KDIGO 2025 IgAN Update:
The Time for Clinical Nihilism is Over

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KDIGO guideline updated – 2012, 2021 to 2025

2025 KDIGO guideline update

2025

The update takes into consideration evidence from randomized controlled trials published through **August 2024**:

- Systematic reviews of relevant studies
- Strength of recommendations following the GRADE approach
- Limitations of the evidence
- Areas of future research

Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. Kidney Inter., Suppl. 2012; 2: 139–274.
KDIGO Glomerular Diseases Work Group. Kidney Int. 2021 Oct;100(4S)S1-S276.
KDIGO 2025 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF IMMUNOGLOBULIN A NEPHROPATHY (IgAN) AND IMMUNOGLOBULIN A VASCULITIS (IgAV)

IGAN IS THE MOST COMMON PRIMARY GLOMERULONEPHRITIS GLOBALLY

Prevalence of IgAN worldwide (Berger disease)

More common:

- Southern Europe
- Asia
- Native Americans

Onset: peak 20 – 30 years

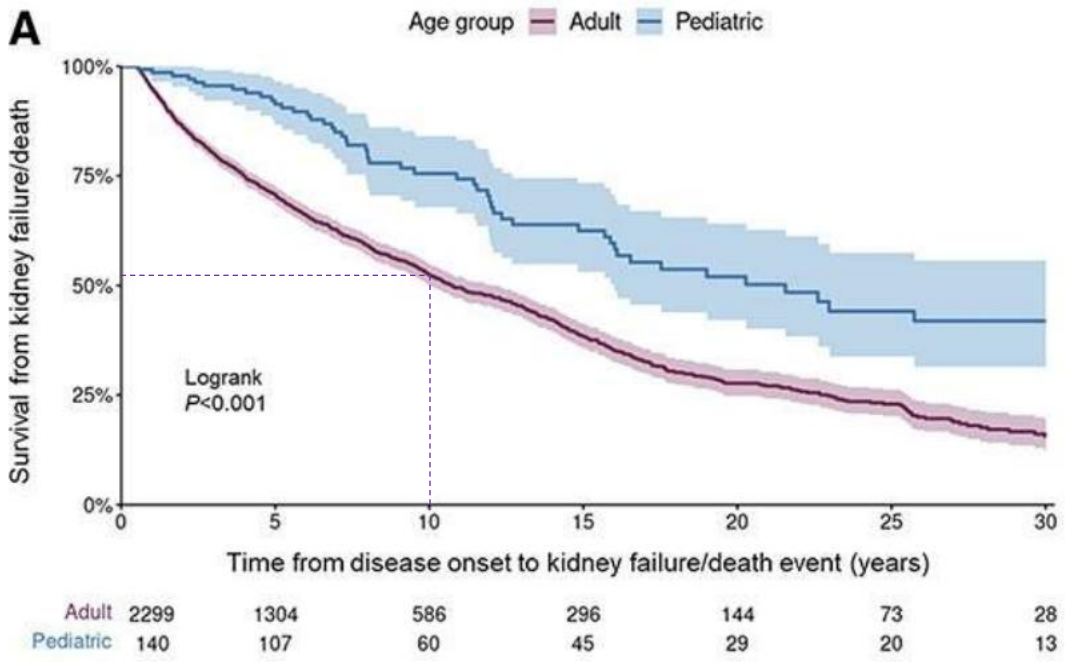
Male : Female ratio:

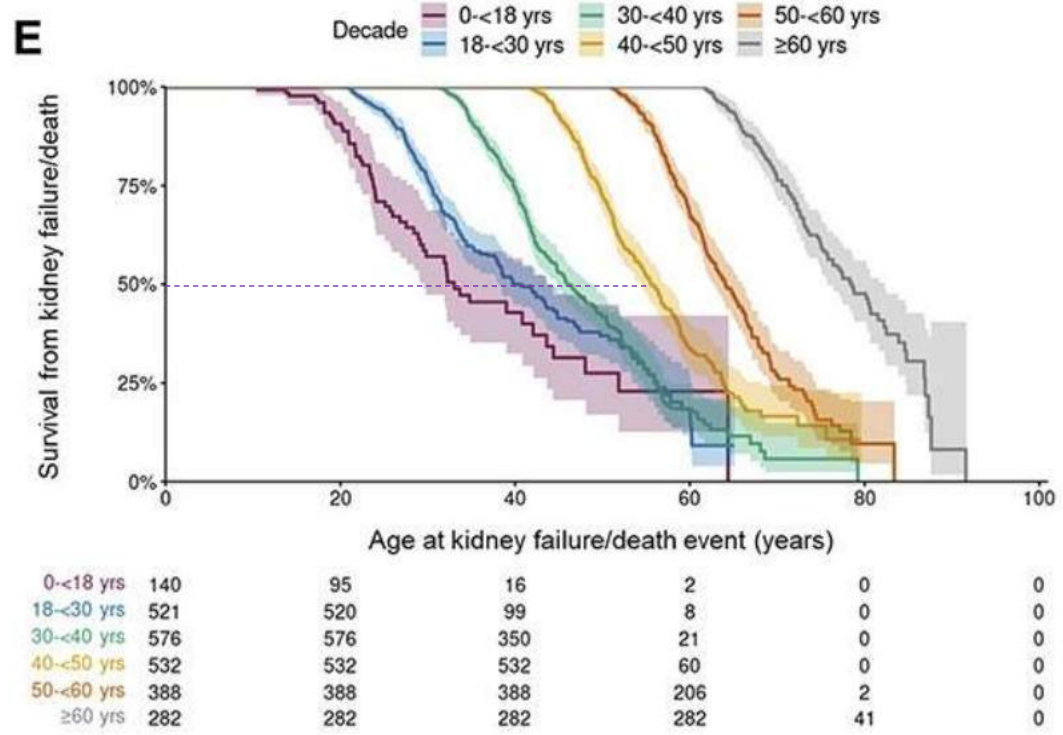
- 2:1 in Europe / U.S
- 1:1 in Asia

Stamellou E et al. Nat Rev Dis Primers. 2023

LONG TERM OUTCOMES IN IGA NEPHROPATHY REMAIN POOR

MOST PATIENTS DEVELOP KIDNEY FAILURE WITHIN THEIR LIFETIME





Pitcher D et al. Clin J Am Soc Nephrol. 2023;18(6):727-738.

PROTEINURIA IS A KEY DETERMINANT OF KIDNEY FAILURE RISK

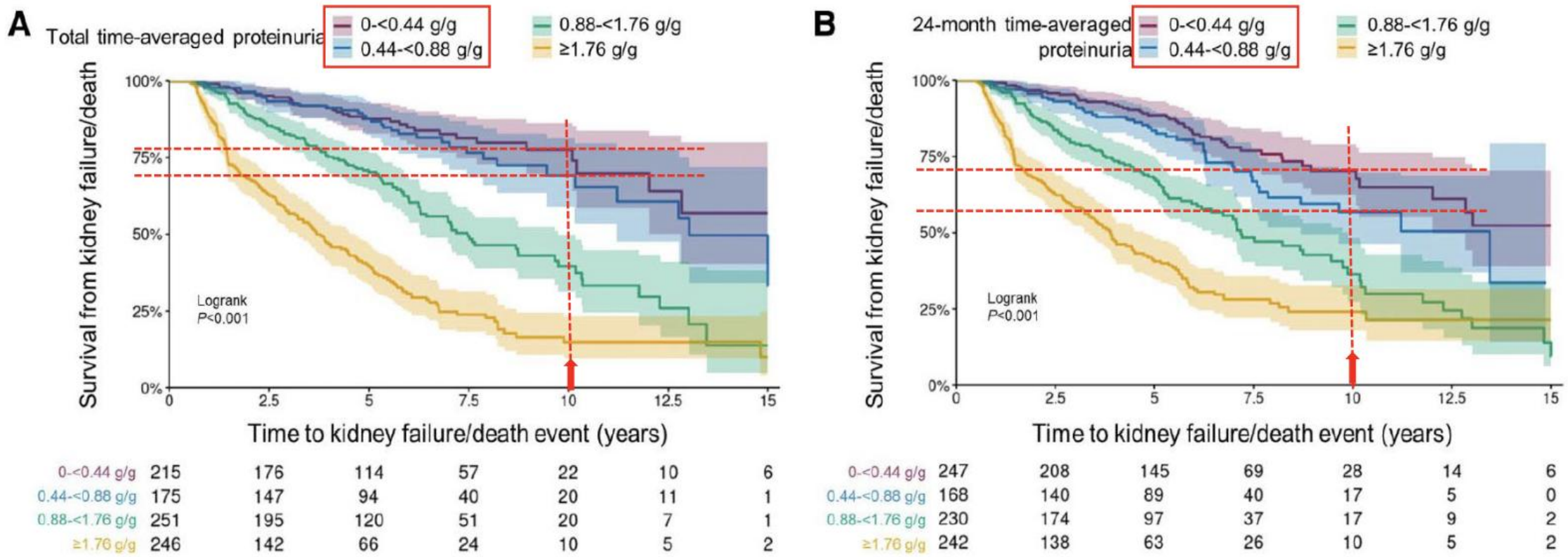
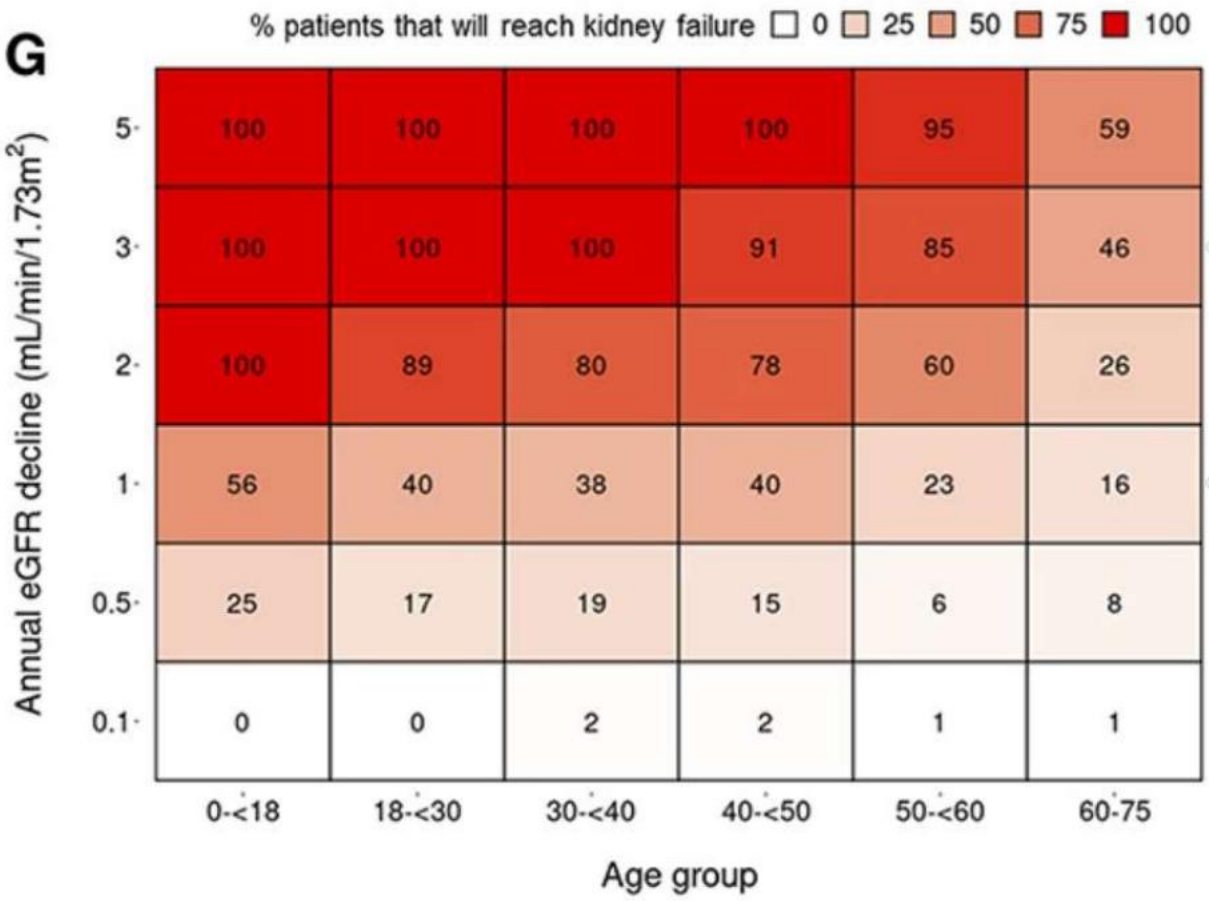


Figure 2. Kaplan–Meier survival curves of time to kidney failure/death event in population 1. (A) Using total follow-up time-averaged proteinuria. (B) Using 24-month time-averaged proteinuria. 0.44 g/g=50 mg/mmol; 0.88 g/g=100 mg/mmol; 1.76 g/g=200 mg/mmol.

Pitcher D et al. Clin J Am Soc Nephrol. 2023;18(6):727-738.

EGFR STABILIZATION IS CRITICAL FOR PREVENTING KIDNEY FAILURE OVER LIFETIME



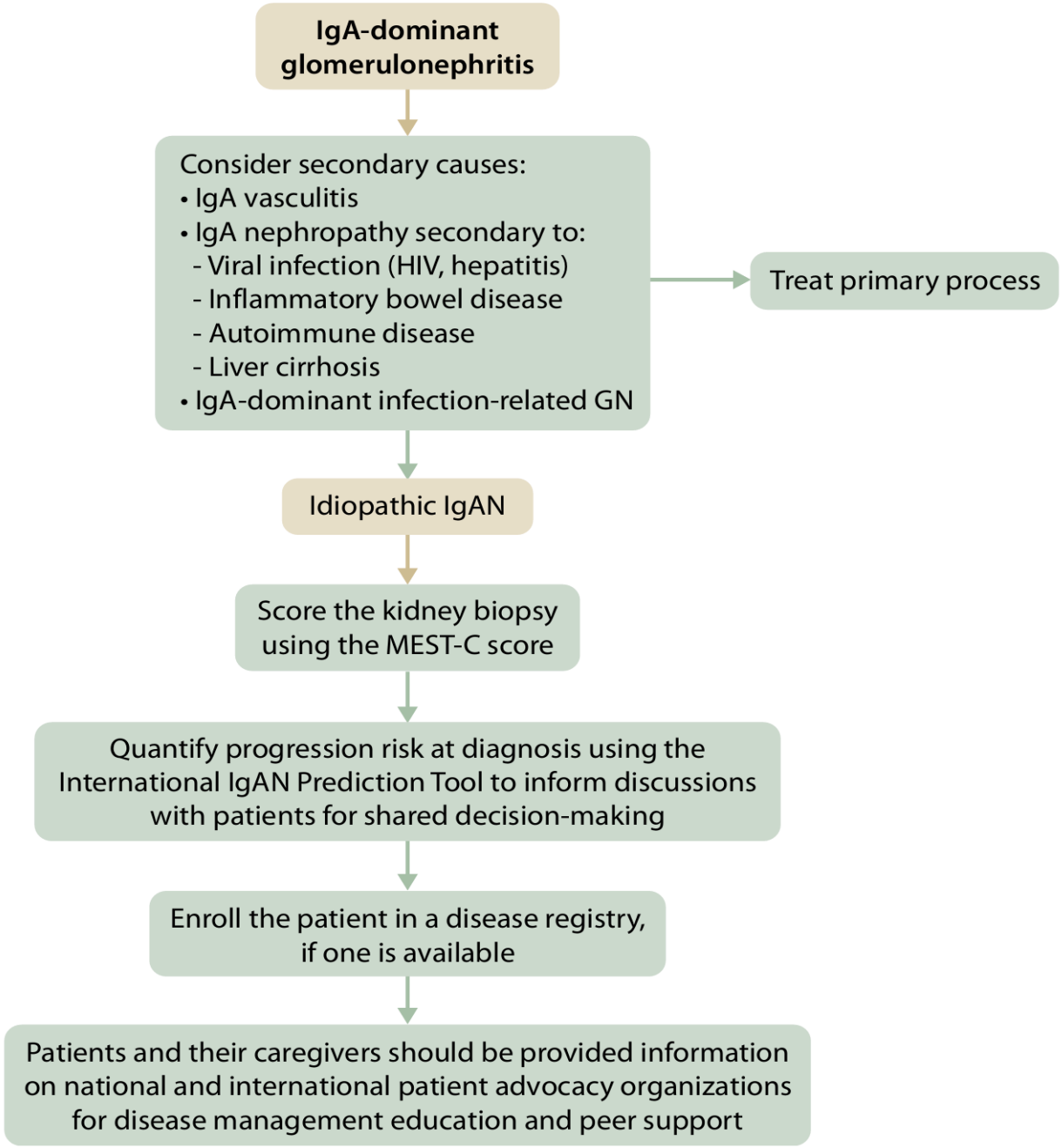
100% of patients diagnosed before age of 40 yr will reach kidney failure

~40% of patients diagnosed before age of 50 yr will reach kidney failure

To avoid kidney failure within lifetime, must target eGFR decline of < 1 ml/min/1.73 m_2 per year

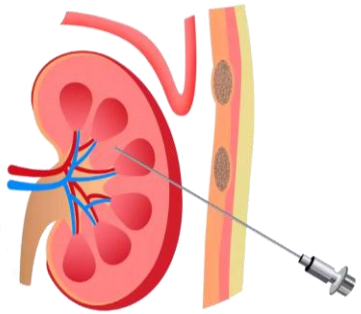
Pitcher D et al. Clin J Am Soc Nephrol. 2023;18(6):727-738.

Initial assessment of the patient with IgAN



2025 KDIGO first indicated the recommended timing to conduct kidney biopsy - proteinuria ≥0.5 g/d (or equivalent)

- IgAN can only diagnosed by **kidney biopsy**



- 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 who do not have a contraindication for kidney biopsy.

Exclude secondary causes:

- IgA vasculitis
- IgAN originated from
  - HIV, hepatitis B/C
  - IBD
  - Autoimmune disease
  - Liver cirrhosis
- IgA dominant post-infectious GN

2025 version mentioned the timing to conduct kidney biopsy to indicate that suspected patients shall be diagnosed early for treatment

Timing of Renal biopsy for IgA Nephropathy

2021 KDIGO

Timing for a kidney biopsy:
- No recommendation

Defining patients with IgAN at high risk of progression in IgAN:
- **Proteinuria ≥0.75-1 g/d**, despite **≥ 90 days** of optimized supportive care

Treatment goal:
- Proteinuria reduction to **< 1 g/d** is a surrogate marker of improved kidney outcome in IgAN, and reduction to under 1 g/d is a reasonable target.

The **management** of patients with IgAN:
- All patients with **proteinuria >0.5 g/d,** irrespective of whether they have hypertension, be treated with either an **ACEi or ARB**
- Patients who remain at high risk of progressive CKD despite maximal supportive care be considered for **a 6-month course of glucocorticoid** therapy.

2025 KDIGO

Timing for a kidney biopsy:
- All adults with **proteinuria ≥0.5 g/d** in whom IgAN is a possible diagnosis

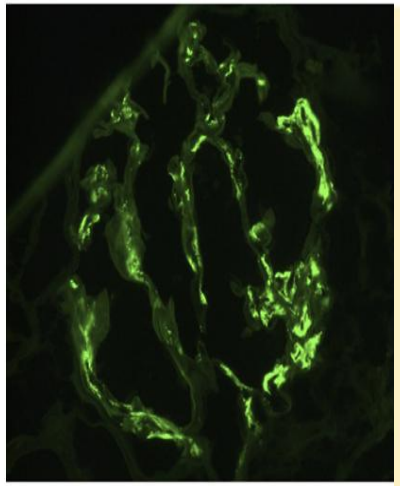
Defining patients with IgAN at risk of progressive kidney function loss:
- **Proteinuria ≥0.5 g/d**, while on or off treatment for IgAN

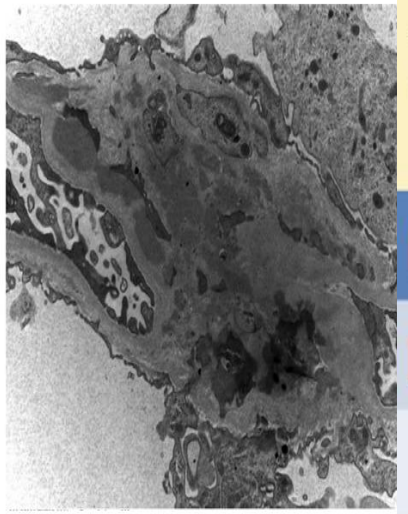
Treatment goal:
- Reduce the rate of loss of kidney function to **<1 ml/min** per year.
- Urine protein excretion should be maintained **<0.5 g/d,** preferably **<0.3 g/d**

The **focus of management** in most patients should be to simultaneously:
- **Prevent or reduce IgA immune complex formation and immune complex mediated glomerular injury.**
  - Nefecon (TRF-Budenoside); reduced-dose systemic glucocorticoid
- Manage the consequences of existing IgAN-induced nephron loss.
  - Control of blood pressure with a target of **≤ 120/70 mm Hg: RAS blockade** / **MRA, SGLT2i**

HALLMARK OF IGAN:

MESANGIAL IGA STAINING IN IF





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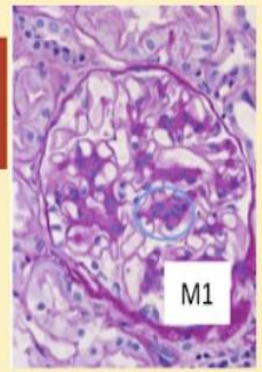
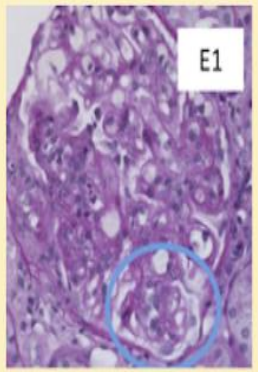


Mesangial hypercellularity

≥4 mesangial cells in any mesangial area of a glomerulus

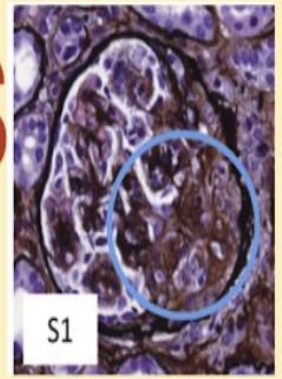
E



Endocapillary hypercellularity

An increased number of cells in glomerular capillary lumen

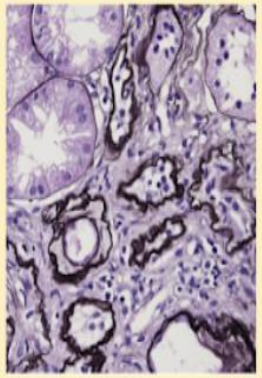
S



Segmental glomerulosclerosis

Adhesion or sclerosis that not involving the entire glomerulus

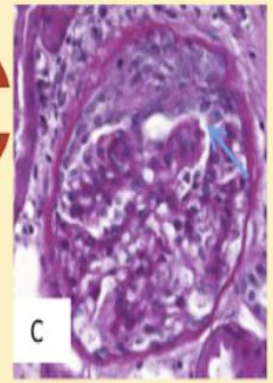
T



Tubular atrophy/ interstitial fibrosis

The percentage of tubular atrophy/ interstitial fibrosis of cortical area

C



Cellular/ fibrocellular crescents

Extracapillary cell proliferation > 2 cell layers thick and <50% matrix

M0 ≤50% of glomeruli	E0 Absence	S0 Absence	T0 0-25%	C0 Absence
M1 >50% of glomeruli	E1 Any presence	S1 Any presence	T1 26%-50%	C1 <25% of glomeruli
			T2 >50%	C2 ≥25% of glomeruli

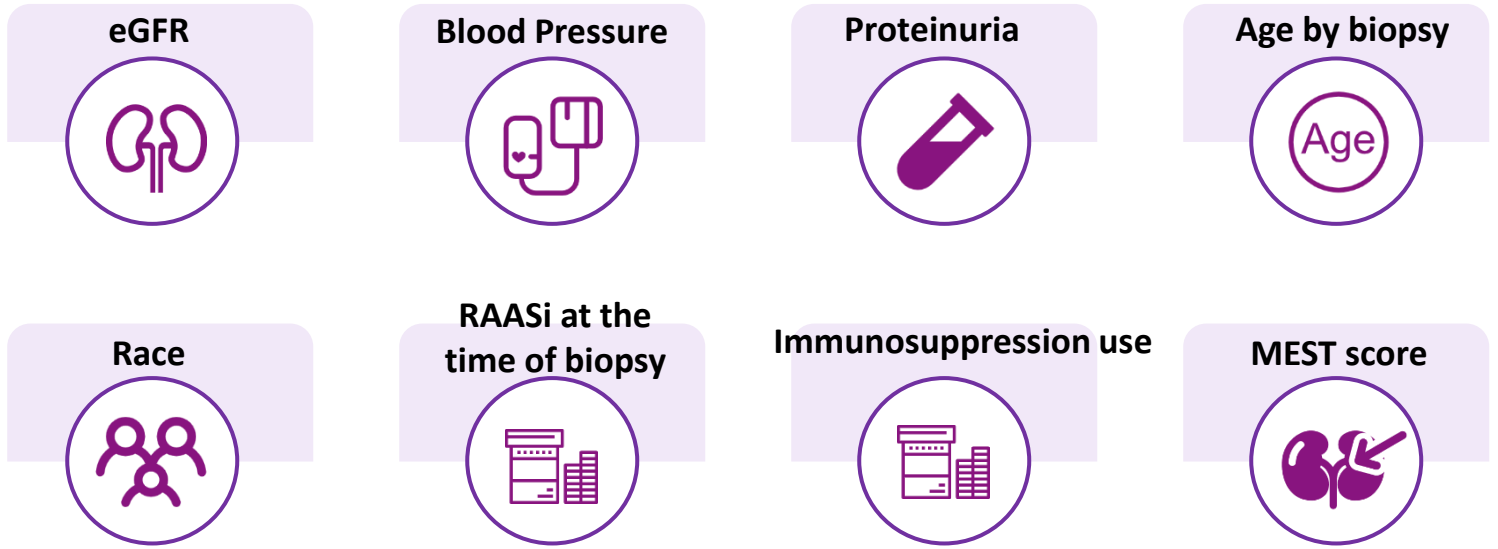
EM: mesangial electron-dense immune deposits

2025 KDIGO suggest to use prediction tools to quantify the prognosis

Tool to predict the risk eGFR decline 50% or risk of renal failure [2] → **Prediction tool at the time of kidney biopsy** [1] → **Risk prediction up to 7 years from kidney biopsy** [1]

- **IgAN International 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. [1]



Except eGFR and proteinuria, there is no validated serum or urine biomarkers to predict prognosis of IgAN [1]

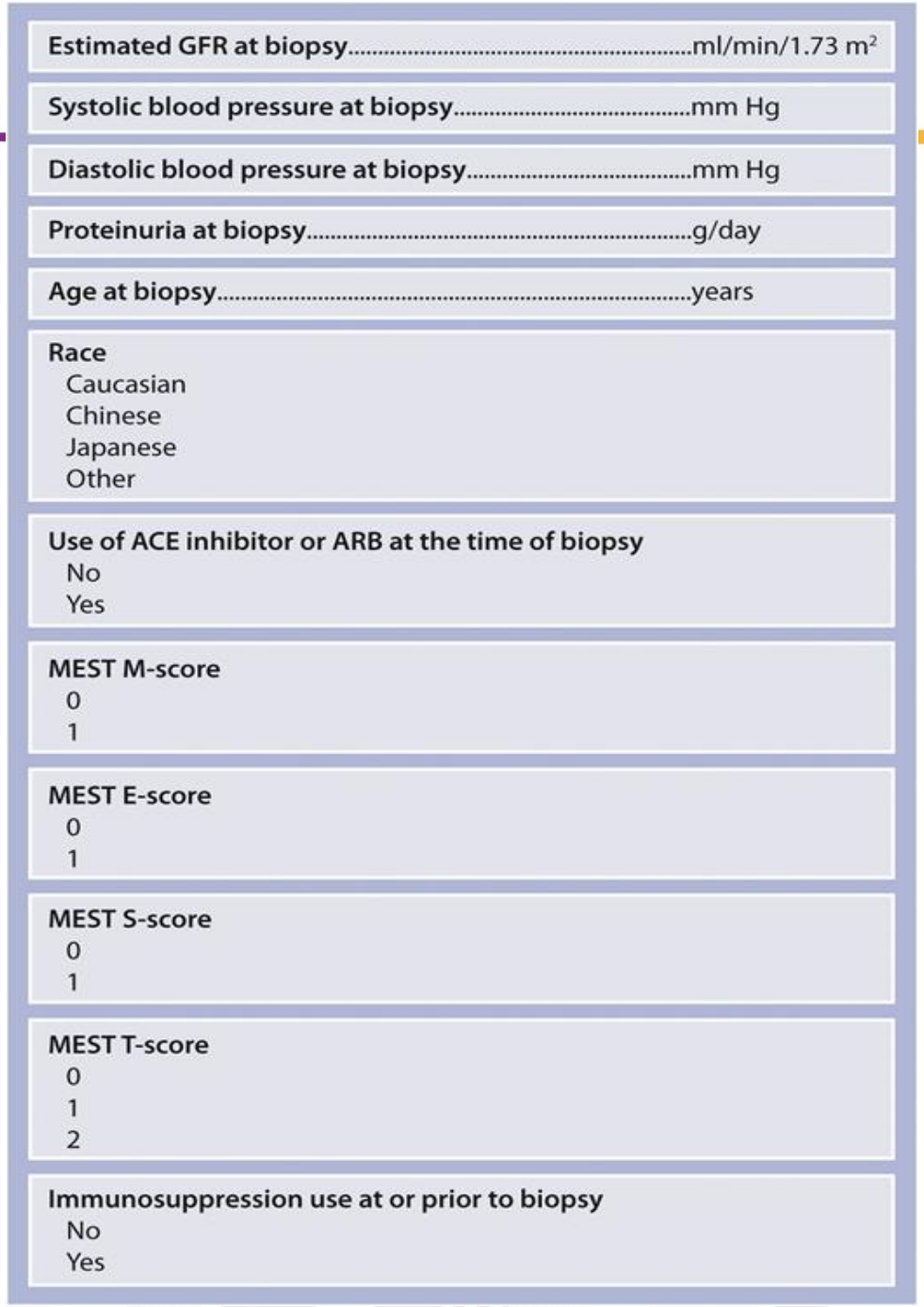
New biomarkers incl. pathology, hematuria, urine and serum are under exploration for prognosis [3]

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).

1. KDIGO 2025 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF IMMUNOGLOBULIN A NEPHROPATHY (IgAN) AND IMMUNOGLOBULIN A VASCULITIS (IgAV)
2. Barbour SJ, et al. Kidney Int 2022;102(1):160-172. 3. Cattran DC, et at. Kidney Int Rep. 2023;8(12):2515-2528.

IgAN - Prognosis

- No validated prognostic serum or urine biomarkers for IgAN other than eGFR and proteinuria.
- **The International IgAN Prediction Tools:** valuable resource to quantify short-term (**up to 7 years from kidney biopsy**) risk of progression
- QxMD calculator: international IgAN prediction tool-adults



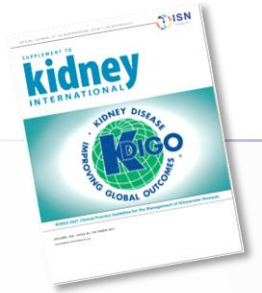
2021 KDIGO guideline: Proteinuria >0.5 g/d patients shall start ACEI/ARB

2012 KDIGO

Proteinuria

1 g/d

- Proteinuria >1 g/d, recommend to long-term use oral ACEI/ARB and adjust dose by BP (1B)
- Proteinuria <1 g/d, IgAN patients' BP shall control at <130/80mmHg; proteinuria>1g/d at <125/75mmHg (no classification)



2021 KDIGO

Proteinuria

>0.5 g/d

- **Recommend all patients undergo BP management, initiate ACEI or ARB if proteinuria >0.5 g/d, regardless BP (1B)**

KDIGO Glomerular Diseases Work Group. Kidney Int. 2021 Oct;100(4S)S1-S276.

2025 KDIGO specify treatment timeline when proteinuria ≥0.5 g/d, and initial treatment is not longer limited at supportive care

2021 version

Treatment timing

- **Proteinuria ＞0.5 g/d → start supportive treatment**
- Additional treatment to be considered after ≥90 days optimized supportive treatment, and the proteinuria still **＞0.75～1 g/d,** as high progression risk patient

2025 version

Treatment timing：

- 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.

2024 version indicated treatment and kidney biopsy timing at proteinuria ≥0.5 g/d, once confirmed diagnosis, supportive treatment is no longer the only option for initial treatment

1. KDIGO 2025 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF IMMUNOGLOBULIN A NEPHROPATHY (IgAN) AND IMMUNOGLOBULIN A VASCULITIS (IgAV)
2. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. Kidney Int. 2021 Oct;100(4S):S1-S276.

2025 KDIGO New treatment goal: to reduce the rate of loss of kidney function to <1 ml/min per year for the rest of the patient's life

2021 version

- **Proteinuria ＜1 g/d**

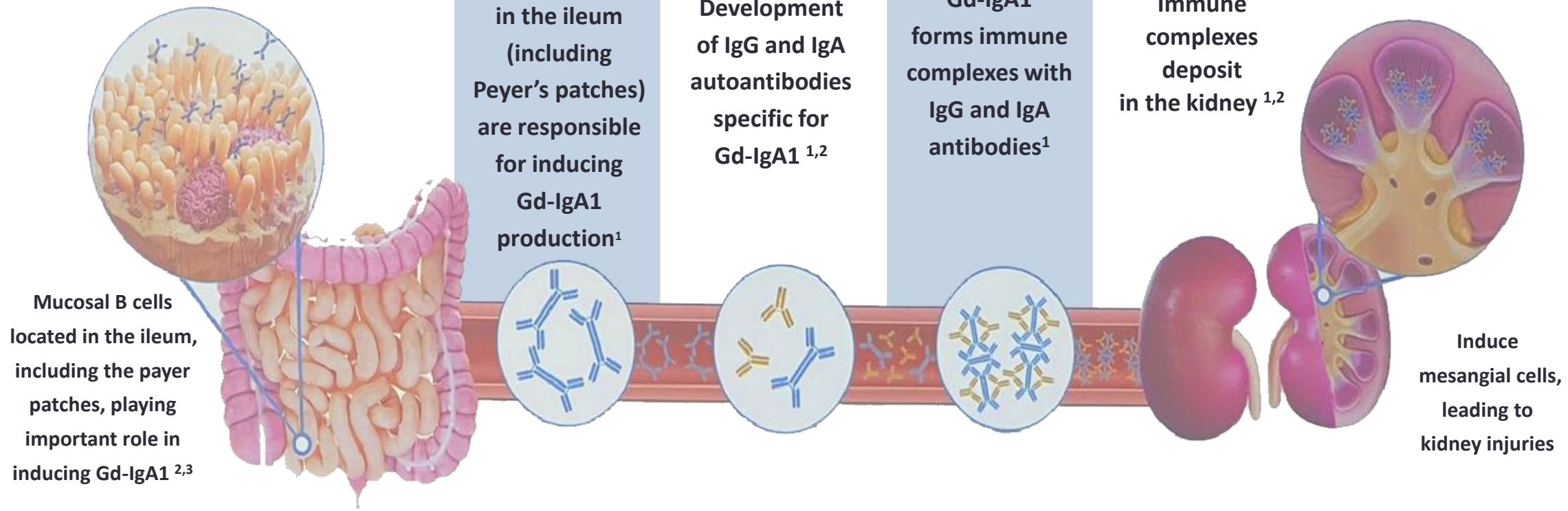
is a reasonable treatment goal

2025 version

- 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)**, multiple drugs are likely to be needed to achieve this.

Firstly highlight the treatment goal is to reduce the rate of loss of kidney function to <1 ml/min per year for the rest of the patient's life. In the meanwhile, based on current evidence-based study, 2025 version indicated the lower proteinuria the better, and even achieve complete remission.

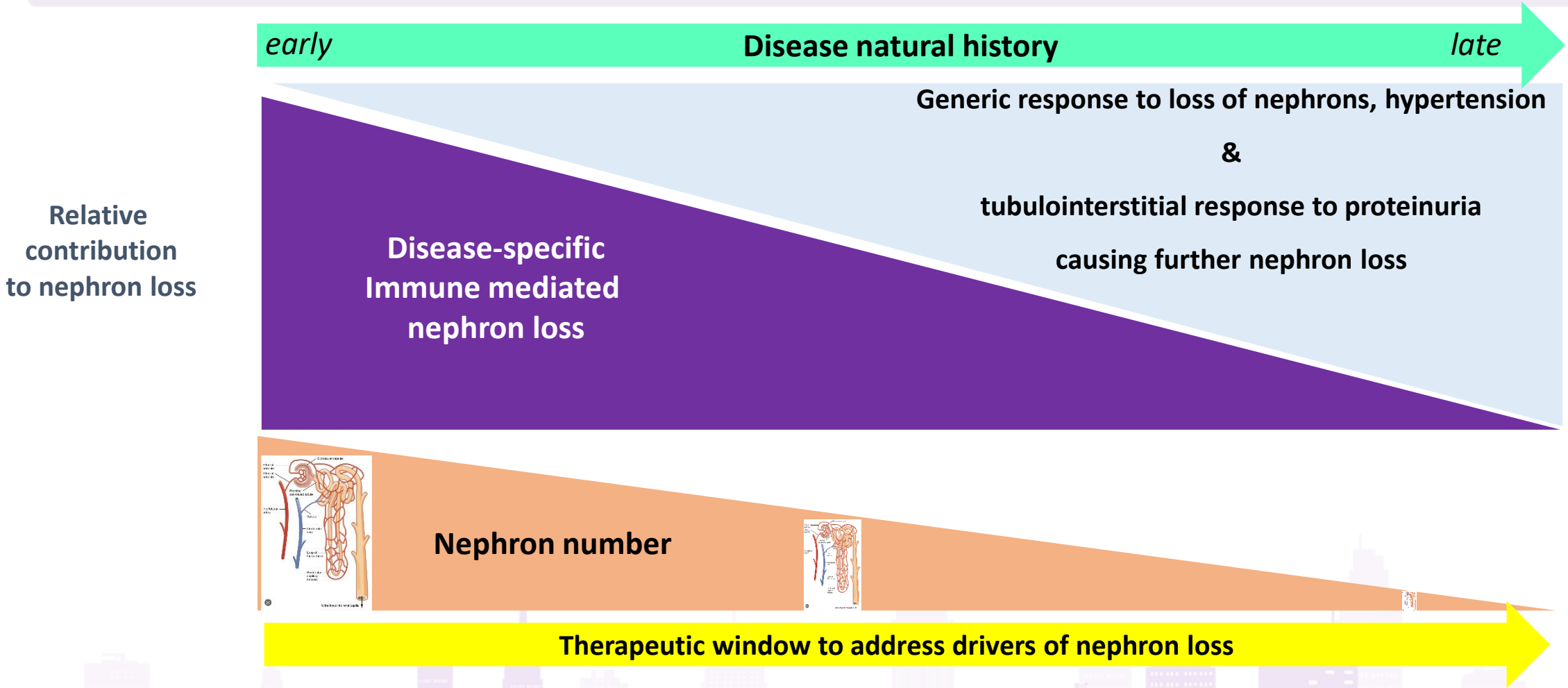
The “Four-Hit Hypothesis” with Gd-IgA1 as the source is currently the widely accepted pathogenesis mechanism for IgAN [1]



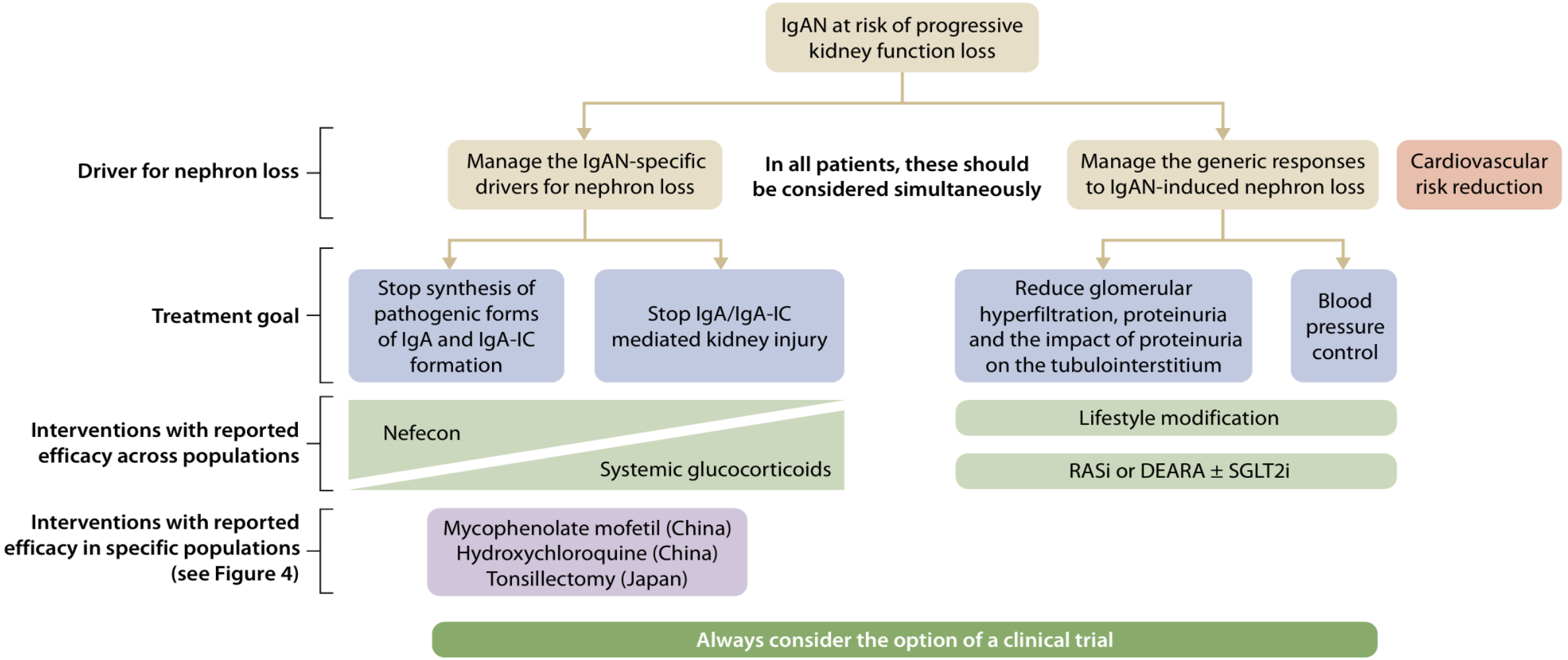
1. Chang S, et al. Front Med (Lousonne). 2020;7:92. 2. Barratt J, et al. Kidney Int Rep. 2020;5(10):1620-1624. 3. Lafayette R, et al. Lancet. 2023;402(10405):859-870.

2025 KDIGO
IgAN are “2 diseases” from early to late disease progression

- ✓ Prevent or reduce IgA immune complex formation and immune complex-mediated glomerular injury.
- ✓ In parallel, manage the consequences of existing IgAN-induced nephron loss.



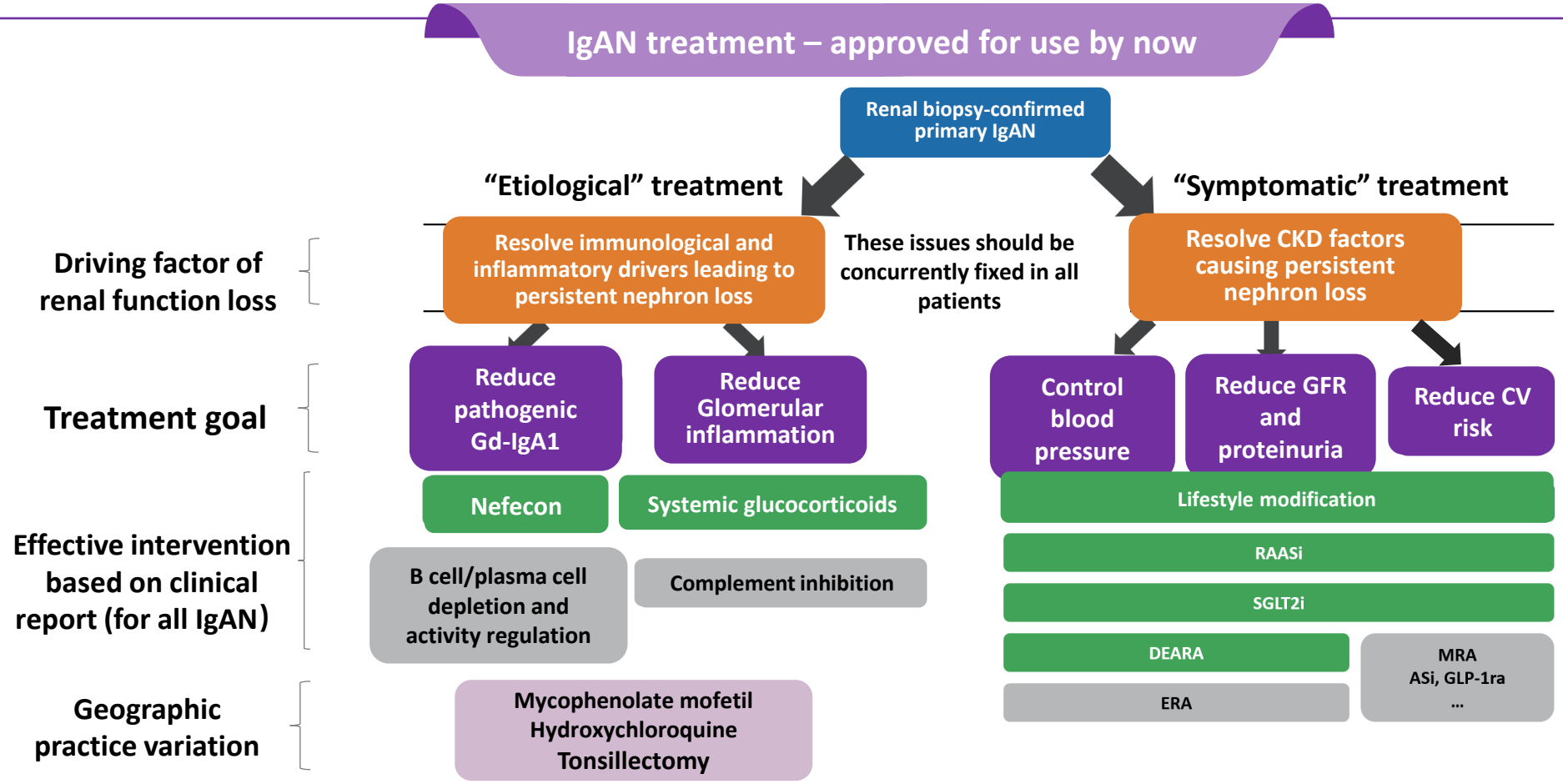
NEW STANDARD OF CARE IGA NEPHROPATHY



KDIGO 2025 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF IMMUNOGLOBULIN A NEPHROPATHY (IgAN) AND IMMUNOGLOBULIN A VASCULITIS (IgAV)

2025 KDIGO : A dual approach of etiological and supportive treatment

- IgAN a dual approach of etiological and supportive treatment：
  - **Resolve immunological and inflammatory drivers leading to persistent nephron loss by reducing pathogenic Gd-IgA1**
  - **Resolve CKD factors causing persistent nephron loss**



High levels of Gd-IgA1 can be associated with poor disease outcomes, including disease progression and kidney failure [1,2]

eGFR

- Serum Gd-IgA1 can be negatively correlated with eGFR[3,4]
- A higher relative degree of galactose deficiency in serum IgA1 has predicted faster eGFR decline and poor kindly survival[5]

CKD progression

- In a study, progression of CKD has been observed with higher serum Gd-IgA1 levels[4]
- A higher serum Gd-IgA1 has been suggested to predict CKD progression in IgAN[4]

Although Gd-IgA1 appears to be an important, emerging biomarker for assessing and predicting IgAN progression, further research in larger studies using standardized assays is needed

1. Zhao N, et al. Kidney Int. 2012;82(7):790-796. 2. Canetta PA, et al. Clin J Am Soc Nephrol, 2014;9(3):617-625.
3. Vaz de Castro PAS, et al. J Nephrol. Published online March 1, 2024. 4. Kim JS, et al. J Clin Med.2020;9(11):3549. 5. Maixnerova D, et al. PLoS One. 2019;14(2):e0212254.

2025 KDIGO treatment recommendations
Managing the IgAN-specific drivers for nephron loss

Reduce the levels of pathogenic forms of IgA and IgA immune complexes

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

Strengths

Nefecon is the only treatment to date proven to reduce the levels of pathogenic forms of IgA and IgA immune complexes

Risk

Possibility of some systemic glucocorticoid related side effects with Nefecon, these are usually **mild and reversible** on treatment cessation.

Treat immune-complex induced glomerular injury

- **Considering affordability and accessibility of Nefecon,** recommend IgAN patients at risk of progression (limited cycles of reduced-dose systemic steroid after considering risk)

Strengths

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

Risk

- Antimicrobial prophylaxis against Pneumocystis jirovecii
- Anti-viral prophylaxis in hepatitis B carriers
- GI bleeding, infection, metabolic, cosmetic, and neuropsychiatric side effects, alongside the potential impact on bone health.

Geographic practice variation

- MMF and Hydroxychloroquine: evidence-based support in China IgAN
- Tonsillectomy: evidence-based support in Japan

Not recommend

- Anti-platelet, anti-coagulant AZA, cyclophosphamide, rituximab, fish oils, calcineurin inhibitors

Other pharmacologic therapies evaluated in IgAN: inconsistency and only in small sample studies

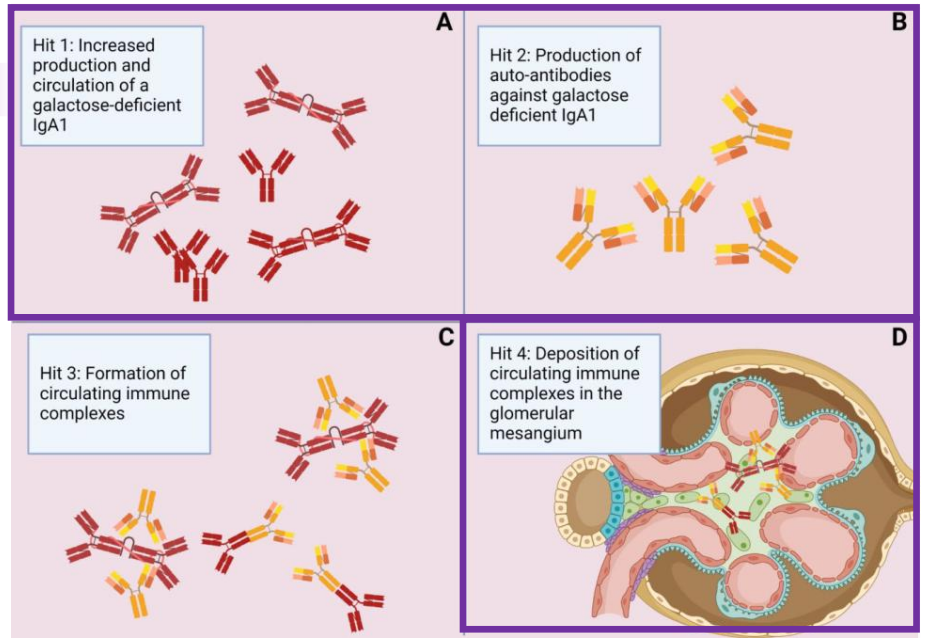
Agent	Suggested usage	Remarks
Antiplatelet agents	Not recommended	No evidence of efficacy
Anticoagulants	Not recommended	No evidence of efficacy
Azathioprine	Not recommended	No evidence of efficacy as monotherapy or when combined with glucocorticoids
Cyclophosphamide	Not recommended	Unless in the setting 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	In Chinese patients	Three small RCT showing superior or non-inferiority in proteinuria reduction and eGFR changes complared to placebo or low-dose glucosteroids
Hydroxychloroquine	In Chinese patients	In those patients who remain at high risk of progression in spite of optimized supportive care

Based on the “Four-Hit Hypothesis”, new drugs continue to emerge; Nefecon targets the intestine, striking at the source

- ✓ Targeting the upstream pathogenic mechanism: **B cells that produce Gd-IgA1 and anti-Gd-IgA1 antibodies**; among these, **Nefecon has received full FDA approval**.
- ✓ Targeting intrarenal damage: Including complement system inhibitors, RASi, and etc; among these, Sparsentan and Iptacopan has received conditional FDA approval.

Therapeutics that target the “four hits”/Drugs in phase 3

Drug	Target	
Nefecon	**Gut mucosal B cells**	FDA approved
Sibeprenlimab	APRIL	FDA approved
Zigakibart	APRIL	
Atacicept	BAFF+APRIL	
Telitacicept	BAFF+APRIL	



Drug	Target	
RO7434656	CFB RNA	
Iptacopan	CFB	FDA approved
Ravulizumab	C5	
Sparsentan	**ERA+ARB**	FDA approved
Atrasentan	ERA	

APRIL: a proliferation-inducing ligand; ARB: angiotensin II receptor blockers; BAFF: B-cell activating factor receptor; CFB: complement factor B; ERA: endothelin receptor antagonist; FDA: Food and Drug Administration; Gd-IgA1: galactose-deficient immunoglobulin A1; IgA: immunoglobulin A; IgAN: immunoglobulin A nephropathy; RASi: renin-angiotensin system inhibitor; RNA: ribonucleic acid

Phase 3 clinical trials open in 2025 evaluating new treatments for IgAN

Drug targets	Drug	Target	Clinical trial Registration number	Status as of July 2024
Drugs targeting the production of pathogenic forms of IgAN	Sibeprenlimab (VIS649)	APRIL	VISIONARY NCT05248646	In follow-up FDA approval 2025/11
	Zigakibart (BION-1301)	APRIL	BEYOND NCT05852938	Recruiting
	Atacicept	APRIL/BAFF	ORIGIN3 NCT04716231	Recruiting
	Telitacicept	APRIL/BAFF	NCT05799287	In follow-up
	Povetacicept	APRIL/BAFF	RAINIER NCT06564142	Recruiting
Drugs targeting IgA-containing immune complex–mediated inflammation	Iptacopan (LNP023)	Complement alternative pathway factor B	APPLAUSE-IgAN NCT04578834	In follow-up FDA approval 2024/08
	Sefaxersen (RO7434656)	Complement alternative pathway factor B	IMAGINATION NCT05797610	Recruiting
	Ravulizumab	Complement terminal pathway C5	I CAN NCT06291376	Recruiting
Drugs targeting the generic downstream consequences of IgAN-induced nephron loss	Atrasentan	Endothelin A receptor	ALIGN NCT04573478	In follow-up FDA approval 2025/03

Take home message

2021 KDIGO

Timing for a kidney biopsy:
- No recommendation

Defining patients with IgAN at high risk of progression in IgAN:
- **Proteinuria ≥0.75-1 g/d**, despite **≥ 90 days** of optimized supportive care

Treatment goal:
- Proteinuria reduction to **< 1 g/d** is a surrogate marker of improved kidney outcome in IgAN, and reduction to under 1 g/d is a reasonable target.

The **management** of patients with IgAN:
- All patients with **proteinuria >0.5 g/d,** irrespective of whether they have hypertension, be treated with either an **ACEi or ARB**
- Patients who remain at high risk of progressive CKD despite maximal supportive care be considered for **a 6-month course of glucocorticoid** therapy.

2025 KDIGO

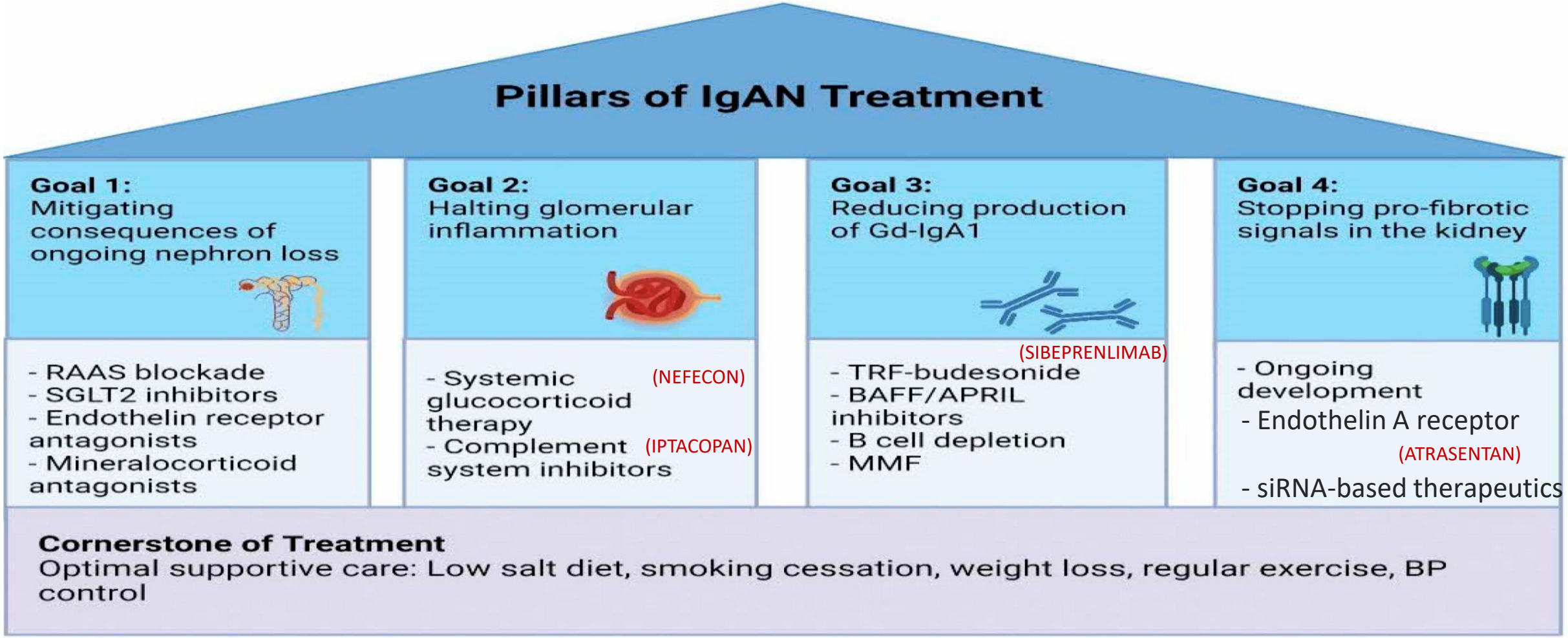
Timing for a kidney biopsy:
- All adults with **proteinuria ≥0.5 g/d** in whom IgAN is a possible diagnosis

Defining prognosis using International IgAN Prediction Tools
- At-biopsy and post-biopsy for adults and children

Treatment goal:
- Reduce the rate of loss of kidney function to **<1 ml/min** per year.
- Urine protein excretion should be maintained **<0.5 g/d,** preferably **<0.3 g/d**

The **focus of management** in most patients should be to simultaneously:
- **Prevent or reduce IgA immune complex formation and immune complex mediated glomerular injury.**
  - Nefecon (TRF-Budenoside); reduced-dose systemic glucocorticoid
- Manage the consequences of existing IgAN-induced nephron loss.
  - Control of blood pressure with a target of **≤ 120/70 mm Hg**
  - Singly or combination: RAS blockade / **DEARA, SGLT2i**

Clinical Nihilism is Over with New Guideline



Always consider the option of a clinical trial

Thank you for your attention