 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 pregnancy category C. Ivermectin is also excreted in breast milk, and use is not recommended during lactation unless delayed maternal treatment outweighs potential risk to the nursing infant.

- Epidemiological 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 IGN4)

Figure IGN4. Global distribution of malaria transmission

Malaria transmission occurs throughout · Malaria transmission occurs in some parts · Malaria transmission is not known to occur
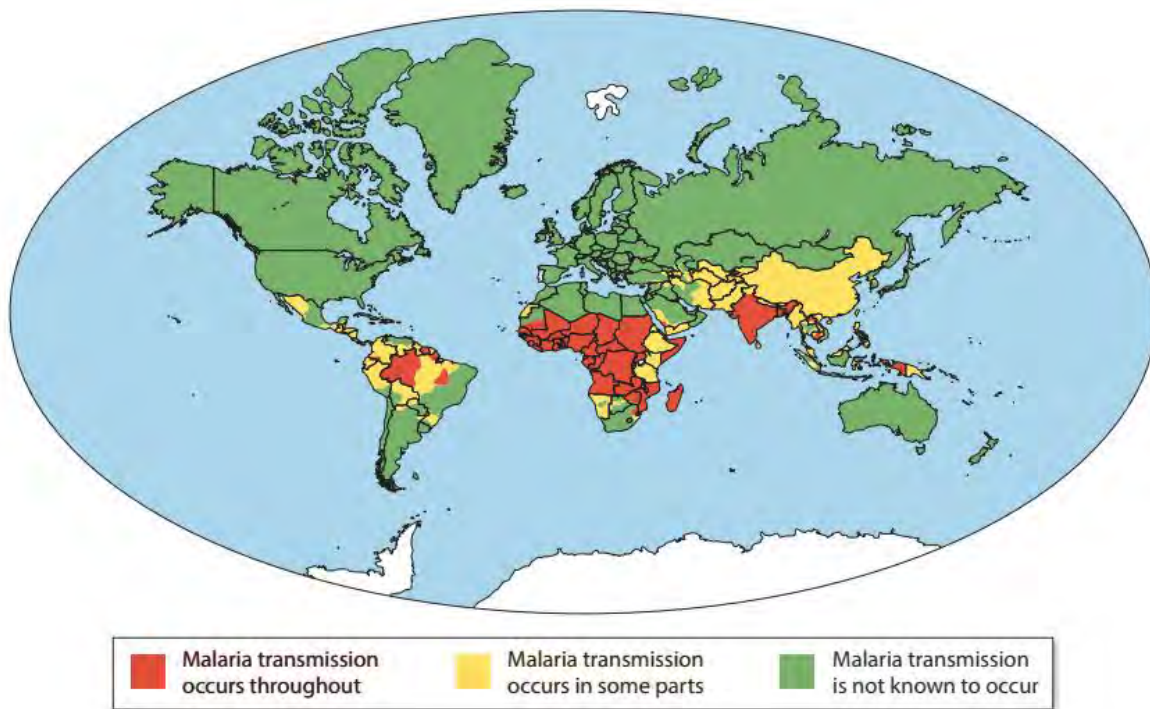
     Malarial infection can cause a diversity of kidney injuries, both acute and chronic. Malarial infection-related GN is believed to primarily be a condition mediated by immune complex formation.

     Malaria-associated AKI can be classified as AKI from acute tubular necrosis (ATN), acute malarial-associated GN (reversible), or chronic and progressive GN (irreversible).[463] 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.[464] (Figure IGN5)

Figure IGN5. Pathophysiology of kidney involvement in malaria[464]
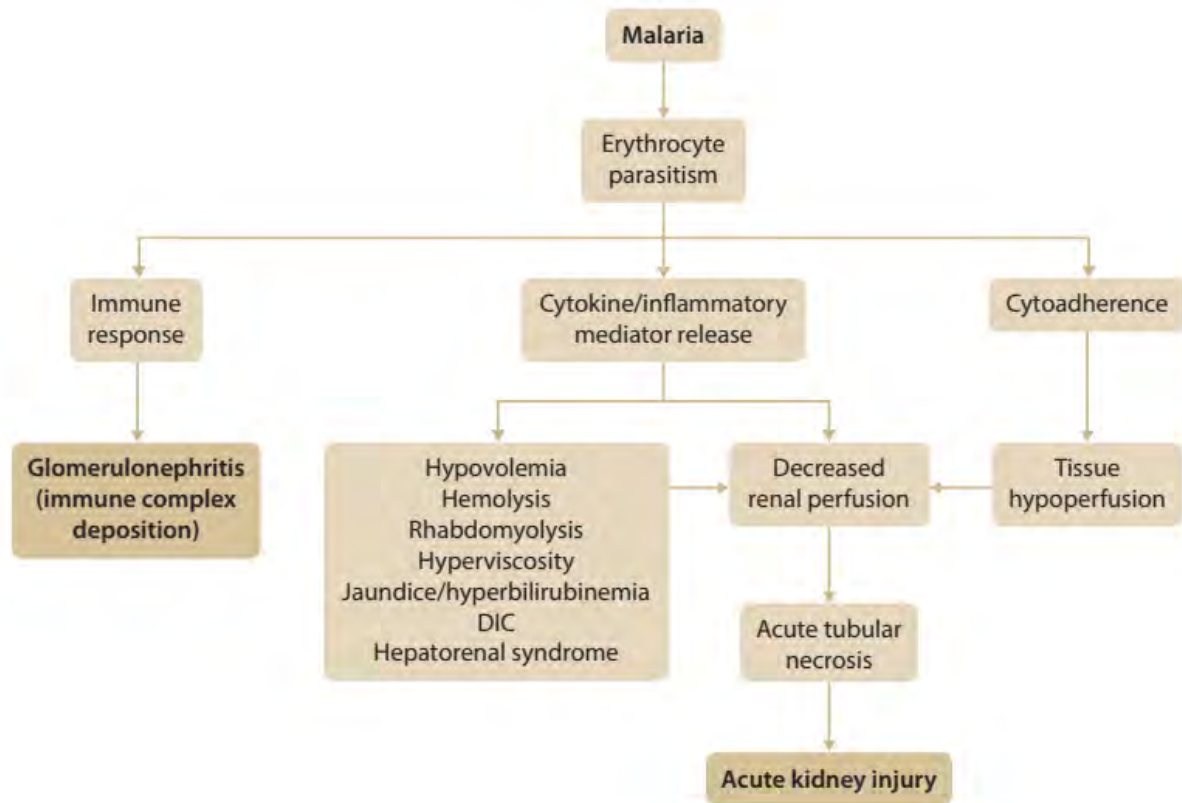
DIC, disseminated intravascular coagulation

The exact incidence of GN in malaria is unknown, estimated to be around 18%.[465] Acute malaria-associated GN can occur with *P. falciparum* or *P. 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 and mesangioproliferative GN.[463]

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).[466, 467] NS, sometimes with impaired kidney function, is a common clinical manifestation. QMN is principally encountered in young children.[464] 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, SLE, rather than QMN.[465, 468, 469]

Table IGN5. Histopathologic staging of quartan malarial nephropathy

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

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.

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 three to five years after primary infection.[470] Complete kidney recovery can be seen in approximately 64% to 79% of cases of AKI or acute GN associated with *P. falciparum* and *P. vivax*.[471-473]

There does not appear to be any role for steroids or immunosuppressant therapy in malarial nephropathy,[466, 467] 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 intravenous or intramuscular artesunate for at least 24 hours, followed by a complete three-day course of ACT once the patient is able to tolerate oral medications.

The World Health Organization also provides detailed recommendations for treatment of malaria.[474]

7.3.3.2. Special situations

In cases of severe malaria in children <6 years when injectable medication cannot be given, the child should receive rectal artesunate and then referred to health care facility where full level of care can be provided.

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 less than six months of age (since G6PD testing can be confounded by fetal hemoglobin in early life), and for women breastfeeding infants less than six months old.

Table IGN6. Antimalarial drugs and pregnancy[475]

Safe	Unsafe
Chloroquine	Halofantrine
Amodiaquine	Tetracycline/doxycycline
Quinine	Primaquine
Azithromycin	
Sulfadoxine–pyrimethamine	
Mefloquine	
Dawson–chlorproguinil	
Artemisinin derivates	
Atovaquone–proguanil	
Lemefantrine	

RESEARCH RECOMMENDATIONS

- Studies of the incidence and prevalence of malarial nephropathy and its response to antimalarial therapy are needed, especially in endemic areas of West Africa.
- RCTs are needed to investigate the role of corticosteroids 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 are needed, as pregnant women are often excluded from clinical trials.[468]

CHAPTER 8. IMMUNOGLOBULIN AND COMPLEMENT-MEDIATED GLOMERULAR DISEASES WITH AN MPGN PATTERN OF INJURY

This chapter replaces the 2012 guidelines 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 diseases that often have a membranoproliferative pattern of injury, including C3 glomerulopathy.[476]

The treatment of MPGN depends upon identification of an underlying cause. In most cases, the MPGN lesion derives from deposition of immunoglobulins and complement 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 IF 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 may be found in many unrelated disorders (Table ICMG1). Identification of the pathogenic mechanisms specific for a disease is critical for appropriate management.

Table ICMG1. Causes of a membranoproliferative pattern of injury

Immunoglobulin/ immune-complex-mediated	**Deposition of antigen–antibody immune complexes as a result of an infection:** • Viral: hepatitis C, 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**
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**
MPGN without immune complexes or complement	• Healing phase of HUS/TTP • Anti-phospholipid (anti-cardiolipin) 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 • Anti-trypsin deficiency
"Idiopathic" forms of MPGN	• None of the conditions above are present

CFB, complement factor B; CFH, complement factor H; CFHR5, complement factor H-related protein 5; CFI, complement factor I; DDD, dense deposit disease; 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

Membranoproliferative lesions were historically classified based on the location of deposits on electron microscopic examination as:

- *Type I MPGN* (MPGN I)-characterized by *subendothelial* and *mesangial* electron-dense deposits consisting of both immunoglobulin and C3

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- *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 the development of a new pathobiology-based classification. The new classification relies on IF examination; deposits are defined as primarily immunoglobulin (monoclonal), codominant polyclonal immunoglobulin and complement, or predominantly complement (Figure ICMG1).[477, 478]

Figure ICMG1. Pathophysiology of MPGN lesions
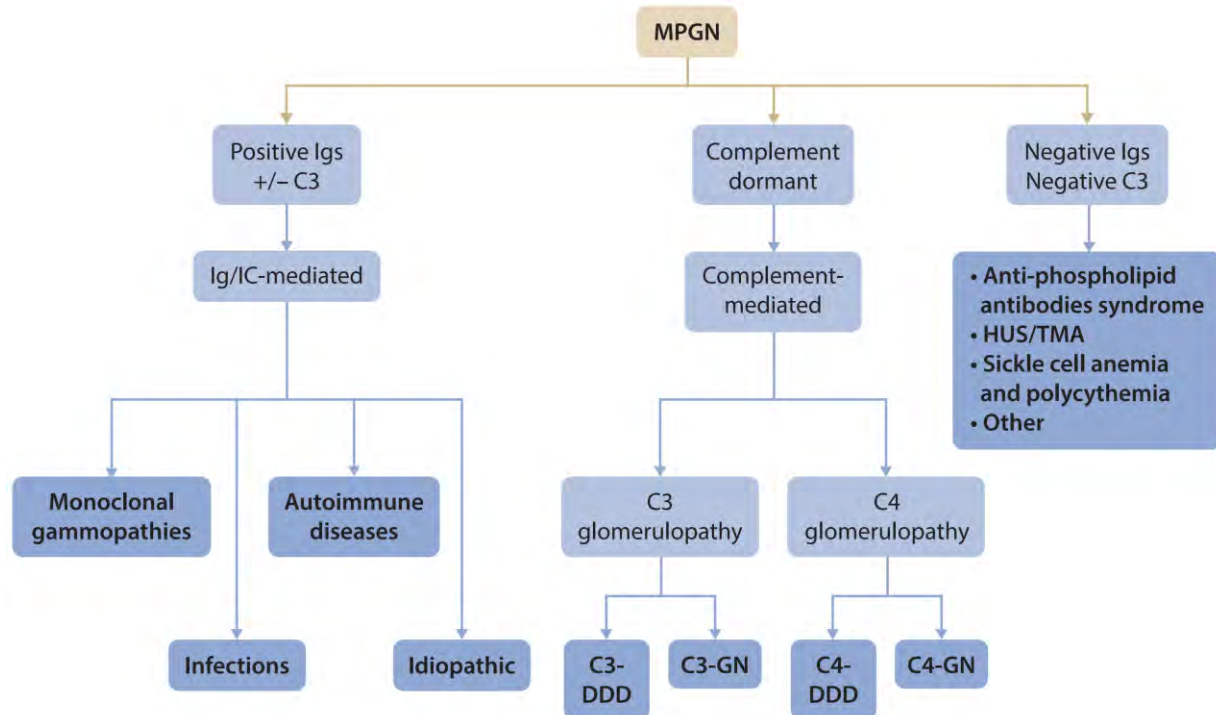
DDD, dense deposit disease, GN, glomerulonephritis; HUS, hemolytic-uremic syndrome; IC, immune complex; Ig, immunoglobulin; MPGN, membranoproliferative glomerulonephritis; TMA, thrombotic microangiopathy

On the basis of the IF findings, MPGN can be broadly divided into immunoglobulin and complement-positive MPGN and complement-dominant MPGN. The presence of immunoglobulin and complement-positive or immunoglobulin alone necessitates evaluation

for infections, autoimmune diseases, and monoclonal gammopathies. 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 LM will depend, in part, on the timing of the kidney biopsy in relation to disease chronicity.[479]

A. Immune complex-mediated GN (ICGN) with an MPGN pattern

ICGN is characterized by the deposition of immune complexes containing both polyclonal immunoglobulins and 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.

B. Glomerulonephritis 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 without overt hematological 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).[480] Kidney injury most commonly results from direct glomerular deposition of the monoclonal immunoglobulin. Examples include immunotactoid glomerulopathy, type I 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.[481] Each type can be differentiated by the distribution and ultrastructural appearance of deposits (i.e., amorphous or organized) by EM.[482] A complete discussion of these entities is beyond the scope of this guideline.

C. Glomerulonephritis with C3 and C4 dominant deposits.

C3 Glomerulopathy (C3G) is a rare entity that is defined by *C3 dominant glomerulonephritis* (a proliferative histologic lesion with C3 deposition at least two orders of magnitude greater than any other immune reactant) on kidney biopsy IF.[483] This category includes both DDD and the newer designation of C3 glomerulonephritis (C3GN).[484] Whereas 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 (i.e., infection-related GN) must be excluded by history where possible. Masked monoclonal immunoglobulin deposits should be considered in patients with a pattern of C3GN when IF shows a small amount of immunoglobulin deposition admixed with C3 deposits. IF studies on paraffin-embedded tissue after pronase digestion may be useful to detect masked glomerular deposits of monoclonal Ig.[485] The MPGN pattern is inconstantly observed in C3G. Hypocomplementemia is present in approximately 50% of cases.[486, 487] The underlying pathophysiological mechanism is presumed to result from dysregulation of the alternative complement pathway.[488] A new entity of complement-mediated GN that is characterized by bright C4d staining but with no or minimal C3 or immunoglobulin deposits on IF studies (C4 glomerulopathy, C4G) has recently been described.[489] Further studies are required to determine its underlying cause.

8.1. Diagnosis
Practice Point 8.1.1. Evaluate patients with ICGN for underlying disease (Table ICGM1).

Consider: 1) 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; 2) 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 hematological malignancy.

Patients with PGNMID by IF must undergo a complete evaluation for a hematological malignancy or an indolent plasma cell or lymphocytic disorder, regardless of age, and must include: 1) serum and urine protein electrophoresis; 2) serum and urine immunofixation; 3) measurement of serum-free light chain levels; 4) hematology consultation to further evaluate for the presence of an underlying B-cell/plasma cell clone producing the monoclonal immunoglobulin.[480] Working with a hematologist is important not only to further evaluate

these patients (i.e., bone marrow biopsy, if indicated) but also because a number of the drugs used to treat these patients are not available to the majority of practicing nephrologists.

Practice Point 8.1.3. If no underlying etiology is found for immunoglobulin/ICGN after extensive workup, evaluate for complement dysregulation (Table ICMG2).

Data support a role for complement dysregulation in ICGN.[490, 491] 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.[492] 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 (Table ICMG2).

Table ICMG2. Evaluation of abnormalities of the alternative pathway of complement*

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, CFHR-5
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)

*Modified from Angioi et al.[31]

†Some complement assays may require referral to specialist/research laboratories and interpretation of complement assays may require expert consultation

‡The presence of a circulating monoclonal gammopathy is less common below the age of 50. Ability to detect a monoclonal protein will depend on the sensitivity of the assay used.

AP50, complement alternate pathway; Bb, activated factor B; C3d, complement component 3d; C4d, complement component 4d; CFB, complement factor B; CFH, complement factor H; CFHRI-5, complement factor H-related protein-5; CFI, complement factor I; CH50, total hemolytic complement; FB, factor B; FH, factor H; FI, factor I; Ig, immunoglobulin; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; 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 C3G.

Both infection-related GN (i.e., in the presence of active infection) and post-infectious GN (i.e., in patients with a preceding infection that resolved) are presumed to be non-recurrent, 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 ICMD1).

C3G in its classic form is a disease of children and young adults[493] 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 is associated with mutations in genes encoding Factor H, Factor I, the complement factor H-related (CFHR), or C3.[488] Recently, the association between the production of a monoclonal protein in older adults and the development of C3G has been described.[487, 494] In patients over the age of 50 with C3G, the prevalence of monoclonal gammopathy ranges from 31% to 83% versus approximately 3% in age-matched controls.[487] However, eight patients, aged 20 to 47, had C3G and a circulating monoclonal protein demonstrating the disease's large age span.[492] The association rests on the epidemiologic findings. Direct evidence demonstrating monoclonal gammopathy as the cause of C3G is lacking in most patients. When evaluated, it appears that a number of monoclonal proteins have complement dysregulating features, primarily through direct activation of the complement alternative pathway.[494] 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.[495] 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 corticosteroids 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 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 (Table ICMD1). In addition, all patients with ICGN are likely to benefit from the usual, routine care considered for other active glomerular disease patients. (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 only 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/day, 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. Since 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, immune suppression 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 steroid-sparing option.

Practice Point 8.2.1.4. For patients with idiopathic ICGN nephrotic syndrome and normal or near-normal serum creatinine, try a limited treatment course of corticosteroids.

Prednisone (or its equivalent) can be initiated at 1 mg/kg per day (maximum dose of 60 to 80 mg/day) for 12 to 16 weeks. If the patient responds, prednisone may be gradually tapered to alternate-day therapy over six to eight months. If there is <30% reduction in proteinuria after 12 to 16 weeks, we recommend tapering and discontinuation of prednisone.

Patients with a contraindication to corticosteroids or unwilling to take steroids can be treated with a CNI. We do not encourage the extended use of steroids, where a steroid-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 corticosteroids and immunosuppressive therapy to supportive care.

Prednisone (or its equivalent) can be initiated at 1 mg/kg per day (maximum dose 60 to 80 mg/day) for 12 to 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 to 16 weeks are considered to have had an unsatisfactory response. In such patients, reduce the dose of prednisone to 20 mg a day and add MMF. If, after six to 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 per day; maximum 200 mg/day in adults) with prednisone (10 mg/day) for three to six 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 one gram followed 14 days later a second dose of one gram, and repeat this two-gram regime at six months.

In patients with persistent disease activity despite at least six months of MMF plus low dose prednisone or after three to six months of daily oral cyclophosphamide plus prednisone or

rituximab, discontinue corticosteroids 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 corticosteroids and cyclophosphamide.

Initiate treatment with intravenous methylprednisolone (1-3 g) followed by oral glucocorticoids and oral cyclophosphamide or oral glucocorticoids and rituximab using a regimen similar to that used for patients with ANCA-associated vasculitis (AAV - see Chapter 9).

Practice Point 8.2.1.7. For most patients with idiopathic ICGN presenting with an eGFR <30 ml/min/1.73m² treat with supportive care alone.

Unless kidney biopsy shows an active necrotizing crescentic glomerulonephritis or other reason that could support use of immunosuppression (i.e., minimal interstitial fibrosis or concomitant acute tubule-interstitial nephritis), these patients should be treated conservatively with referral for kidney transplant evaluation in due course.

8.2.2. C3 glomerulopathy

An optimal treatment strategy for C3 glomerulopathy 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).[496] This opinion is based primarily on four 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, and if this fails, eculizumab.

Consider treating patients with C3G who have proteinuria >1 g/d and hematuria or have 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 C3G patients who received immunosuppressive treatment (corticosteroids alone or combined with other drugs). Immunosuppression did not seem to reduce progression to kidney failure as compared to untreated individuals.[497] Similar results were obtained by Servais *et al*. in a cohort of 85 C3G patients.[491]

More recent data showed encouraging results with MMF. Rabasco *et al*. reported a relative treatment advantage with MMF in a cohort of 60 C3G patients.[498] In a mean follow-up of 47 months, the 22 patients who received MMF plus steroids 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 immune suppression seen in this retrospective cohort provided the support for the current expert opinion on treatment approach for C3G.[496]

Similarly, Avasare *et al*. reported the kidney outcomes for 30 C3G patients after MMF.[499] After a mean follow-up of three years, two-thirds had either a stabilized or reduced SCr and reduced proteinuria. Ravindran *et al*. reported the kidney outcomes on a subcohort of 144 C3G patients.[487] Of 24 patients given MMF (median follow-up 9.6 months), three had improved kidney outcome measures, and four had stable disease. Fifteen patients worsened. Finally, Bomback *et al*. reported the results of a sub-cohort of their 111 C3G patients.[486] 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. The single trial conducted to date involved three patients with DDD (including one kidney transplant recipient) and three patients with C3GN (including two kidney transplant recipients), all of whom had proteinuria >1g/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 three patients. After 12 months of twice-weekly eculizumab, three patients had a kidney response (decrease in SCr levels and/or proteinuria), and one 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, six patients (23%) had a global clinical response, six (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 or limited effect on the complement dysregulation that governs C3G.

In the absence of clear evidence, we consider using eculizumab 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 immune suppression in fully characterized idiopathic ICGN and C3G patients 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-C3 glomerulopathy
- RCTs of clone-targeted chemotherapy versus immunosuppression for the treatment of paraprotein-associated glomerular diseases

CHAPTER 9. ANTI-NEUTROPHIL CYTOPLASMIC ANTIBODIES (ANCA)-ASSOCIATED VASCULITIS (AAV)

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 (MPA), and eosinophilic granulomatosis with polyangiitis (eGPA).[500] The kidney lesion associated with these conditions is a pauci-immune focal and segmental necrotizing and crescentic glomerulonephritis (NCGN). Active pauci-immune small-vessel vasculitis is typically associated with circulating anti-neutrophil cytoplasm antibodies (ANCA), and GPA, MPA, and eGPA were grouped under the term "ANCA-associated vasculitis" in the 2012 Chapel Hill definitions of primary systemic vasculitis.[500] 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 ANCA-associated vasculitis (AAV) and is associated with an increased risk of death.[501] 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 to 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, serological testing and interpretation are of great diagnostic importance. A positive test for anti-GBM antibodies suggests anti-GBM disease (formerly Goodpasture syndrome) and a need for urgent plasma exchange without waiting for a positive diagnostic biopsy (Figure ANCA1), whereas a positive test for ANCA is compatible with a diagnosis of AAV. 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.[502] The 2017 revised international consensus on testing of ANCA in GPA and MPA states that high-quality antigen-specific immunoassays are the preferred screening method for MPO- and PR3-ANCA.[503]

Practice Point 9.1.1. In case of a clinical presentation compatible with small-vessel vasculitis in combination with positive MPO- or 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 ANCA1).

Figure ANCA1. Biopsy strategy in suspected kidney vasculitis
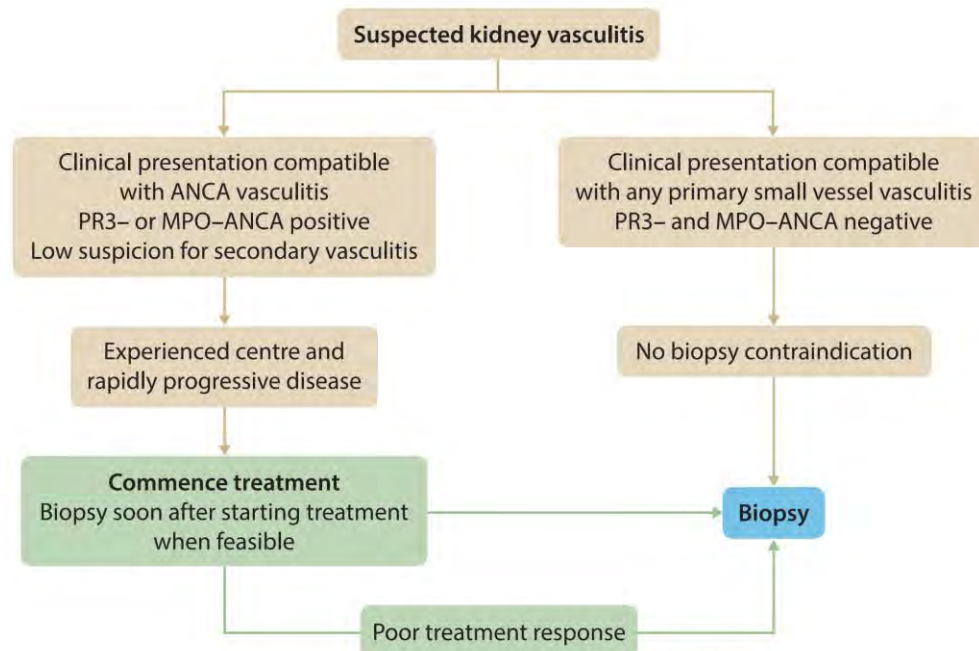
ANCA, anti-neutrophil cytoplasmic antibodies; MPO, myeloperoxidase; PR3, proteinase-3

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. Biopsy remains the gold standard, and in GPA, the diagnostic yield of a kidney biopsy can be as high as 91.5%.[504] The kidney biopsy provides prognostic information through assessment of glomerular, tubule-interstitial, and vascular histopathology.[505] 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 MPA, GPA, or NCGN are persistently ANCA-negative. These patients are treated similarly to ANCA-positive patients, although no study has focused specifically on the treatment of ANCA-negative patients. Considering ANCA-negative patients, it is important to realize that several non-vasculitic diseases may closely mimic small-vessel vasculitis. These include systemic rheumatic diseases, for example, SLE, infections, and malignancies.

Table ANCA1. Definition of disease activity, remission, relapse, and treatment-resistant disease in AAV

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

AAV, ANCA-associated vasculitis; GN, glomerulonephritis

Figure ANCA2. Diagnostic strategy in rapidly progressive glomerulonephritis (RPGN)
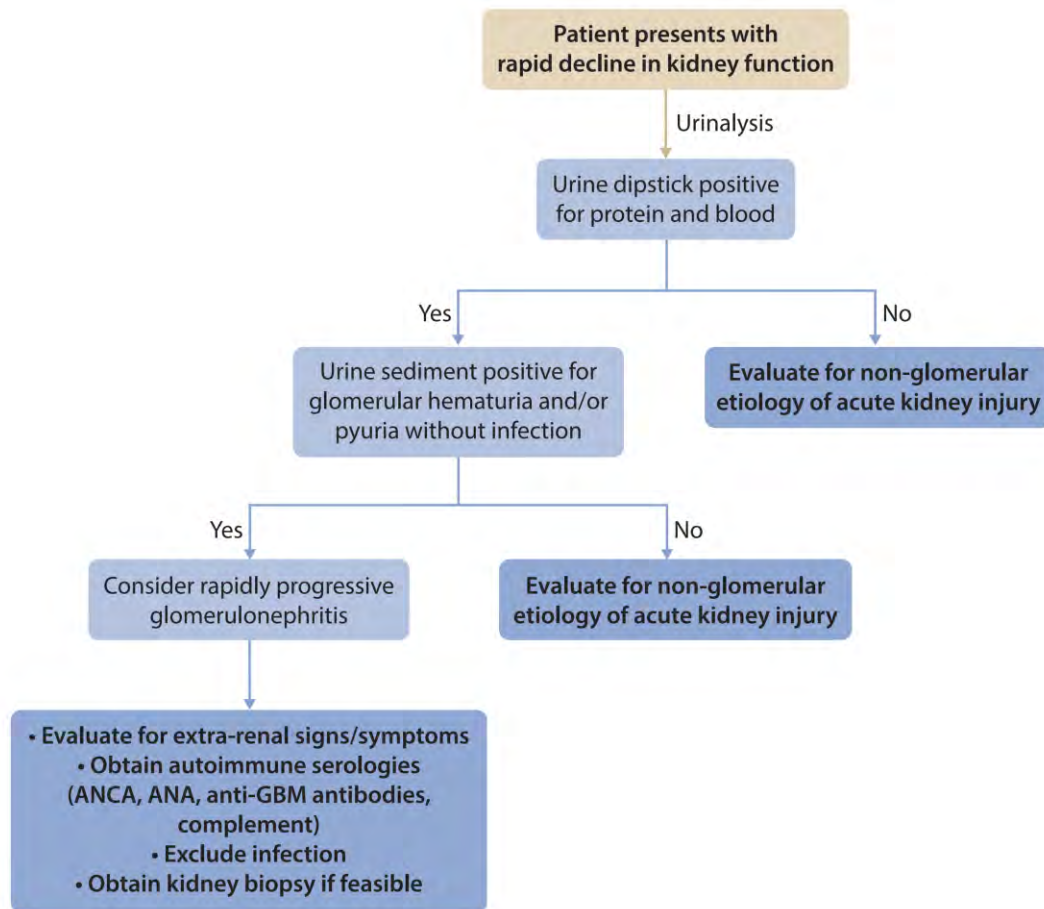
ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibodies; GBM, glomerular basement membrane

Table ANCA2. Frequency of organ involvement in AAV

Organ system	Microscopic polyangiitis (%)	Granulomatosis with polyangiitis (GPA) (%)	Eosinophilic granulomatosis with polyangiitis (EGPA) (%)
Cutaneous	40	40	60
Renal	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

AAV, ANCA-associated vasculitis
*Jenette NEJM 1997

Practice Point 9.1.2. Patients with AAV should be treated at centers with experience in AAV management.

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A center with experience in AAV management is equipped with adequate facilities for rapid diagnosis and management. For diagnosis, adequate serological and histological 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.[506-508] 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 (over 75 years of age) for whom immunosuppressive treatment has been associated with improved survival.[509]

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.[505] Figure ANCA3 and Brix et al.[510]).

Figure ANCA3. Histopathological classification of ANCA-associated glomerulonephritis[*]
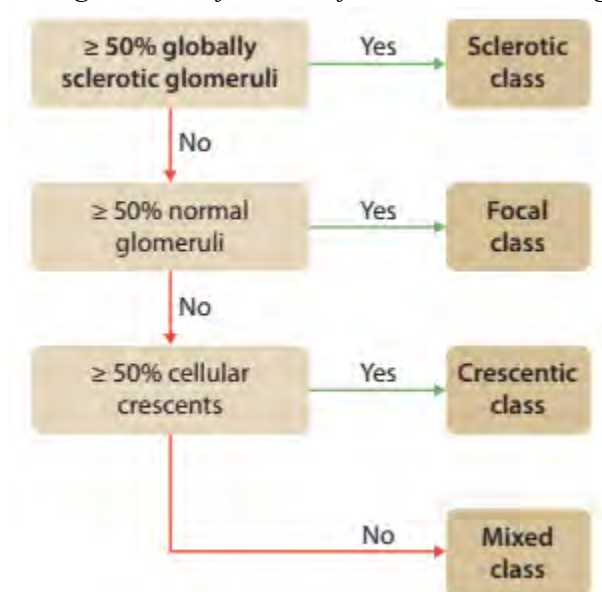
*Biopsies should be scored for glomerular lesions in the following order: globally sclerotic glomeruli, normal glomeruli, and glomeruli with cellular crescents. Biopsies that do not fit into a category based upon a predominant glomerular phenotype will be included in the mixed category (ref Berden JASN, 2010; 21:1628-36).

In validation studies of the histopathological classification by Berden, more than 50% normal glomeruli in the focal class were associated with a favorable outcome, whereas more than 50% sclerotic glomeruli were associated with a poor outcome.[511] Also, in the kidney risk score developed by Brix, a higher percentage of normal glomeruli (above 25%) was associated with favorable kidney outcomes.[510] However, regarding the crescentic class (more than 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 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 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 ANCA1).

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, but 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. PR3-ANCA-positive patients experience more relapses than MPO-positive patients.[512] The achievement of ANCA-negativity after induction treatment is associated with a lower risk of relapse.[513, 514] Both a rise or persistence of ANCA are only modestly predictive of future disease relapse.[515] 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

9.3.1. Induction

Treatment of AAV is generally divided into an initial phase commonly termed "induction", followed by a "maintenance" phase.

> **Recommendation 9.3.1.1. We recommend that corticosteroids 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 >354 µmol/l; >4 mg/dl) kidney disease, limited data for induction therapy with rituximab are available. Only in a small proportion of patients with the non-severe disease (non-life threatening or no RPGN) can methotrexate (MTX) or MMF in combination with corticosteroids be considered as alternative agents, but relapse rates, especially for PR3-ANCA patients, are high with these agents.

Key information
Balance of benefits and harms

Cyclophosphamide, in combination with corticosteroids has been used as induction therapy in several RCTs. In two RCTs, rituximab alone or in combination with two cyclophosphamide pulses was shown to be equally effective as cyclophosphamide, but with a similar rate of infectious complications (Table S30[516-518]). However, *post hoc* analysis of the RAVE trial found a superior remission rate for the PR3-ANCA subgroup at six months treated with rituximab, with an OR of 2.11 (95% CI 1.04, 4.30) in analyses adjusted for age, sex, and new-onset versus relapsing disease at baseline.[519] In patients with PR3-AAV and relapsing disease, more patients achieved remission at six and 12 months with rituximab, with an OR of 3.57 (95% CI 1.43, 8.93) at six months and an OR of 4.32 (95% CI 1.53, 12.15) at 12 months (Table S31[519]). No association between treatment drug and remission was observed in patients with MPO-AAV.

Regarding the route of cyclophosphamide administration oral and intravenous, cyclophosphamide resulted in similar outcomes. With intravenous cyclophosphamide, a reduction of the total cyclophosphamide dosage is achieved compared to oral cyclophosphamide. In the CYCLOPS study, this resulted in a lower rate of leukopenia (Table S32[518, 520]). Nevertheless, more patients tended to experience relapses after intravenous 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 both PR3- and MPO-ANCA patients but a much-increased relapse risk in those with PR3-ANCA in the MYCYC trial (Table S33[518, 521-524]).

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 (Table S34[518, 525, 526]).

Corticosteroids are major contributors to adverse events. Intravenous methyl prednisolone (doses 1-3g) is widely used for more severe presentations but has not been tested in an RCT. Oral prednisolone/prednisone starting at 1.0 mg/kg/day has been used in most RCTs, again without direct RCT support. The rate of reduction of corticosteroids varies between studies with some aiming for withdrawal by month five, while others continue between 5-10 mg/day after six months.[527] The PEXIVAS trial demonstrated that for patients with GFR <50 ml/min/1.73 m^2, a more rapid reduction was as effective but safer than a "standard" corticosteroid tapering regimen. In the RAVE trial, the rituximab group had a lower corticosteroid exposure, and observational studies have supported early corticosteroid removal when rituximab is used (Table ANCA5).

Complement-targeted therapy might be another strategy to reduce glucocorticoid exposition. The CLEAR trial showed that C5a receptor inhibition with CCX168 avacopan might be effective and could potentially replace glucocorticoid treatment in ANCA-associated vasculitis.[528] Subsequently, the ADVOCATE study is a phase 3 study comparing induction with CCX168 avacopan versus standard glucocorticoid induction therapy in combination with rituximab or cyclophosphamide followed by azathioprine.[529] Currently, the data of this study have not been published, and these were not included in the systematic review by the ERT.

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 (Table S34[516-518]). The critical outcome, all-cause mortality, was included; however, there were no cases reported. ESKD was not included as an outcome in the two 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 six 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 one study). There were no differences in kidney outcomes, and those with SCr >354 μmol/l were excluded. Finally, follow-up was short at 18 months.

The studies comparing continuous oral versus intravenous pulse cyclophosphamide were not blinded (participants and study personnel) (Table S35[518, 530-532]). Overall, the quality of evidence on the important endpoints 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 (Table S32[518, 520]). The quality of the evidence was low for all critical outcomes due to imprecision, as there was only one 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 (Table S33[518, 521-524]). 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 and Tunin *et al.* studies had an independent, blinded adjudication committee assess the primary endpoint of complete remission at six months, and hence the quality of the evidence for this outcome has been rated as high.

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 intravenous cyclophosphamide. Patients treated with intravenous pulse cyclophosphamide may have an increased risk of relapse, as reported in the CYCLOPS study.

Corticosteroids 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 corticosteroid requirement, particularly desirable in those at higher risk of corticosteroid toxicity.[517, 533] Alternatively, C5a receptor inhibition with avacopan might be effective and could potentially replace glucocorticoid treatment in ANCA-associated vasculitis.[528] The results of the ADVOCATE study comparing induction with standard glucocorticoids versus CCX168 (avacopan) in combination with rituximab or cyclophosphamide followed by azathioprine have not been published.

Resources and other 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 intravenous 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 both patients treated with intravenous or oral cyclophosphamide, frequent monitoring for treatment toxicity, in particular leukopenia, is important.

Rationale

Cyclophosphamide, in combination with corticosteroids, has been applied as induction therapy in multiple RCTs. In two RCTs, rituximab has been shown equally effective in inducing remission to cyclophosphamide.[516, 517] Rituximab compared to cyclophosphamide probably has little or no difference in relapse rate at one to six 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.[534, 535]

In the RAVE study, patients with relapsing disease more often achieved remission at six and 12 months in the rituximab group compared to the cyclophosphamide-azathioprine group.[536] Analysis of the data according to ANCA status showed that patients with PR3-AAV were significantly more often in complete remission at six months than patients treated with cyclophosphamide-azathioprine.[519]

An important consideration when interpreting the RAVE trial is that it excluded patients with severe kidney disease (SCr >354 µmol/l) and alveolar hemorrhage. In contrast, the RITUXVAS study included such patients and showed that rituximab combined with two cyclophosphamide pulses and glucocorticoids was comparable to cyclophosphamide for remission induction and number of adverse events.[516]

Regarding the administration route of cyclophosphamide, four RCTs compared induction therapy with intravenous pulse versus continuous oral cyclophosphamide.[518, 520, 530-532] Intravenous cyclophosphamide and oral cyclophosphamide resulted in a similar rate of complete remission but less leukopenia was seen in patients given intravenous cyclophosphamide. In the CYCLOPS study, a higher rate of relapse was reported with intravenous pulse cyclophosphamide. This reflects the 50% reduction in cyclophosphamide exposure seen with IV regimens; shorter course oral cyclophosphamide regimens 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.[516, 518, 521, 522] Compared to cyclophosphamide, methotrexate was associated with a higher relapse rate [RR 1.50 (95% CI 1.03, 2.17)].[518, 537] 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/day 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 six months The lower dose regimen was non-inferior for efficacy and safer, thus is preferred.[539] All patients in the PEXIVAS trial received an initial dose of intravenous methylprednisolone between 1 and 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 (Table ANCA6).

Low-dose sulfamethoxazole/trimethoprim, or alternative, is advised for pneumocystis pneumonia prophylaxis for the duration of the cyclophosphamide course or for six months following rituximab. Longer-term use may be considered in those receiving repeated rituximab infusions, for those with structural lung disease or requiring ongoing immunosuppressive or glucocorticoid therapy.

In a retrospective study, the IgG level before rituximab correlated with hypogammaglobulinemia post-rituximab.[540] Therefore, IgG levels should be measured at baseline and every six months for patients treated with rituximab. A low level at baseline (defined as IgG <3 g/l, Table ANCA6) may predict a greater risk of secondary immunodeficiency with rituximab.[540]

Practice Point 9.3.1.1. A recommended treatment algorithm for AAV is given in Figure ANCA4.

Figure ANCA4. Recommended treatment regimen for AAV
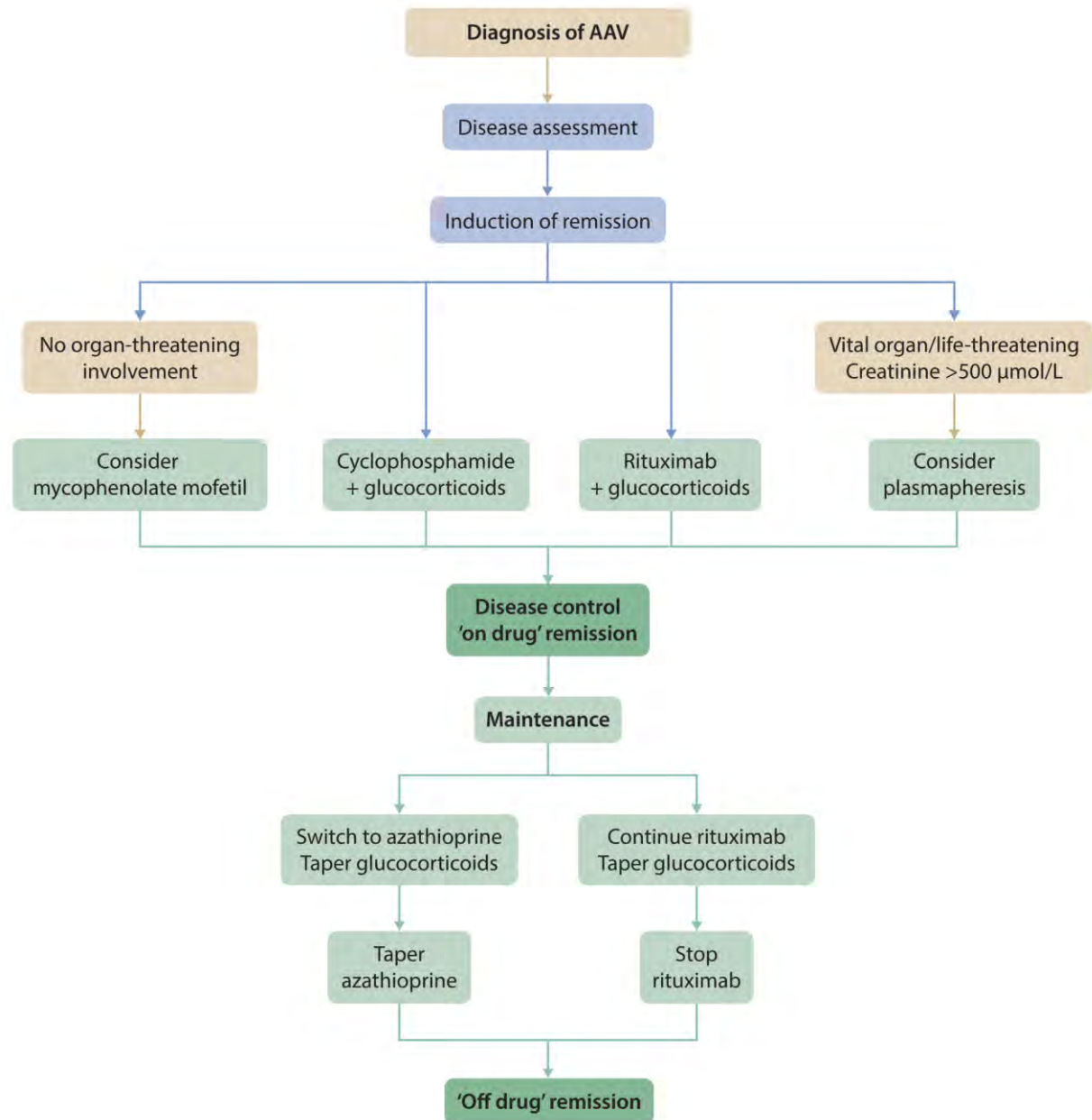
AAV, ANCA-associated vasculitis

Practice Point 9.3.1.2. In patients presenting with markedly reduced or rapidly declining GFR (SCr >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 above 354 μmol/l (>4 mg/dl) 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 four weekly infusions of rituximab and two intravenous cyclophosphamide pulses with glucocorticoids might be an alternative to intravenous cyclophosphamide for three to six months. In the RITUXVAS trial, this resulted in a similar rate of remission and adverse events as cyclophosphamide.[516]

Practice Point 9.3.1.3. Considerations for choosing between rituximab and cyclophosphamide for induction therapy are given in Table ANCA3.

Table ANCA3. Factors for consideration when choosing between rituximab and cyclophosphamide for induction therapy of AAV

Rituximab preferred	Cyclophosphamide preferred
Children and adolescents	Rituximab difficult to access
Pre-menopausal women and men concerned about their fertility	Severe GN (SCr >350 μmol/l at diagnosis), combination of two intravenous pulses of cyclophosphamide with rituximab can be considered
Frail older adults	
Glucocorticoid-sparing especially important	
Relapsing disease	
PR3–ANCA disease	

AAV, ANCA-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibodies; 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 Table ANCA4.

Table ANCA4. Considerations for the route of administration of cyclophosphamide for AAV

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

Practice Point 9.3.1.5. Discontinue immunosuppressive therapy after three months in patients who remain dialysis-dependent and who do not have any extrarenal manifestations of disease.

Practice Point 9.3.1.6. Recommendations for oral corticosteroid tapering are given in Table ANCA5.

     Following cyclophosphamide induction, oral prednisolone should be reduced to a dose of 5 mg/day by six months. Following rituximab induction, prednisolone can be withdrawn by six months.

     The dose of oral prednisolone is 1 mg/kg/day for the first week, then a programmed reduction is followed. (Table ANCA5) Intravenous methylprednisolone is widely used initially for patients with more severe presentations at a dose of 1 to 3 g in total. This is not evidence-based and is likely to contribute to glucocorticoid toxicity.

Table ANCA5. Prednisolone tapering regimen for AAV

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		

Practice Point 9.3.1.7. Recommendations for immunosuppressive dosing are given in Table ANCA6.

Table ANCA6. Immunosuppressive drug dosing for AAV

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			

GFR, glomerular filtration rate; i.v., intravenous; MMF, mycophenolate mofetil

Practice Point 9.3.1.8. Consider plasma exchange for patients requiring dialysis or with rapidly increasing serum creatinine, and in patients with diffuse alveolar hemorrhage who have hypoxemia.

The MEPEX trial showed improved kidney outcomes in patients with severe kidney disease (SCr > 500 µmol/l) who were treated with plasma exchange.[541] Also, a meta-analysis that looked at the addition of plasma exchange showed a reduction in the occurrence of ESKD at three and 12 months after diagnosis (Table S36). The PEXIVAS trial failed to demonstrate that plasma exchange delayed the time to ESKD or death for AAV patients presenting with GFR <50 ml/min/1.73 m² or alveolar hemorrhage over a median follow-up of 2.9 years.[539] *Post hoc* studies of the PEXIVAS dataset and meta-analysis may generate results relevant to future recommendations. The routine use of plasma exchange is not recommended for patients presenting with a GFR <50 ml/min/1.73 m², but plasma exchange can be considered in those with more severe presentations (SCr >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 ANCA-positive patients were also positive for anti-GBM antibodies, and 32% of anti-GBM-positive patients had detectable ANCA.[542] Thus, double-positivity for both ANCA and anti-GBM antibodies is common. These patients behave more like anti-GBM disease than AAV, supporting the initiation of plasma exchange. However, unlike pure anti-GBM disease, these patients have a tendency to relapse and should receive maintenance therapy.

*Table ANCA7. Plasma exchange dosing and frequency for AAV**

Antineutrophil cytoplasmic antibody vasculitis with severe kidney disease	Vasculitis with diffuse pulmonary hemorrhage	Vasculitis in association with anti-glomerular basement membrane 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-glomerular basement membrane antibodies are undetectable

* If a patient is at risk of bleeding, volume replacement should be with fresh, frozen plasma.

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 cyclophosphamide plus glucocorticoids. Maintenance regimens have evolved over time, and several immunosuppressive medications have been evaluated. Azathioprine, given after at least three months of cyclophosphamide induction, was found to be equally effective for relapse prevention with less leukopenia as extending cyclophosphamide for 12 months (Table S37[543]). Compared to azathioprine, MMF maintenance was less effective in relapse prevention and did not have a superior infection profile (Table S38[518, 544]). In contrast, methotrexate and azathioprine were found to be equally effective in relapse prevention with similar toxicity and long-term outcomes (Table S39[518, 545]). Overall, azathioprine has been the standard immunosuppressive used for maintenance of remission in AAV over the last several years.

The duration of azathioprine maintenance has been examined. Compared to tapering maintenance azathioprine after 12 months of treatment, tapering after four years of therapy decreased relapse rate, and the incidence of kidney failure.[526, 544] 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 (Table S40[518, 526, 546]).

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 (MAINRITSAN).[547] However, after rituximab induction for relapsing AAV, rituximab maintenance decreased major and minor disease relapses compared to azathioprine (RITAZAREM).[548] No difference in infection rate was found between azathioprine and rituximab (Table S41[518, 547, 549, 550]).

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) (Table S42[518, 551]).

Addition of trimethoprim/sulfamethaxozole (160/800 mg) compared with placebo in maintenance therapy may have little or no difference on complete remission at one or two years. (Table S43[552, 553])

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 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 confidence intervals and serious imprecision, in particular for the critical outcomes of all-cause mortality and ESKD. The quality of the evidence for azathioprine as maintenance therapy was moderate for relapse and adverse events in RCTs that compared azathioprine with cyclophosphamide (Table S37[518, 543]), methotrexate (Table S43[518, 545]), MMF (Table S38[518, 544]), and RCTs that compared extended with standard azathioprine therapy (Table S40[518, 526, 546]). The quality of the evidence was downgraded because of imprecision, as there was only one study for each comparison. However, the comparison of MMF with azathioprine exhibited low quality of evidence for infection because of very wide confidence intervals 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 was only one RCT that examined this

comparison (Table S41[518, 547]). 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 (Table S42[518, 551]). The quality of the evidence was downgraded from this RCT because of very serious imprecision, as there was only one study and outcomes exhibited very wide confidence intervals 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 REMAIN trial, low-dose steroids were combined with azathioprine maintenance.[526] In a meta-analysis of observational studies and RCTs, a longer course of glucocorticoids in AAV was associated with fewer relapses.[554]

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.[512, 555] In the RAVE study, patients did not receive maintenance therapy after induction with rituximab, and a high relapse rate was seen in both rituximab and cyclophosphamide-azathioprine groups, but corticosteroids were withdrawn before six months.[517] 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 corticosteroids 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.

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.[556] Therefore, in MPO-ANCA patients who are dialysis-dependent and have no extrarenal manifestations of disease, despite thorough review including chest 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 steroids. 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.[557]

Therefore, this Work Group prefers rituximab for maintenance therapy, particularly for patients with known relapsing disease, PR3-AAV, 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 suggests an increasing risk of secondary immunodeficiency in this population.

Resources and other 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 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.[558] 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 one RCT. It probably decreases major relapses; no difference in adverse events was reported (MAINRITSAN).[547] Azathioprine maintenance up to 18 months after induction of remission with cyclophosphamide has been shown to be equally effective as continuing cyclophosphamide (CYCAZAREM) for one year and then switching to azathioprine.[543] MMF has not been shown to be more effective than azathioprine.[544]

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, AZA-ANCA) limits relapse rate after four versus two years.[526, 546]

As the aim of maintenance therapy in 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, cardiovascular, or lung involvement.[512, 555] Persistent ANCA-positivity after induction of remission has also been reported.[526, 559] The RCT that tested extended azathioprine for four years versus azathioprine for two years in PR3-AAV patients that remained ANCA-positive showed a non-significant difference (at four years, 48% vs 24% relapses in standard vs extended) but was underpowered.[546]

Comparison with other guidelines

Considering other guidelines, the EULAR/EDTA prefers azathioprine and glucocorticoids over rituximab for remission maintenance.[527] According to the reviewed evidence by the ERT, rituximab was found superior to azathioprine, due to lower rates of major relapse. Therefore, this panel prefers rituximab over azathioprine for maintenance therapy in AAV. The EULAR/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 four 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 is based on expert opinion, little evidence is available, and no consensus was reached even among experts.

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.

This Work Group's preference based upon observational reports and unpublished data from the RITAZAREM study would be 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

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(RITAZAREM).[548] However, azathioprine combined with corticosteroids 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 MPO-AAV patients 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 committee.

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 four 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 corticosteroid 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 (Table ANCA8).

Table ANCA8. Factors that increase relapse risk for AAV

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

ANCA, anti-neutrophil cytoplasmic antibodies; PR3, proteinase-3

Practice Point 9.3.2.6. Consider methotrexate for maintenance therapy in patients induced with methotrexate or who are intolerant of azathioprine and MMF, but not if GFR is <60 ml/min/1.73 m².

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Practice Point 9.3.2.7. Considerations for choosing rituximab or azathioprine for maintenance therapy are presented in Table ANCA9.

Table ANCA9. Considerations for using rituximab or azathioprine for AAV maintenance therapy

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

ANCA, anti-neutrophil cytoplasmic antibodies; HBsAg, hepatitis c 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 Table ANCA10.

Table ANCA10. Immunosuppressive dosing and duration of AAV maintenance therapy

Rituximab	Azathioprine	MMF
Scheduled dosing protocol: 1. 500 mg infusion at complete remission, and at months 6, 12, and 18 thereafter 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 year after diagnosis then decrease by 25 mg every 3 months	2000 mg/d (divided doses) at complete remission for 2 years
	Extended azathioprine at complete remission until four years after diagnosis; started at 1.5–2 mg/kg/d for 18–24 months, then decrease to a dose of 1 mg/kg/d until four years after diagnosis, then taper by 25 mg every 3 months. Corticosteroids should also be continued at 5–7.5 mg/d for two years and then slowly reduced by 1 mg every 2 months	

MMF, mycophenolate mofetil

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 grams have been associated with the occurrence of malignancies.[560] 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.[519] Rituximab is therefore preferred for relapsing AAV. The RITAZAREM trial studied the effect of rituximab induction in 187 patients with relapsing GPA/MPA – there was a high rate of remission, >90% by four months.[548]

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.[523, 524] However, if non-severe relapses are treated with MMF, there is an increased rate of future relapse, and corticosteroid 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, non-adherence, 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 extra-pulmonary 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, and glucocorticoid use minimized. Plasma exchange and high-dose intravenous 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 at least six 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 to 0.03 per patient year.[561, 562] This relapse rate was not influenced by remission duration or ANCA status before transplantation.[561]

RESEARCH RECOMMENDATIONS
- RCTs are needed 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 are needed 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% to 60%, depending on the demographics of the population studied.[563-566] Kidney involvement in SLE has been associated with higher mortality, especially for patients progressing to kidney failure.[567-569] The ultimate goal of treating LN is to preserve kidney function and reduce the morbidity and mortality associated with chronic kidney disease 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 10.3.3.1.

10.1 Diagnosis
Practice Point 10.1.1. Approach to the diagnosis of kidney involvement in SLE (Figure LN1)

Figure LN1. Diagnosis of kidney involvement in SLE
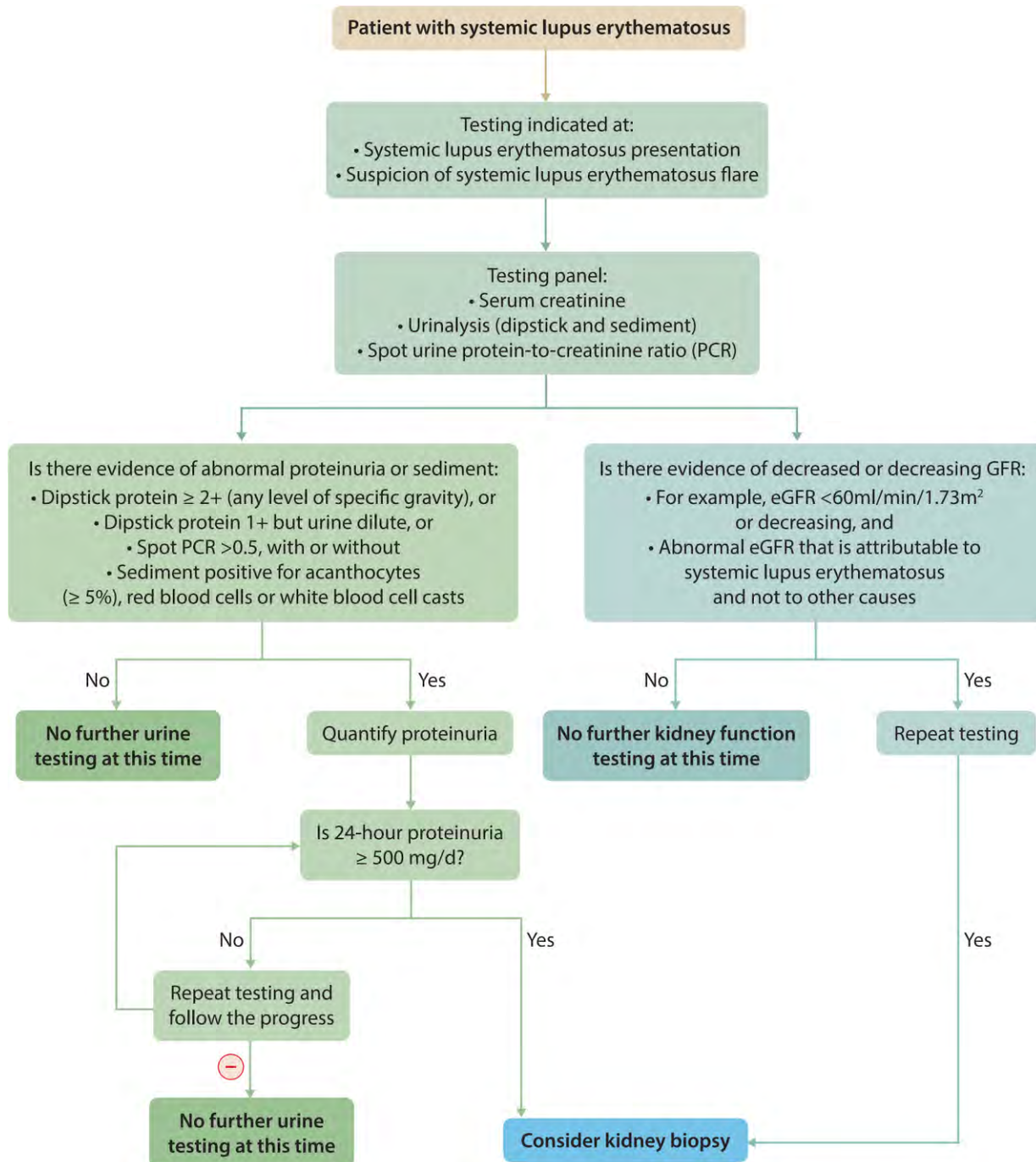
eGFR, estimated glomerular filtration rate

   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.[563-566] There is higher incidence of LN and more severe disease in childhood-onset SLE compared to

adult-onset SLE.[570] Because clinical findings do not always correlate with the extent or severity of kidney involvement,[571, 572] a kidney biopsy is useful to confirm the diagnosis and for the assessment of activity and chronicity features that inform treatment decisions and prognosis.[571-581] Kidney biopsies should be read by an experienced kidney pathologist and classified by the International Society of Neurology and the Renal Pathology Society (ISN/RPS) scheme.[582-584] 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 (Table LN1).

Table LN1. Activity and chronicity items included in LN kidney biopsy report

Items included into the NIH activity score	Evaluation	Points	Score
• Endocapillary hypercellularity • Neutrophils and/or karyorrhexis • Fibrinoid necrosis • Hyaline deposits (wire loop and/or hyaline thrombi) • Cellular/fibrocellular crescents • Interstitial inflammation (interstitial leukocytes)	Not present Present in: <25% 25-50% >50%	0 1 2 3	0–3 0–3 (0–3) × 2 0–3 (0–3) × 2 0–3
		Total activity score	**0–24**
Items included into the NIH chronicity score	**Evaluation**	**Points**	**Score**
• Total glomerulosclerosis (global + segmental) • Fibrous crescents • Interstitial fibrosis • Tubular atrophy	< 10% 10–25% 25–50% > 50%	0 1 2 3	0–3 0–3 0–3 0–3
		Total chronicity score	**0–12**
Other items not included into the scores			
• 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)			

NIH, National Institute of Health

10.2. Treatment

10.2.1. General management of patients with lupus nephritis

Recommendation 10.2.1.1. We recommend that patients with 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,[585, 586] higher response rates to therapy,[585-588] lower incidence of cardiovascular and thrombotic events in patients with antiphospholipid antibodies[589-592] less organ damage,[593-598] improved lipid profile,[599, 600] and better preservation of bone mass.[601]

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.[602-604] 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.[605, 606]

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 randomized, prospective 24-week study 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 an HR of 2.50 (95% CI 1.08, 5.58). The frequency of severe LN flares was also increased but did not reach statistical significance.[607] A systematic review that included 95 reports published between 1982 and 2007, five 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.[608] 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 has been upgraded because of the large reported effect sizes.[582, 587, 596, 609] 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 (Table S44[598, 610]).

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 G6PD deficiency, measurement of G6PD levels is preferred in men, especially those of African, Asian, and Middle Eastern origin, before starting hydroxychloroquine. However, this risk appeared low, according to the findings of a recent report.[611] All patients should have a baseline retinal examination and then annual eye testing, especially after five years of use. Clinicians should be aware that antimalarials may be cardiotoxic (i.e., congestive heart failure, conduction abnormalities) after long-duration therapy or high cumulative exposure. The dosing of hydroxychloroquine is 6.5 mg/kg ideal weight/day or 400 mg/day, and during the maintenance phase, this should be lowered to 4 to 5 mg/kg/day. A 25% lower dose should be given to patients with eGFR <30 ml/min/1.73 m^2.

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 Table LN2.

Table LN2. Measures to minimize the risk of complications related to LN or its treatment

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 • RAAS 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
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

HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; RAAS, renin-angiotensin-aldosterone system

While many of the above recommendations also apply to patients with proteinuric kidney diseases treated with immunosuppression in general (see 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 gender-matched controls in the general population.[612, 613] Infections, cardiovascular complications, and CKD, especially kidney failure, are major causes of death.[567-569, 614] Early deaths are related to infections or disease, while cardiovascular and malignant complications and deaths related to kidney failure account for late mortalities.[615]

Cardiovascular complications in patients with LN

Patients with SLE have both traditional (dyslipidemia, smoking, obesity, etc.) and non-traditional (proteinuria, inflammation, etc.) cardiovascular 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 corticosteroids and CNIs). Regular evaluation of various risk factors and timely treatment are essential to prevent premature cardiovascular complications.[616]

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.[609, 612, 617] 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.[617] Avoidance of over-immunosuppression 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 corticosteroid 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 lupus patients, 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.[620] In a retrospective study from Thailand that included 132 patients with various connective tissue diseases, trimethoprim-sulfamethoxazole was effective in preventing pneumocystis pneumonia, and adverse drug reaction occurred in only 9.4% of SLE patients given prophylaxis.[621] However, a recent retrospective study from Japan reported a drug allergy rate of 41.9% in lupus patients given trimethoprim-sulfamethoxazole prophylaxis with conventional dosing, but only 10.7% in those with gradual introduction of the drug over a nine-day period.[622] Pneumocystis pneumonia is a severe complication in immunosuppressed patients and can result in fatality. Prophylaxis should be actively considered, taking into consideration a patient's allergic diathesis. The rate of *Herpes zoster* is two to ten times higher in patients with SLE than 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 lupus patients, and there is concern whether the adjuvant might affect disease activity. There is also concern that polio vaccination has been associated with lupus flares, while the data on influenza vaccination are conflicting. Response to vaccination is reduced following exposure to high-dose immunosuppression.[623]

Contraception and pregnancy

Pregnancy in patients with LN is associated with increased maternal complications and inferior fetal outcomes compared with healthy individuals, and the risks are higher when LN is active. Some of the frequently used medications in lupus patients are contraindicated during pregnancy, such as MMF, cyclophosphamide, and warfarin. Counseling with regard to contraception and pregnancy should be done early in patients of child-bearing age. 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

Corticosteroid therapy, especially when high doses are used for long durations, increases bone loss.[624, 625] In children, glucocorticoid cumulative dose affects peak bone mass and growth.[626] Individual evaluation of fracture risk can be estimated using patient demographics and clinical history, corticosteroid dose, and the Fracture Risk Assessment Tool (FRAX) score.[627] Calcium (optimal intake 1000-1200 mg/d) and vitamin D supplementation are recommended for LN patients and consideration for oral bisphosphonates according to individual risk assessment.[628, 629]

Malignancies in patients with LN

Patients with SLE have increased risk of malignant tumors, including non-Hodgkin's lymphoma, lung, liver, vulvar/vaginal, thyroid, non-melanoma skin cancer, and the risk (especially with bladder cancer) is increased in patients with a history of exposure to cyclophosphamide.[630, 631] 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.[632] While 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 predispose to the development of SLE or lupus-like disease.[633, 634]

<u>10.2.2. Class I or Class II lupus nephritis</u>

Practice Point 10.2.2.1. Approach to immunosuppressive treatment for patients with Class I or Class II LN (Figure LN2)

Figure LN2. Immunosuppressive treatment for patients with Class I or Class II LN
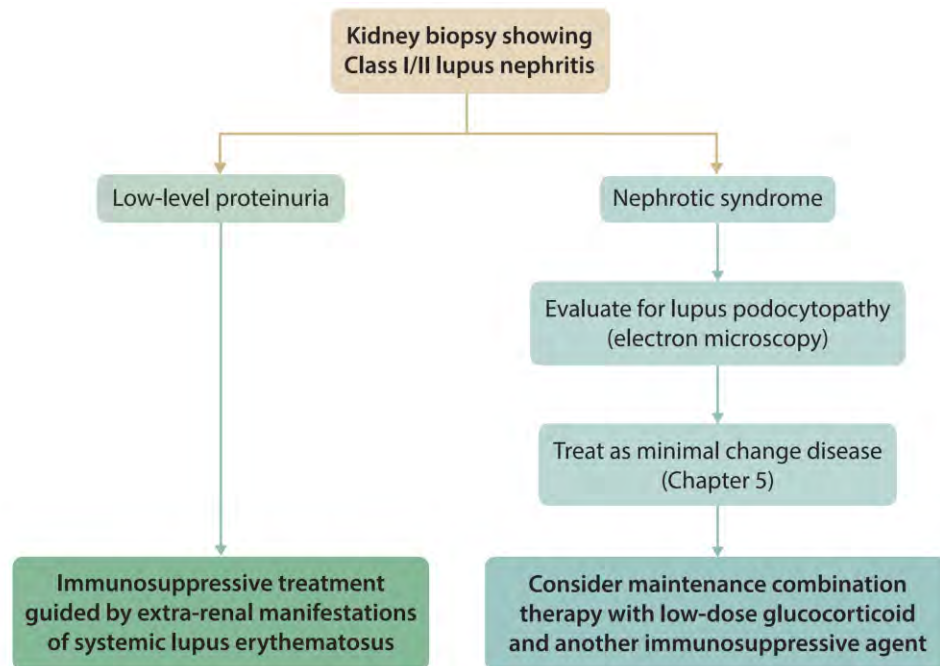
Patients with Class I or Class II LN generally have normal kidney function, low-grade (sub-nephrotic) proteinuria, and sometimes microscopic hematuria. For these patients, no specific immunosuppressive therapy beyond what is being given for non-kidney lupus is needed.[635]

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 EM. Histologically, these patients are similar to patients with MCD, and clinically they behave like MCD and often have a good response to corticosteroid treatment.[636, 637] Although there have been no RCTs, observational data showed that over 90% of patients given corticosteroid monotherapy achieved remission within a median time of four weeks.[636, 638-642] Data on relapse are even more limited, but there appears to be a significant risk of relapse after corticosteroids are tapered.[643] Although optimal duration is not known, maintenance with low-dose corticosteroid 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 corticosteroids plus either low-dose intravenous cyclophosphamide or MPAA *(1B)*.

This recommendation places a high value on the data demonstrating that corticosteroids, 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 recommendation places a relatively lower value on recent data showing comparable efficacy but more rapid achievement of kidney response with triple therapy that included corticosteroids, reduced-dose MPAA, and low-dose tacrolimus when compared to dual therapy that included corticosteroids and cyclophosphamide.

Figure LN3. Recommended approach for initial therapy of active Class III/IV LN
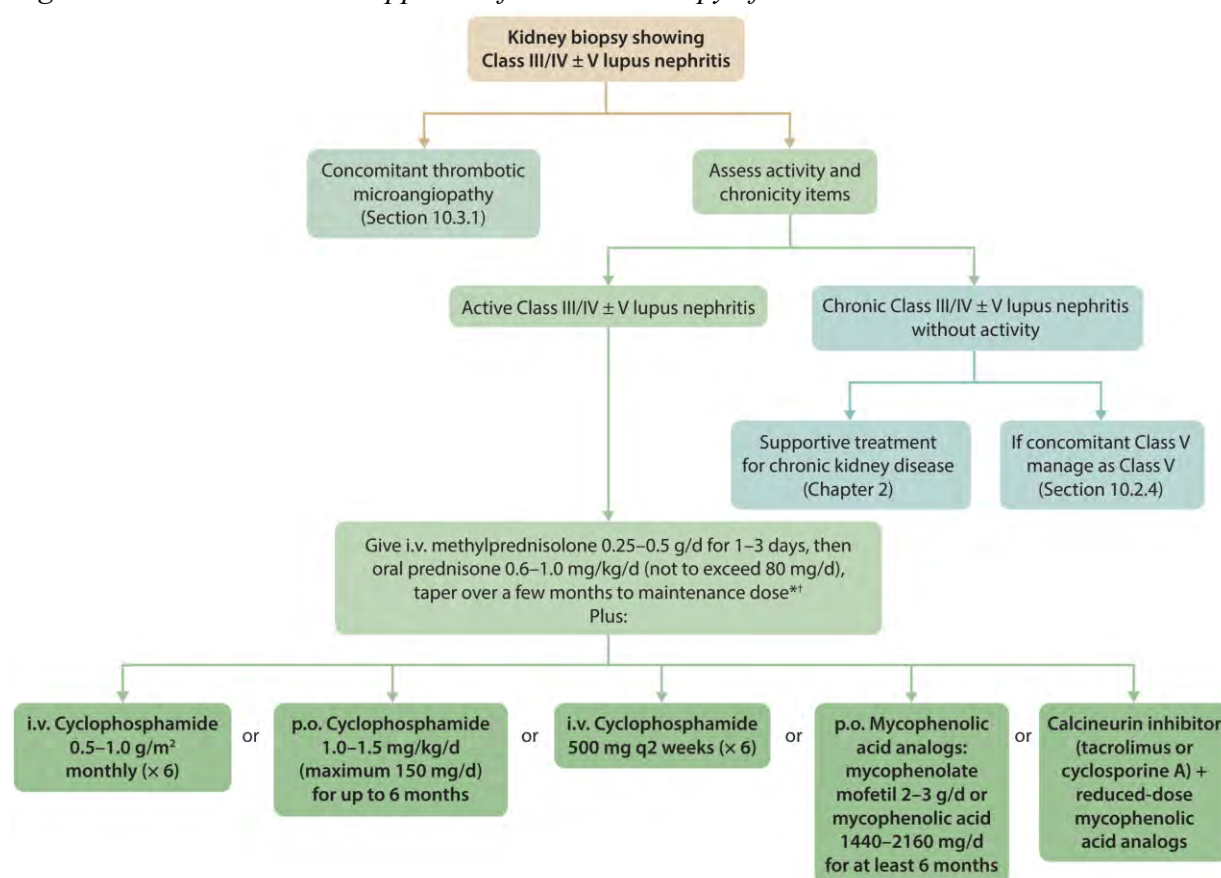
i.v., intravenous; p.o., oral
*Refer to Table LN3 for examples of corticosteroid treatment regimen
†Refer to Table LN4 for comments on cyclophosphamide regimens.

Key information

Balance of benefits and harms

The short-term prognosis of patients with proliferative LN improved dramatically when treatment with high-dose corticosteroids was started in the 1960s.[644] 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 corticosteroids was shown to be superior to treatment with corticosteroids alone in preserving long-term kidney survival in active severe LN.[574, 645-648]

For decades the accepted standard-of-care for proliferative LN was high-dose corticosteroids 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.

MPAA received considerable attention and were shown to have similar efficacy as cyclophosphamide for initial treatment of LN.[649, 650] Although some studies suggested MPAA 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 corticosteroids, and these likely accounted for many treatment-associated adverse events.[573, 575, 651] 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.

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.[578, 652] This regimen was also tested in a short-term trial that included 100 Indian patients and showed similar remission rates when compared to MPAA.[650] In view of the scarcity of data on reduced-dose cyclophosphamide in patients of African or Hispanic descent, there is concern whether this regimen is effective in these patient groups.

Recently, a triple-immunosuppressive "multi-target" regimen of corticosteroids, reduced-dose MPAA, and low-dose tacrolimus was compared to standard-dose cyclophosphamide in a clinical trial from mainland China, and this regimen induced significantly more kidney responses during the first six months of treatment.[580] Extended follow-up data showed comparable kidney response rates in both groups during the second year of treatment.[653] This regimen had a similar incidence but different profile of adverse

events than cyclophosphamide. A study in Japan reported a complete response rate of 80% after six months of treatment with a "multi-target" triple immunosuppressive regimen that included corticosteroids, reduced-dose cyclophosphamide, and tacrolimus.[654]

It is important to note that of all of 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 corticosteroids alone.[646, 647] 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,[576, 652, 655-658] that effective induction of kidney response after initial therapy, especially a complete kidney 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 are associated with significant patient morbidity and mortality and a very high risk of kidney loss. Three distinct approaches have evolved to achieve kidney response and prevent loss of kidney function. The attempt to reduce medication side effects has been only modestly successful, shifting side effect profiles away from the leukopenia, infertility, and future cancers associated with a 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 six RCTs that compared intravenous cyclophosphamide with corticosteroids, there was moderate quality of the 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) (Table S45[574, 645, 646, 648, 659-661]).

High-dose versus low-dose cyclophosphamide has been compared in a few RCTs (Table S46[578, 662-664]). The results from these trials indicate that low-dose cyclophosphamide is associated with fewer adverse events (although in some studies the efficacy also appeared lower than the high-dose regimen) with moderate quality of the evidence because of serious imprecision (only a few events, resulting in wide confidence intervals for 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 intravenous cyclophosphamide. The quality of the evidence was downgraded to moderate because of unclear reporting of allocation concealment in trials (Table S47[573, 649-651, 661, 665-668]).

The very few RCTs that compared triple-therapy regimen of corticosteroids, reduced-dose MPAA, and low-dose tacrolimus with intravenous cyclophosphamide indicate low quality of the evidence because of study limitations and indirectness (Table S48[580, 661, 669]). As the trials have mainly included patients of Asian ethnicity or in China and the trials exclude patients with severe disease; hence, the generalizability of this therapy to the broader LN population is unclear.

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 child-bearing 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 intravenous cyclophosphamide has less risk than standard-dose and is a reasonable alternative to MPAA, but because the data favoring low-dose cyclophosphamide have come from White patients with mild to moderately severe LN, this alternative may not be appropriate for treating severe LN or 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 high nurse-to-patient ratios, 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 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, kidney failure receiving kidney replacement therapy, and patients receiving immunosuppression, especially with high-dose or prolonged administration of corticosteroids. MPAA regimens were associated with higher medication costs but lower facility costs and a superior quality of life compared to intravenous cyclophosphamide.[670-672]

Considerations for implementation

In view of the significant treatment costs,[672-674] 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 intravenous 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 is little data on this group of patients who present with aggressive disease, since their clinical characteristics precluded them from inclusion into 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 higher efficacy,[675, 676] while physicians caring for Chinese patients may want to choose MPAA and corticosteroids or triple immunosuppression with corticosteroids plus low-dose MPAA plus low-dose CNI as opposed to a cyclophosphamide-based regimen.[580, 653]

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 corticosteroids, and subsequently following the adoption of combined immunosuppressive regimens with cyclophosphamide or MPAA as standard therapy.

Corticosteroids 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 corticosteroid treatment alone. Combined immunosuppressive regimens also facilitate steroid minimization, thereby reducing its adverse effects (Table LN3).

Although recent data from mainland China showed comparable short-term response rate between patients treated with triple immunosuppression that included corticosteroids plus

reduced-dose MMF and low-dose tacrolimus and controls treated with corticosteroids plus standard-dose intravenous cyclophosphamide, there is insufficient long-term follow-up data on disease flare rate, kidney survival, patient survival, and also safety data on this 'multi-target' triple immunosuppressive regimen. The risk of infective complications, as suggested by the numerically higher rate of severe infections in the 'multi-target' treatment arm, and CNI nephrotoxicity require further investigation.

Practice Point 10.2.3.1.1. A regimen of reduced-dose corticosteroids may be considered during the initial treatment of active LN (Table LN3).

Table LN3. Example of corticosteroid regimens for LN

	Standard-dose scheme	Reduced-dose scheme
Methylprednisolone pulses	0.25–0.5 g/day × 3	0.25–0.5 g/day × 2–3
Oral prednisone equivalent		
Week 0–2	0.6–1.0 mg/kg (max 80 mg/day)	20–25 mg
Week 3–4	0.3–0.5 mg/kg	20 mg
Week 5–6	20 mg	15 mg
Week 7–8	15 mg	10 mg
Week 9–10	12.5 mg	7.5 mg
Week 11–12	10 mg	5 mg
Week > 12	5.0–7.5 mg	2.5 mg

Corticosteroids 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 is necessary because there is a lag before the immunosuppressive effects of cyclophosphamide, MPAA, and CNIs are seen. The dose, tapering regimen, and duration of corticosteroid schemes vary considerably between clinicians and are largely opinion-based. Examples are given in Table LN3.

The role of intravenous methylprednisolone pulses at the start of treatment is not well-studied but is commonly given as up to three daily doses of 500 mg each (range 250-1000 mg/d), especially in patients who present with a clinical syndrome of rapidly progressive GN - 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 corticosteroids, there is increasing use of initial intravenous corticosteroid pulses followed by a lower starting dose and/or more rapid taper of oral corticosteroid as illustrated in Table LN3.[677] With accumulating data on the efficacy and steroid-sparing role of immunosuppressive medications such as cyclophosphamide and MMF, there is a move towards reducing the exposure to corticosteroids (Table S49[661, 678]).

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 Institute of Health (NIH) regimen or high-dose regimen) and low-dose (also known as the Euro-Lupus regimen). The dosing and duration for these regimens are given in Table LN4.

Table LN4. Cyclophosphamide dosing regimens, combined with corticosteroids, in initial treatment for active Class III/IV LN

	Intravenous cyclophosphamide – modified (NIH regimen)	Intravenous cyclophosphamide (Euro-Lupus regimen)	Oral cyclophosphamide
Cyclophosphamide	i.v. 0.5–1 g/m² monthly for 6 months	i.v. 500 mg every 2 weeks for 3 months	p.o. 1.0–1.5 mg/kg/day (max 150 mg/day) 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

NIH: National Institute of Health

The choice of which regimen to use depends on several factors and can be individualized:

- *Efficacy:* Oral and standard-dose intravenous cyclophosphamide regimens have been used in diverse ethnic populations and for all levels of disease severity and show equivalent efficacy (Table S45[576, 579, 655, 661, 679-682]). Reduced-dose cyclophosphamide (Euro-Lupus regimen) shows equivalent efficacy to standard-dose cyclophosphamide but was tested mainly in White patients.[578, 652] Emerging data suggest low-dose cyclophosphamide is effective in Asians, Hispanics, and Black patients, but these studies did not compare directly to standard-dose intravenous cyclophosphamide (Table S46[650, 661-664, 683]).

- *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 leave work or family activities.
- *Toxicity:* The toxicities of cyclophosphamide may be considered immediate (e.g., GI, susceptibility to infection) or delayed (e.g., loss of fertility, future malignancies).
- Standard-dose intravenous 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 currently recommended (Table S50[574, 661, 682]). The incidence of bladder toxicity is also felt to be less with intravenous cyclophosphamide. Reduced-dose intravenous cyclophosphamide has the most favorable immediate toxicity profile amongst the three 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 constitute 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 should be used as 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 between 2 to 3 g/d. Several studies have shown that MMF has comparable short-term efficacy to oral or intravenous cyclophosphamide for induction of complete and partial kidney responses (Table S47[573, 575, 576, 651, 661, 665-668]). MMF has significant GI 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 mg to 2160 mg is warranted in view of its improved gastrointestinal tolerance.[678]

While MPAA does not predispose to gonadal failure or hematologic malignancies like cyclophosphamide, the ALMS trial (target dose 3 g/d) showed a similar incidence of side effects between patients treated with MMF plus corticosteroids and patients treated with cyclophosphamide plus corticosteroids.[573] In this trial, nine deaths occurred in the MMF group and five in the cyclophosphamide group. Seven of the nine deaths in the MMF group were due to infections, and seven of the nine deaths in MMF-treated patients occurred in Asia. Concomitant high-dose corticosteroids 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.[684] Therefore, consideration of the race or ethnicity of a patient or the geographical locality may also be relevant when deciding on the dose of MPAA to be used in view of the potential differences in the risk profile between patients.

MPA pharmacokinetics varies considerably between 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 to 45 mg/hr/l or trough level of 3.0 to 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.[685-689]

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 intravenous cyclophosphamide to date.[573, 675] 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), while the response to MMF was numerically higher but not statistically different than cyclophosphamide in Black patients (53.9% vs. 40.0%, p=0.39). A higher response rate to MMF in Hispanic patients compared to cyclophosphamide was also reported in cohort studies.[676] In contrast, the response rate to cyclophosphamide was numerically higher but not statistically different than MMF in Asian patients (63.9% vs. 53.2%, p=0.24).[675]

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 at presentation showed a comparable early response to corticosteroids plus either cyclophosphamide or MMF.[690] 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,[577] 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 triple immunosuppressive regimen that includes a calcineurin inhibitor, reduced-dose MPAA, and corticosteroids should be reserved for patients who cannot tolerate standard-dose MPAA and are unfit for or will not use cyclophosphamide-based regimens.

Data from short-term studies with follow-up of six to twelve months suggest that a regimen of corticosteroids combined with cyclosporine or tacrolimus, with or without reduced-

dose MPAA, as initial LN therapy has comparable efficacy to corticosteroids combined with cyclophosphamide. The majority of these trials have been conducted in Asia, and the largest trial combined fixed, relatively low-dose tacrolimus (4 mg/d, achieved trough levels of 5.2-5.5 ng/ml) with low-dose MMF (1 g/d) and reported earlier attainment of kidney response than NIH-cyclophosphamide regimen with a higher complete kidney response rate (46% vs. 26%) after 24 weeks of treatment.[580] Extended follow-up, however, showed comparable kidney response rates in both groups during the second year of treatment.[653] A recent international multicenter phase 2 study compared triple immunosuppression with MMF (2 g/d) plus corticosteroids plus a novel CNI voclosporin against MMF (2 g/d) plus corticosteroids plus placebo, with forced tapering of prednisone to 2.5 mg/d after eight weeks, and demonstrated a higher short-term (6 and 12 months) kidney response rate in voclosporin treated patients.[677]

This study suggests that triple immunosuppressive therapy incorporating a CNI may be applicable to Asians and other ethnicities, although further information on the risk of infection especially in Asian countries, is required.

In both the Chinese tacrolimus study and the international voclosporin study, the incidence of infections appeared higher in patients who received triple immunosuppression, although the difference versus controls was not statistically significant. Additionally, acute and chronic calcineurin nephrotoxicity, metabolic side-effects and hypertension, a significant relapse rate after discontinuation, and the lack of long-term follow-up data are limitations or unclear issues related to treatment regimens that include CNIs.

For these reasons, the Work Group considers calcineurin-based triple therapy as a treatment option only for patients who do not tolerate, or will not use for various reasons, standard LN regimens.

Practice Point 10.2.3.1.5. Other therapies, such as azathioprine or leflunomide combined with corticosteroids, 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.

Azathioprine combined with methylprednisolone pulses showed comparable short-term kidney response rate as prednisolone combined with standard-dose intravenous 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 (Table S51[574, 661, 691, 692]). 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 in pregnant patients.

Short-term studies in Chinese patients compared leflunomide against intravenous cyclophosphamide, both combined with corticosteroids, and reported comparable kidney response rates of approximately 70% after six months.[693, 694]

Other therapies that have not shown significant benefit when added to standard therapy include plasmapheresis (Table S52[579, 661, 695-697]), and the anti-interleukin-6 antibody, sirukumab (Table S53[698]). In a phase 2a trial, laquinimod was associated with a higher kidney response rate (62.5% compared with 33.3% in the placebo group) when added to standard of care treatment with corticosteroids and MMF in patients with active LN (Table S54[699]).

Practice Point 10.2.3.1.6. The place of biologics for the initial treatment of proliferative LN is evolving, and while not yet ready to be recommended as first-line, may be considered for individual patients.

Results from phase 2 and phase 3 clinical trials have failed to demonstrate improved short-term efficacy when B-cell targeted therapies (rituximab, ocrelizumab), costimulatory blockade (abatacept), or anti-interleukin-6 monoclonal antibody were added to standard initial therapy of corticosteroids and either MMF or cyclophosphamide.[698, 700-703] Interestingly, patients treated with rituximab and abatacept in these trials showed more effective suppression of anti-dsDNA levels and complement activation, but this biological efficacy did not translate to conventional clinical indicators of treatment response.[700, 702] The lack of efficacy contrasts with reports of case series that suggested efficacy when patients with suboptimal response to standard therapy were treated with rituximab.[704-708] Nevertheless, the observations do not exclude 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 (Table S55-Table S57).[709]

There are ongoing clinical trials that investigate the role of biologics that target B-cells (obinutuzumab), B-cell activating factor (belimumab), co-stimulatory proteins (iscalimab), and other molecules or cells relevant to disease pathogenesis.

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 decreases the risk of LN relapse compared to azathioprine or no treatment and that MPAA are comparably effective to 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 LN4. Maintenance therapy for Class III and Class IV LN
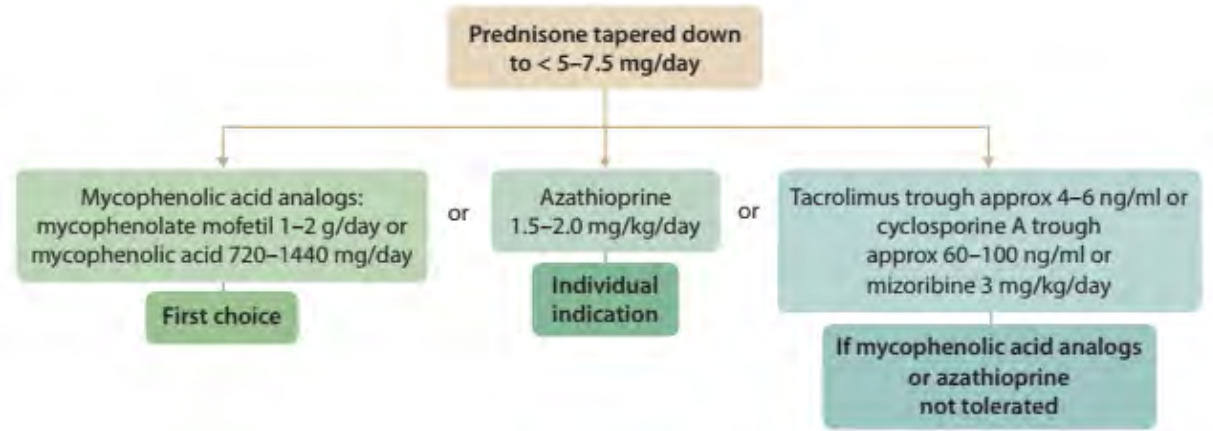
Key information

Balance of benefits and harms

High-intensity immunosuppression for the initial treatment of LN is given for three to six months, depending on the regimen (See 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, 573, 578, 580] and approximately 20% achieve complete histologic remission, defined as an activity index of zero on repeat kidney biopsy.[571] 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 clear that the addition of a cytotoxic agent to corticosteroids during the initial treatment of LN improved long-term kidney survival, patients were kept on oral or, in later studies, intravenous cyclophosphamide for months or years,[659] This led to considerable lifetime cyclophosphamide exposure and toxicity.[710, 711] A study reported in 2004 compared quarterly intravenous 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.[712] 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,[655, 681] 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 two major clinical trials (Table S59[577, 652]). In a LN cohort of 227 ethnically diverse patients, the maintenance phase of ALMS showed that over three years of follow-up the composite treatment failure end-point 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).[577] LN flares occurred in 12.9% of MMF-treated patients and 23.4% of azathioprine-treated patients. In contrast, the MAINTAIN trial randomized 105 predominantly White patients to MMF or azathioprine and corticosteroid maintenance therapy after initial therapy with the low-dose cyclophosphamide regimen and showed no difference in time to kidney flare between the two groups, with a cumulative kidney flare rate of around 20% in both groups after 36 months.[652] 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 corticosteroids ("multi-target" regimen) against azathioprine in responders following "multi-target" regimen or NIH intravenous cyclophosphamide as initial treatment for six months in the two groups respectively, and the results showed similar efficacy in preventing flares in the two groups and a higher incidence of adverse events due to transaminitis in the azathioprine group.[653] However, the follow-up duration of 18 months was relatively short, and the generalizability of data needs further investigation. Also, while the response rate was significantly higher in the "multi-target" group after six months of initial treatment, the cumulative response rate was similar between the two 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 "multi-target" triple immunosuppressive maintenance treatment regimens that comprised corticosteroids with MPAA and either cyclosporine[713, 714] or tacrolimus.[715]

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 one RCT compared long duration (18 months) of cyclophosphamide therapy encompassing both the initial treatment period and the maintenance phase with short duration (six months) of cyclophosphamide therapy as initial treatment followed by maintenance treatment with variable immunosuppressive regimens. Due to study limitations and very serious imprecision (only one study, very wide CIs indicating appreciable benefit and harm), the quality of the evidence for this trial is very low (Table S60[657, 661]).

Similarly, only one 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 one study, wide CIs) (Table S61[712]).

The ALMS trial compared azathioprine with MMF as maintenance therapy in patients with proliferative LN and showed increased rate of composite "treatment failure" endpoint and adverse effects (e.g., leukopenia) in patients who received azathioprine.[577] Despite the large sample size and this being 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 (see Practice Point 10.2.3.2.4.[716-719]).

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 not yet achieved, and in all cases to avoid disease relapses needing re-institution 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 on MPAA, or who place a high value on becoming pregnant may choose azathioprine (or a CNI) over MPAA, as may patients for whom MPAA 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, the major resource implications arise from laboratory monitoring of lupus activity and

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immunosuppression and managing complications of treatment. While the drug cost of MPAA is considerably higher than azathioprine, there are few cost-effectiveness analyses of maintenance treatment for LN.[720] 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 so when azathioprine or MPAA is used, and this also has implications on 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 (see 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 to 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, who do not have access to MPAA, or who consider 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 corticosteroids, is mainly based on data from ALMS and the MAINTAIN trial (Table S59[577, 721]). While the results from the latter showed no statistically significant difference in time to disease flare and 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 corticosteroids combined with azathioprine is 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 less than two years,[576, 658] and that long-term maintenance treatment with MPAA was associated with a low disease flare rate.[722] Overall, while the efficacy and safety data to date favor MPAA as maintenance treatment, azathioprine is an acceptable alternative.

Practice Point 10.2.3.2.2. Corticosteroids should be tapered to the lowest possible dose during maintenance, except when corticosteroids are required for extrarenal lupus manifestations, and discontinuation of corticosteroids should be considered after patients have maintained a complete clinical kidney response for approximately 12 months.

Prolonged corticosteroid exposure is associated with continued and significant organ damage accrual and morbidity.[678, 723] At the end of the initial phase of treatment the goal will have been to reduce most patients to a daily dose of prednisone (or equivalent) that is not higher than 7.5 mg, and preferably as low as possible. The tapering regimen and duration of corticosteroid maintenance therapy vary considerably between 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. Corticosteroid avoidance in maintenance therapy has been attempted with the use of rituximab, but the evidence to support this remains limited to one cohort.[709]

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

The suggested dosages are largely based on data from the ALMS and MAINTAIN trial.[576, 721] As mentioned before, the Work Group recommends to maintain these doses until achievement of complete response and then taper (Table LN5). Due to pharmacogenetic differences, the level of MPA exposure varies considerably between patients receiving the same dose of MPAA. While there is 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.[724]

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 corticosteroids.[716, 725] In a study of 70 Chinese patients who achieved remission after initial therapy with corticosteroids and either intravenous cyclophosphamide or tacrolimus, maintenance therapy with tacrolimus (trough blood level target of 4 to 6 ng/ml) was compared with azathioprine 2 mg/kg/d, both in combination with prednisone 10 mg/d. Over six months of follow-up, kidney relapse occurred in two azathioprine-treated patients and none in the tacrolimus group (Table LN5).[726]

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 corticosteroids and MMF, especially in patients who showed features of MN in their baseline kidney biopsies.[714, 717, 727-729] Caution is required when considering adding CNI for the purpose of decreasing proteinuria. It is desirable that there is histological 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 (Table LN5).

The experience with mizoribine as maintenance therapy in LN is largely limited to Japanese patients.[718, 730] Results from a post-marketing surveillance study that included 559 mizoribine-treated patients showed that nearly all were receiving corticosteroids, 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 two years of mizoribine treatment, and the authors concluded that mizoribine was safe and effective.[731] (Table LN5)

Table LN5. Maintenance immunosuppressive regimens in patients with LN

Maintenance immuno-suppressive regimens	Low-dose corticosteroid AND				
	Mycophenolic acid analogs	Azathioprine	Calcineurin inhibitor	Mizoribine	Mycophenolic acid analogs and calcineurin inhibitor
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

AZA, azathioprine

Practice Point 10.2.3.2.5. The total duration of initial immunosuppression plus combination maintenance immunosuppression for proliferative LN should not be less than 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 the total duration of immunosuppression (initial therapy plus maintenance) for patients with proliferative LN who have achieved a complete kidney response and have no ongoing extrarenal manifestations be at least 36 months, based on considering the following evidence collectively:

- In Chinese patients who received MMF as initial therapy, discontinuation of MMF before two years was associated with an increased risk of disease flare.[576, 658]
- During the third to fourth year of MMF maintenance therapy, kidney flare was associated with low 12-hour trough MPA blood levels, while patients with trough levels of approximately 2 mg/l remained in remission.[732]
- 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 corticosteroids and either MMF or azathioprine.[577]
- In an Italian cohort, immunosuppression was tapered in patients who were in complete remission for over 12 months, and 27% relapsed. One of the predictors of successful treatment discontinuation was a longer duration (median of four years) of prior immunosuppressive therapy.[733]
- Despite at least 36 months of immunosuppression and at least 12 months of sustained complete clinical kidney response, 28% to 50% of patients continue to show inflammatory histologic activity on repeat kidney biopsy.[734-736] 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.[735, 736]

- 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,[734-736] 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 at least three 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 LN5.

Figure LN5. Management of patients with pure Class V LN
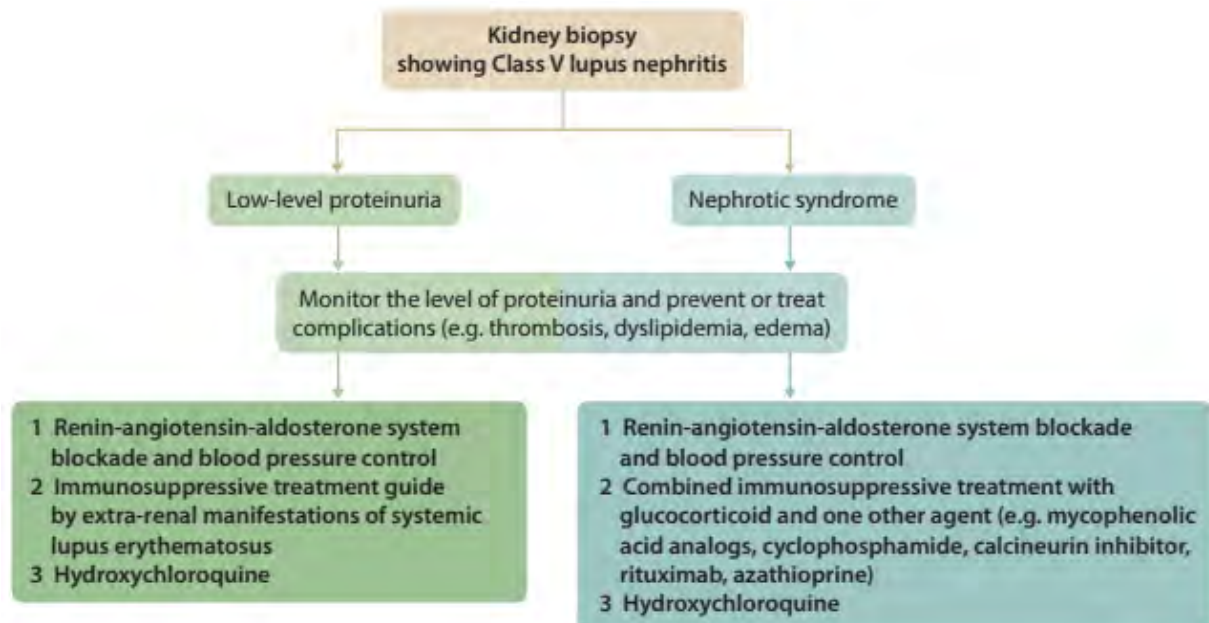
Class V LN accounts for 5% to 10% of all LN cases. Data on clinical management are based on very few controlled trials with small sample size, analyses of pooled data, and observational studies. Because 10% to 30% of patients with Class V LN and nephrotic

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 cardiovascular morbidity and predisposes to thrombosis, treatment of Class V patients who have nephrotic range proteinuria or NS is warranted.[737-740]

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).[679] Pooled data from two studies showed that prednisone plus either cyclophosphamide or MMF had similar efficacy of lowering proteinuria after six months of treatment.[741] Other studies of relatively small sample size reported the efficacy of corticosteroids combined with azathioprine,[588, 740] oral cyclophosphamide,[742] intravenous cyclophosphamide,[679, 743] MMF,[587, 588, 743-746] CNIs,[679, 728, 745, 747-749] and rituximab[709, 750] with response rates of 40% to 60%. Tacrolimus was reported as effective when given together with corticosteroids 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.[717] There is a lack of robust data in the management of Class V LN, especially in patients who present with nephrotic syndrome. The data to date is more in favor of combining corticosteroids with MPAA, a CNI, or short-term cyclophosphamide, than with other options.

In addition to general methods to reduce urine protein, such as RAS inhibition and meticulous blood pressure control, MMF is a reasonable first choice for treating Class V patients with nephrotic range proteinuria. If ineffective, we suggest cyclophosphamide for not more than six 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. (see 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 Table LN6.

Table LN6. Commonly used definitions of response to therapy in LN

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

PCR, protein-creatinine ratio

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.[655, 751-753] However, there are no universally accepted criteria for the level of improvement required, which makes direct comparisons of different clinical trials more difficult.

Table LN6 definitions 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 two large European LN trials showed that favorable kidney outcomes were predicted by achieving a proteinuria level of 0.7 g/d to 0.8 g/d after 12 months of therapy, a conclusion supported by other reports.[657, 754-756]

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 six to 12 months, but improvement of proteinuria and eGFR is continuous over time, and the rate of improvement varies considerably between 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 between patients.[573, 575, 576, 680, 728, 757, 758]

Outside of a formal clinical trial setting, the Work Group suggests that if patients are improving, allowing 18 to 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 eight weeks of treatment.[759]

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), blood pressure control, edema resolution, urine sediment, hemoglobin and albumin improvements, and serological parameters, including double-strand DNA antibodies and serum complements. If 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.[734-736] A repeat kidney biopsy may, therefore, be useful in confirming kidney response, especially before important major treatment decisions such as discontinuation of immunosuppression.[571]

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 LN6.

Figure LN6. Algorithm for the management of patients who show unsatisfactory response to initial therapy for active LN

1	Verify adherence to treatment
2	Ensure adequate dosing of immunosuppressive medications by measuring plasma drug levels if applicable or available (check mycophenolic acid level if on mycophenolic acid analogs/check infusion records if on cyclophosphamide)
3	Repeat biopsy if concern for chronicity or other diagnosis (e.g. thrombotic microangiopathy)
4	Consider switching to an alternative first-line regimen when there is persistent disease activity (mycophenolic acid analogs to cyclophosphamide-based regimen or vice versa)
5	Consider the following in patients refractory to first-line treatment regimens: • Combined mycophenolic acid analogs and calcineurin inhibitor therapy, or • Addition of rituximab, or • Extended course of i.v. pulse cyclophosphamide

i.v., intravenous

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 three to four weeks is clearly unsatisfactory and warrants early appraisal of potential causes for non-response and early intervention, while patients who show response to treatment can be closely observed, and investigated when the level of improvement after three to four months of therapy is suboptimal or below expectation. A two-month time frame to see improvement was suggested based on *post hoc* analysis of data from the ALMS trial,[759] but deterioration needs to be evaluated on an individual basis in terms of rapidity and severity.

The role of non-adherence in unsatisfactory treatment response cannot be over-emphasized. The prevalence of non-adherence in SLE patients could be over 60%.[760-763]

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 intravenous cyclophosphamide, patients who did not show response, defined as improvement by at least 30%, after 12 weeks of treatment were switched to the other treatment arm.[651] Another study reported efficacy of MMF in patients refractory to or who had relapsed after cyclophosphamide treatment.[764] 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% to 80%,[632, 704, 722, 765-776] 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.[777]

Similarly, data from observational cohorts suggested efficacy of CNIs, either combined with corticosteroids and/or MMF, in patients with refractory or relapsing LN.[714, 715, 778-782]

<u>10.2.4.3. Treatment of LN relapse</u>

Relapses of LN are common, and LN flare is an important predictor of poor long-term kidney survival.[783-786] LN flare rates of 10% to 50% have been reported, and relapses occur over time.[787] Failure to achieve complete remission increases the risk of subsequent relapse.[647, 655, 788] 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.[647] Similarly, a hazard ratio of 6.2 for relapse was reported in Chinese patients who did not achieve complete remission after initial therapy.[655]

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 that was 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 a 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.[789] All LN clinical trials testing initial, induction therapies for LN include both types of patients. While these considerations form the basis for Practice Point 10.2.4.3.1., there are several caveats in choosing an approach:

i. 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 older than 32 years with a cumulative exposure of 8 g/m^2 .[790, 791] 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.

ii. If patients relapse during pregnancy, treatment choices are more limited. These are discussed in Section 10.3.2.

iii. Patient preference and/or tolerance of the initial regimen should be considered. Also, patient adherence should be considered in the choice of treatment.

iv. 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

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LN because there is often discordance between clinical findings and histologic findings.[571, 572] The tempo and magnitude of change in proteinuria may help with rapid increases and large changes often reflecting active disease. SLE serologies (e.g., complement, anti-dsDNA) may support a flare diagnosis but need to be evaluated in the context of prior serological 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.[792]

In lieu of waiting to treat LN until it flares, 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%.[793] 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 less than two years, two major relapses (12.5%, both with LN relapse) occurred in the early treatment group compared to 20 relapses (87%), seven of which were major (one 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 over four weeks) or placebo. During a short follow-up (90 days), no patients given prednisone had a severe flare, but six placebo patients did, and three of the flares were kidney.[794] A recently published retrospective study of Chinese LN patients suggested that a moderate increase in immunosuppressive treatment dose was effective in preventing kidney and non-kidney flares without excessive treatment-related adverse effects.[724] Taken together, all of these data suggest that LN flares may be preventable, at least for some patients, but larger RCTs of sufficient duration will be needed before this approach can be endorsed.

10.3. Special situations

10.3.1. LN and thrombotic microangiopathy (TMA)

Practice Point 10.3.1.1. Patients with LN and TMA should be managed according to the underlying etiology of TMA, as shown in Figure LN7.

Figure LN7. Management of patients with LN and TMA[*]
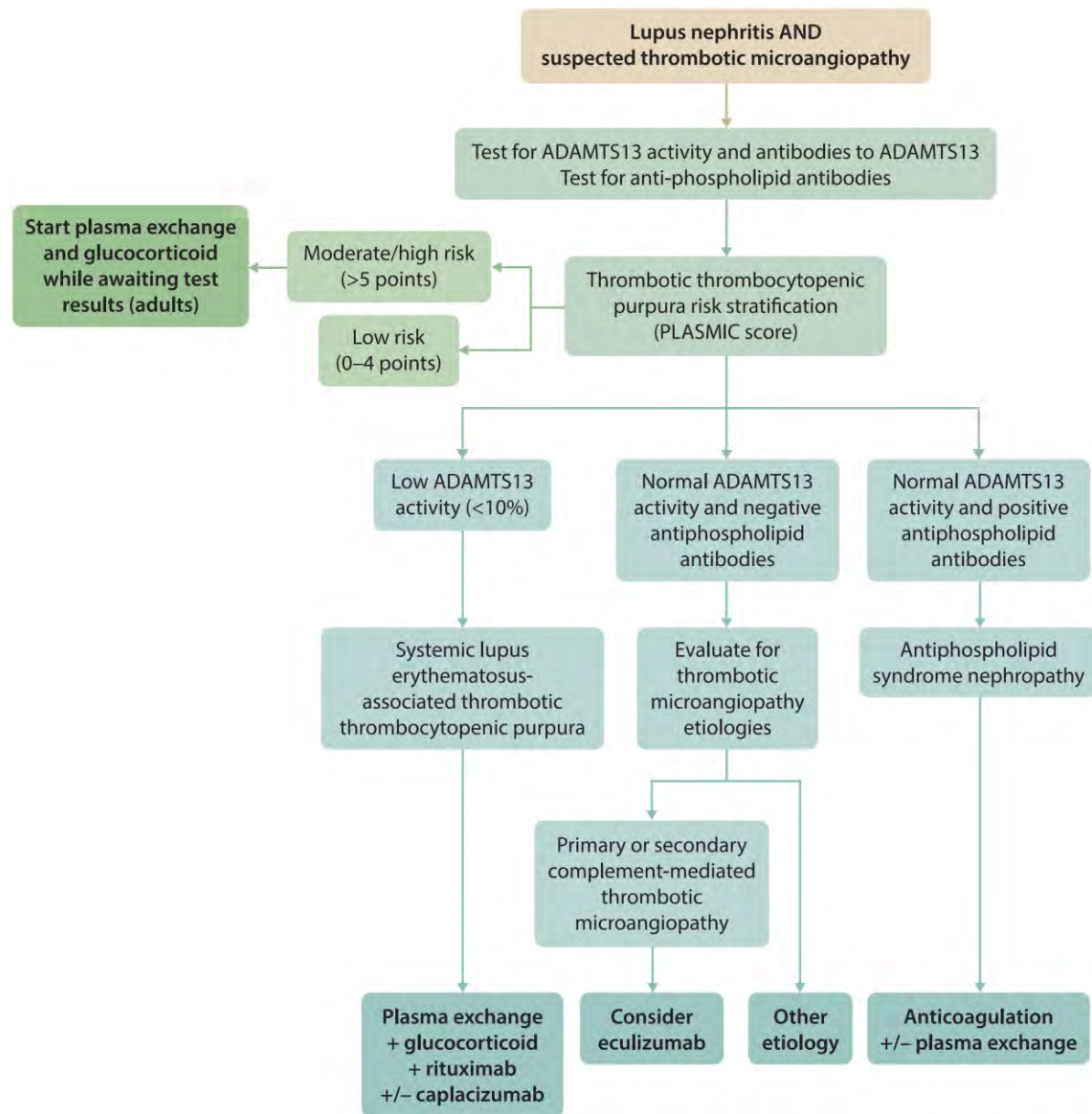
* Bendpudi PK. Lancet Haematol 2017; 4: e57

TMA is a pathologic description of vascular endothelial injury secondary to various etiologies (244). 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.[496, 795] 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 co-managed with an experienced hematologist. However, 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, anti-phospholipid antibodies, and complement studies may not be available and even when available often take considerable time to complete (Figure LN5). If TTP is suspected, one may consider using the PLASMIC score,[796] and if the score defines an intermediate-to-high risk of TTP, adults should be started on plasma exchange and corticosteroids while waiting for the investigation results. In children, TTP is less common and plasma exchange has been associated with considerable morbidity,[797] so it is acceptable to defer plasma exchange for 24 to 48 hours until the ADAMTS13 result is available to confirm that the procedure is indicated.[798]

TMA due to lupus-associated TTP

The diagnosis of TTP is mainly reserved for patients with TMA and low ADAMST13 activity (≤10%).[799, 800] The treatment of confirmed TTP in LN is extrapolated from that of acquired TTP and includes plasma exchange,[801, 802] high-dose corticosteroids,[803-805] rituximab,[806-808] and/or caplacizumab (vWF inhibitor) (Figure LN5).[809, 810]

TMA due to antiphospholipid syndrome (APS)

Antiphospholipid antibodies (aPLA) are found in about 30% of SLE patients and may be associated with venous and/or arterial macro- or microvascular thrombosis, thrombocytopenia, adverse pregnancy outcomes, and neurological abnormalities. Kidney damage is a well-recognized complication of antiphospholipid syndrome (APS), presenting as renal artery thrombosis or stenosis, RVT, or injury to the kidney microvasculature, also known as antiphospholipid syndrome nephropathy (APSN).[811] There are few data on the management of APSN. 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.[812] Complete and partial response rates were 38.1% and 22.6%, respectively, after 12 months of immunosuppressive treatment. Thirty-seven of 61 aPLA-positive patients also received anticoagulation therapy, and anticoagulated patients showed a higher complete response rate (59.5% vs. 30.8%), while 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 APSN with long-term anticoagulation with warfarin. Direct oral anticoagulants are not recommended as they were inferior to warfarin in preventing thromboembolic events.[813, 814]

Catastrophic APS is characterized by thrombosis, often of rapid onset, affecting multiple organs and is associated with high mortality. Treatment includes both total

anticoagulation and high-dose corticosteroids.[27, 815] Plasma exchange is often used in catastrophic APS and has been associated with improved patient survival in retrospective studies.[816] There are recent anecdotal reports on the potential efficacy of rituximab in catastrophic APS.[817, 818] 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.[819-821]

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 should ideally be evaluated with complement studies when available.[31, 496] 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 which 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 corticosteroids and cyclophosphamide, and may best be treated with a complement inhibitor such as eculizumab, although the optimal dose and duration remain controversial.[822-824] The limited data to date show a high response rate with resolution of TMA in 68% of patients with secondary aHUS.[825] Data from 31 adult patients (26 treated with plasma therapy and five plasma-resistant patients treated with eculizumab) showed complete kidney recovery in four of five eculizumab treated patients.[826] Efficacy of eculizumab treatment was also reported in a lupus patient with 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.[827] A recent report on nine patients with TMA associated with SLE and/or APS showed that kidney function improved by 25% in half of the patients after four weeks of eculizumab treatment and two of three patients were able to discontinue dialysis.[828]

Another recent report on 11 patients with TMA and LN showed complement regulatory protein mutations in six patients and response to eculizumab treatment in ten patients.[829]

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.[804, 830, 831] 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 complement factor H 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.[832-835] Data from 31 adult patients (26 treated with plasma therapy and five plasma-resistant patients treated with eculizumab) showed recovery of kidney function in approximately 40% of patients given plasma therapy.[826]

10.3.2. Pregnancy in patients with LN

Practice Point 10.3.2.1. Patients with active LN should be counseled to avoid pregnancy while the disease is active or when treatment with potentially teratogenic drugs is ongoing, and for at least six 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 corticosteroids, 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.[836, 837] 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 SLE patients with 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 lupus patients.[838]

Hydroxychloroquine is considered safe in pregnancy and may decrease the rate of preterm birth and intrauterine growth retardation, while withdrawal of hydroxychloroquine has been associated with LN flare, so it should be continued when an LN patient becomes pregnant.[603, 608, 839] 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.[840, 841] The incidence of LN flare in pregnancy has been reported to be 11% to 28% and is higher if patients have low serum complement levels or high anti-double-stranded DNA antibody titers.[836] Active LN during pregnancy can be treated with corticosteroids plus azathioprine and/or a CNI, although in the first trimester, the use of corticosteroids is associated with an increased risk of gestational diabetes and cleft palate.

10.3.3. Treatment of LN in children

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

Approximately 20% of SLE is diagnosed before the age of 18, and genetic components are more common in childhood-onset SLE.[842-844] There is suggestive evidence that disease is often more severe in the pediatric population. In adolescent SLE patients with isolated proteinuria, orthostatic, or postural proteinuria should be excluded as this phenomenon has been frequently observed in this population.[845, 846]

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 intravenous medications, growth concerns, which may favor limiting corticosteroid exposure, fertility concerns, especially as patients approach adolescence, which may favor limiting cyclophosphamide exposure, and psychosocial concerns around school and socialization with peers. As such, children with LN should be co-managed by pediatric nephrologists and rheumatologists with expertise in lupus, and the expertise of other professionals such as a clinical psychologist may be helpful.

10.3.4. Management of lupus patients with kidney failure
Practice Point 10.3.4.1. LN patients 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. Lupus patients receiving hemodialysis display similar three-year survival rates and mortality due to cardiovascular or infectious complications as patients receiving peritoneal dialysis.[847-849] 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 patients who developed kidney failure due to other types of kidney disease,[850, 851] and transplanted patients have lower mortality than lupus patients who remain on dialysis.[852] As clinical outcomes are better in patients with shorter durations of dialysis,[853, 854] 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,[855] 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.[856-858] One important consideration is that patients who have antiphospholipid antibodies

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may experience dialysis vascular access clotting or allograft thrombosis and may require prophylactic anticoagulation.[859-862]

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 could ideally be used in conjunction with novel, targeted therapies of LN to select the most appropriate treatment, including biologic medications targeting specific pathogenic pathways
- Establish kidney 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 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 steroid-reduction protocols for LN management?

CHAPTER 11. ANTI-GLOMERULAR BASEMENT MEMBRANE ANTIBODY GLOMERULONEPHRITIS

Anti-glomerular basement membrane (GBM) antibody GN is a rare glomerular disease with an incidence of 0.5 to 1 per million population. It is caused by autoantibodies against the non-collagenous 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 disease). Anti-GBM is usually a rapidly progressive crescentic GN, and about 80% of patients have crescents in half or more of their glomeruli.[863] Goodpasture´s syndrome occurs in 40% to 60% of patients, and kidney disease is accompanied by sometimes massive and fatal pulmonary hemorrhage.[864] Anti-GBM disease with pulmonary involvement is more frequent in men (about 80%) and typically occurs during the second decade.[865] Isolated anti-GBM nephritis does not have clear male preponderance and may also occur in older persons.[866] If untreated, anti-GBM disease has very high morbidity with almost all patients going on to kidney failure and can have significant mortality. In patients with Goodpasture´s syndrome, mortality rate was 96% before the introduction of immunosuppression and 47% despite being treated with immunosuppression.[867] Most patients died of respiratory failure.[865] 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-GBM disease should be made urgently in all patients with suspected rapidly progressive glomerulonephritis.

In patients who present with a suspected rapidly progressive GN, 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.[868, 869]

Diagnosis of diffuse alveolar hemorrhage is usually done clinically and confirmed by the high-resolution CT scans. Bronchoscopy and pulmonary functional testing may be useful, but 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 (See Figure AGBM1)

Figure AGBM1. Diagnostic and therapeutic algorithm
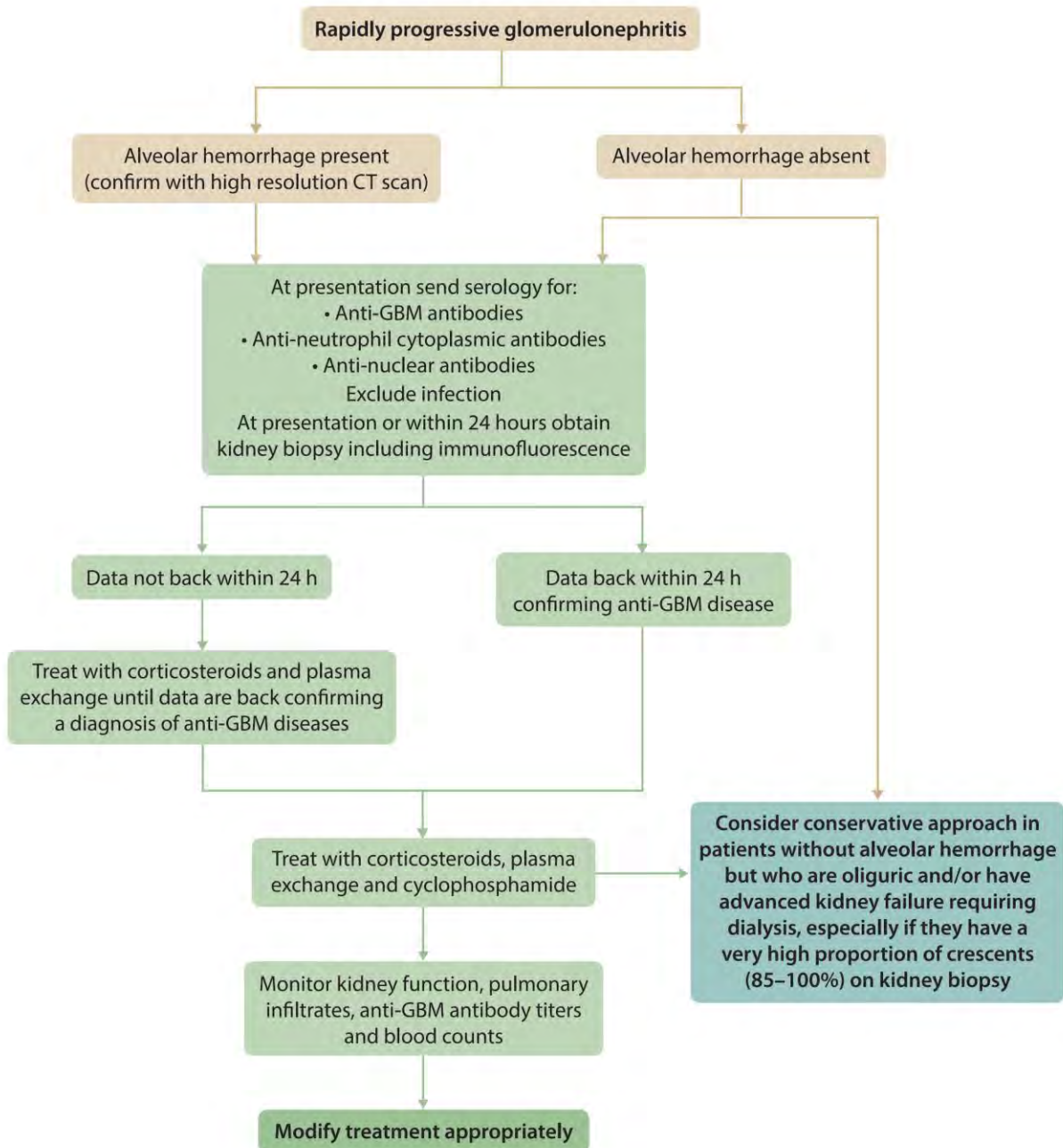
CT, computed tomography; GBM, glomerular basement membrane

11.2. Treatment

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

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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%[865] to 8.5% with plasma exchange and immunosuppression,[866] and five-year patient survival is currently over 90% with treatment.[870] 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 five-year kidney survival of treated patients has improved from about 25% to about 50% probably because of both earlier diagnosis and higher proportion of patients treated with plasma exchange.[870, 871]

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 only been one RCT, which is of very low quality. No systematic review for observational studies was undertaken by the ERT. However, the observational studies that were identified by the Work Group exhibit strong mortality and kidney benefit for patients treated with immunosuppression and plasma exchange compared with incomplete treatment or no treatment. Therefore, the overall quality of evidence was rated as low.

One small (n=17) RCT compared plasma exchange therapy with standard of care in patients with anti-GBM (Table S62[872]). The quality of the evidence for critical outcomes (all-cause mortality, ESKD, and infection) was very low because of study limitations (unclear randomization and allocation concealment methods used) and very serious imprecision (only one study with few patients and very wide CIs indicating less certainty in effect). Other outcomes, like anti-GBM antibodies, were not considered as critical and important outcomes for the guideline.

Because untreated anti-GBM GN and Goodpasture's disease 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. In some regions, some or all of these facilities may not be available. 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.[873] 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 patients.[874] Pulmonary disease is more frequent in smokers,[875] and presence of pulmonary disease may be associated with better kidney outcomes,[876] 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 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 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 eight weeks.[866] 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 h), 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 two to three weeks before anti-GBM antibodies disappear completely.[866, 868, 877] 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 prolonged to two to three months and corticosteroids to about six months.

Formation of anti-GBM antibody ceases spontaneously after six to nine months.[878] However, based on available clinical experience, oral cyclophosphamide daily for three months and gradually tapered corticosteroids completely withdrawn within six months seem to be appropriate in most patients to prevent new antibody production.[866, 879] In patients with persistent anti-GBM antibody after three months of cyclophosphamide, continuation of treatment with either azathioprine or mycophenolate (in combination with corticosteroids) is suggested.[880]

As the risk of infection in patients with kidney failure treated with cyclophosphamide is high,[881] prophylaxis of *Pneumocystis* pneumonia with cotrimoxazole could be considered.[880] In patients with serious infection during treatment with plasma exchange adding intravenous immunoglobulin therapy to antibiotics could be considered. Intravenous immunoglobulin

should be given immediately after plasma exchange to limit its removal, but their real impact is uncertain (Table AGBM1).[882]

Table AGBM1. Treatment of anti-GBM disease

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 haemorrhage 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
Corticosteroids	• 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

According to Kluth and Rees, 1999; McAdoo and Pusey, 2017; and Kaplan *et al.*, 2019

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 antibody had recurrent antibodies or relapsed beyond six months.[868] Individual patients with relapses many years after the first presentation of the disease were, however, reported,[883-886] and repeated relapses may occur in patients who do not cease smoking or are exposed to lung irritants.[887, 888] Treatment of patients who do not have detectable anti-GBM antibodies beyond six months is not recommended. Smoking should be strongly discouraged.

Practice Point 11.2.5. Patients with glomerulonephritis 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.[542]

Double-positive patients also may have severe kidney disease and often have lung hemorrhage at presentation, but 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 patients with AAV and require aggressive early treatment as for anti-GBM disease followed by maintenance immunosuppression as for AAV.[868] (see Chapter 9)

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

Refractory anti-GBM disease is rare (less than 10%).[884] Experience with rituximab in anti-GBM disease is limited to case reports and two small case series of eight patients who incompletely responded to standard treatment and were successfully rescued with rituximab,[889] and four dialysis-dependent patients primarily treated with rituximab instead of cyclophosphamide as first-line therapy for pulmonary remission with no effect on the kidney.[890]

There are several case reports of patients with anti-GBM disease successfully treated with mycophenolate or MPA instead of cyclophosphamide.[891-894] Mycophenolate could be used instead of cyclophosphamide in patients refusing cyclophosphamide, or 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 three anti-GBM disease patients who were dialysis-dependent, but none of these patients recovered independent kidney function.[895] 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 ten patients with anti-GBM disease treated with immunoadsorption dialysis dependency was successfully reversed in three out of six patients.[896]

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 at least six months.

Survival of patients with anti-GBM disease after kidney transplantation is comparable to patients with other causes of kidney failure.[897] 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,[898] but is very rare (<3%) in patients who have no antibodies.[879]

Anti-GBM antibodies form in 5% to 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.[899]

RESEARCH RECOMMENDATIONS

- Compare rituximab to cyclophosphamide plus corticosteroids and plasma exchange for induction of remission in anti-GBM disease.
- Compare MMF to cyclophosphamide plus corticosteroids and plasma exchange for induction of remission in anti-GBM disease.
- Compare immune adsorption to plasma exchange plus background immunosuppression for induction of remission in anti-GBM disease.

METHODS FOR GUIDELINE DEVELOPMENT

AIM

This an update of the *KDIGO Clinical Practice Guideline for Glomerulonephritis* published in 2012.[900] 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 guidelines for the management of glomerulonephritis. The guideline development methods are described below.

OVERVIEW OF THE PROCESS

This guideline adhered to international best practices for guideline development.[901] These guidelines have been conducted and reported in accordance with the AGREE II reporting checklist.[902] The processes undertaken for the development of the *KDIGO 2020 Clinical Practice Guideline on Glomerular Diseases* are described below.

- Appointing Work Group members and the Evidence Review Team (ERT)
- Finalizing guideline development methodology
- Defining scope and topics of the guideline
- Formulating clinical questions – identifying the Population, Intervention, Comparator, Outcomes, 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 pre-defined 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
- Public review in May 2020
- Finalizing and publishing the guideline
- Guideline update

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, dietetics, 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 underlying rationale, as well as grading the strength of the recommendation.

The KDIGO Co-Chairs, KDIGO Methods Chair, Work Group Co-Chairs, and the ERT met for a one-day meeting in Houston, Texas, United States of America in February 2018 to discuss the previous guideline, 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 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 drafted preliminary list of topics and key clinical questions was informed by the previous KDIGO guideline[900] and the KDIGO controversies conference on Glomerular Diseases.[1, 2] Logical 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 Population, Intervention, Comparator, Outcomes (a list of critical and important outcomes was compiled after voting from the Work Group (Table MC1)), and Methods (PICOM) format. The Work Group and the ERT further refined the clinical questions to finalize 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 with 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.[900] Details of the PICOM questions and associated Cochrane Kidney and Transplant systematic reviews are provided in Table MC2. All evidence reviews were conducted in accordance with the Cochrane Handbook,[903] and guideline development adhered to the standards of GRADE (Grades of Recommendation, Assessment, Development, and Evaluation).[904]

Table MC1. Hierarchy of outcomes

Hierarchy	Outcomes
Critical outcomes	- All-cause mortality - End-stage kidney disease (need for dialysis/ eGFR <15 ml/min/1.73 m^2) ≥50% loss of GFR - Infection - Corticosteroid-related adverse events - Malignancy
Important outcomes	- Complete remission/relapse - Annual GFR loss (minimum three years follow-up)

Table MC2. Clinical questions and systematic review topics in PICOM format

Guideline chapter	General Principles in the Management of Glomerular Diseases
Clinical question	In patients with GN, what are patient preferences and values for immunosuppressive and non-immunosuppressive therapy?
Population	Patients with GN
Phenomenon of interest	Preferences and values for immunosuppressive or non-immunosuppressive therapy
Outcomes	Preferences and values
Study design	All study types
Guideline chapter	Immunoglobin A Nephropathy/Immunoglobin A Vasculitis
Clinical question	In patients with biopsy-proven IgAN, what non-immunosuppressive agents compared to no treatment/placebo improve efficacy outcomes and reduce adverse effects?
Population	Patients with IgAN
Intervention	Fish oil, anticoagulants/antiplatelet, antioxidant, tonsillectomy, statins, traditional Chinese medicine, vitamin D, vitamin E, allopurinol, etc.
Comparator	No treatment/placebo
Outcomes	Outcomes listed in Table MC1
Study design	RCTs
Cochrane review	Reid S M, *et al*. Non-immunosuppressive agents for treating IgA nephropathy (Review). Cochrane Database of Systematic Reviews. 2011:3; CD003962.
Clinical question	In patients with biopsy-proven IgAN, what immunosuppressive agents compared to no treatment/placebo improve efficacy outcomes and reduce adverse effects?
Population	Patients with IgAN
Intervention	Immunosuppressive therapy
Comparator	No treatment/placebo
Outcomes	Outcomes listed in Table MC1
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.
Clinical question	In patients with biopsy-proven IgAV (Henoch-Schönlein purura (HSP) nephritis), what immunosuppressive agents compared to no treatment/placebo or standard of care improve efficacy outcomes and reduce adverse effects?
Population	Patients with IgAV (HSP nephritis)
Intervention	Immunosuppressive therapy
Comparator	No treatment/placebo or standard of care
Outcomes	Outcomes listed in Table MC1 Additional outcomes – body mass index
Study design	RCTs
Cochrane 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; CD004128.
Guideline chapter	Membranous Nephropathy
Clinical question	In adults with biopsy-proven idiopathic MN, 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	Critical and important outcomes listed in Table MC1
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.
Guideline chapter	Nephrotic Syndrome in Children
Clinical question	In children (aged 3 to 18 years of age) with SSNS, what corticosteroid therapy regimens compared with no treatment/placebo or standard of care improve efficacy outcomes and reduce adverse effects?

Population	Children (aged 3 to 18 years of age) with SSNS
Intervention	Corticosteroid therapy
Comparator	No treatment/placebo or standard of care
Outcomes	Outcomes listed in Table MC1
Study design	RCTs
Cochrane review	Hahn D, *et al*. Corticosteroid therapy for nephrotic syndrome in children (Review). Cochrane Database of Systematic Reviews. 2015:3; CD001533.
Clinical question	In children (aged 3 to 18 years of age) with SSNS, what non-corticosteroid immunosuppressive regimens compared to no treatment/placebo or standard of care improve efficacy outcomes and reduce adverse effects?
Population	Children (aged 3 to 18 years of age) with SSNS
Intervention	Non-corticosteroid immunosuppressive therapy
Comparator	No treatment/placebo or standard of care
Outcomes	Outcomes listed in Table MC1
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.
Clinical question	In children (aged 3 to 18 years of age) with SRNS, what immunosuppressive therapy compared to no treatment/placebo or other immunosuppressive medication improves efficacy outcomes and reduce adverse effects?
Population	Children (aged 3 to 18 years of age) with SRNS
Intervention	Immunosuppressive therapy
Comparator	No treatment/placebo or other immunosuppressive therapies (including corticosteroids)
Outcomes	Outcomes listed in Table MC1
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
Guideline chapter	Minimal Change Disease in Adults

Clinical question	In adults with biopsy-proven MCD and NS, what immunosuppressive agents compared to no treatment/placebo or other immunosuppressive therapy improves 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	Critical and important outcomes listed in Table MC1
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
Guideline chapter	**Focal Segmental Glomerulosclerosis in Adults**
Clinical question	In adults with biopsy-proven FSGS, what immunosuppressive agents compared to no treatment/placebo or other immunosuppressive therapy improves efficacy outcomes and reduces adverse effects?
Population	Adults with biopsy-proven FSGS
Intervention	Immunosuppressive therapy
Comparator	No treatment/placebo or other immunosuppressive therapies
Outcomes	Critical and important outcomes listed in Table MC1
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.
Guideline chapter	**Infection-Related Glomerulonephritis**
Clinical question	In adult patients with hepatitis B- or hepatitis C-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 hepatitis B- or hepatitis C-related GN
Intervention	Antiviral treatment therapy
Comparator	No treatment/placebo or standard of care
Outcomes	Critical and important outcomes listed in Table MC1
Study design	RCTs

Cochrane systematic reviews	None relevant
Clinical question	In patients with HIV-associated nephropathy, what antiretroviral treatment compared to no treatment/placebo or standard of care improves efficacy outcomes and reduce adverse effects?
Population	HIV-associated nephropathy
Intervention	Highly active antiretroviral therapy (HAART alone or combined with antihypertensive agents, corticosteroids, and immunosuppressive therapies)
Comparator	No treatment/placebo or standard of care
Outcomes	Critical and important outcomes listed in Table MC1
Study design	RCTs
Cochrane systematic reviews	Yahaya I, *et al*. Interventions for HIV-associated nephropathy (Review). Cochrane Database of Systematic Reviews. 2013:1; CD007183.
Guideline chapter	Immunoglobulin and Complement-Mediated Glomerular Diseases with an MPGN Pattern of Injury
Clinical question	In adults with complement-mediated disease, what immunosuppressive agents compared to no treatment/placebo or standard of care improves efficacy outcomes and reduce adverse effects?
Population	Patients with C3 mediated GN, C3 DDD, CFHR5 nephropathy, C4 mediated GN, Idiopathic MPGN, FGRS
Intervention	Immunosuppressive therapy
Comparator	No treatment/placebo or standard of care
Outcomes	Critical and important outcomes listed in Table MC1
Study design	RCTs
Cochrane systematic reviews	None relevant
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, ESKD, complete kidney remission, hematological response, adverse events
Study design	RCTs and observational studies
Cochrane systematic reviews	None relevant
Guideline chapter	Anti-Neutrophil Cytoplasmic Antibodies (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	Critical and important outcomes listed in Table MC1
Study design	RCTs
Cochrane systematic reviews	Walters *et al*. Interventions for renal vasculitis in adults (Review). Cochrane Database of Systematic Reviews. 2020:1; CD003232.
Guideline chapter	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 or placebo with standard of care
Outcomes	Critical and important outcomes listed in Table MC1
Study design	RCTs and observational studies
Cochrane systematic reviews	None relevant
Clinical question	In patients with non-proliferative (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 non-proliferative (Class I, II, V, or VI) LN

Intervention	Immunosuppressive therapy
Comparator	No treatment/placebo or other immunosuppressive therapies
Outcomes	Critical and important outcomes listed in Table MC1
Study design	RCTs
Cochrane systematic reviews	None relevant
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 clinical 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	Critical and important outcomes listed in Table MC1
Study design	RCTs
Cochrane systematic reviews	Tunnicliffe DJ, *et al*. Immunosuppressive treatment for proliferative lupus nephritis. Cochrane Database of Systematic Reviews. 2018:6; CD002922.
Guideline chapter	Anti-Glomerular Basement Membrane Antibody Glomerulonephritis
Clinical question	In patients with biopsy-proven anti-GBM, what immunosuppressive agents compared to no treatment/placebo or other immunosuppressive therapies improve efficacy (all-cause mortality, ESKD, ≥50% loss of GFR, annual loss of GFR, complete remission) outcomes and reduces adverse effects (infection, and malignancy)?
Population	Patients with biopsy-proven anti-GBM
Intervention	Immunosuppressive therapy
Comparator	No treatment/placebo or other immunosuppressive therapies
Outcomes	Critical and important outcomes listed in Table MC1
Study design	RCTs
Cochrane systematic reviews	None relevant

Literature searches and article selection

Searches for RCTs utilized the Cochrane Kidney and Transplant Registry of studies. 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 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 International Clinical Trials Register search portal.

For review topics that matched to 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 only included RCTs and not linked to any an existing Cochrane systematic review. For clinical questions that included other study types, for example, systematic reviews on non-CKD populations, the medical literature databases MEDLINE and Embase were searched. The search strategies are provided in Supplementary Appendix Table S1.

The titles and abstracts resulting from the searches were screened by two 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 21,521 citations were screened. Of these, 447 RCTs and 94 observational studies were included in the evidence review. (Figure MC1)

Figure MC1. Search yield and study flow diagram

Randomized controlled trials (RCTs)
Search May 2018
Cochrane Kidney and Transplant registry of studies
21,521 citations retrieved

Observational studies
Search May 2018
MEDLINE
1739 citations retrieved

Included RCTs
IgA nephropathy – 128 RCTs
IgA vasculitis – 12 RCTs
Primary membranous nephropathy – 60 RCTs
Nephrotic syndrome in children – 109 RCTs
Minimal change disease – 8 RCTs
Focal segmental glomerulosclerosis – 11 RCTs
Infection–related glomerulonephritis – 1 RCT
Complement–mediated glomerulonephritis – 3 RCTs
Anti–neutrophil cytoplasmic antibodies (ANCA)–associated vasculitis – 39 RCTs
Lupus nephritis – 75 RCTs
Anti–glomerular basement membrane antibody glomerulonephritis – 1 RCT

Included observational studies
Patient priorities and preferences – 7 studies
Complement–mediated glomerulonephritis – 74 studies
lupus nephritis (antimalarials) – 13 studies

Included studies
447 RCTs
94 observational studies

Data extraction

Data extraction was performed independently by two members of the ERT. Unclear data were clarified by contacting the author of the study report, and any relevant data obtained in this manner was 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:[905]

- 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)

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- 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 a risk of bias?

All critical appraisal was conducted independently by two 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 outcomes (all-cause mortality, ESKD, ≥50% loss of GFR, infection, malignancy, complete remission/relapse) results were expressed as relative risk (RR) with 95% confidence intervals (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 Mantel-Haenszel random-effects effects model for dichotomous outcomes and 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.[903]

Assessment of heterogeneity – Heterogeneity was assessed by visual inspection of forest plots of standardized mean effect sizes and of risk ratios, and χ^2 tests. A P < 0.1 was used to denote statistical heterogeneity and with an I^2 calculated to measure the proportion of total variation in the estimates of treatment effect that was due to heterogeneity beyond chance.[903] We used conventions of interpretation as defined by Higgins *et al*.[905]

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).[905] Other reasons for the asymmetry of funnel plots were considered.

Subgroup analysis and investigation of heterogeneity – Subgroup analysis was undertaken to explore whether clinical differences between 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: kidney function (GFR, proteinuria, presence of albuminuria, presence of macroscopic hematuria),

histopathological class of disease, primary versus secondary forms of disease, gender, adult versus pediatric. The test of subgroup differences used the I^2 statistic and a P-value of 0.05.[905]

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 the study was conducted in.

However, insufficient data were available to determine the influence of these factors on the effect size of critical and important outcomes.

Grading the quality of the evidence and 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.[904, 906] The GRADE approach 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 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 one study); all indicating concerns about the precision of the results.[904] The final grade for the quality of the evidence for an outcome could be high, moderate, low, or very low (Table MC3).

  For observational studies and other study types, it is possible for the certainty of the evidence to be upgraded from low quality of the evidence according to the specified criteria. For further details on the GRADE approach for rating quality of the evidence, see Table MC4.

Table MC3. Classification for quality and certainty of the evidence

Grade	Quality of evidence	Meaning
A	High	We are confident that the true effect lies 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 effect is very uncertain and often will be far from the truth.

Table MC4. GRADE system for grading quality of evidence

Study design	Staring grade of the quality of the evidence	Step 2 – Lower grade	Step 3 – raise grade for observational studies
RCTs	High	Study limitations: -1 serious -2 very serious	Strength of association +1 large effect size (e.g., 0.5) +2 very large effect size (e.g., 0.2)
	Moderate	Inconsistency: -1 serious -2 very serious	Evidence of a dose-response gradient
Observational studies	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	

Summary of findings tables

Summary of findings tables were developed to include a description of the population, intervention, and comparator. In addition, summary of findings tables included results from the data synthesis as relative and absolute effect estimates. Grading of the quality of evidence for each critical and important outcome is also provided in the summary of findings tables. The summary of findings tables were generated using MAGICapp, an online software application

designed to support guideline development, and are available in the Data Supplement: Appendix C & D – Evidence Tables.

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; Budapest, Hungary, June 2019) and by email communication. The final draft was sent for external public review; reviewers provided open-ended responses. Based on feedback, it was further revised by Work Group Co-Chairs and members. All Work Group members provided feedback on initial and final drafts of the recommendation statement and guideline 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 MC5). 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 preferences and values, resources, and other considerations (Table MC6).

TableMC5. KDIGO nomenclature and description for grading recommendations

Grade	Implications		
	Patients	**Clinicians**	**Policy**
Level 1 "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 "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 MC6. 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 provided.
Quality of the evidence	A higher quality of the evidence, the more likely a strong recommendation is provided. However, there are exceptions where 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 where possible or were assessed in the judgment of the Work Group, where robust evidence was not identified.
Resources and other costs	The higher the costs of an intervention—that is, the more resources consumed—the less likely a strong recommendation is warranted.

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.

The overall quality of the evidence – The overall quality of the evidence was based on the certainty of the evidence for all critical and important outcomes, taking into account relative importance for each outcome to the population of interest. The overall quality of the evidence was graded (A, B, C, or D - Table MC3).

Patient values and preferences – No patients or caregivers were involved in the Work Group. The Work Group, from their experience in managing patients with GN and their understanding of the best available scientific literature made judgments on the preferences and values 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)

Resources and other costs – Healthcare and non-health care resources, including all inputs in the treatment management pathway,[907] 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 supplement recommendations for which a larger quality 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 may also 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 or weak) and the quality of the evidence (A, B, C, D). The recommendation statements are followed by key information (benefits and harms, quality of the evidence, values and preferences, resource use and costs, considerations for implementation), and rationale. Each recommendation is linked to relevant summary of findings tables. An underlying rationale 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 hand searching of journals was not performed for these reviews. In the development of these guidelines, no scoping exercise with patients, searches of the qualitative literature, and formal qualitative evidence synthesis examining patient experiences and priorities were undertaken. As noted, whilst resource implications were considered in the formulation of recommendations, not all topics had formal economic evaluations undertaken.

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REFERENCES

1. Floege J, Barbour SJ, Cattran DC, *et al.* Management and treatment of glomerular diseases (part 1): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2019; **95:** 268-280.

2. Rovin BH, Caster DJ, Cattran DC, *et al.* Management and treatment of glomerular diseases (part 2): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2019; **95:** 281-295.

3. Bartosik LP, Lajoie G, Sugar L, *et al.* Predicting progression in IgA nephropathy. *Am J Kidney Dis* 2001; **38:** 728-735.

4. Hotta O, Taguma Y, Kurosawa K, *et al.* Early intensive therapy for clinical remission of active IgA nephropathy: a three-year follow-up study. *Nihon Jinzo Gakkai Shi* 1993; **35:** 967-973.

5. Kawamura T, Yoshimura M, Miyazaki Y, *et al.* A multicenter randomized controlled trial of tonsillectomy combined with steroid pulse therapy in patients with immunoglobulin A nephropathy. *Nephrol Dial Transplant* 2014; **29:** 1546-1553.

6. Kawasaki Y, Takano K, Suyama K, *et al.* Efficacy of tonsillectomy pulse therapy versus multiple-drug therapy for IgA nephropathy. *Pediatr Nephrol* 2006; **21:** 1701-1706.

7. Reid S, Cawthon PM, Craig JC, *et al.* Non-immunosuppressive treatment for IgA nephropathy. *Cochrane Database Syst Rev* 2011**:** CD003962.

8. Yang D, He L, Peng X, *et al.* The efficacy of tonsillectomy on clinical remission and relapse in patients with IgA nephropathy: a randomized controlled trial. *Ren Fail* 2016; **38:** 242-248.

9. Yata N, Nakanishi K, Shima Y, *et al.* Improved renal survival in Japanese children with IgA nephropathy. *Pediatr Nephrol* 2008; **23:** 905-912.

10. Selewski DT, Ambruzs JM, Appel GB, *et al.* Clinical Characteristics and Treatment Patterns of Children and Adults With IgA Nephropathy or IgA Vasculitis: Findings From the CureGN Study. *Kidney Int Rep* 2018; **3:** 1373-1384.

11. Cambier A, Rabant M, Peuchmaur M, *et al.* Immunosuppressive Treatment in Children With IgA Nephropathy and the Clinical Value of Podocytopathic Features. *Kidney Int Rep* 2018; **3:** 916-925.

12. Working Group of the International IgA Nephropathy Network, The Renal Pathology Society, Coppo R, *et al.* The Oxford IgA nephropathy clinicopathological classification is valid for children as well as adults. *Kidney Int* 2010; **77:** 921-927.

13. Yoshikawa N, Honda M, Iijima K, *et al.* Steroid treatment for severe childhood IgA nephropathy: a randomized, controlled trial. *Clin J Am Soc Nephrol* 2006; **1:** 511-517.

14. Yoshikawa N, Ito H, Sakai T, *et al.* A controlled trial of combined therapy for newly diagnosed severe childhood IgA nephropathy. The Japanese Pediatric IgA Nephropathy Treatment Study Group. *J Am Soc Nephrol* 1999; **10:** 101-109.

15. Coppo R, Peruzzi L, Amore A, *et al.* IgACE: a placebo-controlled, randomized trial of angiotensin-converting enzyme inhibitors in children and young people with IgA nephropathy and moderate proteinuria. *J Am Soc Nephrol* 2007; **18:** 1880-1888.

16. Coppo R. Biomarkers and targeted new therapies for IgA nephropathy. *Pediatr Nephrol* 2017; **32:** 725-731.

17. Yoshikawa N, Ito H. Combined therapy with prednisolone, azathioprine, heparin-warfarin, and dipyridamole for paediatric patients with severe IgA nephropathy--is it relevant for adult patients? *Nephrol Dial Transplant* 1999; **14:** 1097-1099.

18. Lv J, Yang Y, Zhang H, *et al.* Prediction of outcomes in crescentic IgA nephropathy in a multicenter cohort study. *J Am Soc Nephrol* 2013; **24:** 2118-2125.

19. Shima Y, Nakanishi K, Hama T, *et al.* Spontaneous remission in children with IgA nephropathy. *Pediatr Nephrol* 2013; **28:** 71-76.

20. Ozen S, Marks SD, Brogan P, *et al.* European consensus-based recommendations for diagnosis and treatment of immunoglobulin A vasculitis-the SHARE initiative. *Rheumatology (Oxford)* 2019; **58:** 1607-1616.

21. Ozen S, Ruperto N, Dillon MJ, *et al.* EULAR/PReS endorsed consensus criteria for the classification of childhood vasculitides. *Ann Rheum Dis* 2006; **65:** 936-941.

22. Coppo R, Andrulli S, Amore A, *et al.* Predictors of outcome in Henoch-Schonlein nephritis in children and adults. *Am J Kidney Dis* 2006; **47:** 993-1003.

23. Pillebout E, Thervet E, Hill G, *et al.* Henoch-Schonlein Purpura in adults: outcome and prognostic factors. *J Am Soc Nephrol* 2002; **13:** 1271-1278.

24. Shrestha S, Sumingan N, Tan J, *et al.* Henoch Schonlein purpura with nephritis in adults: adverse prognostic indicators in a UK population. *QJM* 2006; **99:** 253-265.

25. Barbour SJ, Coppo R, Zhang H, *et al.* Evaluating a New International Risk-Prediction Tool in IgA Nephropathy. *JAMA Intern Med* 2019; **179:** 942-952.

26. Augusto JF, Sayegh J, Delapierre L, *et al.* Addition of plasma exchange to glucocorticosteroids for the treatment of severe Henoch-Schonlein purpura in adults: a case series. *Am J Kidney Dis* 2012; **59:** 663-669.

27. Schwartz J, Padmanabhan A, Aqui N, *et al.* Guidelines on the Use of Therapeutic Apheresis in Clinical Practice-Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Seventh Special Issue. *J Clin Apher* 2016; **31:** 149-162.

28. Chartapisak W, Opastiraku S, Willis NS, *et al.* Prevention and treatment of renal disease in Henoch-Schonlein purpura: a systematic review. *Arch Dis Child* 2009; **94:** 132-137.

29. Chartapisak W, Opastirakul S, Hodson EM, *et al.* Interventions for preventing and treating kidney disease in Henoch-Schonlein Purpura (HSP). *Cochrane Database Syst Rev* 2009**:** CD005128.

30. Hennies I, Gimpel C, Gellermann J, *et al.* Presentation of pediatric Henoch-Schonlein purpura nephritis changes with age and renal histology depends on biopsy timing. *Pediatr Nephrol* 2018; **33:** 277-286.

31. Angioi A, Fervenza FC, Sethi S, *et al.* Diagnosis of complement alternative pathway disorders. *Kidney Int* 2016; **89:** 278-288.

32. Walker PD, Cavallo T, Bonsib SM, *et al.* Practice guidelines for the renal biopsy. *Mod Pathol* 2004; **17:** 1555-1563.

33. Corwin HL, Schwartz MM, Lewis EJ. The importance of sample size in the interpretation of the renal biopsy. *Am J Nephrol* 1988; **8:** 85-89.

34. Hogan JJ, Mocanu M, Berns JS. The Native Kidney Biopsy: Update and Evidence for Best Practice. *Clin J Am Soc Nephrol* 2016; **11:** 354-362.

35. Rovin BH, Parikh SV, Alvarado A. The kidney biopsy in lupus nephritis: is it still relevant? *Rheum Dis Clin North Am* 2014; **40:** 537-552, ix.

36. Glassock RJ. Evaluation of proteinuria redux. *Kidney Int* 2016; **90:** 938-940.

37. Tangri N, Grams ME, Levey AS, *et al.* Multinational Assessment of Accuracy of Equations for Predicting Risk of Kidney Failure: A Meta-analysis. *JAMA* 2016; **315:** 164-174.

38. Weaver RG, James MT, Ravani P, *et al.* Estimating Urine Albumin-to-Creatinine Ratio from Protein-to-Creatinine Ratio: Development of Equations using Same-Day Measurements. *J Am Soc Nephrol* 2020; **31:** 591-601.

39. Clase CM, St Pierre MW, Churchill DN. Conversion between bromcresol green- and bromcresol purple-measured albumin in renal disease. *Nephrol Dial Transplant* 2001; **16:** 1925-1929.

40. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16:** 31-41.

41. Gaspari F, Perico N, Ruggenenti P, *et al.* Plasma clearance of nonradioactive iohexol as a measure of glomerular filtration rate. *J Am Soc Nephrol* 1995; **6:** 257-263.

42. Perrone RD, Steinman TI, Beck GJ, *et al.* Utility of radioisotopic filtration markers in chronic renal insufficiency: simultaneous comparison of 125I-iothalamate, 169Yb-DTPA, 99mTc-DTPA, and inulin. The Modification of Diet in Renal Disease Study. *Am J Kidney Dis* 1990; **16:** 224-235.

43. Pottel H, Delanaye P, Schaeffner E, *et al.* Estimating glomerular filtration rate for the full age spectrum from serum creatinine and cystatin C. *Nephrol Dial Transplant* 2017; **32:** 497-507.

44. Schwartz GJ, Munoz A, Schneider MF, *et al.* New equations to estimate GFR in children with CKD. *J Am Soc Nephrol* 2009; **20:** 629-637.

45. Stevens LA, Coresh J, Greene T, *et al.* Assessing kidney function--measured and estimated glomerular filtration rate. *N Engl J Med* 2006; **354:** 2473-2483.

46.   Stevens LA, Coresh J, Schmid CH, *et al.* Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. *Am J Kidney Dis* 2008; **51:** 395-406.

47.   Branten AJ, Vervoort G, Wetzels JF. Serum creatinine is a poor marker of GFR in nephrotic syndrome. *Nephrol Dial Transplant* 2005; **20:** 707-711.

48.   Coppo R, Fervenza FC. Persistent Microscopic Hematuria as a Risk Factor for Progression of IgA Nephropathy: New Floodlight on a Nearly Forgotten Biomarker. *J Am Soc Nephrol* 2017; **28:** 2831-2834.

49.   Ray EC, Rondon-Berrios H, Boyd CR, *et al.* Sodium retention and volume expansion in nephrotic syndrome: implications for hypertension. *Adv Chronic Kidney Dis* 2015; **22:** 179-184.

50.   Jentzer JC, DeWald TA, Hernandez AF. Combination of loop diuretics with thiazide-type diuretics in heart failure. *J Am Coll Cardiol* 2010; **56:** 1527-1534.

51.   Fallahzadeh MA, Dormanesh B, Fallahzadeh MK, *et al.* Acetazolamide and Hydrochlorothiazide Followed by Furosemide Versus Furosemide and Hydrochlorothiazide Followed by Furosemide for the Treatment of Adults With Nephrotic Edema: A Randomized Trial. *Am J Kidney Dis* 2017; **69:** 420-427.

52.   Staehr M, Buhl KB, Andersen RF, *et al.* Aberrant glomerular filtration of urokinase-type plasminogen activator in nephrotic syndrome leads to amiloride-sensitive plasminogen activation in urine. *Am J Physiol Renal Physiol* 2015; **309:** F235-241.

53.   Tamargo J, Segura J, Ruilope LM. Diuretics in the treatment of hypertension. Part 2: loop diuretics and potassium-sparing agents. *Expert Opin Pharmacother* 2014; **15:** 605-621.

54.   Leehey DJ, Zhang JH, Emanuele NV, *et al.* BP and Renal Outcomes in Diabetic Kidney Disease: The Veterans Affairs Nephropathy in Diabetes Trial. *Clin J Am Soc Nephrol* 2015; **10:** 2159-2169.

55.   Ontarget Investigators, Yusuf S, Teo KK, *et al.* Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008; **358:** 1547-1559.

56.   Dhaybi OA, Bakris G. Mineralocorticoid antagonists in chronic kidney disease. *Curr Opin Nephrol Hypertens* 2017; **26:** 50-55.

57.   Parving HH, Brenner BM, McMurray JJ, *et al.* Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med* 2012; **367:** 2204-2213.

58.   Coresh J, Heerspink HJL, Sang Y, *et al.* Change in albuminuria and subsequent risk of end-stage kidney disease: an individual participant-level consortium meta-analysis of observational studies. *Lancet Diabetes Endocrinol* 2019; **7:** 115-127.

59.   Heerspink HJL, Greene T, Tighiouart H, *et al.* Change in albuminuria as a surrogate endpoint for progression of kidney disease: a meta-analysis of treatment effects in randomised clinical trials. *Lancet Diabetes Endocrinol* 2019; **7:** 128-139.

60.   Thompson A, Carroll K, L AI, *et al.* Proteinuria Reduction as a Surrogate End Point in Trials of IgA Nephropathy. *Clin J Am Soc Nephrol* 2019; **14:** 469-481.

61. Agrawal S, Zaritsky JJ, Fornoni A, *et al.* Dyslipidaemia in nephrotic syndrome: mechanisms and treatment. *Nat Rev Nephrol* 2018; **14:** 57-70.

62. Vaziri ND. Disorders of lipid metabolism in nephrotic syndrome: mechanisms and consequences. *Kidney Int* 2016; **90:** 41-52.

63. Kong X, Yuan H, Fan J, *et al.* Lipid-lowering agents for nephrotic syndrome. *Cochrane Database Syst Rev* 2013**:** CD005425.

64. Morris AW. Nephrotic syndrome: PCSK9: a target for hypercholesterolaemia in nephrotic syndrome. *Nat Rev Nephrol* 2016; **12:** 510.

65. Pincus KJ, Hynicka LM. Prophylaxis of thromboembolic events in patients with nephrotic syndrome. *Ann Pharmacother* 2013; **47:** 725-734.

66. Sexton DJ, de Freitas DG, Little MA, *et al.* Direct-Acting Oral Anticoagulants as Prophylaxis Against Thromboembolism in the Nephrotic Syndrome. *Kidney Int Rep* 2018; **3:** 784-793.

67. Makani A, Saba S, Jain S, *et al.* The Safety of Anticoagulation for Atrial Fibrillation with DOAC versus Warfarin in Patients with Various Stages of Renal Function. *Journal of the American College of Cardiology* 2019; **73:** 322.

68. Mirrakhimov AE, Ali AM, Barbaryan A, *et al.* Primary Nephrotic Syndrome in Adults as a Risk Factor for Pulmonary Embolism: An Up-to-Date Review of the Literature. *Int J Nephrol* 2014; **2014:** 916760.

69. Gigante A, Barbano B, Liberatori M, *et al.* Nephrotic syndrome and stroke. *Int J Immunopathol Pharmacol* 2013; **26:** 769-772.

70. Carter SA, Lightstone L, Cattran D, *et al.* Standardized Outcomes in Nephrology-Glomerular Disease (SONG-GD): establishing a core outcome set for trials in patients with glomerular disease. *Kidney Int* 2019; **95:** 1280-1283.

71. Levey AS, Gansevoort RT, Coresh J, *et al.* Change in Albuminuria and GFR as End Points for Clinical Trials in Early Stages of CKD: A Scientific Workshop Sponsored by the National Kidney Foundation in Collaboration With the US Food and Drug Administration and European Medicines Agency. *Am J Kidney Dis* 2020; **75:** 84-104.

72. Grams ME, Sang Y, Ballew SH, *et al.* Evaluating Glomerular Filtration Rate Slope as a Surrogate End Point for ESKD in Clinical Trials: An Individual Participant Meta-Analysis of Observational Data. *J Am Soc Nephrol* 2019; **30:** 1746-1755.

73. Greene T, Ying J, Vonesh EF, *et al.* Performance of GFR Slope as a Surrogate End Point for Kidney Disease Progression in Clinical Trials: A Statistical Simulation. *J Am Soc Nephrol* 2019; **30:** 1756-1769.

74. Groopman E, Goldstein D, Gharavi A. Diagnostic Utility of Exome Sequencing for Kidney Disease. Reply. *N Engl J Med* 2019; **380:** 2080-2081.

75. Hamidi H, Kretzler M. Systems biology approaches to identify disease mechanisms and facilitate targeted therapy in the management of glomerular disease. *Curr Opin Nephrol Hypertens* 2018; **27:** 433-439.

76. Hayek SS, Sever S, Ko YA, *et al.* Soluble Urokinase Receptor and Chronic Kidney Disease. *N Engl J Med* 2015; **373:** 1916-1925.

77. Siwy J, Mischak H, Zurbig P. Proteomics and personalized medicine: a focus on kidney disease. *Expert Rev Proteomics* 2019; **16:** 773-782.

78. Ponticelli C, Glassock RJ. Prevention of complications from use of conventional immunosuppressants: a critical review. *J Nephrol* 2019; **32:** 851-870.

79. Blumenfeld Z, Patel B, Leiba R, *et al.* Gonadotropin-releasing hormone agonist may minimize premature ovarian failure in young women undergoing autologous stem cell transplantation. *Fertil Steril* 2012; **98:** 1266-1270 e1261.

80. Lazarus B, Chen Y, Wilson FP, *et al.* Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease. *JAMA Intern Med* 2016; **176:** 238-246.

81. Xie Y, Bowe B, Li T, *et al.* Proton Pump Inhibitors and Risk of Incident CKD and Progression to ESRD. *J Am Soc Nephrol* 2016; **27:** 3153-3163.

82. Meyrier A, Noel LH, Auriche P, *et al.* Long-term renal tolerance of cyclosporin A treatment in adult idiopathic nephrotic syndrome. Collaborative Group of the Societe de Nephrologie. *Kidney Int* 1994; **45:** 1446-1456.

83. Iijima K, Hamahira K, Tanaka R, *et al.* Risk factors for cyclosporine-induced tubulointerstitial lesions in children with minimal change nephrotic syndrome. *Kidney Int* 2002; **61:** 1801-1805.

84. Wiles K, Lightstone L. Glomerular Disease in Women. *Kidney Int Rep* 2018; **3:** 258-270.

85. 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.

86. Oliverio AL, Zee J, Mariani LH, *et al.* Renal Complications in Pregnancy Preceding Glomerulonephropathy Diagnosis. *Kidney Int Rep* 2019; **4:** 159-162.

87. Davison JM, Katz AI, Lindheimer MD. Kidney disease and pregnancy: obstetric outcome and long-term renal prognosis. *Clin Perinatol* 1985; **12:** 497-519.

88. Jungers P, Forget D, Henry-Amar M, *et al.* Chronic kidney disease and pregnancy. *Adv Nephrol Necker Hosp* 1986; **15:** 103-141.

89. Lindheimer MD, Katz AI. Gestation in women with kidney disease: prognosis and management. *Baillieres Clin Obstet Gynaecol* 1994; **8:** 387-404.

90. Park S, Lee SM, Park JS, *et al.* Midterm eGFR and Adverse Pregnancy Outcomes: The Clinical Significance of Gestational Hyperfiltration. *Clin J Am Soc Nephrol* 2017; **12:** 1048-1056.

91. Kattah AG, Garovic VD. Pregnancy and Lupus Nephritis. *Semin Nephrol* 2015; **35:** 487-499.

92. Piccoli GB, Attini R, Cabiddu G, *et al.* Maternal-foetal outcomes in pregnant women with glomerulonephritides. Are all glomerulonephritides alike in pregnancy? *J Autoimmun* 2017; **79:** 91-98.

93. Smyth A, Oliveira GH, Lahr BD, *et al.* A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. *Clin J Am Soc Nephrol* 2010; **5:** 2060-2068.

94. Buyon JP, Kim MY, Guerra MM, *et al.* Predictors of Pregnancy Outcomes in Patients With Lupus: A Cohort Study. *Ann Intern Med* 2015; **163:** 153-163.

95. Moroni G, Doria A, Giglio E, *et al.* Fetal outcome and recommendations of pregnancies in lupus nephritis in the 21st century. A prospective multicenter study. *J Autoimmun* 2016; **74:** 6-12.

96. Ahmed SB, Hovind P, Parving HH, *et al.* Oral contraceptives, angiotensin-dependent renal vasoconstriction, and risk of diabetic nephropathy. *Diabetes Care* 2005; **28:** 1988-1994.

97. Ahmed SB, Kang AK, Burns KD, *et al.* Effects of oral contraceptive use on the renal and systemic vascular response to angiotensin II infusion. *J Am Soc Nephrol* 2004; **15:** 780-786.

98. Kang AK, Duncan JA, Cattran DC, *et al.* Effect of oral contraceptives on the renin angiotensin system and renal function. *Am J Physiol Regul Integr Comp Physiol* 2001; **280:** R807-813.

99. Lidegaard O, Lokkegaard E, Jensen A, *et al.* Thrombotic stroke and myocardial infarction with hormonal contraception. *N Engl J Med* 2012; **366:** 2257-2266.

100. Berthoux F, Mohey H, Laurent B, *et al.* Predicting the risk for dialysis or death in IgA nephropathy. *J Am Soc Nephrol* 2011; **22:** 752-761.

101. Goto M, Wakai K, Kawamura T, *et al.* A scoring system to predict renal outcome in IgA nephropathy: a nationwide 10-year prospective cohort study. *Nephrol Dial Transplant* 2009; **24:** 3068-3074.

102. Pesce F, Diciolla M, Binetti G, *et al.* Clinical decision support system for end-stage kidney disease risk estimation in IgA nephropathy patients. *Nephrol Dial Transplant* 2016; **31:** 80-86.

103. Wakai K, Kawamura T, Endoh M, *et al.* A scoring system to predict renal outcome in IgA nephropathy: from a nationwide prospective study. *Nephrol Dial Transplant* 2006; **21:** 2800-2808.

104. Xie J, Kiryluk K, Wang W, *et al.* Predicting progression of IgA nephropathy: new clinical progression risk score. *PLoS One* 2012; **7:** e38904.

105. Tanaka S, Ninomiya T, Katafuchi R, *et al.* Development and validation of a prediction rule using the Oxford classification in IgA nephropathy. *Clin J Am Soc Nephrol* 2013; **8:** 2082-2090.

106. Chen T, Li X, Li Y, *et al.* Prediction and Risk Stratification of Kidney Outcomes in IgA Nephropathy. *Am J Kidney Dis* 2019; **74:** 300-309.

107. Jafar TH, Stark PC, Schmid CH, *et al.* Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. *Ann Intern Med* 2003; **139:** 244-252.

108. Xie X, Atkins E, Lv J, *et al.* Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. *Lancet* 2016; **387:** 435-443.

109. Xie X, Liu Y, Perkovic V*, et al.* Renin-Angiotensin System Inhibitors and Kidney and Cardiovascular Outcomes in Patients With CKD: A Bayesian Network Meta-analysis of Randomized Clinical Trials. *Am J Kidney Dis* 2016; **67:** 728-741.

110. Nakamura T, Ushiyama C, Suzuki S*, et al.* Effects of angiotensin-converting enzyme inhibitor, angiotensin II receptor antagonist and calcium antagonist on urinary podocytes in patients with IgA nephropathy. *Am J Nephrol* 2000; **20:** 373-379.

111. Horita Y, Tadokoro M, Taura K*, et al.* Low-dose combination therapy with temocapril and losartan reduces proteinuria in normotensive patients with immunoglobulin a nephropathy. *Hypertens Res* 2004; **27:** 963-970.

112. Praga M, Gutierrez E, Gonzalez E*, et al.* Treatment of IgA nephropathy with ACE inhibitors: a randomized and controlled trial. *J Am Soc Nephrol* 2003; **14:** 1578-1583.

113. Shi X, Chen X, Liu S*, et al.* The effects of angiotensin-converting enzyme inhibitor on IgA nephropathy and the influencing factors. *Zhonghua nei ke za zhi [Chinese journal of internal medicine] 41(6):399-403, 2002* 2002; **41:** 399-403.

114. Woo KT, Lau YK, Wong KS*, et al.* ACEI/ATRA therapy decreases proteinuria by improving glomerular permselectivity in IgA nephritis. *Kidney Int* 2000; **58:** 2485-2491.

115. Rauen T, Eitner F, Fitzner C*, et al.* Intensive Supportive Care plus Immunosuppression in IgA Nephropathy. *N Engl J Med* 2015; **373:** 2225-2236.

116. Coppo R, Troyanov S, Bellur S*, et al.* Validation of the Oxford classification of IgA nephropathy in cohorts with different presentations and treatments. *Kidney Int* 2014; **86:** 828-836.

117. Le W, Liang S, Hu Y*, et al.* Long-term renal survival and related risk factors in patients with IgA nephropathy: results from a cohort of 1155 cases in a Chinese adult population. *Nephrol Dial Transplant* 2012; **27:** 1479-1485.

118. Reich HN, Troyanov S, Scholey JW*, et al.* Remission of proteinuria improves prognosis in IgA nephropathy. *J Am Soc Nephrol* 2007; **18:** 3177-3183.

119. Kanno Y, Okada H, Saruta T*, et al.* Blood pressure reduction associated with preservation of renal function in hypertensive patients with IgA nephropathy: a 3-year follow-up. *Clin Nephrol* 2000; **54:** 360-365.

120. Li PK, Leung CB, Chow KM*, et al.* Hong Kong study using valsartan in IgA nephropathy (HKVIN): a double-blind, randomized, placebo-controlled study. *Am J Kidney Dis* 2006; **47:** 751-760.

121. Ruggenenti P, Perna A, Gherardi G*, et al.* Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet* 1999; **354:** 359-364.

122. Inker LA, Mondal H, Greene T*, et al.* Early Change in Urine Protein as a Surrogate End Point in Studies of IgA Nephropathy: An Individual-Patient Meta-analysis. *Am J Kidney Dis* 2016; **68:** 392-401.

123. Geng DF, Sun WF, Yang L*, et al.* Antiproteinuric effect of angiotensin receptor blockers in normotensive patients with proteinuria: a meta-analysis of randomized controlled trials. *J Renin Angiotensin Aldosterone Syst* 2014; **15:** 44-51.

124. Lv J, Zhang H, Wong MG*, et al.* Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA Nephropathy: The TESTING Randomized Clinical Trial. *JAMA* 2017; **318:** 432-442.

125. Lv J, Zhang H, Chen Y*, et al.* Combination therapy of prednisone and ACE inhibitor versus ACE-inhibitor therapy alone in patients with IgA nephropathy: a randomized controlled trial. *Am J Kidney Dis* 2009; **53:** 26-32.

126. Manno C, Torres DD, Rossini M*, et al.* Randomized controlled clinical trial of corticosteroids plus ACE-inhibitors with long-term follow-up in proteinuric IgA nephropathy. *Nephrol Dial Transplant* 2009; **24:** 3694-3701.

127. Pozzi C, Bolasco PG, Fogazzi GB*, et al.* Corticosteroids in IgA nephropathy: a randomised controlled trial. *Lancet* 1999; **353:** 883-887.

128. Dudley J, Smith G, Llewelyn-Edwards A*, et al.* Randomised, double-blind, placebo-controlled trial to determine whether steroids reduce the incidence and severity of nephropathy in Henoch-Schonlein Purpura (HSP). *Arch Dis Child* 2013; **98:** 756-763.

129. Hahn D, Hodson EM, Willis NS*, et al.* Interventions for preventing and treating kidney disease in Henoch-Schonlein Purpura (HSP). *Cochrane Database Syst Rev* 2015**:** CD005128.

130. Huber AM, King J, McLaine P*, et al.* A randomized, placebo-controlled trial of prednisone in early Henoch Schonlein Purpura [ISRCTN85109383]. *BMC Med* 2004; **2:** 7.

131. Islek I, Sezer T, Totan M. *The effect of profilactic prednisolon therapy on renal involvement in henoch schonlein vasculitis [abstract].* Proceedings of the XXXVI Congress of the European Renal Association-European Dialysis & Transplant Association; 1999 September 5-8. Madrid, Spain.

132. Mollica F, Li Volti S, Garozzo R*, et al.* Effectiveness of early prednisone treatment in preventing the development of nephropathy in anaphylactoid purpura. *Eur J Pediatr* 1992; **151:** 140-144.

133. Ronkainen J, Koskimies O, Ala-Houhala M*, et al.* Early prednisone therapy in Henoch-Schonlein purpura: a randomized, double-blind, placebo-controlled trial. *J Pediatr* 2006; **149:** 241-247.

134. Crayne CB, Eloseily E, Mannion ML*, et al.* Rituximab treatment for chronic steroid-dependent Henoch-Schonlein purpura: 8 cases and a review of the literature. *Pediatr Rheumatol Online J* 2018; **16:** 71.

135. Maritati F, Fenoglio R, Pillebout E*, et al.* Brief Report: Rituximab for the Treatment of Adult-Onset IgA Vasculitis (Henoch-Schonlein). *Arthritis Rheumatol* 2018; **70:** 109-114.

136. Du Y, Li J, He F*, et al.* The diagnosis accuracy of PLA2R-AB in the diagnosis of idiopathic membranous nephropathy: a meta-analysis. *PLoS One* 2014; **9:** e104936.

137. Behnert A, Schiffer M, Muller-Deile J*, et al.* Antiphospholipase A(2) receptor autoantibodies: a comparison of three different immunoassays for the diagnosis of idiopathic membranous nephropathy. *J Immunol Res* 2014; **2014:** 143274.

138. Bobart SA, De Vriese AS, Pawar AS*, et al.* Noninvasive diagnosis of primary membranous nephropathy using phospholipase A2 receptor antibodies. *Kidney Int* 2019; **95:** 429-438.

139. Wiech T, Stahl RAK, Hoxha E. Diagnostic role of renal biopsy in PLA2R1-antibody-positive patients with nephrotic syndrome. *Mod Pathol* 2019; **32:** 1320-1328.

140. Howman A, Chapman TL, Langdon MM*, et al.* Immunosuppression for progressive membranous nephropathy: a UK randomised controlled trial. *Lancet* 2013; **381:** 744-751.

141. Seitz-Polski B, Debiec H, Rousseau A*, et al.* Phospholipase A2 Receptor 1 Epitope Spreading at Baseline Predicts Reduced Likelihood of Remission of Membranous Nephropathy. *J Am Soc Nephrol* 2018; **29:** 401-408.

142. Pei Y, Cattran D, Greenwood C. Predicting chronic renal insufficiency in idiopathic membranous glomerulonephritis. *Kidney Int* 1992; **42:** 960-966.

143. van den Brand JA, Hofstra JM, Wetzels JF. Prognostic value of risk score and urinary markers in idiopathic membranous nephropathy. *Clin J Am Soc Nephrol* 2012; **7:** 1242-1248.

144. Hofstra JM, Debiec H, Short CD*, et al.* Antiphospholipase A2 receptor antibody titer and subclass in idiopathic membranous nephropathy. *J Am Soc Nephrol* 2012; **23:** 1735-1743.

145. Rousseau A: Sub-analysis of data from GEMRITUX cohort. Personal Communication received by Wetzels JF. January 15, 2019

146. van den Brand JA, van Dijk PR, Hofstra JM*, et al.* Cancer risk after cyclophosphamide treatment in idiopathic membranous nephropathy. *Clin J Am Soc Nephrol* 2014; **9:** 1066-1073.

147. Ponticelli C, Altieri P, Scolari F*, et al.* A randomized study comparing methylprednisolone plus chlorambucil versus methylprednisolone plus cyclophosphamide in idiopathic membranous nephropathy. *J Am Soc Nephrol* 1998; **9:** 444-450.

148. Branten AJ, Reichert LJ, Koene RA*, et al.* Oral cyclophosphamide versus chlorambucil in the treatment of patients with membranous nephropathy and renal insufficiency. *QJM* 1998; **91:** 359-366.

149. du Buf-Vereijken PW, Branten AJ, Wetzels JF. Idiopathic membranous nephropathy: outline and rationale of a treatment strategy. *Am J Kidney Dis* 2005; **46:** 1012-1029.

150. Ahmed S, Rahman M, Alam MR*, et al.* Methyl prednisolone plus chlorambucil as compared with prednisolone alone for the treatment of idiopathic membranous nephropathy - a preliminary study. *Bangladesh renal journal* 1994; **13:** 51-54.

151. Braun N, Erley CM, Benda N*, et al.* Therapy of membranous glomerulonephritis with nephrotic syndrome. 5 years follow-up of a prospective, randomized multi-centre study [abstract]. *Nephrology Dialysis Transplantation* 1995; **10:** 967.

152. Donadio JV, Jr., Holley KE, Anderson CF*, et al.* Controlled trial of cyclophosphamide in idiopathic membranous nephropathy. *Kidney Int* 1974; **6:** 431-439.

153. Imbasciati E, Cagnoli L, Case N*, et al.* [Controlled study of treatment of steroids and chlorambucil, in alternate months, for membranous nephropathy and focal glomerulosclerosis. Preliminary evaluation of the results]. *Minerva Nefrol* 1980; **27:** 571-575.

154. Jha V, Ganguli A, Saha TK, *et al.* A randomized, controlled trial of steroids and cyclophosphamide in adults with nephrotic syndrome caused by idiopathic membranous nephropathy. *J Am Soc Nephrol* 2007; **18:** 1899-1904.

155. Kosmadakis G, Filiopoulos V, Smirloglou D, *et al.* Comparison of immunosuppressive therapeutic regimens in patients with nephrotic syndrome due to idiopathic membranous nephropathy. *Ren Fail* 2010; **32:** 566-571.

156. Pahari DK, Das S, Dutta BN, *et al.* Prognosis and management of membraneous nephropathy. *J Assoc Physicians India* 1993; **41:** 350-351.

157. Ponticelli C, Zucchelli P, Imbasciati E, *et al.* Controlled trial of methylprednisolone and chlorambucil in idiopathic membranous nephropathy. *N Engl J Med* 1984; **310:** 946-950.

158. Ponticelli C, Zucchelli P, Locatelli F, et al. *Controlled trial of monthly alternated courses of steroid and chlorambucil in idiopathic membranous nephropathy*. Proceedings of the 19th Congress European Dialysis and Transplant Associatio; 1982 September 6-9; Madrid, Spain.

159. Ponticelli C, Zucchelli P, Passerini P, *et al.* Methylprednisolone plus chlorambucil as compared with methylprednisolone alone for the treatment of idiopathic membranous nephropathy. The Italian Idiopathic Membranous Nephropathy Treatment Study Group. *N Engl J Med* 1992; **327:** 599-603.

160. Chen Y, Schieppati A, Chen X, *et al.* Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. *Cochrane Database Syst Rev* 2014**:** CD004293.

161. Dahan K, Debiec H, Plaisier E, *et al.* Rituximab for Severe Membranous Nephropathy: A 6-Month Trial with Extended Follow-Up. *J Am Soc Nephrol* 2017; **28:** 348-358.

162. Fervenza FC, Appel GB, Barbour SJ, *et al.* Rituximab or Cyclosporine in the Treatment of Membranous Nephropathy. *N Engl J Med* 2019; **381:** 36-46.

163. Cattran DC, Appel GB, Hebert LA, *et al.* Cyclosporine in patients with steroid-resistant membranous nephropathy: a randomized trial. *Kidney Int* 2001; **59:** 1484-1490.

164. Cattran DC, Greenwood C, Ritchie S, *et al.* A controlled trial of cyclosporine in patients with progressive membranous nephropathy. Canadian Glomerulonephritis Study Group. *Kidney Int* 1995; **47:** 1130-1135.

165. Chen M, Li H, Li XY, *et al.* Tacrolimus combined with corticosteroids in treatment of nephrotic idiopathic membranous nephropathy: a multicenter randomized controlled trial. *Am J Med Sci* 2010; **339:** 233-238.

166. He L, Peng Y, Liu H, *et al.* Treatment of idiopathic membranous nephropathy with combination of low-dose tacrolimus and corticosteroids. *J Nephrol* 2013; **26:** 564-571.

167. Laurens W, Ruggenenti P, Perna A, *et al.* A randomised and controlled study to assess the effect of cyclosporin in nephrotic patients with membranous nephropathy and reduced renal function (cyclomen). *Journal of nephrology* 1994; **7:** 237-247.

168. Praga M, Barrio V, Fernandez JG, et al. *Tacrolimus monotherapy in membranous nephropathy: a randomized controlled trial [abstract no: S-FC-010]*. Proceedings of the 4th World Congress of

Nephrology 19th International Congress of the International Society of Nephrology (ISN); 2007 April 21-25; Rio de Janeiro, Brazil.

169.   Ramachandran R, Hn HK, Kumar V*, et al.* Tacrolimus combined with corticosteroids versus Modified Ponticelli regimen in treatment of idiopathic membranous nephropathy: Randomized control trial. *Nephrology (Carlton)* 2016; **21:** 139-146.

170.   Ramachandran R, Yadav AK, Kumar V*, et al.* Two-Year Follow-up Study of Membranous Nephropathy Treated With Tacrolimus and Corticosteroids Versus Cyclical Corticosteroids and Cyclophosphamide. *Kidney Int Rep* 2017; **2:** 610-616.

171.   Yuan H, Liu N, Sun GD*, et al.* Effect of prolonged tacrolimus treatment in idiopathic membranous nephropathy with nephrotic syndrome. *Pharmacology* 2013; **91:** 259-266.

172.   Falk RJ, Hogan SL, Muller KE*, et al.* Treatment of progressive membranous glomerulopathy. A randomized trial comparing cyclophosphamide and corticosteroids with corticosteroids alone. The Glomerular Disease Collaborative Network. *Ann Intern Med* 1992; **116:** 438-445.

173.   Reichert LJ, Huysmans FT, Assmann K*, et al.* Preserving renal function in patients with membranous nephropathy: daily oral chlorambucil compared with intermittent monthly pulses of cyclophosphamide. *Ann Intern Med* 1994; **121:** 328-333.

174.   Dussol B, Morange S, Burtey S*, et al.* Mycophenolate mofetil monotherapy in membranous nephropathy: a 1-year randomized controlled trial. *Am J Kidney Dis* 2008; **52:** 699-705.

175.   Chan TM, Lin AW, Tang SC*, et al.* Prospective controlled study on mycophenolate mofetil and prednisolone in the treatment of membranous nephropathy with nephrotic syndrome. *Nephrology (Carlton)* 2007; **12:** 576-581.

176.   Senthil Nayagam L, Ganguli A, Rathi M*, et al.* Mycophenolate mofetil or standard therapy for membranous nephropathy and focal segmental glomerulosclerosis: a pilot study. *Nephrol Dial Transplant* 2008; **23:** 1926-1930.

177.   Choi JY, Kim DK, Kim YW*, et al.* The Effect of Mycophenolate Mofetil versus Cyclosporine as Combination Therapy with Low Dose Corticosteroids in High-risk Patients with Idiopathic Membranous Nephropathy: a Multicenter Randomized Trial. *J Korean Med Sci* 2018; **33:** e74.

178.   Peng L, Wei SY, Li LT*, et al.* Comparison of different therapies in high-risk patients with idiopathic membranous nephropathy. *J Formos Med Assoc* 2016; **115:** 11-18.

179.   Branten AJ, du Buf-Vereijken PW, Vervloet M*, et al.* Mycophenolate mofetil in idiopathic membranous nephropathy: a clinical trial with comparison to a historic control group treated with cyclophosphamide. *Am J Kidney Dis* 2007; **50:** 248-256.

180.   van de Logt AE, Hofstra JM, Wetzels JF. Pharmacological treatment of primary membranous nephropathy in 2016. *Expert Rev Clin Pharmacol* 2016; **9:** 1463-1478.

181.   Gellermann J, Weber L, Pape L*, et al.* Mycophenolate mofetil versus cyclosporin A in children with frequently relapsing nephrotic syndrome. *J Am Soc Nephrol* 2013; **24:** 1689-1697.

182.   Noone DG, Iijima K, Parekh R. Idiopathic nephrotic syndrome in children. *Lancet* 2018; **392:** 61-74.

183. Tune BM, Mendoza SA. Treatment of the idiopathic nephrotic syndrome: regimens and outcomes in children and adults. *J Am Soc Nephrol* 1997; **8:** 824-832.

184. Emma F, Montini G, Gargiulo A. Equations to estimate prednisone dose using body weight. *Pediatr Nephrol* 2019; **34:** 685-688.

185. Feber J, Al-Matrafi J, Farhadi E*, et al.* Prednisone dosing per body weight or body surface area in children with nephrotic syndrome: is it equivalent? *Pediatr Nephrol* 2009; **24:** 1027-1031.

186. Ekka BK, Bagga A, Srivastava RN. Single- versus divided-dose prednisolone therapy for relapses of nephrotic syndrome. *Pediatr Nephrol* 1997; **11:** 597-599.

187. Vivarelli M, Massella L, Ruggiero B*, et al.* Minimal Change Disease. *Clin J Am Soc Nephrol* 2017; **12:** 332-345.

188. Sinha A, Saha A, Kumar M*, et al.* Extending initial prednisolone treatment in a randomized control trial from 3 to 6 months did not significantly influence the course of illness in children with steroid-sensitive nephrotic syndrome. *Kidney Int* 2015; **87:** 217-224.

189. Teeninga N, Kist-van Holthe JE, van Rijswijk N*, et al.* Extending prednisolone treatment does not reduce relapses in childhood nephrotic syndrome. *J Am Soc Nephrol* 2013; **24:** 149-159.

190. Yoshikawa N, Nakanishi K, Sako M*, et al.* A multicenter randomized trial indicates initial prednisolone treatment for childhood nephrotic syndrome for two months is not inferior to six-month treatment. *Kidney Int* 2015; **87:** 225-232.

191. Hahn D, Hodson EM, Willis NS*, et al.* Corticosteroid therapy for nephrotic syndrome in children. *Cochrane Database Syst Rev* 2015**:** CD001533.

192. Webb NJA, Woolley RL, Lambe T*, et al.* Long term tapering versus standard prednisolone treatment for first episode of childhood nephrotic syndrome: phase III randomised controlled trial and economic evaluation. *BMJ* 2019; **365:** l1800.

193. Bagga A, Hari P, Srivastava RN. Prolonged versus standard prednisolone therapy for initial episode of nephrotic syndrome. *Pediatr Nephrol* 1999; **13:** 824-827.

194. Ehrich JH, Brodehl J. Long versus standard prednisone therapy for initial treatment of idiopathic nephrotic syndrome in children. Arbeitsgemeinschaft fur Padiatrische Nephrologie. *Eur J Pediatr* 1993; **152:** 357-361.

195. Jayantha UK. *Comparison of ISKDC regime with a six month steroid regime in the treatment of steroid sensitive nephrotic syndrome [abstract no: FP2B].* Proceedings of the 7th Asian Congress of Pediatric Nephrology; 2000 November 1-4; Singapore.

196. Ksiazek J, Wyszynska T. Short versus long initial prednisone treatment in steroid-sensitive nephrotic syndrome in children. *Acta Paediatr* 1995; **84:** 889-893.

197. Moundekhel S, Khan GS, Afridi U. Management of nephrotic syndrome: ISKDC versus APN. *Pakistan Journal of Medical and Health Sciences* 2012; **6:** 3.

198.   Norero C, Delucchi A, Lagos E, *et al.* [Initial therapy of primary nephrotic syndrome in children: evaluation in a period of 18 months of two prednisone treatment schedules. Chilean Co-operative Group of Study of Nephrotic Syndrome in Children]. *Rev Med Chil* 1996; **124:** 567-572.

199.   Paul SK, Muinuddin G, Jahan S, *et al.* Long versus standard initial prednisolone therapy in children with idiopathic nephrotic syndrome. *Mymensingh Med J* 2014; **23:** 261-267.

200.   Satomura K, Yamaoka K, Shima M, *et al.* Standard vs low initial dose of prednisolone therapy for first episodes of nephrotic syndrome in children [abstract]. *Pediatric Nephrology* 2001; **16:** 1.

201.   Ueda N, Chihara M, Kawaguchi S, *et al.* Intermittent versus long-term tapering prednisolone for initial therapy in children with idiopathic nephrotic syndrome. *J Pediatr* 1988; **112:** 122-126.

202.   Nephrotic syndrome in children: a randomized trial comparing two prednisone regimens in steroid-responsive patients who relapse early. Report of the international study of kidney disease in children. *J Pediatr* 1979; **95:** 239-243.

203.   Tarshish P, Tobin JN, Bernstein J, *et al.* Prognostic significance of the early course of minimal change nephrotic syndrome: report of the International Study of Kidney Disease in Children. *J Am Soc Nephrol* 1997; **8:** 769-776.

204.   MacDonald NE, Wolfish N, McLaine P, *et al.* Role of respiratory viruses in exacerbations of primary nephrotic syndrome. *J Pediatr* 1986; **108:** 378-382.

205.   Aljebab F, Choonara I, Conroy S. Systematic Review of the Toxicity of Long-Course Oral Corticosteroids in Children. *PLoS One* 2017; **12:** e0170259.

206.   Ishikura K, Yoshikawa N, Nakazato H, *et al.* Morbidity in children with frequently relapsing nephrosis: 10-year follow-up of a randomized controlled trial. *Pediatr Nephrol* 2015; **30:** 459-468.

207.   Kyrieleis HA, Lowik MM, Pronk I, *et al.* Long-term outcome of biopsy-proven, frequently relapsing minimal-change nephrotic syndrome in children. *Clin J Am Soc Nephrol* 2009; **4:** 1593-1600.

208.   Lettgen B, Jeken C, Reiners C. Influence of steroid medication on bone mineral density in children with nephrotic syndrome. *Pediatr Nephrol* 1994; **8:** 667-670.

209.   Abeyagunawardena AS, Thalgahagoda RS, Dissanayake PV, *et al.* Short courses of daily prednisolone during upper respiratory tract infections reduce relapse frequency in childhood nephrotic syndrome. *Pediatr Nephrol* 2017; **32:** 1377-1382.

210.   Abeyagunawardena AS, Trompeter RS. Increasing the dose of prednisolone during viral infections reduces the risk of relapse in nephrotic syndrome: a randomised controlled trial. *Arch Dis Child* 2008; **93:** 226-228.

211.   Gulati A, Sinha A, Sreenivas V, *et al.* Daily corticosteroids reduce infection-associated relapses in frequently relapsing nephrotic syndrome: a randomized controlled trial. *Clin J Am Soc Nephrol* 2011; **6:** 63-69.

212.   Mattoo TK, Mahmoud MA. Increased maintenance corticosteroids during upper respiratory infection decrease the risk of relapse in nephrotic syndrome. *Nephron* 2000; **85:** 343-345.

213. Trompeter RS, Lloyd BW, Hicks J, *et al.* Long-term outcome for children with minimal-change nephrotic syndrome. *Lancet* 1985; **1:** 368-370.

214. Fakhouri F, Bocquet N, Taupin P, *et al.* Steroid-sensitive nephrotic syndrome: from childhood to adulthood. *Am J Kidney Dis* 2003; **41:** 550-557.

215. Skrzypczyk P, Panczyk-Tomaszewska M, Roszkowska-Blaim M, *et al.* Long-term outcomes in idiopathic nephrotic syndrome: from childhood to adulthood. *Clin Nephrol* 2014; **81:** 166-173.

216. Tan L, Li S, Yang H, *et al.* Efficacy and acceptability of immunosuppressive agents for pediatric frequently-relapsing and steroid-dependent nephrotic syndrome: A network meta-analysis of randomized controlled trials. *Medicine (Baltimore)* 2019; **98:** e15927.

217. Prospective, controlled trial of cyclophosphamide therapy in children with nephrotic syndrome. Report of the International study of Kidney Disease in Children. *Lancet* 1974; **2:** 423-427.

218. Abramowicz M, Barnett HL, Edelmann CM, Jr*., et al.* Controlled trial of azathioprine in children with nephrotic syndrome. A report for the international study of kidney disease in children. *Lancet* 1970; **1:** 959-961.

219. Alatas H, Wirya IG, Tambunan T, *et al.* Controlled trial of chlorambucil in frequently relapsing nephrotic syndrome in children (a preliminary report). *J Med Assoc Thai* 1978; **61 Suppl 1:** 222-228.

220. Barratt TM, Soothill JF. Controlled trial of cyclophosphamide in steroid-sensitive relapsing nephrotic syndrome of childhood. *Lancet* 1970; **2:** 479-482.

221. Chiu J, McLaine PN, Drummond KN. A controlled prospective study of cyclophosphamide in relapsing, corticosteroid-responsive, minimal-lesion nephrotic syndrome in childhood. *J Pediatr* 1973; **82:** 607-613.

222. Grupe WE, Makker SP, Ingelfinger JR. Chlorambucil treatment of frequently relapsing nephrotic syndrome. *N Engl J Med* 1976; **295:** 746-749.

223. Pravitsitthikul N, Willis NS, Hodson EM, *et al.* Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. *Cochrane Database Syst Rev* 2013**:** CD002290.

224. Sural S, Pahari DK, Mitra K, *et al.* Efficacy of levamisole compared to cyclophosphamide and steroid in frequently relapsing (FR) minimal change nephrotic syndrome (MCNS) [abstract]. *Journal of the American Society of Nephrology* 2001; **12:** 1.

225. Levamisole for corticosteroid-dependent nephrotic syndrome in childhood. British Association for Paediatric Nephrology. *Lancet* 1991; **337:** 1555-1557.

226. Abeyagunawardena AS, Trompeter RS. Efficacy of levamisole as a single agent in maintaining remission in steroid dependant nephrotic syndrome [abstract]. *Pediatric Nephrology* 2006; **21:** 1503.

227. Al-Saran K, Mirza K, Al-Ghanam G, *et al.* Experience with levamisole in frequently relapsing, steroid-dependent nephrotic syndrome. *Pediatr Nephrol* 2006; **21:** 201-205.

228. Dayal U, Dayal AK, Shastry JC, *et al.* Use of levamisole in maintaining remission in steroid-sensitive nephrotic syndrome in children. *Nephron* 1994; **66:** 408-412.

229. Gruppen MP, Bouts AH, Jansen-van der Weide MC, *et al.* A randomized clinical trial indicates that levamisole increases the time to relapse in children with steroid-sensitive idiopathic nephrotic syndrome. *Kidney Int* 2018; **93:** 510-518.

230. Rashid HU, Ahmed S, Fatima N, *et al.* Levamisole in the treatment of steroid dependent or frequent relapsing nephrotic syndrome in children. *Bangladesh Renal Journal* 1996; **15:** 1.

231. Weiss R, GROUP N-N-P-PNS. Randomized, double-blind, placebo (P) controlled trial of levamisole (L) for children (CH) with frequently relapsing/steroid dependant (FR/SD) nephrotic syndrome (NS) [abstract]. *Journal of the American Society of Nephrology* 1993; **4:** 1.

232. Sinha A, Puraswani M, Kalaivani M, *et al.* Efficacy and safety of mycophenolate mofetil versus levamisole in frequently relapsing nephrotic syndrome: an open-label randomized controlled trial. *Kidney Int* 2019; **95:** 210-218.

233. Hoyer PF. Results of the nephrotic syndrome study VIII of the APN: new standard treatment versus new standard treatment plus 8 weeks cyclosporin A [abstract]. *Journal of the American Society of Nephrology* 1999; **10:** 1.

234. Hoyer PF, Brodeh J. Initial treatment of idiopathic nephrotic syndrome in children: prednisone versus prednisone plus cyclosporine A: a prospective, randomized trial. *J Am Soc Nephrol* 2006; **17:** 1151-1157.

235. Anh YH, Kim SH, Han KH, *et al.* Efficacy and safety of rituximab in children with refractory nephrotic syndrome: a multicenter clinical trial [abstract]. *Pediatric Nephrology* 2013; **28:** 1361.

236. Boumediene A, Vachin P, Sendeyo K, *et al.* NEPHRUTIX: A randomized, double-blind, placebo vs Rituximab-controlled trial assessing T-cell subset changes in Minimal Change Nephrotic Syndrome. *J Autoimmun* 2018; **88:** 91-102.

237. Iijima K, Tsuchida N, Sako M: Multicenter double-blind, randomized, placebo-controlled trial of IDEC-C2B8 for the treatment of childhood-onset complicated nephrotic syndrome In, 2010

238. Ravani P, Magnasco A, Edefonti A, *et al.* Short-term effects of rituximab in children with steroid- and calcineurin-dependent nephrotic syndrome: a randomized controlled trial. *Clin J Am Soc Nephrol* 2011; **6:** 1308-1315.

239. Ravani P, Ponticelli A, Siciliano C, *et al.* Rituximab is a safe and effective long-term treatment for children with steroid and calcineurin inhibitor-dependent idiopathic nephrotic syndrome. *Kidney Int* 2013; **84:** 1025-1033.

240. Ravani P, Rossi R, Bonanni A, *et al.* Rituximab in Children with Steroid-Dependent Nephrotic Syndrome: A Multicenter, Open-Label, Noninferiority, Randomized Controlled Trial. *J Am Soc Nephrol* 2015; **26:** 2259-2266.

241. Mishra OP, Basu B, Upadhyay SK, *et al.* Behavioural abnormalities in children with nephrotic syndrome. *Nephrol Dial Transplant* 2010; **25:** 2537-2541.

242. Mitra S, Banerjee S. The impact of pediatric nephrotic syndrome on families. *Pediatr Nephrol* 2011; **26:** 1235-1240.

243.	Arbeitsgemeinschaft fur Padiatrische Nephrologie. Effect of cytotoxic drugs in frequently relapsing nephrotic syndrome with and without steroid dependence. *N Engl J Med* 1982; **306:** 451-454.

244.	Azib S, Macher MA, Kwon T*, et al.* Cyclophosphamide in steroid-dependent nephrotic syndrome. *Pediatr Nephrol* 2011; **26:** 927-932.

245.	Donia AF, Ammar HM, El-Agroudy Ael B*, et al.* Long-term results of two unconventional agents in steroid-dependent nephrotic children. *Pediatr Nephrol* 2005; **20:** 1420-1425.

246.	Ruggenenti P, Ruggiero B, Cravedi P*, et al.* Rituximab in steroid-dependent or frequently relapsing idiopathic nephrotic syndrome. *J Am Soc Nephrol* 2014; **25:** 850-863.

247.	Iijima K, Sako M, Nozu K*, et al.* Rituximab for childhood-onset, complicated, frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome: a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet* 2014; **384:** 1273-1281.

248.	van den Brand J, Ruggenenti P, Chianca A*, et al.* Safety of Rituximab Compared with Steroids and Cyclophosphamide for Idiopathic Membranous Nephropathy. *J Am Soc Nephrol* 2017; **28:** 2729-2737.

249.	Cammas B, Harambat J, Bertholet-Thomas A*, et al.* Long-term effects of cyclophosphamide therapy in steroid-dependent or frequently relapsing idiopathic nephrotic syndrome. *Nephrol Dial Transplant* 2011; **26:** 178-184.

250.	Zagury A, de Oliveira AL, de Moraes CA*, et al.* Long-term follow-up after cyclophosphamide therapy in steroid-dependent nephrotic syndrome. *Pediatr Nephrol* 2011; **26:** 915-920.

251.	Cattran DC, Appel GB, Hebert LA*, et al.* A randomized trial of cyclosporine in patients with steroid-resistant focal segmental glomerulosclerosis. North America Nephrotic Syndrome Study Group. *Kidney Int* 1999; **56:** 2220-2226.

252.	Garin EH, Orak JK, Hiott KL*, et al.* Cyclosporine therapy for steroid-resistant nephrotic syndrome. A controlled study. *Am J Dis Child* 1988; **142:** 985-988.

253.	Lieberman KV, Tejani A. A randomized double-blind placebo-controlled trial of cyclosporine in steroid-resistant idiopathic focal segmental glomerulosclerosis in children. *J Am Soc Nephrol* 1996; **7:** 56-63.

254.	Ponticelli C, Rizzoni G, Edefonti A*, et al.* A randomized trial of cyclosporine in steroid-resistant idiopathic nephrotic syndrome. *Kidney Int* 1993; **43:** 1377-1384.

255.	Trautmann A, Schnaidt S, Lipska-Zietkiewicz BS*, et al.* Long-Term Outcome of Steroid-Resistant Nephrotic Syndrome in Children. *J Am Soc Nephrol* 2017; **28:** 3055-3065.

256.	Gipson DS, Trachtman H, Kaskel FJ*, et al.* Clinical trial of focal segmental glomerulosclerosis in children and young adults. *Kidney Int* 2011; **80:** 868-878.

257.	Li S, Yang H, Guo P*, et al.* Efficacy and safety of immunosuppressive medications for steroid-resistant nephrotic syndrome in children: a systematic review and network meta-analysis. *Oncotarget* 2017; **8:** 73050-73062.

258. Tarshish P, Tobin JN, Bernstein J, *et al.* Cyclophosphamide does not benefit patients with focal segmental glomerulosclerosis. A report of the International Study of Kidney Disease in Children. *Pediatr Nephrol* 1996; **10:** 590-593.

259. Gulati A, Sinha A, Gupta A, *et al.* Treatment with tacrolimus and prednisolone is preferable to intravenous cyclophosphamide as the initial therapy for children with steroid-resistant nephrotic syndrome. *Kidney Int* 2012; **82:** 1130-1135.

260. Plank C, Kalb V, Hinkes B, *et al.* Cyclosporin A is superior to cyclophosphamide in children with steroid-resistant nephrotic syndrome-a randomized controlled multicentre trial by the Arbeitsgemeinschaft fur Padiatrische Nephrologie. *Pediatr Nephrol* 2008; **23:** 1483-1493.

261. Sinha A, Gupta A, Kalaivani M, *et al.* Mycophenolate mofetil is inferior to tacrolimus in sustaining remission in children with idiopathic steroid-resistant nephrotic syndrome. *Kidney Int* 2017; **92:** 248-257.

262. Choudhry S, Bagga A, Hari P, *et al.* Efficacy and safety of tacrolimus versus cyclosporine in children with steroid-resistant nephrotic syndrome: a randomized controlled trial. *Am J Kidney Dis* 2009; **53:** 760-769.

263. Hodson EM, Willis NS, Craig JC. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. *Cochrane Database Syst Rev* 2010**:** CD003594.

264. Valverde S, Hernandez AM, Velasquez L, *et al.* Efficacy of prednisone-tacrolimus vs. prednisone-cyclosporine in steroid-resistant nephrotic syndrome [abstract]. *Pediatric Nephrology* 2010; **25:** 1.

265. Cameron JS. The nephrotic syndrome and its complications. *Am J Kidney Dis* 1987; **10:** 157-171.

266. Elie V, Fakhoury M, Deschenes G, *et al.* Physiopathology of idiopathic nephrotic syndrome: lessons from glucocorticoids and epigenetic perspectives. *Pediatr Nephrol* 2012; **27:** 1249-1256.

267. Appel GB, Radhakrishnan J, D'Agati V. Secondary Glomerular Disease. In: Brenner. BM (ed). *BRENNER & RECTOR'S THE KIDNEY*, 10th edn. Elsevier (November 11, 2015): Philadelphia, 2016, pp 1091-1160.

268. Waldman M, Crew RJ, Valeri A, *et al.* Adult minimal-change disease: clinical characteristics, treatment, and outcomes. *Clin J Am Soc Nephrol* 2007; **2:** 445-453.

269. Nolasco F, Cameron JS, Heywood EF, *et al.* Adult-onset minimal change nephrotic syndrome: a long-term follow-up. *Kidney Int* 1986; **29:** 1215-1223.

270. Black DA, Rose G, Brewer DB. Controlled trial of prednisone in adult patients with the nephrotic syndrome. *Br Med J* 1970; **3:** 421-426.

271. Coggins CH. Adult minimal change nephropathy: experience of the collaborative study of glomerular disease. *Trans Am Clin Climatol Assoc* 1986; **97:** 18-26.

272. Huang JJ, Hsu SC, Chen FF, *et al.* Adult-onset minimal change disease among Taiwanese: clinical features, therapeutic response, and prognosis. *Am J Nephrol* 2001; **21:** 28-34.

273. Mahmoodi BK, ten Kate MK, Waanders F, *et al.* High absolute risks and predictors of venous and arterial thromboembolic events in patients with nephrotic syndrome: results from a large retrospective cohort study. *Circulation* 2008; **117:** 224-230.

274. Radhakrishnan J, Appel AS, Valeri A, *et al.* The nephrotic syndrome, lipids, and risk factors for cardiovascular disease. *Am J Kidney Dis* 1993; **22:** 135-142.

275. Maas RJ, Deegens JK, Beukhof JR, *et al.* The Clinical Course of Minimal Change Nephrotic Syndrome With Onset in Adulthood or Late Adolescence: A Case Series. *Am J Kidney Dis* 2017; **69:** 637-646.

276. Korbet SM, Schwartz MM, Lewis EJ. Primary focal segmental glomerulosclerosis: clinical course and response to therapy. *Am J Kidney Dis* 1994; **23:** 773-783.

277. Mak SK, Short CD, Mallick NP. Long-term outcome of adult-onset minimal-change nephropathy. *Nephrol Dial Transplant* 1996; **11:** 2192-2201.

278. Tse KC, Lam MF, Yip PS, *et al.* Idiopathic minimal change nephrotic syndrome in older adults: steroid responsiveness and pattern of relapses. *Nephrol Dial Transplant* 2003; **18:** 1316-1320.

279. Imbasciati E, Gusmano R, Edefonti A, *et al.* Controlled trial of methylprednisolone pulses and low dose oral prednisone for the minimal change nephrotic syndrome. *Br Med J (Clin Res Ed)* 1985; **291:** 1305-1308.

280. Palmer SC, Nand K, Strippoli GF. Interventions for minimal change disease in adults with nephrotic syndrome. *Cochrane Database Syst Rev* 2008**:** CD001537.

281. Yeung CK, Wong KL, Ng WL. Intravenous methylprednisolone pulse therapy in minimal change nephrotic syndrome. *Aust N Z J Med* 1983; **13:** 349-351.

282. World Health Organization. WHO Model Lists of Essential Medicines. (2017), http://www.who.int/medicines/publications/essentialmedicines/en/ [Accessed September 21, 2019]

283. Hogan J, Radhakrishnan J. The treatment of minimal change disease in adults. *J Am Soc Nephrol* 2013; **24:** 702-711.

284. Nair RB, Date A, Kirubakaran MG, *et al.* Minimal-change nephrotic syndrome in adults treated with alternate-day steroids. *Nephron* 1987; **47:** 209-210.

285. Al-Khader AA, Lien JW, Aber GM. Cyclophosphamide alone in the treatment of adult patients with minimal change glomerulonephritis. *Clin Nephrol* 1979; **11:** 26-30.

286. Cameron JS, Turner DR, Ogg CS, *et al.* The nephrotic syndrome in adults with 'minimal change' glomerular lesions. *Q J Med* 1974; **43:** 461-488.

287. Uldall PR, Feest TG, Morley AR, *et al.* Cyclophosphamide therapy in adults with minimal-change nephrotic syndrome. *Lancet* 1972; **1:** 1250-1253.

288. Matsumoto H, Nakao T, Okada T, *et al.* Favorable outcome of low-dose cyclosporine after pulse methylprednisolone in Japanese adult minimal-change nephrotic syndrome. *Intern Med* 2004; **43:** 668-673.

289. Remy P, Audard V, Natella PA*, et al.* An open-label randomized controlled trial of low-dose corticosteroid plus enteric-coated mycophenolate sodium versus standard corticosteroid treatment for minimal change nephrotic syndrome in adults (MSN Study). *Kidney Int* 2018; **94:** 1217-1226.

290. Boumpas DT, Chrousos GP, Wilder RL*, et al.* Glucocorticoid therapy for immune-mediated diseases: basic and clinical correlates. *Ann Intern Med* 1993; **119:** 1198-1208.

291. Nakayama M, Katafuchi R, Yanase T*, et al.* Steroid responsiveness and frequency of relapse in adult-onset minimal change nephrotic syndrome. *Am J Kidney Dis* 2002; **39:** 503-512.

292. Eguchi A, Takei T, Yoshida T*, et al.* Combined cyclosporine and prednisolone therapy in adult patients with the first relapse of minimal-change nephrotic syndrome. *Nephrol Dial Transplant* 2010; **25:** 124-129.

293. Li X, Li H, Chen J*, et al.* Tacrolimus as a steroid-sparing agent for adults with steroid-dependent minimal change nephrotic syndrome. *Nephrol Dial Transplant* 2008; **23:** 1919-1925.

294. Ponticelli C, Edefonti A, Ghio L*, et al.* Cyclosporin versus cyclophosphamide for patients with steroid-dependent and frequently relapsing idiopathic nephrotic syndrome: a multicentre randomized controlled trial. *Nephrol Dial Transplant* 1993; **8:** 1326-1332.

295. Guitard J, Hebral AL, Fakhouri F*, et al.* Rituximab for minimal-change nephrotic syndrome in adulthood: predictive factors for response, long-term outcomes and tolerance. *Nephrol Dial Transplant* 2014; **29:** 2084-2091.

296. Iwabuchi Y, Takei T, Moriyama T*, et al.* Long-term prognosis of adult patients with steroid-dependent minimal change nephrotic syndrome following rituximab treatment. *Medicine (Baltimore)* 2014; **93:** e300.

297. Munyentwali H, Bouachi K, Audard V*, et al.* Rituximab is an efficient and safe treatment in adults with steroid-dependent minimal change disease. *Kidney Int* 2013; **83:** 511-516.

298. Lee HY, Kim HS, Kang CM*, et al.* The efficacy of cyclosporine A in adult nephrotic syndrome with minimal change disease and focal-segmental glomerulosclerosis: a multicenter study in Korea. *Clin Nephrol* 1995; **43:** 375-381.

299. Meyrier A, Condamin MC, Broneer D. Treatment of adult idiopathic nephrotic syndrome with cyclosporin A: minimal-change disease and focal-segmental glomerulosclerosis. Collaborative Group of the French Society of Nephrology. *Clin Nephrol* 1991; **35 Suppl 1:** S37-42.

300. Day CJ, Cockwell P, Lipkin GW*, et al.* Mycophenolate mofetil in the treatment of resistant idiopathic nephrotic syndrome. *Nephrol Dial Transplant* 2002; **17:** 2011-2013.

301. Sandoval D, Poveda R, Draibe J*, et al.* Efficacy of mycophenolate treatment in adults with steroid-dependent/frequently relapsing idiopathic nephrotic syndrome. *Clin Kidney J* 2017; **10:** 632-638.

302. Li X, Liu Z, Wang L*, et al.* Tacrolimus Monotherapy after Intravenous Methylprednisolone in Adults with Minimal Change Nephrotic Syndrome. *J Am Soc Nephrol* 2017; **28:** 1286-1295.

303. Shirai S, Imai N, Sueki S, *et al.* Combined cyclosporine and prednisolone therapy using cyclosporine blood concentration monitoring for adult patients with new-onset minimal change nephrotic syndrome: a single-center pilot randomized trial. *Clin Exp Nephrol* 2018; **22:** 283-290.

304. D'Agati VD, Fogo AB, Bruijn JA, *et al.* Pathologic classification of focal segmental glomerulosclerosis: a working proposal. *Am J Kidney Dis* 2004; **43:** 368-382.

305. D'Agati VD, Alster JM, Jennette JC, *et al.* Association of histologic variants in FSGS clinical trial with presenting features and outcomes. *Clin J Am Soc Nephrol* 2013; **8:** 399-406.

306. Deegens JK, Steenbergen EJ, Borm GF, *et al.* Pathological variants of focal segmental glomerulosclerosis in an adult Dutch population--epidemiology and outcome. *Nephrol Dial Transplant* 2008; **23:** 186-192.

307. Thomas DB, Franceschini N, Hogan SL, *et al.* Clinical and pathologic characteristics of focal segmental glomerulosclerosis pathologic variants. *Kidney Int* 2006; **69:** 920-926.

308. D'Agati V. The many masks of focal segmental glomerulosclerosis. *Kidney Int* 1994; **46:** 1223-1241.

309. Deegens JK, Dijkman HB, Borm GF, *et al.* Podocyte foot process effacement as a diagnostic tool in focal segmental glomerulosclerosis. *Kidney Int* 2008; **74:** 1568-1576.

310. Kambham N, Markowitz GS, Valeri AM, *et al.* Obesity-related glomerulopathy: an emerging epidemic. *Kidney Int* 2001; **59:** 1498-1509.

311. Chun MJ, Korbet SM, Schwartz MM, *et al.* Focal segmental glomerulosclerosis in nephrotic adults: presentation, prognosis, and response to therapy of the histologic variants. *J Am Soc Nephrol* 2004; **15:** 2169-2177.

312. Hommos MS, De Vriese AS, Alexander MP, *et al.* The Incidence of Primary vs Secondary Focal Segmental Glomerulosclerosis: A Clinicopathologic Study. *Mayo Clin Proc* 2017; **92:** 1772-1781.

313. Praga M, Morales E, Herrero JC, *et al.* Absence of hypoalbuminemia despite massive proteinuria in focal segmental glomerulosclerosis secondary to hyperfiltration. *Am J Kidney Dis* 1999; **33:** 52-58.

314. De Vriese AS, Sethi S, Nath KA, *et al.* Differentiating Primary, Genetic, and Secondary FSGS in Adults: A Clinicopathologic Approach. *J Am Soc Nephrol* 2018; **29:** 759-774.

315. Santin S, Bullich G, Tazon-Vega B, *et al.* Clinical utility of genetic testing in children and adults with steroid-resistant nephrotic syndrome. *Clin J Am Soc Nephrol* 2011; **6:** 1139-1148.

316. Brown EJ, Pollak MR, Barua M. Genetic testing for nephrotic syndrome and FSGS in the era of next-generation sequencing. *Kidney Int* 2014; **85:** 1030-1038.

317. Deegens JK, Steenbergen EJ, Wetzels JF. Review on diagnosis and treatment of focal segmental glomerulosclerosis. *Neth J Med* 2008; **66:** 3-12.

318. Beaufils H, Alphonse JC, Guedon J, *et al.* Focal glomerulosclerosis: natural history and treatment. A report of 70 cases. *Nephron* 1978; **21:** 75-85.

319. Cameron JS, Turner DR, Ogg CS*, et al.* The long-term prognosis of patients with focal segmental glomerulosclerosis. *Clin Nephrol* 1978; **10:** 213-218.

320. Rydel JJ, Korbet SM, Borok RZ*, et al.* Focal segmental glomerular sclerosis in adults: presentation, course, and response to treatment. *Am J Kidney Dis* 1995; **25:** 534-542.

321. Velosa JA, Holley KE, Torres VE*, et al.* Significance of proteinuria on the outcome of renal function in patients with focal segmental glomerulosclerosis. *Mayo Clin Proc* 1983; **58:** 568-577.

322. Troyanov S, Wall CA, Miller JA*, et al.* Focal and segmental glomerulosclerosis: definition and relevance of a partial remission. *J Am Soc Nephrol* 2005; **16:** 1061-1068.

323. Cattran DC, Rao P. Long-term outcome in children and adults with classic focal segmental glomerulosclerosis. *Am J Kidney Dis* 1998; **32:** 72-79.

324. Korbet SM. Treatment of primary FSGS in adults. *J Am Soc Nephrol* 2012; **23:** 1769-1776.

325. Banfi G, Moriggi M, Sabadini E*, et al.* The impact of prolonged immunosuppression on the outcome of idiopathic focal-segmental glomerulosclerosis with nephrotic syndrome in adults. A collaborative retrospective study. *Clin Nephrol* 1991; **36:** 53-59.

326. Goumenos DS, Tsagalis G, El Nahas AM*, et al.* Immunosuppressive treatment of idiopathic focal segmental glomerulosclerosis: a five-year follow-up study. *Nephron Clin Pract* 2006; **104:** c75-82.

327. Pei Y, Cattran D, Delmore T*, et al.* Evidence suggesting under-treatment in adults with idiopathic focal segmental glomerulosclerosis. Regional Glomerulonephritis Registry Study. *Am J Med* 1987; **82:** 938-944.

328. Schwartz MM, Evans J, Bain R*, et al.* Focal segmental glomerulosclerosis: prognostic implications of the cellular lesion. *J Am Soc Nephrol* 1999; **10:** 1900-1907.

329. Nagai R, Cattran DC, Pei Y. Steroid therapy and prognosis of focal segmental glomerulosclerosis in the elderly. *Clin Nephrol* 1994; **42:** 18-21.

330. Jenis EH, Teichman S, Briggs WA*, et al.* Focal segmental glomerulosclerosis. *Am J Med* 1974; **57:** 695-705.

331. Lim VS, Sibley R, Spargo B. Adult lipoid nephrosis: clinicopathological correlations. *Ann Intern Med* 1974; **81:** 314-320.

332. Newman WJ, Tisher CC, McCoy RC*, et al.* Focal glomerular sclerosis: contrasting clinical patterns in children and adults. *Medicine (Baltimore)* 1976; **55:** 67-87.

333. Ponticelli C, Villa M, Banfi G*, et al.* Can prolonged treatment improve the prognosis in adults with focal segmental glomerulosclerosis? *Am J Kidney Dis* 1999; **34:** 618-625.

334. Fujimoto S, Yamamoto Y, Hisanaga S*, et al.* Minimal change nephrotic syndrome in adults: response to corticosteroid therapy and frequency of relapse. *Am J Kidney Dis* 1991; **17:** 687-692.

335. Korbet SM, Schwartz MM, Lewis EJ. Minimal-change glomerulopathy of adulthood. *Am J Nephrol* 1988; **8:** 291-297.

336.   Costello R, Patel R, Humphreys J, *et al.* Patient perceptions of glucocorticoid side effects: a cross-sectional survey of users in an online health community. *BMJ Open* 2017; **7:** e014603.

337.   Duncan N, Dhaygude A, Owen J, *et al.* Treatment of focal and segmental glomerulosclerosis in adults with tacrolimus monotherapy. *Nephrol Dial Transplant* 2004; **19:** 3062-3067.

338.   Velosa JA, Donadio JV, Jr., Holley KE. Focal sclerosing glomerulonephropathy: a clinicopathologic study. *Mayo Clin Proc* 1975; **50:** 121-133.

339.   Ramachandran R, Kumar V, Rathi M, *et al.* Tacrolimus therapy in adult-onset steroid-resistant nephrotic syndrome due to a focal segmental glomerulosclerosis single-center experience. *Nephrol Dial Transplant* 2014; **29:** 1918-1924.

340.   Segarra A, Vila J, Pou L, *et al.* Combined therapy of tacrolimus and corticosteroids in cyclosporin-resistant or -dependent idiopathic focal glomerulosclerosis: a preliminary uncontrolled study with prospective follow-up. *Nephrol Dial Transplant* 2002; **17:** 655-662.

341.   Braun N, Schmutzler F, Lange C, *et al.* Immunosuppressive treatment for focal segmental glomerulosclerosis in adults. *Cochrane Database Syst Rev* 2008**:** CD003233.

342.   Bhaumik SK, Majumdar A, Barman SC. Comparison of pulse methylprednisolone vs cyclosporin based therapy in steroid resistant focal segmental glomerulosclerosis [abstract]. *Indian Journal of Nephrology* 2002; **12**.

343.   Melocoton TL, Kamil ES, Cohen AH, *et al.* Long-term cyclosporine A treatment of steroid-resistant and steroid-dependent nephrotic syndrome. *Am J Kidney Dis* 1991; **18:** 583-588.

344.   Ghiggeri GM, Catarsi P, Scolari F, *et al.* Cyclosporine in patients with steroid-resistant nephrotic syndrome: an open-label, nonrandomized, retrospective study. *Clin Ther* 2004; **26:** 1411-1418.

345.   Heering P, Braun N, Mullejans R, *et al.* Cyclosporine A and chlorambucil in the treatment of idiopathic focal segmental glomerulosclerosis. *Am J Kidney Dis* 2004; **43:** 10-18.

346.   El-Husseini A, El-Basuony F, Mahmoud I, *et al.* Long-term effects of cyclosporine in children with idiopathic nephrotic syndrome: a single-centre experience. *Nephrol Dial Transplant* 2005; **20:** 2433-2438.

347.   Canetta PA, Radhakrishnan J. Impact of the National Institutes of Health Focal Segmental Glomerulosclerosis (NIH FSGS) clinical trial on the treatment of steroid-resistant FSGS. *Nephrol Dial Transplant* 2013; **28:** 527-534.

348.   Glassock RJ, Alvarado A, Prosek J, *et al.* Staphylococcus-related glomerulonephritis and poststreptococcal glomerulonephritis: why defining "post" is important in understanding and treating infection-related glomerulonephritis. *Am J Kidney Dis* 2015; **65:** 826-832.

349.   Montseny JJ, Meyrier A, Kleinknecht D, *et al.* The current spectrum of infectious glomerulonephritis. Experience with 76 patients and review of the literature. *Medicine (Baltimore)* 1995; **74:** 63-73.

350.   Iwata Y, Ohta S, Kawai K, *et al.* Shunt nephritis with positive titers for ANCA specific for proteinase 3. *Am J Kidney Dis* 2004; **43:** e11-16.

351. Boils CL, Nasr SH, Walker PD*, et al.* Update on endocarditis-associated glomerulonephritis. *Kidney Int* 2015; **87:** 1241-1249.

352. Griffin KA, Schwartz MM, Korbet SM. Pulmonary-renal syndrome of bacterial endocarditis mimicking Goodpasture's syndrome. *Am J Kidney Dis* 1989; **14:** 329-332.

353. Nasr SH, D'Agati VD. IgA-dominant postinfectious glomerulonephritis: a new twist on an old disease. *Nephron Clin Pract* 2011; **119:** c18-25.

354. Nasr SH, Fidler ME, Valeri AM*, et al.* Postinfectious glomerulonephritis in the elderly. *J Am Soc Nephrol* 2011; **22:** 187-195.

355. Satoskar AA, Nadasdy G, Plaza JA*, et al.* Staphylococcus infection-associated glomerulonephritis mimicking IgA nephropathy. *Clin J Am Soc Nephrol* 2006; **1:** 1179-1186.

356. Haas M, Racusen LC, Bagnasco SM. IgA-dominant postinfectious glomerulonephritis: a report of 13 cases with common ultrastructural features. *Hum Pathol* 2008; **39:** 1309-1316.

357. Kidney Disease: Improving Global Outcomes Hepatitis C Work Group. KDIGO 2018 Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease. *Kidney Int Suppl.* 2018; **8:** 91-165.

358. European Association For The Study Of The Liver. EASL Clinical Practice Guidelines: management of chronic hepatitis B. *J Hepatol* 2009; **50:** 227-242.

359. Kupin WL. Viral-Associated GN: Hepatitis B and Other Viral Infections. *Clin J Am Soc Nephrol* 2017; **12:** 1529-1533.

360. Sorrell MF, Belongia EA, Costa J*, et al.* National Institutes of Health Consensus Development Conference Statement: management of hepatitis B. *Ann Intern Med* 2009; **150:** 104-110.

361. Hou JH, Zhu HX, Zhou ML*, et al.* Changes in the Spectrum of Kidney Diseases: An Analysis of 40,759 Biopsy-Proven Cases from 2003 to 2014 in China. *Kidney Dis (Basel)* 2018; **4:** 10-19.

362. Raveendran N, Beniwal P, D'Souza AV*, et al.* Profile of glomerular diseases associated with hepatitis B and C: A single-center experience from India. *Saudi J Kidney Dis Transpl* 2017; **28:** 355-361.

363. Lai KN, Li PK, Lui SF*, et al.* Membranous nephropathy related to hepatitis B virus in adults. *N Engl J Med* 1991; **324:** 1457-1463.

364. Shah AS, Amarapurkar DN. Spectrum of hepatitis B and renal involvement. *Liver Int* 2018; **38:** 23-32.

365. Zhou TB, Jiang ZP. Is there an association of hepatitis B virus infection with minimal change disease of nephrotic syndrome? A clinical observational report. *Ren Fail* 2015; **37:** 459-461.

366. Dong HR, Wang YY, Cheng XH*, et al.* Retrospective Study of Phospholipase A2 Receptor and IgG Subclasses in Glomerular Deposits in Chinese Patients with Membranous Nephropathy. *PLoS One* 2016; **11:** e0156263.

367. Xie Q, Li Y, Xue J, *et al.* Renal phospholipase A2 receptor in hepatitis B virus-associated membranous nephropathy. *Am J Nephrol* 2015; **41:** 345-353.

368. De Virgilio A, Greco A, Magliulo G, *et al.* Polyarteritis nodosa: A contemporary overview. *Autoimmun Rev* 2016; **15:** 564-570.

369. Mazzaro C, Dal Maso L, Urraro T, *et al.* Hepatitis B virus related cryoglobulinemic vasculitis: A multicentre open label study from the Gruppo Italiano di Studio delle Crioglobulinemie - GISC. *Dig Liver Dis* 2016; **48:** 780-784.

370. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; **67:** 370-398.

371. Perrillo RP, Gish R, Falck-Ytter YT. American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology* 2015; **148:** 221-244 e223.

372. Makvandi M. Update on occult hepatitis B virus infection. *World J Gastroenterol* 2016; **22:** 8720-8734.

373. Kong D, Wu D, Wang T, *et al.* Detection of viral antigens in renal tissue of glomerulonephritis patients without serological evidence of hepatitis B virus and hepatitis C virus infection. *Int J Infect Dis* 2013; **17:** e535-538.

374. Jiang W, Liu T, Dong H, *et al.* Relationship Between Serum DNA Replication, Clinicopathological Characteristics and Prognosis of Hepatitis B Virus-associated Glomerulonephritis with Severe Proteinuria by Lamivudine Plus Adefovir Dipivoxil Combination Therapy. *Biomed Environ Sci* 2015; **28:** 206-213.

375. Tan Z, Fang J, Lu JH, *et al.* HBV serum and renal biopsy markers are associated with the clinicopathological characteristics of HBV-associated nephropathy. *Int J Clin Exp Pathol* 2014; **7:** 8150-8154.

376. *Recent Advances in IgA nephropathy*. In: Lai. KN (ed). World Scientific: Singapore, 2009.

377. Iida H, Izumino K, Asaka M, *et al.* IgA nephropathy and hepatitis B virus. IgA nephropathy unrelated to hepatitis B surface antigenemia. *Nephron* 1990; **54:** 18-20.

378. Lai KN, Lai FM, Tam JS. IgA nephropathy associated with chronic hepatitis B virus infection in adults: the pathogenetic role of HBsAG. *J Pathol* 1989; **157:** 321-327.

379. Roccatello D, Saadoun D, Ramos-Casals M, *et al.* Cryoglobulinaemia. *Nat Rev Dis Primers* 2018; **4:** 11.

380. Elewa U, Sandri AM, Kim WR, *et al.* Treatment of hepatitis B virus-associated nephropathy. *Nephron Clin Pract* 2011; **119:** c41-49.

381. Lin CY. Treatment of hepatitis B virus-associated membranous nephropathy with recombinant alpha-interferon. *Kidney Int* 1995; **47:** 225-230.

382. Lisker-Melman M, Webb D, Di Bisceglie AM, *et al.* Glomerulonephritis caused by chronic hepatitis B virus infection: treatment with recombinant human alpha-interferon. *Ann Intern Med* 1989; **111:** 479-483.

383. Fabrizi F, Dixit V, Martin P. Meta-analysis: anti-viral therapy of hepatitis B virus-associated glomerulonephritis. *Aliment Pharmacol Ther* 2006; **24:** 781-788.

384. Yang Y, Ma YP, Chen DP*, et al.* A Meta-Analysis of Antiviral Therapy for Hepatitis B Virus-Associated Membranous Nephropathy. *PLoS One* 2016; **11:** e0160437.

385. Yi Z, Jie YW, Nan Z. The efficacy of anti-viral therapy on hepatitis B virus-associated glomerulonephritis: A systematic review and meta-analysis. *Ann Hepatol* 2011; **10:** 165-173.

386. Zhang Y, Zhou JH, Yin XL*, et al.* Treatment of hepatitis B virus-associated glomerulonephritis: a meta-analysis. *World J Gastroenterol* 2010; **16:** 770-777.

387. Zheng XY, Wei RB, Tang L*, et al.* Meta-analysis of combined therapy for adult hepatitis B virus-associated glomerulonephritis. *World J Gastroenterol* 2012; **18:** 821-832.

388. Fang J, Li W, Tan Z*, et al.* Comparison of prednisolone and lamivudine combined therapy with prednisolone monotherapy on carriers of hepatitis B virus with IgA nephropathy: a prospective cohort study. *Int Urol Nephrol* 2014; **46:** 49-56.

389. Javaid MM, Khatri P, Subramanian S. Should antiviral monotherapy with nucleotide analogs be the primary treatment option for focal segmental glomerulosclerosis-related nephrotic syndrome in chronic hepatitis B infection? *Saudi J Kidney Dis Transpl* 2018; **29:** 714-718.

390. Wang L, Ye Z, Liang H*, et al.* The combination of tacrolimus and entecavir improves the remission of HBV-associated glomerulonephritis without enhancing viral replication. *Am J Transl Res* 2016; **8:** 1593-1600.

391. Piaserico S, Messina F, Russo FP. Managing Psoriasis in Patients with HBV or HCV Infection: Practical Considerations. *Am J Clin Dermatol* 2019.

392. Shimura S, Watashi K, Fukano K*, et al.* Cyclosporin derivatives inhibit hepatitis B virus entry without interfering with NTCP transporter activity. *J Hepatol* 2017; **66:** 685-692.

393. Yang Y, Ma L, Wang C*, et al.* Effectiveness of sulodexide might be associated with inhibition of complement system in hepatitis B virus-associated membranous nephropathy: An inspiration from a pilot trial. *Eur J Intern Med* 2016; **32:** 96-104.

394. Tsai MS, Chen JH, Fang YW*, et al.* Membranous nephropathy induced by pegylated interferon alpha-2a therapy for chronic viral hepatitis B. *Clin Nephrol* 2012; **77:** 496-500.

395. Berchtold L, Zanetta G, Dahan K*, et al.* Efficacy and Safety of Rituximab in Hepatitis B Virus-Associated PLA2R-Positive Membranous Nephropathy. *Kidney Int Rep* 2018; **3:** 486-491.

396. Liu T, Yang S, Yue Z*, et al.* Clinical and pathological characteristics of 5 children with HBV surface antigen (HBsAg)-negative hepatitis B virus-associated glomerulonephritis. *J Clin Virol* 2015; **66:** 1-5.

397. 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.

398.   UNAIDS. In (2020). www.UNAIDS.org [Accessed February 19, 2020]

399.   Lucas GM, Jing Y, Sulkowski M*, et al.* Hepatitis C viremia and the risk of chronic kidney disease in HIV-infected individuals. *J Infect Dis* 2013; **208:** 1240-1249.

400.   Shen TC, Huang KY, Chao CH*, et al.* The risk of chronic kidney disease in tuberculosis: a population-based cohort study. *QJM* 2015; **108:** 397-403.

401.   Wen YK, Chen ML. Crescentic glomerulonephritis associated with miliary tuberculosis. *Clin Nephrol* 2009; **71:** 310-313.

402.   Kudose S, Santoriello D, Bomback AS*, et al.* The spectrum of kidney biopsy findings in HIV-infected patients in the modern era. *Kidney Int* 2020; **97:** 1006-1016.

403.   Haas M, Kaul S, Eustace JA. HIV-associated immune complex glomerulonephritis with "lupus-like" features: a clinicopathologic study of 14 cases. *Kidney Int* 2005; **67:** 1381-1390.

404.   Sury K, Perazella MA. The Changing Face of Human Immunodeficiency Virus-Mediated Kidney Disease. *Adv Chronic Kidney Dis* 2019; **26:** 185-197.

405.   Atta MG, Estrella MM, Kuperman M*, et al.* HIV-associated nephropathy patients with and without apolipoprotein L1 gene variants have similar clinical and pathological characteristics. *Kidney Int* 2012; **82:** 338-343.

406.   Dummer PD, Limou S, Rosenberg AZ*, et al.* APOL1 Kidney Disease Risk Variants: An Evolving Landscape. *Semin Nephrol* 2015; **35:** 222-236.

407.   Ahmed S, Siddiqui RK, Siddiqui AK*, et al.* HIV associated thrombotic microangiopathy. *Postgrad Med J* 2002; **78:** 520-525.

408.   Sarmiento M, Balcells ME, Ramirez P. Thrombotic microangiopathy as first manifestation of acute human immunodeficiency virus infection: a case report and review of the literature. *J Med Case Rep* 2016; **10:** 152.

409.   Mocroft A, Neuhaus J, Peters L*, et al.* Hepatitis B and C co-infection are independent predictors of progressive kidney disease in HIV-positive, antiretroviral-treated adults. *PLoS One* 2012; **7:** e40245.

410.   Yoo J, Baumstein D, Kuppachi S*, et al.* Diffuse infiltrative lymphocytosis syndrome presenting as reversible acute kidney injury associated with Gram-negative bacterial infection in patients with newly diagnosed HIV infection. *Am J Kidney Dis* 2011; **57:** 752-755.

411.   Atta MG, Estrella MM, Skorecki KL*, et al.* Association of APOL1 Genotype with Renal Histology among Black HIV-Positive Patients Undergoing Kidney Biopsy. *Clin J Am Soc Nephrol* 2016; **11:** 262-270.

412.   Beckerman P, Bi-Karchin J, Park AS*, et al.* Transgenic expression of human APOL1 risk variants in podocytes induces kidney disease in mice. *Nat Med* 2017; **23:** 429-438.

413.   Fu Y, Zhu JY, Richman A*, et al.* APOL1-G1 in Nephrocytes Induces Hypertrophy and Accelerates Cell Death. *J Am Soc Nephrol* 2017; **28:** 1106-1116.

414.   Kruzel-Davila E, Shemer R, Ofir A, *et al.* APOL1-Mediated Cell Injury Involves Disruption of Conserved Trafficking Processes. *J Am Soc Nephrol* 2017; **28:** 1117-1130.

415.   Ma L, Chou JW, Snipes JA, *et al.* APOL1 Renal-Risk Variants Induce Mitochondrial Dysfunction. *J Am Soc Nephrol* 2017; **28:** 1093-1105.

416.   Palau L, Menez S, Rodriguez-Sanchez J, *et al.* HIV-associated nephropathy: links, risks and management. *HIV AIDS (Auckl)* 2018; **10:** 73-81.

417.   Kasembeli AN, Duarte R, Ramsay M, *et al.* APOL1 Risk Variants Are Strongly Associated with HIV-Associated Nephropathy in Black South Africans. *J Am Soc Nephrol* 2015; **26:** 2882-2890.

418.   Fine DM, Wasser WG, Estrella MM, *et al.* APOL1 risk variants predict histopathology and progression to ESRD in HIV-related kidney disease. *J Am Soc Nephrol* 2012; **23:** 343-350.

419.   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.

420.   Szczech LA, Gupta SK, Habash R, *et al.* The clinical epidemiology and course of the spectrum of renal diseases associated with HIV infection. *Kidney Int* 2004; **66:** 1145-1152.

421.   Cohen SD, Kimmel PL. Immune complex renal disease and human immunodeficiency virus infection. *Semin Nephrol* 2008; **28:** 535-544.

422.   Booth JW, Hamzah L, Jose S, *et al.* Clinical characteristics and outcomes of HIV-associated immune complex kidney disease. *Nephrol Dial Transplant* 2016; **31:** 2099-2107.

423.   Fine DM, Perazella MA, Lucas GM, *et al.* Kidney biopsy in HIV: beyond HIV-associated nephropathy. *Am J Kidney Dis* 2008; **51:** 504-514.

424.   Gerntholtz TE, Goetsch SJ, Katz I. HIV-related nephropathy: a South African perspective. *Kidney Int* 2006; **69:** 1885-1891.

425.   Han TM, Naicker S, Ramdial PK, *et al.* A cross-sectional study of HIV-seropositive patients with varying degrees of proteinuria in South Africa. *Kidney Int* 2006; **69:** 2243-2250.

426.   Choi AI, Li Y, Parikh C, *et al.* Long-term clinical consequences of acute kidney injury in the HIV-infected. *Kidney Int* 2010; **78:** 478-485.

427.   Insight Start Study Group, Lundgren JD, Babiker AG, *et al.* Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. *N Engl J Med* 2015; **373:** 795-807.

428.   Temprano Anrs Study Group, Danel C, Moh R, *et al.* A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. *N Engl J Med* 2015; **373:** 808-822.

429.   World Health Organization. Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations. Geneva, Switzerland, 2014.

430.   Yahaya I, Uthman OA, Uthman MM. Interventions for HIV-associated nephropathy. *Cochrane Database Syst Rev* 2013**:** CD007183.

431. Szczech LA, Hoover DR, Feldman JG*, et al.* Association between renal disease and outcomes among HIV-infected women receiving or not receiving antiretroviral therapy. *Clin Infect Dis* 2004; **39:** 1199-1206.

432. Strategies for Management of Antiretroviral Therapy Study Group, El-Sadr WM, Lundgren J*, et al.* CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med* 2006; **355:** 2283-2296.

433. Kalayjian RC, Franceschini N, Gupta SK*, et al.* Suppression of HIV-1 replication by antiretroviral therapy improves renal function in persons with low CD4 cell counts and chronic kidney disease. *AIDS* 2008; **22:** 481-487.

434. Krawczyk CS, Holmberg SD, Moorman AC*, et al.* Factors associated with chronic renal failure in HIV-infected ambulatory patients. *AIDS* 2004; **18:** 2171-2178.

435. Gupta SK, Parker RA, Robbins GK*, et al.* The effects of highly active antiretroviral therapy on albuminuria in HIV-infected persons: results from a randomized trial. *Nephrol Dial Transplant* 2005; **20:** 2237-2242.

436. Gupta SK, Smurzynski M, Franceschini N*, et al.* The effects of HIV type-1 viral suppression and non-viral factors on quantitative proteinuria in the highly active antiretroviral therapy era. *Antivir Ther* 2009; **14:** 543-549.

437. Longenecker CT, Scherzer R, Bacchetti P*, et al.* HIV viremia and changes in kidney function. *AIDS* 2009; **23:** 1089-1096.

438. Babut-Gay ML, Echard M, Kleinknecht D*, et al.* Zidovudine and nephropathy with human immunodeficiency virus (HIV) infection. *Ann Intern Med* 1989; **111:** 856-857.

439. Ifudu O, Rao TK, Tan CC*, et al.* Zidovudine is beneficial in human immunodeficiency virus associated nephropathy. *Am J Nephrol* 1995; **15:** 217-221.

440. Kirchner JT. Resolution of renal failure after initiation of HAART: 3 cases and a discussion of the literature. *AIDS Read* 2002; **12:** 103-105, 110-102.

441. Szczech LA, Edwards LJ, Sanders LL*, et al.* Protease inhibitors are associated with a slowed progression of HIV-related renal diseases. *Clin Nephrol* 2002; **57:** 336-341.

442. Ingulli E, Tejani A, Fikrig S*, et al.* Nephrotic syndrome associated with acquired immunodeficiency syndrome in children. *J Pediatr* 1991; **119:** 710-716.

443. Smith MC, Austen JL, Carey JT*, et al.* Prednisone improves renal function and proteinuria in human immunodeficiency virus-associated nephropathy. *Am J Med* 1996; **101:** 41-48.

444. Barsoum RS. Schistosomiasis and the kidney. *Semin Nephrol* 2003; **23:** 34-41.

445. Bezerrada G, Junior S, Duartea DB*, et al.* Schistosomiasis-associated kidney disease: A review. *Asian Pacific Journal of Tropical Disease* 2013; **3:** 79-84.

446. Barsoum RS, Sersawy G, Haddad S*, et al.* Hepatic macrophage function in schistosomal glomerulopathy. *Nephrol Dial Transplant* 1988; **3:** 612-616.

447.   Martinelli R, Pereira LJ, Brito E, *et al.* Renal involvement in prolonged Salmonella bacteremia: the role of schistosomal glomerulopathy. *Rev Inst Med Trop Sao Paulo* 1992; **34:** 193-198.

448.   Abdul-Fattah MM, Yossef SM, Ebraheem ME, *et al.* Schistosomal glomerulopathy: a putative role for commonly associated Salmonella infection. *J Egypt Soc Parasitol* 1995; **25:** 165-173.

449.   Hsiao A, Toy T, Seo HJ, *et al.* Interaction between Salmonella and Schistosomiasis: A Review. *PLoS Pathog* 2016; **12:** e1005928.

450.   Martinelli R, Pereira LJ, Rocha H. The influence of anti-parasitic therapy on the course of the glomerulopathy associated with Schistosomiasis mansoni. *Clin Nephrol* 1987; **27:** 229-232.

451.   Ross AG, Bartley PB, Sleigh AC, *et al.* Schistosomiasis. *N Engl J Med* 2002; **346:** 1212-1220.

452.   Barsoum RS. Urinary schistosomiasis: review. *J Adv Res* 2013; **4:** 453-459.

453.   Pakasa NM, Nseka NM, Nyimi LM. Secondary collapsing glomerulopathy associated with Loa loa filariasis. *Am J Kidney Dis* 1997; **30:** 836-839.

454.   Ormerod AD, Petersen J, Hussey JK, *et al.* Immune complex glomerulonephritis and chronic anaerobic urinary infection--complications of filariasis. *Postgrad Med J* 1983; **59:** 730-733.

455.   Pillay VK, Kirch E, Kurtzman NA. Glomerulopathy associated with filarial loiasis. *JAMA* 1973; **225:** 179.

456.   Hall CL, Stephens L, Peat D, *et al.* Nephrotic syndrome due to loiasis following a tropical adventure holiday: a case report and review of the literature. *Clin Nephrol* 2001; **56:** 247-250.

457.   Dreyer G, Ottesen EA, Galdino E, *et al.* Renal abnormalities in microfilaremic patients with Bancroftian filariasis. *Am J Trop Med Hyg* 1992; **46:** 745-751.

458.   Langhammer J, Birk HW, Zahner H. Renal disease in lymphatic filariasis: evidence for tubular and glomerular disorders at various stages of the infection. *Trop Med Int Health* 1997; **2:** 875-884.

459.   Cruel T, Arborio M, Schill H, *et al.* [Nephropathy and filariasis from Loa loa. Apropos of 1 case of adverse reaction to a dose of ivermectin]. *Bull Soc Pathol Exot* 1997; **90:** 179-181.

460.   Ngu JL, Mate A, Leke R, *et al.* Proteinuria associated with diethylcarbamazine treatment of onchocerciasis (abstract). *Lancet* 1980; **315**.

461.   Abel L, Ioly V, Jeni P, *et al.* Apheresis in the management of loiasis with high microfilariaemia and renal disease. *Br Med J (Clin Res Ed)* 1986; **292:** 24.

462.   World Health Organization. Lymphatic filariasis: Treatment and prevention. https://www.who.int/lymphatic_filariasis/epidemiology/treatment/en/ [Accessed March 17, 2020]

463.   Arogundade FA, Hassan MO, Omotoso BA, *et al.* Spectrum of kidney diseases in Africa: malaria, schistosomiasis, sickle cell disease, and toxins. *Clin Nephrol* 2016; **86 (2016):** 53-60.

464.   Silva GBDJ, Pinto JR, Barros EJG, *et al.* Kidney involvement in malaria: an update. *Rev Inst Med Trop Sao Paulo* 2017; **59:** e53.

465.   Olowu WA, Ademola A, Ajite AB*, et al.* Childhood nephrotic syndrome in tropical Africa: then and now. *Paediatr Int Child Health* 2017; **37:** 259-268.

466.   Barsoum RS. Malarial nephropathies. *Nephrol Dial Transplant* 1998; **13:** 1588-1597.

467.   Eiam-Ong S. Malarial nephropathy. *Semin Nephrol* 2003; **23:** 21-33.

468.   Doe JY, Funk M, Mengel M*, et al.* Nephrotic syndrome in African children: lack of evidence for 'tropical nephrotic syndrome'? *Nephrol Dial Transplant* 2006; **21:** 672-676.

469.   Olowu WA, Adelusola KA, Adefehinti O*, et al.* Quartan malaria-associated childhood nephrotic syndrome: now a rare clinical entity in malaria endemic Nigeria. *Nephrol Dial Transplant* 2010; **25:** 794-801.

470.   Gomes AP, Vitoria RR, Costa AP*, et al.* Malaria grave por Plasmodium falciparum. *Revista Brasileira de Terapia Intensiva* 2011; **23:** 11.

471.   Naqvi R. Plasmodium Vivax causing acute kidney injury: A foe less addressed. *Pak J Med Sci* 2015; **31:** 1472-1475.

472.   Naqvi R, Akhtar F, Ahmed E*, et al.* Malarial acute kidney injury: 25 years experience from a center in an endemic region. *British Journal of Medicine and Medical Research* 2016; **12:** 6.

473.   Shukla VS, Singh RG, Rathore SS*, et al.* Outcome of malaria-associated acute kidney injury: a prospective study from a single center. *Ren Fail* 2013; **35:** 801-805.

474.   World Health Organization. Malaria: Overview of Malaria Treatment. https://www.who.int/lymphatic_filariasis/epidemiology/treatment/en/ [Accessed March 17, 2020]

475.   Nosten F, McGready R, d'Alessandro U*, et al.* Antimalarial drugs in pregnancy: a review. *Curr Drug Saf* 2006; **1:** 1-15.

476.   Fervenza FC, Sethi S, Glassock RJ. Idiopathic membranoproliferative glomerulonephritis: does it exist? *Nephrol Dial Transplant* 2012; **27:** 4288-4294.

477.   Sethi S, Fervenza FC. Membranoproliferative glomerulonephritis: pathogenetic heterogeneity and proposal for a new classification. *Semin Nephrol* 2011; **31:** 341-348.

478.   Sethi S, Fervenza FC. Membranoproliferative glomerulonephritis--a new look at an old entity. *N Engl J Med* 2012; **366:** 1119-1131.

479.   Lorenz EC, Sethi S, Leung N*, et al.* Recurrent membranoproliferative glomerulonephritis after kidney transplantation. *Kidney Int* 2010; **77:** 721-728.

480.   Leung N, Bridoux F, Batuman V*, et al.* The evaluation of monoclonal gammopathy of renal significance: a consensus report of the International Kidney and Monoclonal Gammopathy Research Group. *Nat Rev Nephrol* 2019; **15:** 45-59.

481.   Bhutani G, Nasr SH, Said SM*, et al.* Hematologic characteristics of proliferative glomerulonephritides with nonorganized monoclonal immunoglobulin deposits. *Mayo Clin Proc* 2015; **90:** 587-596.

482. Bridoux F, Leung N, Hutchison CA*, et al.* Diagnosis of monoclonal gammopathy of renal significance. *Kidney Int* 2015; **87:** 698-711.

483. Pickering MC, D'Agati VD, Nester CM*, et al.* C3 glomerulopathy: consensus report. *Kidney Int* 2013; **84:** 1079-1089.

484. Servais A, Fremeaux-Bacchi V, Lequintrec M*, et al.* Primary glomerulonephritis with isolated C3 deposits: a new entity which shares common genetic risk factors with haemolytic uraemic syndrome. *J Med Genet* 2007; **44:** 193-199.

485. Messias NC, Walker PD, Larsen CP. Paraffin immunofluorescence in the renal pathology laboratory: more than a salvage technique. *Mod Pathol* 2015; **28:** 854-860.

486. Bomback AS, Santoriello D, Avasare RS*, et al.* C3 glomerulonephritis and dense deposit disease share a similar disease course in a large United States cohort of patients with C3 glomerulopathy. *Kidney Int* 2018; **93:** 977-985.

487. Ravindran A, Fervenza FC, Smith RJH*, et al.* C3 Glomerulopathy: Ten Years' Experience at Mayo Clinic. *Mayo Clin Proc* 2018; **93:** 991-1008.

488. Smith RJH, Appel GB, Blom AM*, et al.* C3 glomerulopathy - understanding a rare complement-driven renal disease. *Nat Rev Nephrol* 2019; **15:** 129-143.

489. Sethi S, Quint PS, O'Seaghdha CM*, et al.* C4 Glomerulopathy: A Disease Entity Associated With C4d Deposition. *Am J Kidney Dis* 2016; **67:** 949-953.

490. Ruggenenti P, Daina E, Gennarini A*, et al.* C5 Convertase Blockade in Membranoproliferative Glomerulonephritis: A Single-Arm Clinical Trial. *Am J Kidney Dis* 2019; **74:** 224-238.

491. Servais A, Noel LH, Roumenina LT*, et al.* Acquired and genetic complement abnormalities play a critical role in dense deposit disease and other C3 glomerulopathies. *Kidney Int* 2012; **82:** 454-464.

492. Nasr SH, Valeri AM, Appel GB*, et al.* Dense deposit disease: clinicopathologic study of 32 pediatric and adult patients. *Clin J Am Soc Nephrol* 2009; **4:** 22-32.

493. Lu DF, McCarthy AM, Lanning LD*, et al.* A descriptive study of individuals with membranoproliferative glomerulonephritis. *Nephrol Nurs J* 2007; **34:** 295-302; quiz 303.

494. Chauvet S, Roumenina LT, Aucouturier P*, et al.* Both Monoclonal and Polyclonal Immunoglobulin Contingents Mediate Complement Activation in Monoclonal Gammopathy Associated-C3 Glomerulopathy. *Front Immunol* 2018; **9:** 2260.

495. Chauvet S, Fremeaux-Bacchi V, Petitprez F*, et al.* Treatment of B-cell disorder improves renal outcome of patients with monoclonal gammopathy-associated C3 glomerulopathy. *Blood* 2017; **129:** 1437-1447.

496. Goodship TH, Cook HT, Fakhouri F*, et al.* Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. *Kidney Int* 2017; **91:** 539-551.

497. Medjeral-Thomas NR, O'Shaughnessy MM, O'Regan JA*, et al.* C3 glomerulopathy: clinicopathologic features and predictors of outcome. *Clin J Am Soc Nephrol* 2014; **9:** 46-53.

498. Rabasco C, Cavero T, Roman E*, et al.* Effectiveness of mycophenolate mofetil in C3 glomerulonephritis. *Kidney Int* 2015; **88:** 1153-1160.

499. Avasare RS, Canetta PA, Bomback AS*, et al.* Mycophenolate Mofetil in Combination with Steroids for Treatment of C3 Glomerulopathy: A Case Series. *Clin J Am Soc Nephrol* 2018; **13:** 406-413.

500. Jennette JC, Falk RJ, Bacon PA*, et al.* 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013; **65:** 1-11.

501. Mohammad AJ, Mortensen KH, Babar J*, et al.* Pulmonary Involvement in Antineutrophil Cytoplasmic Antibodies (ANCA)-associated Vasculitis: The Influence of ANCA Subtype. *J Rheumatol* 2017; **44:** 1458-1467.

502. Damoiseaux J, Csernok E, Rasmussen N*, et al.* Detection of antineutrophil cytoplasmic antibodies (ANCAs): a multicentre European Vasculitis Study Group (EUVAS) evaluation of the value of indirect immunofluorescence (IIF) versus antigen-specific immunoassays. *Ann Rheum Dis* 2017; **76:** 647-653.

503. Bossuyt X, Cohen Tervaert JW, Arimura Y*, et al.* Position paper: Revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis. *Nat Rev Rheumatol* 2017; **13:** 683-692.

504. Aasarod K, Bostad L, Hammerstrom J*, et al.* Renal histopathology and clinical course in 94 patients with Wegener's granulomatosis. *Nephrol Dial Transplant* 2001; **16:** 953-960.

505. Berden AE, Ferrario F, Hagen EC*, et al.* Histopathologic classification of ANCA-associated glomerulonephritis. *J Am Soc Nephrol* 2010; **21:** 1628-1636.

506. Flossmann O, Berden A, de Groot K*, et al.* Long-term patient survival in ANCA-associated vasculitis. *Ann Rheum Dis* 2011; **70:** 488-494.

507. Heijl C, Mohammad AJ, Westman K*, et al.* Long-term patient survival in a Swedish population-based cohort of patients with ANCA-associated vasculitis. *RMD Open* 2017; **3:** e000435.

508. Mukhtyar C, Flossmann O, Hellmich B*, et al.* Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism systemic vasculitis task force. *Ann Rheum Dis* 2008; **67:** 1004-1010.

509. Weiner M, Goh SM, Mohammad AJ*, et al.* Outcome and treatment of elderly patients with ANCA-associated vasculitis. *Clin J Am Soc Nephrol* 2015; **10:** 1128-1135.

510. Brix SR, Noriega M, Tennstedt P*, et al.* Development and validation of a renal risk score in ANCA-associated glomerulonephritis. *Kidney Int* 2018; **94:** 1177-1188.

511. Berden AE. Best Practice & Research. *Clinical Rheumatology* 2018; **32:** 83-93.

512. Walsh M, Flossmann O, Berden A*, et al.* Risk factors for relapse of antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2012; **64:** 542-548.

513. McClure ME, Wason J, Gopaluni S, *et al.* Evaluation of PR3-ANCA Status After Rituximab for ANCA-Associated Vasculitis. *J Clin Rheumatol* 2019; **25:** 217-223.

514. Sanders JS, Huitma MG, Kallenberg CG, *et al.* Prediction of relapses in PR3-ANCA-associated vasculitis by assessing responses of ANCA titres to treatment. *Rheumatology (Oxford)* 2006; **45:** 724-729.

515. Tomasson G, Grayson PC, Mahr AD, *et al.* Value of ANCA measurements during remission to predict a relapse of ANCA-associated vasculitis--a meta-analysis. *Rheumatology (Oxford)* 2012; **51:** 100-109.

516. Jones RB, Tervaert JW, Hauser T, *et al.* Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med* 2010; **363:** 211-220.

517. Stone JH, Merkel PA, Spiera R, *et al.* Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010; **363:** 221-232.

518. Walters G, Willis NS, Craig JC. Interventions for renal vasculitis in adults. *Cochrane Database Syst Rev* 2015**:** CD003232.

519. Unizony S, Villarreal M, Miloslavsky EM, *et al.* Clinical outcomes of treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis based on ANCA type. *Ann Rheum Dis* 2016; **75:** 1166-1169.

520. de Groot K, Harper L, Jayne DR, *et al.* Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med* 2009; **150:** 670-680.

521. Han F, Liu G, Zhang X, *et al.* Effects of mycophenolate mofetil combined with corticosteroids for induction therapy of microscopic polyangiitis. *Am J Nephrol* 2011; **33:** 185-192.

522. Hu W, Liu C, Xie H, *et al.* Mycophenolate mofetil versus cyclophosphamide for inducing remission of ANCA vasculitis with moderate renal involvement. *Nephrol Dial Transplant* 2008; **23:** 1307-1312.

523. Jones RB, Hiemstra TF, Ballarin J, *et al.* Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: a randomised, non-inferiority trial. *Ann Rheum Dis* 2019; **78:** 399-405.

524. Tuin J, Stassen PM, Bogdan DI, *et al.* Mycophenolate Mofetil Versus Cyclophosphamide for the Induction of Remission in Nonlife-Threatening Relapses of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis: Randomized, Controlled Trial. *Clin J Am Soc Nephrol* 2019; **14:** 1021-1028.

525. De Groot K, Rasmussen N, Bacon PA, *et al.* Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2005; **52:** 2461-2469.

526. Karras A, Pagnoux C, Haubitz M, *et al.* Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis. *Ann Rheum Dis* 2017; **76:** 1662-1668.

527. Yates M, Watts RA, Bajema IM, *et al.* EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. *Ann Rheum Dis* 2016; **75:** 1583-1594.

528. Jayne DRW, Bruchfeld AN, Harper L, *et al.* Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis. *J Am Soc Nephrol* 2017; **28:** 2756-2767.

529. A Phase 3 Clinical Trial of CCX168 (Avacopan) in Patients With ANCA-Associated Vasculitis (ADVOCATE). In clinicaltrials.gov, U.S. National Library of Medicine, 2016.

530. Adu D, Pall A, Luqmani RA, *et al.* Controlled trial of pulse versus continuous prednisolone and cyclophosphamide in the treatment of systemic vasculitis. *QJM* 1997; **90:** 401-409.

531. Guillevin L, Cordier JF, Lhote F, *et al.* A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis. *Arthritis Rheum* 1997; **40:** 2187-2198.

532. Haubitz M, Schellong S, Gobel U, *et al.* Intravenous pulse administration of cyclophosphamide versus daily oral treatment in patients with antineutrophil cytoplasmic antibody-associated vasculitis and renal involvement: a prospective, randomized study. *Arthritis Rheum* 1998; **41:** 1835-1844.

533. Pepper RJ, McAdoo SP, Moran SM, *et al.* A novel glucocorticoid-free maintenance regimen for anti-neutrophil cytoplasm antibody-associated vasculitis. *Rheumatology (Oxford)* 2019; **58:** 260-268.

534. McClure M, Gopaluni S, Jayne D, *et al.* B cell therapy in ANCA-associated vasculitis: current and emerging treatment options. *Nat Rev Rheumatol* 2018; **14:** 580-591.

535. van Daalen EE, Rizzo R, Kronbichler A, *et al.* Effect of rituximab on malignancy risk in patients with ANCA-associated vasculitis. *Ann Rheum Dis* 2017; **76:** 1064-1069.

536. Specks U, Merkel PA, Seo P, *et al.* Efficacy of remission-induction regimens for ANCA-associated vasculitis. *N Engl J Med* 2013; **369:** 417-427.

537. Maritati F, Alberici F, Oliva E, *et al.* Methotrexate versus cyclophosphamide for remission maintenance in ANCA-associated vasculitis: A randomised trial. *PLoS One* 2017; **12:** e0185880.

538. Plasma Exchange and Glucocorticoids for Treatment of Anti-Neutrophil Cytoplasm Antibody (ANCA) - Associated Vasculitis (PEXIVAS). In clinicaltrials.gov, U.S. National Library of Medicine, 2009

539. Walsh M, Merkel PA, Jayne D. The Effects of Plasma Exchange and Reduced-Dose Glucocorticoids during Remission-Induction for Treatment of Severe ANCA-Associated Vasculitis [abstract]. *Arthritis Rheumatology* 2018; **70**.

540. Roberts DM, Jones RB, Smith RM, *et al.* Rituximab-associated hypogammaglobulinemia: incidence, predictors and outcomes in patients with multi-system autoimmune disease. *J Autoimmun* 2015; **57:** 60-65.

541. Jayne DR, Gaskin G, Rasmussen N, *et al.* Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol* 2007; **18:** 2180-2188.

542. Levy JB, Hammad T, Coulthart A, *et al.* Clinical features and outcome of patients with both ANCA and anti-GBM antibodies. *Kidney Int* 2004; **66:** 1535-1540.

543. Hiemstra TF, Walsh M, Mahr A, *et al.* Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. *JAMA* 2010; **304:** 2381-2388.

544. Sanders JS, de Joode AA, DeSevaux RG, *et al.* 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. *Nephrol Dial Transplant* 2016; **31:** 1453-1459.

545. Pagnoux C, Mahr A, Hamidou MA, *et al.* Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. *N Engl J Med* 2008; **359:** 2790-2803.

546. Guillevin L, Pagnoux C, Karras A, *et al.* Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med* 2014; **371:** 1771-1780.

547. Charles P, Terrier B, Perrodeau E, *et al.* Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2). *Ann Rheum Dis* 2018; **77:** 1143-1149.

548. Smith R, Jayne D, Merkel P. A Randomized, Controlled Trial of Rituximab versus Azathioprine After Induction of Remission with Rituximab for Patients with ANCA-associated Vasculitis and Relapsing Disease [abstract]. *Arthritis Rheumatology* 2019; **71**.

549. Guillevin L, Pagnoux C, Karras A, *et al.* Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *New England Journal of Medicine* 2014; **371:** 1771-1780.

550. Walters G, Willis NS, Craig JC. Interventions for renal vasculitis in adults. *Cochrane Database of Systematic Reviews* 2015.

551. Stegeman CA, Tervaert JW, de Jong PE, *et al.* Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. Dutch Co-Trimoxazole Wegener Study Group. *N Engl J Med* 1996; **335:** 16-20.

552. Jayne D, Rasmussen N, Andrassy K, *et al.* A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med* 2003; **349:** 36-44.

553. Zycinska K, Wardyn KA, Zielonka TM, *et al.* Co-trimoxazole and prevention of relapses of PR3-ANCA positive vasculitis with pulmonary involvement. *Eur J Med Res* 2009; **14 Suppl 4:** 265-267.

554. Walsh M, Merkel PA, Mahr A, *et al.* Effects of duration of glucocorticoid therapy on relapse rate in antineutrophil cytoplasmic antibody-associated vasculitis: A meta-analysis. *Arthritis Care Res (Hoboken)* 2010; **62:** 1166-1173.

555. Pagnoux C, Hogan SL, Chin H, *et al.* Predictors of treatment resistance and relapse in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis: comparison of two independent cohorts. *Arthritis Rheum* 2008; **58:** 2908-2918.

556. Romeu M, Couchoud C, Delaroziere JC, *et al.* Survival of patients with ANCA-associated vasculitis on chronic dialysis: data from the French REIN registry from 2002 to 2011. *QJM* 2014; **107:** 545-555.

557. Pugnet G, Pagnoux C, Terrier B*, et al.* Rituximab versus azathioprine for ANCA-associated vasculitis maintenance therapy: impact on global disability and health-related quality of life. *Clin Exp Rheumatol* 2016; **34:** S54-59.

558. Mukhtyar C, Lee R, Brown D*, et al.* Modification and validation of the Birmingham Vasculitis Activity Score (version 3). *Ann Rheum Dis* 2009; **68:** 1827-1832.

559. Slot MC, Tervaert JW, Boomsma MM*, et al.* Positive classic antineutrophil cytoplasmic antibody (C-ANCA) titer at switch to azathioprine therapy associated with relapse in proteinase 3-related vasculitis. *Arthritis Rheum* 2004; **51:** 269-273.

560. Faurschou M, Sorensen IJ, Mellemkjaer L*, et al.* Malignancies in Wegener's granulomatosis: incidence and relation to cyclophosphamide therapy in a cohort of 293 patients. *J Rheumatol* 2008; **35:** 100-105.

561. Geetha D, Eirin A, True K*, et al.* Renal transplantation in antineutrophil cytoplasmic antibody-associated vasculitis: a multicenter experience. *Transplantation* 2011; **91:** 1370-1375.

562. Goceroglu A, Rahmattulla C, Berden AE*, et al.* The Dutch Transplantation in Vasculitis (DUTRAVAS) Study: Outcome of Renal Transplantation in Antineutrophil Cytoplasmic Antibody-associated Glomerulonephritis. *Transplantation* 2016; **100:** 916-924.

563. Alarcon GS, McGwin G, Jr., Petri M*, et al.* Baseline characteristics of a multiethnic lupus cohort: PROFILE. *Lupus* 2002; **11:** 95-101.

564. Bastian HM, Roseman JM, McGwin G, Jr.*, et al.* Systemic lupus erythematosus in three ethnic groups. XII. Risk factors for lupus nephritis after diagnosis. *Lupus* 2002; **11:** 152-160.

565. Feldman CH, Hiraki LT, Liu J*, et al.* Epidemiology and sociodemographics of systemic lupus erythematosus and lupus nephritis among US adults with Medicaid coverage, 2000-2004. *Arthritis Rheum* 2013; **65:** 753-763.

566. Pons-Estel BA, Catoggio LJ, Cardiel MH*, et al.* The GLADEL multinational Latin American prospective inception cohort of 1,214 patients with systemic lupus erythematosus: ethnic and disease heterogeneity among "Hispanics". *Medicine (Baltimore)* 2004; **83:** 1-17.

567. Mok CC, Kwok RC, Yip PS. Effect of renal disease on the standardized mortality ratio and life expectancy of patients with systemic lupus erythematosus. *Arthritis Rheum* 2013; **65:** 2154-2160.

568. Sule S, Fivush B, Neu A*, et al.* Increased risk of death in pediatric and adult patients with ESRD secondary to lupus. *Pediatr Nephrol* 2011; **26:** 93-98.

569. Yap DY, Tang CS, Ma MK*, et al.* Survival analysis and causes of mortality in patients with lupus nephritis. *Nephrol Dial Transplant* 2012; **27:** 3248-3254.

570. Hiraki LT, Feldman CH, Liu J*, et al.* Prevalence, incidence, and demographics of systemic lupus erythematosus and lupus nephritis from 2000 to 2004 among children in the US Medicaid beneficiary population. *Arthritis Rheum* 2012; **64:** 2669-2676.

571. Malvar A, Pirruccio P, Alberton V*, et al.* Histologic versus clinical remission in proliferative lupus nephritis. *Nephrol Dial Transplant* 2017; **32:** 1338-1344.

572. Zickert A, Sundelin B, Svenungsson E, *et al.* Role of early repeated renal biopsies in lupus nephritis. *Lupus Sci Med* 2014; **1:** e000018.

573. Appel GB, Contreras G, Dooley MA, *et al.* Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. *J Am Soc Nephrol* 2009; **20:** 1103-1112.

574. Austin HA, 3rd, Klippel JH, Balow JE, *et al.* Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. *N Engl J Med* 1986; **314:** 614-619.

575. Chan TM, Li FK, Tang CS, *et al.* Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong-Guangzhou Nephrology Study Group. *N Engl J Med* 2000; **343:** 1156-1162.

576. Chan TM, Tse KC, Tang CS, *et al.* Long-term study of mycophenolate mofetil as continuous induction and maintenance treatment for diffuse proliferative lupus nephritis. *J Am Soc Nephrol* 2005; **16:** 1076-1084.

577. Dooley MA, Jayne D, Ginzler EM, *et al.* Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. *N Engl J Med* 2011; **365:** 1886-1895.

578. Houssiau FA, Vasconcelos C, D'Cruz D, *et al.* Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. *Arthritis Rheum* 2002; **46:** 2121-2131.

579. Lewis EJ, Hunsicker LG, Lan SP, *et al.* A controlled trial of plasmapheresis therapy in severe lupus nephritis. The Lupus Nephritis Collaborative Study Group. *N Engl J Med* 1992; **326:** 1373-1379.

580. Liu Z, Zhang H, Liu Z, *et al.* Multitarget therapy for induction treatment of lupus nephritis: a randomized trial. *Ann Intern Med* 2015; **162:** 18-26.

581. Pollak VE, Pirani CL, Schwartz FD. The Natural History of the Renal Manifestations of Systemic Lupus Erythematosus. *J Lab Clin Med* 1964; **63:** 537-550.

582. Bajema IM, Wilhelmus S, Alpers CE, *et al.* Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices. *Kidney Int* 2018; **93:** 789-796.

583. Markowitz GS, D'Agati VD. The ISN/RPS 2003 classification of lupus nephritis: an assessment at 3 years. *Kidney Int* 2007; **71:** 491-495.

584. Weening JJ, D'Agati VD, Schwartz MM, *et al.* The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol* 2004; **15:** 241-250.

585. Galindo-Izquierdo M, Rodriguez-Almaraz E, Pego-Reigosa JM, *et al.* Characterization of Patients With Lupus Nephritis Included in a Large Cohort From the Spanish Society of Rheumatology Registry of Patients With Systemic Lupus Erythematosus (RELESSER). *Medicine (Baltimore)* 2016; **95:** e2891.

586. Pons-Estel GJ, Alarcon GS, Burgos PI, *et al.* Mestizos with systemic lupus erythematosus develop renal disease early while antimalarials retard its appearance: data from a Latin American cohort. *Lupus* 2013; **22:** 899-907.

587.   Kasitanon N, Fine DM, Haas M, *et al.* Hydroxychloroquine use predicts complete renal remission within 12 months among patients treated with mycophenolate mofetil therapy for membranous lupus nephritis. *Lupus* 2006; **15:** 366-370.

588.   Mejia-Vilet JM, Cordova-Sanchez BM, Uribe-Uribe NO, *et al.* Immunosuppressive treatment for pure membranous lupus nephropathy in a Hispanic population. *Clin Rheumatol* 2016; **35:** 2219-2227.

589.   Kaiser R, Cleveland CM, Criswell LA. Risk and protective factors for thrombosis in systemic lupus erythematosus: results from a large, multi-ethnic cohort. *Ann Rheum Dis* 2009; **68:** 238-241.

590.   Petri M. Use of hydroxychloroquine to prevent thrombosis in systemic lupus erythematosus and in antiphospholipid antibody-positive patients. *Curr Rheumatol Rep* 2011; **13:** 77-80.

591.   Ruiz-Irastorza G, Egurbide MV, Pijoan JI, *et al.* Effect of antimalarials on thrombosis and survival in patients with systemic lupus erythematosus. *Lupus* 2006; **15:** 577-583.

592.   Tektonidou MG, Laskari K, Panagiotakos DB, *et al.* Risk factors for thrombosis and primary thrombosis prevention in patients with systemic lupus erythematosus with or without antiphospholipid antibodies. *Arthritis Rheum* 2009; **61:** 29-36.

593.   Fessler BJ, Alarcon GS, McGwin G, Jr., *et al.* Systemic lupus erythematosus in three ethnic groups: XVI. Association of hydroxychloroquine use with reduced risk of damage accrual. *Arthritis Rheum* 2005; **52:** 1473-1480.

594.   Pakchotanon R, Gladman DD, Su J, *et al.* More Consistent Antimalarial Intake in First 5 Years of Disease Is Associated with Better Prognosis in Patients with Systemic Lupus Erythematosus. *J Rheumatol* 2018; **45:** 90-94.

595.   Pokroy-Shapira E, Gelernter I, Molad Y. Evolution of chronic kidney disease in patients with systemic lupus erythematosus over a long-period follow-up: a single-center inception cohort study. *Clin Rheumatol* 2014; **33:** 649-657.

596.   Pons-Estel GJ, Alarcon GS, McGwin G, Jr., *et al.* Protective effect of hydroxychloroquine on renal damage in patients with lupus nephritis: LXV, data from a multiethnic US cohort. *Arthritis Rheum* 2009; **61:** 830-839.

597.   Shaharir SS, Ghafor AH, Said MS, *et al.* A descriptive study of the factors associated with damage in Malaysian patients with lupus nephritis. *Lupus* 2014; **23:** 436-442.

598.   Siso A, Ramos-Casals M, Bove A, *et al.* Previous antimalarial therapy in patients diagnosed with lupus nephritis: influence on outcomes and survival. *Lupus* 2008; **17:** 281-288.

599.   Hodis HN, Quismorio FP, Jr., Wickham E, *et al.* The lipid, lipoprotein, and apolipoprotein effects of hydroxychloroquine in patients with systemic lupus erythematosus. *J Rheumatol* 1993; **20:** 661-665.

600.   Tam LS, Gladman DD, Hallett DC, *et al.* Effect of antimalarial agents on the fasting lipid profile in systemic lupus erythematosus. *J Rheumatol* 2000; **27:** 2142-2145.

601.   Lakshminarayanan S, Walsh S, Mohanraj M, *et al.* Factors associated with low bone mineral density in female patients with systemic lupus erythematosus. *J Rheumatol* 2001; **28:** 102-108.

602.   Eudy AM, Siega-Riz AM, Engel SM, *et al.* Effect of pregnancy on disease flares in patients with systemic lupus erythematosus. *Ann Rheum Dis* 2018; **77:** 855-860.

603.   Leroux M, Desveaux C, Parcevaux M, *et al.* Impact of hydroxychloroquine on preterm delivery and intrauterine growth restriction in pregnant women with systemic lupus erythematosus: a descriptive cohort study. *Lupus* 2015; **24:** 1384-1391.

604.   Liu E, Liu Z, Zhou Y. Feasibility of hydroxychloroquine adjuvant therapy in pregnant women with systemic lupus erythematosus. *Biomedical Research (India)* 2018; **29:** 980-983.

605.   Serre J, Buob D, Boffa JJ. Hydroxychloroquine-induced podocytopathy mimicking Fabry disease. *BMJ Case Rep* 2019; **12**.

606.   Sperati CJ, Rosenberg AZ. Hydroxychloroquine-induced mimic of renal Fabry disease. *Kidney Int* 2018; **94:** 634.

607.   Canadian Hydroxychloroquine Study Group. A randomized study of the effect of withdrawing hydroxychloroquine sulfate in systemic lupus erythematosus. *N Engl J Med* 1991; **324:** 150-154.

608.   Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, *et al.* Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. *Ann Rheum Dis* 2010; **69:** 20-28.

609.   Feldman CH, Hiraki LT, Winkelmayer WC, *et al.* Serious infections among adult Medicaid beneficiaries with systemic lupus erythematosus and lupus nephritis. *Arthritis Rheumatol* 2015; **67:** 1577-1585.

610.   Zheng ZH, Zhang LJ, Liu WX, *et al.* Predictors of survival in Chinese patients with lupus nephritis. *Lupus* 2012; **21:** 1049-1056.

611.   Mohammad S, Clowse MEB, Eudy AM, *et al.* Examination of Hydroxychloroquine Use and Hemolytic Anemia in G6PDH-Deficient Patients. *Arthritis Care Res (Hoboken)* 2018; **70:** 481-485.

612.   Cervera R, Khamashta MA, Font J, *et al.* Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. *Medicine (Baltimore)* 2003; **82:** 299-308.

613.   Fors Nieves CE, Izmirly PM. Mortality in Systemic Lupus Erythematosus: an Updated Review. *Curr Rheumatol Rep* 2016; **18:** 21.

614.   Tselios K, Gladman DD, Sheane BJ, *et al.* All-cause, cause-specific and age-specific standardised mortality ratios of patients with systemic lupus erythematosus in Ontario, Canada over 43 years (1971-2013). *Ann Rheum Dis* 2019; **78:** 802-806.

615.   Yurkovich M, Vostretsova K, Chen W, *et al.* Overall and cause-specific mortality in patients with systemic lupus erythematosus: a meta-analysis of observational studies. *Arthritis Care Res (Hoboken)* 2014; **66:** 608-616.

616.   Steiman AJ, Gladman DD, Ibanez D, *et al.* Outcomes in patients with systemic lupus erythematosus with and without a prolonged serologically active clinically quiescent period. *Arthritis Care Res (Hoboken)* 2012; **64:** 511-518.

617. Thong KM, Chan TM. Infectious complications in lupus nephritis treatment: a systematic review and meta-analysis. *Lupus* 2019; **28:** 334-346.

618. Liebling M, Rubio E, Ie S. Prophylaxis for Pneumocystis jiroveci pneumonia: is it a necessity in pulmonary patients on high-dose, chronic corticosteroid therapy without AIDS? *Expert Rev Respir Med* 2015; **9:** 171-181.

619. Schmajuk G, Jafri K, Evans M*, et al.* Pneumocystis jirovecii pneumonia (PJP) prophylaxis patterns among patients with rheumatic diseases receiving high-risk immunosuppressant drugs. *Semin Arthritis Rheum* 2019; **48:** 1087-1092.

620. Petri M, Allbritton J. Antibiotic allergy in systemic lupus erythematosus: a case-control study. *J Rheumatol* 1992; **19:** 265-269.

621. Vananuvat P, Suwannalai P, Sungkanuparph S*, et al.* Primary prophylaxis for Pneumocystis jirovecii pneumonia in patients with connective tissue diseases. *Semin Arthritis Rheum* 2011; **41:** 497-502.

622. Suyama Y, Okada M, Rokutanda R*, et al.* Safety and efficacy of upfront graded administration of trimethoprim-sulfamethoxazole in systemic lupus erythematosus: A retrospective cohort study. *Mod Rheumatol* 2016; **26:** 557-561.

623. Murdaca G, Orsi A, Spano F*, et al.* Vaccine-preventable infections in Systemic Lupus Erythematosus. *Hum Vaccin Immunother* 2016; **12:** 632-643.

624. Angeli A, Guglielmi G, Dovio A*, et al.* High prevalence of asymptomatic vertebral fractures in post-menopausal women receiving chronic glucocorticoid therapy: a cross-sectional outpatient study. *Bone* 2006; **39:** 253-259.

625. Curtis JR, Westfall AO, Allison J*, et al.* Population-based assessment of adverse events associated with long-term glucocorticoid use. *Arthritis Rheum* 2006; **55:** 420-426.

626. Hansen KE, Kleker B, Safdar N*, et al.* A systematic review and meta-analysis of glucocorticoid-induced osteoporosis in children. *Semin Arthritis Rheum* 2014; **44:** 47-54.

627. Centre for Metabolic Bone Diseases. Fracture Risk Assessment Tool. In (2020) https://www.sheffield.ac.uk/FRAX/ [Accessed February 23, 2020]

628. Buckley L, Guyatt G, Fink HA*, et al.* 2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. *Arthritis Rheumatol* 2017; **69:** 1521-1537.

629. Zhang Y, Milojevic D. Protecting Bone Health in Pediatric Rheumatic Diseases: Pharmacological Considerations. *Paediatr Drugs* 2017; **19:** 193-211.

630. Choi MY, Flood K, Bernatsky S*, et al.* A review on SLE and malignancy. *Best Pract Res Clin Rheumatol* 2017; **31:** 373-396.

631. Goobie GC, Bernatsky S, Ramsey-Goldman R*, et al.* Malignancies in systemic lupus erythematosus: a 2015 update. *Curr Opin Rheumatol* 2015; **27:** 454-460.

632.   Tessier-Cloutier B, Clarke AE, Pineau CA, *et al.* What investigations are needed to optimally monitor for malignancies in SLE? *Lupus* 2015; **24:** 781-787.

633.   Gatto M, Agmon-Levin N, Soriano A, *et al.* Human papillomavirus vaccine and systemic lupus erythematosus. *Clin Rheumatol* 2013; **32:** 1301-1307.

634.   Pellegrino P, Carnovale C, Perrone V, *et al.* Human papillomavirus vaccine in patients with systemic lupus erythematosus. *Epidemiology* 2014; **25:** 155-156.

635.   Baldwin DS, Gluck MC, Lowenstein J, *et al.* Lupus nephritis. Clinical course as related to morphologic forms and their transitions. *Am J Med* 1977; **62:** 12-30.

636.   Hu W, Chen Y, Wang S, *et al.* Clinical-Morphological Features and Outcomes of Lupus Podocytopathy. *Clin J Am Soc Nephrol* 2016; **11:** 585-592.

637.   Lewis EJ. Chapter 8. Lupus Podocytopathy. In: Lewis EJ, Schwartz MM, Korbet SM, Chan TM (eds). *Lupus Nephritis, 2nd ed*. Oxford University Press, 2010.

638.   Gutierrez S, Petiti JP, De Paul AL, *et al.* Lupus-related podocytopathy. Could it be a new entity within the spectrum of lupus nephritis? *Nefrologia* 2012; **32:** 245-246.

639.   Han TS, Schwartz MM, Lewis EJ. Association of glomerular podocytopathy and nephrotic proteinuria in mesangial lupus nephritis. *Lupus* 2006; **15:** 71-75.

640.   Kraft SW, Schwartz MM, Korbet SM, *et al.* Glomerular podocytopathy in patients with systemic lupus erythematosus. *J Am Soc Nephrol* 2005; **16:** 175-179.

641.   Shea-Simonds P, Cairns TD, Roufosse C, *et al.* Lupus podocytopathy. *Rheumatology (Oxford)* 2009; **48:** 1616-1618.

642.   Wang SF, Chen YH, Chen DQ, *et al.* Mesangial proliferative lupus nephritis with podocytopathy: a special entity of lupus nephritis. *Lupus* 2018; **27:** 303-311.

643.   Hu WX, Chen YH, Bao H, *et al.* Glucocorticoid with or without additional immunosuppressant therapy for patients with lupus podocytopathy: a retrospective single-center study. *Lupus* 2015; **24:** 1067-1075.

644.   Gladman DD, Urowitz MB, Rahman P, *et al.* Accrual of organ damage over time in patients with systemic lupus erythematosus. *J Rheumatol* 2003; **30:** 1955-1959.

645.   Donadio JV, Jr., Holley KE, Ferguson RH, *et al.* Treatment of diffuse proliferative lupus nephritis with prednisone and combined prednisone and cyclophosphamide. *N Engl J Med* 1978; **299:** 1151-1155.

646.   Gourley MF, Austin HA, 3rd, Scott D, *et al.* Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. A randomized, controlled trial. *Ann Intern Med* 1996; **125:** 549-557.

647.   Illei GG, Austin HA, Crane M, *et al.* Combination therapy with pulse cyclophosphamide plus pulse methylprednisolone improves long-term renal outcome without adding toxicity in patients with lupus nephritis. *Ann Intern Med* 2001; **135:** 248-257.

648. Steinberg AD, Kaltreider HB, Staples PJ, *et al.* Cyclophosphamide in lupus nephritis: a controlled trial. *Ann Intern Med* 1971; **75:** 165-171.

649. Li X, Ren H, Zhang Q, *et al.* Mycophenolate mofetil or tacrolimus compared with intravenous cyclophosphamide in the induction treatment for active lupus nephritis. *Nephrol Dial Transplant* 2012; **27:** 1467-1472.

650. Rathi M, Goyal A, Jaryal A, *et al.* Comparison of low-dose intravenous cyclophosphamide with oral mycophenolate mofetil in the treatment of lupus nephritis. *Kidney Int* 2016; **89:** 235-242.

651. Ginzler EM, Dooley MA, Aranow C, *et al.* Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med* 2005; **353:** 2219-2228.

652. Houssiau FA, Vasconcelos C, D'Cruz D, *et al.* The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide. *Ann Rheum Dis* 2010; **69:** 61-64.

653. Zhang H, Liu Z, Zhou M, *et al.* Multitarget Therapy for Maintenance Treatment of Lupus Nephritis. *J Am Soc Nephrol* 2017; **28:** 3671-3678.

654. Sakai R, Kurasawa T, Nishi E, *et al.* Efficacy and safety of multitarget therapy with cyclophosphamide and tacrolimus for lupus nephritis: a prospective, single-arm, single-centre, open label pilot study in Japan. *Lupus* 2018; **27:** 273-282.

655. Chan TM, Tse KC, Tang CS, *et al.* Long-term outcome of patients with diffuse proliferative lupus nephritis treated with prednisolone and oral cyclophosphamide followed by azathioprine. *Lupus* 2005; **14:** 265-272.

656. Chen YE, Korbet SM, Katz RS, *et al.* Value of a complete or partial remission in severe lupus nephritis. *Clin J Am Soc Nephrol* 2008; **3:** 46-53.

657. Dall'Era M, Cisternas MG, Smilek DE, *et al.* Predictors of long-term renal outcome in lupus nephritis trials: lessons learned from the Euro-Lupus Nephritis cohort. *Arthritis Rheumatol* 2015; **67:** 1305-1313.

658. Yap DY, Ma MK, Mok MM, *et al.* Long-term data on corticosteroids and mycophenolate mofetil treatment in lupus nephritis. *Rheumatology (Oxford)* 2013; **52:** 480-486.

659. Boumpas DT, Austin HA, 3rd, Vaughn EM, *et al.* Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. *Lancet* 1992; **340:** 741-745.

660. Sesso R, Monteiro M, Sato E, *et al.* A controlled trial of pulse cyclophosphamide versus pulse methylprednisolone in severe lupus nephritis. *Lupus* 1994; **3:** 107-112.

661. Tunnicliffe DJ, Palmer SC, Henderson L, *et al.* Immunosuppressive treatment for proliferative lupus nephritis. *Cochrane Database Syst Rev* 2018; **6:** CD002922.

662. Mehra S, Usdadiya JB, Jain VK, *et al.* Comparing the efficacy of low-dose vs high-dose cyclophosphamide regimen as induction therapy in the treatment of proliferative lupus nephritis: a single center study. *Rheumatol Int* 2018; **38:** 557-568.

663. Mitwalli AH, Al Wakeel JS, Hurraib S, *et al.* Comparison of high and low dose of cyclophosphamide in lupus nephritis patients: a long-term randomized controlled trial. *Saudi J Kidney Dis Transpl* 2011; **22:** 935-940.

664. Sabry A, Abo-Zenah H, Medhat T, *et al.* A comparative study of two intensified pulse cyclophosphamide remission-inducing regimens for diffuse proliferative lupus nephritis: an Egyptian experience. *Int Urol Nephrol* 2009; **41:** 153-161.

665. El-Shafey EM, Abdou SH, Shareef MM. Is mycophenolate mofetil superior to pulse intravenous cyclophosphamide for induction therapy of proliferative lupus nephritis in Egyptian patients? *Clin Exp Nephrol* 2010; **14:** 214-221.

666. Mendonca S, Gupta D, Ali S, *et al.* Mycophenolate mofetil or cyclophosphamide in indian patients with lupus nephritis: Which is better? A single-center experience. *Saudi J Kidney Dis Transpl* 2017; **28:** 1069-1077.

667. Ong LM, Hooi LS, Lim TO, *et al.* Randomized controlled trial of pulse intravenous cyclophosphamide versus mycophenolate mofetil in the induction therapy of proliferative lupus nephritis. *Nephrology (Carlton)* 2005; **10:** 504-510.

668. Sedhain A, Hada R, Agrawal RK, *et al.* Low dose mycophenolate mofetil versus cyclophosphamide in the induction therapy of lupus nephritis in Nepalese population: a randomized control trial. *BMC Nephrol* 2018; **19:** 175.

669. Bao H, Liu ZH, Xie HL, *et al.* Successful treatment of class V+IV lupus nephritis with multitarget therapy. *J Am Soc Nephrol* 2008; **19:** 2001-2010.

670. Mohara A, Perez Velasco R, Praditsitthikorn N, *et al.* A cost-utility analysis of alternative drug regimens for newly diagnosed severe lupus nephritis patients in Thailand. *Rheumatology (Oxford)* 2014; **53:** 138-144.

671. Tse KC, Tang CS, Lam MF, *et al.* Cost comparison between mycophenolate mofetil and cyclophosphamide-azathioprine in the treatment of lupus nephritis. *J Rheumatol* 2009; **36:** 76-81.

672. Wilson EC, Jayne DR, Dellow E, *et al.* The cost-effectiveness of mycophenolate mofetil as firstline therapy in active lupus nephritis. *Rheumatology (Oxford)* 2007; **46:** 1096-1101.

673. Meacock R, Dale N, Harrison MJ. The humanistic and economic burden of systemic lupus erythematosus : a systematic review. *Pharmacoeconomics* 2013; **31:** 49-61.

674. Sahay M, Saivani Y, Ismal K, *et al.* Mycophenolate versus Cyclophosphamide for Lupus Nephritis. *Indian J Nephrol* 2018; **28:** 35-40.

675. Isenberg D, Appel GB, Contreras G, *et al.* Influence of race/ethnicity on response to lupus nephritis treatment: the ALMS study. *Rheumatology (Oxford)* 2010; **49:** 128-140.

676. Mejia-Vilet JM, Arreola-Guerra JM, Cordova-Sanchez BM, *et al.* Comparison of Lupus Nephritis Induction Treatments in a Hispanic Population: A Single-center Cohort Analysis. *J Rheumatol* 2015; **42:** 2082-2091.

677. Rovin BH, Solomons N, Pendergraft WF, 3rd, *et al.* A randomized, controlled double-blind study comparing the efficacy and safety of dose-ranging voclosporin with placebo in achieving remission in patients with active lupus nephritis. *Kidney Int* 2019; **95:** 219-231.

678. Zeher M, Doria A, Lan J, *et al.* Efficacy and safety of enteric-coated mycophenolate sodium in combination with two glucocorticoid regimens for the treatment of active lupus nephritis. *Lupus* 2011; **20:** 1484-1493.

679. Austin HA, 3rd, Illei GG, Braun MJ, *et al.* Randomized, controlled trial of prednisone, cyclophosphamide, and cyclosporine in lupus membranous nephropathy. *J Am Soc Nephrol* 2009; **20:** 901-911.

680. McKinley A, Park E, Spetie D, *et al.* Oral cyclophosphamide for lupus glomerulonephritis: an underused therapeutic option. *Clin J Am Soc Nephrol* 2009; **4:** 1754-1760.

681. Mok CC, Ho CT, Chan KW, *et al.* Outcome and prognostic indicators of diffuse proliferative lupus glomerulonephritis treated with sequential oral cyclophosphamide and azathioprine. *Arthritis Rheum* 2002; **46:** 1003-1013.

682. Yee CS, Crabtree N, Skan J, *et al.* Prevalence and predictors of fragility fractures in systemic lupus erythematosus. *Ann Rheum Dis* 2005; **64:** 111-113.

683. Access Trial Group. Treatment of lupus nephritis with abatacept: the Abatacept and Cyclophosphamide Combination Efficacy and Safety Study. *Arthritis Rheumatol* 2014; **66:** 3096-3104.

684. Ciancio G, Miller J, Gonwa TA. Review of major clinical trials with mycophenolate mofetil in renal transplantation. *Transplantation* 2005; **80:** S191-200.

685. Alexander S, Fleming DH, Mathew BS, *et al.* Pharmacokinetics of concentration-controlled mycophenolate mofetil in proliferative lupus nephritis: an observational cohort study. *Ther Drug Monit* 2014; **36:** 423-432.

686. Kittanamongkolchai W, Rukrung C, Supasiri T, *et al.* Therapeutic drug monitoring of mycophenolate mofetil for the treatment of severely active lupus nephritis. *Lupus* 2013; **22:** 727-732.

687. Lertdumrongluk P, Somparn P, Kittanamongkolchai W, *et al.* Pharmacokinetics of mycophenolic acid in severe lupus nephritis. *Kidney Int* 2010; **78:** 389-395.

688. Neumann I, Fuhrmann H, Fang IF, *et al.* Association between mycophenolic acid 12-h trough levels and clinical endpoints in patients with autoimmune disease on mycophenolate mofetil. *Nephrol Dial Transplant* 2008; **23:** 3514-3520.

689. van Gelder T, Berden JH, Berger SP. To TDM or not to TDM in lupus nephritis patients treated with MMF? *Nephrol Dial Transplant* 2015; **30:** 560-564.

690. Rovin BH, Parikh SV, Hebert LA, *et al.* Lupus nephritis: induction therapy in severe lupus nephritis-- should MMF be considered the drug of choice? *Clin J Am Soc Nephrol* 2013; **8:** 147-153.

691. Grootscholten C, Bajema IM, Florquin S, *et al.* Treatment with cyclophosphamide delays the progression of chronic lesions more effectively than does treatment with azathioprine plus methylprednisolone in patients with proliferative lupus nephritis. *Arthritis Rheum* 2007; **56:** 924-937.

692. Grootscholten C, Ligtenberg G, Hagen EC, *et al.* Azathioprine/methylprednisolone versus cyclophosphamide in proliferative lupus nephritis. A randomized controlled trial. *Kidney Int* 2006; **70:** 732-742.

693. Wang HY, Cui TG, Hou FF, *et al.* Induction treatment of proliferative lupus nephritis with leflunomide combined with prednisone: a prospective multi-centre observational study. *Lupus* 2008; **17:** 638-644.

694. Zhang M, Qi C, Zha Y, *et al.* Leflunomide versus cyclophosphamide in the induction treatment of proliferative lupus nephritis in Chinese patients: a randomized trial. *Clin Rheumatol* 2019; **38:** 859-867.

695. Clark WF, Lindsay RM, Cattran DC, *et al.* Monthly plasmapheresis for systemic lupus erythematosus with diffuse proliferative glomerulonephritis: a pilot study. *Can Med Assoc J* 1981; **125:** 171-174.

696. Doria A, Piccoli A, Vesco P, *et al.* Therapy of lupus nephritis. A two-year prospective study. *Ann Med Interne (Paris)* 1994; **145:** 307-311.

697. Wallace DJ, Goldfinger D, Pepkowitz SH, *et al.* Randomized controlled trial of pulse/synchronization cyclophosphamide/apheresis for proliferative lupus nephritis. *J Clin Apher* 1998; **13:** 163-166.

698. Rovin BH, van Vollenhoven RF, Aranow C, *et al.* A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Treatment With Sirukumab (CNTO 136) in Patients With Active Lupus Nephritis. *Arthritis Rheumatol* 2016; **68:** 2174-2183.

699. Jayne D, Appel G, Chan TM, *et al.* LB0003: A randomized controlled study of laquinimod in active lupus nephritis patients in combination with standard of care. *Ann Rheum Dis* 2013; **72:** A164.

700. Furie R, Nicholls K, Cheng TT, *et al.* Efficacy and safety of abatacept in lupus nephritis: a twelve-month, randomized, double-blind study. *Arthritis Rheumatol* 2014; **66:** 379-389.

701. Mysler EF, Spindler AJ, Guzman R, *et al.* Efficacy and safety of ocrelizumab in active proliferative lupus nephritis: results from a randomized, double-blind, phase III study. *Arthritis Rheum* 2013; **65:** 2368-2379.

702. Rovin BH, Furie R, Latinis K, *et al.* Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. *Arthritis Rheum* 2012; **64:** 1215-1226.

703. Wofsy D, Hillson JL, Diamond B. Abatacept for lupus nephritis: alternative definitions of complete response support conflicting conclusions. *Arthritis Rheum* 2012; **64:** 3660-3665.

704. Gunnarsson I, Sundelin B, Jonsdottir T, *et al.* Histopathologic and clinical outcome of rituximab treatment in patients with cyclophosphamide-resistant proliferative lupus nephritis. *Arthritis Rheum* 2007; **56:** 1263-1272.

705. Karim MY, Pisoni CN, Khamashta MA. Update on immunotherapy for systemic lupus erythematosus-- what's hot and what's not! *Rheumatology (Oxford)* 2009; **48:** 332-341.

706. Li EK, Tam LS, Zhu TY, *et al.* Is combination rituximab with cyclophosphamide better than rituximab alone in the treatment of lupus nephritis? *Rheumatology (Oxford)* 2009; **48:** 892-898.

707. Lu TY, Ng KP, Cambridge G, *et al.* A retrospective seven-year analysis of the use of B cell depletion therapy in systemic lupus erythematosus at University College London Hospital: the first fifty patients. *Arthritis Rheum* 2009; **61:** 482-487.

708. Ramos-Casals M, Soto MJ, Cuadrado MJ, *et al.* Rituximab in systemic lupus erythematosus: A systematic review of off-label use in 188 cases. *Lupus* 2009; **18:** 767-776.

709. Condon MB, Ashby D, Pepper RJ, *et al.* Prospective observational single-centre cohort study to evaluate the effectiveness of treating lupus nephritis with rituximab and mycophenolate mofetil but no oral steroids. *Ann Rheum Dis* 2013; **72:** 1280-1286.

710. Mok CC, Lau CS, Wong RW. Risk factors for ovarian failure in patients with systemic lupus erythematosus receiving cyclophosphamide therapy. *Arthritis Rheum* 1998; **41:** 831-837.

711. Radis CD, Kahl LE, Baker GL, *et al.* Effects of cyclophosphamide on the development of malignancy and on long-term survival of patients with rheumatoid arthritis. A 20-year followup study. *Arthritis Rheum* 1995; **38:** 1120-1127.

712. Contreras G, Pardo V, Leclercq B, *et al.* Sequential therapies for proliferative lupus nephritis. *N Engl J Med* 2004; **350:** 971-980.

713. Aragon E, Resontoc LP, Chan YH, *et al.* Long-term outcomes with multi-targeted immunosuppressive protocol in children with severe proliferative lupus nephritis. *Lupus* 2016; **25:** 399-406.

714. Kasitanon N, Boripatkosol P, Louthrenoo W. Response to combination of mycophenolate mofetil, cyclosporin A and corticosteroid treatment in lupus nephritis patients with persistent proteinuria. *Int J Rheum Dis* 2018; **21:** 200-207.

715. Choi CB, Won S, Bae SC. Outcomes of multitarget therapy using mycophenolate mofetil and tacrolimus for refractory or relapsing lupus nephritis. *Lupus* 2018; **27:** 1007-1011.

716. Karasawa K, Uchida K, Kodama M, *et al.* Long-term effects of tacrolimus for maintenance therapy of lupus nephritis: a 5-year retrospective study at a single center. *Rheumatol Int* 2018; **38:** 2271-2277.

717. Yap DY, Ma MK, Mok MM, *et al.* Long-term data on tacrolimus treatment in lupus nephritis. *Rheumatology (Oxford)* 2014; **53:** 2232-2237.

718. Yumura W, Suganuma S, Uchida K, *et al.* Effects of long-term treatment with mizoribine in patients with proliferative lupus nephritis. *Clin Nephrol* 2005; **64:** 28-34.

719. Zavada J, Sinikka Pesickova S, Rysava R, *et al.* Extended follow-up of the CYCLOFA-LUNE trial comparing two sequential induction and maintenance treatment regimens for proliferative lupus nephritis based either on cyclophosphamide or on cyclosporine A. *Lupus* 2014; **23:** 69-74.

720. Nee R, Rivera I, Little DJ, *et al.* Cost-Utility Analysis of Mycophenolate Mofetil versus Azathioprine Based Regimens for Maintenance Therapy of Proliferative Lupus Nephritis. *Int J Nephrol* 2015; **2015:** 917567.

721. Houssiau FA, D'Cruz D, Sangle S, *et al.* Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial. *Ann Rheum Dis* 2010; **69:** 2083-2089.

722. Yap DYH, Tang C, Ma MKM, *et al.* Longterm Data on Disease Flares in Patients with Proliferative Lupus Nephritis in Recent Years. *J Rheumatol* 2017; **44:** 1375-1383.

723. Ruiz-Arruza I, Lozano J, Cabezas-Rodriguez I, *et al.* Restrictive Use of Oral Glucocorticoids in Systemic Lupus Erythematosus and Prevention of Damage Without Worsening Long-Term Disease Control: An Observational Study. *Arthritis Care Res (Hoboken)* 2018; **70:** 582-591.

724. Yap DYH, Kwan LPY, Ma MKM, *et al.* Preemptive immunosuppressive treatment for asymptomatic serological reactivation may reduce renal flares in patients with lupus nephritis: a cohort study. *Nephrol Dial Transplant* 2019; **34:** 467-473.

725. Tanaka H, Watanabe S, Aizawa-Yashiro T, *et al.* Long-term tacrolimus-based immunosuppressive treatment for young patients with lupus nephritis: a prospective study in daily clinical practice. *Nephron Clin Pract* 2012; **121:** c165-173.

726. Chen W, Liu Q, Chen W, *et al.* Outcomes of maintenance therapy with tacrolimus versus azathioprine for active lupus nephritis: a multicenter randomized clinical trial. *Lupus* 2012; **21:** 944-952.

727. Cortes-Hernandez J, Torres-Salido MT, Medrano AS, *et al.* Long-term outcomes--mycophenolate mofetil treatment for lupus nephritis with addition of tacrolimus for resistant cases. *Nephrol Dial Transplant* 2010; **25:** 3939-3948.

728. Tse KC, Lam MF, Tang SC, *et al.* A pilot study on tacrolimus treatment in membranous or quiescent lupus nephritis with proteinuria resistant to angiotensin inhibition or blockade. *Lupus* 2007; **16:** 46-51.

729. Uchino A, Tsukamoto H, Nakashima H, *et al.* Tacrolimus is effective for lupus nephritis patients with persistent proteinuria. *Clin Exp Rheumatol* 2010; **28:** 6-12.

730. Sugiyama S. Long-term therapy of mizoribine on lupus nephritis in joint multi-center study. *Journal of Cliinical Therapuetics and Medicine* 1996; **12:** 215-219.

731. Takeuchi T, Okada K, Yoshida H, *et al.* Post-marketing surveillance study of the long-term use of mizoribine for the treatment of lupus nephritis: 2-Year results. *Mod Rheumatol* 2018; **28:** 85-94.

732. Yap DYH, Tam CH, Yung S, *et al.* Pharmacokinetics and pharmacogenomics of mycophenolic acid and its clinical correlations in maintenance immunosuppression for lupus nephritis. *Nephrol Dial Transplant* 2018.

733. Moroni G, Longhi S, Giglio E, *et al.* What happens after complete withdrawal of therapy in patients with lupus nephritis. *Clin Exp Rheumatol* 2013; **31:** S75-81.

734. Alvarado AS, Malvar A, Lococo B, *et al.* The value of repeat kidney biopsy in quiescent Argentinian lupus nephritis patients. *Lupus* 2014; **23:** 840-847.

735. De Rosa M, Azzato F, Toblli JE, *et al.* A prospective observational cohort study highlights kidney biopsy findings of lupus nephritis patients in remission who flare following withdrawal of maintenance therapy. *Kidney Int* 2018; **94:** 788-794.

736. Malvar A, Alberton V, Lococo B, *et al.* Kidney biopsy-based management of maintenance immunosuppression is safe and may ameliorate flare rate in lupus nephritis. *Kidney Int* 2020; **97:** 156-162.

737. Appel GB, Cohen DJ, Pirani CL, *et al.* Long-term follow-up of patients with lupus nephritis. A study based on the classification of the World Health Organization. *Am J Med* 1987; **83:** 877-885.

738. Mercadal L, Montcel ST, Nochy D, *et al.* Factors affecting outcome and prognosis in membranous lupus nephropathy. *Nephrol Dial Transplant* 2002; **17:** 1771-1778.

739. Mok CC. Membranous nephropathy in systemic lupus erythematosus: a therapeutic enigma. *Nat Rev Nephrol* 2009; **5:** 212-220.

740. Mok CC, Ying KY, Yim CW, *et al.* Very long-term outcome of pure lupus membranous nephropathy treated with glucocorticoid and azathioprine. *Lupus* 2009; **18:** 1091-1095.

741. Radhakrishnan J, Moutzouris DA, Ginzler EM, *et al.* Mycophenolate mofetil and intravenous cyclophosphamide are similar as induction therapy for class V lupus nephritis. *Kidney Int* 2010; **77:** 152-160.

742. Chan TM, Li FK, Hao WK, *et al.* Treatment of membranous lupus nephritis with nephrotic syndrome by sequential immunosuppression. *Lupus* 1999; **8:** 545-551.

743. Cramer CH, 2nd, Mills M, Valentini RP, *et al.* Clinical presentation and outcome in a cohort of paediatric patients with membranous lupus nephritis. *Nephrol Dial Transplant* 2007; **22:** 3495-3500.

744. Borba EF, Guedes LK, Christmann RB, *et al.* Mycophenolate mofetil is effective in reducing lupus glomerulonephritis proteinuria. *Rheumatol Int* 2006; **26:** 1078-1083.

745. Mok CC, Ying KY, Yim CW, *et al.* Tacrolimus versus mycophenolate mofetil for induction therapy of lupus nephritis: a randomised controlled trial and long-term follow-up. *Ann Rheum Dis* 2016; **75:** 30-36.

746. Spetie DN, Tang Y, Rovin BH, *et al.* Mycophenolate therapy of SLE membranous nephropathy. *Kidney Int* 2004; **66:** 2411-2415.

747. Chen W, Tang X, Liu Q, *et al.* Short-term outcomes of induction therapy with tacrolimus versus cyclophosphamide for active lupus nephritis: A multicenter randomized clinical trial. *Am J Kidney Dis* 2011; **57:** 235-244.

748. Szeto CC, Kwan BC, Lai FM, *et al.* Tacrolimus for the treatment of systemic lupus erythematosus with pure class V nephritis. *Rheumatology (Oxford)* 2008; **47:** 1678-1681.

749. Yap DY, Yu X, Chen XM, *et al.* Pilot 24 month study to compare mycophenolate mofetil and tacrolimus in the treatment of membranous lupus nephritis with nephrotic syndrome. *Nephrology (Carlton)* 2012; **17:** 352-357.

750. Chavarot N, Verhelst D, Pardon A, *et al.* Rituximab alone as induction therapy for membranous lupus nephritis: A multicenter retrospective study. *Medicine (Baltimore)* 2017; **96:** e7429.

751. Houssiau FA, Vasconcelos C, D'Cruz D, *et al.* Early response to immunosuppressive therapy predicts good renal outcome in lupus nephritis: lessons from long-term followup of patients in the Euro-Lupus Nephritis Trial. *Arthritis Rheum* 2004; **50:** 3934-3940.

752. Korbet SM, Lewis EJ, Collaborative Study G. Severe lupus nephritis: the predictive value of a >/= 50% reduction in proteinuria at 6 months. *Nephrol Dial Transplant* 2013; **28:** 2313-2318.

753. Korbet SM, Lewis EJ, Schwartz MM, *et al.* Factors predictive of outcome in severe lupus nephritis. Lupus Nephritis Collaborative Study Group. *Am J Kidney Dis* 2000; **35:** 904-914.

754. Tamirou F, D'Cruz D, Sangle S, *et al.* Long-term follow-up of the MAINTAIN Nephritis Trial, comparing azathioprine and mycophenolate mofetil as maintenance therapy of lupus nephritis. *Ann Rheum Dis* 2016; **75:** 526-531.

755. Tamirou F, Lauwerys BR, Dall'Era M, *et al.* A proteinuria cut-off level of 0.7 g/day after 12 months of treatment best predicts long-term renal outcome in lupus nephritis: data from the MAINTAIN Nephritis Trial. *Lupus Sci Med* 2015; **2:** e000123.

756. Ugolini-Lopes MR, Seguro LPC, Castro MXF, *et al.* Early proteinuria response: a valid real-life situation predictor of long-term lupus renal outcome in an ethnically diverse group with severe biopsy-proven nephritis? *Lupus Sci Med* 2017; **4:** e000213.

757. Ioannidis JP, Boki KA, Katsorida ME, *et al.* Remission, relapse, and re-remission of proliferative lupus nephritis treated with cyclophosphamide. *Kidney Int* 2000; **57:** 258-264.

758. Touma Z, Urowitz MB, Ibanez D, *et al.* Time to recovery from proteinuria in patients with lupus nephritis receiving standard treatment. *J Rheumatol* 2014; **41:** 688-697.

759. Dall'Era M, Stone D, Levesque V, *et al.* Identification of biomarkers that predict response to treatment of lupus nephritis with mycophenolate mofetil or pulse cyclophosphamide. *Arthritis Care Res (Hoboken)* 2011; **63:** 351-357.

760. Bruce IN, Gladman DD, Urowitz MB. Factors associated with refractory renal disease in patients with systemic lupus erythematosus: the role of patient nonadherence. *Arthritis Care Res* 2000; **13:** 406-408.

761. Costedoat-Chalumeau N, Pouchot J, Guettrot-Imbert G, *et al.* Adherence to treatment in systemic lupus erythematosus patients. *Best Pract Res Clin Rheumatol* 2013; **27:** 329-340.

762. Marengo MF, Waimann CA, de Achaval S, *et al.* Measuring therapeutic adherence in systemic lupus erythematosus with electronic monitoring. *Lupus* 2012; **21:** 1158-1165.

763. Petri M, Perez-Gutthann S, Longenecker JC, *et al.* Morbidity of systemic lupus erythematosus: role of race and socioeconomic status. *Am J Med* 1991; **91:** 345-353.

764. Rivera F, Merida E, Illescas ML, *et al.* Mycophenolate in refractory and relapsing lupus nephritis. *Am J Nephrol* 2014; **40:** 105-112.

765. Bang SY, Lee CK, Kang YM, *et al.* Multicenter retrospective analysis of the effectiveness and safety of rituximab in korean patients with refractory systemic lupus erythematosus. *Autoimmune Dis* 2012; **2012:** 565039.

766. Contis A, Vanquaethem H, Truchetet ME*, et al.* Analysis of the effectiveness and safety of rituximab in patients with refractory lupus nephritis: a chart review. *Clin Rheumatol* 2016; **35:** 517-522.

767. Diaz-Lagares C, Croca S, Sangle S*, et al.* Efficacy of rituximab in 164 patients with biopsy-proven lupus nephritis: pooled data from European cohorts. *Autoimmun Rev* 2012; **11:** 357-364.

768. Garcia-Carrasco M, Mendoza-Pinto C, Sandoval-Cruz M*, et al.* Anti-CD20 therapy in patients with refractory systemic lupus erythematosus: a longitudinal analysis of 52 Hispanic patients. *Lupus* 2010; **19:** 213-219.

769. Iaccarino L, Bartoloni E, Carli L*, et al.* Efficacy and safety of off-label use of rituximab in refractory lupus: data from the Italian Multicentre Registry. *Clin Exp Rheumatol* 2015; **33:** 449-456.

770. Iwata S, Saito K, Hirata S*, et al.* Efficacy and safety of anti-CD20 antibody rituximab for patients with refractory systemic lupus erythematosus. *Lupus* 2018; **27:** 802-811.

771. Koike R, Harigai M, Atsumi T*, et al.* Japan College of Rheumatology 2009 guidelines for the use of tocilizumab, a humanized anti-interleukin-6 receptor monoclonal antibody, in rheumatoid arthritis. *Mod Rheumatol* 2009; **19:** 351-357.

772. Kotagiri P, Martin A, Hughes P*, et al.* Single-dose rituximab in refractory lupus nephritis. *Intern Med J* 2016; **46:** 899-901.

773. Melander C, Sallee M, Trolliet P*, et al.* Rituximab in severe lupus nephritis: early B-cell depletion affects long-term renal outcome. *Clin J Am Soc Nephrol* 2009; **4:** 579-587.

774. Tanaka Y, Takeuchi T, Miyasaka N*, et al.* Efficacy and safety of rituximab in Japanese patients with systemic lupus erythematosus and lupus nephritis who are refractory to conventional therapy. *Mod Rheumatol* 2016; **26:** 80-86.

775. Vigna-Perez M, Hernandez-Castro B, Paredes-Saharopulos O*, et al.* Clinical and immunological effects of Rituximab in patients with lupus nephritis refractory to conventional therapy: a pilot study. *Arthritis Res Ther* 2006; **8:** R83.

776. Weidenbusch M, Rommele C, Schrottle A*, et al.* Beyond the LUNAR trial. Efficacy of rituximab in refractory lupus nephritis. *Nephrol Dial Transplant* 2013; **28:** 106-111.

777. Alshaiki F, Obaid E, Almuallim A*, et al.* Outcomes of rituximab therapy in refractory lupus: A meta-analysis. *Eur J Rheumatol* 2018; **5:** 118-126.

778. Fei Y, Wu Q, Zhang W*, et al.* Low-dose tacrolimus in treating lupus nephritis refractory to cyclophosphamide: a prospective cohort study. *Clin Exp Rheumatol* 2013; **31:** 62-68.

779. Jesus D, Rodrigues M, da Silva JAP*, et al.* Multitarget therapy of mycophenolate mofetil and cyclosporine A for induction treatment of refractory lupus nephritis. *Lupus* 2018; **27:** 1358-1362.

780. Mok CC, To CH, Yu KL*, et al.* Combined low-dose mycophenolate mofetil and tacrolimus for lupus nephritis with suboptimal response to standard therapy: a 12-month prospective study. *Lupus* 2013; **22:** 1135-1141.

781. Ogawa H, Kameda H, Amano K, *et al.* Efficacy and safety of cyclosporine A in patients with refractory systemic lupus erythematosus in a daily clinical practice. *Lupus* 2010; **19:** 162-169.

782. Sheikholeslami M, Hajialilo M, Rasi Hashemi SS, *et al.* Low dose cyclosporine A in the treatment of resistant proliferative lupus nephritis. *Mod Rheumatol* 2018; **28:** 523-529.

783. Arriens C, Chen S, Karp DR, *et al.* Prognostic significance of repeat biopsy in lupus nephritis: Histopathologic worsening and a short time between biopsies is associated with significantly increased risk for end stage renal disease and death. *Clin Immunol* 2017; **185:** 3-9.

784. Moroni G, Quaglini S, Gallelli B, *et al.* The long-term outcome of 93 patients with proliferative lupus nephritis. *Nephrol Dial Transplant* 2007; **22:** 2531-2539.

785. Mosca M, Bencivelli W, Neri R, *et al.* Renal flares in 91 SLE patients with diffuse proliferative glomerulonephritis. *Kidney Int* 2002; **61:** 1502-1509.

786. Parikh SV, Nagaraja HN, Hebert L, *et al.* Renal flare as a predictor of incident and progressive CKD in patients with lupus nephritis. *Clin J Am Soc Nephrol* 2014; **9:** 279-284.

787. Morris HK, Canetta PA, Appel GB. Impact of the ALMS and MAINTAIN trials on the management of lupus nephritis. *Nephrol Dial Transplant* 2013; **28:** 1371-1376.

788. Hanaoka H, Iida H, Kiyokawa T, *et al.* Early achievement of deep remission predicts low incidence of renal flare in lupus nephritis class III or IV. *Arthritis Res Ther* 2018; **20:** 86.

789. Mejia-Vilet JM, Parikh SV, Song H, *et al.* Immune gene expression in kidney biopsies of lupus nephritis patients at diagnosis and at renal flare. *Nephrol Dial Transplant* 2019; **34:** 1197-1206.

790. Ioannidis JP, Katsifis GE, Tzioufas AG, *et al.* Predictors of sustained amenorrhea from pulsed intravenous cyclophosphamide in premenopausal women with systemic lupus erythematosus. *J Rheumatol* 2002; **29:** 2129-2135.

791. Katsifis GE, Tzioufas AG. Ovarian failure in systemic lupus erythematosus patients treated with pulsed intravenous cyclophosphamide. *Lupus* 2004; **13:** 673-678.

792. Parikh SV, Alvarado A, Malvar A, *et al.* The Kidney Biopsy in Lupus Nephritis: Past, Present, and Future. *Semin Nephrol* 2015; **35:** 465-477.

793. Bootsma H, Spronk P, Derksen R, *et al.* Prevention of relapses in systemic lupus erythematosus. *Lancet* 1995; **345:** 1595-1599.

794. Tseng CE, Buyon JP, Kim M, *et al.* The effect of moderate-dose corticosteroids in preventing severe flares in patients with serologically active, but clinically stable, systemic lupus erythematosus: findings of a prospective, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2006; **54:** 3623-3632.

795. Brocklebank V, Wood KM, Kavanagh D. Thrombotic Microangiopathy and the Kidney. *Clin J Am Soc Nephrol* 2018; **13:** 300-317.

796.   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.

797.   Johnson S, Stojanovic J, Ariceta G, *et al.* An audit analysis of a guideline for the investigation and initial therapy of diarrhea negative (atypical) hemolytic uremic syndrome. *Pediatr Nephrol* 2014; **29:** 1967-1978.

798.   Loirat C, Fakhouri F, Ariceta G, *et al.* An international consensus approach to the management of atypical hemolytic uremic syndrome in children. *Pediatr Nephrol* 2016; **31:** 15-39.

799.   George JN, Nester CM. Syndromes of thrombotic microangiopathy. *N Engl J Med* 2014; **371:** 654-666.

800.   Scully M, Hunt BJ, Benjamin S, *et al.* Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. *Br J Haematol* 2012; **158:** 323-335.

801.   Rock GA, Shumak KH, Buskard NA, *et al.* Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. *N Engl J Med* 1991; **325:** 393-397.

802.   von Baeyer H. Plasmapheresis in thrombotic microangiopathy-associated syndromes: review of outcome data derived from clinical trials and open studies. *Ther Apher* 2002; **6:** 320-328.

803.   Allford SL, Hunt BJ, Rose P, *et al.* Guidelines on the diagnosis and management of the thrombotic microangiopathic haemolytic anaemias. *Br J Haematol* 2003; **120:** 556-573.

804.   Bell WR, Braine HG, Ness PM, *et al.* Improved survival in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Clinical experience in 108 patients. *N Engl J Med* 1991; **325:** 398-403.

805.   Westwood JP, Thomas M, Alwan F, *et al.* Rituximab prophylaxis to prevent thrombotic thrombocytopenic purpura relapse: outcome and evaluation of dosing regimens. *Blood Adv* 2017; **1:** 1159-1166.

806.   Froissart A, Buffet M, Veyradier A, *et al.* Efficacy and safety of first-line rituximab in severe, acquired thrombotic thrombocytopenic purpura with a suboptimal response to plasma exchange. Experience of the French Thrombotic Microangiopathies Reference Center. *Crit Care Med* 2012; **40:** 104-111.

807.   Scully M, Cohen H, Cavenagh J, *et al.* Remission in acute refractory and relapsing thrombotic thrombocytopenic purpura following rituximab is associated with a reduction in IgG antibodies to ADAMTS-13. *Br J Haematol* 2007; **136:** 451-461.

808.   Scully M, McDonald V, Cavenagh J, *et al.* A phase 2 study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura. *Blood* 2011; **118:** 1746-1753.

809.   Peyvandi F, Scully M, Kremer Hovinga JA, *et al.* Caplacizumab for Acquired Thrombotic Thrombocytopenic Purpura. *N Engl J Med* 2016; **374:** 511-522.

810.   Scully M, Cataland SR, Peyvandi F, *et al.* Caplacizumab Treatment for Acquired Thrombotic Thrombocytopenic Purpura. *N Engl J Med* 2019; **380:** 335-346.

811. Tektonidou MG. Antiphospholipid Syndrome Nephropathy: From Pathogenesis to Treatment. *Front Immunol* 2018; **9:** 1181.

812. Sciascia S, Yazdany J, Dall'Era M, *et al.* Anticoagulation in patients with concomitant lupus nephritis and thrombotic microangiopathy: a multicentre cohort study. *Ann Rheum Dis* 2019; **78:** 1004-1006.

813. Dufrost V, Risse J, Reshetnyak T, *et al.* Increased risk of thrombosis in antiphospholipid syndrome patients treated with direct oral anticoagulants. Results from an international patient-level data meta-analysis. *Autoimmun Rev* 2018; **17:** 1011-1021.

814. Pengo V, Denas G, Zoppellaro G, *et al.* Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. *Blood* 2018; **132:** 1365-1371.

815. Kazzaz NM, McCune WJ, Knight JS. Treatment of catastrophic antiphospholipid syndrome. *Curr Opin Rheumatol* 2016; **28:** 218-227.

816. Bucciarelli S, Espinosa G, Cervera R, *et al.* Mortality in the catastrophic antiphospholipid syndrome: causes of death and prognostic factors in a series of 250 patients. *Arthritis Rheum* 2006; **54:** 2568-2576.

817. Dioszegi A, Tarr T, Nagy-Vincze M, *et al.* Microthrombotic renal involvement in an SLE patient with concomitant catastrophic antiphospholipid syndrome: the beneficial effect of rituximab treatment. *Lupus* 2018; **27:** 1552-1558.

818. Rymarz A, Niemczyk S. The complex treatment including rituximab in the Management of Catastrophic Antiphospholid Syndrome with renal involvement. *BMC Nephrol* 2018; **19:** 132.

819. Guillot M, Rafat C, Buob D, *et al.* Eculizumab for catastrophic antiphospholipid syndrome-a case report and literature review. *Rheumatology (Oxford)* 2018; **57:** 2055-2057.

820. Ruffatti A, Tarzia V, Fedrigo M, *et al.* Evidence of complement activation in the thrombotic small vessels of a patient with catastrophic antiphospholipid syndrome treated with eculizumab. *Autoimmun Rev* 2019; **18:** 561-563.

821. Tinti MG, Carnevale V, Inglese M, *et al.* Eculizumab in refractory catastrophic antiphospholipid syndrome: a case report and systematic review of the literature. *Clin Exp Med* 2019; **19:** 281-288.

822. Legendre CM, Licht C, Muus P, *et al.* Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. *N Engl J Med* 2013; **368:** 2169-2181.

823. Licht C, Greenbaum LA, Muus P, *et al.* Efficacy and safety of eculizumab in atypical hemolytic uremic syndrome from 2-year extensions of phase 2 studies. *Kidney Int* 2015; **87:** 1061-1073.

824. Wijnsma KL, Duineveld C, Wetzels JFM, *et al.* Eculizumab in atypical hemolytic uremic syndrome: strategies toward restrictive use. *Pediatr Nephrol* 2019; **34:** 2261-2277.

825. Cavero T, Rabasco C, Lopez A, *et al.* Eculizumab in secondary atypical haemolytic uraemic syndrome. *Nephrol Dial Transplant* 2017; **32:** 466-474.

826. Cao M, Leite BN, Ferreiro T, *et al.* Eculizumab Modifies Outcomes in Adults with Atypical Hemolytic Uremic Syndrome with Acute Kidney Injury. *Am J Nephrol* 2018; **48:** 225-233.

827.   de Holanda MI, Porto LC, Wagner T, *et al.* Use of eculizumab in a systemic lupus erythemathosus patient presenting thrombotic microangiopathy and heterozygous deletion in CFHR1-CFHR3. A case report and systematic review. *Clin Rheumatol* 2017; **36:** 2859-2867.

828.   Kello N, Khoury LE, Marder G, *et al.* Secondary thrombotic microangiopathy in systemic lupus erythematosus and antiphospholipid syndrome, the role of complement and use of eculizumab: Case series and review of literature. *Semin Arthritis Rheum* 2019; **49:** 74-83.

829.   Park MH, Caselman N, Ulmer S, *et al.* Complement-mediated thrombotic microangiopathy associated with lupus nephritis. *Blood Adv* 2018; **2:** 2090-2094.

830.   Caprioli J, Noris M, Brioschi S, *et al.* Genetics of HUS: the impact of MCP, CFH, and IF mutations on clinical presentation, response to treatment, and outcome. *Blood* 2006; **108:** 1267-1279.

831.   Loirat C, Sonsino E, Hinglais N, *et al.* Treatment of the childhood haemolytic uraemic syndrome with plasma. A multicentre randomized controlled trial. The French Society of Paediatric Nephrology. *Pediatr Nephrol* 1988; **2:** 279-285.

832.   Ariceta G, Besbas N, Johnson S, *et al.* Guideline for the investigation and initial therapy of diarrhea-negative hemolytic uremic syndrome. *Pediatr Nephrol* 2009; **24:** 687-696.

833.   Kaplan BS, Ruebner RL, Spinale JM, *et al.* Current treatment of atypical hemolytic uremic syndrome. *Intractable Rare Dis Res* 2014; **3:** 34-45.

834.   Reid VL, Mullan A, Erwig LP. Rapid recovery of membrane cofactor protein (MCP; CD46) associated atypical haemolytic uraemic syndrome with plasma exchange. *BMJ Case Rep* 2013; **2013**.

835.   Sengul Samanci N, Ayer M, Ergen A, *et al.* An effective treatment of atypical hemolytic uremic syndrome with plasma exchange and eculizumab: A case report. *Transfus Apher Sci* 2015; **52:** 314-316.

836.   Buyon JP, Kim MY, Guerra MM, *et al.* Kidney Outcomes and Risk Factors for Nephritis (Flare/De Novo) in a Multiethnic Cohort of Pregnant Patients with Lupus. *Clin J Am Soc Nephrol* 2017; **12:** 940-946.

837.   Clowse ME, Jamison M, Myers E, *et al.* A national study of the complications of lupus in pregnancy. *Am J Obstet Gynecol* 2008; **199:** 127 e121-126.

838.   Andreoli L, Bertsias GK, Agmon-Levin N, *et al.* EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. *Ann Rheum Dis* 2017; **76:** 476-485.

839.   Kroese SJ, de Hair MJH, Limper M, *et al.* Hydroxychloroquine Use in Lupus Patients during Pregnancy Is Associated with Longer Pregnancy Duration in Preterm Births. *J Immunol Res* 2017; **2017:** 2810202.

840.   Meher S, Duley L, Hunter K, *et al.* Antiplatelet therapy before or after 16 weeks' gestation for preventing preeclampsia: an individual participant data meta-analysis. *Am J Obstet Gynecol* 2017; **216:** 121-128 e122.

841.   Xu TT, Zhou F, Deng CY, *et al.* Low-Dose Aspirin for Preventing Preeclampsia and Its Complications: A Meta-Analysis. *J Clin Hypertens (Greenwich)* 2015; **17:** 567-573.

842.   Remmers EF, Plenge RM, Lee AT, *et al.* STAT4 and the risk of rheumatoid arthritis and systemic lupus erythematosus. *N Engl J Med* 2007; **357:** 977-986.

843.   Silva CA, Avcin T, Brunner HI. Taxonomy for systemic lupus erythematosus with onset before adulthood. *Arthritis Care Res (Hoboken)* 2012; **64:** 1787-1793.

844.   Wenderfer SE, Ruth NM, Brunner HI. Advances in the care of children with lupus nephritis. *Pediatr Res* 2017; **81:** 406-414.

845.   Chandar J, Gomez-Marin O, del Pozo R, *et al.* Role of routine urinalysis in asymptomatic pediatric patients. *Clin Pediatr (Phila)* 2005; **44:** 43-48.

846.   Sebestyen JF, Alon US. The teenager with asymptomatic proteinuria: think orthostatic first. *Clin Pediatr (Phila)* 2011; **50:** 179-182.

847.   Contreras G, Pagan J, Chokshi R, *et al.* Comparison of mortality of ESRD patients with lupus by initial dialysis modality. *Clin J Am Soc Nephrol* 2014; **9:** 1949-1956.

848.   Levy B, Couchoud C, Rougier JP, *et al.* Outcome of patients with systemic lupus erythematosus on chronic dialysis: an observational study of incident patients of the French National Registry 2002-2012. *Lupus* 2015; **24:** 1111-1121.

849.   Mejia-Vilet JM, Tejeda-Maldonado J, Correa-Rotter R. Comment on "Clinical Practice Guidelines for the Treatment of Systemic Lupus Erythematosus by the Mexican College of Rheumatology". *Reumatol Clin* 2018.

850.   O'Shaughnessy MM, Liu S, Montez-Rath ME, *et al.* Kidney Transplantation Outcomes across GN Subtypes in the United States. *J Am Soc Nephrol* 2017; **28:** 632-644.

851.   Park ES, Ahn SS, Jung SM, *et al.* Renal outcome after kidney-transplantation in Korean patients with lupus nephritis. *Lupus* 2018; **27:** 461-467.

852.   Jorge A, Wallace ZS, Lu N, *et al.* Renal Transplantation and Survival Among Patients With Lupus Nephritis: A Cohort Study. *Ann Intern Med* 2019; **170:** 240-247.

853.   Goldfarb-Rumyantzev A, Hurdle JF, Scandling J, *et al.* Duration of end-stage renal disease and kidney transplant outcome. *Nephrol Dial Transplant* 2005; **20:** 167-175.

854.   Plantinga LC, Patzer RE, Drenkard C, *et al.* Association of time to kidney transplantation with graft failure among U.S. patients with end-stage renal disease due to lupus nephritis. *Arthritis Care Res (Hoboken)* 2015; **67:** 571-581.

855.   Cheigh JS, Kim H, Stenzel KH, *et al.* Systemic lupus erythematosus in patients with end-stage renal disease: long-term follow-up on the prognosis of patients and the evolution of lupus activity. *Am J Kidney Dis* 1990; **16:** 189-195.

856.   Contreras G, Mattiazzi A, Guerra G, *et al.* Recurrence of lupus nephritis after kidney transplantation. *J Am Soc Nephrol* 2010; **21:** 1200-1207.

857.   Pham PT, Pham PC. Graft loss due to recurrent lupus nephritis in living-related kidney donation. *Clin J Am Soc Nephrol* 2011; **6:** 2296-2299.

858. Ponticelli C, Moroni G, Glassock RJ. Recurrence of secondary glomerular disease after renal transplantation. *Clin J Am Soc Nephrol* 2011; **6:** 1214-1221.

859. Bataille S, Burtey S, Decourt A*, et al.* [Antiphospholipids antibodies and hemodialysis: a frequent association linked to arteriovenous fistula thrombosis]. *Nephrol Ther* 2015; **11:** 27-33.

860. Morales JM, Serrano M, Martinez-Flores JA*, et al.* Antiphospholipid Syndrome and Renal Allograft Thrombosis. *Transplantation* 2019; **103:** 481-486.

861. Vaidya S, Gugliuzza K, Daller JA. Efficacy of anticoagulation therapy in end-stage renal disease patients with antiphospholipid antibody syndrome. *Transplantation* 2004; **77:** 1046-1049.

862. Wagenknecht DR, Fastenau DR, Torry RJ*, et al.* Risk of early renal allograft failure is increased for patients with antiphospholipid antibodies. *Transpl Int* 2000; **13 Suppl 1:** S78-81.

863. Jennette JC. Rapidly progressive crescentic glomerulonephritis. *Kidney Int* 2003; **63:** 1164-1177.

864. McAdoo SP, Pusey CD. Anti-Glomerular Basement Membrane Disease. *Clin J Am Soc Nephrol* 2017; **12:** 1162-1172.

865. Wilson CB, Dixon FJ. Anti-glomerular basement membrane antibody-induced glomerulonephritis. *Kidney Int* 1973; **3:** 74-89.

866. Savage CO, Pusey CD, Bowman C*, et al.* Antiglomerular basement membrane antibody mediated disease in the British Isles 1980-4. *Br Med J (Clin Res Ed)* 1986; **292:** 301-304.

867. Benoit FL, Rulon DB, Theil GB*, et al.* Goodpasture's Syndrome: A Clinicopathologic Entity. *Am J Med* 1964; **37:** 424-444.

868. McAdoo SP, Tanna A, Hruskova Z*, et al.* Patients double-seropositive for ANCA and anti-GBM antibodies have varied renal survival, frequency of relapse, and outcomes compared to single-seropositive patients. *Kidney Int* 2017; **92:** 693-702.

869. Salama AD, Dougan T, Levy JB*, et al.* Goodpasture's disease in the absence of circulating anti-glomerular basement membrane antibodies as detected by standard techniques. *Am J Kidney Dis* 2002; **39:** 1162-1167.

870. Marques C, Carvelli J, Biard L*, et al.* Prognostic Factors in Anti-glomerular Basement Membrane Disease: A Multicenter Study of 119 Patients. *Front Immunol* 2019; **10:** 1665.

871. van Daalen EE, Jennette JC, McAdoo SP*, et al.* Predicting Outcome in Patients with Anti-GBM Glomerulonephritis. *Clin J Am Soc Nephrol* 2018; **13:** 63-72.

872. Johnson JP, Moore J, Jr., Austin HA, 3rd*, et al.* Therapy of anti-glomerular basement membrane antibody disease: analysis of prognostic significance of clinical, pathologic and treatment factors. *Medicine (Baltimore)* 1985; **64:** 219-227.

873. Alchi B, Griffiths M, Sivalingam M*, et al.* Predictors of renal and patient outcomes in anti-GBM disease: clinicopathologic analysis of a two-centre cohort. *Nephrol Dial Transplant* 2015; **30:** 814-821.

874. Li FK, Tse KC, Lam MF, *et al.* Incidence and outcome of antiglomerular basement membrane disease in Chinese. *Nephrology (Carlton)* 2004; **9:** 100-104.

875. Donaghy M, Rees AJ. Cigarette smoking and lung haemorrhage in glomerulonephritis caused by autoantibodies to glomerular basement membrane. *Lancet* 1983; **2:** 1390-1393.

876. Lazor R, Bigay-Game L, Cottin V, *et al.* Alveolar hemorrhage in anti-basement membrane antibody disease: a series of 28 cases. *Medicine (Baltimore)* 2007; **86:** 181-193.

877. Lockwood CM, Boulton-Jones JM, Lowenthal RM, *et al.* Recovery from Goodpasture's syndrome after immunosuppressive treatment and plasmapheresis. *Br Med J* 1975; **2:** 252-254.

878. Flores JC, Taube D, Savage CO, *et al.* Clinical and immunological evolution of oligoanuric anti-GBM nephritis treated by haemodialysis. *Lancet* 1986; **1:** 5-8.

879. Levy JB, Turner AN, Rees AJ, *et al.* Long-term outcome of anti-glomerular basement membrane antibody disease treated with plasma exchange and immunosuppression. *Ann Intern Med* 2001; **134:** 1033-1042.

880. Kaplan AA, Appel GB, Pusey CE, *et al.*: Treatment of anti-GBM antibody (Goodpasture´s disease). In (vol 2020), UpToDate, UpToDate, 2017

881. Jefferson JA. Complications of Immunosuppression in Glomerular Disease. *Clin J Am Soc Nephrol* 2018; **13:** 1264-1275.

882. Schmaldienst S, Mullner M, Goldammer A, *et al.* Intravenous immunoglobulin application following immunoadsorption: benefit or risk in patients with autoimmune diseases? *Rheumatology (Oxford)* 2001; **40:** 513-521.

883. Borza DB, Chedid MF, Colon S, *et al.* Recurrent Goodpasture's disease secondary to a monoclonal IgA1-kappa antibody autoreactive with the alpha1/alpha2 chains of type IV collagen. *Am J Kidney Dis* 2005; **45:** 397-406.

884. Huart A, Josse AG, Chauveau D, *et al.* Outcomes of patients with Goodpasture syndrome: A nationwide cohort-based study from the French Society of Hemapheresis. *J Autoimmun* 2016; **73:** 24-29.

885. Levy JB, Lachmann RH, Pusey CD. Recurrent Goodpasture's disease. *Am J Kidney Dis* 1996; **27:** 573-578.

886. Mehler PS, Brunvand MW, Hutt MP, *et al.* Chronic recurrent Goodpasture's syndrome. *Am J Med* 1987; **82:** 833-835.

887. Gu B, Magil AB, Barbour SJ. Frequently relapsing anti-glomerular basement membrane antibody disease with changing clinical phenotype and antibody characteristics over time. *Clin Kidney J* 2016; **9:** 661-664.

888. Liu P, Waheed S, Boujelbane L, *et al.* Multiple recurrences of anti-glomerular basement membrane disease with variable antibody detection: can the laboratory be trusted? *Clin Kidney J* 2016; **9:** 657-660.

889. Touzot M, Poisson J, Faguer S, *et al.* Rituximab in anti-GBM disease: A retrospective study of 8 patients. *J Autoimmun* 2015; **60:** 74-79.

890.	Heitz M, Carron PL, Clavarino G*, et al.* Use of rituximab as an induction therapy in anti-glomerular basement-membrane disease. *BMC Nephrol* 2018; **19:** 241.

891.	Garcia-Canton C, Toledo A, Palomar R*, et al.* Goodpasture's syndrome treated with mycophenolate mofetil. *Nephrol Dial Transplant* 2000; **15:** 920-922.

892.	Kiykim AA, Horoz M, Gok E. Successful treatment of resistant antiglomerular basement membrane antibody positivity with mycophenolic acid. *Intern Med* 2010; **49:** 577-580.

893.	Mori M, Nwaogwugwu U, Akers GR*, et al.* Anti-glomerular basement membrane disease treated with mycophenolate mofetil, corticosteroids, and plasmapheresis. *Clin Nephrol* 2013; **80:** 67-71.

894.	Olivier M, Watson H, Lee D*, et al.* Monotypic IgG1-kappa Atypical Anti-Glomerular Basement Membrane Nephritis: A Case Report. *Case Rep Nephrol Dial* 2019; **9:** 8-14.

895.	Soveri I, Molne J, Uhlin F*, et al.* The IgG-degrading enzyme of Streptococcus pyogenes causes rapid clearance of anti-glomerular basement membrane antibodies in patients with refractory anti-glomerular basement membrane disease. *Kidney Int* 2019; **96:** 1234-1238.

896.	Biesenbach P, Kain R, Derfler K*, et al.* Long-term outcome of anti-glomerular basement membrane antibody disease treated with immunoadsorption. *PLoS One* 2014; **9:** e103568.

897.	Tang W, McDonald SP, Hawley CM*, et al.* Anti-glomerular basement membrane antibody disease is an uncommon cause of end-stage renal disease. *Kidney Int* 2013; **83:** 503-510.

898.	Choy BY, Chan TM, Lai KN. Recurrent glomerulonephritis after kidney transplantation. *Am J Transplant* 2006; **6:** 2535-2542.

899.	Kashtan CE. Renal transplantation in patients with Alport syndrome. *Pediatr Transplant* 2006; **10:** 651-657.

900.	Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. *Kidney Int Suppl.* 2012; **2:** 139–274

901.	Institute of Medicine Committee on Standards for Developing Trustworthy Clinical Practice Guidelines: Graham R, Mancher M, Miller Wolman D, Greenfield S*, et al.* (eds). *Clinical Practice Guidelines We Can Trust*: Washington (DC), 2011.

902.	Brouwers MC, Kho ME, Browman GP*, et al.* AGREE II: advancing guideline development, reporting and evaluation in health care. *J Clin Epidemiol* 2010; **63:** 1308-1311.

903.	*Cochrane Handbook for Systematic Reviews of Interventions*. John Wiley & Sons: Chichester UK, 2019.

904.	Guyatt GH, Oxman AD, Kunz R*, et al.* GRADE guidelines 6. Rating the quality of evidence--imprecision. *J Clin Epidemiol* 2011; **64:** 1283-1293.

905.	Higgins JP, Altman DG, Gotzsche PC*, et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343:** d5928.

906.   Guyatt GH, Oxman AD, Schunemann HJ, *et al.* GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. *J Clin Epidemiol* 2011; **64:** 380-382.

907.   Brunetti M, Shemilt I, Pregno S, *et al.* GRADE guidelines: 10. Considering resource use and rating the quality of economic evidence. *J Clin Epidemiol* 2013; **66:** 140-150.