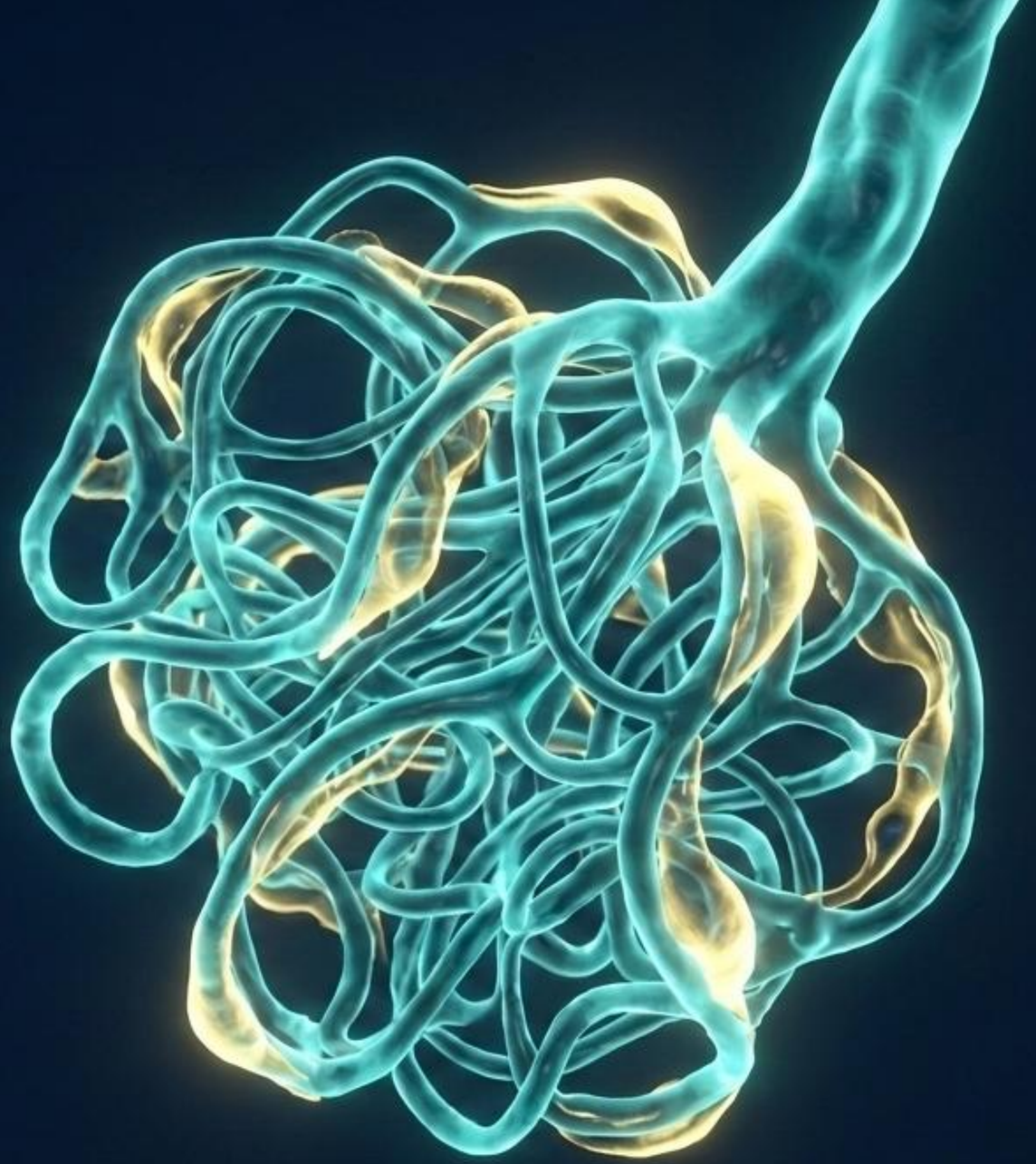
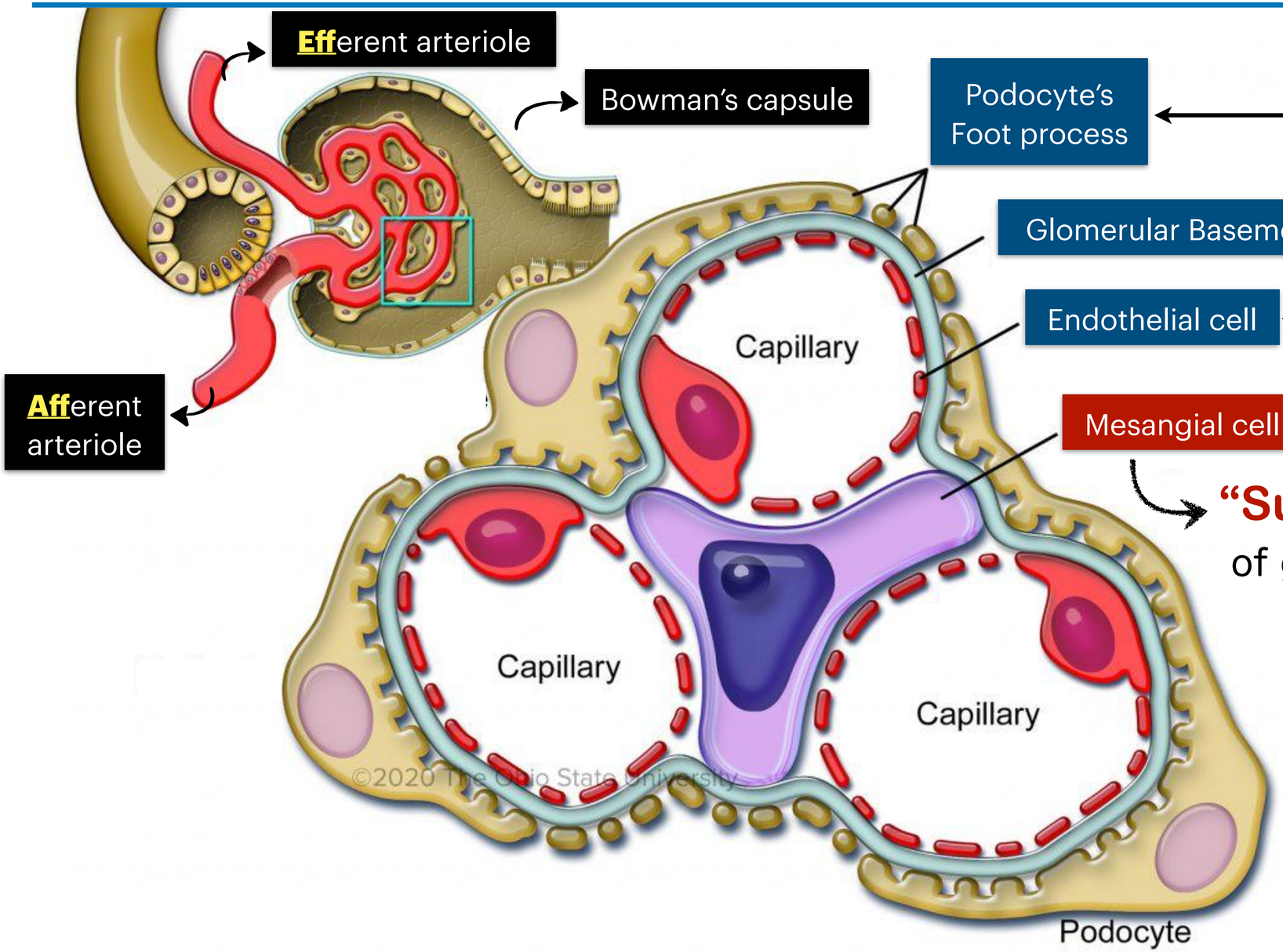
Common Glomerular Disorder

For Internist



Panthita Sornhiran
Nephrology unit
Department of Internal Medicine
Police General Hospital

Glomerular Structure



Podocyte's Foot process

Glomerular Basement Membrane (GBM)

Endothelial cell

Mesangial cell & matrix

"Filtration" barrier

"Supportive" structure of glomerulus

- Size > 50 Aº (Larger than albumin)
- NEGATIVELY charge

Brenner & Rector's the kidney, 11th edition

Stepwise Approach

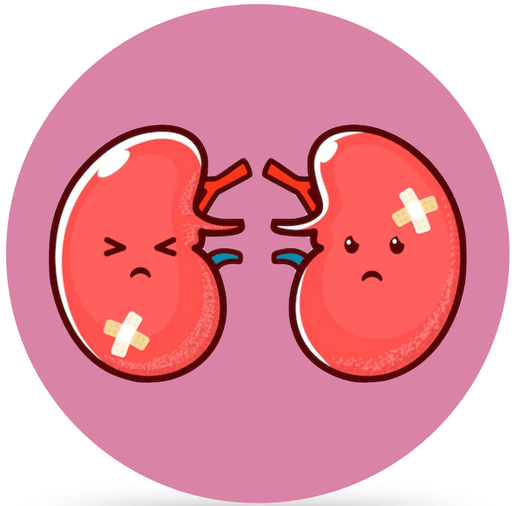
- Glomerular disease?
- Glomerular syndrome?
- Primary or Secondary?
- Differential diagnosis?
- Treatment (Specific & Supportive)?

Clinical Manifestation

Edema

Proteinuria

Hematuria



Kidney function decline

How to approach "Proteinuria"

Intermittent proteinuria

(Proteinuria <1-2 g/day, no active sediments, normal eGFR)

Functional proteinuria

- **Increase intra-glomerular pressure**
- Fever, Exercise, CHF, Acute illness

Orthostatic proteinuria

- Abnormal **proteinuria in upright** position
- Age of onset < 30 years
- 7 am-11 pm: proteinuria > 150 mg/16h
- 11 pm - 7am: proteinuria < 50 mg/8h
- Self-limited

Persistent proteinuria

Tubular proteinuria (Proteinuria < 2 g/day)

- **↓Tubular** protein **reabsorption** (Proximal tubule)
- eg. ATIN, CTIN, Fanconi syndrome

Overflow proteinuria

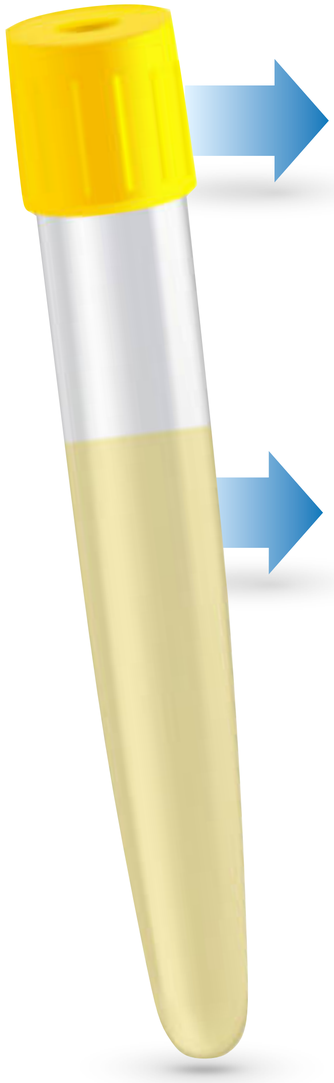
- **↑LMW Protein production** > Tubular protein reabsorption
- LMW proteinuria* (**UPCR & UACR disproportion**)
- eg. Multiple Myeloma (Light chain), Hemolysis (Hemoglobin), Rhabdomyolysis (Myoglobin)

Glomerular proteinuria

- Glomerular injury → ↓Barrier function
- **Proteinuria > 2-3 g/day** ± Urine sediments

Brenner & Rector's the kidney, 11th edition

Urine test for "Proteinuria"



Semiquantitative Method

- **Urine protein dipstick** (albumin only)
- Sulfosalicylic acid test (albumin + non-albumin)
- Urinary lysozyme (albumin + lysozyme)

Limitation

- Radiocontrast
- UpH > 8
- Gross hematuria
- Antiseptic eg. Chlorhexidine

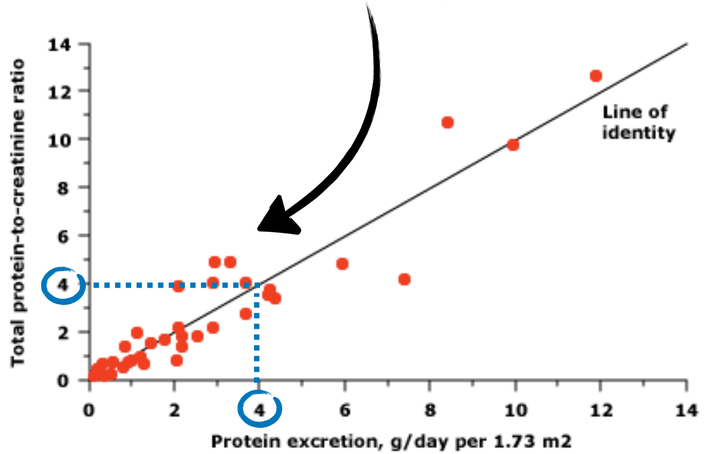
Quantitative Method

- **24-hour urine protein** **Gold standard**
  - Normal: < 150 mg/day
  - Adequate: Urine Cr >15-20 MKD (Female), >20-25 MKD (Male)
- **Spot urine protein** (UPCR & UACR)

  Limitation
  - Influence of the urine Cr
  - Variety of protein excretion throughout the day

UPCR ≥ 4g/gCr

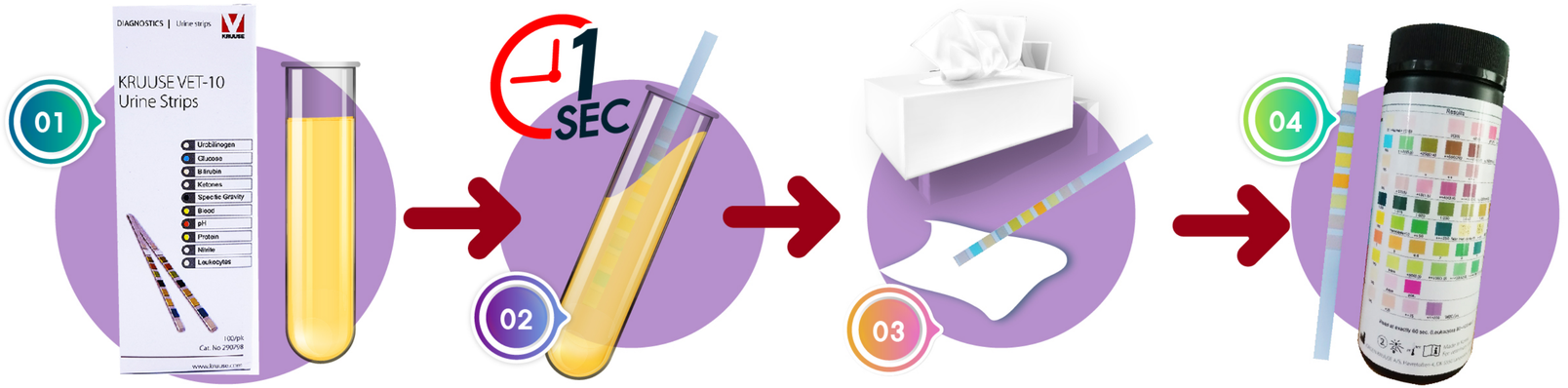
may "NOT" precisely correlated with 24h urine protein



N Engl J Med. 1983;309:1543-1546.

Urine test for “Proteinuria”

Urine Dipstick	Urine albumin (mg/dL)
Negative	< 10
Trace	**15**-30
1(+)	**30**-100
2(+)	**100**-300
3(+)	**300**-1000
4(+)	**> 1000**

	Urine protein categories		
			
UACR (mg/gCr)	<30	30-300	>300
UPCR (mg/gCr)	<150	150-500	>500

Urine test for “Proteinuria”

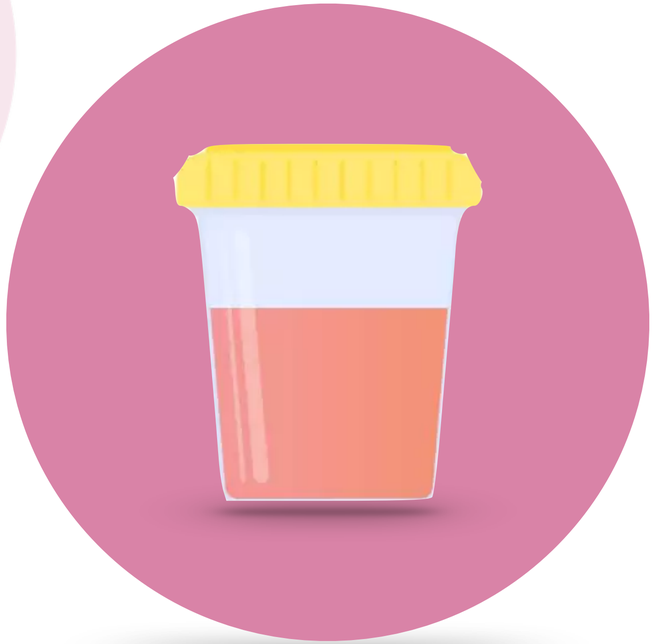
Urine Dipstick	Urine albumin (mg/dL)
Negative	< 10
Trace	**15**-30
1(+)	**30**-100
2(+)	**100**-300
3(+)	**300**-1000
4(+)	**> 1000**

Urine Test	Urine protein categories		
	A1 (Normal to mildly increased)	**A2** (Moderately increased)	**A3** (Severely increased)
Urine Dipstick	Negative to trace	1+ to 2+	≥ 2+
UACR (mg/gCr)	<30	30-300	>300
UPCR (mg/gCr)	<150	150-500	>500

Clinical Manifestation

Edema

Proteinuria



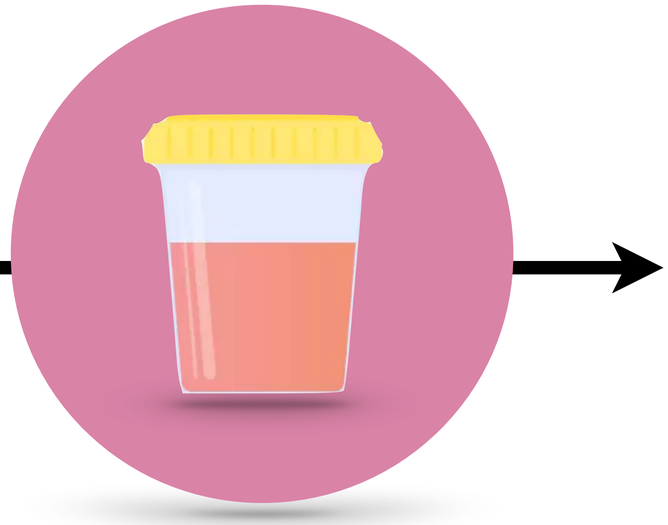
Hematuria

Kidney function decline

How to approach "Hematuria"

Glomerular cause

- "NO" clot
- Proteinuria > 500 mg/gCr
- Dysmorphic RBCs
- RBC Cast



Non-Glomerular cause

- Clot
- Proteinuria < 500 mg/gCr
- "NO" Dysmorphic RBCs
- "NO" RBC Cast

Ddx

- Glomerulonephritis (**GN**)
- **GN Mimics** (TMA)
- Others
  - ✓ **Alport** syndrome
  - ✓ **Thin basement membrane**

Ddx

- **Renal** (Infection/ Inflammation/ Stone/ Ruptured cyst/Tumor)
- **Extrarenal**
  - ✓ **Genitourethral** (Infection/ Inflammation/ Stone/ Trauma/ Tumor)
  - ✓ **Vascular** (eg. Renal vein thrombosis)
  - ✓ **Systemic** bleeding

Brenner & Rector's the kidney, 11th edition

Stepwise Approach

- ✓ Glomerular disease?
- ◉ **Glomerular syndrome?**
- ◉ Primary or Secondary?
- ◉ Differential diagnosis?
- ◉ Treatment (Specific & Supportive)?

Glomerular syndrome

1 Asymptomatic

- Isolated proteinuria 150 mg to 3 g/day
- Hematuria > 2 RBC/HPF in spun urine

2 Nephrotic syndrome

- Generalized **edema**
- **Proteinuria > 3.5 g/24h** (UPCR > 3)
- **Hypoalbuminemia** < 3.5 g/dL
- **Hypercholesterolemia** > 250 mg/dL
- Lipiduria (Oval fat body)

Glomerulonephritis (GN)

- Glomerular **hematuria**
- Proteinuria (**< 3g/day**)
- **Azotemia** / Oliguria
- Edema
- **Hypertension** (Accelerated/New-onset)

3 Acute GN

< 7 days

4 RPGN*

Weeks to months

5 Chronic GN

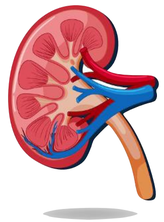
> 3 months

*RPGN: Rapid Progressive Glomerulonephritis

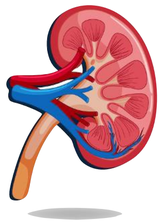
Stepwise Approach

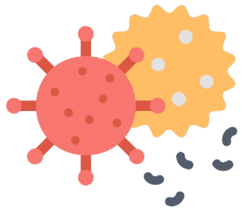
- ✓ Glomerular disease?
- ✓ Glomerular syndrome?
- ◉ **Primary or Secondary?**
- ◉ Differential diagnosis?
- ◉ Treatment (Specific & Supportive)?

Glomerular Disease: Etiology

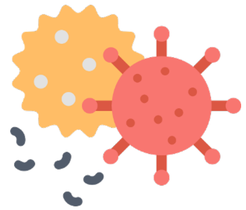


PRIMARY
glomerular disease





SECONDARY
glomerular disease



Disease	Nephrotic features	Nephritic features
MCD	++++	-
MN	++++	+
FSGS	+++	++
IgAN	++	+++
MPGN	++	+++
PSGN	+	++++
ANCA	+	++++
Anti-GBM	+	++++

- **Infection** (**HBV**, **HCV**, **HIV**, Syphillis, Parasite)
- **Autoimmune** (**SLE**, RA, Systemic vasculitis)
- **Drug** (**NSAIDs**, Lithium, Gold, Penicillamine)
- **Malignancy** (Hematologic/Solid organ **tumor**)
- **Metabolic cause** (**DM**)
- **Paraproteinemia** (**Amyloidosis**)
- **Genetics**
- **Others** (Obesity, Pre-eclampsia, Allergy)

Comprehensive Clinical Nephrology, 7th edition

Stepwise Approach

✓ Glomerular disease?

✓ Glomerular syndrome?

✓ Primary or Secondary?

- **Differential diagnosis?**
- **Treatment (Specific & Supportive)?**

Glomerular syndrome

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- **Hypertension** (Accelerated/New-onset)

3 Acute GN

< 7 days

4 RPGN*

Weeks to months

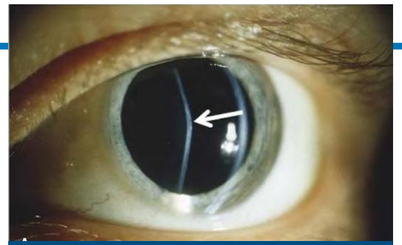
5 Chronic GN

> 3 months

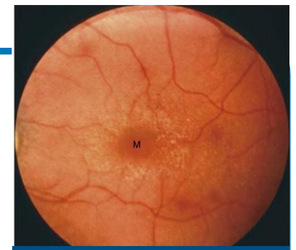
*RPGN: Rapid Progressive Glomerulonephritis

Asymptomatic: Inherited GBM disorder

Alport Syndrome (AS)



Anterior lenticonus



Perimacular flecks

- **Etiology**: Mutation of **"Type IV collagen"** (COL4A3, COL4A4, COL4A5)
- **Inheritance**: **X-linked (85%)** > AR (15%) > AD (5%)
- **Clinical**:
  - ✓ **Renal:** Persistent microscopic hematuria, proteinuria (rare; male with XLAS > female with ARAS)
  - ✓ **Extrarenal: SNHL**, **Anterior lenticonus**, **Maculopathy** (Perimacular flecks), Leiomyomatosis (Esophagus/Tracheobronchus)
- **Management**: RAAS blockade & supportive Rx

Thin Basement Membrane Disease

- **Etiology**: Mutation of **"Type IV collagen"** (COL4A3, COL4A4)
- **Inheritance**: **AD**
- **Clinical**: Asymptomatic microscopic hematuria

Comprehensive Clinical Nephrology, 7th edition
Brenner & Rector's the kidney, 11th edition

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How to approach "Nephrotic Syndrome"?

1 2º Nephrotic Syndrome	2 1º Nephrotic Syndrome	3 Secondary causes
DKD	**Minimal Change Disease** [MCD] 1ºAbrupt, 2º Insidious, Bimodal age	· **Infection**: Virus, Strogyloides · **Autoimmune**: SLE (LN I), Myasthenia · **Drug**: NSAIDs, Lithium · **Malignancy**: Lymphoma, Leukemia · **Allergy**: Pollen, Bee sting, Food allergens
LN class V	**Membranous Nephropathy** [MN] Insidious onset, Elderly	· **Infection**: HBeAg, Syphillis · **Autoimmune**: SLE (LN V) · **Drug**: Gold, Penicillamine · **Malignancy**: Solid organ tumor
Amyloidosis	**Focal Segmental Glomerulosclerosis** [FSGS] 1ºAbrupt, 2ºInsidious, various character	· **Infection**: HIV, Parvovirus B19, EBV · **Autoimmune**: SLE (LN VI) · **Drug**: Pamidronate, Lithium, Heroin, IFN · **Others**: Obesity, HT, Genetic

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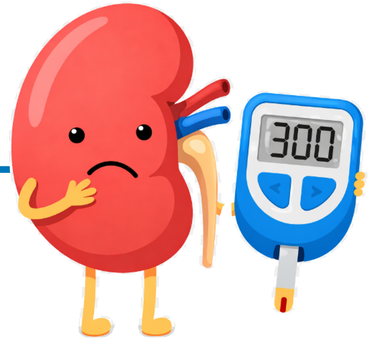
LN class V	**Membranous Nephropathy** [MN] Insidious onset, Elderly	Autoimmune
Amyloidosis	**Focal Segmental Glomerulosclerosis** [FSGS] 1ºAbrupt, 2ºInsidious, various character	Drug
		Malignancy

- Malignancy: Lymphoma, Leukemia
- Autoimmune: SLE (LN V)
- Infection: HIV, Parvovirus B19, EBV

Diabetic Kidney Disease (DKD)



DM → **Macroalbuminuria** (MAU > 300 mg/gCr) OR

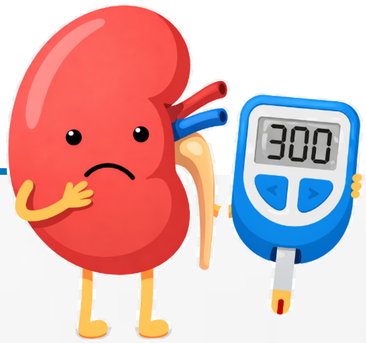
DM → **Microalbuminuria** (MAU 30-300 mg/gCr) + → **Type 1 DM** OR

→ **Diabetic Retinopathy**

	Diabetic Kidney Disease	Other Nephrotic Syndrome
DM Duration	≥ 10 years	< 5 years
Proteinuria	Slow progression	Rapid onset & progression
CKD progression	Slow progression	Rapid onset & progression
Urine sediments	Bland	Active urine sediments
Diabetic retinopathy	T1D (90%), T2D (50%)	±

Diabetic Kidney Disease (DKD)

Guideline-Directed Medical Therapy (GDMT)



RAS
inhibitors

SGLT2
inhibitors

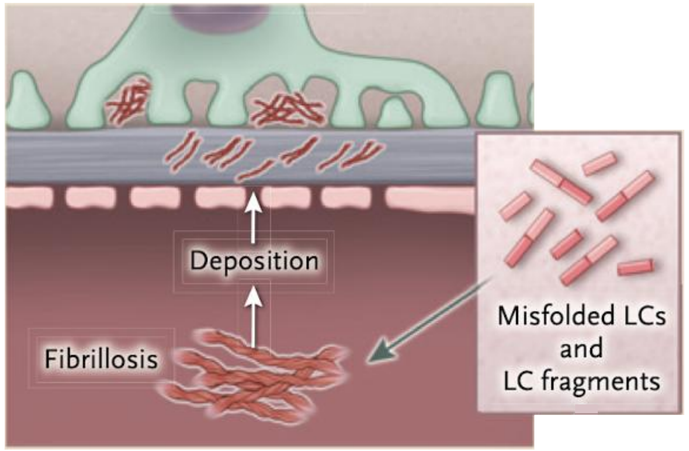
Non-steroidal
MRA

GLP1
Receptor agonist

Amyloidosis

Pathogenesis

Organ deposition of abnormal folding protein



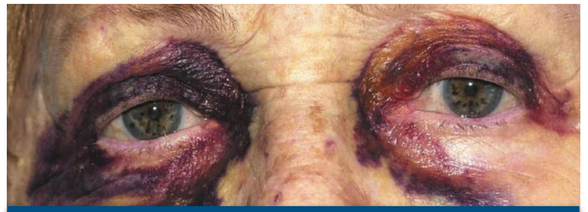
Glomerulus
deposition

Nephrotic Syndrome

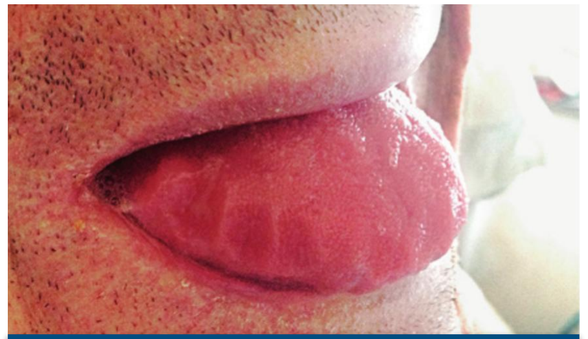
Renal Manifestation

- Glomerulus: **Proteinuria** (albuminuria)
- Tubulointestitium: **ATI**, **Nephrogenic DI**, **RTA**
- Vascular: **Hypertension**

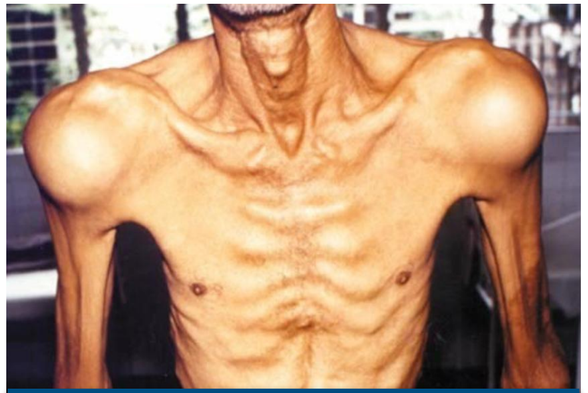
Extrarenal Manifestation



Pinch purpura



Macroglossia with tongue indentation



Shoulder pad sign

Organomegaly

- ✓ **Restrictive cardiomyopathy***
- ✓ Hepatomegaly
- ✓ Macroglossia
- ✓ Shoulder pad sign

Autonomic dysfunction

- ✓ GI pseudo-obstruction (↓ GI Motility)
- ✓ Autonomic neuropathy

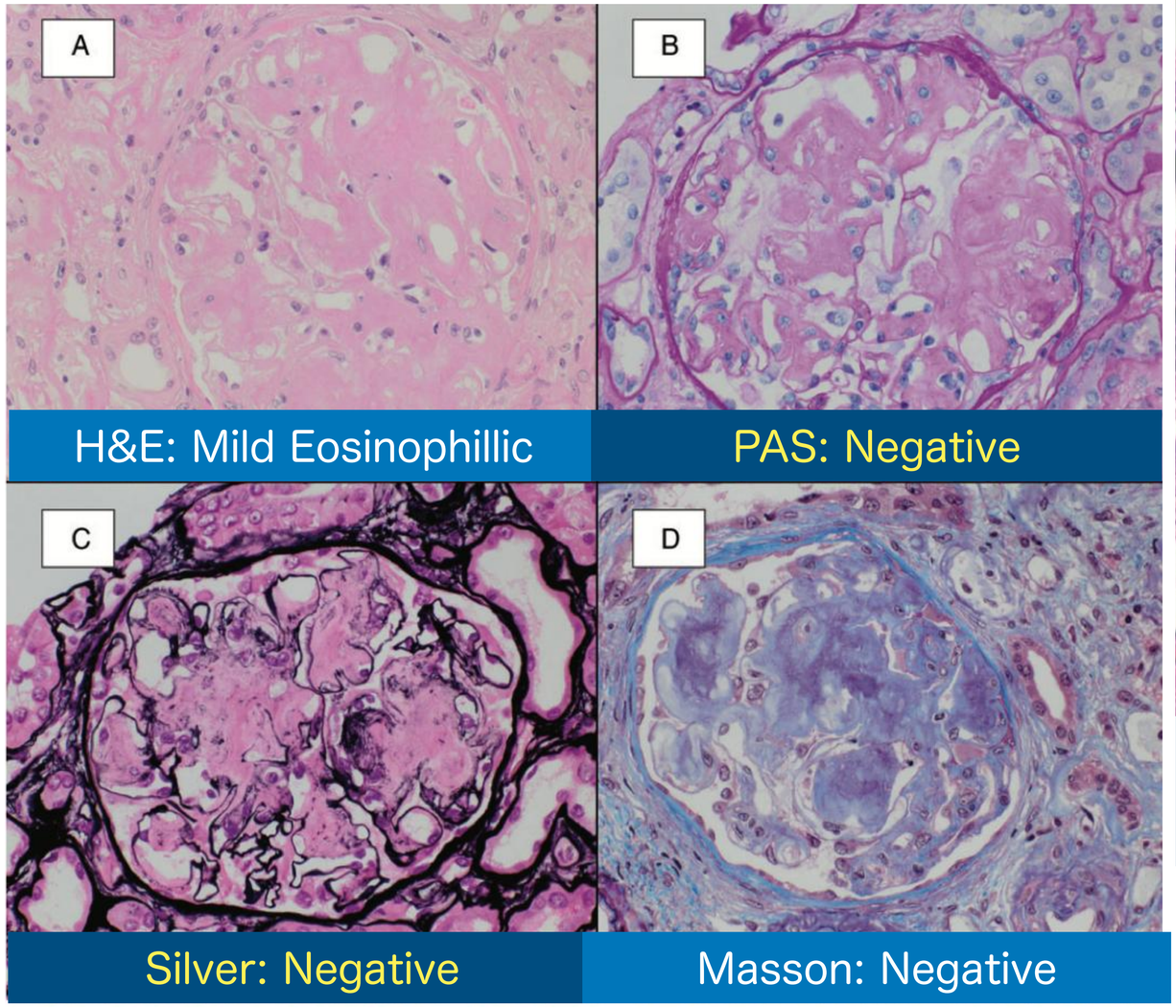
Hematologic disorder

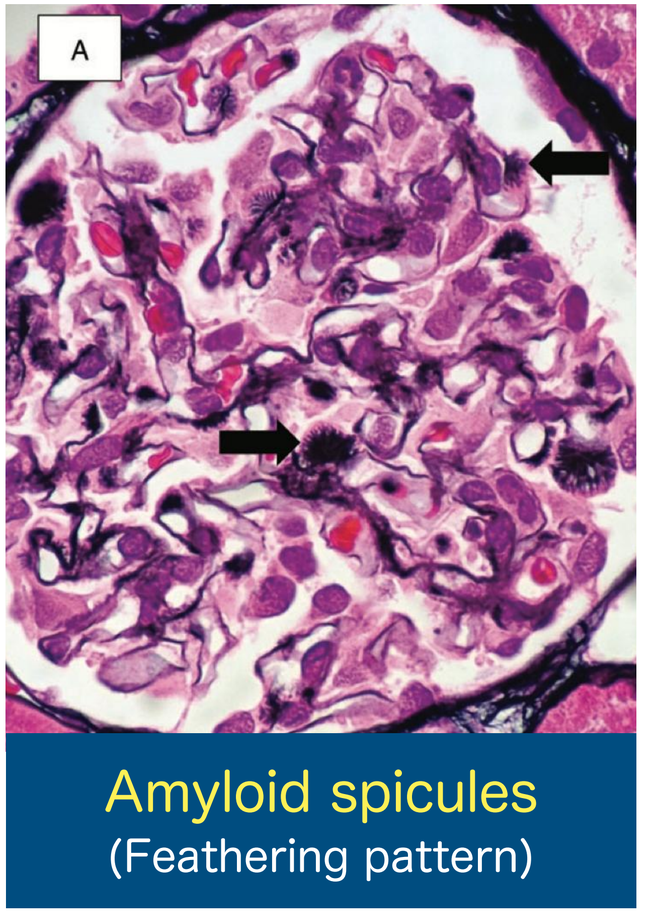
- ✓ Anemia
- ✓ Acquired FIX & X deficiency
  - Skin purpura
  - Spontaneous bleeding

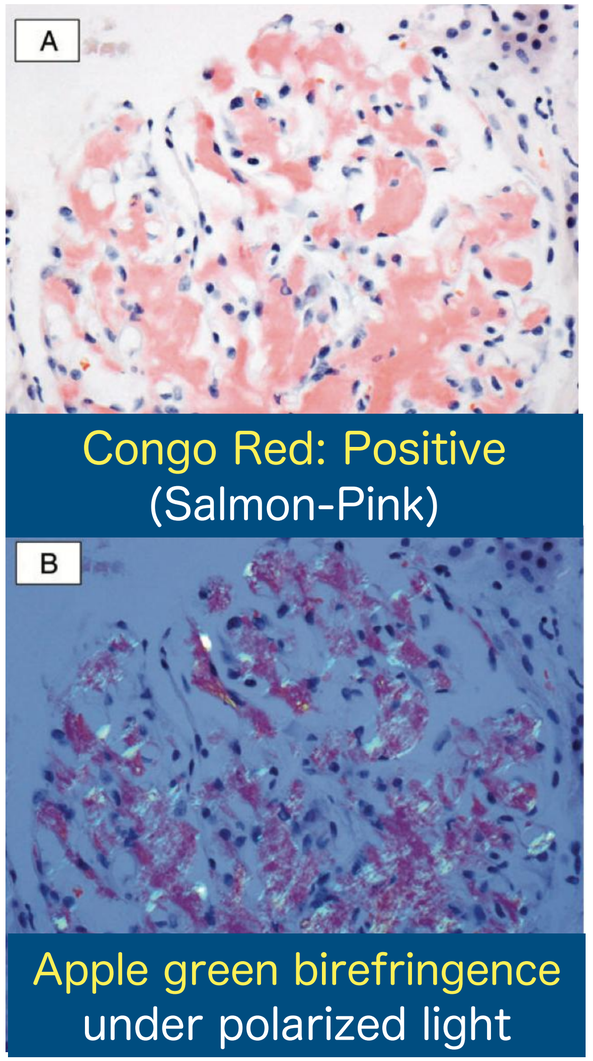
N Engl J Med; 2004; 351:e23
N Engl J Med; 2007; 356:2406
N Engl J Med; 2018; 378:2321

Amyloidosis: Renal Histopathology

"Amorphous material with nodular expansion on mesangium & capillary walls"







Clin Kidney J(2014) 7:97-106

Amyloidosis: Treatment

	AL (Acquired)	AA (Acquired)	DAR (Acquired)	ATTR	
				Acquired (Wild)	Hereditary
Underlying condition	**Ig-related** disorder	**Chronic inflammation**	**Long Dialysis vintage**	↑ Age	TTR gene mutation
Precursor protein	**Light chain** (Variable region)	Serum amyloid A protein (**SAA**)	**ß2M**	**TTR protein**	
Renal manifestation	Proteinuria>500mg/d or ↓eGFR	Proteinuria>500mg/d or ↓eGFR	N/A	Rare	Unusual until late stage
Extrarenal involvement	**Cardio(RCM)**~75%, Polyarthritis, Hepatomegaly Coagulation defect	Cardiomyopathy (Rare)	CTS, **Polyneuropathy**, Guitar string sign	CMP, CTS	**Peripheral neuropathy** & Autonomic dysfunction
Specific Treatment	**Combined ASCT/HDM** or Melphalan-based Rx	**Rx Inflammation** Targeted Rx (Eprodisate, CPCHPC)	**ß2M clearance**	**Orthotopic liver transplant ± KT**	
Kidney Transplantation	5-yr graft survival 74% Recurrence 28%	Recurrence 14%	Best Choice !!		

How to approach "Nephrotic Syndrome"?

1 2º Nephrotic Syndrome	2 1º Nephrotic Syndrome	3 Secondary causes
DKD	**Minimal Change Disease** [MCD] 1ºAbrupt, 2º Insidious, Bimodal age	· Infection: Virus, Strogyloides · Autoimmune: SLE (LN I), Myasthenia · Drug: NSAIDs, Lithium · Malignancy: Lymphoma, Leukemia · Allergy: Pollen, Bee sting, Food allergens
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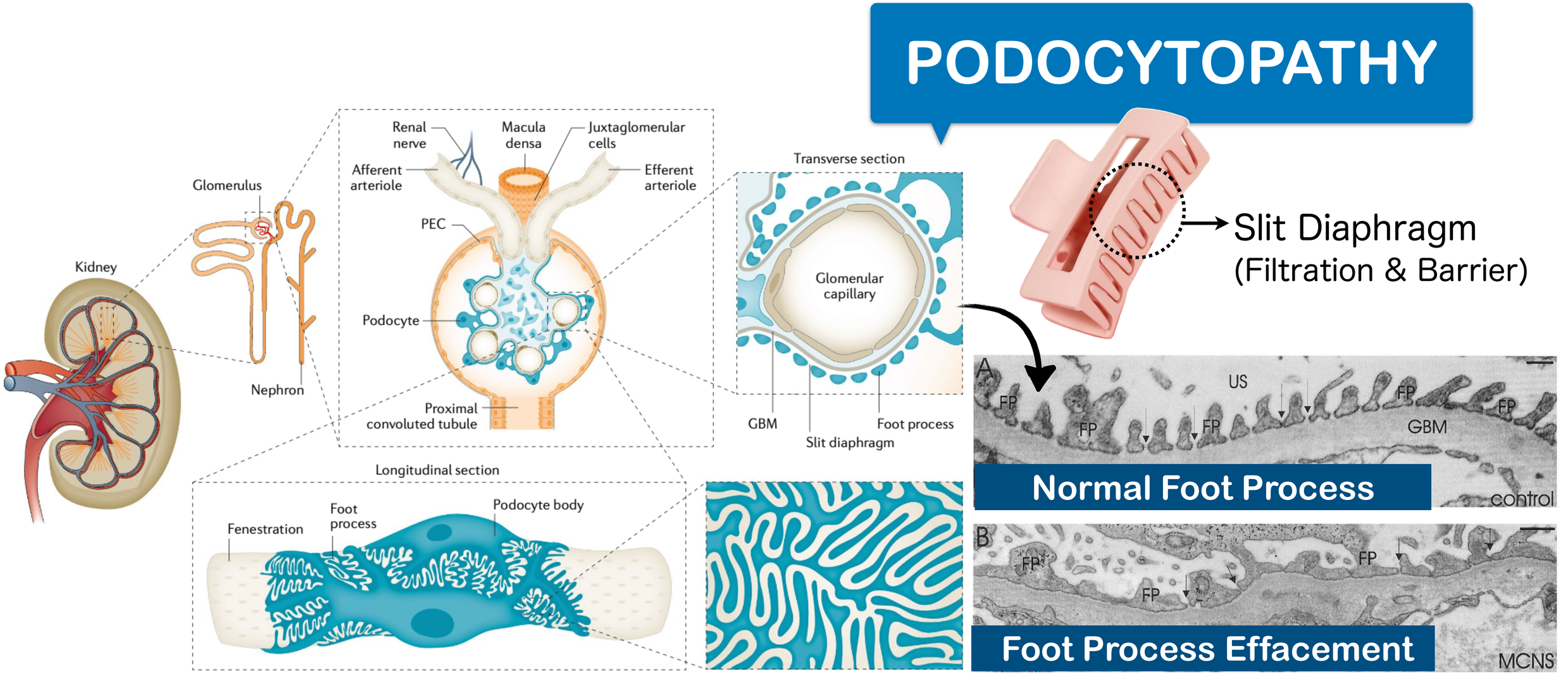
Minimal Change Disease (MCD)

Focal Segmental Glomerulosclerosis (FSGS)



Nat Rev Dis Primers 6, 68(2020)

MCD Vs FSGS: Clinical features & Treatment

	MCD	FSGS
Age of onset	**Bimodal age**	Variable
Onset	◉ Primary: Abrupt onset ◉ Secondary: Insidious onset	◉ Primary: Abrupt onset ◉ Secondary: Insidious onset
Clinical	**100% Full-blown NS**	70% NS, **20-50% GN features**
2º cause	✓ Infection: **Virus**, Parasite (**Strongyloides**), Mycoplasma ✓ Autoimmune: LN Class I, Myasthenia ✓ Drug: **NSAIDs**, Lithium ✓ Malignancy (Hematologic): Lymphoma (**HD**), Leukemia ✓ Allergy: Pollen, Bee sting, Food allergen	✓ Infection: **HIV**, Parvovirus B19, EBV ✓ Autoimmune: **LN Class VI** ✓ Drug: Heroin, **Pamidronate**, Lithium, **IFN** ✓ Others: Hypertension, **Obesity**, Sickle cell ✓ Genetic: Familial FSGS
Treatment	· **Prednisolone 1 MKD** (Max 80 mg) OD, or 2 mg/kg (Max 120 mg) AD X **4-16 wks** → **taper off 6 months** (**Begin tapering at 2 weeks after CR**) · Contraindications: Severe hyperglycemia, Steroid-induced psychosis, Osteoporosis/Osteopenia · If Contraindicated/ Frequent relapse/ Steroid dependent: POCY, CNI, RTX, MMF/MPA	

Kidney International (2021) 100, S1-S276

MCD Vs FSGS: Treatment response

- **Complete Remission:** **Proteinuria < 0.3** g/d, **Stable serum Cr**, Serum **Alb > 3.5** g/dL
- **Partial Remission:** **↓Proteinuria to 0.3-3.5 g/d** "AND" **↓>50%** from baseline
- **Relapse:** **Proteinuria > 3.5 g/d after complete remission** has been achieved
- **Steroid-resistant MCD:** Persistence of **proteinuria > 3.5 g/d** with **↓<50%** from baseline **despite prednisolone 1 MKD** or 2 mg/kg AD for **>16 weeks**
- **Frequently relapsing MCD:** **≥ 2 relapses per 6 months** or **≥ 4 relapses per 12 months**
- **Steroid-dependent MCD:** **Relapse** occurring **during, or within 2 weeks** of completing steroid Rx

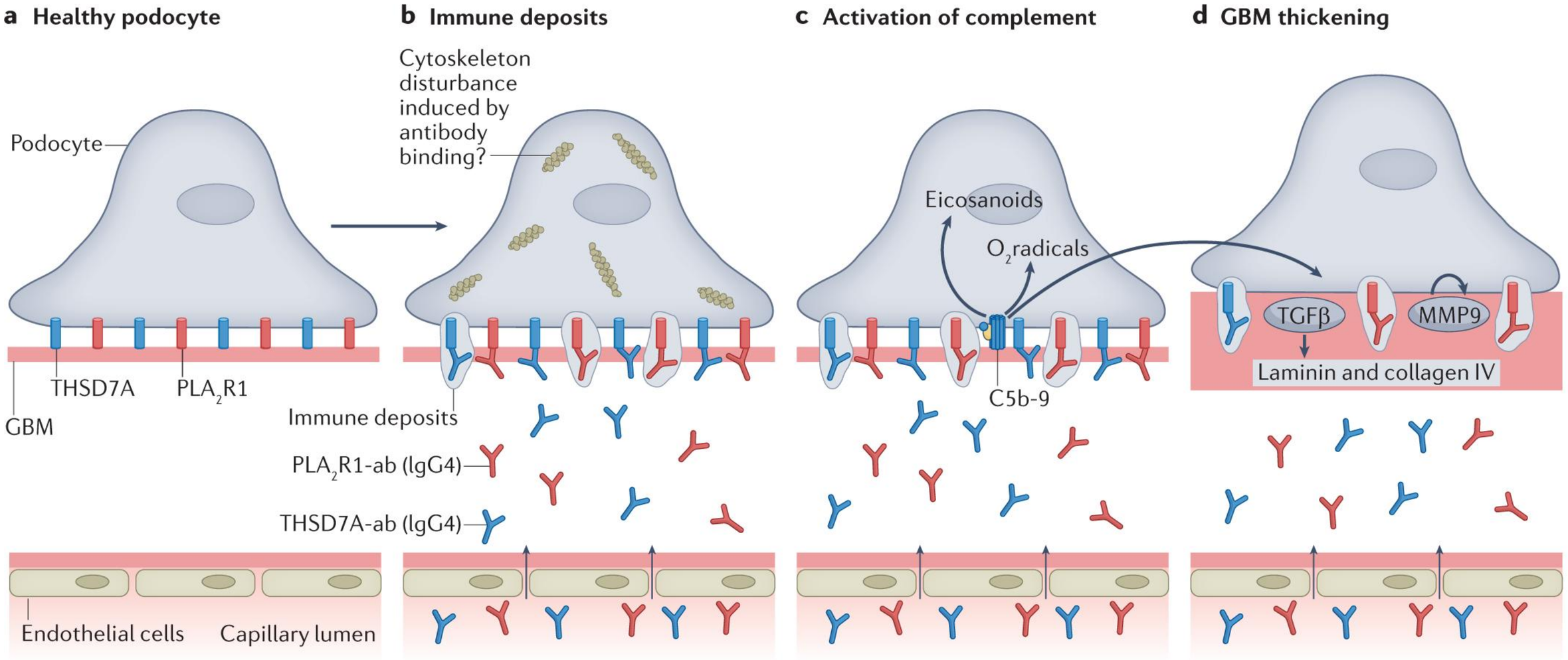
Kidney International (2021) 100, S1-S276

How to approach "Nephrotic Syndrome"?

1 2º Nephrotic Syndrome	2 1º Nephrotic Syndrome	3 Secondary causes
DKD	**Minimal Change Disease** [MCD] 1ºAbrupt, 2º Insidious, Bimodal age	· Infection: Virus, Strogyloides · Autoimmune: SLE (LN I), Myasthenia · Drug: NSAIDs, Lithium · Malignancy: Lymphoma, Leukemia · Allergy: Pollen, Bee sting, Food allergens
LN class V	**Membranous Nephropathy** [MN] Insidious onset, Elderly	· Infection: HBeAg, Syphillis · Autoimmune: SLE (LN V) · Drug: Gold, Penicillamine · Malignancy: Solid organ tumor
Amyloidosis	**Focal Segmental Glomerulosclerosis** [FSGS] 1ºAbrupt, 2ºInsidious, various character	· Infection: HIV, Parvovirus B19, EBV · Autoimmune: SLE (LN VI) · Drug: Pamidronate, Lithium, Heroin, IFN · Others: Obesity, HT, Genetic

Membranous Nephropathy (MN)

Pathogenesis

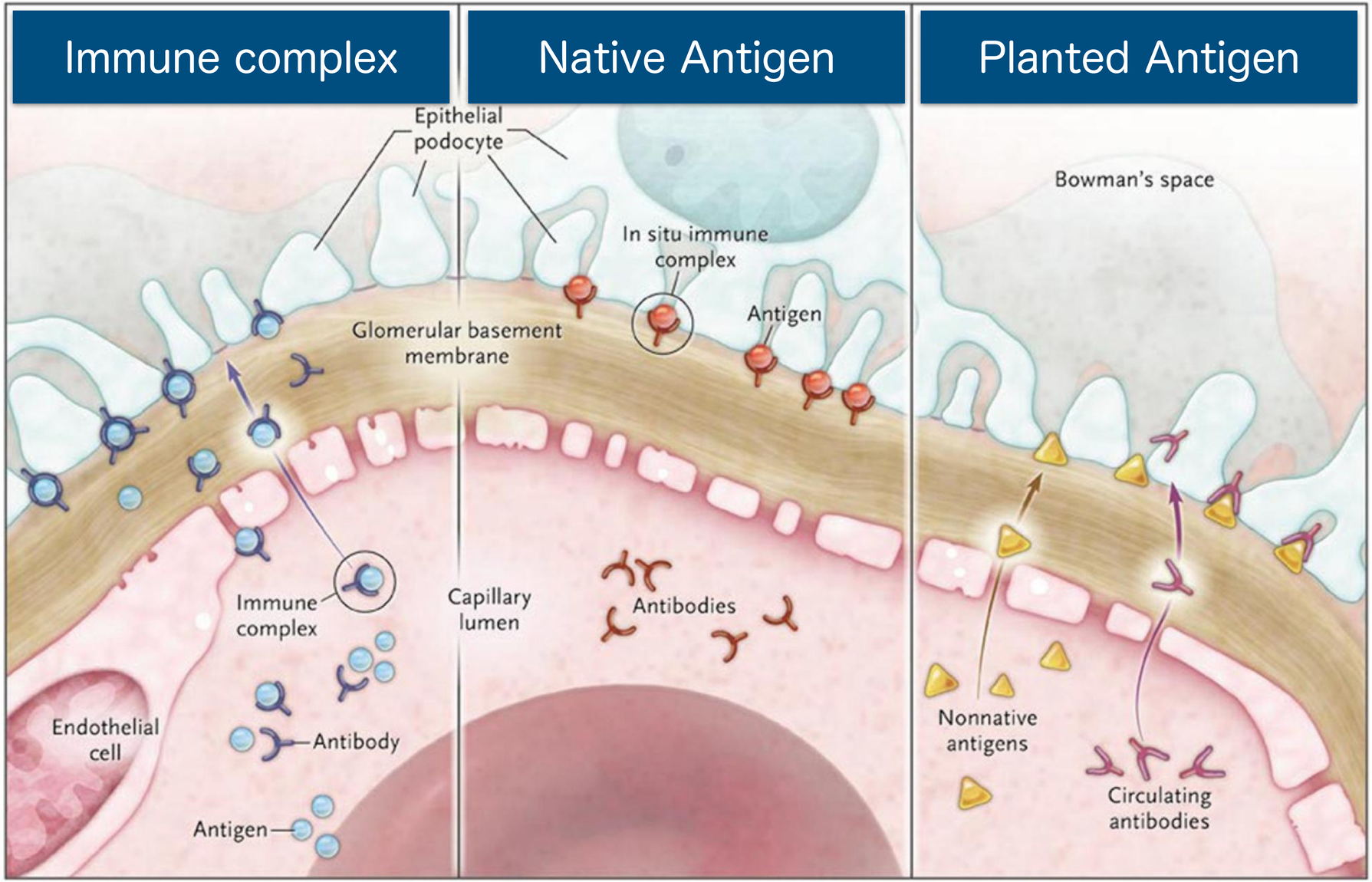


Nat Rev Nephrol 18, 466-478(2022)

Membranous Nephropathy (MN)

Pathogenesis

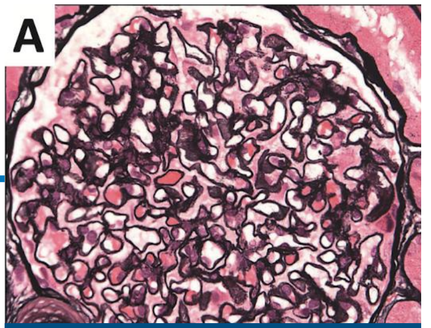
- ✓ Immune complex
  - LN Class V
- ✓ Native Antigen
  - PLA2R
  - THSD7A
  - NELL-1
- ✓ Planted Antigen
  - HBeAg
  - Syphyllis
  - Solid organ tumor
  - Drug



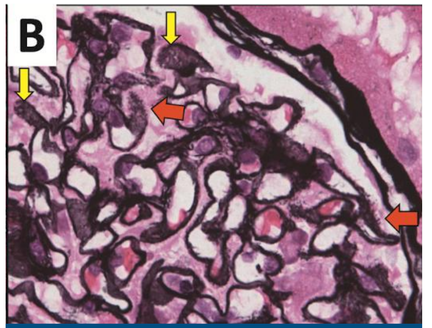
N Engl J Med 2009; 361:81-83

Membranous Nephropathy (MN)

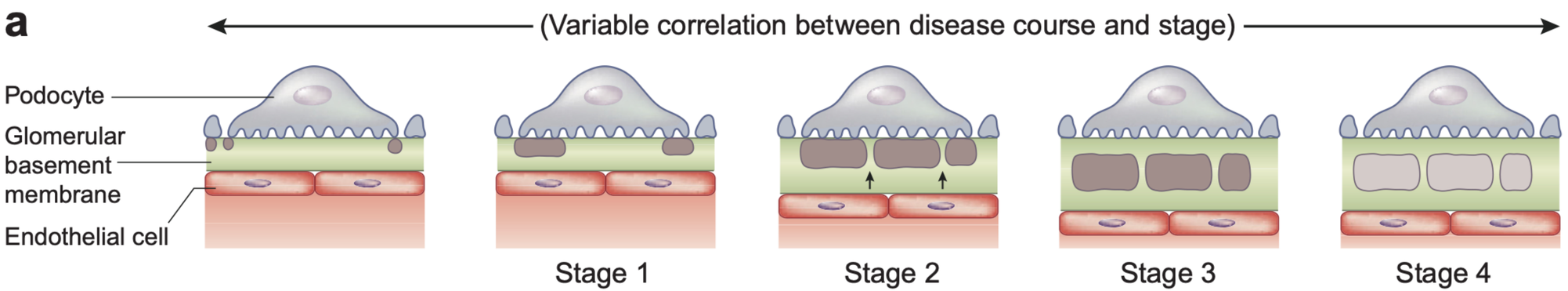
Histopathology

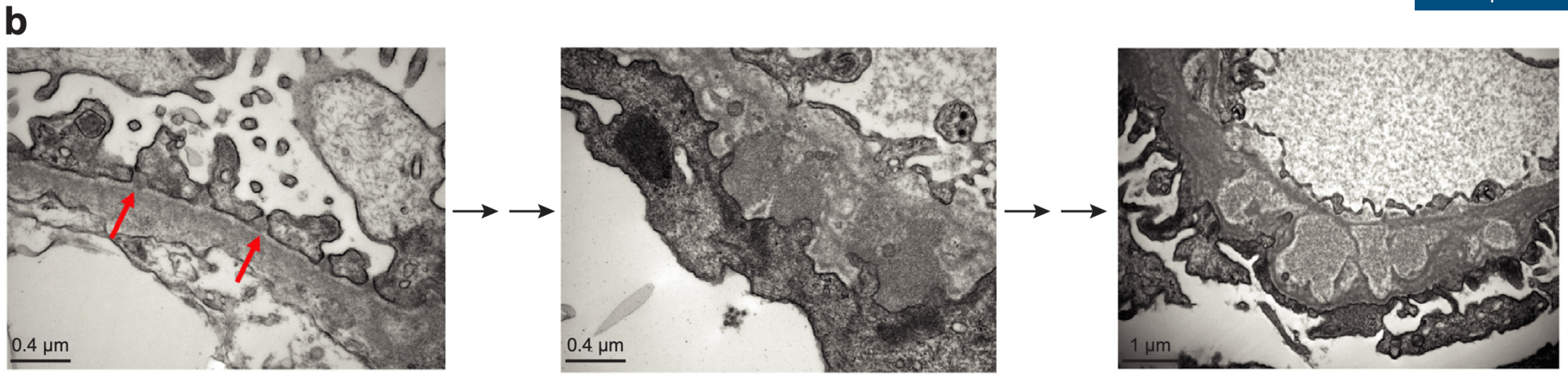


GBM Thickening



Spikes & Holes





Peri-slit diaphragm immune deposits[#]

Stage 2 immune deposits[#]

Stage 4 immune deposits

Kidney International, 2021;100,289-300

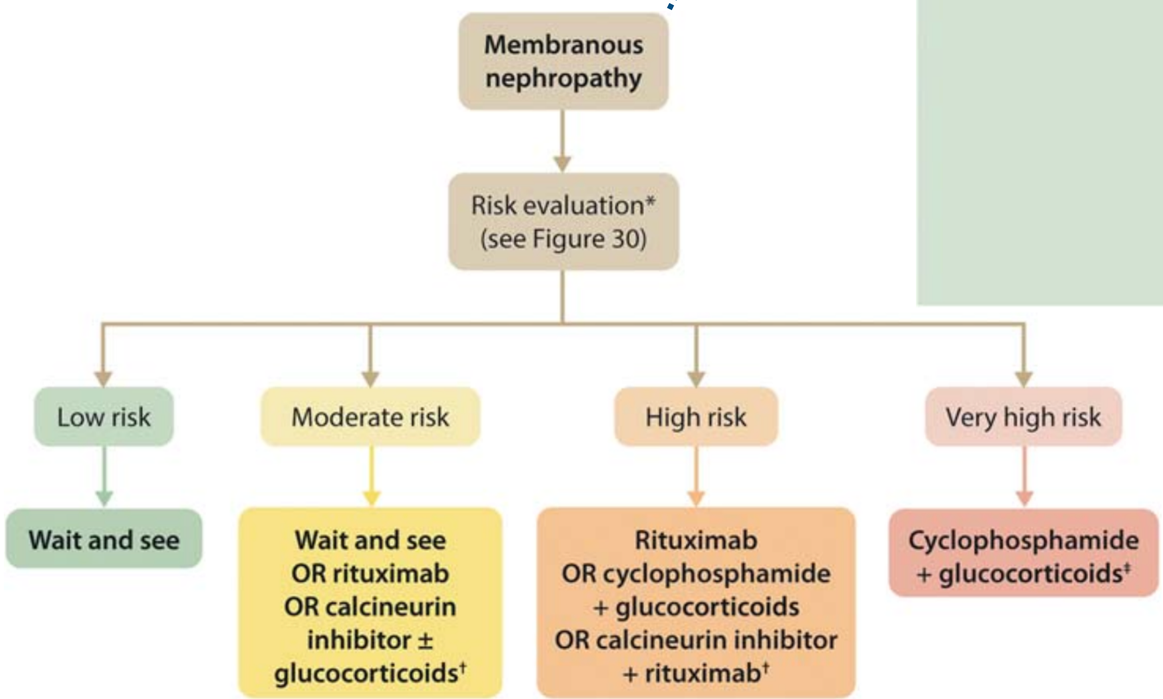
Membranous Nephropathy (MN): Clinical features

Age of onset	> 40 years
Onset	**Insidious** onset
Special characters **Disease of "30"**	✓ 30% Spontaneous **remission**
	✓ 30% **Stable** disease
	✓ 30% **Progression** of disease
Secondary causes	◉ Infection: HBV (**HBeAg**), Syphillis (Treponemal Ab)
	◉ Autoimmune: **LN Class V**, Autoimmune thyroiditis
	◉ Drug: **Gold**, **D-Penicillamine**, **NSAIDs**
	◉ Malignancy: **Solid** organ tumor (Lung, Colon, Kidney, Prostate), NHL

Membranous Nephropathy (MN)

Management

- Low: Wait & See
- Moderate: **RTX** > CNI/Steroid
- High: **RTX** > CY/Steroid > CNI/RTX
- Very high: **CY/Steroid**



Low risk	Moderate risk	High risk	Very high risk
• Normal eGFR, proteinuria <3.5 g/d and serum albumin >30 g/l OR • Normal eGFR, proteinuria <3.5 g/d or a decrease >50% after 6 months of conservative therapy with ACEi/ARB	• Normal eGFR, proteinuria >3.5 g/d and no decrease >50% after 6 months of conservative therapy with ACEi/ARB AND • Not fulfilling high-risk criteria	• eGFR <60 ml/min/1.73 m²* and/or proteinuria >8 g/d for >6 months OR • Normal eGFR, proteinuria >3.5 g/d and no decrease >50% after 6 months of conservative therapy with ACEi/ARB AND at least one of the following: • Serum albumin <25 g/l† • PLA2Rab >50 RU/ml‡ • Urinary α_1 -microglobulin >40 µg/min • Urinary IgG >1 µg/min • Urinary β_2-microglobulin >250 mg/d • Selectivity index >0.20§	• Life-threatening nephrotic syndrome OR • Rapid deterioration of kidney function not otherwise explained

- **Rituximab** 1 g IV q 1 wk x 2 Dose
- **CY/Steroid (Modified Ponticelli regimen)**
  - ✓ **IVMP 1g x 3 d** then, **Pred 0.5 MKD** at month **1, 3, 5**
  - ✓ **POCY 2.5 MKD** at month **2, 4, 6**

Kidney International (2021) 100, S1-S276

Complication in Nephrotic syndrome

- Acute kidney injury (AKI)
- Hypercoagulability
- Dyslipidemia

Nephrotic syndrome complication: AKI

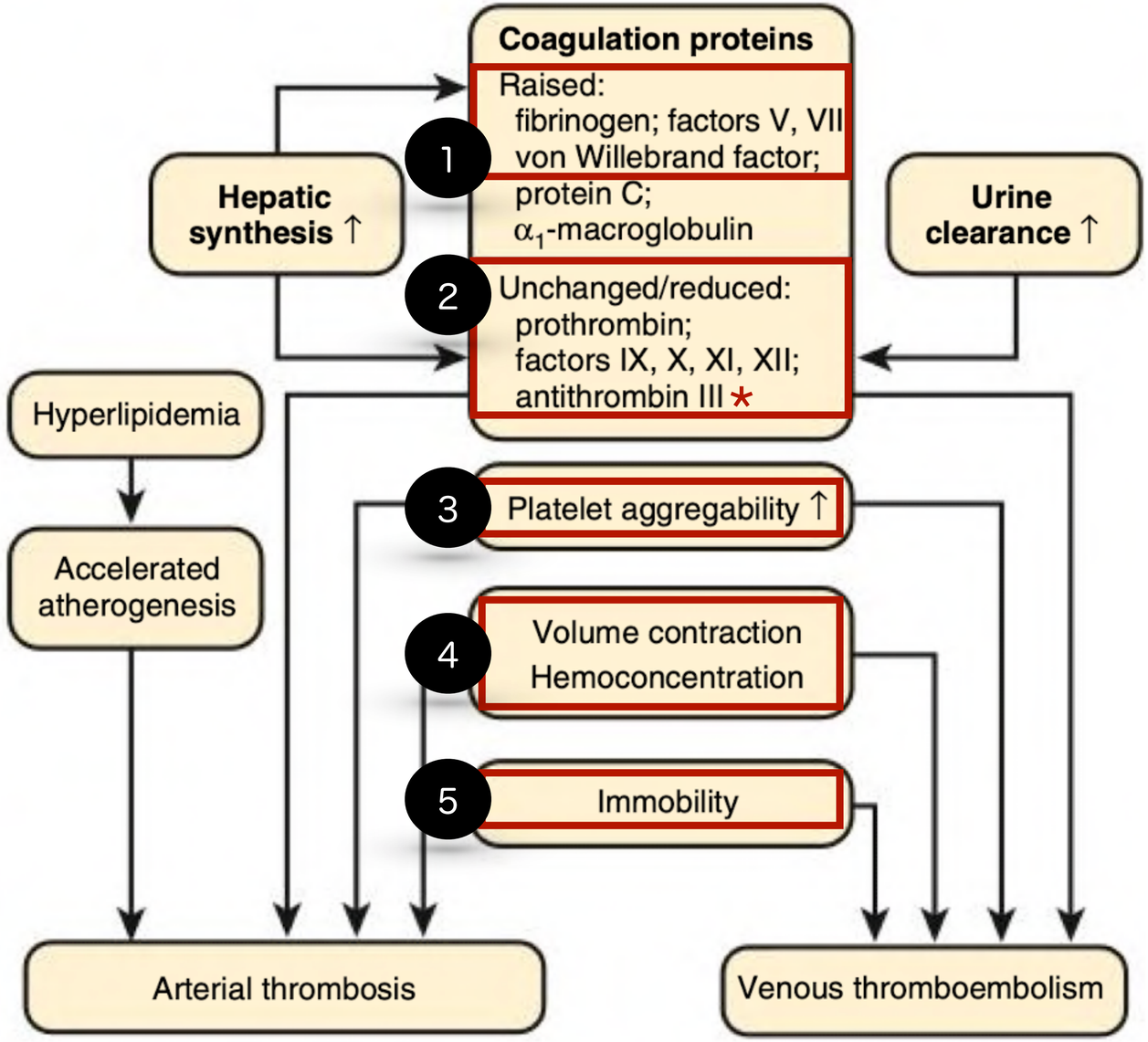
AKI in Nephrotic syndrome

ATN/AIN	· Low ECV (Hypoalbuminemia, overdiuresis) · Nephrotoxic (NSAIDs, CNI, contrast, ATB), RAAS blocker
Nephrosarca	· Interstitial edema & collapsed tubule
Bilateral RVT	· ↓ Anti-coagulable protein · ↑ Immune complex (MN) activate coagulation process or FXII
Aggressive disease	· Worsening disease (Collapsing FSGS)
Crescentic GN superimposition	· New-onset or worsening glomerular hematuria (ANCA/ Anti-GBM)

Kidney International (2018) 94, 861-869
Medicina 2019, 55, 365
Curr Opin Crit Care 2019, 25:573-579

Nephrotic syndrome complication: Hypercoagulability

Onset	**First 6 months** of diagnosis
Age	**Adults** > Children
Affected vessels	**Venous** > Arterial [Common: **DVT, RVT**]
Etiology	**MN** (Most common) > Other type NS
Main risk factors	✓ **Histologic** Diagnosis ✓ Severity of **proteinuria** ✓ Serum **Alb < 2.5** g/dL
Additional risk factors	Prior thrombosis, Antiphospholipid Ab+, Obesity, Genetic, Surgery, Malignancy, Pregnancy



Comprehensive Clinical Nephrology, 7th edition

Nephrotic syndrome complication: Hypercoagulability

Treatment

For thromboembolic events, full-dose anticoagulation is required for 6–12 months and/or for the duration of the nephrotic syndrome

- Venous thrombosis
- Arterial thrombosis
- Pulmonary embolus
- Nonvalvular atrial fibrillation

Prophylaxis

- **B:** BMI > 35 kg/m^2
- **I:** Immobilization
- **G:** Genetic
- **S:** Surgery (Recent)
- **I:** -
- **H:** HF NYHA class III-IV
- **P:** proteinuria > 10 g/d

*https://www.med.unc.edu/gntools/bleedrisk.html.

Kidney International (2021) 100, S1-S276

Nephrotic syndrome complication: Dyslipidemia

Pathogenesis

1. Hypoalbuminemia →↑**Hepatic synthesis** of LDL, VLDL, Lp(a)
2. **Defective peripheral lipoprotein lipase** activity → ↑VLDL
3. Urinary **loss of HDL** → ↓HDL
4. ↑Hepatic & Kidney **PCSK9 overexpression**
5. Treatment complications: Steroid, mTORi, CNI

Treatment

- ✓Treat as general population
- ✓When **statins combined with CNI** may ↑risk of **myalgia/myositis**
- ✓**Lipid aphaeresis** may use in hyperlipidemia in **steroid-resistant NS**

Comprehensive Clinical Nephrology, 7th edition
Kidney International (2021) 100, S1-S276

Glomerular syndrome

1 Asymptomatic

- Isolated proteinuria 150 mg to 3 g/day
- Hematuria > 2 RBC/HPF in spun urine

2 Nephrotic syndrome

- Generalized **edema**
- **Proteinuria > 3.5 g/24h** (UPCR > 3)
- **Hypoalbuminemia** < 3.5 g/dL
- **Hypercholesterolemia** > 250 mg/dL
- Lipiduria (Oval fat body)

Glomerulonephritis (GN)

- Glomerular **hematuria**
- Proteinuria (**< 3g/day**)
- **Azotemia** / Oliguria
- Edema
- **Hypertension** (Accelerated/New-onset)

3 Acute GN

< 7 days

4 RPGN*

Weeks to months

5 Chronic GN

> 3 months

*RPGN: Rapid Progressive Glomerulonephritis

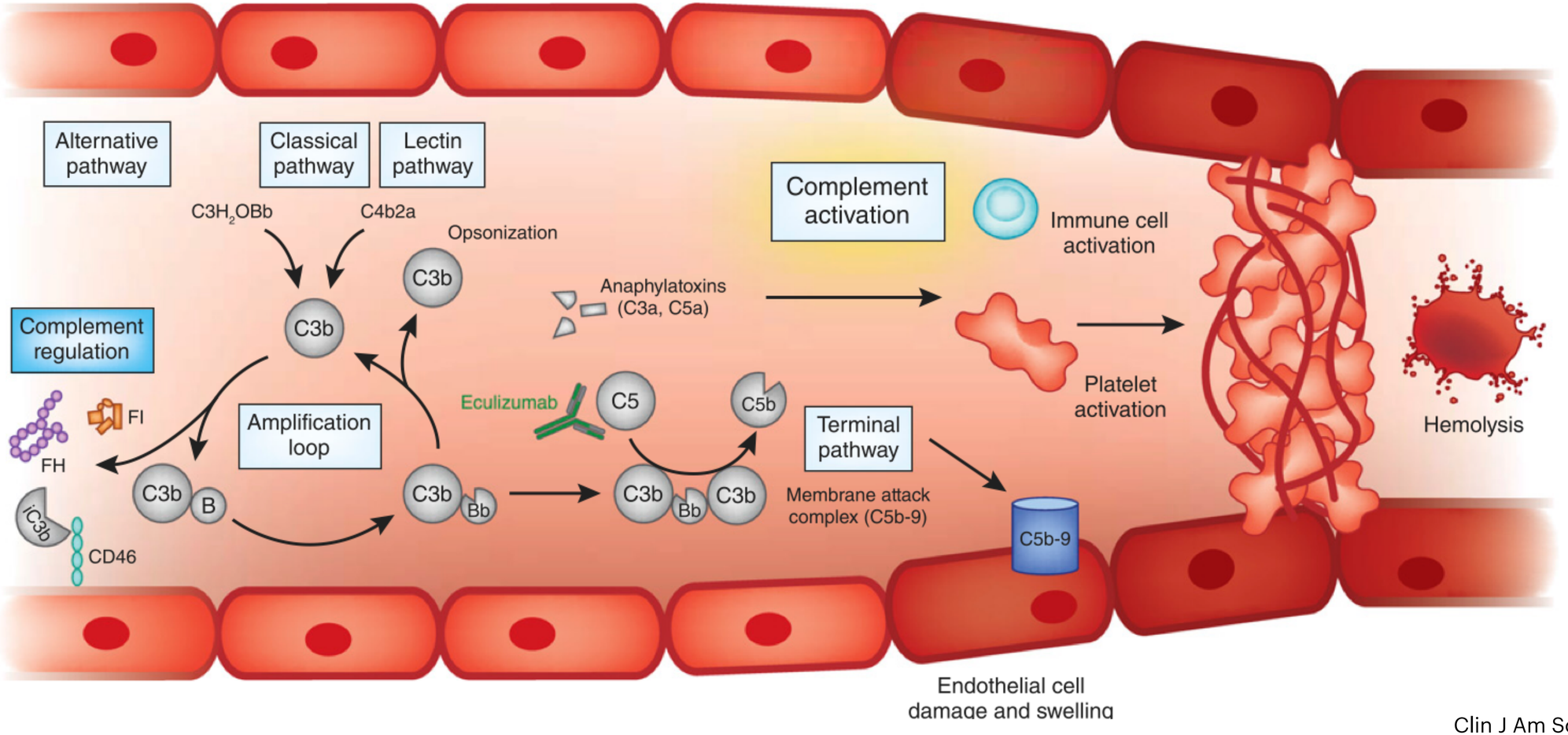
How to approach "Glomerulonephritis" ?

RPGN Mimicker	Immune complex			Anti-GBM		Pauci-immune	
	Young adult, Acute to RPGN			Bimodal age, RPGN		Elderly, insidious onset	
←→ C3, C4	←→ C3, C4	↓C3	↓C3, ↓C4	←→ C3, C4		←→ C3, C4	
• TMA • Alport syndrome • ATN/AIN • Renovascular disease • Papillary necrosis	IgAN	• IRGN • C3GN	• LN • Cryoglobulinemia (↓ ↓C4) • MPGN	No Pulmonary hemorrhage	Pulmonary hemorrhage	C-ANCA (Anti-PR3)	P-ANCA (Anti-MPO)
				Anti-GBM disease	Goodpasture syndrome	GPA	• EGPA • MPA • Drug-induced ANCA

Thrombotic microangiopathy (TMA)

Pathogenesis:

Complement hyperactivation → **Endothelial injury**, **Microthrombi**, and **Hemolysis**



Clin J Am Soc Nephrol 13: 300–317, February, 2018

Thrombotic microangiopathy (TMA)

Ddx TMA from DIC
Normal Coag !!

Clinical Manifestation

1. **Thrombocytopenia:** Platelet < 150,000/mm^3 or ↓ > 25% from baseline
2. **MAHA** blood picture
3. **End organ damage**

Renal	Extrarenal
· **Microscopic hematuria** (78%)	· **Neuro**: AOC, Seizure
· **Subnephrotic range proteinuria** (75%)	· **CVS**: Myocardial infarction
· Sterile pyuria (31%)	· **GI**: Bowel necrosis, diarrhea
· Cast (24%)	· **Others**: pulmonary, ocular

1 + 2 + **Renal involvement** = **HUS**

Etiology: **Genetic**, Precipitating factors (**Infection**, **Pregnancy**)

Treatment: **Eculizumab** ± TPE with FFP

1 + 2 + **Neuro + AKI + Fever** = **TTP**

Etiology: **↓ADAMTS13** (<10%)

Treatment: **TPE with FFP**

Brenner & Rector's the kidney, 11th edition

How to approach “Glomerulonephritis” ?

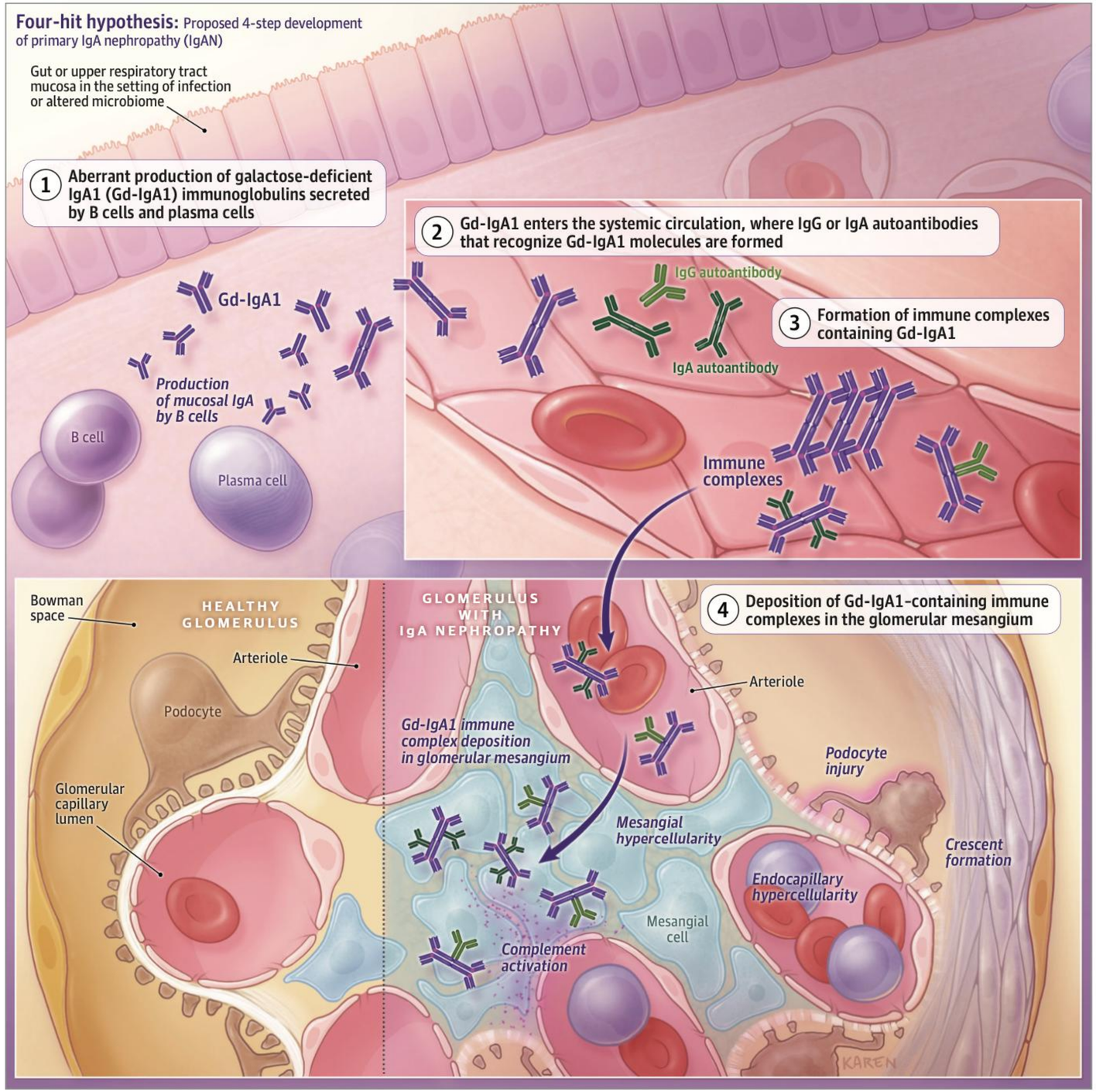
RPGN Mimicker	Immune complex			Anti-GBM		Pauci-immune	
	Young adult, Acute to RPGN			Bimodal age, RPGN		Elderly, insidious onset	
←→ C3, C4	←→ C3, C4	↓C3	↓C3, ↓C4	←→ C3, C4		←→ C3, C4	
				No Pulmonary hemorrhage	Pulmonary hemorrhage	C-ANCA (Anti-PR3)	P-ANCA (Anti-MPO)
• TMA • Alport syndrome • ATN/AIN • Renovascular disease • Papillary necrosis	IgAN	• IRGN • C3GN	• LN • Cryoglobulinemia (↓ ↓C4) • MPGN	Anti-GBM disease	Goodpasture syndrome	GPA	• EGPA • MPA • Drug-induced ANCA

IgA Nephropathy

Pathogenesis

4-HIT Hypothesis

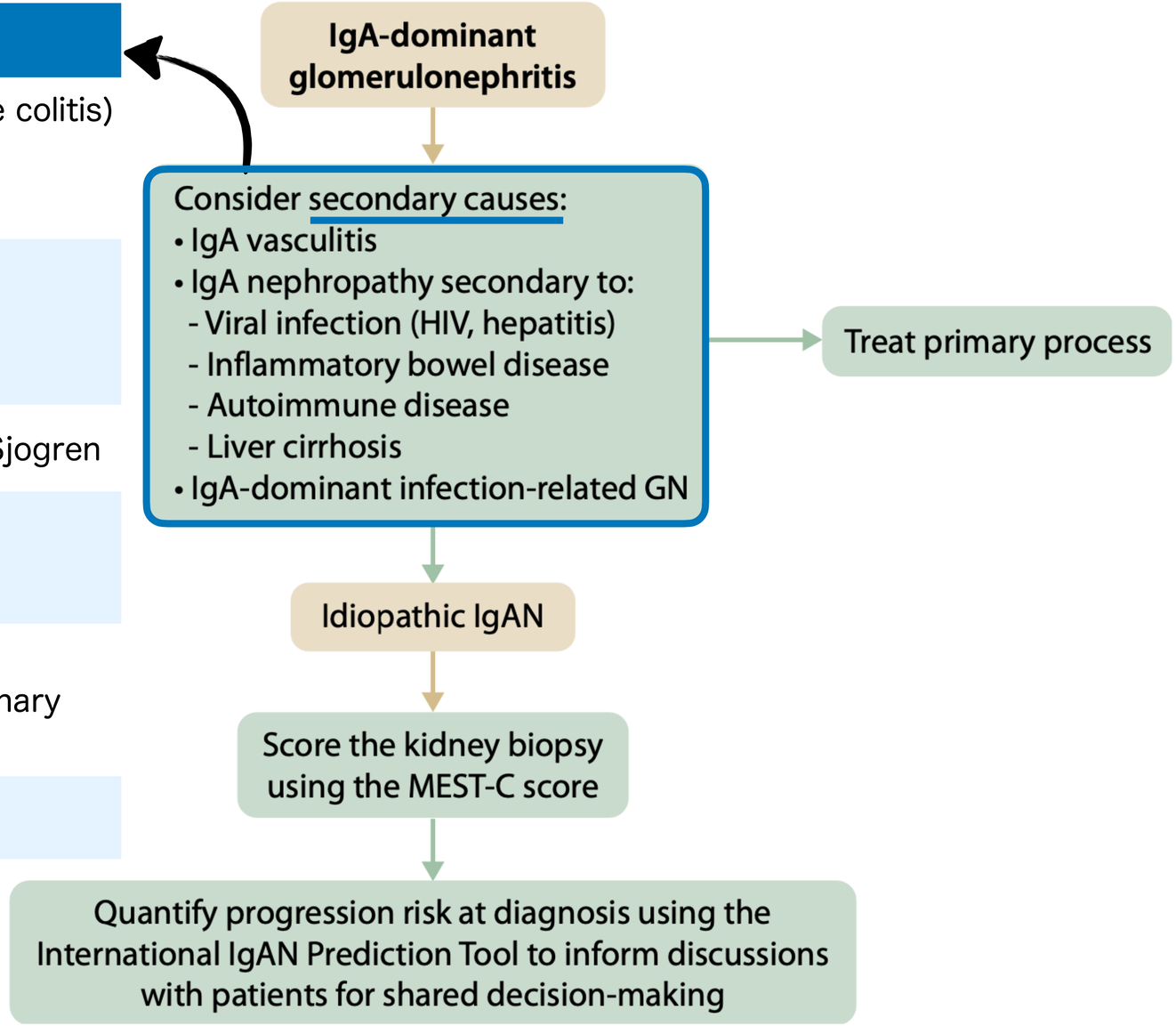
1. Production of **Gd-IgA1**
2. **Anti-Gd-IgA1 Ab** formation (IgG or IgA Autoantibodies)
3. Gd-IgA1-containing **immune complex** formation
4. **Deposition** of immune complexes at glomerular **mesangium**



JAMA. 2026;335(9):799-813.

IgA Nephropathy: Approach

Group	Disease
GI & liver diseases	– **Inflammatory bowel disease** (Crohn, Ulcerative colitis) – Celiac disease – **Cirrhosis**
Infection	– HCV, HBV, **HIV** infection – Tuberculosis – **Leprosy**
Autoimmune	– **Ankylosing spondylitis**, Rheumatoid arthritis, Sjogren
Malignancy	– Solid: Lung cancer, Renal cell carcinoma – Hematologic: **Lymphoma**, **IgA myeloma**
Respiratory	– Sarcoidosis – **Bronchiolitis obliterans**, Cystic fibrosis, Pulmonary fibrosis
Skin	– **Dermatitis herpetiformis**, **Psoriasis**

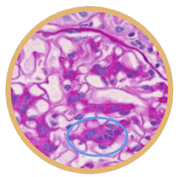


Kidney International (2025) 108 (Suppl 4S), S1-S71.

IgA Nephropathy: Approach

Group	Disease
GI & liver diseases	– **Inflammatory bowel disease** (Crohn, Ulcerative colitis) – Celiac disease, **Cirrhosis**
Infection	– HCV, HBV, **HIV** infection – Tuberculosis, **Leprosy**
Autoimmune	– **Ankylosing spondylitis**, Rheumatoid arthritis, Sjogren
Malignancy	– Solid: Lung cancer, Renal cell carcinoma – Hematologic: **Lymphoma**, **IgA myeloma**
Respiratory	– Sarcoidosis – **Bronchiolitis obliterans**, Cystic fibrosis, Pulmonary fibrosis
Skin	– **Dermatitis herpetiformis**, **Psoriasis**

M



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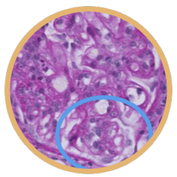
Mesangial hypercellularity[1]
≥4 mesangial cells in any mesangial area of a glomerulus

E



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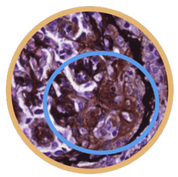
Endocapillary hypercellularity[1]
An increased number of cells in glomerular capillary lumen

S



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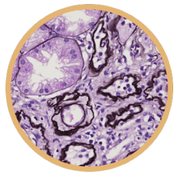
Segmental glomerulosclerosis[1]
Adhesion or sclerosis not involving the entire glomerulus

T



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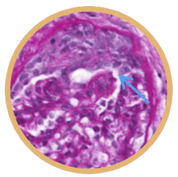
Tubular atrophy/interstitial fibrosis[1,2]
The percentage of tubular atrophy/interstitial fibrosis of cortical area

C



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Cellular/fibrocellular crescent[1]
Extracapillary cell proliferation >2 cell layers thick and <50% matrix

M	E	S	T	C
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

IgA-dominant glomerulonephritis

Consider secondary causes:
- IgA vasculitis
- IgA nephropathy secondary to:
  - Viral infection (HIV, hepatitis)
  - Inflammatory bowel disease
  - Autoimmune disease
  - Liver cirrhosis
- IgA-dominant infection-related GN

→ **Treat primary process**

Idiopathic IgAN

Score the kidney biopsy using the MEST-C score

Quantify progression risk at diagnosis using the International IgAN Prediction Tool to inform discussions with patients for shared decision-making

Kidney International (2025) 108 (Suppl 4S), S1-S71.

IgA Nephropathy: Treatment

Treatment initiation may considered
proteinuria ≥ 0.5 g/d

Steroid CAUTION

- eGFR < 30
- DM & Pre-DM
- Obesity
- Latent infection
- Active PU
- Psychi
- Osteoporosis
- Cataracts

IgAN at risk of progressive kidney function loss

1

2

Driver for nephron loss

Manage the IgAN-specific drivers for nephron loss

In all patients, these should be considered simultaneously

Manage the generic responses to IgAN-induced nephron loss

Cardiovascular risk reduction

Treatment goal

Stop synthesis of pathogenic forms of IgA and IgA-IC formation

Stop IgA/IgA-IC mediated kidney injury

Reduce glomerular hyperfiltration, proteinuria and the impact of proteinuria on the tubulointerstitium

Blood pressure control

1st

9-months course of Nefecon [2B]

Interventions with reported efficacy across populations

Nefecon

Systemic glucocorticoids

Lifestyle modification

[1B] RASi or DEARA ± SGLT2i [2B]

Goal

Proteinuria < 0.5 g/d
(Ideally < 0.3 g/d)

Interventions with reported efficacy in specific populations (see Figure 4)

Mycophenolate mofetil (China)
Hydroxychloroquine (China)
Tonsillectomy (Japan)

If Nefecon are not available
Reduced-dose systemic steroid & Antimicrobial prophylaxis [2B]

0.4 MKD (Methylpred) ~ **Pred 1 MKD x 2 mo**
Then, ↓4 mg (Methylpred)/mo ~ **↓5mg (Pred)/mo**
(Total = **6-9 mo**)

Always consider the option of a clinical trial

Kidney International (2025) 108 (Suppl 4S), S1-S71.

How to approach “Glomerulonephritis” ?

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←→ C3, C4	←→ C3, C4	↓C3	↓C3, ↓C4	←→ C3, C4		←→ C3, C4	
• TMA • Alport syndrome • ATN/AIN • Renovascular disease • Papillary necrosis	IgAN	• IRGN • C3GN	• LN • Cryoglobulinemia (↓ ↓C4) • MPGN	No Pulmonary hemorrhage	Pulmonary hemorrhage	C-ANCA (Anti-PR3)	P-ANCA (Anti-MPO)
				Anti-GBM disease	Goodpasture syndrome	GPA	• EGPA • MPA • Drug-induced ANCA

Post-infectious Glomerulonephritis (PIGN)

Pathogenic Factor	**Nephritogenic streptococcal antigen** ✓ Nephritis-associated plasmin receptor (**NAPlr**) ✓ Streptococcal pyrogen exotoxin B (**SPEB**)
High-risk group	Children, Elderly, Immunocompromised host
History	**Pre-existing infection** ✓ Pharyngitis: **1-2 weeks** ✓ Impetigo: **4-6 weeks**
Physical exam	± Active skin or tonsil infection
LAB	· Glomerulonephritis picture · **↓↓C3, ↓C4** · Positive **ASO** (~30% in URI), **Anti-DNAse B** (~70% in impetigo) or **Anti-hyaluronidase Ab**
Prognosis	· Children: Excellent short-term prognosis · **Elderly: Poor prognosis** for those who develop persistent albuminuria (Mortality up to 20%) · Persistent **low C3 > 12 weeks** may be indicated for kidney biopsy to exclude **C3GN**
Treatment	· Antibiotic for treat underlying infection · Data of high-dose steroid remains unproven

Recovery

- ✓ GN features **~ 2 weeks**
- ✓ Complement **~ 2 months**
- ✓ Hematuria **~ 6 months**
- ✓ Proteinuria **> 1 year**

How to approach “Glomerulonephritis” ?

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←→ C3, C4	←→ C3, C4	↓C3	↓C3, ↓C4	←→ C3, C4		←→ C3, C4	
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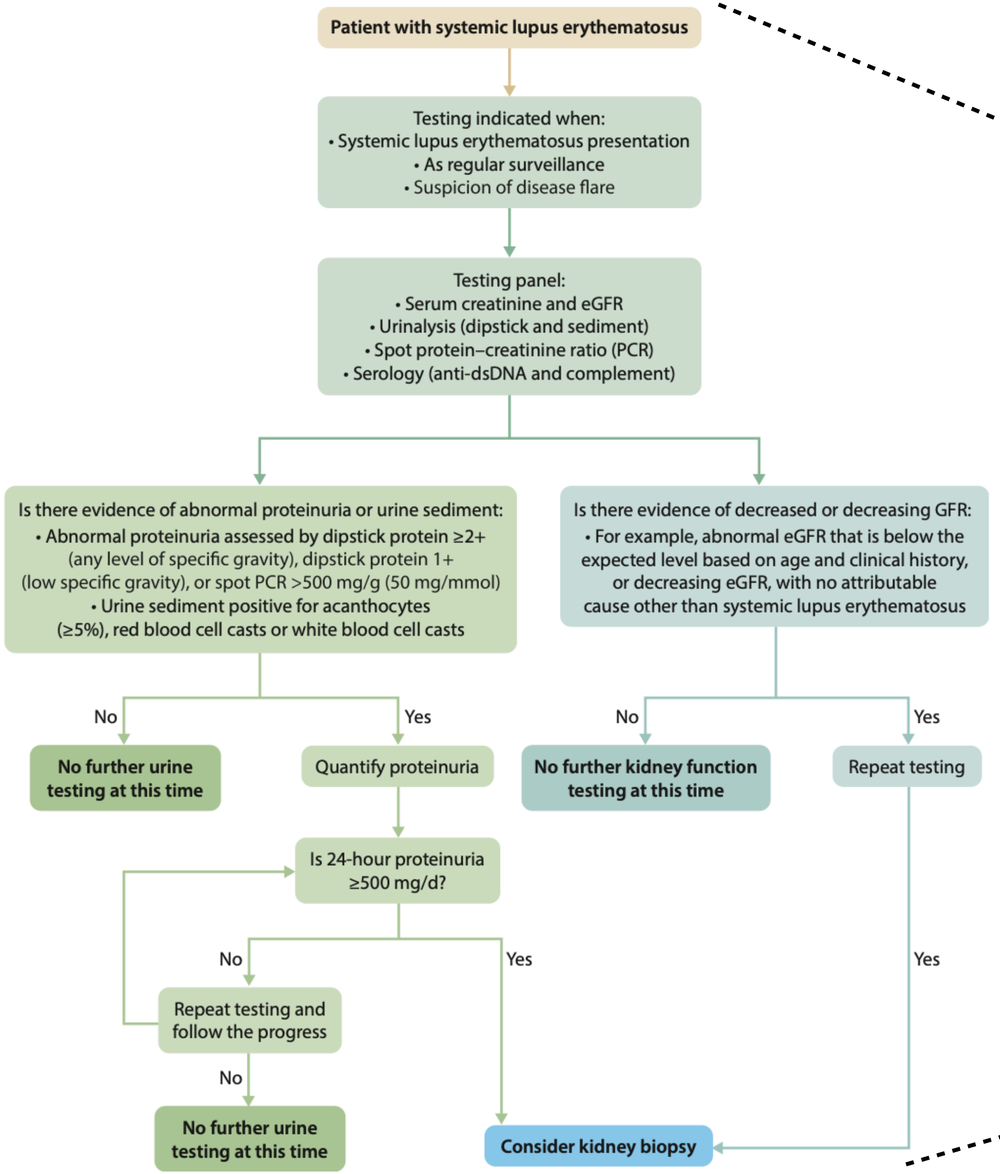
				Anti-GBM disease	Goodpasture syndrome	GPA	• EGPA • MPA • Drug-induced ANCA

Lupus Nephritis: Diagnostic approach



Simplified Version

"SLE"

24h proteinuria ≥ 500 mg/day

↓ eGFR

Yes

Yes

Kidney Biopsy

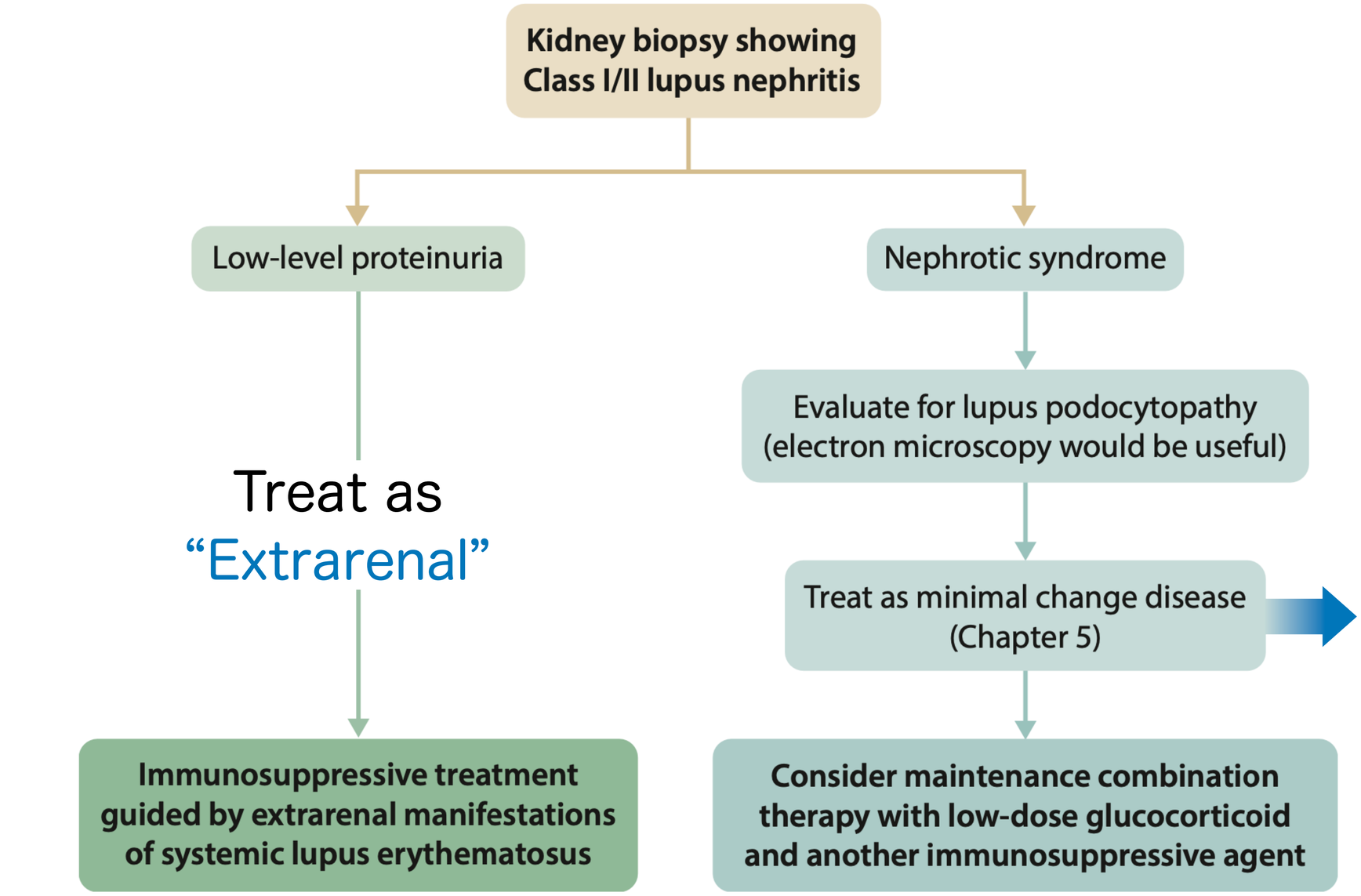
Kidney International (2024) 105(Suppl 1S), S1-S69

Lupus Nephritis: Classification

Revision LN classification ISN/RPS 2018		
Class	**Pathological findings**	**Clinical**
Class I	Minimal Mesangial LN	**Asymptomatic** or **mild** symptoms
Class II	Mesangial proliferative LN	
Class III	Focal proliferative LN (<50% of glomeruli)	**Acute GN** or **RPGN**
Class IV	Diffuse proliferative LN (>50% of glomeruli)	
Class V	Membranous LN	**Nephrotic** syndrome
Class VI	Advanced sclerosing LN (>90%Sclerotic glomeruli)	**Chronic** GN

Immunofluorescence: **"Full house"** (IgA, IgG, IgM, C3, C1q)

Lupus Nephritis Class I/II: Treatment



Prednisolone

- Dose:
  - **1 MKD** upto 80 mg od "OR"
  - 2 MKD unto 120 mg AD
- Duration: **4-16 weeks**
- Taper down: upto **6 months**

Kidney International (2024) 105(Suppl 1S), S1-S69

Lupus Nephritis Class III/IV ± V: Induction

Steroid

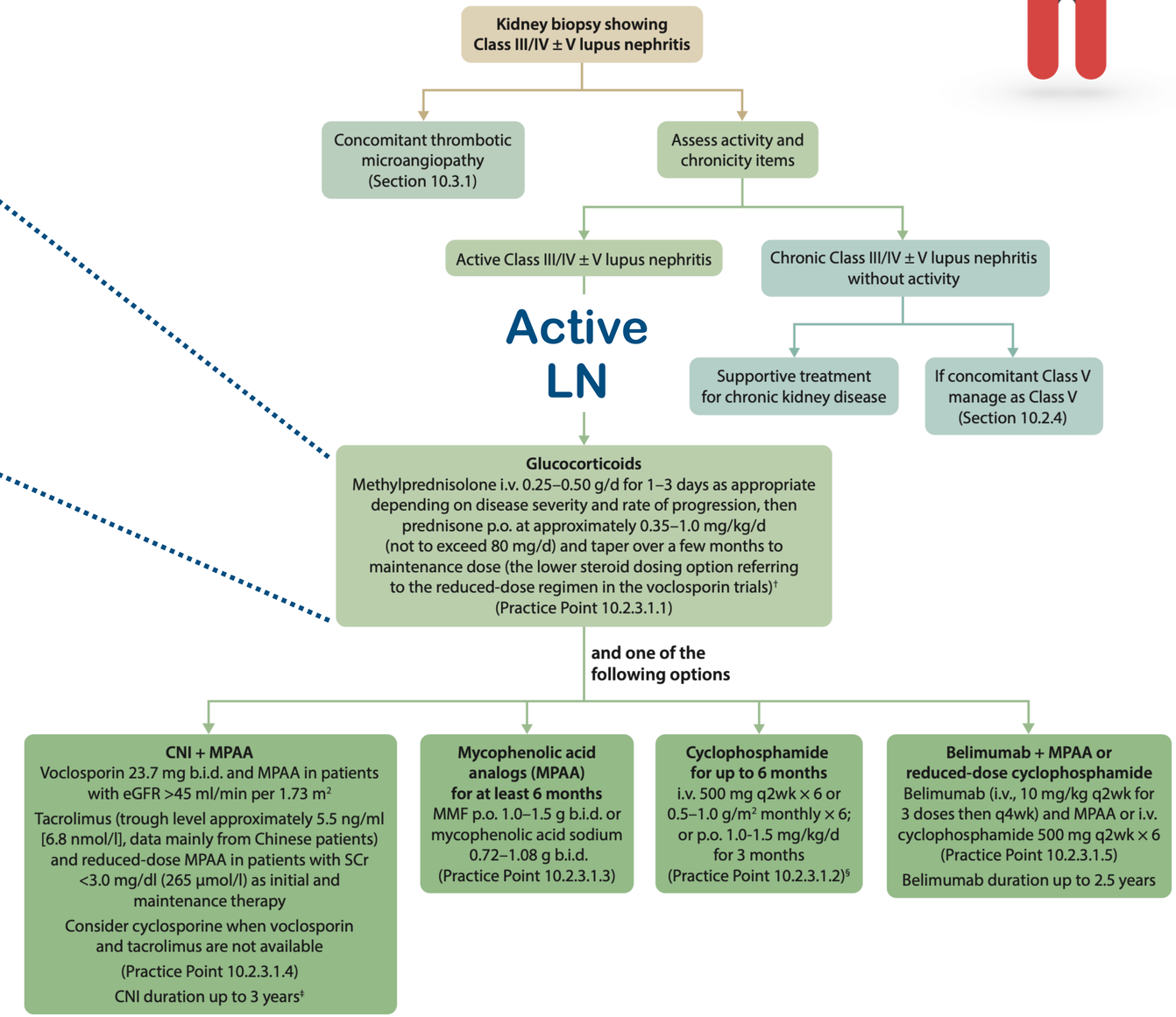
IVMP 0.25-0.50 g/d x 1-3 days

Then, **Prednisolone 0.35-1.0 MKD**

(Max 80 mg/day)

Taper over a few months

1



Kidney International (2024) 105(Suppl 1S), S1-S69

Lupus Nephritis Class III/IV ± V: Induction

Steroid tapering strategies

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

Kidney International (2024) 105(Suppl 1S), S1-S69

Lupus Nephritis Class III/IV ± V: Induction

Steroid

IVMP 0.25-0.50 g/d x 1-3 days

Then, **Prednisolone 0.35-1.0 MKD**

(Max 80 mg/day)

Taper over a few months

Immunosuppressive Rx

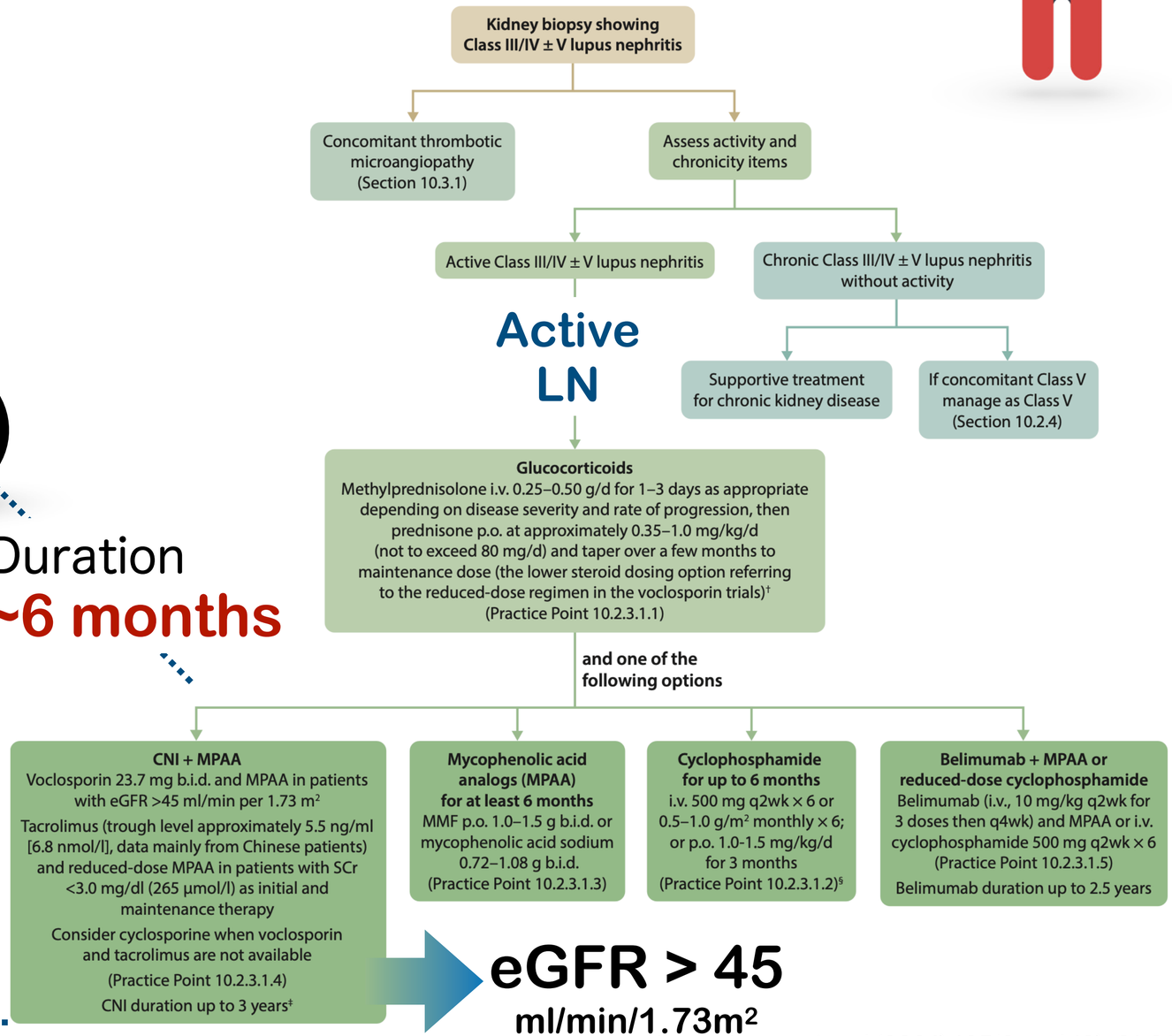
2

Recommendation 10.2.3.1.1: We recommend that patients with active Class III or IV LN, with or without a membranous component, be treated initially with glucocorticoids plus any *one* of the following:

i. **mycophenolic acid analogs (MPAAs) *(1B)*; or**
ii. **low-dose intravenous cyclophosphamide *(1B)*; or**
iii. **belimumab and either MPAA or low-dose intravenous cyclophosphamide *(1B)*; or**
iv. **MPAA and a calcineurin inhibitor (CNI) when kidney function is not severely impaired (i.e., estimated glomerular filtration rate [eGFR] ≤45 ml/min per 1.73 m^2) *(1B)*.**

Duration

~6 months



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Lupus Nephritis Class III/IV ± V: Maintenance

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

✓ Induction + Maintenance Duration ≥ **36 months**

✓ Consider STOP Steroid **after CR ≥ 12 months**

Reduce prednisone to <5 mg/d

1st

First choice

- **MMF** 750-1000 mg bid
- **MPA** 540-720 mg bid

Mycophenolic acid analogs: mycophenolate mofetil 1–2 g/d or mycophenolic acid 720–1440 mg/d

or

Patients who received triple immunosuppression as initial therapy for active nephritis (refer to Recommendation 10.2.3.1.1 and Figure 5)

Continue with the maintenance triple immunosuppression as described in Figure 5 as appropriate, Practice Point 10.2.3.2.5, and Figure 9

or

Individual cases or when no access to MPAA

Azathioprine 1.5–2.0 mg/kg/d

or

If MPAA or azathioprine not tolerated or available

CNI (tacrolimus, level ≈4–6 ng/ml; cyclosporine, level ≈50–100 ng/ml) or mizoribine ≈3–5 mg/kg/d or leflunomide ≈10–20 mg/d

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Lupus Nephritis Class III/IV ± V

Criteria	Definition
Complete response*	• Reduction in proteinuria <0.5 g/g (50 mg/mmol) measured as the PCR from a 24-h urine collection • Stabilization or improvement in kidney function (±10%–15% of baseline) • Within 6–12 mo of starting therapy, but could take more than 12 mo
Primary efficacy renal response	• PCR ≤0.7 g/g (70 mg/mmol) • eGFR that was no worse than 20% below the pre-flare value or ≥60 ml/min per 1.73 m^2 • No use of rescue therapy for treatment failure
Partial response	• Reduction in proteinuria by at least 50% and to <3 g/g (300 mg/mmol) measured as the PCR from a 24-h urine collection • Stabilization or improvement in kidney function (±10%–15% of baseline) • Within 6–12 mo of starting therapy
No kidney response	• Failure to achieve a partial or complete response within 6–12 mo of starting therapy

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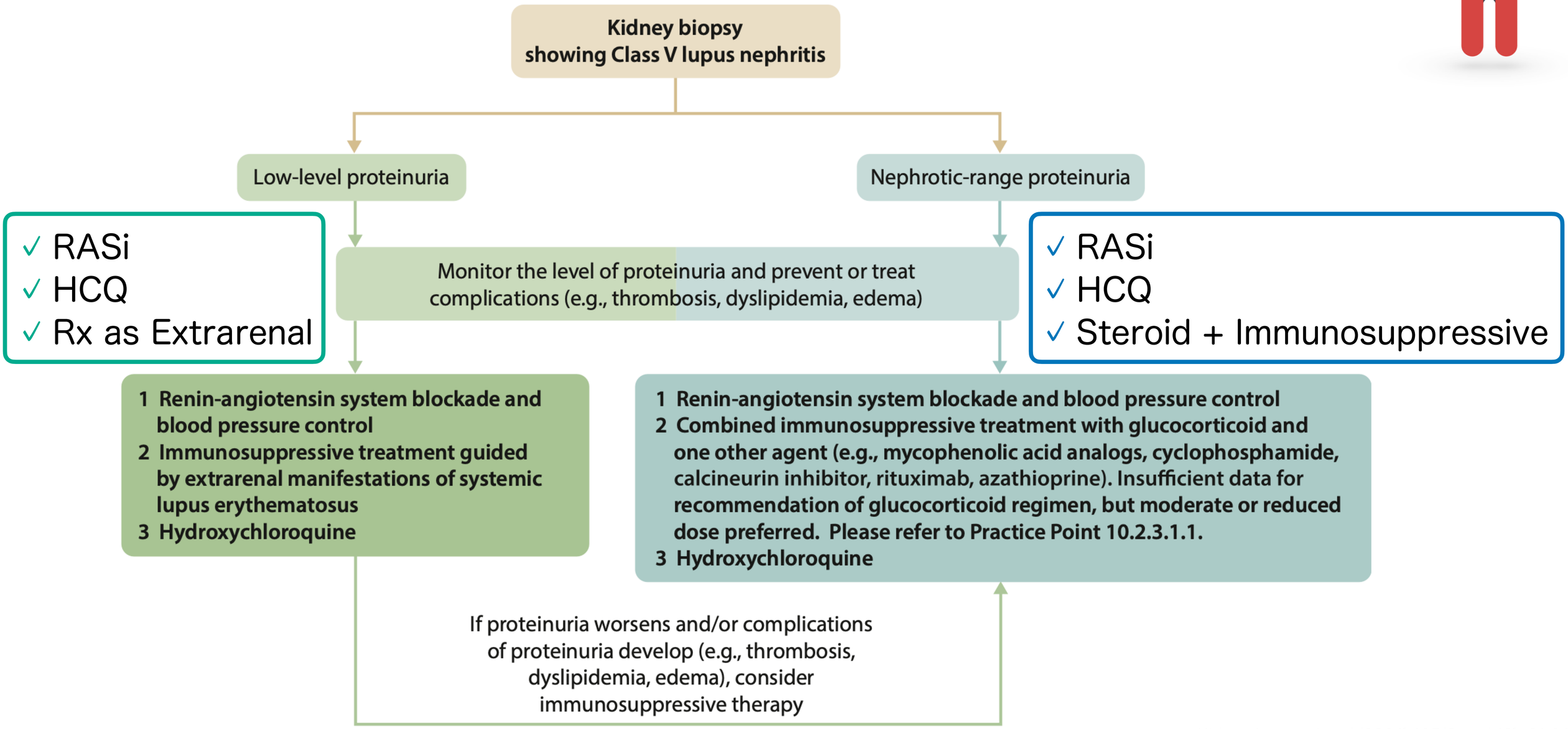
Lupus Nephritis Class V: Treatment



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How to approach “Glomerulonephritis” ?

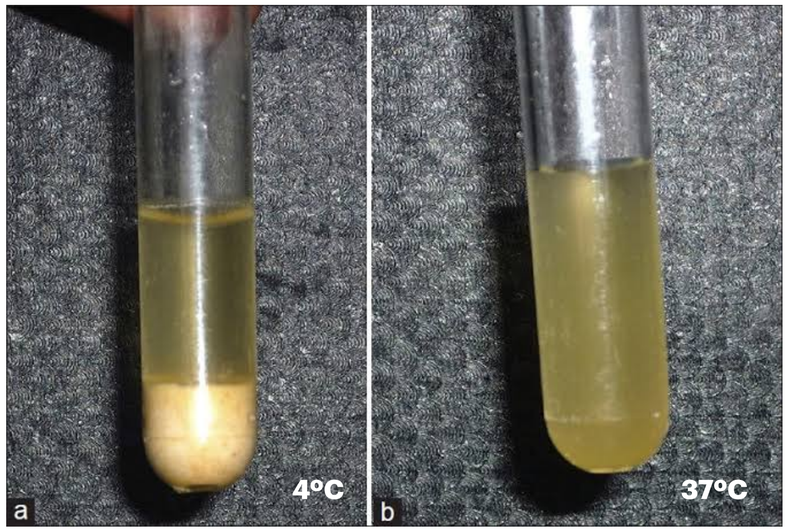
RPGN Mimicker	Immune complex			Anti-GBM		Pauci-immune	
	Young adult, Acute to RPGN			Bimodal age, RPGN		Elderly, insidious onset	
←→ C3, C4	←→ C3, C4	↓C3	↓C3, ↓C4	←→ C3, C4		←→ C3, C4	
				No Pulmonary hemorrhage	Pulmonary hemorrhage	C-ANCA (Anti-PR3)	P-ANCA (Anti-MPO)
• TMA • Alport syndrome • ATN/AIN • Renovascular disease • Papillary necrosis	IgAN	• IRGN • C3GN	• LN • Cryoglobulinemia (↓ ↓C4) • MPGN	Anti-GBM disease	Goodpasture syndrome	GPA	• EGPA • MPA • Drug-induced ANCA

Cryoglobulinemic Glomerulonephritis

What is “Cryoglobulin” ?

Abnormal circulating immunoglobulin

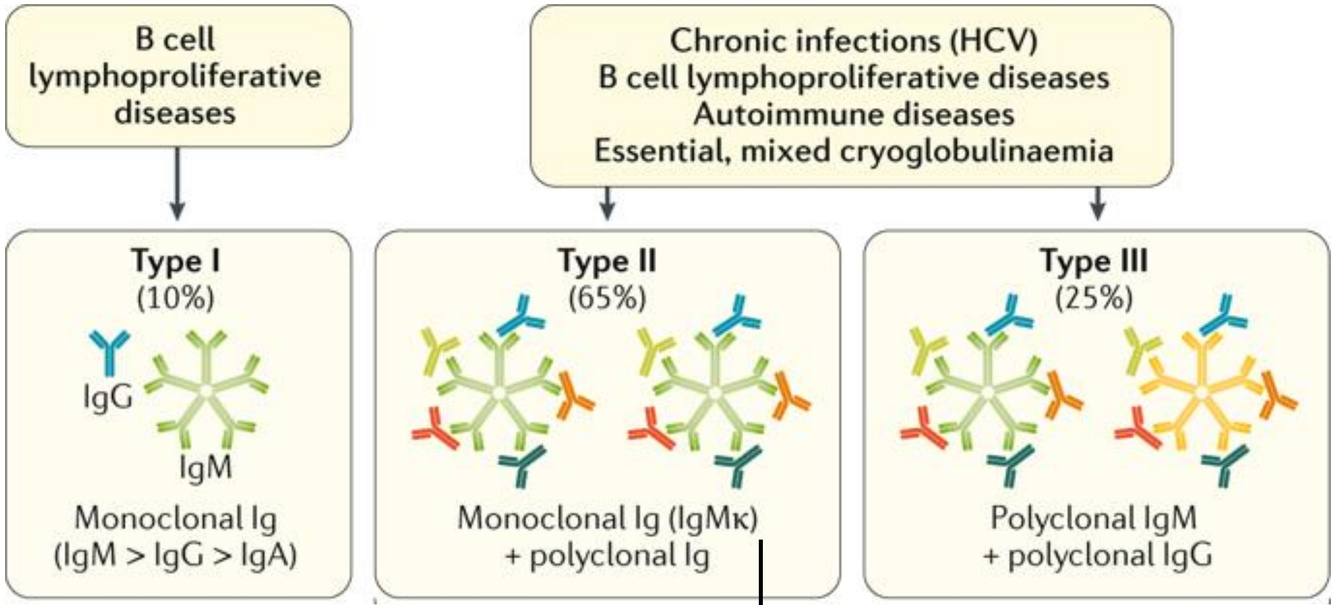
Cold: precipitation, **Warm**: resoluble



Diagnostic test

- Cryoglobulin > 0.05 g/L, Cryocrit ≥ 2%
- Rhematoid Factors +
- Hypocomplementenemia (↓ C4 > ↓ C3)

The Brouet Classification Criteria



- Against polyclonal IgG **“IgM-κ”**
- **Rheumatoid factor activity**
- Binding capacity with **Cellular Fibronectin** (Mesangium)

Nat Rev Dis Primers. 2018 Aug 2;4(1):11.

Cryoglobulinemic Glomerulonephritis

	Type I (10%)	Type II (65%)	Type III (25%)
Abnormal Ig	Monoclonal Ig (**IgM** > IgG > IgA)	**IgMκ** > 90%, Polyclonal Ig	Polyclonal IgG & IgM
Associated disease	Waldenstorm's / Myeloma	**Chronic HCV Infection,** B cell lymphoproliferative disease, **Autoimmune disease**	
Clinical	**Capillary occlusion** (Gangrene, Acrocyanosis)	**Small vessel vasculitis**, Glomerulonephritis, **Meltzer's triad** (Purpura, arthralgia, weakness)	
Pathological Findings			
LM	**MPGN** pattern with strongly **PAS+ cryoglobulin plugs** within capillary loops ± double-contour pattern of GBM in silver stain		
IF	Monoclonal Ig (**IgM** > IgG > IgA)	**IgM**, IgG, κ- and λ- light chain, C3, C1q	
EM	Organized deposits of **curvilinear parallel microtubular** substructures with a diameter of 20-35 nm in subendothelial area		

****Treatment of HCV-associated cryoglobulinemic flare [RPGN]: DAA + RTX or IVMP/POCY ± PLEX**

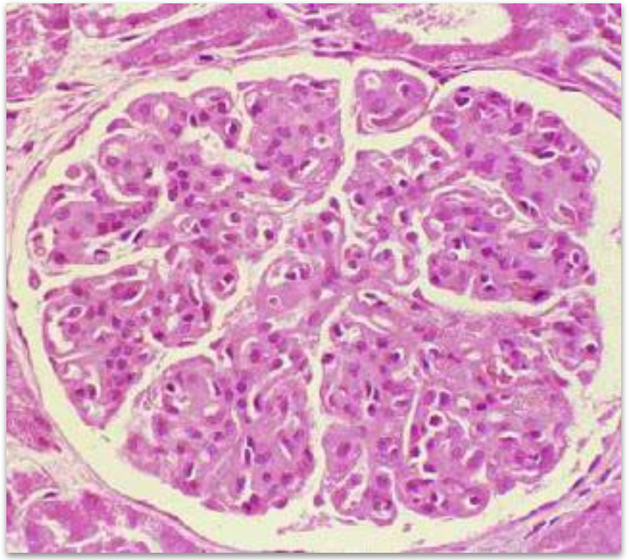
Brenner & Rector's the kidney, 11th edition

How to approach “Glomerulonephritis” ?

RPGN Mimicker	Immune complex			Anti-GBM		Pauci-immune	
	Young adult, Acute to RPGN			Bimodal age, RPGN		Elderly, insidious onset	
←→ C3, C4	←→ C3, C4	↓C3	↓C3, ↓C4	←→ C3, C4		←→ C3, C4	
				No Pulmonary hemorrhage	Pulmonary hemorrhage	C-ANCA (Anti-PR3)	P-ANCA (Anti-MPO)
• TMA • Alport syndrome • ATN/AIN • Renovascular disease • Papillary necrosis	IgAN	• IRGN • C3GN	• LN • Cryoglobulinemia (↓ ↓C4) • MPGN	Anti-GBM disease	Goodpasture syndrome	GPA	• EGPA • MPA • Drug-induced ANCA

Membranoproliferative Glomerulonephritis

MPGN



Membrano
[Thickened GBM]

+

Proliferative
[Intraglomerular cell proliferation]

Mx
1. Determine cause
2. Steroid + CY (RPGN)

MPGN pattern of injury

- Positive Ig +/– C3
  - Ig/IC-mediated
    - Monoclonal gammopathies → Hematologic Malignancy
    - Autoimmune diseases → SLE*, Sjogren, RA
    - Infections → HCV*, HBV, IE, Schistosomiasis
    - Idiopathic
- Complement-dominant
  - Complement-mediated
    - C3 glomerulopathy
      - C3-DDD
      - C3-GN
    - C4 glomerulopathy
      - C4-DDD
      - C4-GN

Mx
1. Steroid + MMF
2. ± Eculizumab

- Negative Ig Negative C3
  - Antiphospholipid antibody syndrome
  - HUS/TMA
  - Sickle cell anemia and polycythemia
  - Other

Kidney International (2021) 100, S1-S276

How to approach “Glomerulonephritis” ?

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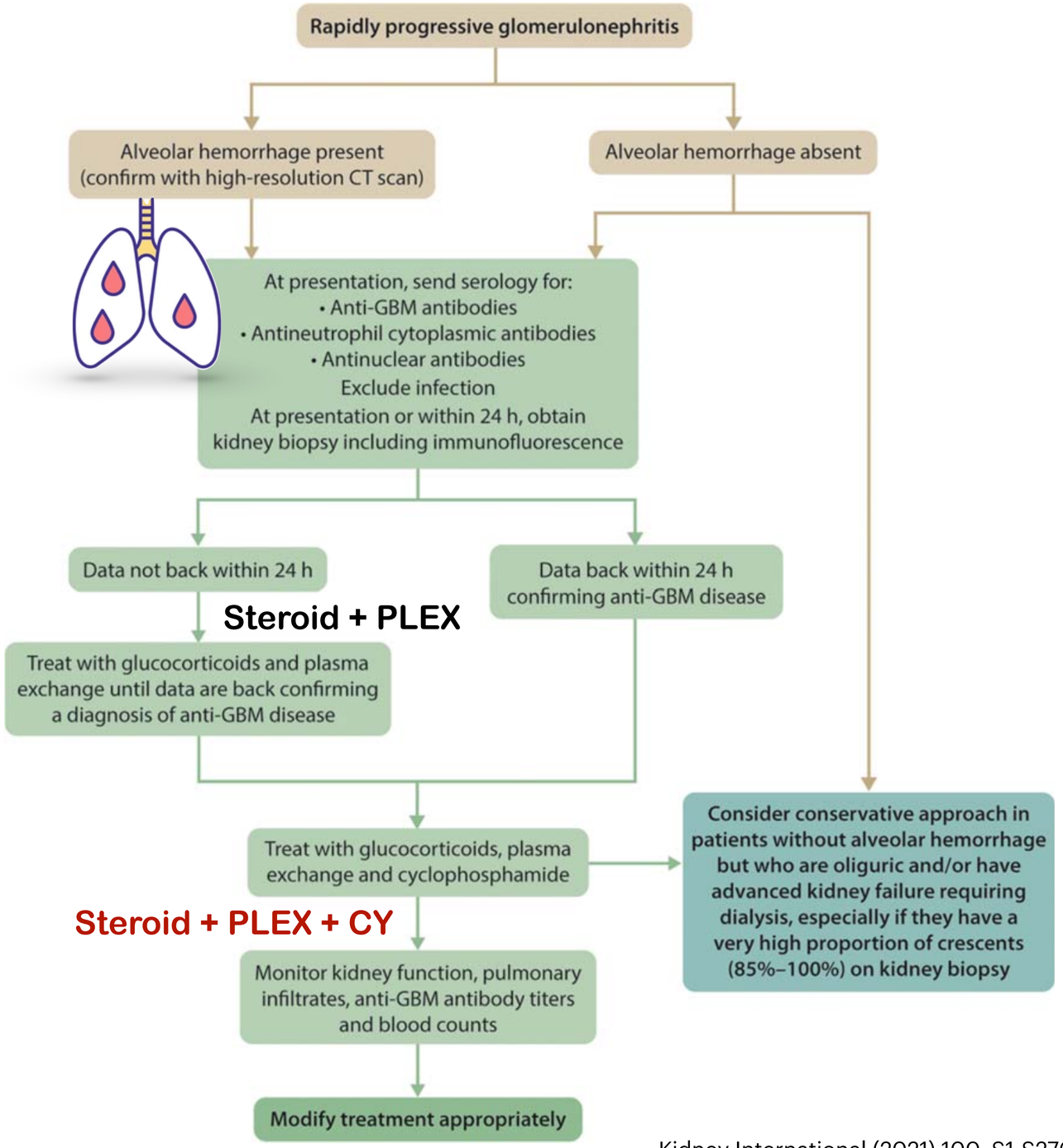
	Young adult, Acute to RPGN			Bimodal age, RPGN		Elderly, insidious onset	
←→ C3, C4	←→ C3, C4	↓C3	↓C3, ↓C4	←→ C3, C4		←→ C3, C4	
• TMA • Alport syndrome • ATN/AIN • Renovascular disease • Papillary necrosis	IgAN	• IRGN • C3GN	• LN • Cryoglobulinemia (↓ ↓C4) • MPGN	No Pulmonary hemorrhage	Pulmonary hemorrhage	C-ANCA (Anti-PR3)	P-ANCA (Anti-MPO)
				Anti-GBM disease	Goodpasture syndrome	GPA	• EGPA • MPA • Drug-induced ANCA

Anti-GBM disease

Etiology	**AutoAb** to non-collagenous domain (**NC1**) of **type IV collagen**
Age	**Bimodal age** ◉ 20-30 yrs: ↑ Pulmonary hemorrhage ◉ >60 years: Renal-limited
Clinical	✓ Rapid progressive glomerulonephritis **(RPGN)** ✓ **Pulmonary hemorrhage** (Goodpasture syndrome)
Lab	✓ Positive **Anti-GBM ~ 95%** ✓ Positive Anti-MPO ~15% (Good prognosis)
Mx	**Steroid + PLEX + CY** in "all" cases **EXCEPT !!** ✓ **Dialysis** at presentation ✓ **100% Crescents** or **> 50% global sclerosis** ✓ **"NO" pulmonary hemorrhage**



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Anti-GBM disease: Treatment

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

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How to approach “Glomerulonephritis” ?

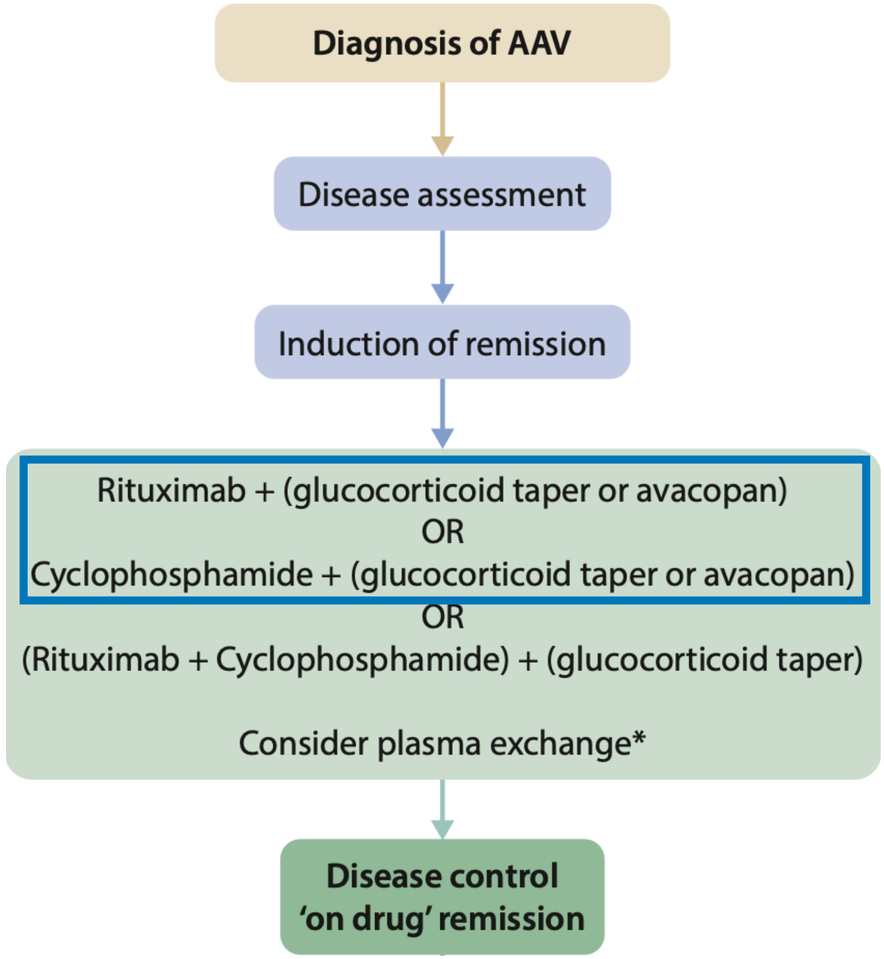
RPGN Mimicker	Immune complex			Anti-GBM		Pauci-immune	
	Young adult, Acute to RPGN			Bimodal age, RPGN		Elderly, insidious onset	
←→ C3, C4	←→ C3, C4	↓C3	↓C3, ↓C4	←→ C3, C4		←→ C3, C4	
				No Pulmonary hemorrhage	Pulmonary hemorrhage	C-ANCA (Anti-PR3)	P-ANCA (Anti-MPO)
• TMA • Alport syndrome • ATN/AIN • Renovascular disease • Papillary necrosis	IgAN	• IRGN • C3GN	• LN • Cryoglobulinemia (↓ ↓C4) • MPGN	Anti-GBM disease	Goodpasture syndrome	GPA	• EGPA • MPA • Drug-induced ANCA

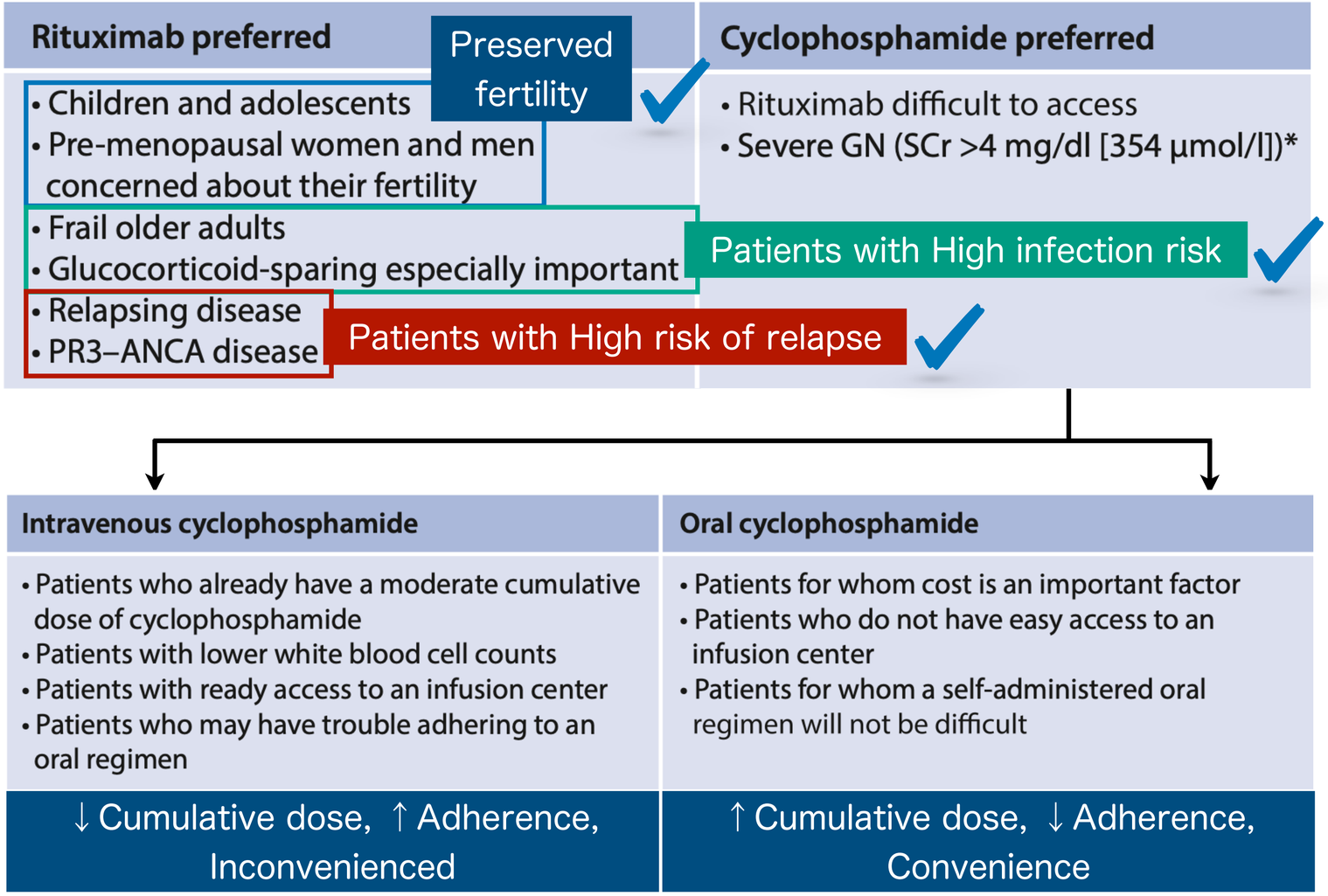
ANCA-Associated Vasculitis (AAV)

	GPA (Granulomatosis with Polyangiitis)	EGPA (Eosinophillic, Granulomatosis with Polyangiitis)	MPA (Microscopic Polyangiitis)
Age of onset	30-40 years	30-40 years	50-60 years
Renal Histopathology	Necrotizing, granulomatous vasculitis	Eosinophillic, necrotizing, granulomatous vasculitis	Necrotizing vasculitis without immune deposit
Extrarenal	・Upper* respiratory tract ✓Saddle nose ✓Recurrent sinusitis ・Lower respiratory tract ✓Abnormal pulmonary infiltration	・Lower respiratory tract ✓Late onset asthma ・Mononeuropathy ・Eosinophilia (>10%) ・Myocarditis	Pulmonary capillaritis
LAB	c-ANCA (Anti-PR3)	p-ANCA (Anti-MPO)	p-ANCA (Anti-MPO)

ANCA-Associated Vasculitis (AAV): Induction

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





Kidney International (2024) 106, 160-165

ANCA-Associated Vasculitis (AAV): Induction

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

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

Remission

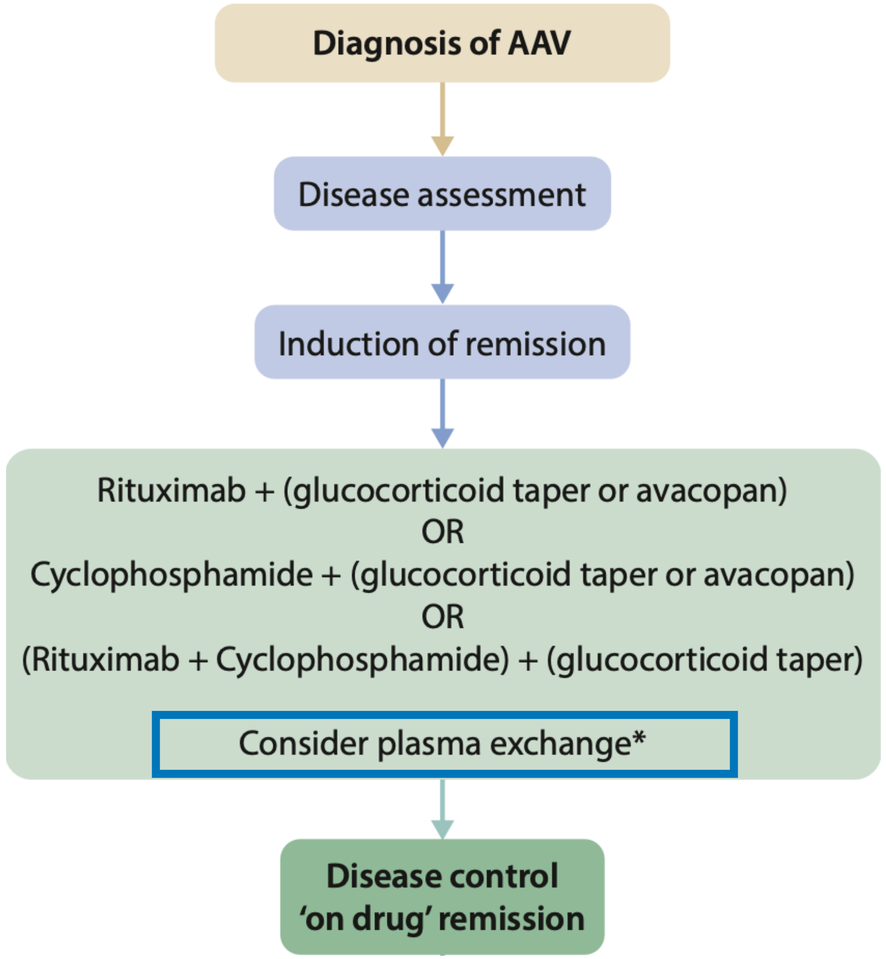
Absence of manifestation of **vasculitis & GN** (**BVAS = 0**)

- ✓ Absence of GN = **Stable or improved GFR**
- ✓ Persistence hematuria or proteinuria does not necessarily imply active disease

Kidney International (2024) 106, 160-165

ANCA-Associated Vasculitis (AAV): Induction

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



When to consider plasma exchange?

- ✓ Cr > 3.4 mg/dL
- ✓ Requiring dialysis
- ✓ Rapidly increasing SCr
- ✓ Diffuse alveolar hemorrhage and hypoxemia

DOSE: 60 ml/kg

ANCA vasculitis with severe kidney disease	Vasculitis with diffuse pulmonary hemorrhage	Vasculitis in association with anti-GBM antibodies
Seven treatments over a maximum of 14 days, 60 ml/kg volume replacement, albumin substitution	Daily until bleeding stops, replace albumin with fresh, frozen plasma	Daily for 14 days or until anti-GBM antibodies are undetectable

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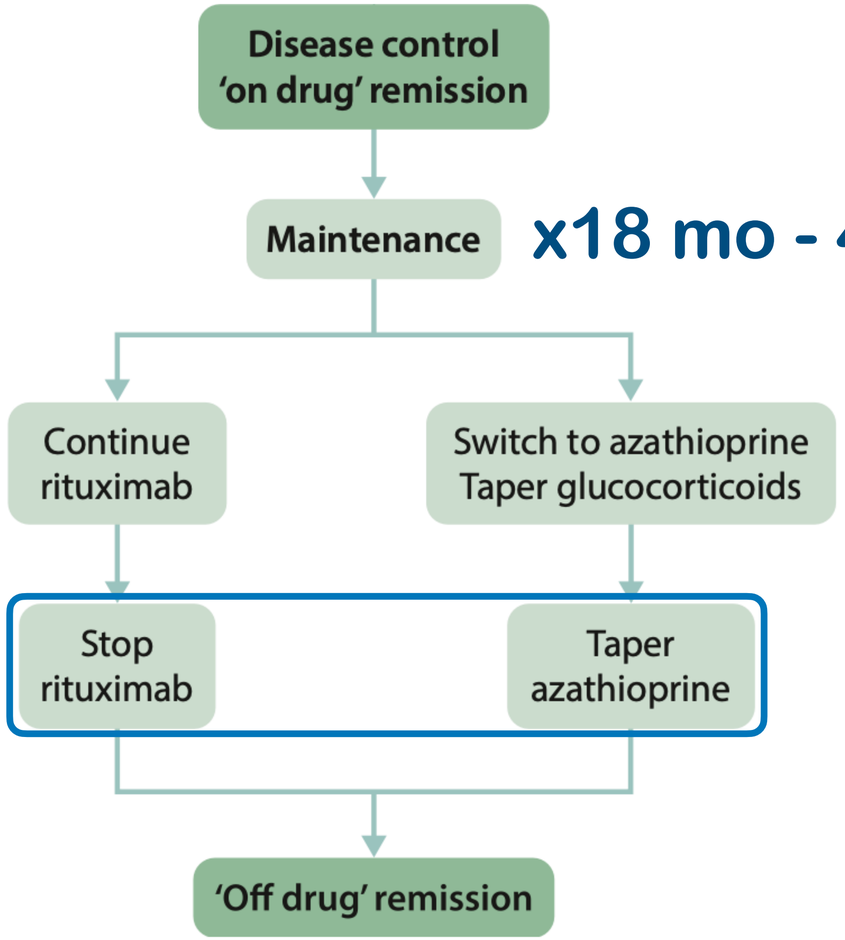
ANCA-Associated Vasculitis (AAV): Maintenance

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



Rituximab preferred	Azathioprine preferred
• Relapsing disease • PR3–ANCA disease High risk relapse group • Frail older adults • Glucocorticoid-sparing especially important High infection risk group • Azathioprine allergy	• Low baseline IgG (<300 mg/dl) • Limited availability of rituximab

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

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General Management in Glomerular Disease

A	**ACEi** or **ARB**: 1st-line Rx in patients with HT & proteinuria
B	**BP:** Target SBP < 120 mmHg (Goal: proteinuria < 1g/day)
C	**CV:** - Start Statin as 1st-line Rx for DLP (particularly in high CV risk) - Smoking cessation - Weight normalization & Regular exercise
D	**Diet:** - Total calories: 30-35 kcal/kg/day - Total protein: 0.8-1 g/kg/day + 1g/g of protein loss (Max 5 g)
E	**Embolism prophylaxis:**
F	**Fluid management:** - Loop diuretic: 1st-line for Rx edema in NS - Restrict Na < 2 g/day
I	**Infection:** - Prophylactic TMP-SMX: High-dose prednisolone, RTX, or CY - Vaccine: Pneumococcal, Influenza, Zoster (Shingrix)

A	Albumin < 2.5 g/dL

"AND"

B	BMI > 35 kg/m2
I	Immobilization
G	Genetic
S	Surgery (Orthopedic/Sx)
H	HF NYHA class III-IV
I	—
P	Proteinuria > 10 g/day

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Specific Management in Glomerular Disease

MCD, FSGS	**Prednisolone** 1 MKD x 4-16 wks → taper off within 6 months
MN	· **Low risk**: wait & See · **Moderate & High**: **RTX** 1 g/wk x 2 dose · **Very high**: **IVMP** 1g/d x 3 days, Then **Pred** 0.5 MKD at month 1,3,5 & **POCY** 2.5 MKD at month 2, 4, 6
TMA	· **HUS**: **Eculizumab** ± TPE with FFP · **TTP**: **TPE** with FFP
IgAN	· **IgAN-specific**: **Nefecon** > **Reduced-dose Pred** > MMF & HCQ (China), Tonsillectomy (Japan) · **General**: RASi (1B), DEARA (2B), SGLT2i (2B)
LN	· **Class I & II**: Low-level proteinuria (Rx as extra-renal), Nephrotic syndrome (Rx as MCD) · **Class III & IV**: Steroid + Immunosuppressive agent (CY/ MPAA/ Belimumab/ CNI) → Maintain: MPAA > Aza · **Class V**: Low-level proteinuria (Rx as extra-renal), Nephrotic syndrome (Steroid + Immunosuppressive agent)
MPGN	· **IC-mediated**: Rx cause, If RPGN → Rx: Steroid + CY · **Complement-mediated**: Steroid + MMF ± Eculizumab
ANCA	Steroid + CY ± **PLEX** **if Cr > 3.4 mg/dL, RPGN, Dialysis, DAH**
Anti-GBM	Steroid + CY + **PLEX** in all cases **EXCEPT Dialysis at presentation + 100% Crescent/ > 50% Sclerosis + no DAH**


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Thank you
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