KDIGO 2024 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF IMMUNOGLOBULIN A NEPHROPATHY (IgAN) AND IMMUNOGLOBULIN A VASCULITIS (IgAV)

PUBLIC REVIEW DRAFT
AUGUST 2024

This is a draft document shared for public review and feedback only. The content of this draft will change based on the feedback received, and should not be used for any other purpose beyond its original intent.

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SUPPLEMENTARY MATERIAL

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NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

Within each recommendation, the strength of recommendation is indicated as **Level 1** or **Level 2**, and the certainty 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	Certainty of evidence	Meaning
A	High	We are confident that the true effect is close to the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of the effect is very uncertain, and often it will be far from the true effect.

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CKD is <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.

KDIGO: Prognosis of CKD by GFR and albuminuria categories

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

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk.

GFR, glomerular filtration rate

CONVERSION FACTORS OF CONVENTIONAL UNITS TO SI UNITS

	Conventional unit	Conversion factor	SI Unit
Albumin	g/dl	10	g/l
Creatinine	mg/dl	88.4	µmol/l
Creatinine clearance	ml/min	0.01667	ml/s
Cyclosporine	ng/ml	0.832	nmol/l
Mycophenolic acid	µg/ml	3.12	µmol/l
PCR	mg/g	0.113	mg/mmol

PCR, protein-to-creatinine ratio; SI, International System of Units
Note: Conventional unit x conversion factor = SI unit

RELATIONSHIP AMONG CATEGORIES FOR ALBUMINURIA AND PROTEINURIA

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

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

ABBREVIATIONS AND ACRONYMS

ACEi	angiotensin-converting enzyme inhibitor(s)
ARB	angiotensin II receptor blocker
CI	confidence interval
CKD	chronic kidney disease
DAPA-CKD	Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease
DEARA	dual endothelin angiotensin receptor antagonism
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EMPA-KIDNEY	The Study of Heart and Kidney Protection With Empagliflozin
ERT	Evidence Review Team
FDA	Food and Drug Administration
gd-IgA1	galactose deficient IgA1
GFR	glomerular filtration rate
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IgAN	immunoglobulin A nephropathy
IgAV	immunoglobulin A vasculitis
IgAVN	IgAV-associated nephritis
KDIGO	Kidney Disease: Improving Global Outcomes
MCD	minimal change disease
MD	mean difference
MEST-C	mesangial [M] and endocapillary [E] hypercellularity, segmental sclerosis [S], interstitial fibrosis/tubular atrophy [T], and crescents [C]
NefIgArd	Efficacy and Safety of Nefecon in Patients With Primary IgA Nephropathy
PCR	protein-to-creatinine ratio
PICOD	population, intervention, comparator, outcomes, study design
PROTECT	A Study of the Effect and Safety of Sparsentan in the Treatment of Patients With IgA Nephropathy
RAS	renin-angiotensin system
RASi	renin-angiotensin system inhibitor
RCT	randomized controlled trial
RPGN	rapidly progressive glomerulonephritis
RR	risk ratio
SAE	serious adverse events
SCr	serum creatinine
SGLT2i	sodium-glucose cotransporter-2 inhibition/inhibitors
STOP-IgA	The Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy
TA-P	time-averaged proteinuria
TEAE	treatment emergent adverse events
TESTING	Therapeutic Effects of Steroids in IgA Nephropathy Global
WHO	World Health Organization

NOTICE

SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINE

This Clinical Practice Guideline document is based upon literature searches last conducted in July 2022 and updated in April 2023. It is designed to assist decision-making. It is not intended to define a standard of care and should not be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians consider the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Healthcare professionals using these recommendations should decide how to apply them to their own clinical practice.

SECTION II: DISCLOSURE

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.

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ABSTRACT

The Kidney Disease: Improving Global Outcomes (KDIGO) 2024 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV) represents a focused update of Chapter 2: Immunoglobulin A nephropathy (IgAN)/immunoglobulin A vasculitis (IgAV) from the KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. The aim is to assist clinicians caring for people with IgAN or IgAV. The update takes into consideration evidence from randomized controlled trials published through April 2023. As in 2021, this guideline provides guidance related to diagnosis, prognosis, treatment, and special situations. Based on the new evidence, this update is mostly related to the guidance relevant to IgAN. Development of this guideline 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 certainty of the evidence and the strength of recommendations following the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) approach. Limitations of the evidence are discussed and areas of future research are also presented.

Keywords: evidence-based; glomerular diseases; guideline; KDIGO; IgAN; IgAV; systematic review

SUMMARY OF RECOMMENDATION STATEMENTS AND PRACTICE POINTS

IMMUNOGLOBULIN A NEPHROPATHY

2.1 Diagnosis

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

- **IgAN can only be diagnosed with a kidney biopsy, as there are no validated diagnostic serum or urine biomarkers for IgAN.**
- **To ensure an early diagnosis and prompt treatment of IgAN, a kidney biopsy should be performed in all adults with proteinuria ≥0.5 g/d (or equivalent) in whom IgAN is a possible diagnosis and who do not have a contraindication for kidney biopsy.**
- **Once a diagnosis of IgAN is made, assess for secondary causes.**
- **In cases of primary IgAN, determine the MEST-C score (mesangial [M] and endocapillary [E] hypercellularity, segmental sclerosis [S], interstitial fibrosis/tubular atrophy [T], and crescents [C]) according to the revised Oxford Classification.**[80]

2.2 Prognosis

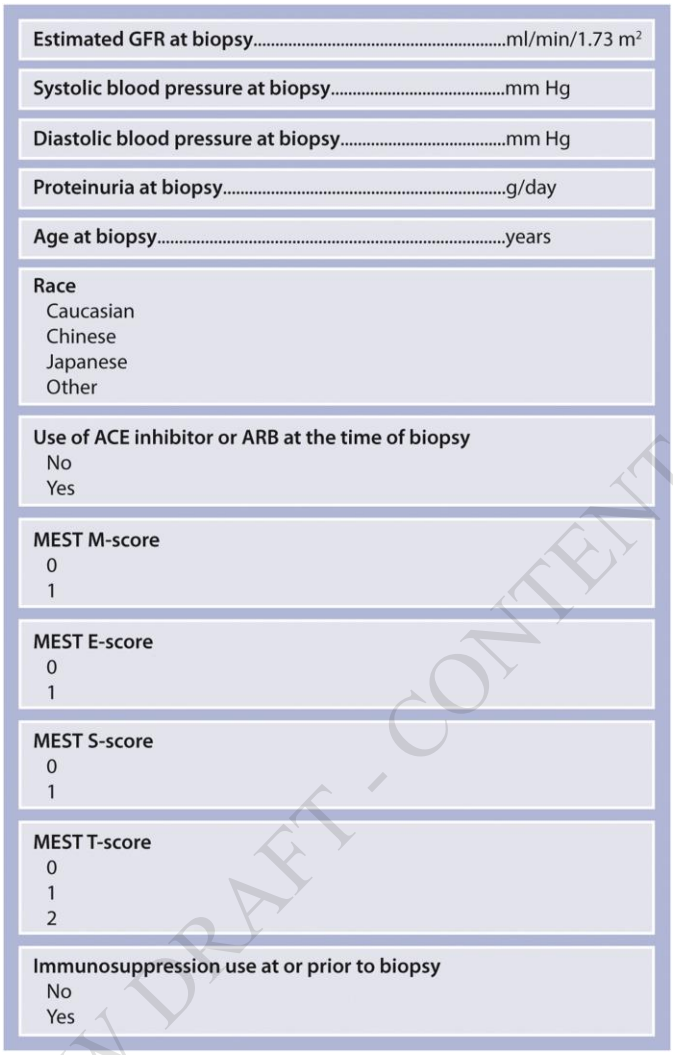

Figure 1 | The data elements included in the International Immunoglobulin A Nephropathy (IgAN) Prediction Tools. Using clinical and histologic data at the time of kidney biopsy, or up to 2 years post kidney biopsy, users can calculate the risk of a 50% decline in eGFR or kidney failure up to 7 years from kidney biopsy in adults and children. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; GFR, glomerular filtration rate; MEST, mesangial (M) and endocapillary (E) hypercellularity, segmental sclerosis (S), and interstitial fibrosis/tubular atrophy (T).

Practice Point 2.2.1: Considerations regarding the prognosis of primary IgAN:

- **Clinical and histologic data at the time of kidney biopsy can be used to risk stratify patients.**
- **The International IgAN Prediction Tools are a valuable resource to quantify short term (up to 7 years from kidney biopsy) risk of progression and inform shared decision-making with patients.**
  - ***International IgAN Prediction Tool at biopsy - Adults***
  - ***International IgAN Prediction Tool post-biopsy - Adults***
  - ***International IgAN Prediction Tool at biopsy - Pediatrics***
  - ***International IgAN Prediction Tool post-biopsy – Pediatric***
- **The International IgAN Prediction Tools incorporate clinical information at the time of kidney biopsy or at 1 or 2 years post-biopsy (Figure 1).**
- **There are no validated prognostic serum or urine biomarkers for IgAN other than estimated glomerular filtration rate (eGFR) and proteinuria.**

Practice Point 2.2.2: The initial assessment of the patient with IgAN (Figure 2)

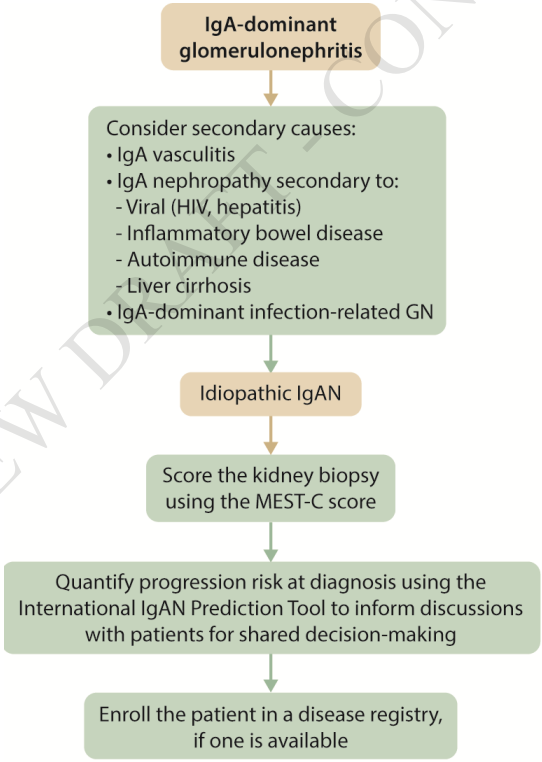

Figure 2 | Initial assessment and management of the patient with immunoglobulin A nephropathy (IgAN). GN, glomerulonephritis; HIV, human immunodeficiency virus; Ignaz, immunoglobulin A nephropathy; MEST-C, mesangial (M) and endocapillary (E) hypercellularity, segmental sclerosis (S), interstitial fibrosis/tubular atrophy (T), and crescents (C).

2.3 Treatment

2.3.1 Defining patients with IgAN at risk of progressive loss of kidney function requiring treatment

Practice Point 2.3.1.1: A patient with IgAN is at risk of progressive loss of kidney function if they have proteinuria ≥0.5 g/d (or equivalent), while on or off treatment for IgAN, and treatment/additional treatment should be started in all cases.

2.3.2 Defining a treatment goal in patients with IgAN at risk of progressive loss of kidney function

Practice Point 2.3.2.1: The treatment goal in patients with IgAN at risk of progressive loss of kidney function is to reduce the rate of loss of kidney function to <1 ml/min per year for the rest of the patient's life. The only validated early biomarker to help guide clinical decision-making is urine protein excretion, which should be maintained at <0.5 g/d (or equivalent), preferably <0.3 g/d (or equivalent), accepting that in some patients with extensive kidney scarring this may not be possible and that multiple drugs are likely to be needed to achieve this.

Practice Point 2.3.2.2: Treatment of patients with IgAN who are at risk of progressive kidney function decline and do not have a variant form of primary IgAN (Figure 3):

- **The focus of management in most patients should be to *simultaneously*:**
  - **Prevent or reduce IgA immune complex formation and immune complex-mediated glomerular injury.**
  - **In parallel, manage the consequences of existing IgAN-induced nephron loss.**
- **Reduction or prevention of IgA immune complex formation should incorporate treatments that have been proven to reduce pathogenic forms of IgA (commonly measured as galactose deficient IgA1 [gd-IgA1]).**
- **Prevention of immune complex-mediated injury should incorporate treatments with proven anti-inflammatory effects, and ideally should be used in combination with, and not as a replacement for, treatments that prevent or reduce IgA immune complex formation.**
- **Management of the consequences of IgAN-induced nephron loss should include:**
  - **Lifestyle advice, including information on dietary sodium restriction, smoking cessation, weight control, and exercise, as appropriate,**
  - **Control of blood pressure with a target of ≤120/70 mm Hg,**
  - **Measures to reduce glomerular hyperfiltration and the impact of proteinuria on the tubulointerstitium, using singly or in combination, renin-angiotensin system (RAS) blockade or dual endothelin angiotensin receptor antagonism (DEARA), and sodium-glucose cotransporter-2 inhibition (SGLT2i), and**
  - **A thorough cardiovascular risk assessment and commencement of appropriate interventions, as necessary.**

- **The key factors to consider when making treatment choices are summarized in Tables 1 and 2.**
- **Issues related to accessibility and affordability of newly approved treatments for IgAN, alongside the requirement for continual or cyclical dosing, mean that it is unlikely that these treatments will be used in resource-limited settings, where cheaper and more easily resourced drugs will be used.**
- **In all patients in whom treatments that target the production of pathogenic forms of IgA or glomerular inflammation are being considered, a detailed discussion of the risks and benefits of each drug should be undertaken.**
- **There is insufficient evidence to support the use of the Oxford Classification MEST-C score in determining which drug should be commenced in IgAN.**
- **There is insufficient evidence to base treatment decisions on the presence and number of crescents in the kidney biopsy alone. Histopathological features must be interpreted in the context of clinical features, in particular, the rate of change of eGFR.**
- **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 the relative merits of different treatments may change.**

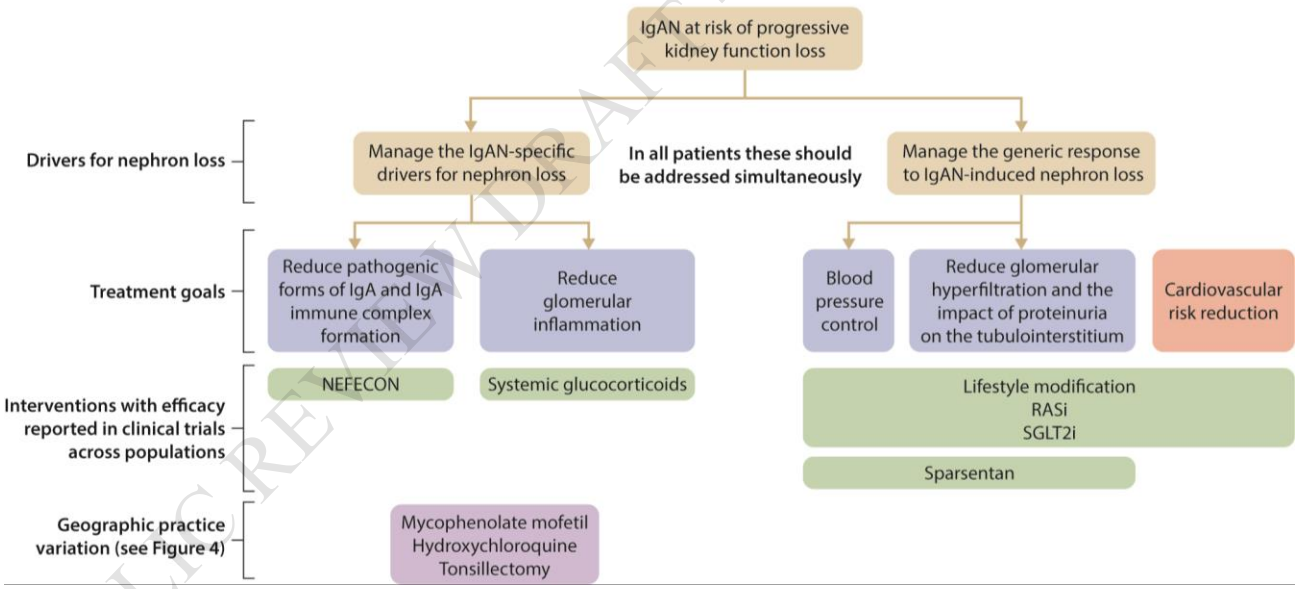

Figure 3 | Treatment targets in immunoglobulin A nephropathy (IgAN) and available to-date approved treatment options. *Measures to reduce glomerular hyperfiltration and the impact of proteinuria on the tubulointerstitium, using singly or in combination, renin-angiotensin system (RAS) blockade sparsentan, and sodium-glucose cotransporter-2 inhibition (SGLT2i). RASi, renin-angiotensin system inhibitors.

Table 1 | Factors to consider when choosing a treatment and or treatment combinations for patients with immunoglobulin A nephropathy (IgAN) at risk of progressive kidney function loss

Questions	Considerations
Is the clinical trial population in which the drug was tested representative of the patient being treated (Table 2)?	**Age:** In the trials of SGLT2i, patients were on average 6-8 years older than those recruited into the NefIgArd and PROTECT trials and 15-17 years older than those recruited to the STOP-IgAN and TESTING study.
	Race: The TESTING study was almost exclusively conducted in Asian patients, STOP-IgAN was exclusively in Caucasians, in the NefIgArd and PROTECT studies Asian patients were relatively under-represented compared to trials of SGLT2i and systemic glucocorticoids.
	eGFR: In the trials of SGLT2i the average eGFR at inclusion was 12–14 ml/min lower than that of patients included in the NefIgArd, PROTECT, STOP-IgAN and TESTING studies.
	Concomitant medications: In all recent studies in IgAN, patients were required to be on a RASi prior to enrolment, requirements for optimized maximally tolerated dosing was not required in the trials of SGLT2i.
	Optimization of RAS blockade: The only trial to formally uptitrate RASi was the PROTECT trial, in the NefIgArd and TESTING studies participants were required to be on local physician attested optimized maximally tolerated RASi.
What is the labelled indication for the drug?	With the new approval pathway for drugs in IgAN the labelled indication may vary dependent upon the country and whether the drug has an accelerated approval/conditional market authorization, where assessment of efficacy has been made on the basis of proteinuria, or a full approval, based on its effect on rate of loss of kidney function.
What are the key advantages of available treatment options?	Nefecon is the only treatment to date proven to reduce the levels of pathogenic forms of IgA and IgA immune complexes
	Systemic glucocorticoids are highly effective anti-inflammatory drugs but have no proven impact on levels of pathogenic forms of IgA or IgA immune complexes at the doses recommended in this guideline.
	SGLT2i have been shown to not only reduce the rate of progression of kidney function loss but also reduce the incidence of adverse cardiovascular events, particularly in people with diabetes. They are also generally well tolerated.
	The DEARA, sparsentan, is the only drug to have shown efficacy beyond in-trial uptitrated RASi. Of note, more patients were included in the PROTECT trial than in all the trials of RASi in IgAN combined.
	RASi effectively reduce proteinuria and have an extensive efficacy and safety data in CKD and cardiovascular disease.
What are the key risks of available treatment options?	As there is some systemic absorption of budesonide patients and clinicians should be aware of the possibility of some systemic glucocorticoid related side effects with nefecon, these are usually mild and reversible on treatment cessation.
	When using systemic glucocorticoids, a reduced-dose protocol should be followed, antimicrobial prophylaxis against *Pneumocystis jirovecii* and anti-viral prophylaxis in hepatitis B carriers should be used, and the patient should be made aware of the risks of gastrointestinal bleeding, infection,

	metabolic, cosmetic, and neuropsychiatric side effects, alongside the potential impact on bone health.
	As with all endothelin receptor antagonists, there is a significant risk of embryofetal toxicity, and females of child-bearing potential must use a reliable form of contraception and undergo monthly pregnancy testing.

GI, gastrointestinal; NefIgArd, Efficacy and Safety of Nefecon in Patients With Primary IgA Nephropathy; PROTECT, A Study of the Effect and Safety of Sparsentan in the Treatment of Patients With IgA Nephropathy; RAS, renin-angiotensin system; RASi, renin-angiotensin system inhibitor(s); SGLT2i, sodium-glucose cotransporter-2 inhibitor(s); STOP-IgAN, The Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy; TESTING, Therapeutic Effects of Steroids in IgA Nephropathy Global.

Table 2 | Baseline characteristics and key inclusion criteria for recently reported trials in immunoglobulin A nephropathy (IgAN) and including significant numbers of patients with IgAN

Characteristic	DAPA-CKD		EMPA-KIDNEY	NefIgArd		PROTECT		STOP-IgAN		TESTING	
	Dapagliflozin (n = 137)	Placebo (n=133)	Empagliflozin (n = 817)	Nefecon (n=182)	Placebo (n=182)	Sparsentan (n=202)	Placebo (n=202)	Supportive care (n=80)	Immunosuppression (n=82)	Methylprednisolone (n=257)	Placebo (n=246)
Age inclusion criteria	≥18 years		≥18 years	≥18 years		≥18 years		≥18 years		≥18 years	
Age, mean (SD), yr	52.2 (13.1)	50.1 (13.1)	50.6 (12.7)	43 (36–50)	42 (34–49)	46.6 (12.8)	45.4 (12.1)	45.8 (12.5)	42.8 (13.1)	35.6 (29.4–46.3)	36.6 (29.0–45.9)
Female sex, n (%)	44 (32.1)	44 (33.1)	282 (34.5)	65 (36)	59 (32)	63 (31)	59 (29)	15 (19)	19 (24)	102 (40)	96 (39)
Race, n (%)											
• White	54 (39.4)	54 (40.6)	361 (44.2)	138 (76)	137 (75)	130 (64)	142 (70)	80 (100)	82 (100)	13 (5)	12 (5)
• Black	0 (0)	1 (0.8)	1 (0.1)	0 (0)	0(0)	1 (<1)	3 (1)	0	0	0 (0)	0 (0)
• Asian	82 (59.9)	77 (57.9)	442 (54.1)	43 (24)	40 (22)	67 (33)	48 (24)	0	0	244 (95)	233 (95)
• Other	1 (0.7)	1 (0.8)	13 (1.6)	1 (1)	5 (3)	4 (2)	10 (5)	0	0	0 (0)	1 (<1)
BMI, mean (SD), kg/m^2	26.3 (4.2)	27.6 (6.1)	26.8 (5.5)	N/A	N/A	N/A	N/A	28.6 (5.3)	27.0 (5.0)	Median: 24.2 (IQR: 21.6–26.7)	Median: 24.7 (IQR: 22.0–28.0)
Blood pressure, mean (SD), mm Hg											
• Systolic	127.7 (16.2)	127.0 (13.9)	131.8 (15.1)	126 (121–132)	124 (117–130)	128.0 (14.4)	129.9 (12.4)	127 (8.5)	124 (9.7)	Median: 123.8 (IQR: 115.0–132.5)	Median: 125.0 (IQR: 115.5–131.0)
• Diastolic	78.7 (11.8)	79.5 (10.1)	82.5 (10.4)	79 (76–84)	79 (74–84)	81.6 (10.6)	83.2 (10.6)	78 (7.0)	77 (7.0)	Median: 80.0 (IQR: 73.5–85.0)	Median: 80.0 (IQR: 74.0–86.0)
eGFR inclusion criteria, ml/min per 1.73 m^2	25–75		≥20 to <45, OR ≥45 to <90 & ACR ≥200 mg/g or PCR ≥300 mg/g	≥35 and ≤90		≥30		30-90		≥30 and ≤120	
eGFR, mean (SD), ml/min per 1.73 m^2	44.3 (12.4)	43.2 (12.0)	43.3 (17.5)	Median: 56.14 (IQR: 45.50-70.97)	Median: 55.11 (IQR: 45.96-67.74)	56.8 (24.3)	57.1 (23.6)	57.4 (24.9)	61.1 (29.0)	Median: 56.1 (IQR: 43.2–75.0)	Median: 59.0 (IQR: 42.0–77.6)
Urinary ACR ratio inclusion criteria	200-5000		See eGFR criteria	N/A		N/A		N/A	N/A	N/A	
Urinary ACR, median (Q1–Q3), mg/g	889.5 (557.5–1472.0)	902.5 (500.5-1633.0)	662 (331–1265)	990 (680-1400)	980 (660-1420)	N/A	N/A	N/A	N/A	N/A	N/A
Urinary protein excretion inclusion criteria	N/A		See eGFR criteria	≥1 g/d		≥1 g/d		>0.75 g/d		≥1 g/d	
Urinary protein excretion, median (Q1-Q3), g/24h	N/A	N/A	N/A	2.29 (1.61-3.14)	2.17 (1.53-3.39)	1.8 (1.2-2.9)	1.8 (1.3-2.6)	1.6 (0.7)	1.8 (0.8)	1.99 (1.36–3.09)	1.93 (1.38–2.88)
Type 2 diabetes diagnosis, n (%)	24 (17.5)	14 (10.5)	58 (7.1)	16 (9)	8 (4)	N/A	N/A	0	0	7 (3)	10 (4)
Baseline medication, n (%)											
• ACEi	44 (32.1)	41 (30.8)	770 (94.2)	179 (98)	179 (98)	202 (100)	202 (100)	27 (34)	40 (49)	140 (54.5)	128 (52.0)
• ARB	89 (65.0)	96 (72.2)						24 (30)	12 (15)	119 (46.3)	120 (48.8)
• ACEi + ARB	--	--	--	--	--	--	--	26 (32)	30 (36)		

Levels of RASi as a percentage of maximum allowable dose at screening, n (%)											
• <50%	N/A	N/A	N/A	39 (22%)	34 (19%)	0	0	N/A	N/A	30 (11.7)	35 (14.2)
• >50%	N/A	N/A	N/A	141 (78%)	145 (81%)	202 (100%)	202 (100%)	N/A	N/A	222 (86.4)	201 (81.7)
• 100%	N/A	N/A	N/A	N/A	N/A	130 (64%)	125 (62%)	61 (76)	58 (71)	N/A	N/A
• Immunosuppression	0 (0)	0 (0)	53 (6.5)	0 (0)	0 (0)	0 (0)	0 (0)	0	0	0 (0)	0 (0)

ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; BMI, body mass index; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; eGFR, estimated glomerular filtration rate; EMPA-KIDNEY, The Study of Heart and Kidney Protection With Empagliflozin; NefIgArd, Efficacy and Safety of Nefecon in Patients With Primary IgA Nephropathy; PCR, protein-to-creatinine ratio; PROTECT, A Study of the Effect and Safety of Sparsentan in the Treatment of Patients With IgA Nephropathy; Q1, quartile 1; Q3, quartile 3; RASi, renin-angiotensin system inhibitor; SD standard deviation; STOP-IgAN, The Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy; TESTING, Therapeutic Effects of Steroids in IgA Nephropathy Global.

2.3.3 Managing the IgAN-specific drivers for nephron loss

2.3.3.1 Reducing the production of pathogenic forms of IgA and IgA immune complex formation

Recommendation 2.3.3.1.1: We suggest treatment with a 9-month course of nefecon for patients who are at risk of progressive kidney function loss with IgAN *(2B)*.

Practice Point 2.3.3.1.1: Factors to consider before using nefecon in patients with IgAN

- **A single 9-month treatment course of nefecon is unlikely to produce a sustained clinical response in terms of proteinuria reduction or stabilization of eGFR and it is likely that many patients will need either repeated 9-month treatment cycles or a reduced-dose maintenance regimen**
- **The approval status, labelled indication and availability vary globally.**

Practice Point 2.3.3.1.2: Other pharmacologic therapies evaluated in IgAN:

- **Multiple agents have been evaluated in often small studies, in restricted populations and have failed to show a consistent benefit in IgAN (Figure 4)**

Agent	Suggested usage	Remarks
Antiplatelet agents	Not recommended	No evidence of efficacy
Anticoagulants	Not recommended	No evidence of efficacy
Azathioprine	Not recommended	No evidence for efficacy as monotherapy or when combined wit glucocorticoids
Cyclophosphamide	Not recommended	Unless in the setting of rapidly progressive IgAN
Calcineurin inhibitors	Not recommended	No evidence of efficacy
Rituximab	Not recommended	No evidence of efficacy
Fish oil	Not recommended	Patients who wish to take fish oil should be advised of the dose and formulation used in the published clinical trials that reported efficacy.
Mycophenolate mofetil (MMF)	**Chinese patients** In those patients in whom glucocorticoids are being considered MMF may be used as a glucocorticoid-sparing agent	Three RCTs have been conducted in China: the first from Hong Kong (n=40, eGFR ~51 ml/min/1.73 m²) showed a significant reduction in time-averaged proteinuria after MMF (1.5 to 2.0 g/day for 6 months) was added to SC in patients with proteinuria >1 g/d.[1] An extended 6-year follow-up showed a lesser slope of eGFR decline and lower probability of reaching kidney failure in MMF-treated patients;[2] the second from around Jiangsu (n=176, eGFR >90 ml/min/1.73 m²) showed that MMF with low-dose glucocorticoids (0.4–0.6 mg/kg/d prednisone) for 6 months was non-inferior to standard-dose glucocorticoids (0.8–1.0 mg/kg/d) for the treatment of incident IgAN presenting with proliferative histologic lesions (E or C lesions with or without necrosis) on kidney biopsy and proteinuria >1.0 g/d.[3] There were significantly fewer glucocorticoid-related side-effects in the combination-therapy arm; the third from Guangdong (n=170, eGFR 50 ml/min/1.73 m²) showed that MMF (initially, 1.5 g/d for 12 months, maintained at 0.75–1.0 g/d for at least 6 months) and SC reduced the frequency of the primary composite outcome (doubling of serum creatinine, kidney failure, or death due to kidney or cardiovascular causes, aHR 0.23; 95% CI, 0.09–0.63) and CKD progression (aHR 0.23; 95% CI, 0.1–0.57) compared to SC alone.[4] MMF was well tolerated in all the 3 trials.
	Non-Chinese patients There is insufficient evidence to support the use of MMF	In three smaller RCTs of MMF in non-Chinese patients there was no evidence for efficacy of MMF monotherapy: these were from Belgium (n=34, inulin clearance ~71 ml/min/1.73 m²),[5] New York (n=32, eGFR ~39 ml/min/1.73 m² and required glomerulosclerosis or tubulointerstitial atrophy and fibrosis on kidney biopsy reflecting relatively advanced CKD already)[6] and US/Canada (n=44, eGFR >90 ml/min/1.73 m², MMF versus omega-3 fatty acid).[7]
Hydroxychloroquine	**Chinese patients** In those patients who remain at high risk of progression in spite of optimized supportive care	In a small, short-term RCT conducted in China, hydroxychloroquine introduced to patients with proteinuria of 0.75–3.5 g/d despite optimized ACEi/ARB reduced proteinuria by 48% versus 10% in the placebo group at 6 months.[(6)]
	Non-Chinese patients There is insufficient evidence to support the use in those patients	Hydroxychloroquine has not been evaluated in non-Chinese patients.

Figure 4 | Other pharmacologic therapies evaluated in immunoglobulin A nephropathy (IgAN). [1]Tang *et al.*[28], [2]Tang *et al.*[29], [3]Hou *et al.*[30], [4]Hou *et al.* [31], [5]Maes *et al.*,[32] [6]Frisch *et al*,.[33] [7]Hogg *et al.*,[34] [8]Liu *et al.*[35], ACEi, angiotensin-converting enzyme inhibitor; aHR, adjusted hazard ratio; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; CI, confidence interval; IgAN, immunoglobulin A nephropathy; KRT, kidney replacement therapy; MMF, mycophenolate mofetil; RCT, randomized controlled trial; SC, standard of care; SCr, serum creatinine.

Practice Point 2.3.3.1.3: Tonsillectomy in IgAN:

- **Tonsillectomy alone or with pulsed glucocorticoids may improve kidney survival and partial or complete remission of hematuria and proteinuria, based on multiple, mostly retrospective studies from Japan (Supplementary Table S5[36-40]).[36-38, 40-42]**
- **Tonsillectomy is recommended in the Japanese Society of Nephrology Guidelines for the treatment of patients with IgAN.**
- **Tonsillectomy should not be performed as a treatment for IgAN in non-Japanese patients.**

2.3.1.2 Managing glomerular inflammation

Recommendation 2.3.1.2.1: In settings where nefecon is not available, we suggest that patients who are at risk of progressive kidney function loss with IgAN be treated with a limited course of a reduced-dose systemic glucocorticoid regimen combined with antimicrobial prophylaxis after a thorough toxicity risk assessment *(2B)*.

Practice Point 2.3.1.2.1: Reduced-dose systemic glucocorticoid regimen:

- **Methylprednisolone (or equivalent) 0.4 mg/kg per day (maximum: 32 mg/d) for 2 months followed by dose tapering by 4 mg/d each month for a total of 6–9 months.**
- **The conversion of methylprednisolone to commonly used forms of systemic glucocorticoids is: 1 mg methylprednisolone equals 1.3 mg of prednisone or prednisolone.**
- **Treatment with systemic glucocorticoids should incorporate antimicrobial prophylaxis against *Pneumocystis jirovecii* and anti-viral prophylaxis in hepatitis B carriers , along with gastroprotection and bone protection according to local guidelines.**

Practice Point 2.3.1.2.2: Factors to consider before using systemic glucocorticoids in IgAN:

- **Systemic glucocorticoids are effective anti-inflammatory drugs, but there is no evidence at the doses recommended in this guideline that they reduce the formation of pathogenic forms of IgA or immune complexes at the recommended doses.**
- **The dose and duration of systemic glucocorticoid treatment required to manage glomerular inflammation when used in combination with a therapy to reduce pathogenic forms of IgA is not known but should not exceed, and is likely to be much less than, the reduced-dose scheme for systemic glucocorticoids for active lupus nephritis, suggested in Practice Point 10.2.3.1.1 of the KDIGO 2024 Clinical Practice Guideline For The Management Of Lupus Nephritis.[45]**
- **The following patient characteristics are likely to increase the risks of systemic glucocorticoid related toxicity:**
  - **eGFR <30 ml/min per 1.73 m^2,**
  - **Diabetes and prediabetes,**
  - **Obesity,**
  - **Latent infections (e.g., viral hepatitis, tuberculosis),**
  - **Active peptic ulceration,**

- **Uncontrolled psychiatric illness,**
- **Osteoporosis, and**
- **Cataracts.**

- **There is insufficient evidence to support the use of the Oxford Classification MEST-C score in determining when systemic glucocorticoids should be commenced.**
- **There are no data to support efficacy or reduced toxicity of alternate-day systemic glucocorticoid regimens.**

2.3.4 Managing the responses to IgAN-induced nephron loss

Practice Point 2.3.4.1: Interventions for all patients with IgAN:

- **Control blood pressure to a target of ≤120/70 mm Hg, using a RASi as the first choice drug intervention**
- **Lifestyle advice should be given, where appropriate, on smoking cessation, weight reduction, dietary sodium restriction (<2 g/d) and regular exercise.**
- **A cardiovascular risk assessment should be undertaken and interventions commenced as per local guidelines.**

Recommendation 2.3.4.1: We recommend all patients who are at risk of progressive kidney function loss with IgAN be treated with an optimized maximally tolerated dose of either an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) *(1B)*.

Recommendation 2.3.4.2: We suggest that patients who are at risk of progressive kidney function loss with IgAN be treated with a sodium-glucose cotransporter-2 inhibitor (SGLT2i) *(2B)*.

Practice Point 2.3.4.2: Factors to consider before using an SGLT2i in patients with IgAN:

- **There was no requirement for patients with IgAN to be on an optimized maximally tolerated dose of RASi for a minimum of 3 months for inclusion in The Study of Heart and Kidney Protection With Empagliflozin (EMPA-KIDNEY) and Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trials.**
- **IgAN patients included in EMPA-KIDNEY and DAPA-CKD likely had longstanding disease, based on the age and eGFR at randomization; therefore, there is uncertainty over the value of SGLT2i in patients with IgAN and a relatively preserved eGFR (>60 ml/min per 1.73 m^2) (see Table 2).**

Recommendation 2.3.4.3: We suggest that patients who are at risk of progressive kidney function loss with IgAN be treated with sparsentan *(2B)*.

Practice Point 2.3.4.3: Factors to consider before using sparsentan in patients with IgAN

- **Sparsentan is a dual endothelin angiotensin receptor antagonist (DEARA) and should not be prescribed together with a RASi.**

- **The approval status, labelled indication and availability vary globally.**

2.4 Special situations

Practice Point 2.4.1: IgAN with nephrotic syndrome:

- **Rarely, patients with IgAN present with nephrotic syndrome (including edema and both hypoalbuminemia and nephrotic-range proteinuria >3.5 g/d).**
- **In these cases, mesangial IgA deposition can be associated with light and electron microscopy features otherwise consistent with a podocytopathy resembling minimal change disease (MCD).**
- **It is unclear whether this is a specific podocytopathic variant of IgAN or the existence of MCD in a patient with IgAN.**
- **Patients with a kidney biopsy demonstrating mesangial IgA deposition and light and electron microscopy features otherwise consistent with MCD should be treated in accordance with the guidelines for MCD in Chapter 5 of the KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases.[12]**
- **Peoples with nephrotic syndrome whose kidney biopsy has coexistent features of a mesangioproliferative glomerulonephritis (MPGN) should be managed in the same way as those patients who are at risk of progressive kidney function loss from IgAN.**
- **Nephrotic-range proteinuria without nephrotic syndrome may also be seen in IgAN, and this commonly reflects coexistent secondary focal segmental glomerulosclerosis (FSGS) (e.g., obesity, uncontrolled hypertension) or development of extensive glomerulosclerosis and tubulointerstitial fibrosis.**

Practice Point 2.4.2: IgAN with AKI:

- **AKI can occur in people with IgAN in the context of severe visible hematuria, commonly in association with an upper respiratory tract infection. A repeat kidney biopsy should be considered in patients who fail to show improvement in kidney function within 2 weeks following cessation of the hematuria. Immediate management of AKI with visible hematuria should focus on supportive care for AKI.**
- **IgAN may also present with AKI either *de novo* or during its natural history due to a rapidly progressive glomerulonephritis (RPGN), often with extensive crescent formation, commonly in the absence of visible hematuria. In the absence of visible hematuria and when other causes of an RPGN (e.g., antineutrophil cytoplasmic antibody [ANCA]-associated vasculitis [AAV], anti-glomerular basement membrane [GBM] disease) and reversible causes (e.g., drug toxicity, common pre- and post-kidney causes) have been excluded, a kidney biopsy should be performed as soon as possible.**

Practice Point 2.4.3: IgAN with RPGN:

- **Rapidly progressive IgAN is defined as a ≥50% decline in eGFR over ≤3 months, where other causes of an RPGN (e.g., AAV, anti-GBM disease) and reversible**

causes (e.g., drug toxicity, common pre- and post-kidney causes) have been excluded.

- **A kidney biopsy is essential in these cases and will commonly demonstrate mesangial and endocapillary hypercellularity, and a high proportion of glomeruli affected by crescents with areas of focal necrosis.**
- **The presence of crescents in a kidney biopsy in the absence of a concomitant change in serum creatinine (SCr) does not constitute rapidly progressive IgAN; however, these patients require close follow-up to ensure prompt detection of any glomerular filtration rate (GFR) decline. If this occurs, a second kidney biopsy may be considered.**
- **Patients with rapidly progressive IgAN should be offered treatment with cyclophosphamide and systemic glucocorticoids in accordance with the KDIGO 2024 Clinical Practice Guideline for the Management of ANCA-Associated Vasculitis.[44]**
- **Prophylactic measures that should accompany immunosuppression are discussed in Chapter 1 of the KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases.[12]**
- **There is insufficient evidence to support the use of rituximab for the treatment of rapidly progressive IgAN.**

Practice Point 2.4.4: IgAN and pregnancy planning:

- **IgAN is a disease predominantly of young adults, and all women of childbearing potential should be offered preconception counselling when appropriate.**
- **Preconception counselling should include a discussion on cessation of RASi, SGLT2i, sparsentan, and nefecon. Blood pressure control should be optimized with alternative antihypertensive medications prior to conception.**
- **In those women at risk of progressive loss of kidney function, a trial of treatments to optimally suppress production of pathogenic forms of IgA and IgA immune complexes and glomerular inflammation prior to conception may be preferable to initiation of these treatments during pregnancy.**
- **RASi, SGLT2i, and sparsentan must not be used during pregnancy and breastfeeding.**
- **The evidence to date suggests that first trimester systemic glucocorticoid use may confer a small increase in the odds of cleft lip with or without cleft palate, although data are conflicting and it is unknown to what extent the underlying maternal disease may contribute. Systemic glucocorticoid use in pregnancy does not increase the risks of preterm birth, low birth weight, or preeclampsia.**
- **The use of nefecon in pregnancy is not advised, however, studies examining the use of budesonide by pregnant women with inflammatory bowel disease have not identified any harmful effects. Budesonide has a Food and Drug Administration (FDA) Pregnancy Category C Risk designation, so risk cannot be ruled out.**

Practice Point 2.4.5: IgAN in children:

General considerations for children with IgAN

- **A more extensive review of the management of IgAN in children can be found in the 2024 International Pediatric Nephrology Association Guidelines for the Management of IgA nephropathy and IgA vasculitis (submitted)**
- **In this guideline, we define children as those aged <18 years, but it is acknowledged that post-pubertal children in some respects may have a similar course and response to treatment as adults with IgAN. However, there are insufficient data currently to recommend that they be managed as adults with IgAN.**
- **Visible hematuria is more frequent in children than in adults, and this may account for earlier diagnosis in children.[56]**
- **Children generally have higher eGFR, lower urine protein excretion, and more hematuria than adults at diagnosis.[55]**

Kidney biopsy in children with IgAN

- **A kidney biopsy is usually performed at presentation of symptoms (hematuria, proteinuria, normal C3) to confirm the diagnosis (and rule out other diagnoses) and assess the degree of inflammation/presence of necrosis.**
- **In particular, a kidney biopsy should be performed promptly in children with persistent (>2-3 weeks) or recurrent hematuria and nephrotic-range proteinuria and/or reduced eGFR.[88]**
- **A kidney biopsy should also be performed in children with persistent or recurrent hematuria and PCR >500 mg/g (50 mg/mmol) in ≥2 measurements on clear urine 1–2 weeks apart.[88]**
- **In children with persistent or recurrent hematuria and PCR between 200–500 mg/g (20-50 mg/mmol) in ≥3 measurements on clear urine 1–2 weeks apart, performing a kidney biopsy should be considered.[88]**
- **Inflammation, mesangial, and endocapillary hypercellularity tend to be more prevalent in kidney biopsies of IgAN in children than in those of adults.[89-92]**

Treatment of children with IgAN

- **There is strong evidence suggesting a benefit of RAS blockade in children.**[132] **All children with IgAN and proteinuria >200 mg/d or PCR >200 mg/g (>20 mg/mmol) should receive RAS blockade, advice on moderating dietary salt intake below 3–5 g/d, and optimal lifestyle and blood pressure control (systolic blood pressure [SBP] <90th percentile for age, sex, and height).**
- **It is widely acknowledged that treatment of IgAN with immunosuppression differs between adults and children, and that in children, the use of immunosuppressants is more widespread, particularly the use of systemic glucocorticoids. However, RCTs and specific expert consensus-driven indications are lacking.[89, 91-96]**
- **Evidence derived mostly from retrospective studies suggests that treatment with systemic glucocorticoids (plus second-line immunosuppression) leads to improved kidney survival.[56, 97]**

- **The risk-benefit balance of glucocorticoid side effects must be considered. Systemic oral glucocorticoids are used in selected settings, in children with clinical risk of progression (i.e., a) PCR 500–1000 mg/g (50–100 mg/mmol) despite 3–6 months of RASB or b) PCR >1000 mg/g (>100 mg/mmol) despite 4 weeks of RAS, or c) active MEST-C scores [≥1 of the following scores: M1, E1, S1 with podocyte lesions, C1], and/or PCR consistently [i.e., persisting over 2–3 weeks in ≥2 measurements 1–2 weeks apart, >1000 mg/g (100 mg/mmol) in addition to RAS blockade].**
  - **Duration of treatment is not established, but usually 2 mg/kg per day (max 60 mg/m^2 per day) of oral prednisone/prednisolone [or equivalent] for a maximum of 4 weeks followed by alternate-day dosing tapered over 5–6 months are given.**
  - **Further extension of the duration may be useful in some cases. Lower doses as those emerging from the adult TESTING trial (0.4 mg/kg per day of prednisone/prednisolone [or equivalent] for 2 months, tapering over 6 months) should be considered.**
- **Regimens including intravenous methylprednisolone are also used on an individual basis in patients with higher clinical and histological risk for progression, such as a) children with acute onset of IgAN and worsening of kidney function (eGFR <90 ml/min per 1.73 m^2) and/or PCR >1000 mg/g (100 mg/mmol) with active severe MEST-C scores (≥2 of the following scores: M1, E1, S1 with podocyte lesions, C1) or b) children with crescentic forms of IgAN (C2).**
  - **In cases with C1 or C2 in the absence of any other MEST-C score >0 the level of proteinuria must be considered.[55, 89, 91, 98]**
  - **In cases with C2, irrespective of proteinuria, treatment of rapidly progressive IgAN is suggested (see below). Dosing regimens may be as follows: 3 methylprednisolone intravenous pulses given at the dose of 15 mg/kg per day each (maximum dose: 500 mg/dose) on 3 consecutive or alternate days followed by oral prednisone/prednisolone as indicated above.**
    - **Alternatively, the intravenous pulses can be repeated 3 times at 2-month intervals, with oral prednisone/prednisolone given at 0.5 mg/kg per day for 2 months between pulse cycles, for a total of 6 months.[99, 100]**
- **Children with IgAN not benefiting from adequate diet, RAS blockade, and glucocorticoids alone, should, whenever possible, be enrolled in clinical trials. Another potential approach is the use of immunosuppressants (e.g., calcineurin inhibitors, cyclophosphamide, mizoribine where available, mycophenolate mofetil or rituximab) in addition to glucocorticoids in these children.**
- **As for adults, IgAN with MCD may be found, and it should be treated as steroid-sensitive nephrotic syndrome (SSNS; Chapter 4).**
- **As in adults, children with rapidly progressive IgAN have a poor outcome, and despite limited evidence, this subgroup should be offered treatment with systemic glucocorticoids (usually as methylprednisolone pulses) and cyclophosphamide.[53, 89, 91]**

Follow-up of children with IgAN

- **Aim for proteinuria ≤200 mg/d (≤400 mg/1.73 m^2 per d) or PCR ≤200 mg/g (≤0.2 g/g [≤20 mg/mmol]).**
- **Aim for SBP at <90th percentile for age, sex, and height.**

- **Continue to follow patients after complete remission, as they can relapse even after many years.[101] In particular, yearly monitoring of blood pressure and urinalysis for patients with a history of pediatric IgAN is necessary.**

2.5 Global implementation of the updated IgAN KDIGO Guideline

[No recommendations and practice points]

2.6 Horizon scanning for future new drug approvals and updates to the Guideline

[No recommendations and practice points]

IMMUNOGLOBULIN A VASCULITIS

2.7 Diagnosis

Practice Point 2.7.1: Considerations for the diagnosis of immunoglobulin A vasculitis associated nephritis (IgAVN):

- **There are no internationally agreed upon criteria for the diagnosis of IgAV in adults**
- **In children, a clinical diagnosis of IgAV can be made based on international criteria.[102-104]**
- **A diagnosis of IgAVN can only be made with a kidney biopsy**
- **A kidney biopsy should be performed in adults with suspected IgAV if there are signs of significant end organ tissue damage: proteinuria ≥0.5 g/d persistent for >4 weeks, kidney function impairment or an RPGN.**
- **Assess all adult patients with IgAV and IgAVN for secondary causes and for malignancy, with age- and sex-appropriate screening tests.**

2.8 Prognosis

Practice Point 2.8.1: Considerations regarding the prognosis of IgAVN:

- **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.[105-107]**
- **The utility of the Oxford MEST-C classification has recently been studied. [108] This showed that in patients treated with immunosuppression E1 lesions were strongly associated with initial improvement followed by progressive decline in kidney function.**
- **The International IgAN Prediction Tool[9] is not designed for determining prognosis of IgAVN.**

2.9 Treatment

2.9.1 Prevention of nephritis in IgAV

Recommendation 2.9.1.1: We recommend not using systemic glucocorticoids to prevent nephritis in patients with isolated extrarenal IgAV *(1B)*.

Practice Point 2.9.1.1: Considerations for the management of all patients with IgAV-associated nephritis (IgAVN) who are at risk of progressive kidney function decline and do not have a rapidly progressive glomerulonephritis:

- **Proteinuria ≥0.5 per day (while on or off treatment for IgAVN) identifies a patient with IgAVN at increased risk of progressive loss of kidney function.**
- **The aspiration for the management of IgAVN, like IgAN, should be to *simultaneously***
  - **Prevent or reduce IgA immune complex formation, mesangial deposition, and immune complex mediated glomerular injury.**
  - **In parallel, manage the consequences of existing IgAVN-induced nephron loss.**
- **Unlike IgAN, there are no treatments proven to prevent/reduce IgA immune complex formation in IgAVN.**
- **Prevention of immune complex-mediated injury should incorporate treatments with proven anti-inflammatory effects, and ideally should be used in combination with, and not as a replacement for, treatments that prevent/reduce IgA immune complex formation.**
  - **In all patients in whom systemic glucocorticoids are being considered, a detailed discussion of the risks and benefits of each drug should be undertaken with the patient.**
  - **In those patients who wish to try systemic glucocorticoids, a reduced-dose regimen as described for IgAN should be employed with antimicrobial prophylaxis.**
- **Management of the consequences of IgAVN-induced nephron loss should include:**
  - **Lifestyle advice, including information on dietary sodium restriction, smoking cessation, weight control, and exercise, as appropriate,**
  - **Control blood pressure to a target of ≤120/70 mm Hg, using a RASi as the first choice drug intervention**
  - **Measures to reduce glomerular hyperfiltration and the impact of proteinuria on the tubulointerstitium, using singly or in combination, RASi and SGLT2i, and**
  - **A thorough cardiovascular risk assessment and commencement of appropriate interventions, as necessary.**
- **Offer participation in a clinical trial if one is available.**
- **There is insufficient evidence to support the use of the Oxford Classification MEST-C score in determining which drug should be commenced in IgAVN.**
- **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.**

2.10 Special situations

Practice Point 2.10.1: IgAV with RPGN:

- **The potential risks and benefits of immunosuppression should be evaluated at the individual patient level and discussed with the patient.**
- **Patients agreeing to treatment should be treated in accordance with the KDIGO 2024 Clinical Practice Guideline for the Management of ANCA-Associated Vasculitis.[44]**
- **IgAVN with RPGN, as well as other presentations of IgAVN, may be associated with significant extrarenal involvement (pulmonary, gastrointestinal, and skin), which may dictate alternative immunosuppressive strategies.**
- **There are insufficient data to determine the efficacy of plasma exchange in IgAVN with RPGN. However, uncontrolled case series describe the potential role for the addition of plasma exchange to glucocorticoid therapy to accelerate recovery in patients with life- or organ-threatening extrarenal complications of IgAV.[115]**

2.10.1 IgAV-associated nephritis in children

Practice Point 2.10.1.1: In this guideline, we define children as those aged <18 years, but it is acknowledged that post-pubertal children in some respects may have a similar course and response to treatment as adults with IgAN. However, there are insufficient data currently to recommend that they be managed as adults with IgAN.

Practice Point 2.10.1.2: A more extensive review of the management of IgAVN in children can be found in the 2024 International Pediatric Nephrology Association Guidelines for the Management of IgA nephropathy and IgA vasculitis (submitted).

Briefly:

- **The majority of children who will develop nephritis do so within 3 months of presentation. Urinary monitoring is necessary at onset of vasculitis and then at least monthly for ≥6 months from initial presentation of systemic disease.**
- **A kidney biopsy should be promptly performed in children with nephrotic-range proteinuria or impaired GFR (<90 ml/min per 1.73 m^2).**
- **In children with IgAV and moderate proteinuria (PCR 1000–2000 mg/g or 100-200 mg/mmol) for 2–4 weeks or mild proteinuria (PCR 200-500 mg/g or 20–50 mg/mmol) for >4 weeks a kidney biopsy should be considered.**
- **In children with confirmed IgAVN, a pediatric nephrologist should be consulted.**
- **In children with IgAVN and persistent proteinuria for >3 months, ACEi or ARB treatment should be considered.**
- **There are no data supporting the use of glucocorticoids to prevent nephritis in children with IgAV and absent evidence of kidney involvement or with isolated microhematuria.[116, 117]**
- **Oral prednisone/prednisolone for 3–6 months or pulsed intravenous methylprednisolone should be considered in children with IgAVN and nephrotic-range proteinuria (PCR >2000 mg/g or 200 mg/mmol) or RPGN and histological risk for progression (International Study of Kidney Disease in Children [ISKDC] ≥II).**

- **Other immunosuppressive agents in addition to glucocorticoids (e.g., calcineurin inhibitors, cyclophosphamide, mizoribine where available, mycophenolate mofetil or rituximab) should be considered in the following indications: to reduce the glucocorticoid dose and/or if PCR >2000 mg/g (200 mg/mmol) and/or insufficient response to glucocorticoids.**
- **Children with IgAVN with nephrotic syndrome and/or rapidly deteriorating kidney function are treated in the same way as those with rapidly progressive IgAN.**
- **Monitoring children with IgAVN with evaluation of urinalysis, eGFR, and blood pressure should be considered for ≥5 years after the initial episode. Lifelong monitoring, individualized according to the severity and response to treatment, appears prudent for children who received therapy for their IgAVN.**

IMMUNOGLOBULIN A NEPHROPATHY

Immunoglobulin A (IgA) nephropathy (IgAN) is the most common pattern of primary glomerular disease worldwide and remains a leading cause of chronic kidney disease (CKD) and kidney failure. Although IgAN is characterized by a single histopathologic criterion of predominant or codominant IgA deposits on kidney biopsy, it is now well recognized that this "disease" exhibits marked heterogeneity in its clinical and pathological features. There is good evidence that the epidemiology, clinical presentation, disease progression, and long-term outcomes 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 descent, followed by people of European descent, and is relatively rare in people 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.

At the time of diagnosis, the majority of patients will have already suffered significant nephron loss, with an estimated glomerular filtration rate (eGFR) on average between 50–60 ml/min per 1.73 m^2. As the average age at diagnosis is between 30–40 years and typical life expectancy in countries with a high prevalence of IgAN is 70–80 years, there needs to be an immediate focus on the introduction of therapies to preserve all remaining nephrons if kidney failure is to be avoided in the lifetime of the patient.

For the first time it is now possible to simultaneously target the 2 fundamental drivers for continued nephron loss in IgAN. The first driver is the IgAN-specific pathogenic pathways leading to production of pathogenic forms of IgA, the formation of IgA immune-complexes, glomerular IgA accumulation, and consequent activation of proinflammatory and profibrotic pathways within the kidneys. As with all forms of progressive kidney disease, the second driver is the intrarenal responses to IgAN-induced nephron loss, which include the development of glomerular hypertension/hyperfiltration, the tubulointerstitial response to persistent proteinuria, and the initiation and/or worsening of systemic hypertension.

As most people already have established CKD at the time of diagnosis, a dual approach will most commonly be needed to slow or prevent continued nephron loss. Since the Kidney Disease: Improving Global Outcomes (KDIGO) 2021 Guideline, a number of new drugs have been approved in various countries for the treatment of both CKD and IgAN, and over the next 5 years, there are likely to be further drug approvals, offering nephrologists a number of new opportunities to slow or stop the loss of kidney function in IgAN.

This guideline makes treatment recommendations for adults with IgAN and provides practice points on how to apply these recommendations to children aged 1–18 years. A more comprehensive review of the management of children with IgAN (and IgA vasculitis) has been produced by the International Pediatric Nephrology Association (submitted, Pediatric Nephrology). Where possible, we have highlighted possible racial differences in response to particular treatment regimens.

IgA vasculitis (Henoch–Schönlein purpura) is discussed later in this guideline.

2.1 Diagnosis

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

- **IgAN can only be diagnosed with a kidney biopsy, as there are no validated diagnostic serum or urine biomarkers for IgAN.**

- **To ensure an early diagnosis and prompt treatment of IgAN, a kidney biopsy should be performed in all adults with proteinuria ≥0.5 g/d (or equivalent) in whom IgAN is a possible diagnosis and who do not have a contraindication for kidney biopsy.**
- **Once a diagnosis of IgAN is made, assess for secondary causes.**
- **In cases of primary IgAN, determine the MEST-C score (mesangial [M] and endocapillary [E] hypercellularity, segmental sclerosis [S], interstitial fibrosis/tubular atrophy [T], and crescents [C]) according to the revised Oxford Classification.**[80]

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.[1-6] More recently, the standardized MEST-C score as defined in the revised Oxford Classification has been incorporated into development of prognostic scoring systems[7] and machine-learning used to select predictive variables.[8] The largest study to date developed a prognostic score in a multinational and multiracial cohort, including sizeable training and validation populations, over 4000 subjects.[9] The initial prediction tool calculates the risk of a 50% decline in eGFR or progression to kidney failure up to 5 years from kidney biopsy in adults. It incorporates the MEST-C histologic scores and clinical variables measured at the time of kidney biopsy. The prediction tool has been updated for use in children.[10] It has also been updated so that it can be applied 1 or 2 years after kidney biopsy.[11] These tools are available as online calculators to assist in discussions with patients regarding outcome. At present, the tools cannot be used to make inferences about treatment. However, it is envisioned that these tools could be used to aid clinical trial design and analysis in the future. Variables included in the prediction tools are listed in Figure 1.

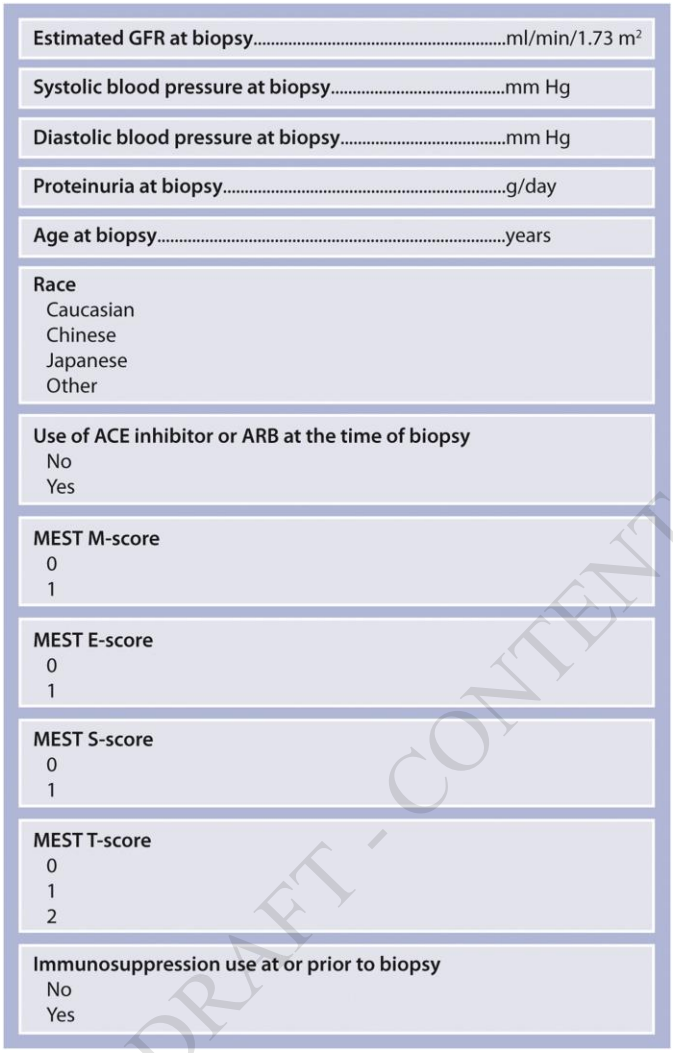

Figure 1 | The data elements included in the International Immunoglobulin A Nephropathy (IgAN) Prediction Tools. Using clinical and histologic data at the time of kidney biopsy, or up to 2 years post kidney biopsy, users can calculate the risk of a 50% decline in eGFR or kidney failure up to 7 years from kidney biopsy in adults and children. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; GFR, glomerular filtration rate; MEST, mesangial (M) and endocapillary (E) hypercellularity, segmental sclerosis (S), and interstitial fibrosis/tubular atrophy (T).

Practice Point 2.2.1: Considerations regarding the prognosis of primary IgAN:

- **Clinical and histologic data at the time of kidney biopsy can be used to risk stratify patients.**
- **The International IgAN Prediction Tools are a valuable resource to quantify short term (up to 7 years from kidney biopsy) risk of progression and inform shared decision-making with patients.**
  - ***International IgAN Prediction Tool at biopsy - Adults***
  - ***International IgAN Prediction Tool post-biopsy - Adults***
  - ***International IgAN Prediction Tool at biopsy - Pediatrics***
  - ***International IgAN Prediction Tool post-biopsy – Pediatric***
- **The International IgAN Prediction Tools incorporate clinical information at the time of kidney biopsy or at 1 or 2 years post-biopsy (Figure 1).**
- **There are no validated prognostic serum or urine biomarkers for IgAN other than estimated glomerular filtration rate (eGFR) and proteinuria.**

Practice Point 2.2.2: The initial assessment of the patient with IgAN (Figure 2)

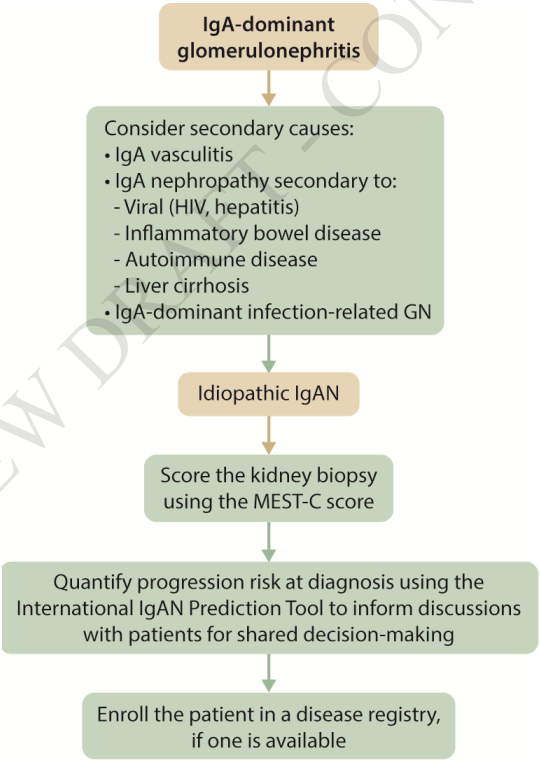

Figure 2 | Initial assessment and management of the patient with immunoglobulin A nephropathy (IgAN). GN, glomerulonephritis; HIV, human immunodeficiency virus; Ignaz, immunoglobulin A nephropathy; MEST-C, mesangial (M) and endocapillary (E) hypercellularity, segmental sclerosis (S), interstitial fibrosis/tubular atrophy (T), and crescents (C).

2.3 Treatment

With the development and recent approval of new therapies for the treatment of IgAN, there has been a fundamental shift in the focus of how to treat this immune complex-mediated glomerular disease since publication of the KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases.[12] The development of drugs that can target the production of pathogenic forms of IgA and reduce IgA immune complex formation means that it is now possible to simultaneously target the 2 fundamental drivers for continued nephron loss in IgAN: (1) IgA immune complex-mediated glomerular injury and (2) the responses in the kidney to IgAN-induced nephron loss. In most countries, a diagnosis of IgAN is made late in the natural history of the disease and, therefore at the time of presentation, it is essential that both of these drivers of continued nephron loss are considered when treatment decisions are being made. In those countries with active population-wide urinalysis screening programs (Japan, South Korea, Taiwan) identification of patients typically occurs much earlier in the natural history of the disease where the focus for treatment is likely to be on limiting immune complex-mediated glomerular injury rather than on the responses in the kidney to IgAN-induced nephron loss, which have yet to become established.

2.3.1 Defining patients with IgAN at risk of progressive loss of kidney function requiring treatment

Practice Point 2.3.1.1: A patient with IgAN is at risk of progressive loss of kidney function if they have proteinuria ≥0.5 g/d (or equivalent), while on or off treatment for IgAN, and treatment/additional treatment should be started in all cases.

The International IgAN Prediction Tools are a valuable resource to quantify short-term risk of progression and inform shared decision-making with patients but have only been validated for use within the first 2 years following a kidney biopsy. Furthermore, there are no data about what threshold of short term (5-year) risk of kidney disease progression would justify commencement of any particular intervention. It is important to realize that even a low risk of kidney failure at 5 years may translate into a very high risk at 15 years or longer.[13]

The traditional indicator for defining patients with IgAN at risk of kidney disease progression requiring treatment throughout most of the natural history of the disease has been the presence of sustained proteinuria. Typically, a threshold of proteinuria of ≥1 g/d has been used to define an increased risk of kidney disease progression; however, there are multiple studies supporting a lower threshold of proteinuria (≥0.5 g/d) as being a biomarker of increased risk of kidney disease progression in IgAN.

In a study of 1155 Chinese patients, the 10-, 15-, and 20-year cumulative kidney survival rates, calculated by Kaplan-Meier method, were 83%, 74%, and 64%, respectively, and patients with a time-averaged proteinuria (TA-P) <0.5 g/d had the highest kidney survival rates compared to those patients with TA-P 0.5–1.0 g/d (who had a 9.1-fold increased risk of developing kidney failure during follow-up; P <0.001) and those with TA-P >1.0 g/d (who had a 46.5-fold increased risk; P <0.001).[14] A study of the United Kingdom National Registry of Rare Kidney Diseases (RaDaR) IgA nephropathy cohort (2299 adults and 140 children) reported that 30% of patients with TA-P of 0.5 to <1.0 g/d and approximately 20% of patients with TA-P <0.5 g/d developed kidney failure within 10 years of diagnosis.[13] These data are supported by the European Validation Study of the Oxford Classification of IgAN (VALIGA), which included 1147 adults and children with IgAN from 13 European countries, in which there was a significant increase in the risk of a 50% decrease in eGFR and/or kidney failure with increasing TA-P: TA-P <0.5 g/d

vs. 0.5–0.9 g/d (*P*<0.001); TA-P 0.5–0.9 g/d vs. 1.0–1.4 g/d (*P*=0.001); and TA-P 1.0–1.4 g/d vs. 1.5–1.9 g/d (*P*=0.04).[15]

These findings, together with the consideration that the average age at diagnosis is between 30–40 years and typical life expectancy in countries with a high prevalence of IgAN is 70–80 years, suggests that a urine protein excretion of ≥0.5 g/d (whether on or off treatment for IgAN) indicates that a person with IgAN is at high risk of progressive loss of kidney function and, ultimately, kidney failure.

It is important to make a distinction between the increased risk of progression relevant in clinical practice (i.e., proteinuria ≥0.5 g/d), in the context of lifetime risk of kidney failure, and the "high risk" of progression (e.g., proteinuria ≥1.0 g/d on renin-angiotensin system inhibitors [RASi]) typically required for inclusion into clinical trials which are looking for changes in rates of deterioration in kidney function over a short time period (e.g., 2 years) in a relatively small number of study participants. The consequence of the need for short clinical studies means that currently many people at increased risk of progressive loss of kidney function with IgAN are excluded from clinical trials.

As IgAN can only be diagnosed with a kidney biopsy, and a diagnosis of IgAN is required to justify the use of the new approved therapies, alongside those that are likely to be approved in the coming years, the threshold to perform a kidney biopsy in an adult with signs of end-organ tissue damage (proteinuria, with or without nonvisible hematuria and/or a low eGFR and/or systemic hypertension) should coincide with the proteinuria threshold, ≥0.5g/d, that delineates a person with IgAN being at risk of progressive kidney function decline .

2.3.2 Defining a treatment goal in patients with IgAN at risk of progressive loss of kidney function

Practice Point 2.3.2.1: The treatment goal in patients with IgAN at risk of progressive loss of kidney function is to reduce the rate of loss of kidney function to <1 ml/min per year for the rest of the patient's life. The only validated early biomarker to help guide clinical decision-making is urine protein excretion, which should be maintained at <0.5 g/d (or equivalent), preferably <0.3 g/d (or equivalent), accepting that in some patients with extensive kidney scarring this may not be possible and that multiple drugs are likely to be needed to achieve this.

Currently the only validated short-term, modifiable biomarker that informs the future risk of kidney function decline is proteinuria. Regardless of the nature of the intervention, reduction in proteinuria in observational studies has independently been associated with improved kidney outcomes.[16] An individual patient-level meta-analysis of available data from randomized controlled trials (RCTs) has demonstrated an association between treatment effects on proteinuria and treatment effects on kidney survival (composite of the time to doubling of serum creatinine [SCr], kidney failure, or death),[17] thereby establishing reduction in proteinuria as a reasonably likely surrogate endpoint for a treatment's effect on progression to kidney failure in IgAN.[17]

Increases in proteinuria may be driven by both IgAN-specific, immune-mediated drivers of nephron loss and the responses in viable nephrons to IgAN-induced nephron loss (and be positively impacted by interventions in both of these areas), as well as by irreversible glomerular scarring and the loss of the protein resorptive capacity of the nephron due to tubular loss (which

will not be impacted by therapeutic interventions).[18] As such, it is not possible to use proteinuria to determine which therapeutic approach is required in an individual patient.

There are emerging data that the kidney function protection associated with proteinuria reduction delivered by drugs that reduce proteinuria through a predominant glomerular hemodynamic effect may be different to that that is associated with proteinuria reduction achieved through the reduction of pathogenic forms of IgA.[19-22] It is also important to acknowledge that suppressing proteinuria solely through a hemodynamic effect is likely to diminish the ability of proteinuria to reflect ongoing glomerular inflammation and injury. This may explain why in global cohorts patients with proteinuria <0.5 g/d, most of whom were on RASi, remained at increased risk of kidney failure.[14, 15]

Practice Point 2.3.2.2: Treatment of patients with IgAN who are at risk of progressive kidney function decline and do not have a variant form of primary IgAN (Figure 3):

- **The focus of management in most patients should be to *simultaneously*:**
  - **Prevent or reduce IgA immune complex formation and immune complex-mediated glomerular injury.**
  - **In parallel, manage the consequences of existing IgAN-induced nephron loss.**
- **Reduction or prevention of IgA immune complex formation should incorporate treatments that have been proven to reduce pathogenic forms of IgA (commonly measured as galactose deficient IgA1 [gd-IgA1]).**
- **Prevention of immune complex-mediated injury should incorporate treatments with proven anti-inflammatory effects, and ideally should be used in combination with, and not as a replacement for, treatments that prevent or reduce IgA immune complex formation.**
- **Management of the consequences of IgAN-induced nephron loss should include:**
  - **Lifestyle advice, including information on dietary sodium restriction, smoking cessation, weight control, and exercise, as appropriate,**
  - **Control of blood pressure with a target of ≤120/70 mm Hg,**
  - **Measures to reduce glomerular hyperfiltration and the impact of proteinuria on the tubulointerstitium, using singly or in combination, renin-angiotensin system (RAS) blockade or dual endothelin angiotensin receptor antagonism (DEARA), and sodium-glucose cotransporter-2 inhibition (SGLT2i), and**
  - **A thorough cardiovascular risk assessment and commencement of appropriate interventions, as necessary.**
- **The key factors to consider when making treatment choices are summarized in Tables 1 and 2.**
- **Issues related to accessibility and affordability of newly approved treatments for IgAN, alongside the requirement for continual or cyclical dosing, mean that it is unlikely that these treatments will be used in resource-limited settings, where cheaper and more easily resourced drugs will be used.**

- **In all patients in whom treatments that target the production of pathogenic forms of IgA or glomerular inflammation are being considered, a detailed discussion of the risks and benefits of each drug should be undertaken.**
- **There is insufficient evidence to support the use of the Oxford Classification MEST-C score in determining which drug should be commenced in IgAN.**
- **There is insufficient evidence to base treatment decisions on the presence and number of crescents in the kidney biopsy alone. Histopathological features must be interpreted in the context of clinical features, in particular, the rate of change of eGFR.**
- **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 the relative merits of different treatments may change.**

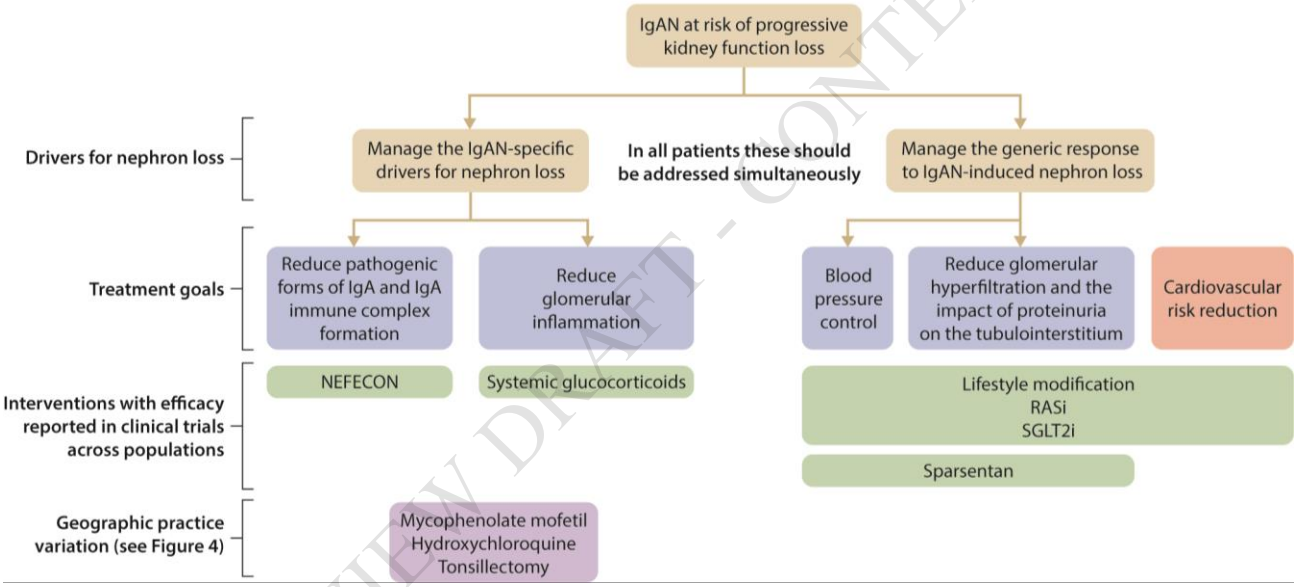

Figure 3 | Treatment targets in immunoglobulin A nephropathy (IgAN) and available to-date approved treatment options. *Measures to reduce glomerular hyperfiltration and the impact of proteinuria on the tubulointerstitium, using singly or in combination, renin-angiotensin system (RAS) blockade or dual endothelin angiotensin receptor antagonism (DEARA), and sodium-glucose cotransporter-2 inhibition (SGLT2i). RASi, renin-angiotensin system inhibitors.

Table 1 | Factors to consider when choosing a treatment and or treatment combinations for patients with immunoglobulin A nephropathy (IgAN) at risk of progressive kidney function loss

Questions	Considerations
Is the clinical trial population in which the drug was tested representative of the patient being treated (Table 2)?	**Age:** In the trials of SGLT2i, patients were on average 6-8 years older than those recruited into the NefIgArd and PROTECT trials and 15-17 years older than those recruited to the STOP-IgAN and TESTING study.
	Race: The TESTING study was almost exclusively conducted in Asian patients, STOP-IgAN was exclusively in Caucasians, in the NefIgArd and PROTECT studies Asian patients were relatively under-represented compared to trials of SGLT2i and systemic glucocorticoids.
	eGFR: In the trials of SGLT2i the average eGFR at inclusion was 12–14 ml/min lower than that of patients included in the NefIgArd, PROTECT, STOP-IgAN and TESTING studies.
	Concomitant medications: In all recent studies in IgAN, patients were required to be on a RASi prior to enrolment, requirements for optimized maximally tolerated dosing was not required in the trials of SGLT2i.
	Optimization of RAS blockade: The only trial to formally uptitrate RASi was the PROTECT trial, in the NefIgArd and TESTING studies participants were required to be on local physician attested optimized maximally tolerated RASi.
What is the labelled indication for the drug?	With the new approval pathway for drugs in IgAN the labelled indication may vary dependent upon the country and whether the drug has an accelerated approval/conditional market authorization, where assessment of efficacy has been made on the basis of proteinuria, or a full approval, based on its effect on rate of loss of kidney function.
What are the key advantages of available treatment options?	Nefecon is the only treatment to date proven to reduce the levels of pathogenic forms of IgA and IgA immune complexes
	Systemic glucocorticoids are highly effective anti-inflammatory drugs but have no proven impact on levels of pathogenic forms of IgA or IgA immune complexes at the doses recommended in this guideline.
	SGLT2i have been shown to not only reduce the rate of progression of kidney function loss but also reduce the incidence of adverse cardiovascular events, particularly in people with diabetes. They are also generally well tolerated.
	The DEARA, sparsentan, is the only drug to have shown efficacy beyond in-trial uptitrated RASi. Of note, more patients were included in the PROTECT trial than in all the trials of RASi in IgAN combined.
	RASi effectively reduce proteinuria and have an extensive efficacy and safety data in CKD and cardiovascular disease.
What are the key risks of available treatment options?	As there is some systemic absorption of budesonide patients and clinicians should be aware of the possibility of some systemic glucocorticoid related side effects with nefecon, these are usually mild and reversible on treatment cessation.
	When using systemic glucocorticoids, a reduced-dose protocol should be followed, antimicrobial prophylaxis against *Pneumocystis jirovecii* and anti-viral prophylaxis in hepatitis B carriers should be used, and the patient should be made aware of the risks of gastrointestinal bleeding, infection,

	metabolic, cosmetic, and neuropsychiatric side effects, alongside the potential impact on bone health.
	As with all endothelin receptor antagonists, there is a significant risk of embryofetal toxicity, and females of child-bearing potential must use a reliable form of contraception and undergo monthly pregnancy testing.

GI, gastrointestinal; NefIgArd, Efficacy and Safety of Nefecon in Patients With Primary IgA Nephropathy; PROTECT, A Study of the Effect and Safety of Sparsentan in the Treatment of Patients With IgA Nephropathy; RAS, renin-angiotensin system; RASi, renin-angiotensin system inhibitor(s); SGLT2i, sodium-glucose cotransporter-2 inhibitor(s); STOP-IgAN, The Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy; TESTING, Therapeutic Effects of Steroids in IgA Nephropathy Global.

Table 2 | Baseline characteristics and key inclusion criteria for recently reported trials in immunoglobulin A nephropathy (IgAN) and including significant numbers of patients with IgAN

Characteristic	DAPA-CKD		EMPA-KIDNEY	NefIgArd		PROTECT		STOP-IgAN		TESTING	
	Dapagliflozin (n = 137)	Placebo (n=133)	Empagliflozin (n = 817)	Nefecon (n=182)	Placebo (n=182)	Sparsentan (n=202)	Placebo (n=202)	Supportive care (n=80)	Immunosuppression (n=82)	Methylprednisolone (n=257)	Placebo (n=246)
Age inclusion criteria	≥18 years		≥18 years	≥18 years		≥18 years		≥18 years		≥18 years	
Age, mean (SD), yr	52.2 (13.1)	50.1 (13.1)	50.6 (12.7)	43 (36–50)	42 (34–49)	46.6 (12.8)	45.4 (12.1)	45.8 (12.5)	42.8 (13.1)	35.6 (29.4–46.3)	36.6 (29.0–45.9)
Female sex, n (%)	44 (32.1)	44 (33.1)	282 (34.5)	65 (36)	59 (32)	63 (31)	59 (29)	15 (19)	19 (24)	102 (40)	96 (39)
Race, n (%)											
• White	54 (39.4)	54 (40.6)	361 (44.2)	138 (76)	137 (75)	130 (64)	142 (70)	80 (100)	82 (100)	13 (5)	12 (5)
• Black	0 (0)	1 (0.8)	1 (0.1)	0 (0)	0(0)	1 (<1)	3 (1)	0	0	0 (0)	0 (0)
• Asian	82 (59.9)	77 (57.9)	442 (54.1)	43 (24)	40 (22)	67 (33)	48 (24)	0	0	244 (95)	233 (95)
• Other	1 (0.7)	1 (0.8)	13 (1.6)	1 (1)	5 (3)	4 (2)	10 (5)	0	0	0 (0)	1 (<1)
BMI, mean (SD), kg/m^2	26.3 (4.2)	27.6 (6.1)	26.8 (5.5)	N/A	N/A	N/A	N/A	28.6 (5.3)	27.0 (5.0)	Median: 24.2 (IQR: 21.6–26.7)	Median: 24.7 (IQR: 22.0–28.0)
Blood pressure, mean (SD), mm Hg											
• Systolic	127.7 (16.2)	127.0 (13.9)	131.8 (15.1)	126 (121–132)	124 (117–130)	128.0 (14.4)	129.9 (12.4)	127 (8.5)	124 (9.7)	Median: 123.8 (IQR: 115.0–132.5)	Median: 125.0 (IQR: 115.5–131.0)
• Diastolic	78.7 (11.8)	79.5 (10.1)	82.5 (10.4)	79 (76–84)	79 (74–84)	81.6 (10.6)	83.2 (10.6)	78 (7.0)	77 (7.0)	Median: 80.0 (IQR: 73.5–85.0)	Median: 80.0 (IQR: 74.0–86.0)
eGFR inclusion criteria, ml/min per 1.73 m^2	25–75		≥20 to <45, OR ≥45 to <90 & ACR ≥200 mg/g or PCR ≥300 mg/g	≥35 and ≤90		≥30		30-90		≥30 and ≤120	
eGFR, mean (SD), ml/min per 1.73 m^2	44.3 (12.4)	43.2 (12.0)	43.3 (17.5)	Median: 56.14 (IQR: 45.50-70.97)	Median: 55.11 (IQR: 45.96-67.74)	56.8 (24.3)	57.1 (23.6)	57.4 (24.9)	61.1 (29.0)	Median: 56.1 (IQR: 43.2–75.0)	Median: 59.0 (IQR: 42.0–77.6)
Urinary ACR ratio inclusion criteria	200-5000		See eGFR criteria	N/A		N/A		N/A	N/A	N/A	
Urinary ACR, median (Q1–Q3), mg/g	889.5 (557.5–1472.0)	902.5 (500.5-1633.0)	662 (331–1265)	990 (680-1400)	980 (660-1420)	N/A	N/A	N/A	N/A	N/A	N/A
Urinary protein excretion inclusion criteria	N/A		See eGFR criteria	≥1 g/d		≥1 g/d		>0.75 g/d		≥1 g/d	
Urinary protein excretion, median (Q1-Q3), g/24h	N/A	N/A	N/A	2.29 (1.61-3.14)	2.17 (1.53-3.39)	1.8 (1.2-2.9)	1.8 (1.3-2.6)	1.6 (0.7)	1.8 (0.8)	1.99 (1.36–3.09)	1.93 (1.38–2.88)
Type 2 diabetes diagnosis, n (%)	24 (17.5)	14 (10.5)	58 (7.1)	16 (9)	8 (4)	N/A	N/A	0	0	7 (3)	10 (4)
Baseline medication, n (%)											
• ACEi	44 (32.1)	41 (30.8)	770 (94.2)	179 (98)	179 (98)	202 (100)	202 (100)	27 (34)	40 (49)	140 (54.5)	128 (52.0)
• ARB	89 (65.0)	96 (72.2)						24 (30)	12 (15)	119 (46.3)	120 (48.8)
• ACEi + ARB	--	--	--	--	--	--	--	26 (32)	30 (36)		

Levels of RASi as a percentage of maximum allowable dose at screening, n (%)											
• <50%	N/A	N/A	N/A	39 (22%)	34 (19%)	0	0	N/A	N/A	30 (11.7)	35 (14.2)
• >50%	N/A	N/A	N/A	141 (78%)	145 (81%)	202 (100%)	202 (100%)	N/A	N/A	222 (86.4)	201 (81.7)
• 100%	N/A	N/A	N/A	N/A	N/A	130 (64%)	125 (62%)	61 (76)	58 (71)	N/A	N/A
• Immunosuppression	0 (0)	0 (0)	53 (6.5)	0 (0)	0 (0)	0 (0)	0 (0)	0	0	0 (0)	0 (0)

ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; BMI, body mass index; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; eGFR, estimated glomerular filtration rate; EMPA-KIDNEY, The Study of Heart and Kidney Protection With Empagliflozin; NefIgArd, Efficacy and Safety of Nefecon in Patients With Primary IgA Nephropathy; PCR, protein-to-creatinine ratio; PROTECT, A Study of the Effect and Safety of Sparsentan in the Treatment of Patients With IgA Nephropathy; Q1, quartile 1; Q3, quartile 3; RASi, renin-angiotensin system inhibitor; SD standard deviation; STOP-IgAN, The Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy; TESTING, Therapeutic Effects of Steroids in IgA Nephropathy Global.

2.3.3 Managing the IgAN-specific drivers for nephron loss

The key initiators of nephron loss in IgAN are: (1) production of pathogenic forms of IgA and formation of IgA immune complexes; mesangial deposition of these immune complexes and triggering of (2) inflammatory and (3) profibrotic responses within the glomerulus. Ultimately, blocking the production of pathogenic IgA would be expected to switch off all downstream pathogenic pathways. However, this is likely to take time and at presentation, patients may already have significant glomerular inflammation evident in their kidney biopsy. Accordingly, an immediate anti-inflammatory (and when available antifibrotic) approach may be desirable alongside starting treatment to stop production of pathogenic forms of IgA.

2.3.3.1 Reducing the production of pathogenic forms of IgA and IgA immune complex formation

There are several drugs currently in development whose mechanisms of action are to reduce the levels of pathogenic forms of IgA and IgA immune complexes in the circulation, either through B cell/plasma cell depletion or modulation of B cell/plasma cell function.[23] In 2024, nefecon is the only approved therapy that has been shown to significantly reduce pathogenic forms of IgA and IgA immune complex formation. A number of other immunomodulatory approaches, including surgical debulking of the mucosal-associated lymphoid tissue by tonsillectomy, have been evaluated in IgAN with no consistent evidence of disease modification across diverse populations (Practice Point 2.3.3.1.3 and Figure 4).

Recommendation 2.3.3.1.1: We suggest treatment with a 9-month course of nefecon for patients who are at risk of progressive kidney function loss with IgAN *(2B)*.

Practice Point 2.3.3.1.1: Factors to consider before using nefecon in patients with IgAN

- **A single 9-month treatment course of nefecon is unlikely to produce a sustained clinical response in terms of proteinuria reduction or stabilization of eGFR and it is likely that many patients will need either repeated 9-month treatment cycles or a reduced-dose maintenance regimen**
- **The approval status, labelled indication and availability vary globally.**

Nefecon, which localizes release of budesonide to the terminal ileum, is designed to suppress mucosal IgA synthesis by the gut-associated lymphoid tissue and thereby reduce serum levels of pathogenic forms of IgA1 and IgA immune complex formation. A single phase 3 RCT of nefecon in IgAN has been conducted, the Efficacy and Safety of Nefecon in Patients With Primary IgA Nephropathy (NefIgArd) study. Based on the primary efficacy endpoint of a statistically significant reduction in proteinuria at 9 months of treatment compared to placebo, nefecon received accelerated United States Food and Drug Agency (FDA) approval for use in IgAN in 2021 and conditional market authorization by the European Medicines Agency (EMA) in 2022. The full 2-year study demonstrated that treatment with nefecon reduced the rate of eGFR decline compared to placebo, and nefecon received full approval by the FDA in 2023, by the National Medical Products Administration (NMPA) in China in 2024 and by the EMA in 2024. Rates of adverse events were low and generally mild to moderate in severity and reversible following cessation of nefecon, as expected for a locally acting budesonide product.

Key information

Balance of benefits and harms

Benefits. In the NefIgArd study 364 adult patients with IgAN, eGFR 35−90 ml/min per 1.73 m^2, and persistent proteinuria (urine protein-to-creatinine ratio [PCR] ≥0.8 g/g or proteinuria ≥1 g/24 h) despite physician attested optimized RASi were randomized (1:1) to receive 16 mg/d of nefecon or placebo for 9 months, followed by a 15-month observational follow-up period off study drug. Treatment with a 9-month course of nefecon in addition to physician attested optimized maximally tolerated RASi resulted in a 27% reduction in proteinuria at 9 months compared to physician attested optimized maximally tolerated RASi plus placebo.[24] This was consistent with the proteinuria reduction observed in the phase 2b Targeted-release budesonide versus placebo in patients with IgA nephropathy [NEFIGAN] trial.[25] Over the 2 years of the study, a 9-month course of nefecon resulted in statistically significant treatment benefit with nefecon versus placebo (difference 5.05 ml/min per 1.73 m^2; 95% confidence interval [CI]: 3.24–7.38; P <0.0001), with a time-weighted average change of –2.47 ml/min per 1.73 m² (95% CI: –3.88 to –1.02) reported with nefecon and –7.52 ml/min per 1.73 m² (95% CI: –8.83 to –6.18) reported with placebo.[20] After 2 years, the change in eGFR from baseline was –6.11 ml/min per 1.73 m² (95% CI: –8.04 to –4.11) in the nefecon group, compared with –12.00 ml/min per 1.73 m² (95% CI: –13.76 to –10.15) in the placebo group. These changes corresponded to a difference in the 2-year total eGFR slope of 2.95 ml/min per 1.73 m² per year (95% CI: 1.67–4.58; P <0.0001) in favor of nefecon. The time from randomization to confirmed 30% reduction in eGFR or kidney failure was significantly delayed with nefecon versus placebo (hazard ratio [HR]: 0.45; 95% CI: 0.26−0.75; P=0.0014); 12% of patients in the nefecon group and 21% of patients in the placebo group had a confirmed event.

Harms. During the 9-month treatment period, treatment-emergent serious adverse events were reported in 10% of patients in the nefecon group and 5% of patients in the placebo group. The most commonly reported treatment-emergent adverse events (TEAE) during treatment with nefecon were peripheral oedema (17% vs. 4%), hypertension (12% vs. 3%), muscle spasms (12% vs. 4%), acne (11% vs. 1%), and headache (10% vs. 8%). Discontinuations due to TEAEs occurred in 9% of the nefecon group and 2% of the placebo group. During the 15-month observational follow-up, the incidence of TEAEs and treatment-emergent serious adverse events was similar between the groups and the frequencies of the most commonly reported TEAEs were similar in both treatment groups. Four participants who were prediabetic at baseline and received nefecon progressed to overt diabetes during the 9-month treatment period.[20]

Certainty of evidence

Moderate certainty of evidence supports the benefits of nefecon treatment in patients with IgAN, when used together with physician attested optimized maximally tolerated RASi (Supplementary Table S4). Two trials, NEFIGAN and NefIgArd, compared nefecon with placebo for 9 months, during which all patients received physician attested optimized maximally tolerated RASi.[20, 25] These studies had consistent findings among 480 patients in total. The 2 studies provided high certainty of evidence that treatment with nefecon prevents eGFR loss (mean difference [MD]: 5.4 ml/min per 1.73 m^2) and has a substantial impact on lowering proteinuria (MD: 29%) during the 9-month treatment period. One of the trials provided moderate certainty evidence that prevention of loss of eGFR, including prevention of kidney failure or eGFR reduction by ≥30%, in addition to reduced proteinuria, all persist for up to 24 months.[25] Due to small numbers of events, and thus serious imprecision, there is low certainty of evidence that

nefecon may make little or no difference in risk of severe infections or upper respiratory infections.

Values and preferences

The Work Group judged that most patients would place a high value on a treatment that possesses a disease-modifying effect by suppressing production of pathogenic forms of IgA and IgA immune complexes and that reduces proteinuria and slows the loss of kidney function, and that is generally well-tolerated. Healthcare providers should, however, advise patients of the potential adverse events associated with systemic absorption of budesonide before commencing nefecon. Healthcare providers should also advise that it is possible that repeated 9-month cycles of nefecon or a reduced-dose maintenance regimen may be required to maintain disease remission, as an increase in proteinuria and decline in eGFR was observed on stopping nefecon treatment.

Resource use and costs

In 2024, nefecon is approved for use in a limited number of countries where there is a high prevalence of IgAN. This, combined with the high cost of nefecon means it is unlikely to be commonly used in resource-limited settings. In addition, repeated 9-month cycles of nefecon or a lower dose maintenance regimen are likely to be needed in many patients to maintain disease remission. This will further impact on the affordability and accessibility of nefecon in resource-limited settings. There are no randomized data supporting the use of any other formulation of oral budesonide in IgAN.

Considerations for implementation

Treatment with nefecon requires no specific monitoring; however, due to the potential for limited systemic absorption of budesonide, healthcare providers should be aware of the potential for some systemic glucocorticoid-related adverse events. These are commonly mild and reversible on cessation of nefecon. In those people with prediabetes, changes in glycemic control may occur and during nefecon treatment, more intensive blood glucose monitoring may be justified. As an increase in proteinuria and decline in eGFR was observed on stopping nefecon treatment repeated 9-month cycles or a lower dose maintenance regimen may be required to maintain disease remission.

Rationale

There is a large body of research evidence supporting a pathogenic link between the mucosal associated lymphoid tissue, and in particular the gut-associated lymphoid tissue, and the generation of pathogenic forms of IgA and immune complex formation in IgAN.[26]

Both the NEFIGAN and NefIgArd clinical trials showed that 9-month treatment with nefecon in addition to RASi resulted in a significant reduction in proteinuria at 9 months and the NefIgArd trial showed that this proteinuria reduction was associated with an eGFR benefit at 2 years. In a study examining biomarker changes in the NEFIGAN study, 16 mg/d of nefecon was shown to result in significant reductions in pathogenic forms of IgA (measured as gd-IgA1) and IgA immune complexes, alongside a pattern of changes in serum cytokines, chemokines, and markers of lymphocyte activation consistent with an effect on the intestinal immune network for IgA production.[27] These data have subsequently been validated in analyses of samples from the NefIgArd study.

The beneficial effects on pathogenic forms of IgA, urine protein excretion and rate of eGFR decline mean that nefecon is the first approved disease-modifying treatment for IgAN. These effects have not been shown with other oral formulations of budesonide. Adverse effects of

nefecon were generally mild and reversible in the NefIgArd study and consistent with some systemic absorption of budesonide, which may offer an immediate anti-inflammatory effect within the kidney. On this basis, the Work Group believe that nefecon should be considered in all patients with IgAN at risk of progressive kidney function loss.

The rise in proteinuria and decline in eGFR observed in the NefIgArd trial after cessation of nefecon indicate that repeated treatment 9-month cycles of nefecon, or a lower dose maintenance regimen, are likely to be needed to achieve sustained benefit, however efficacy and safety data on such regimens is currently not available.

The high cost of nefecon means it is unlikely to be commonly used in resource-limited settings and therefore global adoption of this recommendation is likely to be highly variable.

Practice Point 2.3.3.1.2: Other pharmacologic therapies evaluated in IgAN:

- **Multiple agents have been evaluated in often small studies, in restricted populations and have failed to show a consistent benefit in IgAN (Figure 4)**

Agent	Suggested usage	Remarks
Antiplatelet agents	Not recommended	No evidence of efficacy
Anticoagulants	Not recommended	No evidence of efficacy
Azathioprine	Not recommended	No evidence for efficacy as monotherapy or when combined wit glucocorticoids
Cyclophosphamide	Not recommended	Unless in the setting of rapidly progressive IgAN
Calcineurin inhibitors	Not recommended	No evidence of efficacy
Rituximab	Not recommended	No evidence of efficacy
Fish oil	Not recommended	Patients who wish to take fish oil should be advised of the dose and formulation used in the published clinical trials that reported efficacy.
Mycophenolate mofetil (MMF)	**Chinese patients** In those patients in whom glucocorticoids are being considered MMF may be used as a glucocorticoid-sparing agent	Three RCTs have been conducted in China: the first from Hong Kong (n=40, eGFR ~51 ml/min/1.73 m²) showed a significant reduction in time-averaged proteinuria after MMF (1.5 to 2.0 g/day for 6 months) was added to SC in patients with proteinuria >1 g/d.[1] An extended 6-year follow-up showed a lesser slope of eGFR decline and lower probability of reaching kidney failure in MMF-treated patients;[2] the second from around Jiangsu (n=176, eGFR >90 ml/min/1.73 m²) showed that MMF with low-dose glucocorticoids (0.4–0.6 mg/kg/d prednisone) for 6 months was non-inferior to standard-dose glucocorticoids (0.8–1.0 mg/kg/d) for the treatment of incident IgAN presenting with proliferative histologic lesions (E or C lesions with or without necrosis) on kidney biopsy and proteinuria >1.0 g/d.[3] There were significantly fewer glucocorticoid-related side-effects in the combination-therapy arm; the third from Guangdong (n=170, eGFR 50 ml/min/1.73 m²) showed that MMF (initially, 1.5 g/d for 12 months, maintained at 0.75–1.0 g/d for at least 6 months) and SC reduced the frequency of the primary composite outcome (doubling of serum creatinine, kidney failure, or death due to kidney or cardiovascular causes, aHR 0.23; 95% CI, 0.09–0.63) and CKD progression (aHR 0.23; 95% CI, 0.1–0.57) compared to SC alone.[4] MMF was well tolerated in all the 3 trials.
	Non-Chinese patients There is insufficient evidence to support the use of MMF	In three smaller RCTs of MMF in non-Chinese patients there was no evidence for efficacy of MMF monotherapy: these were from Belgium (n=34, inulin clearance ~71 ml/min/1.73 m²),[5] New York (n=32, eGFR ~39 ml/min/1.73 m² and required glomerulosclerosis or tubulointerstitial atrophy and fibrosis on kidney biopsy reflecting relatively advanced CKD already)[6] and US/Canada (n=44, eGFR >90 ml/min/1.73 m², MMF versus omega-3 fatty acid).[7]
Hydroxychloroquine	**Chinese patients** In those patients who remain at high risk of progression in spite of optimized supportive care	In a small, short-term RCT conducted in China, hydroxychloroquine introduced to patients with proteinuria of 0.75–3.5 g/d despite optimized ACEi/ARB reduced proteinuria by 48% versus 10% in the placebo group at 6 months.[(6)]
	Non-Chinese patients There is insufficient evidence to support the use in those patients	Hydroxychloroquine has not been evaluated in non-Chinese patients.

Figure 4 | Other pharmacologic therapies evaluated in immunoglobulin A nephropathy (IgAN). [1]Tang *et al.*[28], [2]Tang *et al.*[29], [3]Hou *et al.*[30], [4]Hou *et al.* [31], [5]Maes *et al.*,[32] [6]Frisch *et al*,.[33] [7]Hogg *et al.*,[34] [8]Liu *et al.*[35], ACEi, angiotensin-converting enzyme inhibitor; aHR, adjusted hazard ratio; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; CI, confidence interval; IgAN, immunoglobulin A nephropathy; KRT, kidney replacement therapy; MMF, mycophenolate mofetil; RCT, randomized controlled trial; SC, standard of care; SCr, serum creatinine.

Practice Point 2.3.3.1.3: Tonsillectomy in IgAN:

- **Tonsillectomy alone or with pulsed glucocorticoids may improve kidney survival and partial or complete remission of hematuria and proteinuria, based on multiple, mostly retrospective studies from Japan (Supplementary Table S5[36-40]).[36-38, 40-42]**
- **Tonsillectomy is recommended in the Japanese Society of Nephrology Guidelines for the treatment of patients with IgAN.**
- **Tonsillectomy should not be performed as a treatment for IgAN in non-Japanese patients.**

2.3.1.2 Managing glomerular inflammation

Systemic glucocorticoids are the most commonly employed anti-inflammatory drugs used for the treatment of immune mediated glomerular diseases.[12] While glucocorticoids have pleiotropic effects on the immune system[43] in 2024, there are no data to suggest that systemic glucocorticoids, at the dose suggested in this guideline, have a direct effect on the production of pathogenic forms of IgA; therefore, in the absence of such data, their use should be assumed to provide a local anti-inflammatory effect within the kidney.

In other forms of inflammatory glomerular disease, systemic glucocorticoids are used in combination with treatments targeting the production of pathogenic antibodies (e.g., double-stranded DNA [dsDNA], antineutrophil cytoplasmic antibody [ANCA], M-type phospholipase A2 receptor [PLA2R]). Across these diseases,[12, 44, 45] there has been a progressive movement to limit both the dose and duration of exposure to systemic glucocorticoids due to their many side effects and poor patient tolerability. In contrast to all other inflammatory glomerular diseases, systemic glucocorticoids have largely been assessed as monotherapy in IgAN, given at high dose for a prolonged period of time. It is likely that as accessibility and affordability of therapies capable of suppressing production of pathogenic forms of IgA and IgA immune complex formation increases, the requirement for significant doses of prolonged systemic glucocorticoids will diminish.

Recommendation 2.3.1.2.1: In settings where nefecon is not available, we suggest that patients who are at risk of progressive kidney function loss with IgAN be treated with a limited course of a reduced-dose systemic glucocorticoid regimen combined with antimicrobial prophylaxis after a thorough toxicity risk assessment *(2B)*.

Practice Point 2.3.1.2.1: Reduced-dose systemic glucocorticoid regimen:

- **Methylprednisolone (or equivalent) 0.4 mg/kg per day (maximum: 32 mg/d) for 2 months followed by dose tapering by 4 mg/d each month for a total of 6–9 months.**
- **The conversion of methylprednisolone to commonly used forms of systemic glucocorticoids is: 1 mg methylprednisolone equals 1.3 mg of prednisone or prednisolone.**
- **Treatment with systemic glucocorticoids should incorporate antimicrobial prophylaxis against *Pneumocystis jirovecii* and anti-viral prophylaxis in hepatitis B carriers , along with gastroprotection and bone protection according to local guidelines.**

Practice Point 2.3.1.2.2: Factors to consider before using systemic glucocorticoids in IgAN:

- **Systemic glucocorticoids are effective anti-inflammatory drugs, but there is no evidence at the doses recommended in this guideline that they reduce the formation of pathogenic forms of IgA or immune complexes at the recommended doses.**
- **The dose and duration of systemic glucocorticoid treatment required to manage glomerular inflammation when used in combination with a therapy to reduce pathogenic forms of IgA is not known but should not exceed, and is likely to be much less than, the reduced-dose scheme for systemic glucocorticoids for active lupus nephritis, suggested in Practice Point 10.2.3.1.1 of the KDIGO 2024 Clinical Practice Guideline For The Management Of Lupus Nephritis.[45]**
- **The following patient characteristics are likely to increase the risks of systemic glucocorticoid related toxicity:**
  - **eGFR <30 ml/min per 1.73 m^2,**
  - **Diabetes and prediabetes,**
  - **Obesity,**
  - **Latent infections (e.g., viral hepatitis, tuberculosis),**
  - **Active peptic ulceration,**
  - **Uncontrolled psychiatric illness,**
  - **Osteoporosis, and**
  - **Cataracts.**
- **There is insufficient evidence to support the use of the Oxford Classification MEST-C score in determining when systemic glucocorticoids should be commenced.**
- **There are no data to support efficacy or reduced toxicity of alternate-day systemic glucocorticoid regimens.**

The largest available RCT of systemic glucocorticoids is the Therapeutic Effects of Steroids in IgA Nephropathy Global (TESTING) study. The 503 participants in this study included patients at high risk of disease progression. Subjects had an average level of proteinuria of 2.46 g/d at randomization despite optimized supportive care, a mean eGFR of 61.5 ml/min per 1.73 m^2, and 95% were of Asian descent. The full dose of methylprednisolone used in the initial TESTING protocol was associated with an unacceptable risk of harms, particularly infections. The study had to be paused with a lower dose employed combined with antimicrobial prophylaxis for the remainder of the study. About half the study participants received the standard, full-dose regimen; most of the remainder received a reduced-dose regimen. The reduced dose of methylprednisolone was associated with a significant reduction in the frequency of a 40% eGFR decline, kidney failure, or death due to kidney disease. Serious adverse events were less frequent with reduced-dose methylprednisolone and antimicrobial prophylaxis, with a reduced frequency of infections requiring hospitalization; however, one patient died from infection.

Key information

Balance of benefits and harms

Benefits. Participants on the reduced-dose methylprednisolone regimen in the TESTING study experienced a significant reduction in the frequency of the composite primary outcome (a 40% eGFR decline, kidney failure, or death due to kidney disease) compared to those who received

placebo (7/121 vs. 22/120 events, HR: 0.24; 95% CI: 0.10–0.58, *P*=0.002).[46] Overall, the mean annual eGFR slope was –0.7 ml/min per 1.73 m^2 per year in the reduced-dose methylprednisolone arm and –3.0 ml/min per 1.73 m^2 per year in the placebo arm (MD: 2.3 ml/min per 1.73 m^2 per year; 95% CI: 0.0–4.6; *P*=0.05). The mean between-group difference in total eGFR slope over 3 years using a linear spline model was 2.9 ml/min per 1.73 m^2 per year; 95% CI: 0.6–5.2; *P*=0.01). The mean difference in the reduction in proteinuria and eGFR from baseline between the 2 groups was –1.15 g/d and 7.9 ml/min per 1.73 m^2 (*P* <0.001) at 12 months, respectively. The proteinuria and eGFR benefit were lost over time once methylprednisolone was stopped. These data are in contrast to a lack of benefit of systemic glucocorticoids (methylprednisolone, administered intravenously at a dose of 1 g/d for 3 days at the start of months 1, 3, and 5; and oral prednisolone at a dose of 0.5 mg/kg per 48 hours on the other days) seen in The Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy (STOP-IgAN) study in terms of time to first occurrence of the same composite outcome used in the TESTING study after a median follow-up of 7.4 years (inter quartile range: 5.7–8.3 years).[47, 48] Two other small studies, published in 2009, included a total of 160 patients; both evaluated an ACEi with or without prednisone.[49, 50] These studies each found that individuals treated with prednisone had lower risks of progression of kidney disease.

Harms. The TESTING study protocol was revised once it became evident that the use of higher dose methylprednisolone (0.6–0.8 mg/kg per day for 2 months, maximum 48 mg/d, tapering by 8 mg/d each month for a total treatment period of 6–8 months) was associated with an unacceptable risk of harm.[51] The number of patients with at least one serious adverse event (SAE) was greater with methylprednisolone versus placebo (11% vs. 3%), mostly due to an excess of hospitalizations (10% vs. 3%) and serious infections (7% vs. 1%).[51] The excess in patients with at least one SAE was primarily observed with the full-dose methylprednisolone regimen (16% methylprednisolone vs. 3% placebo), rather than the reduced-dose regimen (5% methylprednisolone vs. 3% placebo). Four SAEs were fatal, all of which were in the methylprednisolone group (1.6%), and infection-related, including 3 in the full-dose protocol (2.2%) and 1 in the reduced-dose protocol (0.8%). In the 3 years of the STOP-IgAN trial, more patients in the systemic glucocorticoid group than in the supportive-care group had severe infections, impaired glucose tolerance, and weight gain of more than 5 kg in the first year of treatment.[47, 52]

Certainty of evidence

Moderate-certainty evidence supports the benefits of systemic glucocorticoid therapy, although with low certainty risk of infections (Supplementary Table S6). Four trials evaluated various systemic glucocorticoid regimens in patients with IgAN (excluding studies of nefecon).[48-53] The largest of these, TESTING (n=503), was conducted in a mostly Chinese population (75%, with an additional 19% from South and South-East Asia). The earlier studies were conducted in more racially diverse populations. Across studies, there was moderate certainty of evidence that systemic glucocorticoid therapy reduces kidney failure (risk ratio [RR]: 0.42; 95% CI: 0.17–1.03; 4 studies), ≥50% glomerular filtration rate (GFR) loss (RR: 0.62; 95% CI: 0.45–0.84; TESTING trial), and doubling of SCr (RR: 0.22; 95% CI: 0.07–0.76; 2 studies), together with high certainty of evidence that systemic glucocorticoid plus supportive therapy reduces annual GFR loss (MD: 5.4 ml/min per 1.73 m^2 per year; 95% CI: 2.3–8.6; 2 studies). Due to few events and, thus, serious imprecision, there is very low certainty of evidence regarding the effect of systemic glucocorticoids on all-cause mortality (over an average of about 2.5 years). There is low certainty of evidence that systemic glucocorticoids may increase complete remission (RR: 1.78; 95% CI: 1.09–2.89; with serious inconsistency across 4 trials). There is low certainty of evidence that (reduced-dose) glucocorticoids may increase infections based on the TESTING trial (RR: 2.31; 95% CI: 0.61–8.74).

Values and preferences

The Work Group judged that most patients would place a high value on a treatment that slows the loss of kidney function but also place a high value on the potential toxicity of such a treatment. High doses of systemic glucocorticoid therapy were associated with an excess risk of serious and potentially fatal infections in the initial protocol of the TESTING study. The reduced-dose regimen combined with antimicrobial prophylaxis was associated with a reduced rate of hospitalizations and deaths due to infection. The more frequent metabolic, cosmetic, and neuropsychiatric complications of systemic glucocorticoid use were not reported in the TESTING study, but have been reported in other studies of systemic glucocorticoids in IgAN.[30, 47, 52] Healthcare providers must engage in a thorough discussion of risks and benefits of systemic glucocorticoids and consider individual patient characteristics that may place them at higher risk of toxicity (see Practice Point 2.3.1.2.2). Healthcare providers should advise patients that it is likely that repeated cycles of systemic glucocorticoids may be required to maintain disease remission, as an increase in proteinuria and decline in eGFR was observed on stopping methylprednisolone in the TESTING study.

Resource use and costs

Systemically acting glucocorticoids are included in the World Health Organization (WHO) Model List of Essential Medicines (2019[54]) and are generally readily accessible and inexpensive in all countries where there is a high prevalence of IgAN. Consequently, their use is likely to be higher in resource-limited settings where access to newly approved therapies is likely to be limited.

Considerations for implementation

Healthcare providers should provide individualized assessment of patient risk of progression and risk of treatment-emergent toxicity with systemic glucocorticoids. Healthcare providers may choose to not consider systemic glucocorticoids as a treatment option in patients without signs of glomerular inflammation on kidney biopsy or in those with particular clinical characteristics placing them at higher risk of treatment-emergent toxicity (see Practice Point 2.3.1.2.2).

Rationale

The Work Group acknowledged that rapidly reversing glomerular inflammation is an important goal in the treatment of those people with IgAN who have significant glomerular inflammation as evidenced by the presence of endocapillary hypercellularity and/or cellular crescents in their kidney biopsy, and that systemic glucocorticoids are highly effective anti-inflammatory drugs. There have, however, been no studies combining systemic glucocorticoids with a therapy that reduces pathogenic forms of IgA and so it is unknown what dose and duration of systemic glucocorticoid treatment is required to manage glomerular inflammation when used in combination with a therapy that simultaneously reduces pathogenic forms of IgA.

An initial series of small, placebo-controlled RCTs supported greater reduction in proteinuria with systemic glucocorticoids compared to supportive therapy alone, with or without uniform use of RASi.[41, 55, 56] However, the confidence in estimates of efficacy and toxicity for these studies is low due to small sample size. While the STOP-IgAN study, conducted in White Europeans, failed to show a benefit of systemic glucocorticoids (or combination immunosuppression) on GFR endpoints),[47, 48] the larger TESTING study, conducted in an almost exclusively Asian population, did show a significant reduction in the frequency of the primary kidney outcome (composite 40% reduction in eGFR, kidney failure, death due to kidney disease) with methylprednisolone.[46] The

baseline characteristics of patients included in the 2 trials are different (see Table 2) and this may account for the differences in the baseline rates of eGFR loss during the trial periods in the 2 studies and the reported efficacies of systemic glucocorticoids.

The TESTING trial halted enrollment after randomization of 262 of a planned 750 subjects, due to an 11% greater risk of SAEs in the systemic glucocorticoid group (95% CI: 4.8%–18.2%).[40] This included 2 deaths related to infectious complications. The number of patients with at least one SAE continued to be higher with lower-dose methylprednisolone versus placebo (5% vs. 3%, HR: 1.97; 95% CI: 0.49–7.90), mostly due to an excess of hospitalizations and serious infections (4% vs. 2%). One SAE was fatal. In the STOP-IgAN study an excess of severe infections was also reported.

Based on data from the TESTING trial, in an almost exclusive Asian population, at 2.5 years, the numbers needed to treat to prevent one primary composite outcome was 6 (95% CI: 4.6–8.9). The number needed to treat to cause harm in one person was 41 (95% CI: –116.1 to 17.4).

As the proteinuria and eGFR benefit in the TESTING study were lost over time following cessation of methylprednisolone, repeated treatment cycles of systemic glucocorticoids or a lower dose maintenance regimen are likely to be needed to achieve sustained benefit. This is unlikely to be acceptable to most patients and healthcare providers due to the infectious, metabolic, cosmetic and neuropsychiatric complications of systemic glucocorticoids. With the advent of treatments that target production of pathogenic forms of IgA and immune complex formation long-term use of anti-inflammatory therapies, such as systemic glucocorticoids, are unlikely to be needed and the focus should be on shorter courses of systemic glucocorticoids with a rapid tapering of dose to zero as quickly as possible.

The low cost and easy accessibility of systemic glucocorticoids, however, means that they are likely, for the foreseeable future, to continue to be commonly used as a monotherapy to treat IgAN in resource-limited settings as an alternative to the newly approved more costlier therapies.

2.3.4 Managing the responses to IgAN-induced nephron loss

Progressive and significant nephron loss from any cause leads to the initiation and propagation of a characteristic pattern of initially adaptive but ultimately maladaptive responses within the remaining nephrons that accelerates further nephron loss.[57] In addition, the proteinuria that develops as a consequence of glomerular injury potentiates further nephron loss through direct activation of, and ultimately, damage to tubular epithelial cells by promoting tubulointerstitial inflammation and fibrosis.[58] These processes are compounded by an increased risk of systemic hypertension and collectively these responses result in a significantly increased risk of cardiovascular disease.[59]

Practice Point 2.3.4.1: Interventions for all patients with IgAN:

- **Control blood pressure to a target of ≤120/70 mm Hg, using a RASi as the first choice drug intervention**
- **Lifestyle advice should be given, where appropriate, on smoking cessation, weight reduction, dietary sodium restriction (<2 g/d) and regular exercise.**
- **A cardiovascular risk assessment should be undertaken and interventions commenced as per local guidelines.**

Recommendation 2.3.4.1: We recommend all patients who are at risk of progressive kidney function loss with IgAN be treated with an optimized maximally tolerated dose of

either an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) *(1B)*.

This recommendation is based on an extensive body of evidence in proteinuric CKD showing that treatment with RASi reduces the risk of progression to kidney failure . Data specifically in IgAN, while not extensive, are consistent with these observations. In the judgment of the Work Group, a strong recommendation is warranted because of the consistency of the benefits for RASi across the spectrum of kidney diseases, the generally low risk of harm for RASi, and the lack of rationale for a different recommendation for IgAN specifically.

Key information

Balance of benefits and harms

Benefits. Epidemiologic studies of large IgAN cohorts in North America, Asia, and Europe consistently identify sustained increases in proteinuria as an independent risk factor for progression in IgAN.[14, 15, 60] Retrospective data from large registries show that people with IgAN treated with an ACEi have a lower rate of annual loss of kidney function than similar patients not treated with ACEi or ARB.[60] A meta-analysis of 8 trials involving 866 patients with CKD evaluated the antiproteinuric effect of ARB in people who were normotensive with proteinuria. Compared with a control group, the use of an ARB was associated with a significant reduction in urinary protein excretion in patients with diabetes and moderately increased albuminuria, and nephropathy with overt proteinuria without diabetes. This effect was consistently seen in both Western and Asian populations.[61] Included in this meta-analysis was a small study in IgAN that included 32 people who were normotensive aged 18–54 years with proteinuria (1–3 g/d) and normal kidney function (creatinine clearance >80 ml/min) who were randomly divided into 4 treatment groups (verapamil 120 mg/d; trandolapril 2 mg/d; candesartan cilexetil 8 mg/d; and placebo).[62] 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). An RCT of 44 people with IgAN demonstrated a benefit of an ACEi (enalapril) on progressive kidney disease (better kidney survival and reduction in proteinuria) compared to equivalent blood pressure control with alternative antihypertensives (nifedipine, amlodipine, atenolol, diuretics, and doxazosin).[60] 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.[63] 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, kidney failure, or death in IgAN, and this was consistent across studies.[16] This effect was independent of the presence or absence of hypertension. Reducing proteinuria to slow progression of CKD also reduces cardiovascular risk in general CKD populations.[64, 65]

Harms. There is no evidence that the harms (e.g., angioedema, orthostatic hypotension and adverse drug reactions) are different for people with IgAN compared to those experienced by people with other forms of CKD, and there is some evidence that they are similar. In normotensive people, RASi should be initiated cautiously, and we outline a potential approach in the section on *Considerations for implementation*.

Certainty of evidence

Moderate certainty of evidence supports the benefits of reduction of proteinuria with RASi for slowing of kidney disease progression in patients with IgAN. There is high-certainty evidence to

support the benefits of reduction of proteinuria for slowing of kidney disease progression in all CKD populations.[43] The Work Group believe there is no *a priori* reason to suspect that the larger body of evidence is not generalizable to people with IgAN. Limited data specific to patients IgAN provides low certainty of evidence of clinical effects of RASi and low to moderate certainty of evidence on improvements in intermediate outcomes (Supplementary Table S7[39, 62, 63, 66]). One study provides low certainty of evidence of no effect of RASi on kidney failure or doubling of SCr in patients with IgAN, but with a very imprecise estimate due to small number of events (RR: 0.25; 95% CI: 0.03–2.21). Another small study provides low certainty of evidence of no effect on complete remission of proteinuria, again due to imprecision (RR: 5.29; 95% CI: 0.27–102.49). However, 3 studies provide moderate certainty of evidence that RASi decreases proteinuria (MD: −0.73 g/24 hours; 95% CI: −1.06 to −0.39) and low certainty of evidence that RASi may maintain creatinine clearance; although, with imprecision (MD: 7.0 ml/min; 95% CI: −0.6 to 14.5).

Values and preferences

The Work Group judged that most patients would place a higher value on the potential benefits of antiproteinuric treatment compared to the potential harms associated with treatment. However, younger patients with low or normal blood pressure may place a lower value on the potential benefits of RASi due to the risk of orthostatic hypotension.

Resource use and costs

According to the WHO's Global Health Observatory data repository, ACEi are widely, but not uniformly, available in high IgAN–prevalence areas.[67] It is important to note, however, that in some countries, the use of RASi in patients who are normotensive but have proteinuria is widely implemented but not always supported by health insurers.

Considerations for implementation

When commencing RASi in patients who are normotensive, it is imperative that patients are started on low-dose therapy initially, and that dose escalation is controlled with the aim for the patient to be treated with the maximal tolerated dose of either ACEi or ARB to achieve the maximal reduction in proteinuria while minimizing side effects, in particular orthostatic hypotension. The maximum tolerated dose will often be less than the recommended maximal dose. There are no RCT data available on the efficacy or safety of dual blockade with an ACEi and ARB in IgAN. A *post hoc* analysis of the STOP-IgAN trial demonstrated no additional benefit with dual blockade.[68]

Rationale

The severity of proteinuria has consistently been shown in studies from North America, Europe, and Asia to be an independent risk factor for progression in IgAN.[14, 15, 60] Clinical trial data in CKD consistently show that a sustained reduction in proteinuria with RASi is associated with a slowing in the rate of loss of kidney function,[69-77] and this has also been shown in IgAN).[78] While there is limited data on the use of RASi specifically in IgAN there is no *a priori* reason to suspect that the larger body of evidence of RASi use in CKD is not generalizable to people with IgAN.

In both versions of the KDIGO Clinical Practice Guideline for the Management of Glomerular Diseases, RASi was recommended as the initial treatment for all people with IgAN. A notable change in this guideline is that we recommend simultaneous commencement of disease-modifying therapy and therapies to manage the consequences of IgAN-induced nephron loss.

Indeed, when an early diagnosis is made and eGFR is still preserved the focus of treatment should be on limiting immune complex-mediated glomerular injury rather than on the responses in the kidney to IgAN-induced nephron loss, which have yet to become established.

Consistent with the KDIGO guidelines, all current trials in IgAN mandate that patients must be on an optimized maximally tolerated dose of RASi before screening and therefore all new treatments are being tested in combination with RASi. The A Study of the Effect and Safety of Sparsentan in the Treatment of Patients With IgA Nephropathy (PROTECT) trial calls into question whether an "RASi first" approach to manage the consequences of IgAN-induced nephron loss is the correct one in IgAN. In the PROTECT trial, combined endothelin receptor and angiotensin receptor antagonist was more effective than angiotensin receptor blockade alone at reducing proteinuria and slowing the loss of kidney function in people with well-controlled blood pressure, suggesting that there may be more effective immediate ways to manage the consequences of IgAN-induced nephron loss than RASi alone. This requires further exploration and consideration.

Recommendation 2.3.4.2: We suggest that patients who are at risk of progressive kidney function loss with IgAN be treated with a sodium-glucose cotransporter-2 inhibitor (SGLT2i) *(2B)*.

Practice Point 2.3.4.2: Factors to consider before using an SGLT2i in patients with IgAN:

- **There was no requirement for patients with IgAN to be on an optimized maximally tolerated dose of RASi for a minimum of 3 months for inclusion in The Study of Heart and Kidney Protection With Empagliflozin (EMPA-KIDNEY) and Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trials.**
- **IgAN patients included in EMPA-KIDNEY and DAPA-CKD likely had longstanding disease, based on the age and eGFR at randomization; therefore, there is uncertainty over the value of SGLT2i in patients with IgAN and a relatively preserved eGFR (>60 ml/min per 1.73 m^2) (see Table 2).**

This recommendation is based on an extensive body of evidence in the general CKD population and is consistent in principle with the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease.[79] While there are data specifically in IgAN, these data were not generated in an IgAN population comparable to those patients included in current phase 3 IgAN focused clinical trials and were generated in a generally older patient population with more advanced CKD in which there was a less strict requirement for adherence to optimized maximally tolerated RASi.

Key information

Balance of benefits and harms

Benefits. For the general CKD population, benefits include a reduced risk of kidney disease progression and a reduction in the risk of AKI.[79] In a collaborative meta-analysis of people with CKD, SGLT2i use was also shown to reduce the risk of the composite of cardiovascular death or hospitalization for heart failure by 23%, although there were limited numbers of cardiovascular

events in people with CKD without diabetes.[80] In the EMPA-KIDNEY[81] and DAPA-CKD[82] trials, use of an SGLT2i was associated with a lower rate of loss of kidney function in those people with IgAN. Patients in both of these trials, however, were generally older, with more advanced CKD, and with a less strict requirement for optimized maximally tolerated RASi than are typically recruited into IgAN clinical trials (Table 2).

Harms. SGLT2i are generally well-tolerated. There is no risk of hypoglycemia; however, there is an increased risk of urinary tract infections and mycotic genital infections (in men and women).

Certainty of evidence

High-certainty evidence supports the benefits of SGLT2 inhibitors in the general CKD population, as summarized in the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease.[79] Data specific to the treatment of IgAN is limited to those with IgAN included in the EMPA-KIDNEY and DAPA-CKD trials who were likely to have had longstanding disease, based on the age at randomization, with more advanced CKD and where adherence to optimized maximally tolerated RASi was uncertain (Table 2).[81, 82] For patients with IgAN, there is, overall moderate certainty of evidence based on indirectness of the high-certainty evidence from the general CKD population and moderate certainty of evidence specific to patients with IgAN (Supplementary Table S8). Reported data from the 2 SGLT2i trials provide high certainty of evidence for reduction in kidney disease progression (defined as halving of eGFR, sustained low eGFR, kidney failure, or death from kidney failure) based on an existing systematic review (RR: 0.49; 95% CI: 0.32–0.74),[80] but (due to reporting from a single trial of dapagliflozin), moderate certainty of evidence of reduction in kidney failure (RR: 0.30; 95% CI: 0.11–0.80), annual GFR loss (MD: 1.2 (95% CI: −0.12 to 2.51), and proteinuria (MD: −26%; 95% CI: −37 to −14). There is also low certainty of evidence of fewer adverse events with dapagliflozin than placebo (RR: 0.63; 95% CI: 0.39–1.02), due to imprecision.

Values and preferences

The Work Group judged that most patients with IgAN with an indication for an SGLT2i would choose to receive an SGLT2i for their proven benefits on risk of CKD progression, AKI, and a range of cardiovascular outcomes, alongside their generally good safety profile. Healthcare providers should, however, advise patients of the increased risk of urinary tract infections and mycotic genital infections.

Resource use and costs

There is significant global variability in the affordability of SGLT2i, particularly in resource-limited settings with a high prevalence of IgAN. The availability of generic SGLT2i is likely to improve accessibility and affordability over the coming years.

Considerations for implementation

Commencement of an SGLT2i can be associated with a reversible dip in eGFR but there is no associated risk of either AKI or hyperkalemia. Initiating an SGLT2i does not necessitate alteration of frequency of laboratory monitoring, and it is not routinely necessary to recheck blood tests after initiating an SGLT2i in adults with CKD.

Rationale

There is a very clear rationale for the use of SGLT2i in CKD with and without diabetes based on data from large trials of individual SGLT2i and from meta-analyses combining clinical trials.

It should, however, be acknowledged that the IgAN patients included in EMPA-KIDNEY and DAPA-CKD likely had longstanding disease,[81, 82] based on the age and eGFR at randomization and, therefore, there is uncertainty over the value of SGLT2i in patients with IgAN and a relatively preserved eGFR (>60 ml/min per 1.73 m^2). In light of this, the Work Group felt that SGLT2i should be considered in those people with IgAN and proteinuria ≥0.5 g/d in distinction to the recommendations in the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease[79] for kidney disease with and without diabetes. Use of SGLT2i should not be used as a replacement for disease-modifying therapies in IgAN, and for those patients with an eGFR>60 ml/min per 1.73 m^2, not using an SGLT2i may be appropriate in the absence of other risk factors such as diabetes and cardiovascular disease.

Recommendation 2.3.4.3: We suggest that patients who are at risk of progressive kidney function loss with IgAN be treated with sparsentan *(2B)*.

Practice Point 2.3.4.3: Factors to consider before using sparsentan in patients with IgAN

- **Sparsentan is a dual endothelin angiotensin receptor antagonist (DEARA) and should not be prescribed together with a RASi.**
- **The approval status, labelled indication and availability vary globally.**

This recommendation is based on a single global, randomized, double-blind, active comparator clinical trial undertaken in 406 patients with IgAN at risk of progressive kidney function decline despite physician attested optimized maximally tolerated RASi, where the effect of sparsentan 400 mg on proteinuria and eGFR slope was compared against irbesartan 300 mg over 2 years. Based on the primary efficacy endpoint of a reduction in proteinuria at 9 months of treatment compared to irbesartan, sparsentan received accelerated FDA approval for use in IgAN in 2023 and conditional market authorization by the EMA in 2024. The full 2-year study demonstrated that treatment with sparsentan reduced the rate of eGFR decline compared to irbesartan.

Key information

Balance of benefits and harms

Benefits. The PROTECT trial[22, 83] enrolled 406 patients (Table 2) with biopsy-proven primary IgAN and a 24-hour proteinuria of ≥1.0 g/d, despite physician attested optimized maximally tolerated RASi (with all participants required to be on at least half maximal RASi dose) for at least 12 weeks, an eGFR of ≥30 ml/min per 1.73 m^2, and controlled blood pressure.[22, 83] The study was designed to test the efficacy and safety of sparsentan 400 mg once daily versus irbesartan 300 mg once daily to determine whether sparsentan reduced proteinuria and the risk of CKD progression. At week 36, the reduction in PCR was statistically significantly greater in the sparsentan group (–49.8%) than the irbesartan group (–15.1%; least squares mean ratio: 0.59; 95% CI: 0.51–0.69; P<0.0001). At week 110, the change from baseline in the PCR was −42.8% (95% CI: −49.8 to −35.0) with sparsentan versus −4.4% (95% CI: 15.8–8.7) with irbesartan (geometric least-squares mean ratio: 0.60; 95% CI: 0.50–0.72). Sparsentan treatment also led to a lower loss in the eGFR compared with the irbesartan group (–5.8 vs. –9.5 ml/min per 1.73 m^2 per year, respectively). The 2-year chronic eGFR slope (weeks 6–110) was −2.7 ml/min per 1.73 m^2

per year (95% CI: −3.4 to −2.1) with sparsentan, statistically significantly lower compared with irbesartan (−3.8 ml/min per 1.73 m^2 per year [95% CI: −4.6 to −3.1]; difference 1.1 ml/min per 1.73 m^2 per year [95% CI: 0.1–2.1]; *P*=0.037). The 2-year total eGFR slope (day 1–week 110) was −2.9 ml/min per 1.73 m^2 per year (95% CI: −3.6 to −2.2) with sparsentan and −3.9 ml/min per 1.73 m^2 per year (95% CI: −4.6 to −3.1) with irbesartan (difference: 1.0 ml/min per 1.73 m^2 per year, 95% CI: −0.03 to 1.94; *P*=0.058). Fewer sparsentan-treated patients reached the composite kidney failure endpoint (40% eGFR reduction, kidney failure, or all-cause mortality) compared with irbesartan.

Harms. In the PROTECT study, TEAEs were reported in 93% of patients in the sparsentan group and 88% of patients in the irbesartan group. TEAEs that occurred more frequently with sparsentan than irbesartan (≥5 percentage points) included dizziness (15% vs. 6%) and hypotension (13% vs. 4%). Serious TEAEs were reported in 37% of patients in the sparsentan group and 35% of patients in the irbesartan group, and TEAEs led to treatment discontinuation in 10% and 9% of patients, respectively. Peripheral edema and use of diuretics were similar in both groups, with no increases in body weight. Regarding liver function, 2% of sparsentan-treated patients had an alanine aminotransferase or aspartate aminotransferase elevation of ≥3 times upper limit of normal versus 3% of irbesartan-treated patients. No cases of drug-induced liver injury occurred in either group.

Certainty of evidence

There is moderate-certainty evidence, derived from a single, phase 3 trial, regarding the effect of sparsentan, compared to the ARB irbesartan, in patients with IgAN (Supplementary Table S9[22, 83]). Due to small numbers of events, there is only very low certainty of evidence (very imprecise estimates) for the effect on sparsentan on all-cause mortality and kidney failure. However, there is moderate certainty of evidence that sparsentan greatly increases the likelihood of complete remission (RR: 2.70; 95% CI: 1.74–4.17); the certainty was downgraded because only a single study has been reported. There is also moderate certainty of evidence that sparsentan reduces proteinuria (MD: −40%; 95% CI: −50 to −28), but, due to imprecision, low certainty of evidence that sparsentan reduces annual GFR loss (MD: 1.0; 95% CI: −0.03 to 1.94). There is also low certainty of evidence that sparsentan may not have different risk of adverse events than irbesartan (RR: 1.06; 95% CI: 0.81–1.37); the certainty was downgraded for indirectness since COVID-19 infections were included among adverse events, likely biasing any estimate of treatment-related adverse events toward the null.

Values and preferences

The Work Group judged that most patients would place a high value on a treatment that reduces proteinuria and slows the loss of kidney function, and that is generally well-tolerated. Healthcare providers should, however, advise female patients of the increased risk of fetal toxicity and the need for contraception where appropriate and regular pregnancy testing.

Resource use and costs

In 2024, sparsentan is approved for use in a limited number of countries where there is a high prevalence of IgAN. This, combined with the cost of sparsentan and the fact that it is a life-long therapy, means it is unlikely to be commonly used in resource-limited settings.

Considerations for implementation

In the United States, the FDA mandates a Risk Evaluation and Mitigation Strategy (REMS) requiring all patients to have transaminases and bilirubin measured before initiating treatment and

monthly for the first 12 months, and then every 3 months during treatment. This is not a requirement in Europe. In addition, pregnancy testing is required before the initiation of treatment, during treatment, and 1 month after discontinuation of treatment. People who can become pregnant must use effective contraception before the initiation of treatment, during treatment, and for 1 month after discontinuation of treatment with sparsentan.

Rationale

In IgAN, the endothelin system is activated inducing pathophysiological responses that augment those associated with activation of the RAS.[84] Both systems mediate kidney injury through mechanisms including changes in glomerular hemodynamics, inflammation, and fibrosis. In this context, endothelin receptor antagonism combined with RASi has been shown in numerous preclinical models, including a mouse model of IgAN, and human studies to reduce proteinuria and slow the progression of kidney disease.[85] [86]

In the PROTECT trial treatment with sparsentan resulted in a greater sustained reduction in proteinuria than an ARB alone.[22, 83] Two different measures of eGFR change over the duration of the study were reported and these were dictated by the different regulatory agencies. Chronic eGFR slope (i.e., rate of eGFR change over weeks 6–110, requested by the EMA) and total eGFR slope over the full double-blind treatment period (i.e., day 1–week 110, requested by the FDA) have been reported for the PROTECT trial. There remains considerable debate over which measure is the most appropriate, particularly for drugs that have an acute negative effect on eGFR that opposes the chronic beneficial effects of the drug, as is seen with RASi, SGLT2i, and sparsentan. Total slope was more strongly and precisely associated with a doubling of SCr, eGFR <15 ml/min per 1.73 m^2, or kidney failure with replacement therapy in an individual participant data meta-regression of 66 RCTs.[87] However, in simulations, when an acute negative effect was present, chronic slope had a higher statistical power to detect an effect than total slope. This may explain why in the PROTECT trial there was a significant difference in chronic but not total eGFR slope with sparsentan.

The PROTECT trial required all patients to have persistent proteinuria despite first taking optimized maximally tolerated RASi. The observed greater proteinuria reduction and eGFR preservation with combined blockade of the renin-angiotensin and endothelin systems suggests that a dual approach may be an appropriate first-line approach to manage the responses of IgAN-induced nephron loss in the future.

2.4 Special situations

Practice Point 2.4.1: IgAN with nephrotic syndrome:

- **Rarely, patients with IgAN present with nephrotic syndrome (including edema and both hypoalbuminemia and nephrotic-range proteinuria >3.5 g/d).**
- **In these cases, mesangial IgA deposition can be associated with light and electron microscopy features otherwise consistent with a podocytopathy resembling minimal change disease (MCD).**
- **It is unclear whether this is a specific podocytopathic variant of IgAN or the existence of MCD in a patient with IgAN.**
- **Patients with a kidney biopsy demonstrating mesangial IgA deposition and light and electron microscopy features otherwise consistent with MCD should be treated in**

accordance with the guidelines for MCD in Chapter 5 of the KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases.[12]

- **Peoples with nephrotic syndrome whose kidney biopsy has coexistent features of a mesangioproliferative glomerulonephritis (MPGN) should be managed in the same way as those patients who are at risk of progressive kidney function loss from IgAN.**
- **Nephrotic-range proteinuria without nephrotic syndrome may also be seen in IgAN, and this commonly reflects coexistent secondary focal segmental glomerulosclerosis (FSGS) (e.g., obesity, uncontrolled hypertension) or development of extensive glomerulosclerosis and tubulointerstitial fibrosis.**

Practice Point 2.4.2: IgAN with AKI:

- **AKI can occur in people with IgAN in the context of severe visible hematuria, commonly in association with an upper respiratory tract infection. A repeat kidney biopsy should be considered in patients who fail to show improvement in kidney function within 2 weeks following cessation of the hematuria. Immediate management of AKI with visible hematuria should focus on supportive care for AKI.**
- **IgAN may also present with AKI either *de novo* or during its natural history due to a rapidly progressive glomerulonephritis (RPGN), often with extensive crescent formation, commonly in the absence of visible hematuria. In the absence of visible hematuria and when other causes of an RPGN (e.g., antineutrophil cytoplasmic antibody [ANCA]-associated vasculitis [AAV], anti-glomerular basement membrane [GBM] disease) and reversible causes (e.g., drug toxicity, common pre- and post-kidney causes) have been excluded, a kidney biopsy should be performed as soon as possible.**

Practice Point 2.4.3: IgAN with RPGN:

- **Rapidly progressive IgAN is defined as a ≥50% decline in eGFR over ≤3 months, where other causes of an RPGN (e.g., AAV, anti-GBM disease) and reversible causes (e.g., drug toxicity, common pre- and post-kidney causes) have been excluded.**
- **A kidney biopsy is essential in these cases and will commonly demonstrate mesangial and endocapillary hypercellularity, and a high proportion of glomeruli affected by crescents with areas of focal necrosis.**
- **The presence of crescents in a kidney biopsy in the absence of a concomitant change in serum creatinine (SCr) does not constitute rapidly progressive IgAN; however, these patients require close follow-up to ensure prompt detection of any glomerular filtration rate (GFR) decline. If this occurs, a second kidney biopsy may be considered.**
- **Patients with rapidly progressive IgAN should be offered treatment with cyclophosphamide and systemic glucocorticoids in accordance with the KDIGO 2024 Clinical Practice Guideline for the Management of ANCA-Associated Vasculitis.[44]**

- **Prophylactic measures that should accompany immunosuppression are discussed in Chapter 1 of the KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases.[12]**
- **There is insufficient evidence to support the use of rituximab for the treatment of rapidly progressive IgAN.**

Practice Point 2.4.4: IgAN and pregnancy planning:

- **IgAN is a disease predominantly of young adults, and all women of childbearing potential should be offered preconception counselling when appropriate.**
- **Preconception counselling should include a discussion on cessation of RASi, SGLT2i, sparsentan, and nefecon. Blood pressure control should be optimized with alternative antihypertensive medications prior to conception.**
- **In those women at risk of progressive loss of kidney function, a trial of treatments to optimally suppress production of pathogenic forms of IgA and IgA immune complexes and glomerular inflammation prior to conception may be preferable to initiation of these treatments during pregnancy.**
- **RASi, SGLT2i, and sparsentan must not be used during pregnancy and breastfeeding.**
- **The evidence to date suggests that first trimester systemic glucocorticoid use may confer a small increase in the odds of cleft lip with or without cleft palate, although data are conflicting and it is unknown to what extent the underlying maternal disease may contribute. Systemic glucocorticoid use in pregnancy does not increase the risks of preterm birth, low birth weight, or preeclampsia.**
- **The use of nefecon in pregnancy is not advised, however, studies examining the use of budesonide by pregnant women with inflammatory bowel disease have not identified any harmful effects. Budesonide has a Food and Drug Administration (FDA) Pregnancy Category C Risk designation, so risk cannot be ruled out.**

Practice Point 2.4.5: IgAN in children:

General considerations for children with IgAN

- **A more extensive review of the management of IgAN in children can be found in the 2024 International Pediatric Nephrology Association Guidelines for the Management of IgA nephropathy and IgA vasculitis (submitted)**
- **In this guideline, we define children as those aged <18 years, but it is acknowledged that post-pubertal children in some respects may have a similar course and response to treatment as adults with IgAN. However, there are insufficient data currently to recommend that they be managed as adults with IgAN.**
- **Visible hematuria is more frequent in children than in adults, and this may account for earlier diagnosis in children.[56]**
- **Children generally have higher eGFR, lower urine protein excretion, and more hematuria than adults at diagnosis.[55]**

Kidney biopsy in children with IgAN

- **A kidney biopsy is usually performed at presentation of symptoms (hematuria, proteinuria, normal C3) to confirm the diagnosis (and rule out other diagnoses) and assess the degree of inflammation/presence of necrosis.**
- **In particular, a kidney biopsy should be performed promptly in children with persistent (>2-3 weeks) or recurrent hematuria and nephrotic-range proteinuria and/or reduced eGFR.[88]**
- **A kidney biopsy should also be performed in children with persistent or recurrent hematuria and PCR >500 mg/g (50 mg/mmol) in ≥2 measurements on clear urine 1–2 weeks apart.[88]**
- **In children with persistent or recurrent hematuria and PCR between 200–500 mg/g (20-50 mg/mmol) in ≥3 measurements on clear urine 1–2 weeks apart, performing a kidney biopsy should be considered.[88]**
- **Inflammation, mesangial, and endocapillary hypercellularity tend to be more prevalent in kidney biopsies of IgAN in children than in those of adults.[89-92]**

Treatment of children with IgAN

- **There is strong evidence suggesting a benefit of RAS blockade in children.[132] All children with IgAN and proteinuria >200 mg/d or PCR >200 mg/g (>20 mg/mmol) should receive RAS blockade, advice on moderating dietary salt intake below 3–5 g/d, and optimal lifestyle and blood pressure control (systolic blood pressure [SBP] <90th percentile for age, sex, and height).**
- **It is widely acknowledged that treatment of IgAN with immunosuppression differs between adults and children, and that in children, the use of immunosuppressants is more widespread, particularly the use of systemic glucocorticoids. However, RCTs and specific expert consensus-driven indications are lacking.[89, 91-96]**
- **Evidence derived mostly from retrospective studies suggests that treatment with systemic glucocorticoids (plus second-line immunosuppression) leads to improved kidney survival.[56, 97]**
- **The risk-benefit balance of glucocorticoid side effects must be considered. Systemic oral glucocorticoids are used in selected settings, in children with clinical risk of progression (i.e., a) PCR 500–1000 mg/g (50–100 mg/mmol) despite 3–6 months of RASB or b) PCR >1000 mg/g (>100 mg/mmol) despite 4 weeks of RAS, or c) active MEST-C scores [≥1 of the following scores: M1, E1, S1 with podocyte lesions, C1], and/or PCR consistently [i.e., persisting over 2–3 weeks in ≥2 measurements 1–2 weeks apart, >1000 mg/g (100 mg/mmol) in addition to RAS blockade].**
    - **Duration of treatment is not established, but usually 2 mg/kg per day (max 60 mg/m^2 per day) of oral prednisone/prednisolone [or equivalent] for a maximum of 4 weeks followed by alternate-day dosing tapered over 5–6 months are given.**
    - **Further extension of the duration may be useful in some cases. Lower doses as those emerging from the adult TESTING trial (0.4 mg/kg per day of prednisone/prednisolone [or equivalent] for 2 months, tapering over 6 months) should be considered.**
- **Regimens including intravenous methylprednisolone are also used on an individual basis in patients with higher clinical and histological risk for progression, such as a)**

children with acute onset of IgAN and worsening of kidney function (eGFR <90 ml/min per 1.73 m^2) and/or PCR >1000 mg/g (100 mg/mmol) with active severe MEST-C scores (≥2 of the following scores: M1, E1, S1 with podocyte lesions, C1) or b) children with crescentic forms of IgAN (C2).

- **In cases with C1 or C2 in the absence of any other MEST-C score >0 the level of proteinuria must be considered.[55, 89, 91, 98]**
- **In cases with C2, irrespective of proteinuria, treatment of rapidly progressive IgAN is suggested (see below). Dosing regimens may be as follows: 3 methylprednisolone intravenous pulses given at the dose of 15 mg/kg per day each (maximum dose: 500 mg/dose) on 3 consecutive or alternate days followed by oral prednisone/prednisolone as indicated above.**
  - **Alternatively, the intravenous pulses can be repeated 3 times at 2-month intervals, with oral prednisone/prednisolone given at 0.5 mg/kg per day for 2 months between pulse cycles, for a total of 6 months.[99, 100]**

- **Children with IgAN not benefiting from adequate diet, RAS blockade, and glucocorticoids alone, should, whenever possible, be enrolled in clinical trials. Another potential approach is the use of immunosuppressants (e.g., calcineurin inhibitors, cyclophosphamide, mizoribine where available, mycophenolate mofetil or rituximab) in addition to glucocorticoids in these children.**
- **As for adults, IgAN with MCD may be found, and it should be treated as steroid-sensitive nephrotic syndrome (SSNS; Chapter 4).**
- **As in adults, children with rapidly progressive IgAN have a poor outcome, and despite limited evidence, this subgroup should be offered treatment with systemic glucocorticoids (usually as methylprednisolone pulses) and cyclophosphamide.[53, 89, 91]**

Follow-up of children with IgAN

- **Aim for proteinuria ≤200 mg/d (≤400 mg/1.73 m^2 per d) or PCR ≤200 mg/g (≤0.2 g/g [≤20 mg/mmol]).**
- **Aim for SBP at <90th percentile for age, sex, and height.**
- **Continue to follow patients after complete remission, as they can relapse even after many years.[101] In particular, yearly monitoring of blood pressure and urinalysis for patients with a history of pediatric IgAN is necessary.**

2.5 Global implementation of the updated IgAN KDIGO Guideline

At the time of finalizing this update a number of new therapies have been approved in a limited number of countries for the treatment of both CKD and IgAN and these have been included in this guideline update. However, the Work Group acknowledges that the cost and limited approval status of these therapies in most resource-poor countries with a high prevalence of IgAN mean many nephrologists will be unable to implement the updated KDIGO guideline in their clinical practice.

According to a recent global survey of clinical practice patterns in IgAN, nephrologists from low- and middle-resource settings where >75% of the world's population live and where CKD is

most prevalent (primarily in Asia, South America, and Africa), reported that <30% of sites enrolled patients with IgAN in clinical trials and that systemic glucocorticoids, which are affordable and widely available, were the most common treatment for patients with IgAN with persistent proteinuria. In Latin America and the Caribbean, only 5 of 33 nations (15%) have participated in IgAN clinical trials, highlighting the poor representation of these populations in clinical trial reports. In Asia, only China, Japan, Hong Kong, South Korea, Taiwan, and a small number of Southeast Asian countries have contributed patients to IgAN clinical trials, with poor representation from the Middle East and South Asia, particularly India. IgAN is a highly heterogeneous disease and a lack of clinical trial data from a large proportion of countries where IgAN has a higher prevalence than in most resource-rich countries, challenges the translation of the current clinical trial data to a large proportion of the worlds "at risk" population.

The lack of clinical trial activity in many resource-limited settings is multifaceted and includes a shortage of trained staff and infrastructure, skepticism about the value of clinical trials, and administrative and regulatory barriers. A particular, and now pressing, challenge in many resource-limited settings, including those that have contributed patients to clinical trials in IgAN, is that once a clinical trial has completed, sponsors may not prioritize these countries for drug approval and marketing. This is becoming a significant disincentive to many investigators from resource-limited settings who question the appropriateness of running clinical trials where patients are exposed to novel therapies with unproven safety, and there is a limited expectation that the drug with be available or affordable to them once the trial is completed.

This guideline acknowledges the challenges faced with respect to accessibility and affordability of each treatment included in the update and the Work Group acknowledges that there are also significant global disparities in access to clinical trials in IgAN and that for at least 80% of the world's population, a number of the treatments included in the update will be unattainable. The Work Group hopes that treatment alternatives that target the key drivers of continued nephron loss in IgAN quickly become accessible globally.

The kidney community must work with drug developers to ensure that clinical trials in IgAN are conducted in a truly representative global "at risk" population and that there is a commitment to make these potentially transformative drugs available to the global IgAN patient population.

2.6 Horizon scanning for future new drug approvals and updates to the Guideline

With a greater understanding of the pathogenesis of IgAN, in particular, the factors promoting the generation of pathogenic forms of IgA, the process of immune complex formation, and the importance of processes such as complement activation in the generation of glomerular inflammation, a number of new therapeutic approaches are being tested in clinical trials in IgAN. In parallel, there have been significant advances in targeting those pathways activated following cumulative nephron loss, and a number of drugs initially evaluated in diabetic kidney disease are now transitioning to CKD without diabetes, and as we have seen in the trials of SGLT2i, a significant proportion of these patients will have IgAN. Equally exciting, we are beginning to see trials of drug combinations, mirroring what we are likely to utilize in clinical practice.

Table 3 summarizes those phase 3 trials currently underway, with the hope that there will be up to eight new drugs approved for the treatment of IgAN in the next 4–5 years, targeting novel pathways in IgAN, including B cell modulation and complement activation. Similarly, there are likely to be new additions to the treatment of non-diabetic CKD that will need to be reviewed as

part of the management of the responses to IgAN-induced nephron loss. It is therefore likely that this guideline will require frequent updating for the foreseeable future.

Table 3 | Phase 3 clinical trials open in 2024 evaluating new treatments in IgAN

	Drug	Target	Clinical trial Registration number	Status July 2024
Drugs targeting the production of pathogenic forms of IgAN	Sibeprenlimab (Vis649)	APRIL	VISIONARY NCT05248646	In follow-up
	Zigakibart (BION1301)	APRIL	BEYOND NCT05852938	Recruiting
	Atacicept	APRIL/BAFF	ORIGIN3 NCT04716231	Recruiting
	Telitacicept	APRIL/BAFF	NCT05799287	Recruiting
Drugs targeting IgA immune complex mediated inflammation	Iptacopan (LNP023)	Complement alternative pathway Factor B	APPLAUSE-IgAN NCT04578834	In follow-up
	RO7434656	Complement alternative pathway Factor B	IMAGINATION NCT05797610	Recruiting
	Raviluzumab	Complement terminal pathway C5	I CAN NCT04564339	Recruiting
Drugs targeting the generic downstream consequences of IgAN-induced nephron loss	Atrasentan	Endothelin A receptor	ALIGN NCT 04573478	In follow-up

ALIGN, A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Atrasentan in Patients With IgA Nephropathy at Risk of Progressive Loss of Renal Function; APPLAUSE-IgAN, A Multi-center, Randomized, Double-blind, Placebo-controlled, Parallel Group, Phase III Study to Evaluate the Efficacy and Safety of LNP023 in Primary IgA Nephropathy Patients; APRIL, a proliferation-inducing ligand; BAFF, B cell-activating factor of the TNF family; BEYOND, A Phase 3, Randomized, Double-blind, Placebo-controlled Study of BION-1301 in Adults With IgA Nephropathy; I CAN, A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ravulizumab in Adult Participants With Proliferative Lupus Nephritis or Immunoglobulin A Nephropathy; IgAN, immunoglobulin A nephropathy; IMAGINATION, A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of RO7434656, an Antisense Inhibitor of Complement Factor B, in Patients With Primary IgA Nephropathy at High Risk of Progression; ORIGIN3, A Phase 2b/3, Multi-part, Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Atacicept in Subjects With IgA Nephropathy (IgAN); VISIONARY, A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy and Safety of Sibeprenlimab Administered Subcutaneously in Subjects With Immunoglobulin A Nephropathy.

Research recommendations

The following areas are of high priority for future research to improve the treatment and outcomes of patients with IgAN:

- **Risk stratification:** This is important for both patient evaluation and design of clinical trials. The International IgAN Prediction Tool should be:
    1. validated in additional racial populations not included in the original cohorts,
    2. further developed to enable prediction of progression risk serially during follow-up,
    3. evaluated in relation to specific treatment responses, and
    4. evaluated in populations with optimized CKD therapy (RASi, SGLT2i, sparsentan),
    5. evaluated to guide clinicians in understanding what percentage ranges define low, moderate, high, or very high risk of progression in line with other risk calculators.
- **Biomarker discovery and validation:** Identification and validation of serum, plasma, urine, and/or kidney biomarkers to inform:
    1. prognosis,
    2. treatment selection, particularly around the need for anti-inflammatory therapy, and
    3. monitoring response to treatment.
- **A better understanding of disease heterogeneity:** Incorporating studies of fundamental biology and continued transcontinental collaborative research to identify genetic, gender, and environmental factors influencing disease phenotype across races.
- **Clearer definition on the mechanism of action of the treatments being studied in IgAN**:
    1. Do RASi, SGLT2i, endothelin receptor antagonism, nefecon, B cell-activating factor of the TNF family (BAFF) and/or a proliferation-inducing ligand (APRIL) inhibition have a direct anti-inflammatory and antifibrotic effect in the kidney?
    2. Do systemic glucocorticoids at the dose recommended for the treatment of IgAN modulate production of pathogenic forms of IgA and immune complexes?
    3. Does complement inhibition have effects outside the glomerulus in terms of modulating tubulointerstitial inflammation and scarring?
- **Clearer definition of what constitutes glomerular inflammation requiring specific anti-inflammatory treatment:** Global studies should be undertaken to determine the glomerular lesions (presence and extent) that necessitate the addition of an anti-inflammatory treatment to a therapy that suppresses production of pathogenic forms of IgA and immune complexes.
- **Determination of the dose and duration of systemic glucocorticoid therapy required to treat glomerular inflammation when used in combination with a treatment that reduces production of pathogenic forms of IgA.**
- **Clinical trial design in IgAN:** The establishment of using earlier surrogate biomarkers of disease progression as a pathway to regulatory approval of novel therapies in IgAN has led to the rapid expansion of industry-sponsored studies targeting novel pathways to prevent progressive loss of kidney function in IgAN. These include ongoing, phase 3

studies of agents targeting pathways regulating IgA production and activity of the alternate complement pathway (Table 3). Data from completed phase 3/4 clinical trials with the emergence of approved therapies now challenges the ability to execute placebo-controlled trials in this disease. As new treatments come to market, patients in lengthy placebo-controlled studies with perceived inadequate treatment response are at risk of receiving off-protocol agents, potentially contaminating the treatment arms in a disproportionate manner. Thought must now be given to the use of an active comparator arm consisting of a therapy with proven efficacy. This will undoubtedly make future clinical trials more complex and emphasizes the need to identify even earlier surrogate biomarkers of an intervention's long-term benefit on kidney function decline, thereby allowing a reduction in the duration of clinical studies, thereby limiting the period of time patients are exposed to novel agents rather than the current standard of care treatments. Thought must also be given to treating people with IgAN currently excluded from major trials (e.g., those with proteinuria <1 g/d or those with a baseline eGFR <30 ml/min per 1.73 m^2).

- Finally, none of the available IgAN therapies are curative. Further research is required to establish the optimal combinations, sequencing and duration of treatments required to deliver maximal efficacy and minimal toxicity.

IMMUNOGLOBULIN A VASCULITIS

IgA vasculitis (IgAV), formerly Henoch–Schönlein purpura, is a form of vasculitis marked by IgA deposition within the blood vessels of affected tissues. IgAV commonly affects the small blood vessels of the skin, joints, intestines, and kidneys. Rarely, it can affect the lungs and central nervous system. It is the most common form of vasculitis in children. When IgAV occurs in children <16 years old, it is often self-limiting. Adults may have more severe and relapsing disease. Kidney involvement in IgAV is histopathologically indistinguishable from that seen in the kidney-limited disease IgAN. This guideline outlines management guidance for adults with IgAV-associated nephritis (IgAVN) and provides a practice point for children aged 1–18 years. A more extensive review of the management of IgAVN in children can be found in the 2024 International Pediatric Nephrology Association Guidelines for the Management of IgA nephropathy and IgA vasculitis (submitted).

The evidence base in IgAVN is extremely limited. This guideline, thus, heavily relies on extrapolating data from IgAN to IgAVN, although there is still no clear understanding of how these diseases are related. We make no specific recommendations on how to treat extrarenal organ involvement, in particular gastrointestinal vasculitis and pulmonary hemorrhage, which can be life-threatening and require immunosuppressive therapy independent of any kidney involvement.

2.7 Diagnosis

Practice Point 2.7.1: Considerations for the diagnosis of immunoglobulin A vasculitis associated nephritis (IgAVN):

- **There are no internationally agreed upon criteria for the diagnosis of IgAV in adults**
- **In children, a clinical diagnosis of IgAV can be made based on international criteria.[102-104]**
- **A diagnosis of IgAVN can only be made with a kidney biopsy**
- **A kidney biopsy should be performed in adults with suspected IgAV if there are signs of significant end organ tissue damage: proteinuria ≥0.5 g/d persistent for >4 weeks, kidney function impairment or an RPGN.**
- **Assess all adult patients with IgAV and IgAVN for secondary causes and for malignancy, with age- and sex-appropriate screening tests.**

2.8 Prognosis

Practice Point 2.8.1: Considerations regarding the prognosis of IgAVN:

- **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.[105-107]**
- **The utility of the Oxford MEST-C classification has recently been studied. [108] This showed that in patients treated with immunosuppression E1 lesions were strongly associated with initial improvement followed by progressive decline in kidney function.**

- **The International IgAN Prediction Tool[9] is not designed for determining prognosis of IgAVN.**

2.9 Treatment

2.9.1 Prevention of nephritis in IgAV

Recommendation 2.9.1.1: We recommend not using systemic glucocorticoids to prevent nephritis in patients with isolated extrarenal IgAV *(1B)*.

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

Key information

Balance of benefits and harms

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 systemic glucocorticoids in extrarenal IgAV does not reduce the incidence of kidney involvement. In an RCT of 352 children with IgAV, early treatment with prednisolone did not reduce the prevalence of proteinuria 12 months after disease onset.[109] This finding was replicated in 171 children showing that early use of prednisolone did not prevent the development of nephritis.[110] A meta-analysis of 5 RCTs in which 789 children were examined for the effects of short-duration systemic glucocorticoids (2–4 weeks) at presentation on preventing persistent nephritis at 6 and 12 months after the presentation concluded that such treatment had no preventive effect on onset of persistent nephritis.[111]

Certainty of evidence

There is moderate-certainty evidence based on five RCTs of prednisone versus placebo or supportive care in patients with IgAV (Supplementary Table S10[109-114]). The studies did not report on the critical and important outcomes of mortality, kidney failure, or ≥50% GFR loss, but had moderate certainty that prednisone did not significantly reduce the development of kidney disease any time after treatment (RR: 0.74; 95% CI: 0.42 to 1.32) or alter the presence of continuing kidney disease at 6 months (RR: 0.51; 95% CI: 0.24 to 1.11). There was also low certainty of evidence that prednisone did not affect the risk of continuing kidney disease at 12 months (RR: 1.06; 95% CI: 0.38 to 2.91) or development of severe kidney disease at about 4 years (RR: 1.58; 95% CI: 0.42 to 6.0). The certainty of evidence was downgraded for methodological concerns in the trials (inadequate allocation concealment, lack of blinding) and imprecision.

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

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

Practice Point 2.9.1.1: Considerations for the management of all patients with IgAV-associated nephritis (IgAVN) who are at risk of progressive kidney function decline and do not have a rapidly progressive glomerulonephritis:

- **Proteinuria ≥0.5 per day (while on or off treatment for IgAVN) identifies a patient with IgAVN at increased risk of progressive loss of kidney function.**
- **The aspiration for the management of IgAVN, like IgAN, should be to *simultaneously***
  - **Prevent or reduce IgA immune complex formation, mesangial deposition, and immune complex mediated glomerular injury.**
  - **In parallel, manage the consequences of existing IgAVN-induced nephron loss.**
- **Unlike IgAN, there are no treatments proven to prevent/reduce IgA immune complex formation in IgAVN.**
- **Prevention of immune complex-mediated injury should incorporate treatments with proven anti-inflammatory effects, and ideally should be used in combination with, and not as a replacement for, treatments that prevent/reduce IgA immune complex formation.**
  - **In all patients in whom systemic glucocorticoids are being considered, a detailed discussion of the risks and benefits of each drug should be undertaken with the patient.**
  - **In those patients who wish to try systemic glucocorticoids, a reduced-dose regimen as described for IgAN should be employed with antimicrobial prophylaxis.**
- **Management of the consequences of IgAVN-induced nephron loss should include:**
  - **Lifestyle advice, including information on dietary sodium restriction, smoking cessation, weight control, and exercise, as appropriate,**
  - **Control blood pressure to a target of ≤120/70 mm Hg, using a RASi as the first choice drug intervention**
  - **Measures to reduce glomerular hyperfiltration and the impact of proteinuria on the tubulointerstitium, using singly or in combination, RASi and SGLT2i, and**

- **A thorough cardiovascular risk assessment and commencement of appropriate interventions, as necessary.**

- **Offer participation in a clinical trial if one is available.**
- **There is insufficient evidence to support the use of the Oxford Classification MEST-C score in determining which drug should be commenced in IgAVN.**
- **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.**

2.10 Special situations

Practice Point 2.10.1: IgAV with RPGN:

- **The potential risks and benefits of immunosuppression should be evaluated at the individual patient level and discussed with the patient.**
- **Patients agreeing to treatment should be treated in accordance with the KDIGO 2024 Clinical Practice Guideline for the Management of ANCA-Associated Vasculitis.[44]**
- **IgAVN with RPGN, as well as other presentations of IgAVN, may be associated with significant extrarenal involvement (pulmonary, gastrointestinal, and skin), which may dictate alternative immunosuppressive strategies.**
- **There are insufficient data to determine the efficacy of plasma exchange in IgAVN with RPGN. However, uncontrolled case series describe the potential role for the addition of plasma exchange to glucocorticoid therapy to accelerate recovery in patients with life- or organ-threatening extrarenal complications of IgAV.[115]**

2.10.1 IgAV-associated nephritis in children

Practice Point 2.10.1.1: In this guideline, we define children as those aged <18 years, but it is acknowledged that post-pubertal children in some respects may have a similar course and response to treatment as adults with IgAN. However, there are insufficient data currently to recommend that they be managed as adults with IgAN.

Practice Point 2.10.1.2: A more extensive review of the management of IgAVN in children can be found in the 2024 International Pediatric Nephrology Association Guidelines for the Management of IgA nephropathy and IgA vasculitis (submitted).

Briefly:

- **The majority of children who will develop nephritis do so within 3 months of presentation. Urinary monitoring is necessary at onset of vasculitis and then at least monthly for ≥6 months from initial presentation of systemic disease.**

- **A kidney biopsy should be promptly performed in children with nephrotic-range proteinuria or impaired GFR (<90 ml/min per 1.73 m^2).**
- **In children with IgAV and moderate proteinuria (PCR 1000–2000 mg/g or 100-200 mg/mmol) for 2–4 weeks or mild proteinuria (PCR 200-500 mg/g or 20–50 mg/mmol) for >4 weeks a kidney biopsy should be considered.**
- **In children with confirmed IgAVN, a pediatric nephrologist should be consulted.**
- **In children with IgAVN and persistent proteinuria for >3 months, ACEi or ARB treatment should be considered.**
- **There are no data supporting the use of glucocorticoids to prevent nephritis in children with IgAV and absent evidence of kidney involvement or with isolated microhematuria.[116, 117]**
- **Oral prednisone/prednisolone for 3–6 months or pulsed intravenous methylprednisolone should be considered in children with IgAVN and nephrotic-range proteinuria (PCR >2000 mg/g or 200 mg/mmol) or RPGN and histological risk for progression (International Study of Kidney Disease in Children [ISKDC] ≥II).**
- **Other immunosuppressive agents in addition to glucocorticoids (e.g., calcineurin inhibitors, cyclophosphamide, mizoribine where available, mycophenolate mofetil or rituximab) should be considered in the following indications: to reduce the glucocorticoid dose and/or if PCR >2000 mg/g (200 mg/mmol) and/or insufficient response to glucocorticoids.**
- **Children with IgAVN with nephrotic syndrome and/or rapidly deteriorating kidney function are treated in the same way as those with rapidly progressive IgAN.**
- **Monitoring children with IgAVN with evaluation of urinalysis, eGFR, and blood pressure should be considered for ≥5 years after the initial episode. Lifelong monitoring, individualized according to the severity and response to treatment, appears prudent for children who received therapy for their IgAVN.**

Research recommendations

- Unlike IgAN, there are currently few clinical trials of novel therapies in IgAVN. 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.
- In light of preliminary observational data,[118, 119] suggesting a potential benefit with rituximab, we recommend a dedicated prospective RCT of rituximab in IgAV.
- A better understanding of the natural history and pathogenesis of IgAVN, and identification of factors predictive of future kidney function decline in IgAVN is warranted and this may be possible by utilizing large national registries and biorepositories in North America, the United Kingdom, and Europe.

METHODS FOR GUIDELINE DEVELOPMENT

Aim

This is an update of the IgAN and IgAV chapter (Chapter 2) of the KDIGO Clinical Practice Guideline for Glomerulonephritis published in 2021.[120] Based on recently published evidence in the field, it was decided that a guideline update was required.

The objective of this project was to update the evidence-based clinical practice guideline for the management of IgAN and IgAV. The guideline development methods are described below.

Overview of the process

This guideline adhered to international best practices for guideline development (Appendix B: Supplementary Tables S2 and S3).[121] This guideline has been developed and reported in accordance with the AGREE II reporting checklist.[122] The processes undertaken for the development of the KDIGO 2024 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV) are described below.

- Appointing Work Group members and the Evidence Review Team (ERT)
- Finalizing guideline development methodology
- Defining scope of the guideline
- Implementing literature search strategies to update the evidence base for the guideline
- Selecting studies according to predefined inclusion criteria
- Conducting data extraction and critical appraisal of the literature
- Updating evidence synthesis and meta-analysis to included newly identified studies
- Updating the certainty of the evidence for each outcome across studies
- Grading the strength of the recommendation, based on the certainty of the evidence and other considerations
- Convening a public review in August 2024
- Amending the guideline based on the external review feedback and updating the literature search
- Finalizing and publishing the guideline

Commissioning of Work Group and ERT

The KDIGO Co-Chairs appointed the Work Group Co-Chairs, who then assembled the Work Group, to include content experts in adult nephrology, epidemiology, and public health. The Work Group was responsible for writing the recommendations, practice points, and underlying rationale, as well as grading the strength of each recommendation.

For the 2024 update, the Brown University School of Public Health Center for Evidence Synthesis in Health was contracted to update the systematic evidence review and provide

expertise in guideline development methodology. The Brown ERT consisted of a senior physician-methodologist who led the ERT for the KDIGO 2012 Clinical Practice Guideline for Glomerulonephritis, an adult nephrologist, and a librarian–methodologist, all with expertise in evidence synthesis and guideline development, including for KDIGO guidelines. Cochrane Kidney and Transplant was contracted to conduct systematic evidence review and provide expertise in guideline development methodology for the 2021 guideline.

Defining scope and topics and formulating key clinical questions

Due to resourcing and the probability of practice-changing studies, clinical questions on effectiveness and safety of interventions included in the guideline update were limited to randomized controlled trials (RCTs) to avoid bias by design. Guideline topics and clinical questions focusing on nonrandomized studies were not included in the guideline update (Supplementary Table S1). The guideline Work Group, with assistance from the ERT, determined the overall scope of the guideline. A preliminary list of topics and key clinical questions was informed by the previous KDIGO guideline.[120] Clinical questions adhered to the population, intervention, comparator, outcomes, and study design (PICOD) format (a list of critical and important outcomes was compiled after voting by the Work Group [Table 4]). Clinical questions were mapped to existing Cochrane Kidney and Transplant systematic reviews. These systematic reviews were updated accordingly. For clinical questions that did not map to any Cochrane Kidney and Transplant systematic reviews, *de novo* systematic reviews were undertaken. The previous guideline was reviewed to ensure all identified studies were included in the evidence review.[120] Details of the PICOD questions and associated Cochrane Kidney and Transplant systematic reviews are provided in Table 5.[123-125] All evidence reviews were conducted in accordance with the Cochrane Handbook,[126] and guideline development adhered to the standards of GRADE (Grading of Recommendations, Assessment, Development, and Evaluation).[127]

Table 4 | Hierarchy of outcomes

Hierarchy	Outcomes
Critical outcomes	• All-cause mortality • Kidney failure • ≥50% loss of GFR • Infection • Glucocorticoid-related adverse events • Malignancy
Important outcomes	• Complete remission/relapse • Annual GFR loss (minimum 3 years follow-up)

GFR, glomerular filtration rate.
The critical and important outcomes were voted on by the Work Group using an adapted Delphi process (1–9 Likert scale). Critical outcomes were rated 7–9, and important outcomes were rated 4–6 on the 9-point scale.

Table 5 | Clinical questions and systematic review topics in PICOD format

PICOD criteria	**IgAN or IgAV**
Clinical question	**In patients with biopsy-proven IgAN, what non-immunosuppressive agents, compared to no treatment, placebo, or standard of care, improve efficacy outcomes and reduce adverse effects?**
Population	Patients with IgAN
Intervention	Non-immunosuppressive agents or treatments: Sparsentan, sodium-glucose cotransporter-2 inhibitors (SGLT2i), fish oil, anticoagulants or antiplatelets, antioxidants, tonsillectomy, statins, allopurinol, etc. Exclude: traditional Chinese medicine, complementary and alternative medicine, diets
Comparator	No treatment, placebo, standard of care, or other non-immunosuppressive agents or treatments
Outcomes	Outcomes listed in Table 4
Study design	2021 Guideline: RCTs and observational studies 2024 Guideline: RCTs published in peer-reviewed journals (or meta-analysis based on RCTs)
Cochrane systematic review	Reid SM, *et al*. Non-immunosuppressive agents for treating IgA nephropathy (Review). *Cochrane Database of Systematic Reviews.* 2011:3;CD003962[39]
SoF tables	Supplementary Tables S5, S7–S9, and S31–S52
Clinical question	**In patients with biopsy-proven IgAN, what immunosuppressive agents, compared to no treatment, placebo, or standard of care, improve efficacy outcomes and reduce adverse effects?**
Population	Patients with IgAN
Intervention	Immunosuppressive therapy
Comparator	No treatment, placebo, standard of care, or other immunosuppressive therapies
Outcomes	Outcomes listed in Table 4
Study design	2021 Guideline: RCTs and observational studies 2024 Guideline: RCTs published in peer-reviewed journals (or meta-analysis based on RCTs)
Cochrane systematic review	Natale P, *et al*. Immunosuppressive agents for treating IgA nephropathy (Review). *Cochrane Database of Systematic Reviews.* 2020:3;CD003965[128]

SoF tables	Supplementary Tables S4, S6, and S11–S30
Clinical question	**In patients with biopsy-proven IgAV (Henoch-Schönlein purpura), what immunosuppressive agents, compared to no treatment, placebo, or standard of care, improve efficacy outcomes and reduce adverse effects?**
Population	Patients with IgAV with nephritis
Intervention	Immunosuppressive therapy
Comparator	No treatment, placebo, standard of care, or other immunosuppressive therapies
Outcomes	Outcomes listed in Table 4
Study design	2021 Guideline: RCTs and observational studies 2024 Guideline: RCTs published in peer-reviewed journals (or meta-analysis based on RCTs)
Cochrane systematic review	Hahn D, *et al*. Interventions for preventing and treating kidney disease in Henoch-Schönlein purpura (HSP) (Review). *Cochrane Database of Systematic Reviews.* 2015:8;CD005128[111]
SoF tables	Supplementary Tables S10 and S53–S61

IgAN, immunoglobulin A nephropathy; IgAV, immunoglobulin A vasculitis; PICOD, Population, Intervention, Comparator, Outcomes, Study design; RCT, randomized controlled trial; SoF, summary of findings.

Literature searches and article selection

For the KDIGO 2024 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV), updated literature searches were conducted in MEDLINE (via PubMed), Embase, and the Cochrane Central Register of Controlled Trials (Appendix A: Supplementary Table S1). The searches were restricted to records entered into the databases since January 1, 2020. This was done to provide a 6-month overlap with the prior searches. The searches were conducted on April 19, 2023. These search updates included terms for IgAN, IgAV, nephrotic syndrome (NS), and minimal change disease (MCD) (which all underwent concurrent updates).

The titles and abstracts resulting from the searches were screened by the 3 members of the ERT who independently assessed retrieved abstracts, and for accepted abstracts, the full text, to determine which studies satisfied the inclusion criteria. Disagreement about inclusion was resolved by discussion among the 3 members of the ERT.

For the KDIGO 2021 guideline, a total of 25,925 citations were screened. Of these, 479 RCTs and 102 observational studies were included in the evidence review for all diseases. For the current 2024 update, a total of 4094 citations were screened (for IgAN/IgAV, NS, and MCD) (Figure 5). From these, we found 20 new eligible articles on IgAN, representing 16 new RCTs.

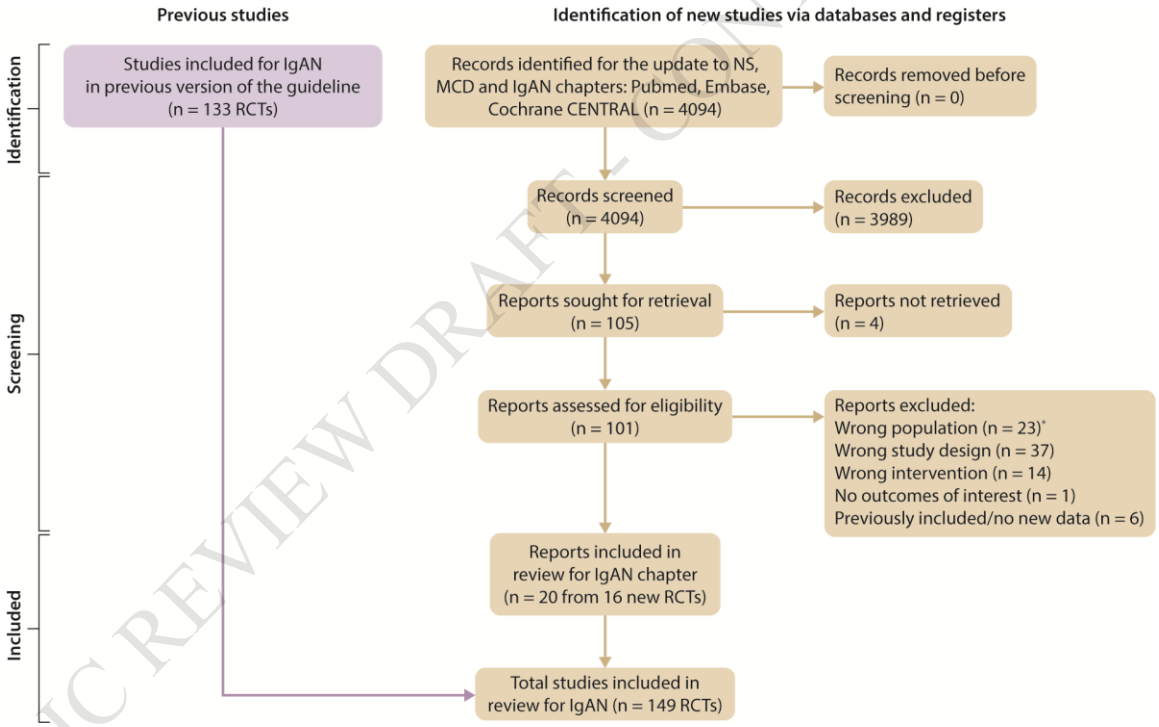

Figure 5 | Search yield and study flow diagram. *Includes 19 studies identified for guideline updates relevant to Minimal Change Disease (MCD) and Nephrotic Syndrome (NS) in Children. IgAN, immunoglobulin A nephropathy; RCT, randomized controlled trial

Data extraction

For the KDIGO 2024 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV), data extraction was performed by 1 member of the Brown ERT and confirmed by the 2 other members of the ERT. The Brown ERT extracted data into the forms designed by the Cochrane ERT. The Cochrane 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 update included only RCTs. For these studies, the Cochrane Risk of Bias tool was used to assess individual study limitations based on the following items[129]:

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at risk of bias?

All critical appraisal was conducted independently by 2 members of the ERT, with disagreements regarding the risk of bias adjudications resolved by consultation with a third review author.

Evidence synthesis and meta-analysis

Measures of treatment effect

Dichotomous outcome (all-cause mortality, kidney failure, ≥50% loss of GFR, infection, malignancy, and complete remission/relapse) results were expressed as RR with 95% CI. The continuous scale outcome annual GFR loss was evaluated as a MD with 95% CI.

Data synthesis

Data were pooled using the Mantel-Haenszel random-effects model for dichotomous outcomes and the inverse variance random-effects model for continuous outcomes. The random-effects model was chosen because it provides a conservative estimate of effect in the presence of known and unknown heterogeneity.[126]

Assessment of heterogeneity

Heterogeneity was assessed by visual inspection of forest plots of standardized mean effect sizes, and of RRs, and by the I2 statistic, which measures the proportion of total variation in the estimates of treatment effect that was due to heterogeneity beyond chance.365 We used conventions of interpretation as defined by Higgins et al.[130]

Assessment of publication bias

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).[126] Other reasons for the asymmetry of funnel plots were considered.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was undertaken to explore whether there were clinical differences among the studies that may have systematically influenced the differences that were observed in the critical and important outcomes. However, subgroup analyses are hypothesis-forming rather than hypothesis-testing and should be interpreted with caution. The following subgroups were considered: baseline kidney function (GFR, proteinuria, presence of albuminuria, presence of macroscopic hematuria), histopathologic class of disease, primary versus secondary forms of disease, sex, and adult versus pediatric. The test of subgroup differences used the I^2 statistic and a *P* value of 0.10 (noting that this is a weak test).[126]

Sensitivity analysis

The following sensitivity analyses were considered:

- Repeating the analysis excluding unpublished studies
- Repeating the analysis, taking account of the risk of bias, as specified
- Repeating the analysis excluding any very long or large studies, to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: language of publication, source of funding (industry vs. other), and country in which the study was conducted.

However, the available data were insufficient to determine the influence of these factors on the effect size of critical and important outcomes.

Grading the certainty of the evidence and the strength of a guideline recommendation

Grading the certainty of the evidence for each outcome across studies

The overall certainty of the evidence related to each critical and important outcome was assessed using the GRADE approach,[127, 131] which assesses the certainty of the evidence for each outcome. For all outcomes, the data were from RCTs; thus, the initial grade for the certainty of the evidence is considered to be high. The certainty 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, we considered the width of the 95% CI, such that for RR, if the 95% CI extended beyond both 0.5 and 2.0, the evidence was considered very imprecise. We also considered sparse data (only 1 study) to be imprecise.[131] The final grade for the certainty of the evidence for an outcome could be high, moderate, low, or very low (Table 6). For further details on the GRADE approach for rating certainty of the evidence, see Table 7.

Table 6 | Classification for certainty of the evidence

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

Table 7 | GRADE system for grading certainty of evidence

Study design	Step 1—Starting grade for the certainty of evidence	Step 2—Lower grade	Step 3—Raise grade for observational evidence
RCT	High	Study limitations: –1, serious –2, very serious	Strength of association +1, large effect size (e.g., <0.5 or >2) +2, very large effect size (e.g., <0.2 or >5)
	Moderate	Inconsistency: –1, serious –2, very serious	Evidence of a dose–response gradient
Observational	Low	Indirectness: –1, serious –2, very serious	All plausible confounding would reduce the demonstrated effect
	Very low	Imprecision: –1, serious –2, very serious –3, extremely serious	
		Publication bias: –1, strongly suspected	

RCT, randomized controlled trial; GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

Summary of findings (SoF) tables

The SoF tables were developed to include a description of the population, intervention, and comparator. In addition, the SoF tables included results from the data synthesis as relative and absolute effect estimates. The grading of the certainty of evidence for each critical and important

outcome is also provided in the SoF tables. For the 2024 update, the SoF tables were updated or created manually. The SoF tables are available in the Data Supplement: Appendix C and Appendix D.

Developing the recommendations

For the KDIGO 2024 Clinical Practice Guideline, the existing recommendations were reviewed and revised, as necessary, and new recommendations were drafted by the Work Group and Co-Chairs. Recommendations were revised in a multistep process by email and teleconferences. The Brown ERT participated in these discussions to ensure consistency with the evidence base and to provide additional feedback.

The final draft was sent for external public review, and reviewers provided open-ended responses. Based on the external stakeholder feedback, the draft was further revised by the Work Group. All Work Group members provided feedback on initial and final drafts of the guideline statements and text, and approved the final version of the guideline. The ERT also provided a descriptive summary of the certainty of evidence in support of the recommendations.

Grading the strength of the recommendations

The strength of a recommendation is graded as Level 1, "we recommend" or Level 2, "we suggest" (Table 8). 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 certainty of the evidence, patient values and preferences, resource use and costs, and considerations for implementation (Table 9).

Table 8 | KDIGO nomenclature and description for grading of 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 9 | Determinants of the strength of recommendation

Factors	Comment
Balance of benefits and harms	The larger the difference between the desirable and undesirable effects, the more likely a strong recommendation is provided. The narrower the gradient, the more likely a weak recommendation is warranted.
Certainty of evidence	The higher the certainty of evidence, the more likely a strong recommendation is warranted. However, there are exceptions for which low or very low certainty of the evidence will warrant a strong recommendation.
Values and preferences	The more variability in values and preferences, or the more uncertainty in values and preferences, the more likely a weak recommendation is warranted. Values and preferences were obtained from the literature, when possible, or were assessed by the judgment of the Work Group when robust evidence was not identified.
Resource use and costs	The higher the costs of an intervention—that is, the more resources consumed—the less likely a strong recommendation is warranted.

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.

Overall certainty of evidence

The overall certainty of the evidence was based on the certainty of the evidence for all critical and important outcomes, taking into account the relative importance of each outcome to the population of interest. The overall certainty of the evidence was graded (A, B, C, or D—Table 6).

Patient values and preferences

No patients or caregivers participated in the Work Group. The Work Group, from their experience in managing patients with glomerular diseases and their understanding of the best available scientific literature, made judgments on the values and preferences of patients. Formal qualitative evidence synthesis on patient priorities and preferences was undertaken by the Cochrane ERT for the 2021 update, but there was limited evidence available to inform the formulation of guideline recommendations (Appendix D).

Resource use and costs

Healthcare and non-healthcare resources, including all inputs in the treatment management pathway,[132] were considered in grading the strength of a recommendation. The following resources were considered: direct healthcare costs; non-healthcare resources, such as

transportation and social services; informal caregiver resources (e.g., time of family and caregivers); and changes in productivity. Economic evaluations, including cost-effectiveness analysis, were not conducted for any of the guideline topics.

Practice points

In addition to graded recommendations, KDIGO guidelines now include "practice points" to help clinicians better evaluate and implement the guidance from the expert Work Group. Practice points are consensus statements about a specific aspect of care, and they supplement recommendations for which a larger quantity of evidence was identified. They are issued when a clinical question was not supported by a systematic review, often to help readers implement the guidance from graded recommendation. Practice points represent the expert judgment of the guideline Work Group, but they also may be based on limited evidence. For example, practice points were provided on monitoring, factors for consideration in treating patients with IgAN/IgAV, dosing adjustments, 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 (Level 1 or Level 2) and the certainty of the evidence (A, B, C, D). The recommendation statements are followed by Key information (*Balance of benefits and harms, Certainty of the evidence, Values and preferences, Resource use and costs, Considerations for implementation*), and Rationale. Each recommendation is linked to relevant SoF 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. The reviews were not exhaustive, as specialty or regional databases were not searched, and manual searching of journals was not performed for these reviews. In the development of these guidelines, no scoping exercise with patients, limited searches of the qualitative literature, nor formal qualitative evidence synthesis examining patient experiences and priorities were undertaken. As noted, although resource implications were considered in the formulation of recommendations, formal economic evaluations were not undertaken for all topics.

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