

# Akut és krónikus glomerulonephritisek

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Centrum

2021. Május 27. - online

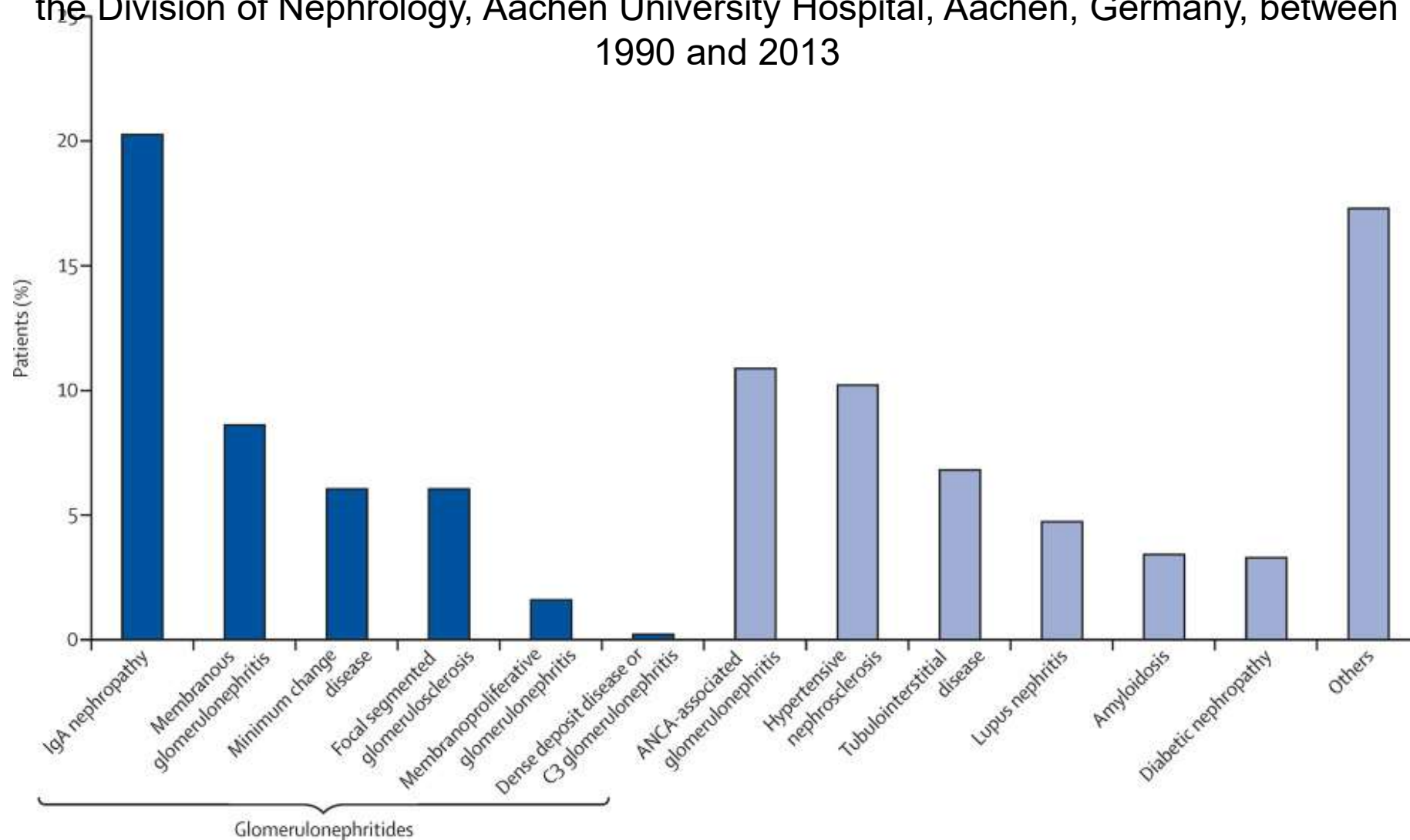


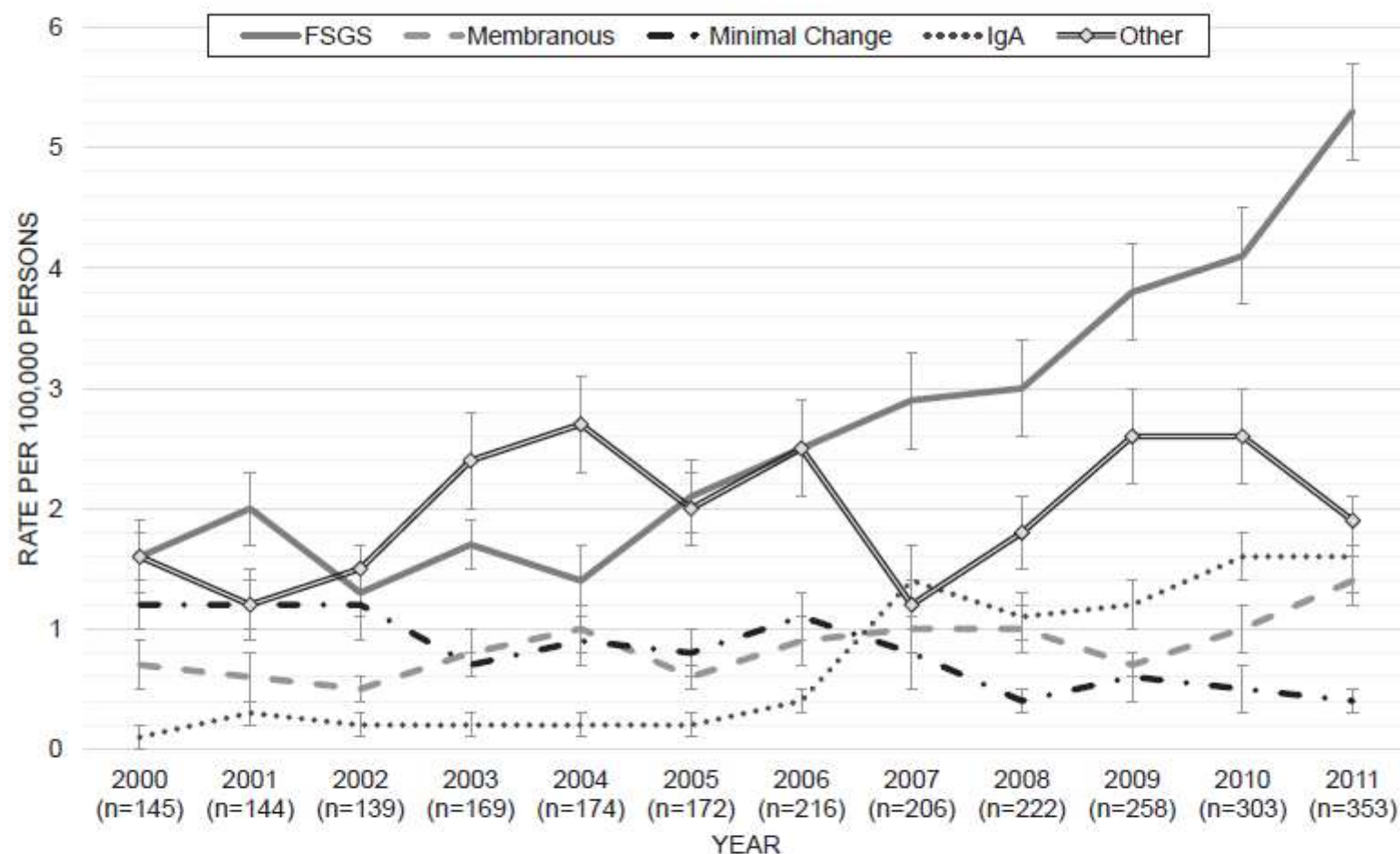
# Primary glomerulonephritides

*Jürgen Floege, Kerstin Amann*

Most glomerulonephritides, even the more common types, are rare diseases. They are nevertheless important since they frequently affect young people, often cannot be cured, and can lead to chronic kidney disease, including end-stage renal failure, with associated morbidity and cost. For example, in young adults, IgA nephropathy is the most common cause of end-stage renal disease. In this Seminar, we summarise existing knowledge of clinical signs, pathogenesis, prognosis, and treatment of glomerulonephritides, with a particular focus on data published between 2008 and 2015, and the most common European glomerulonephritis types, namely IgA nephropathy, membranous glomerulonephritis, minimal change disease, focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, and the rare complement-associated glomerulonephritides such as dense deposit disease and C3 glomerulonephritis.

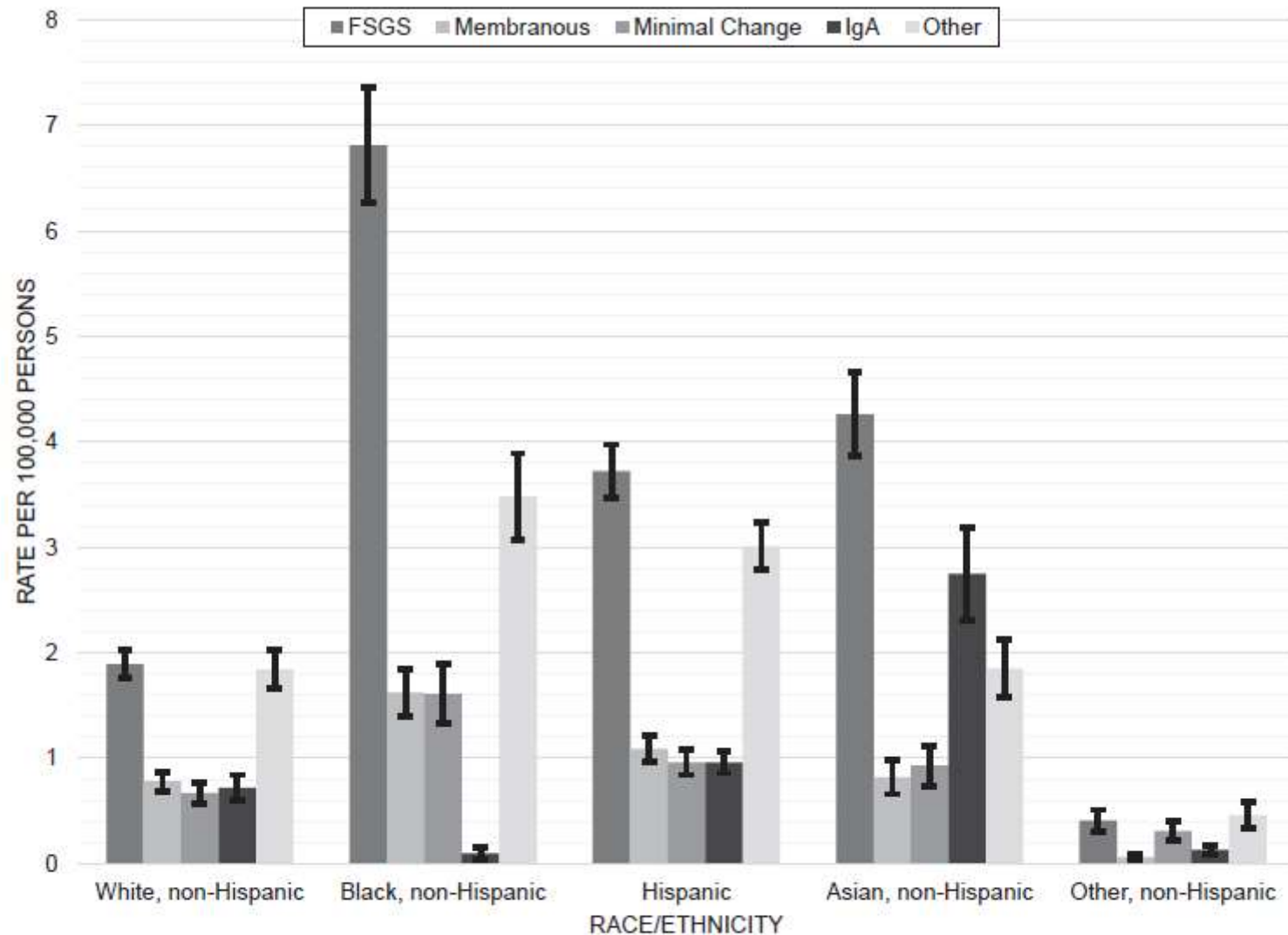
Kidney biopsy diagnoses in 2243 adult patients undergoing native kidney biopsy at the Division of Nephrology, Aachen University Hospital, Aachen, Germany, between 1990 and 2013





**Figure 2.** The distribution of primary glomerulonephropathy in the 12-year observation window. Focal segmental glomerulosclerosis (FSGS) rates, and to a lesser degree immunoglobulin A (IgA) nephropathy rates, increased throughout the period. Minimal change disease and membranous glomerulonephritis rates remained flat throughout our observation period. The “other” category included immune complex glomerulonephritis not otherwise specified, pauci-immune/antineutrophil cytoplasmic antibody-associated glomerulonephritis, thin basement membrane disease, membranoproliferative glomerulonephritis, crescentic glomerulonephritis not otherwise specified, postinfectious glomerulonephritis, anti-glomerular basement membrane disease, fibrillary glomerulonephritis, dense deposit disease, and others.





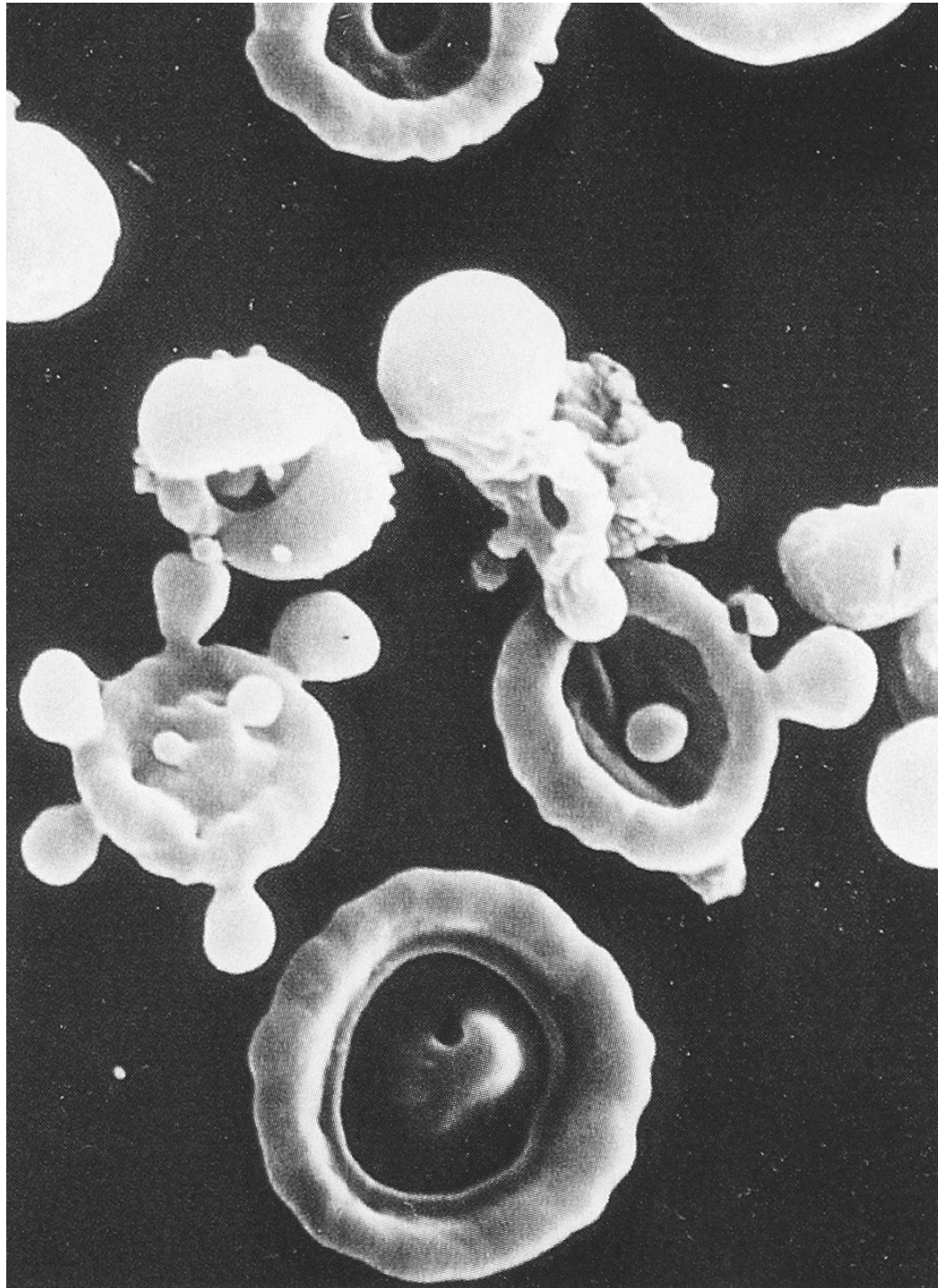
**Figure 3.** Average annual age- and sex-adjusted rates for the most common primary glomerulonephropathy disease states by race and ethnicity, 2000 to 2011. Rates for the primary glomerulonephropathy and by different race and ethnic groups were similar to the distribution for the entire period. Abbreviations: FSGS, focal segmental glomerulosclerosis; IgA, immunoglobulin A.

<http://dx.doi.org/10.1053/j.ajkd.2016.03.416>

- Klinikai kép
  - Nephritis, nephrosis, olygosymptomas, AVE (AKI), KVE (CKD)
- Vesebiopszia
- IgA nephropathia
- Minimal change nephropathia
- Focalis segmentalis glomerulosclerosis
- Membranosus glomerulonephritis/nephropathia
- Gyorsprogressziójú glomerulonephritis
- Autoimmun kórképekhez társuló nephritisek
- Membranoproliferatív (mesangiocapillaris) glomerulonephritis

# Klinikai kép I.

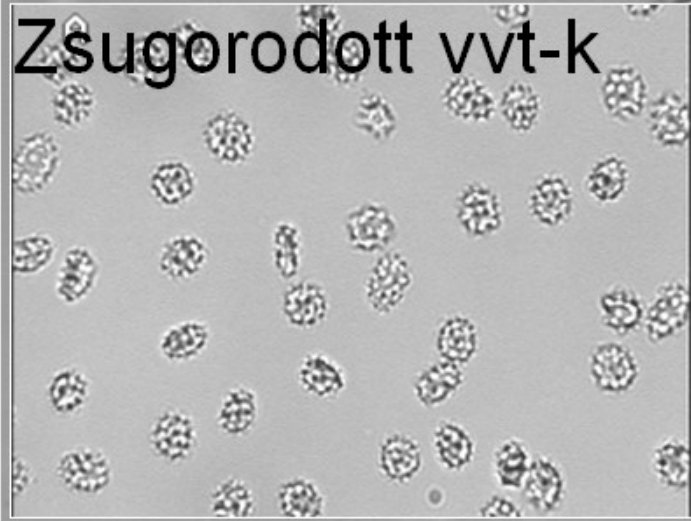
- A. Nephritis syndrome
  - HU dysmorph vvt-kel (!)
  - különböző fokú, ált. enyhe PU (150 mg-2 g/die)
  - GFR ↓ v. norm
  - HT (ált. enyhe)



Glomeruláris eredetű vvt-k



Zsugorodott vvt-k



Ép vvt-k





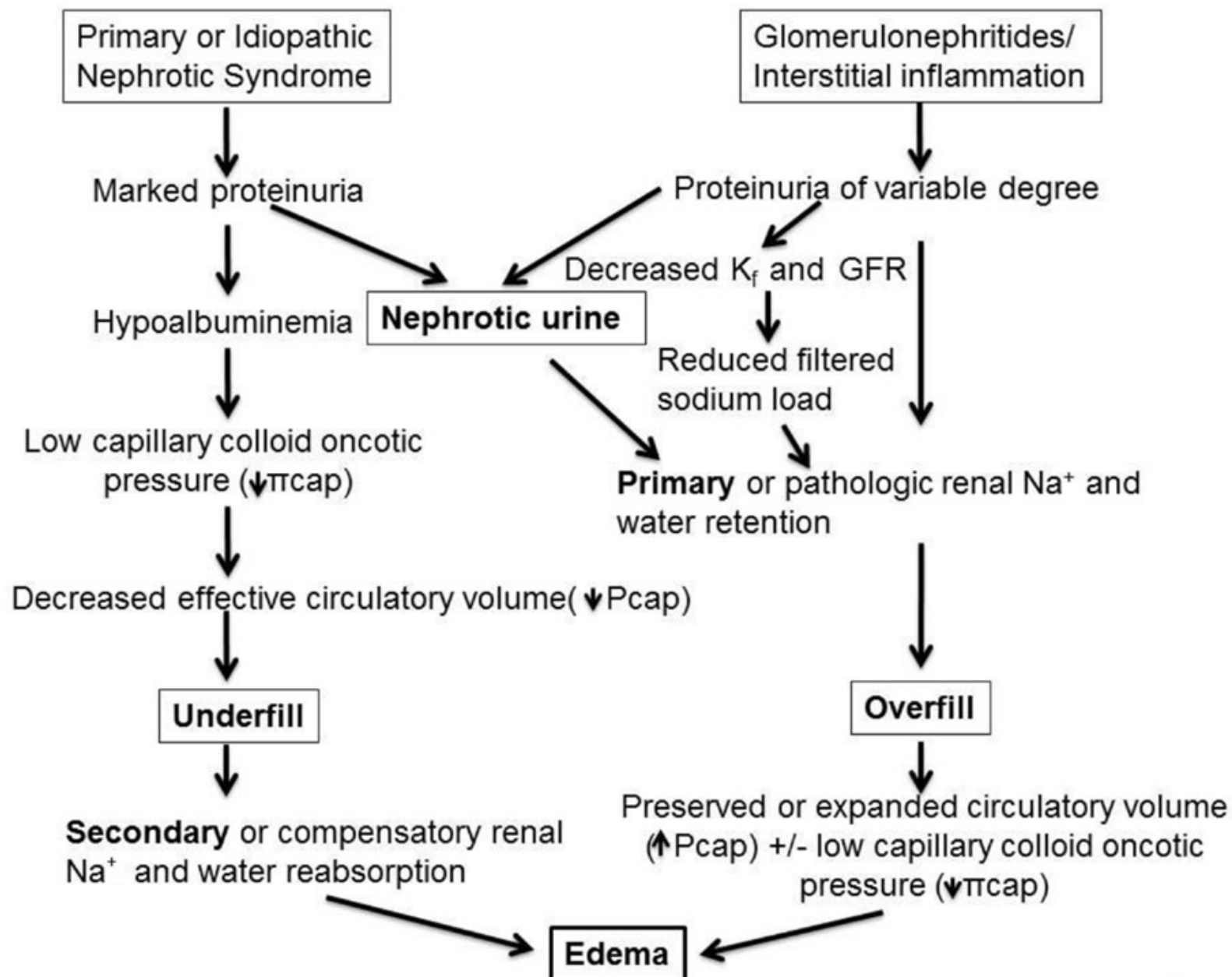
# Jellemző kórképek

- Akut diffúz proliferatív GN
  - Poststreptococcalis
  - Postinfectiozus GN
- Focalis vagy diffúz proliferatív GN
  - IgA nephropathia
  - Lupus nephritis
- Membranoproliferatív (mesangiocapillaris) GN

# Klinikai kép II.

- B. Nephrosis syndroma
  - súlyos proteinuria ( $>3,5$  g/die)
  - hypalbuminaemia ( $<35$  g/l)
  - oedema
  - (hypercholesterinaemia, lipiduria)

## Nephrosis kialakulásának két hypothesise



## Felnőttkori nephrosis syndroma leggyakoribb okai

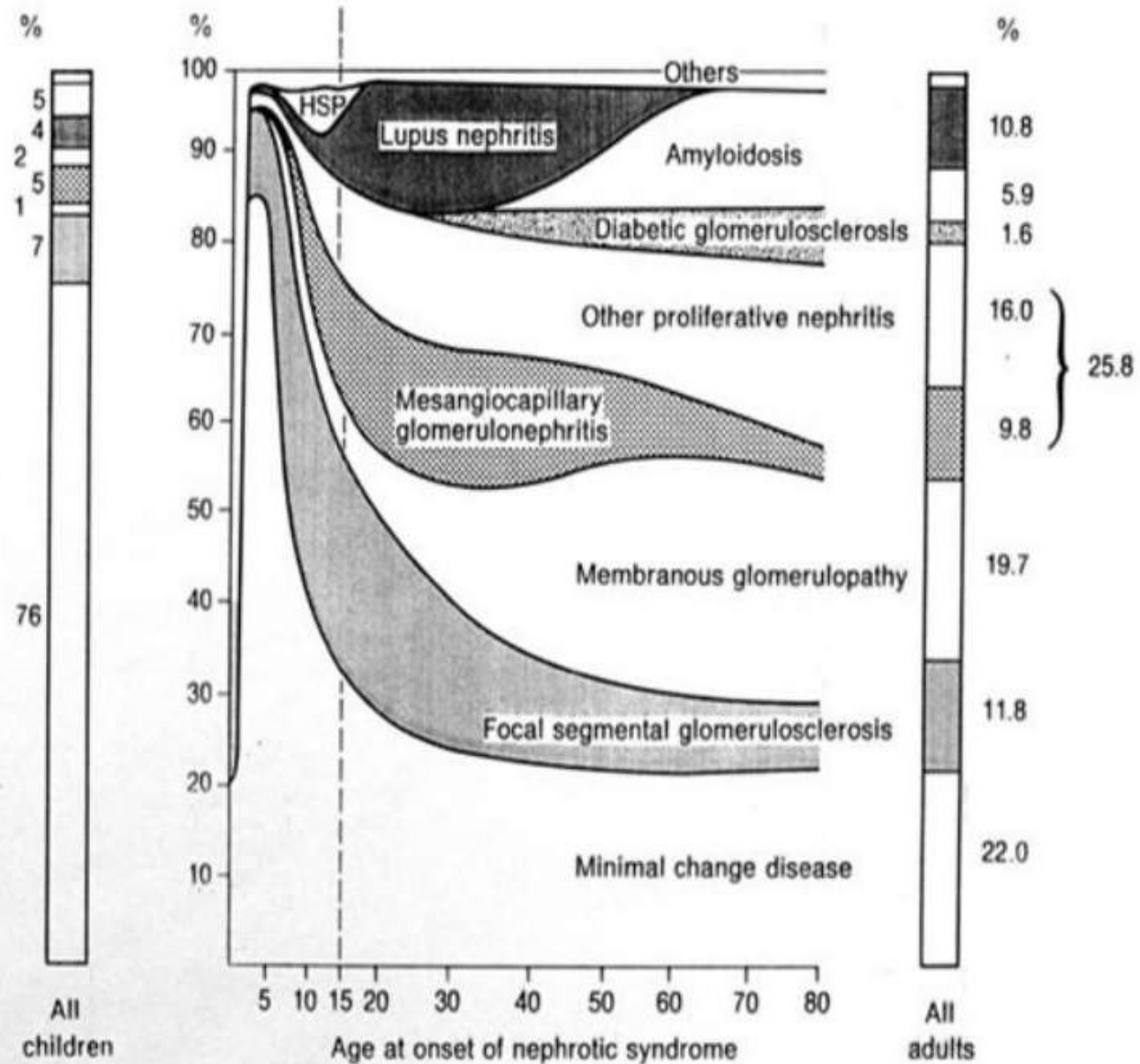
Betegség	Kiváltó/társuló elváltozás	Szerológiai teszt
Minimal change disease (MCD)	Allergia, atopia, NSAIDs, Hodgkin kór	nincs
Focalis segmentalis glomerulosclerosis (FSGS)	African Americans HIV infekció Heroin, pamidronate	— HIV at —
Membranous nephropathia (MN)	Idiopathias Gyógyszer: arany, penicillamine, NSAIDs Infekció: hepatitis B,C; malária Lupus nephritis Tumor: emlő, tüdő, GI	Anti-PLA <sub>2</sub> R at Hepatitis B surface ag, anti-hepatitis C virus at Anti-DNA at —
Membranoproliferative GN (MPGN) I típus	C4 nephritic factor	C3 ↓, C4 ↓
Dense deposit disease (MPGN II típus)	C3 nephritic factor	C3 ↓, C4 normal
Cryoglobulinaemia MPGN	Hepatitis C	Anti-hepatitis C virus at, rheumatoid factor, C3 ↓, C4 ↓, CH50 ↓
Amyloidosis	Myeloma Rheumatoid arthritis, bronchiectasia, Crohn betegség (más krónikus gyulladásos állapot), familial Mediterranean fever	Plasma könnyű láncok Serum fehérje elfo, vizelet immunelfo C-reactive protein
Diabeteses nephropathia	Other diabetic microangiopathy	None

# Nephrosis syndoma háttérében előforduló szövettani kórképek

	Gyerek	Fiatal felnőtt	Középkorú és idős
Minimal change	78	23	21
FSGS	8	19	13
Membranosus GN	2	24	37
Membranoprolif.	6	13	4
Amyloid	0	5	13
Egyéb	6	14	12



**Fig. 6.** Underlying histologic appearance and relative frequencies of various etiologies of nephrotic syndrome according to age at onset. HSP, Henoch-Schönlein purpura. (From [17]; reproduced by kind permission of the authors and publishers)



# Hypercoagulabilitás patophysiologiája nephrosis syndromában

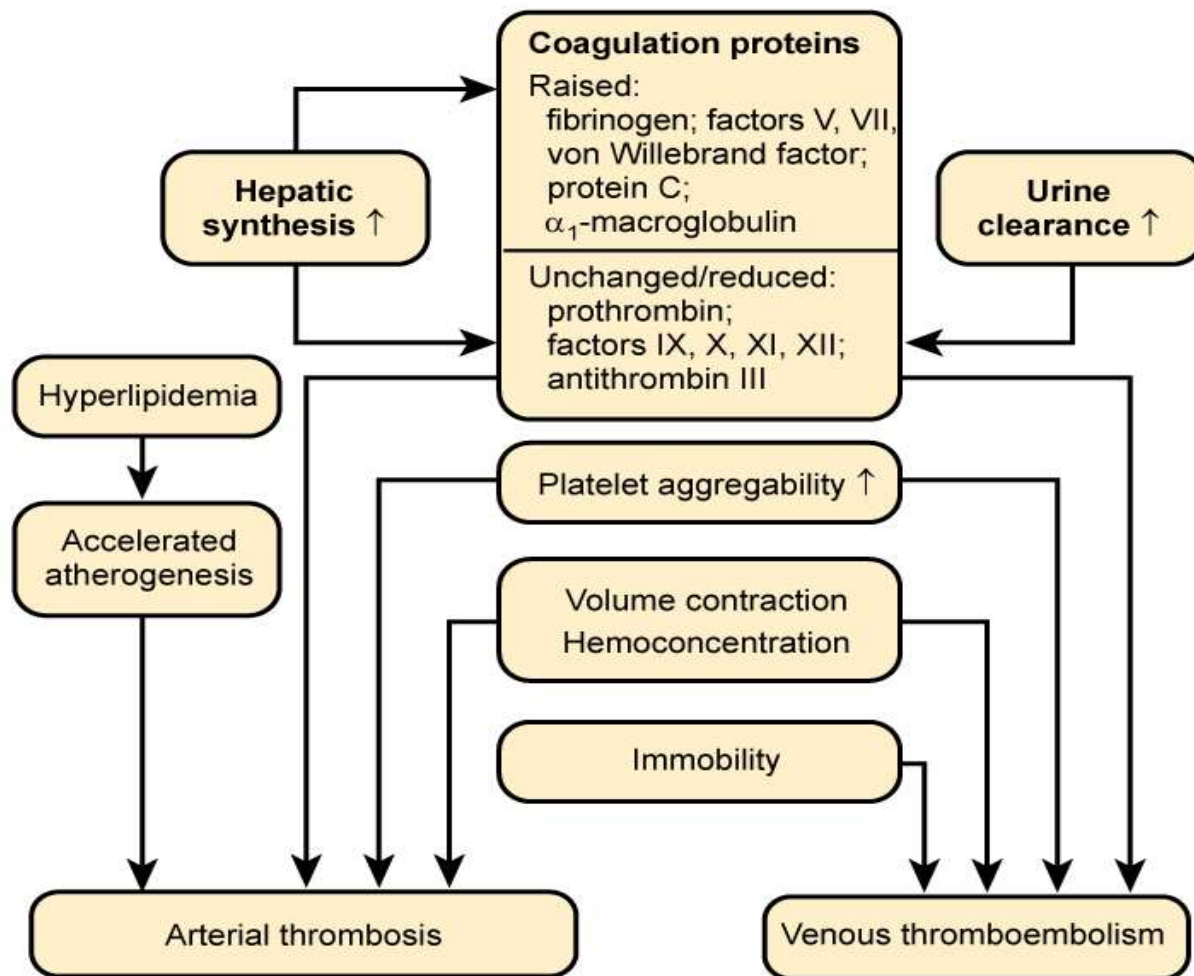


Fig. 15-10. Coagulation abnormalities in nephrotic syndrome.

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**Antikoagulálás, ha se-albumin < 20-25 g/l**

# Nephrosis syndrome prothrombotikus állapot (különböző mértékben)

	Anti-Thrombotic	Pro-Thrombotic
Procoagulant	N or ↓factor XI (160) <sup>8</sup> ↑, N, or ↓ factor II (69) <sup>8</sup> ↑, N, or ↓ factor VII (50) <sup>8</sup> ↑, N, or ↓ factor IX (56) <sup>8</sup> ↑, N, or ↓ factor X (56) <sup>8</sup> ↓ or ↑ Plt Function <sup>8,48</sup>	N or ↓ factor XII (80) <sup>8,49</sup> ↑Plt Count <sup>8,50,51</sup> ↑vWF (variable) <sup>8</sup> ↑↑fibrinogen (340) <sup>8</sup> ↑↑factor V (330) <sup>8</sup> ↑↑factor VIII (330) <sup>8</sup>
Anticoagulant	↑protein C (62) <sup>8,14,54,55</sup> ↑, N, or ↓ protein S (69) <sup>8,14,54</sup>	↓ protein Z (62) <sup>43,54</sup> ↓ or ↓↓ AT (65) <sup>8,14,54</sup>
Profibrinolytic	↑, N, or ↓ α <sub>2</sub> -AP (70) <sup>8</sup>	↓ Plasminogen (92) <sup>8</sup> ↓, N, or ↓ tPA (72) <sup>8,55</sup>
Antifibrinolytic	↓ α <sub>1</sub> -AT (54) <sup>8</sup> ↓ or ↑ PAI (52) <sup>8,42</sup>	↑ Lp(a) (~500) <sup>8</sup> ↑↑ α <sub>2</sub> -M (725) <sup>8</sup>
Other	*Thrombophilia #APL	↑RBC Aggregation <sup>8</sup> Clot Structure <sup>8,62</sup> Hyperlipidemia <sup>8</sup>

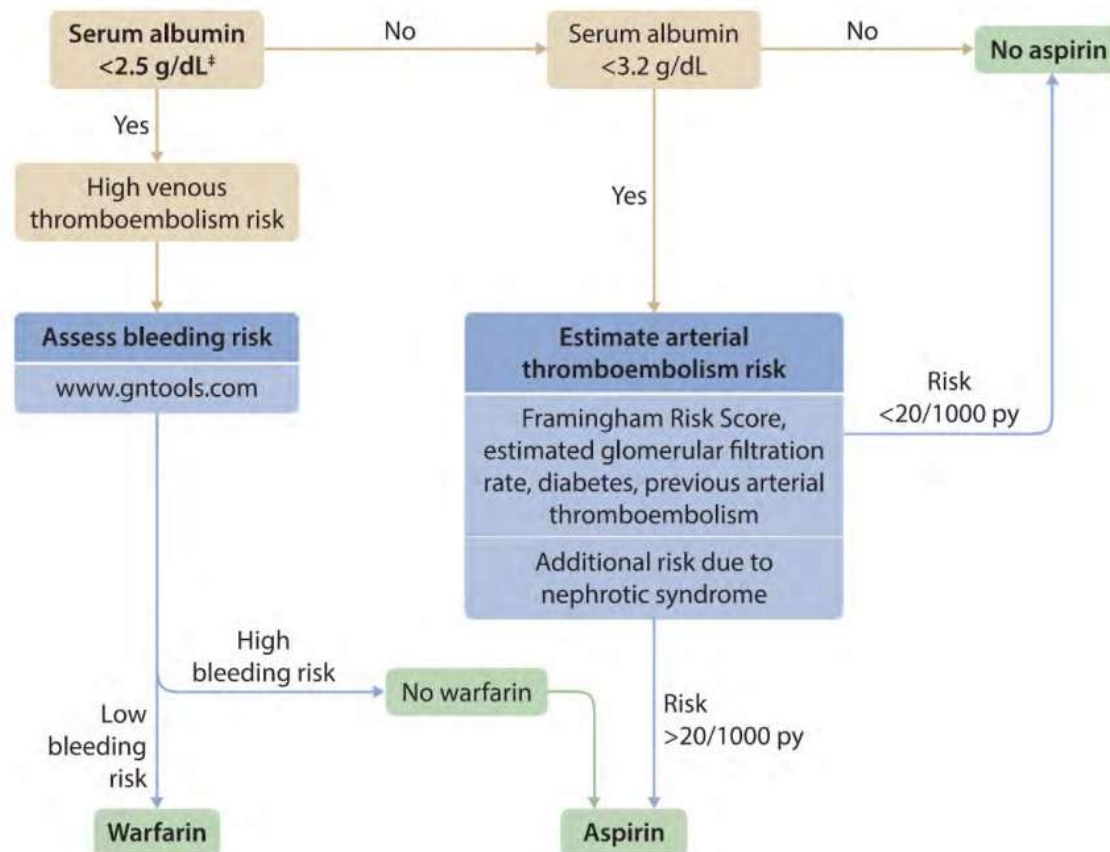


sum hemostatic potential is variably increased

Bryce A. Kerlin et al. CJASN 2012;7:513-520

## Antikoaguláns terápia nephrosis syndromában

Figure GP7. Glomerulonephritis/nephrotic syndrome algorithm for prophylactic anticoagulation<sup>\*†</sup>



<sup>\*</sup>Hofstra, JM. *et al.* Kidney International. 2016; 89 (5): 981 - 983

<sup>†</sup>Note: This algorithm was developed for patients with membranous GN. Its value is unknown for patients with nephrotic syndrome due to other underlying diseases

<sup>‡</sup> Albumin value of 2.5 g/dl is measured using bromocresol green (BCG)

# Nephrotikus ödéma kezelése

- **Maximális RAS gátlás (ACEI±ARB±AldoA)**
- **Diuretikum**
  - **Thiazid(szerű), amilorid**
  - **Kacsdiauretikum (p.o. majd i.v.) – 80-120 mg**
- **Só és folyadék bevitel megszorítása**
- **Albumin (?)**
- **Diéta (?)**
- **Ultrafiltráció**
- **Statinok (simva, atorva, cave: rosuva)**



# Definíció

- **Remisszió** – negative urinalysis on 1<sup>st</sup> morning urine for 3 consecutive mornings
- **Relapszus** – 3+ proteinuria on 3 or more consecutive 1<sup>st</sup> morning urines
- **Gyakori relapszus** – 2 or more relapses within 6 months of diagnosis; or 4 or more relapses per year
- **Szteroid rezisztencia** – no remission after 4 weeks of prednisolone 60mg/m<sup>2</sup>/day

# Klinikai kép III.

- C. kevert forma = „színezett nephrosis”
  - a + b
  - GFR ↓
  - HT

Jellemző kórkép:

Membranoproliferatív GN

Lupus nephritis, (ritkán ) IgAN

# Klinikai kép IV.

- D. Olygosymptomás GN
  - enyhe HU és/vagy PU
  - macroHU attackok

# Jellemző kórképek

- Asymptomatikus proeinuria
  - FSGS, Mesangioproliferativ GN
- Asymptomatikus hematuria
  - Vékony basal membran sy, IgAN, Alport sy.
- Macroscopos hematuria
  - Vékony basal membran sy, IgAN, Alport sy.

# Klinikai kép V.

## E. Akut vese károsodás (AKI)

- Napok, hetek alatt kialakuló veseelégtelenség
- proteinuria (?)
- hematuria (?)
- HT (gyakran hiányozhat)



# Jellemző glomeruláris kórképek

- Gyors progressziójú (crescentes) GN
  - Anti GBM
  - Immunkomplex
  - ANCA
- Vese-tüdő sy
  - Goodpasture sy
  - Lupus nephritis
  - Vasculitisek (Wegener, Churg Strauss, microscopic polyangitis)

# Klinikai kép VI.

## **F. Krónikus veseelégtelenség**

- Hónapok alatt kialakuló veseelégtelenség (súlyos laboreltérések, relatíve enyhe tünetekkel)
- proteinuria
- HT
- Uraemias bőrszín stb.

# Vesebiopsia abszolút indikációi

(terápiás következmény gyakori)

- **Nephrosis syndrome vagy >2g/nap proteinuria haematuria nélkül.** Kivétel: ismert diabetes mellitus, igazolt amyloidosis. Gyakori kórképek: MCD, MNP, FSGS, DNP, amyloidosis
- **Jelentős haematuria proteinuriával.** Kivétel: típusos poststreptococcalis GN. Gyakori kórképek: acut GN, RPGN, MPGN.
- **Acut parenchymalis vesekárosodás** (pre és postrenalis okok kizárása után). Kivétel: egyértelmű acut tubuláris nekrózis, Kórképek: acut GN, RPGN, ATiN, ATN
- **Szisztémás autoimmun betegség** veseérintettség gyanújakor

## **Vesebiopsia relatív indikációi**

(terápiás következmény általában nincs, diagnosztikai, prognosztikai jelentősége van)

**Idült enyhe haematuria (+ enyhe proteinuria)** (vvt  $<10^5$ /ml, proteinuria  $<1$ g/n, normális creatinin).

Gyakori kórképek: IgAN, vékony basalismembran NP.

**Idült enyhe v. mérsékelt proteinuria** ( $<1$  g/n, normális s-creatinin).

Gyakori kórképek: TIN, CGN, urológiai ok.

**Idült veseelégtelenség.** Általában nem indokolt, kivéve, ha aktivitási jelek vannak (szisztémás tünet, üledék, szerológia). Ha a vesenagyság  $<8,5$ cm, a vérzésveszély nagy, az információs érték kicsi.

## Teendők a vesebiopszia előtt

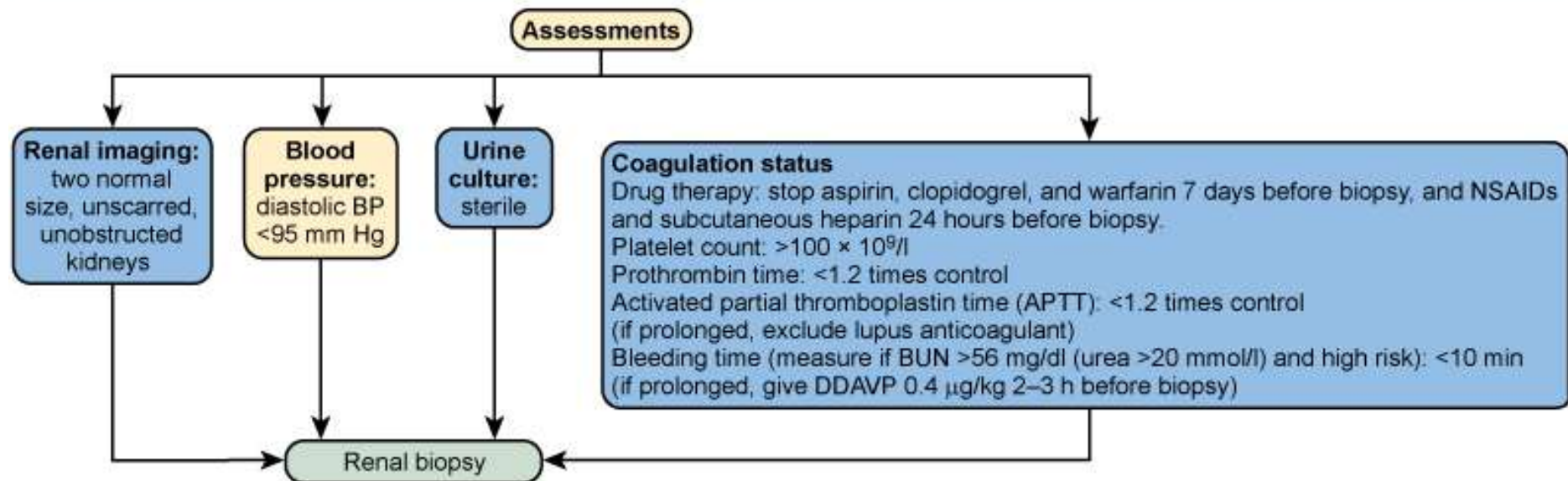
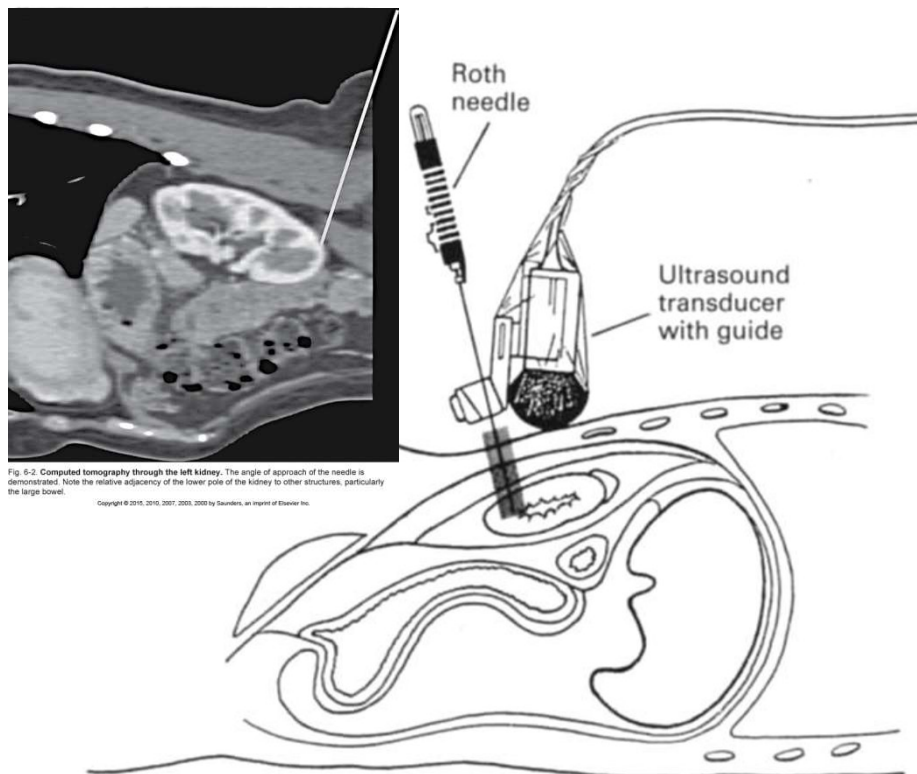


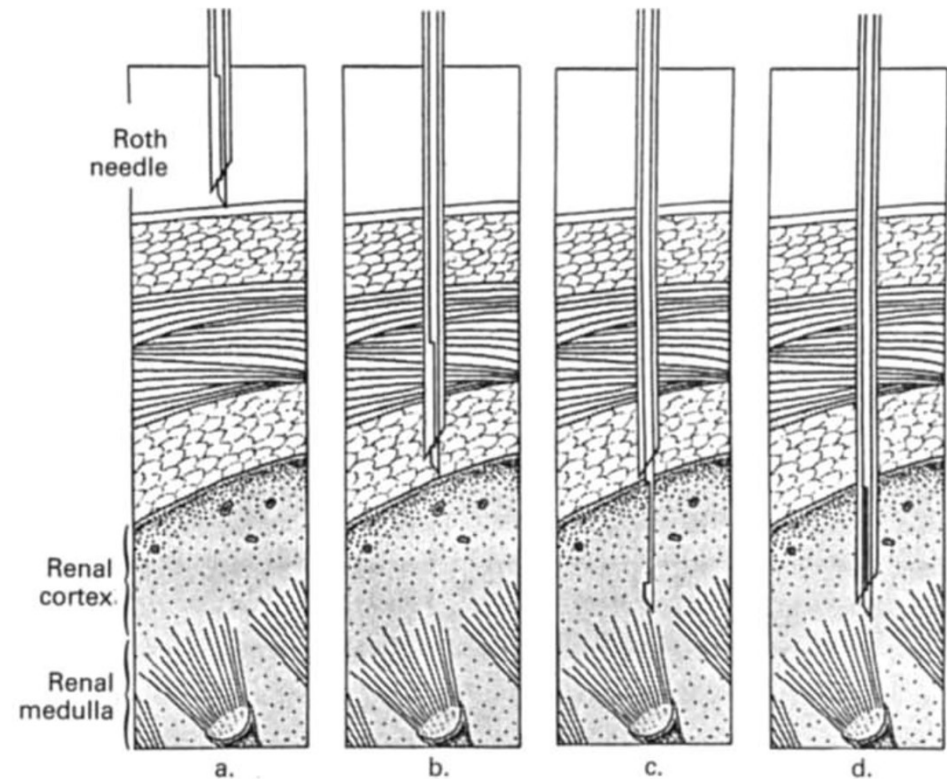
Fig. 6-1. **Workup for renal biopsy.** NSAID, Nonsteroidal anti-inflammatory drug; BUN, blood urea nitrogen; DDAVP, desmopressin.

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# Vesebiopszia technikája



**Fig. 2.** Schematic illustration of biopsy technique.

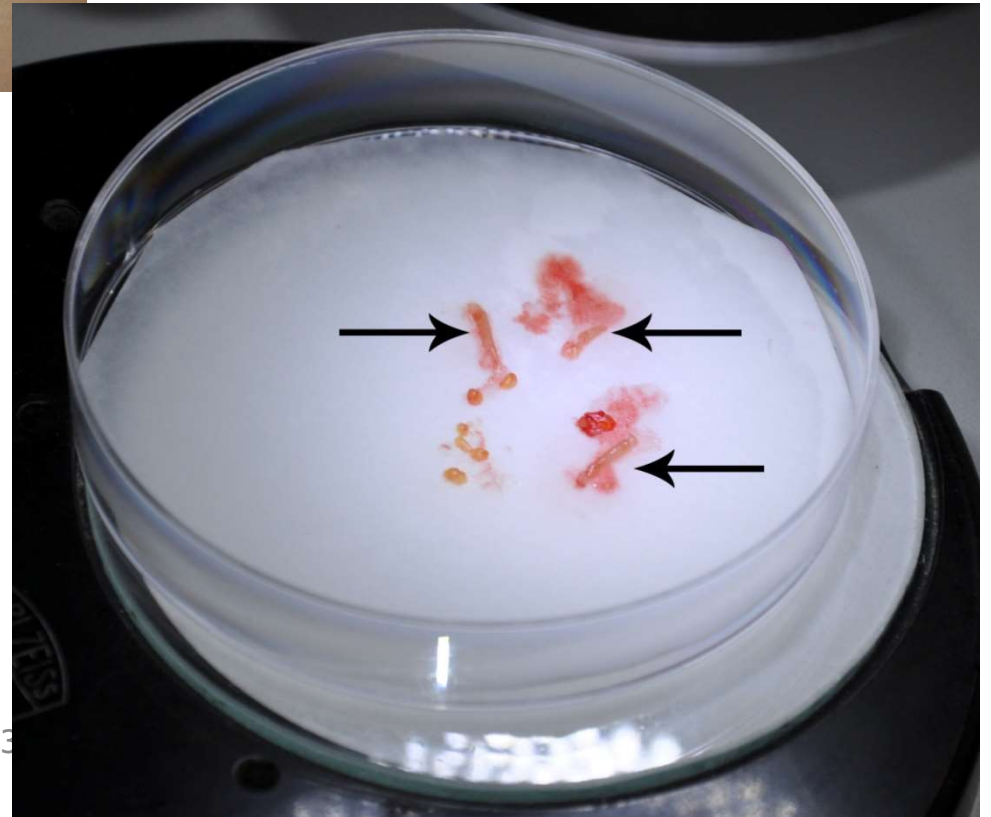


**Fig. 3.** Enlarged view of biopsy site illustrating the biopsy sequence.







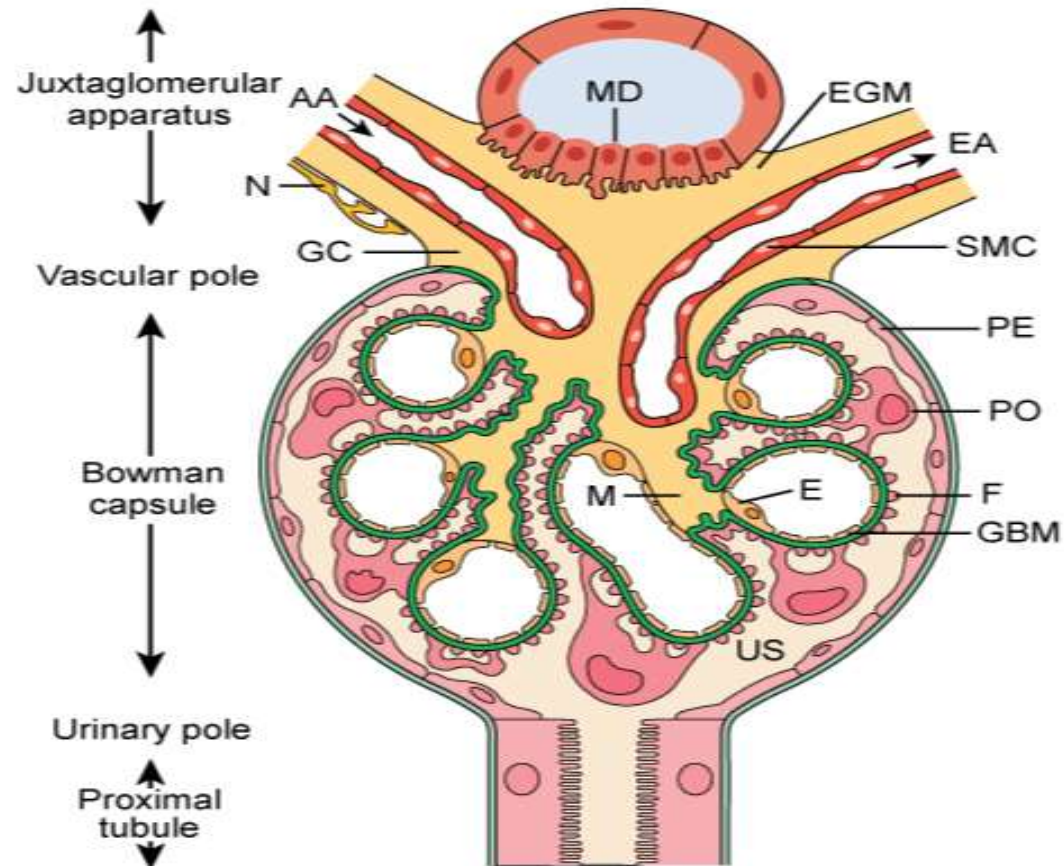




# Vesebiopszia szövődményei

- Perirenalis hematoma (50-80%)
  - Arteriovenosus fistula (<15%)
  - Macroscopos hematuria (<8%)
  - Transfusio, sebészi beavatkozás, nephrectomia (<0,5%)
- } Nem igényel beavatkozást
- A szövődmények 1/3-a 8 órán túl alakul ki!

## Renal Corpuscle and Juxtaglomerular Apparatus

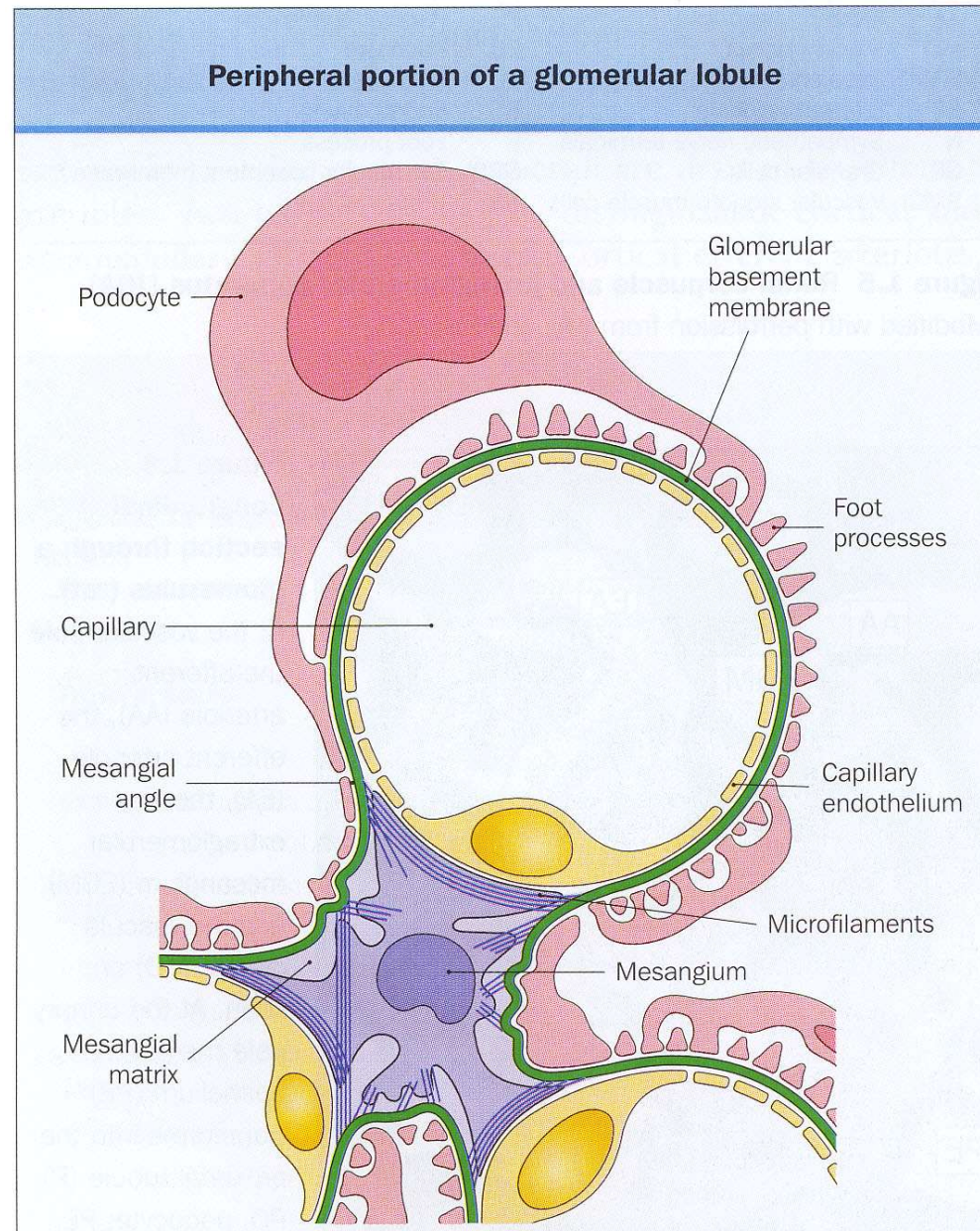


AA Afferent arteriole  
MD Macula densa  
EGM Extraglomerular mesangium  
EA Efferent arteriole  
N Sympathetic nerve terminals  
GC Granular cells  
SMC Vascular smooth muscle cells

PE Parietal epithelium  
PO Podocyte  
M Mesangium  
E Endothelium  
F Foot process  
GBM Glomerular basement membrane  
US Urinary space

*Modified with permission from reference 1.*

Fig. 1-4. Renal corpuscle and juxtaglomerular apparatus.



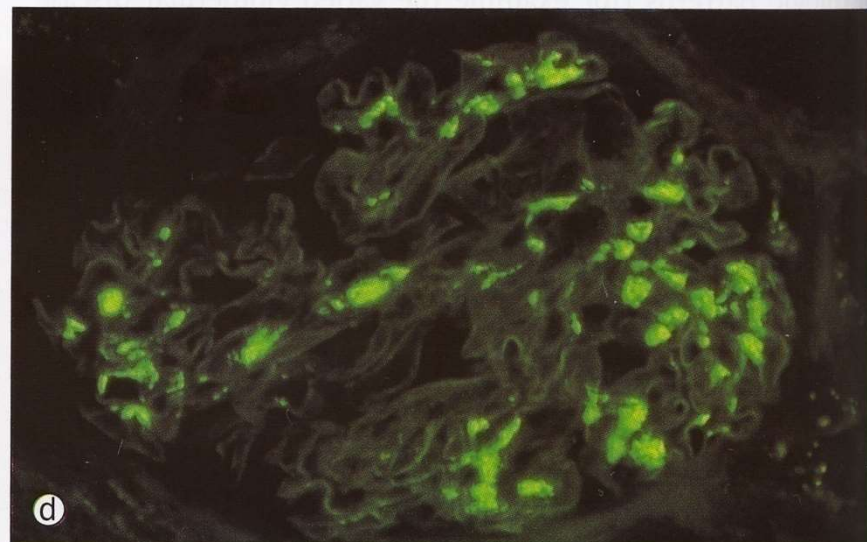
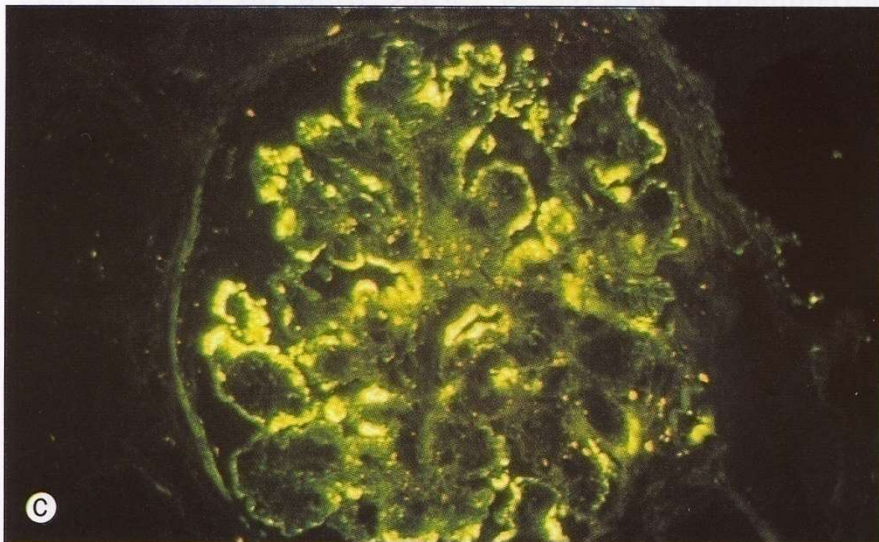
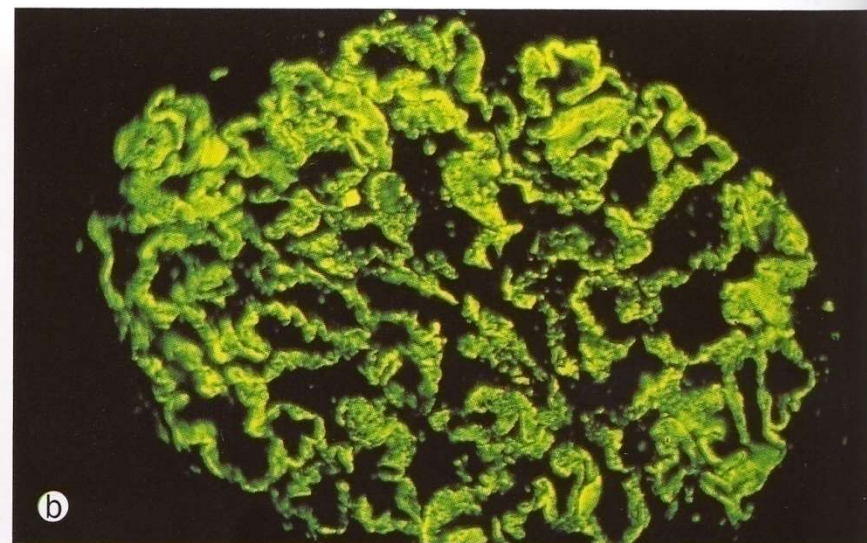
**Figure 1.7 The peripheral portion of a glomerular lobule.** This shows a capillary, the axial position of the mesangium, and the visceral epithelium (podocytes). At the capillary–mesangial interface the capillary endothelium directly abuts the mesangium.

# Vesebiopsziás minta feldolgozása

- Immunhisztológiai
  - Fénymikroszkópos
  - Elektronmikroszkópos
- 
- Glomerulusok
  - Tubulointerstitium
  - Erek



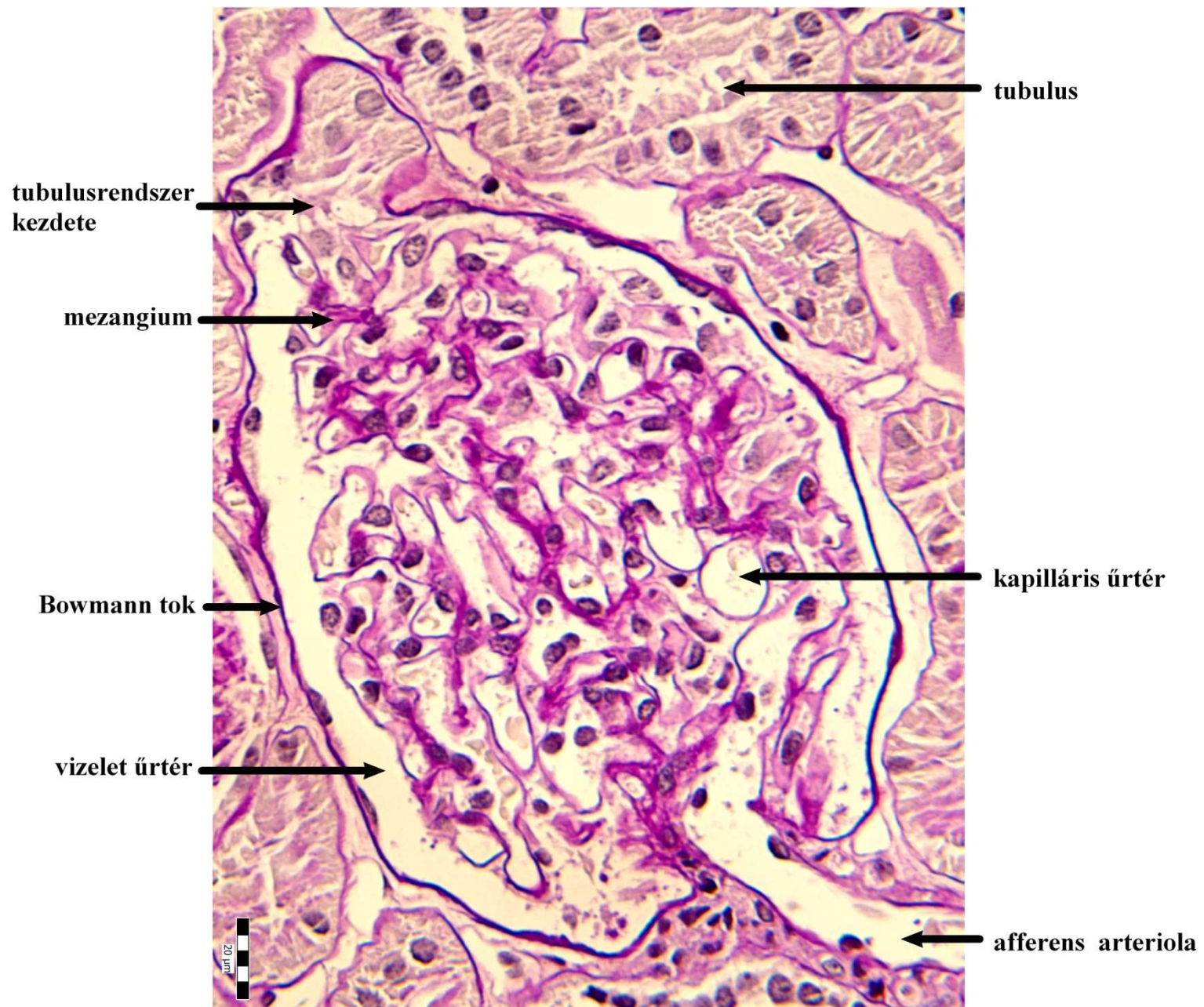
# Immunhisztológiai vizsgálat

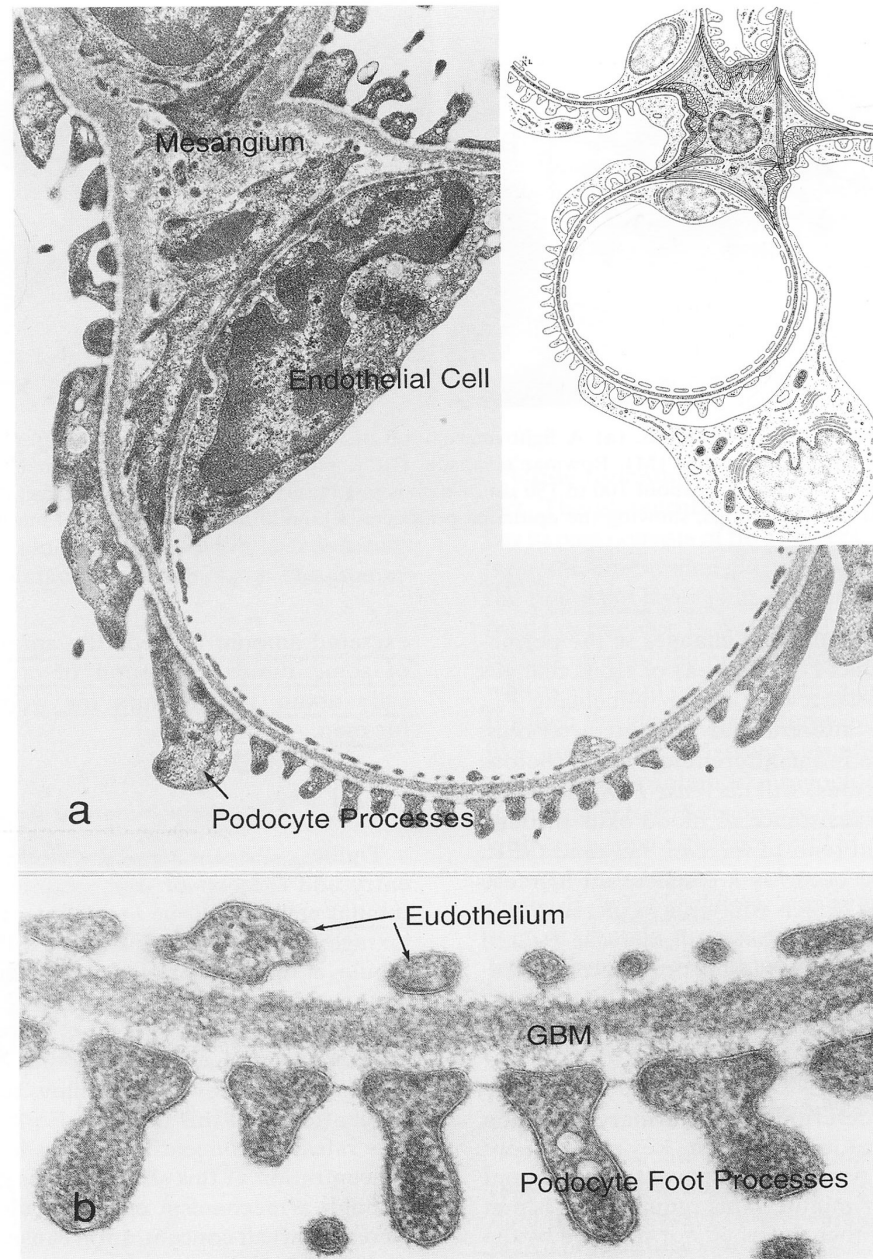


**Figure 20.2 Pathology of glomerular disease: immunofluorescence microscopy.** Common patterns of glomerular staining found by immunofluorescence. (a) Linear capillary wall IgG: antiglomerular basement

membrane disease. (b) Fine granular capillary wall IgG: membranous nephropathy. (c) Coarse granular capillary wall IgG-membranoproliferative GN type I. (d) Granular mesangial IgA/IgG nephropathy.



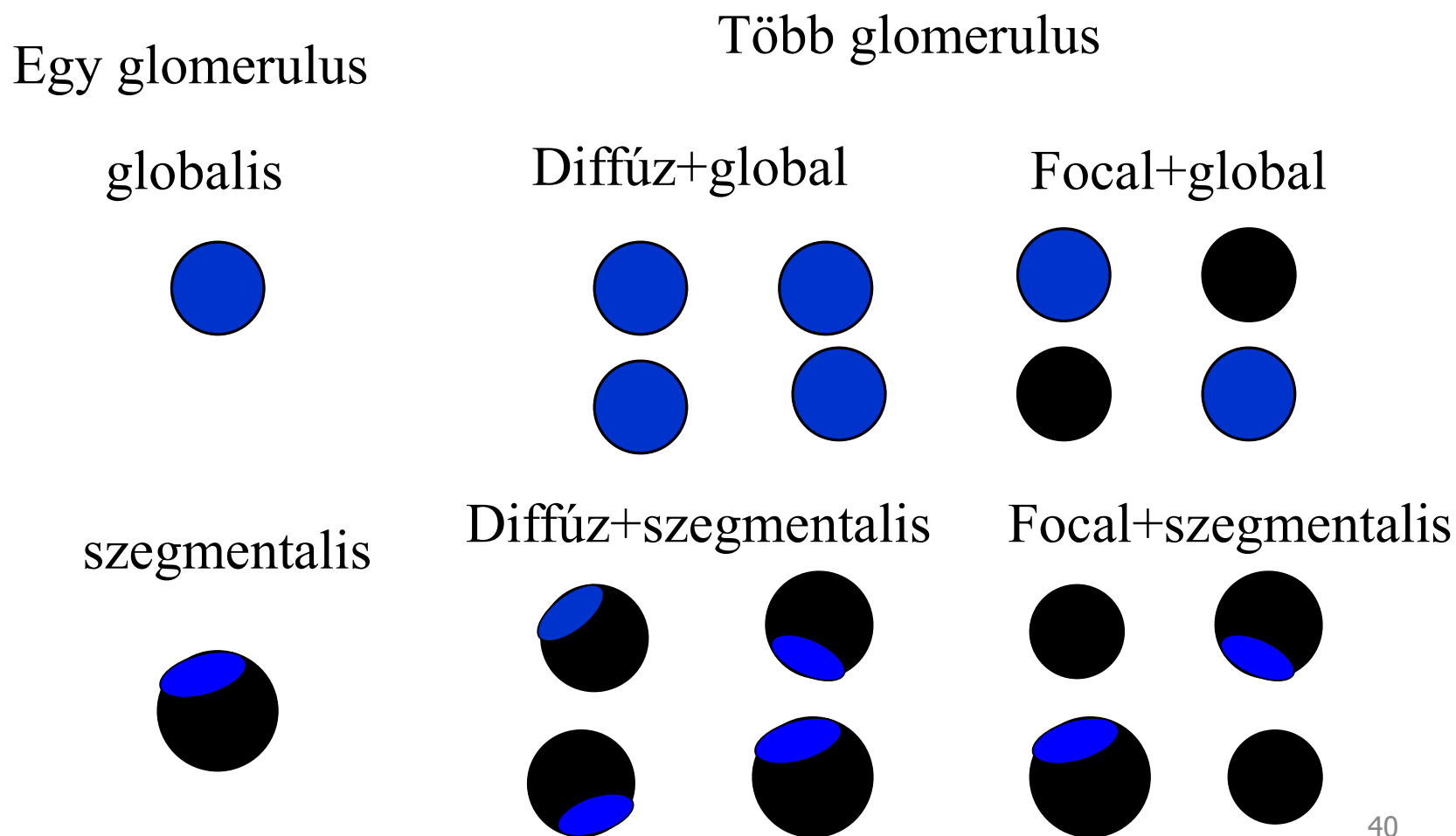




**FIGURE 5** Structure of the glomerular capillary loop and the filtration barrier. (a) A single capillary loop showing the endothelial and foot process layers and the attachments of the basement membrane to the mesangium. Pressure in the glomerular capillary bed is substantially higher than in other capillaries. As shown in the diagrammatic insert, the mesangium provides the structural supports which permit these cells to withstand these high pressures. (b) The glomerular filtration barrier.

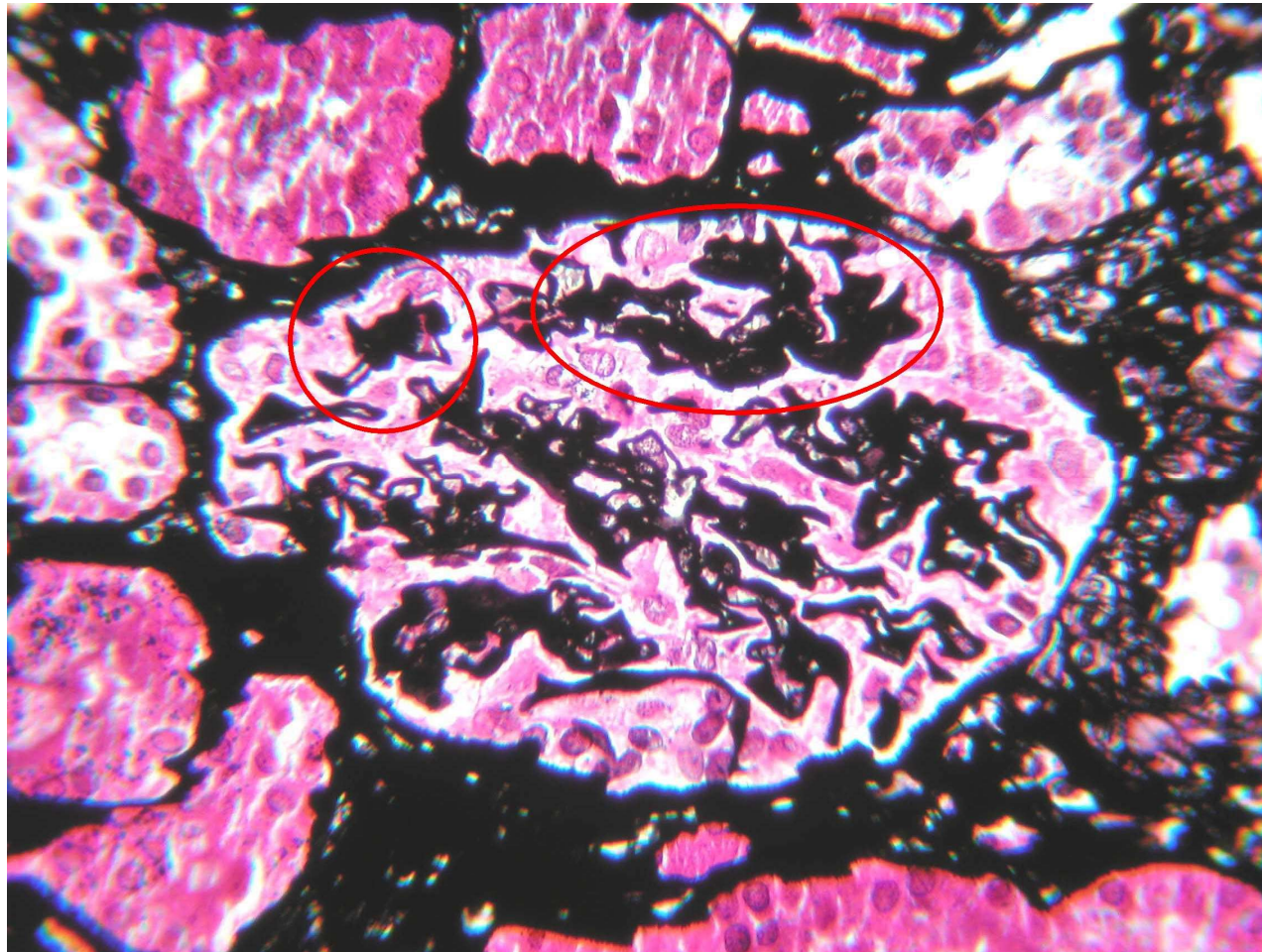
# Szöveti elváltozások a vesében

## a. glomerulus

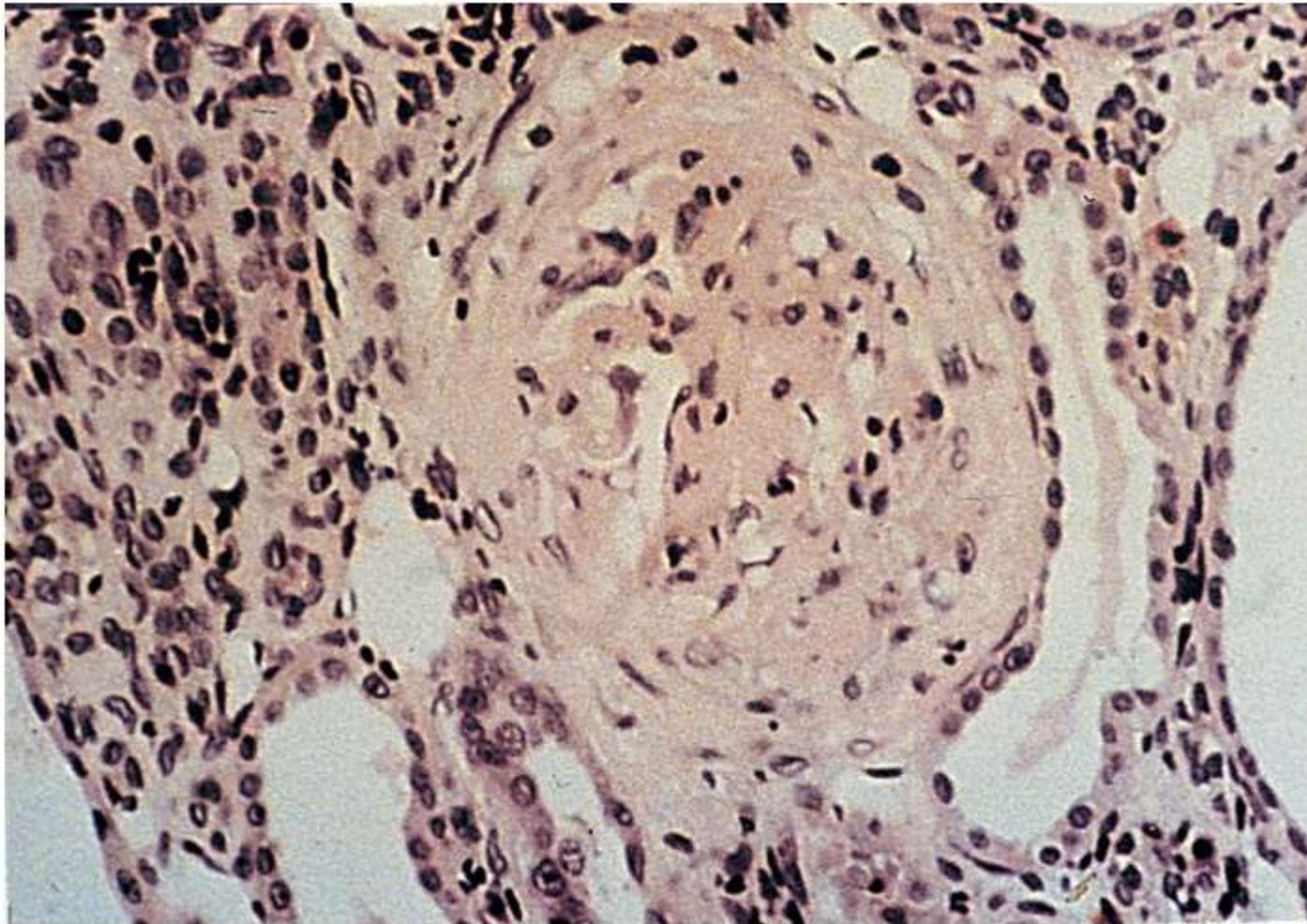




# Szegmentalis sclerosis

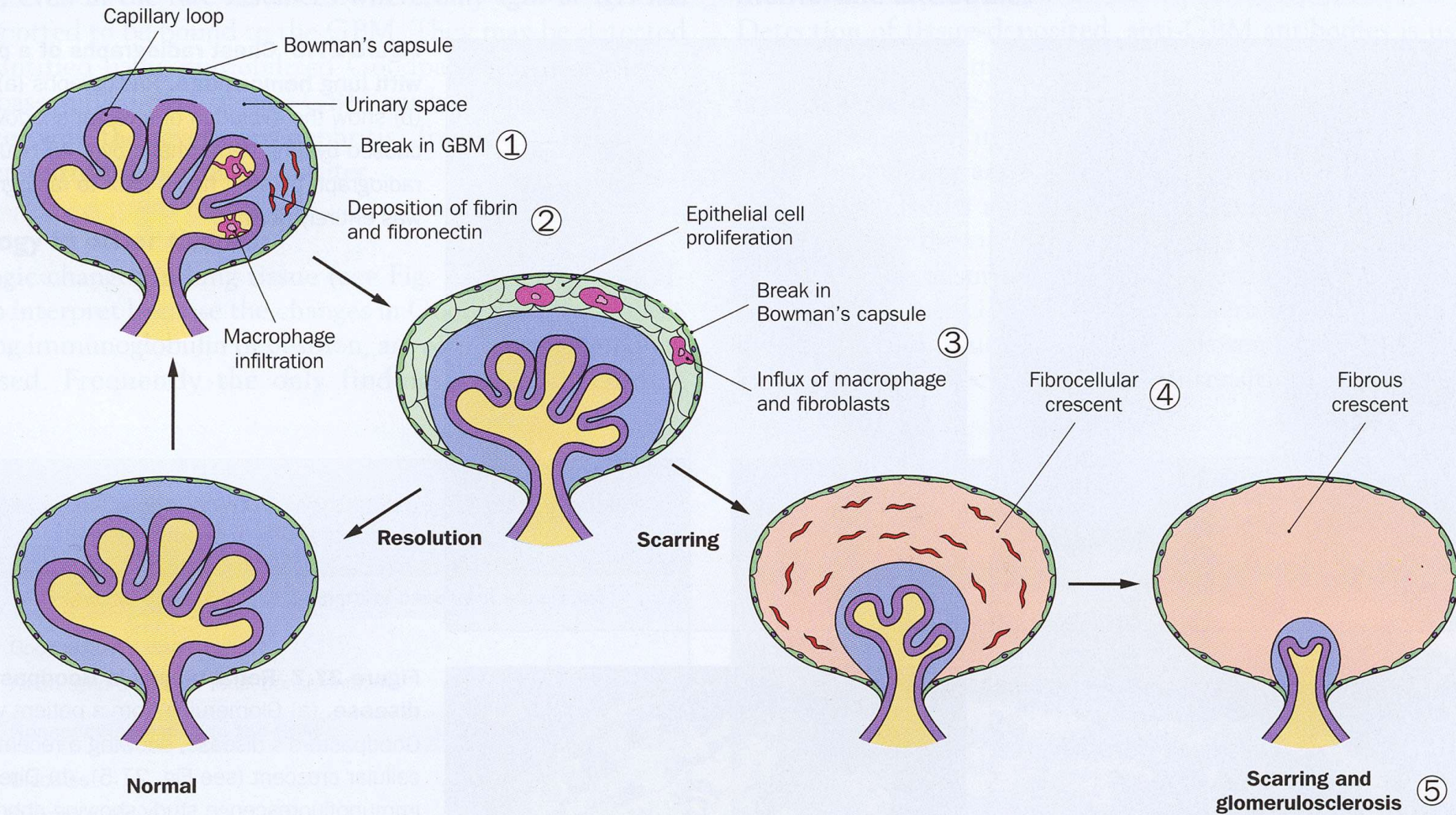


# Globalsclerotikus glomerulus





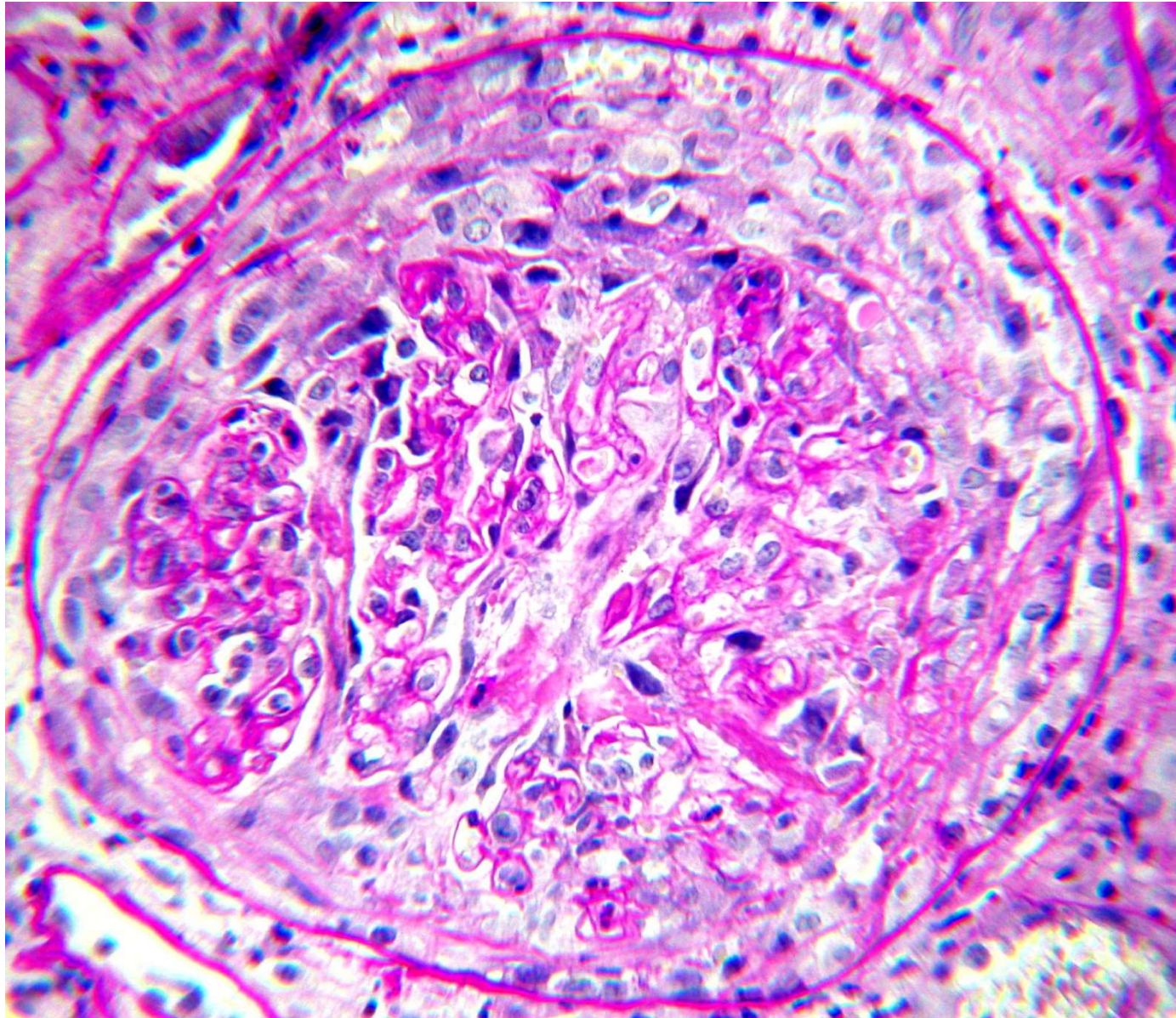
## Crescent formation



**Figure 27.5 Crescent formation.** Following fractures and perforations of the glomerular basement membrane [GBM] (1), deposition of fibrin and serum proteins (2) stimulates proliferation of epithelial cells to form a cellular crescent. Macrophages contribute to this to a variable degree; this may in part depend on whether the disease process also causes perforations of Bowman's capsule (3). Such perforations also permit influx of fibroblasts, and this may influence whether or not there is resolution of the crescent, or formation of fibrocellular crescents (4) and glomerulosclerosis (5). In experimental models crescent formation can be inhibited by defibrination or anticoagulation, although these have not so far proved to be practical therapies in man. Formation of crescents is also T-lymphocyte dependent, and is blocked by T cell depletion or by inhibition of their activation. It is not clear whether this effect is mediated through reduction of initial tissue damage (and thus of GBM or Bowman's capsule fractures) or by inhibition of some secondary step.



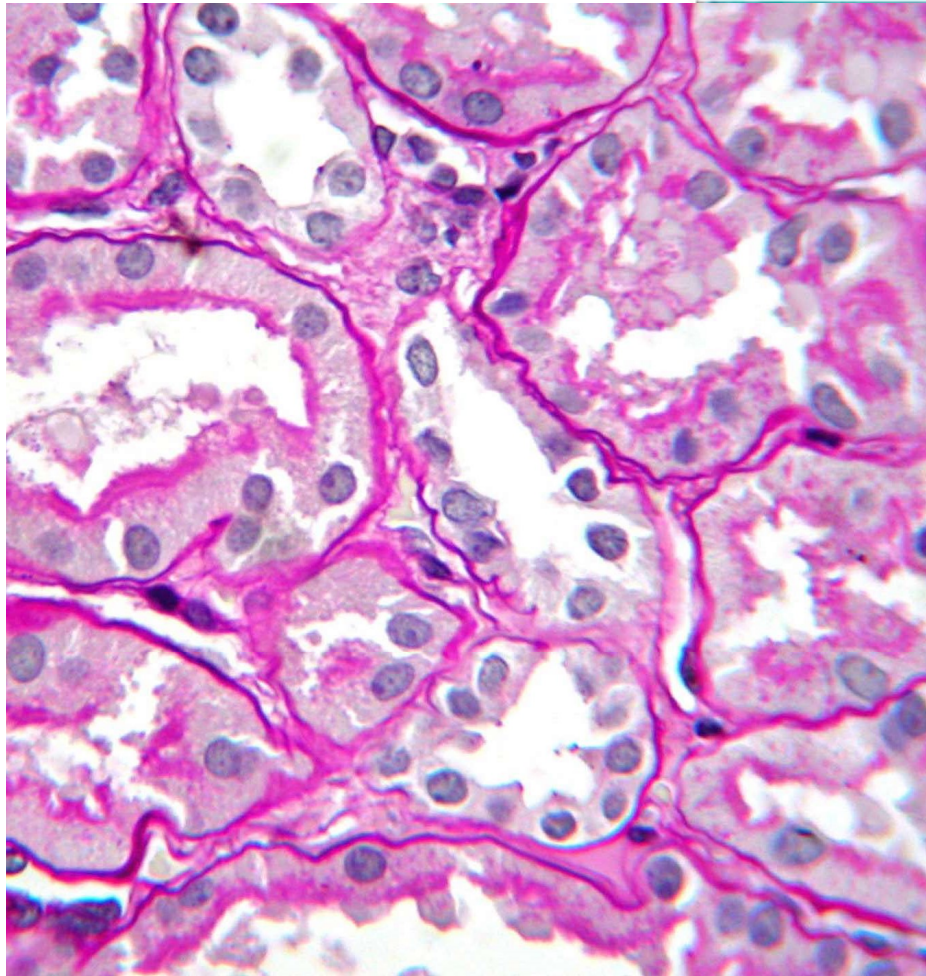
# Crescent (félhold)



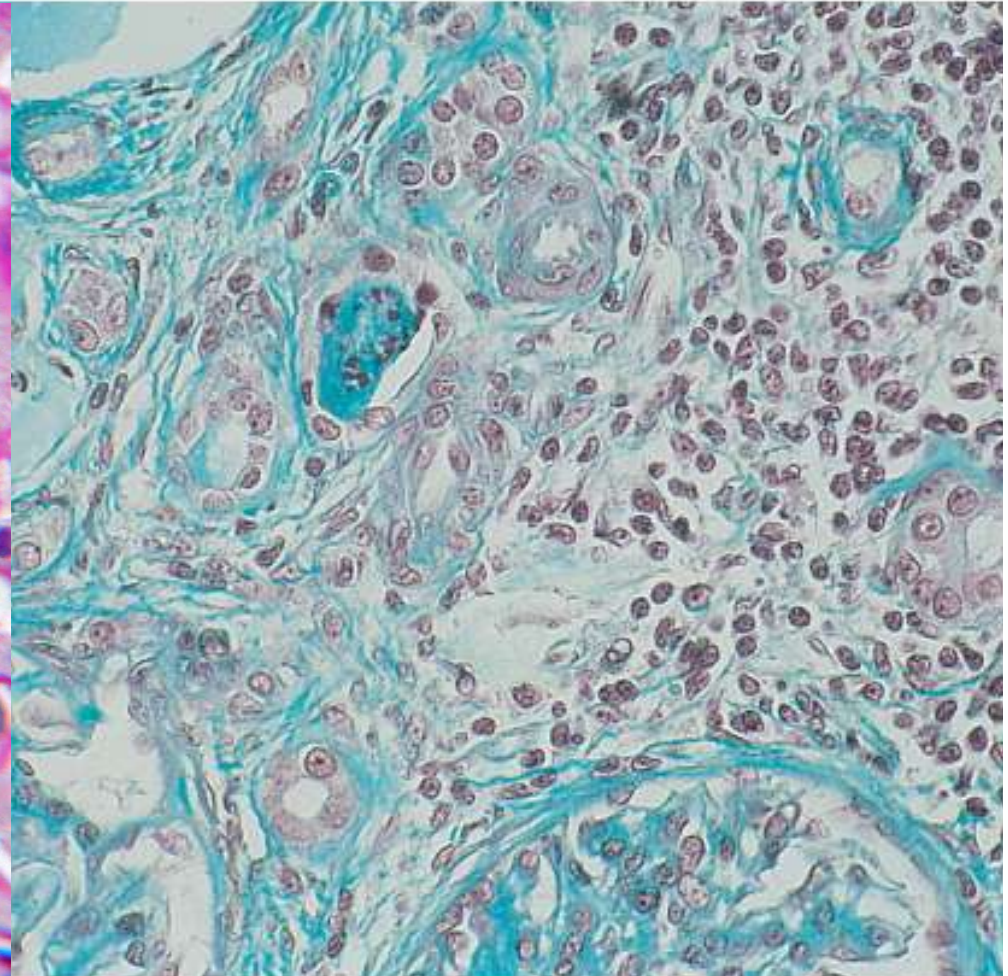


# Tubulointerstitium

Ép



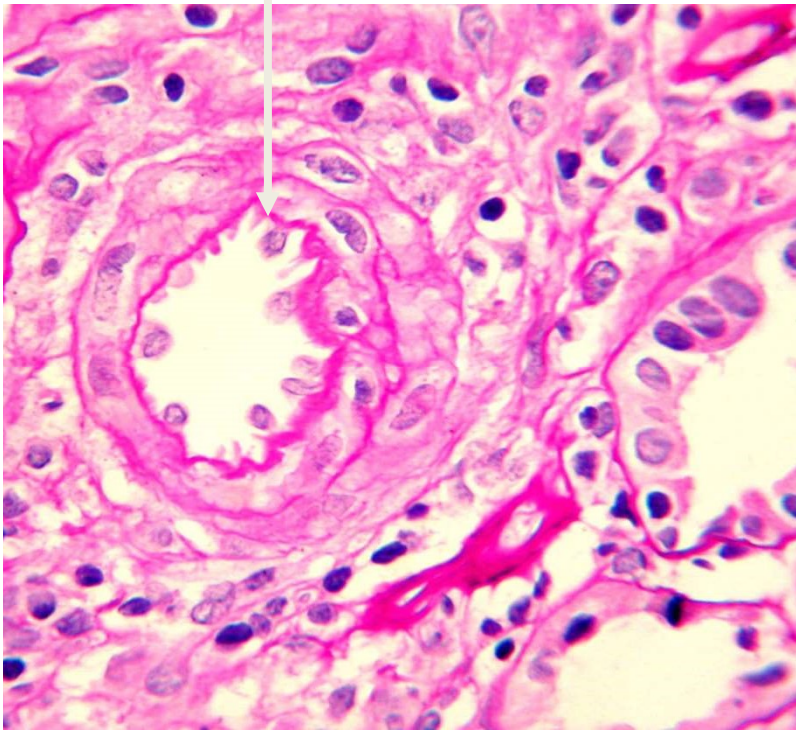
Kereksejtes beszűrődés, hegesedés



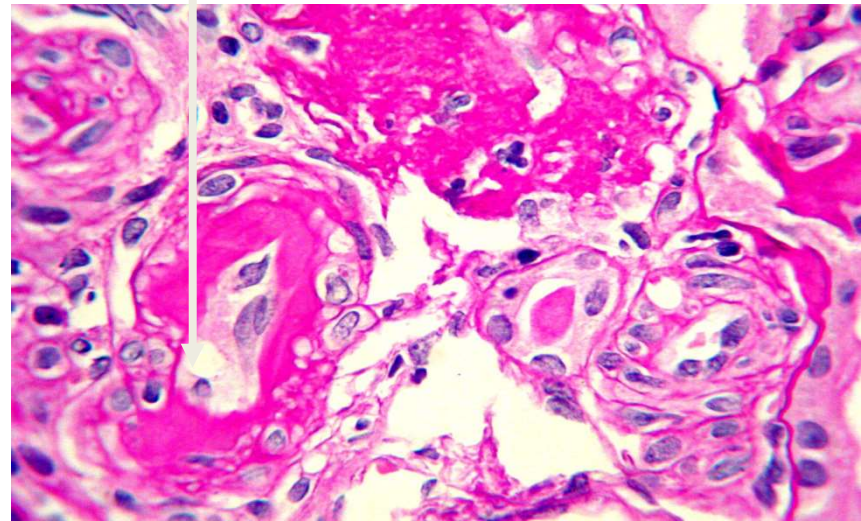


# Kiserek állapota

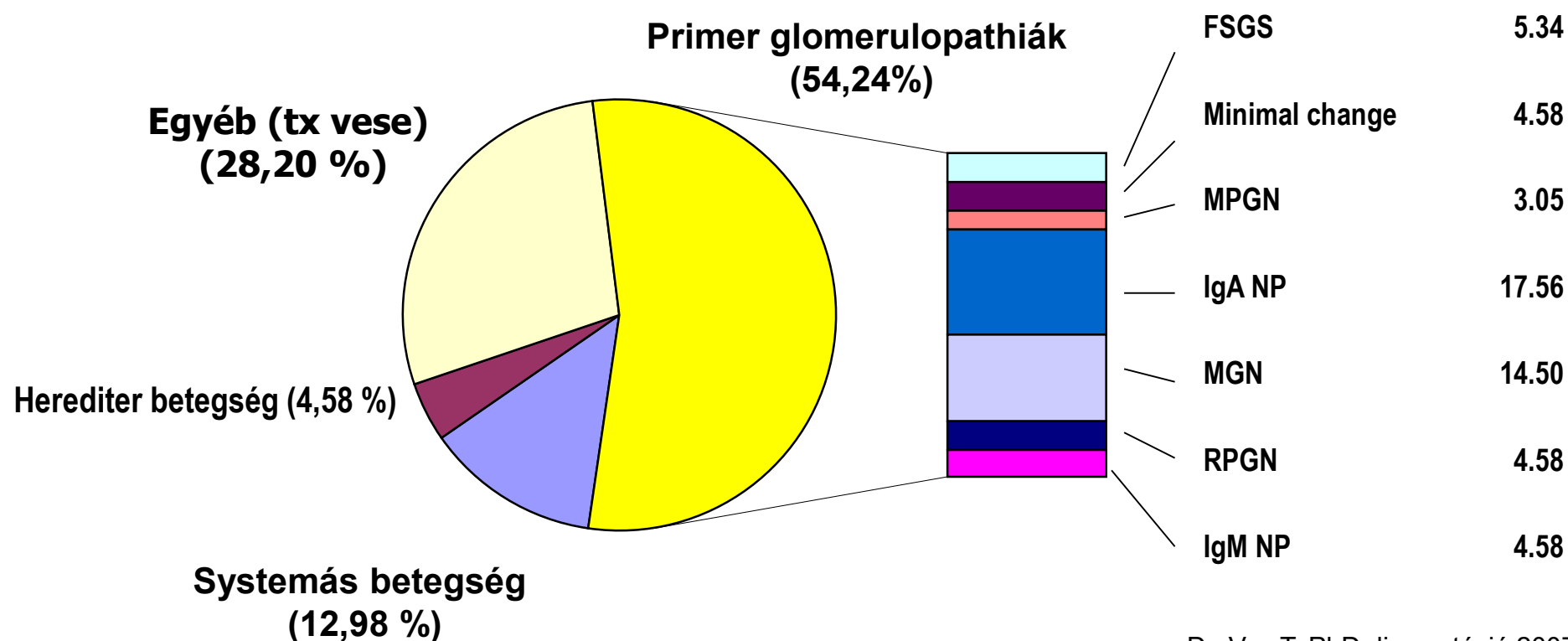
**ép**



**súlyos hyalinos**



# A felnőtt, Baranya megyei lakosok klinikánkon végzett vesebiopsziáinak szövettani eredmény szerinti megoszlása (2003-2005; n=384)



# IgA nephropathia

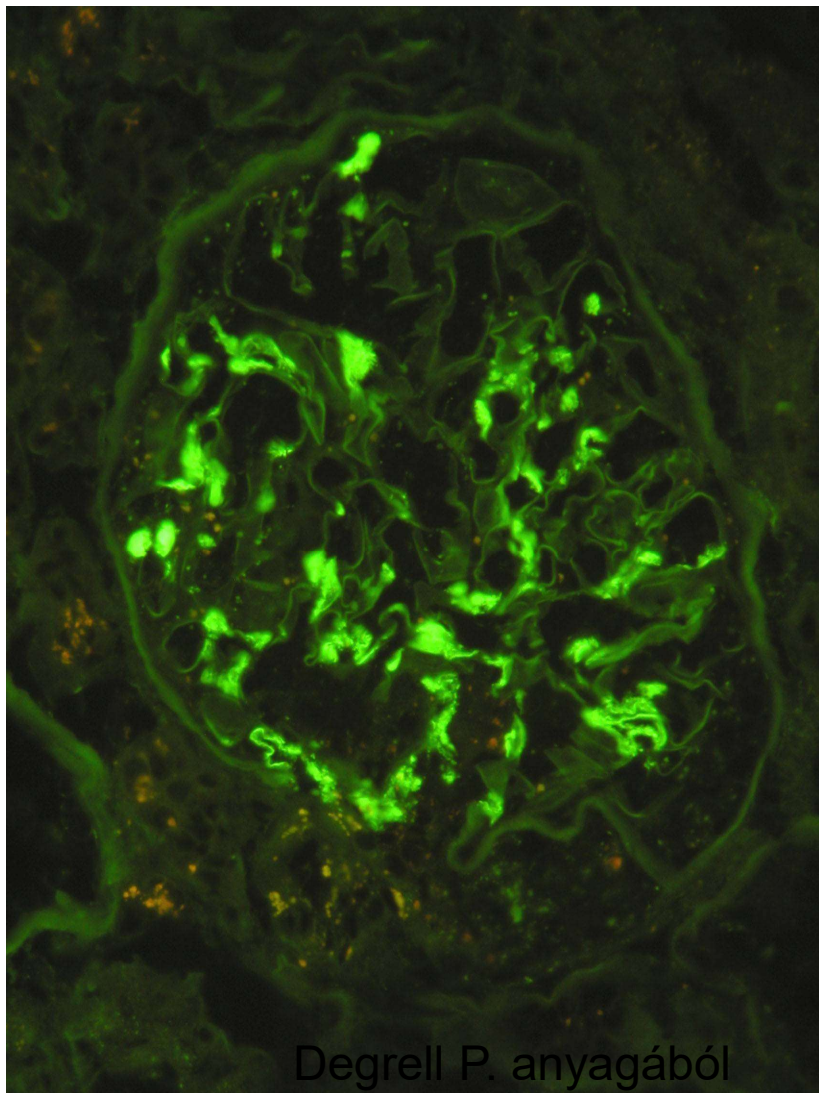
- Dg: döntően IgA granularis lerakódás a mesangiumban FM: mesangioprolif GN

## Klinikai kép

- oligosymptomás (40-50%),
- infekciót követő macroHU ( $\approx 40\%$ )
- nephrosis, RPGN ( $\approx 10\%$ )
- Primer / Secunder forma

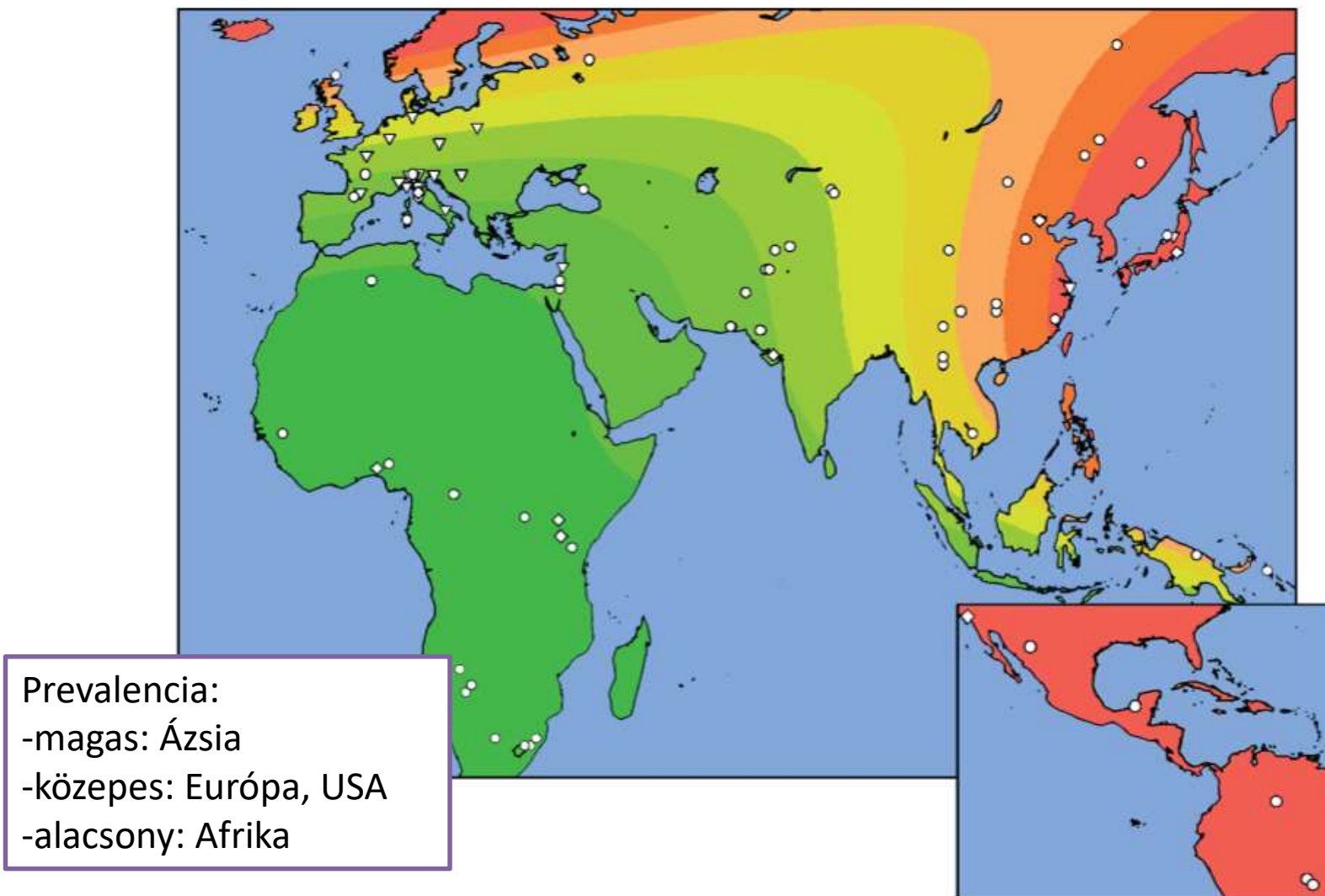


# IgA nephropathia – Berger kór



Degrell P. anyagából

- Berger & Hinglais 1966
- Dominálón IgA1 lerakódás (C3, IgG,  $\lambda$ ,  $\kappa$  is kísérheti)
- Dominálón a mesangiumban



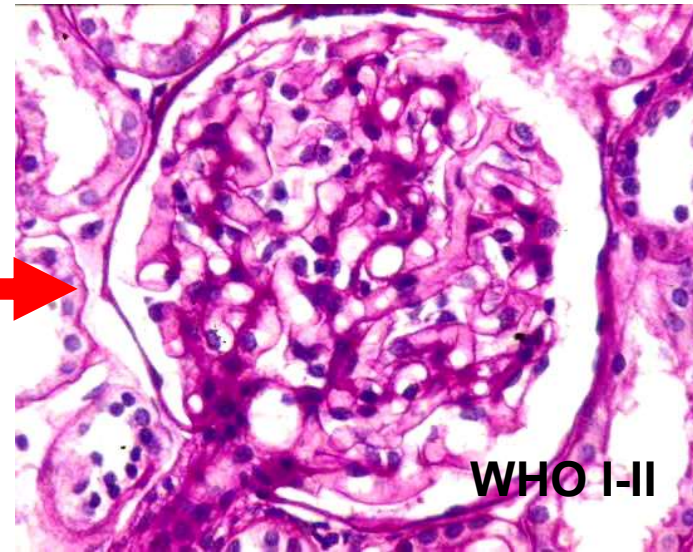
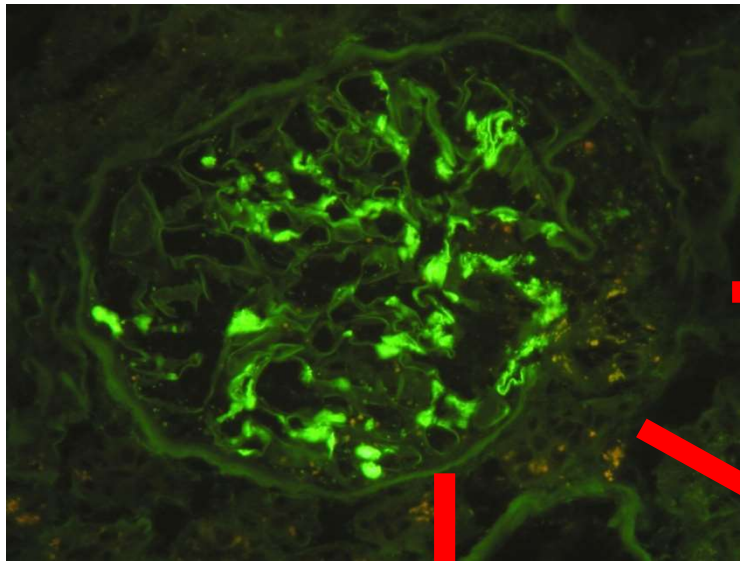
*From reference 11.*

**Fig. 23-2. Geographical variation in genetic risk for IgA nephropathy.** Genome-wide association studies indicate a geographical gradient of risk from green (low risk) to red (high risk).



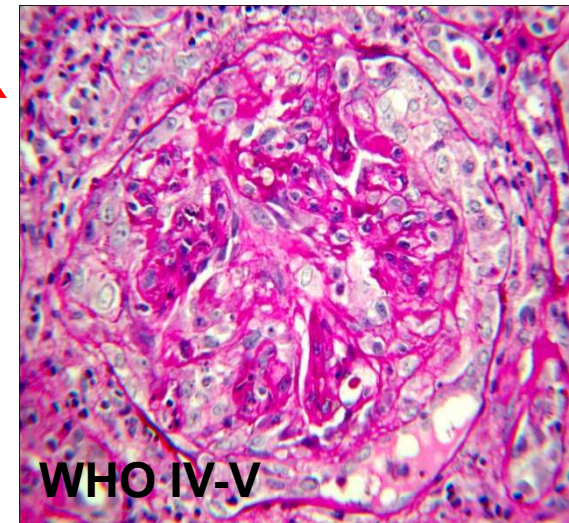
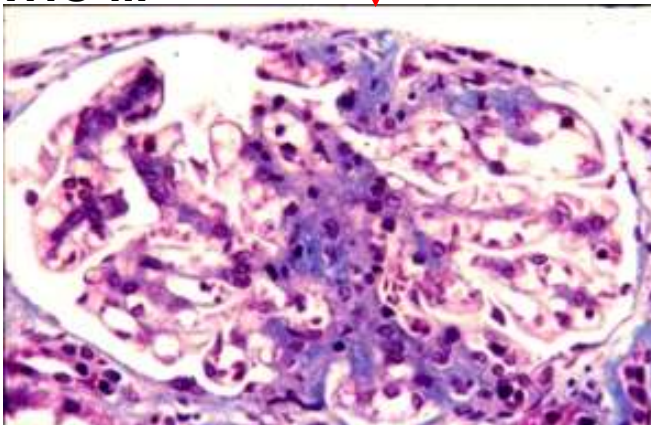
# IgA nephropathia szövettana

(Degrell P. anyaga)



**WHO I-II**

**WHO III**



**WHO IV-V**

# Oxford-MEST klasszifikáció

**Table 8 | Recommended elements in renal biopsy report for a case of IgA nephropathy**

---

*Detailed description of the features present on*

Light microscopy

Immunohistochemistry

Electron microscopy

*Summary of four key pathological features*

Mesangial score  $\leq 0.5$  (M0) or  $> 0.5$  (M1)

Segmental glomerulosclerosis absent (S0) or present (S1)

Endocapillary hypercellularity absent (E0) or present (E1)

Tubular atrophy/interstitial fibrosis  $\leq 25\%$  (T0), 26–50% (T1), or  $> 50\%$  (T2)

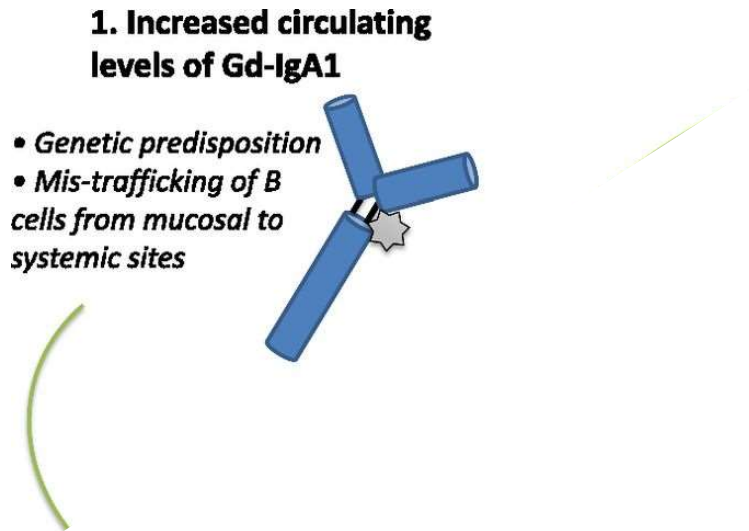
Total number of glomeruli

Number of glomeruli with endocapillary hypercellularity, extracapillary proliferation, global glomerulosclerosis, and segmental glomerulosclerosis

---

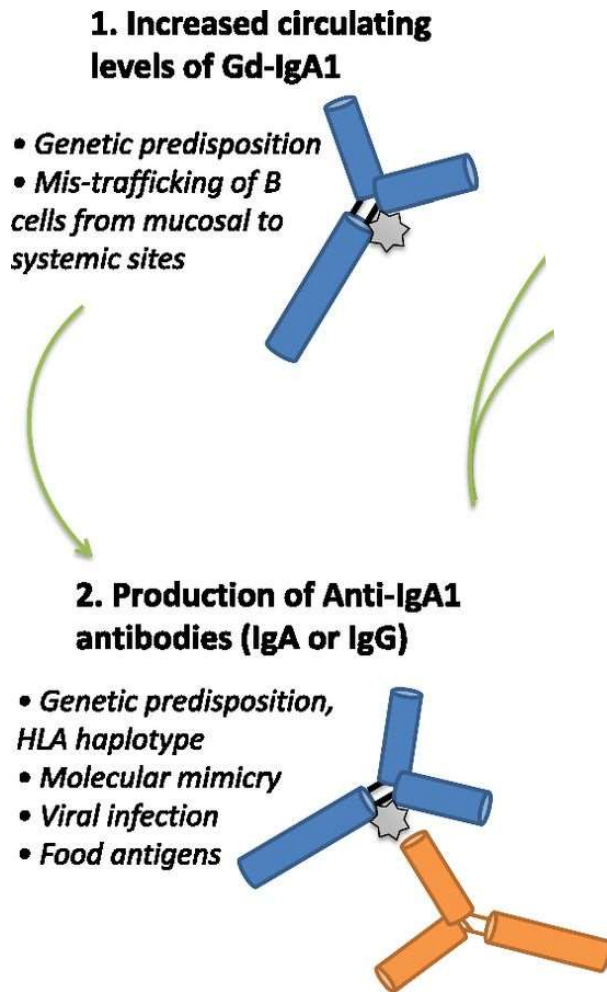
Az IgA nephropathia pathogenezise: 4 lépcsős modell;  
genetikai, környezeti, innate és szerzett immunitás interakciói  
**Canetta CJASN 2014 alapján**

# Az IgA nephropathia pathogenezise: 4 lépcsős modell; genetikai, környezeti, innate és szerzett immunitás interakciói

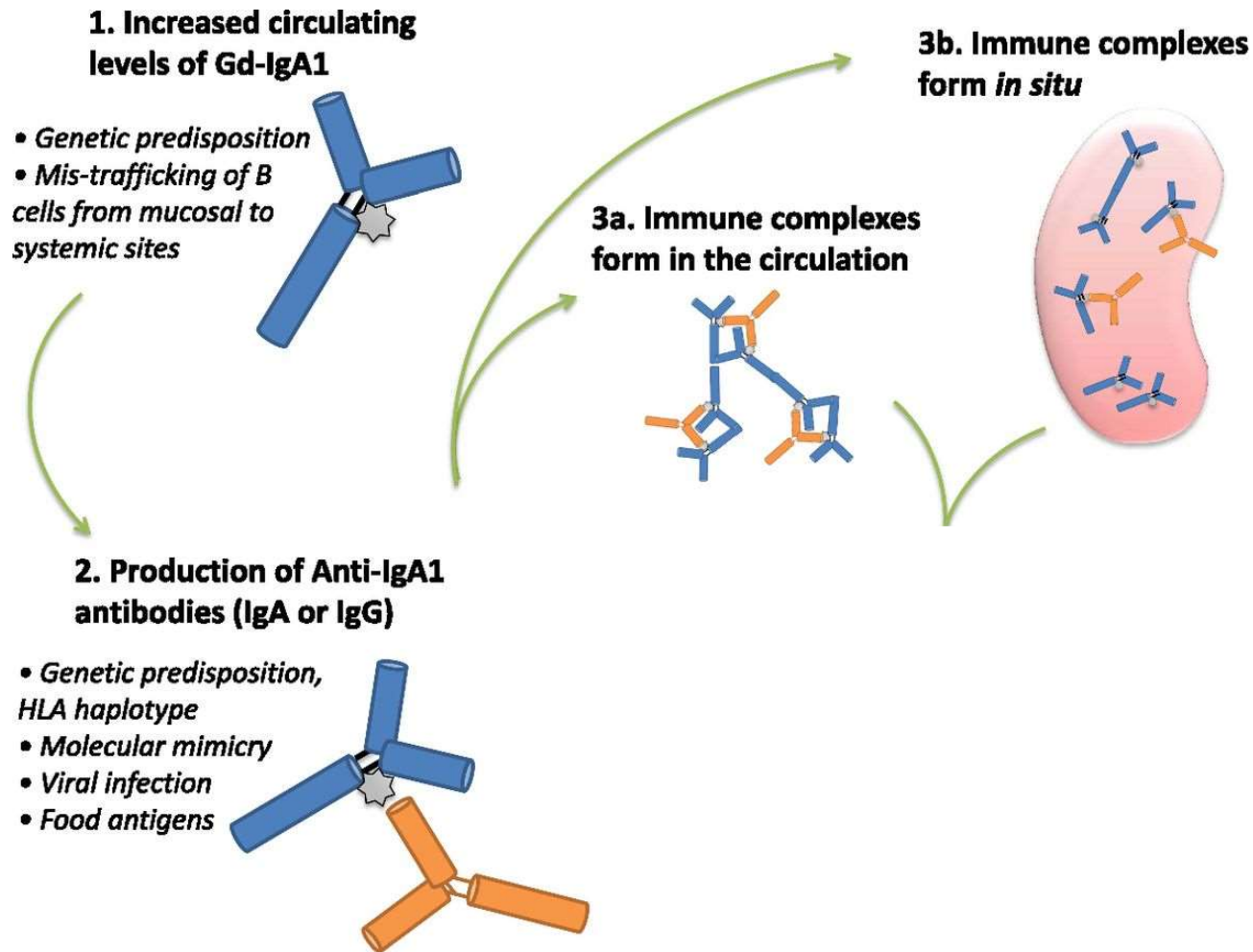


Gd-IgA1: galaktóz deficiens IgA1

# Az IgA nephropathia pathogenezise: 4 lépcsős modell; genetikai, környezeti, innate és szerzett immunitás interakciói

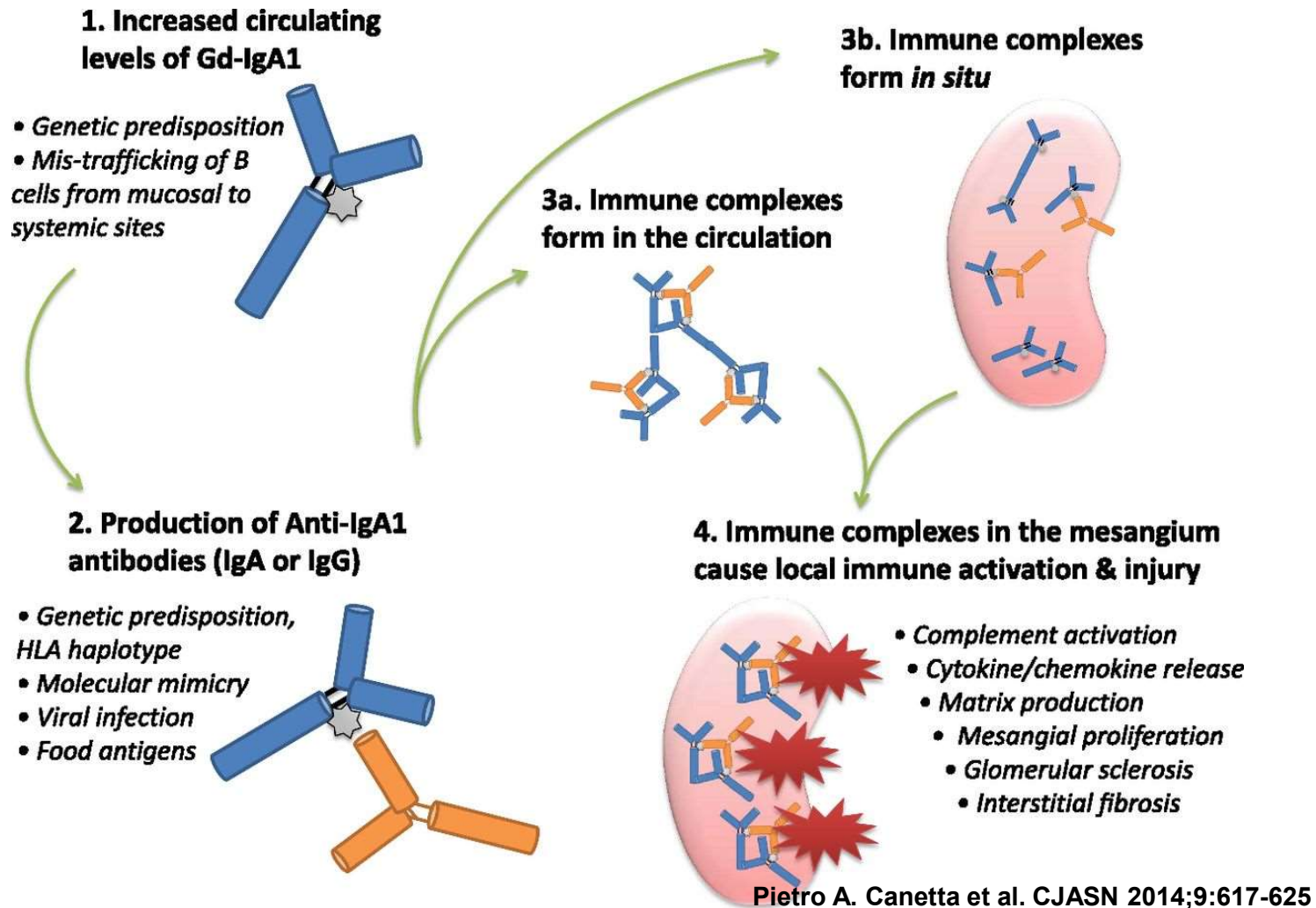


# Az IgA nephropathia pathogenezise: 4 lépcsős modell; genetikai, környezeti, innate és szerzett immunitás interakciói

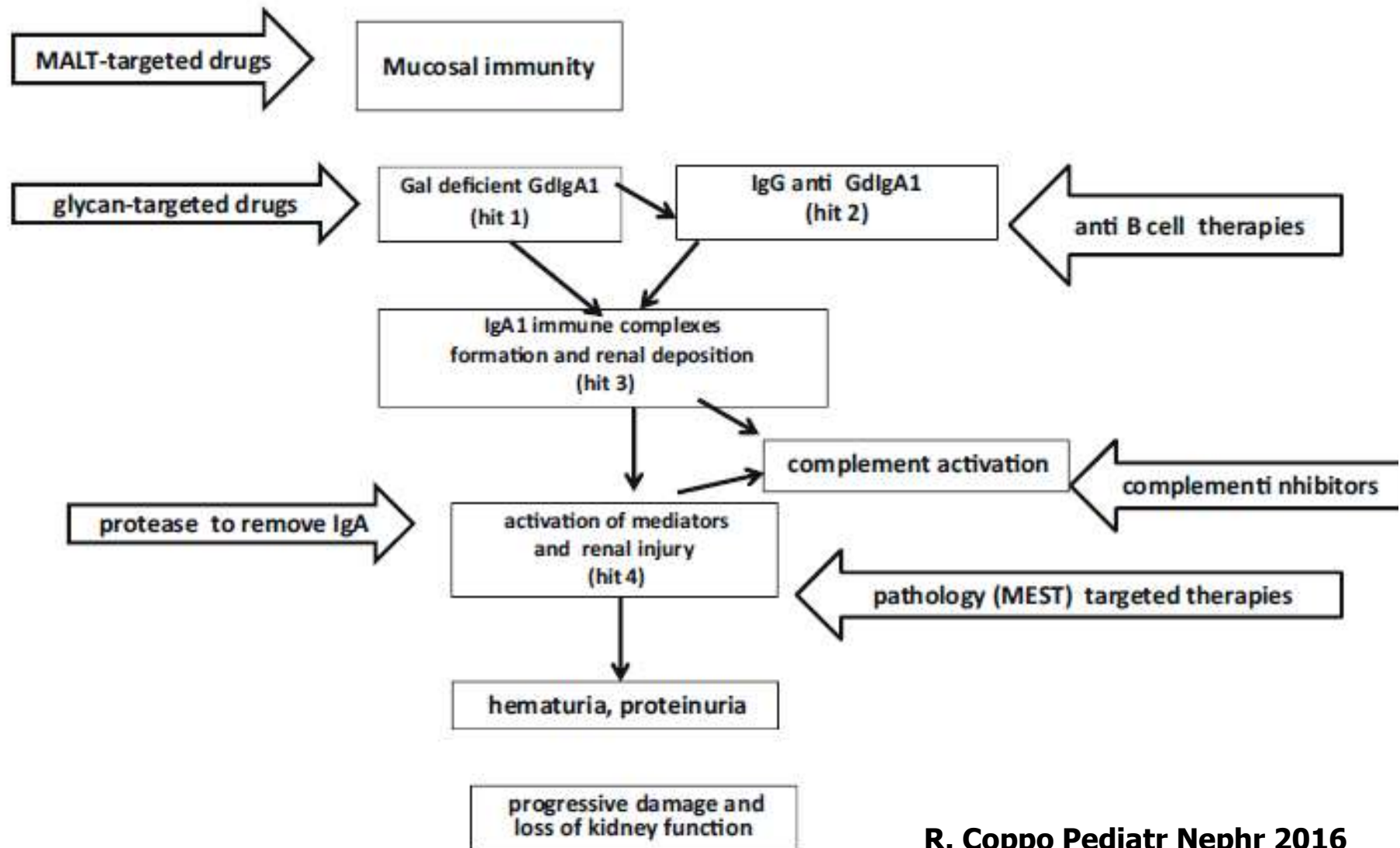




# Az IgA nephropathia pathogenezise: 4 lépcsős modell; genetikai, környezeti, innate és szerzett immunitás interakciói

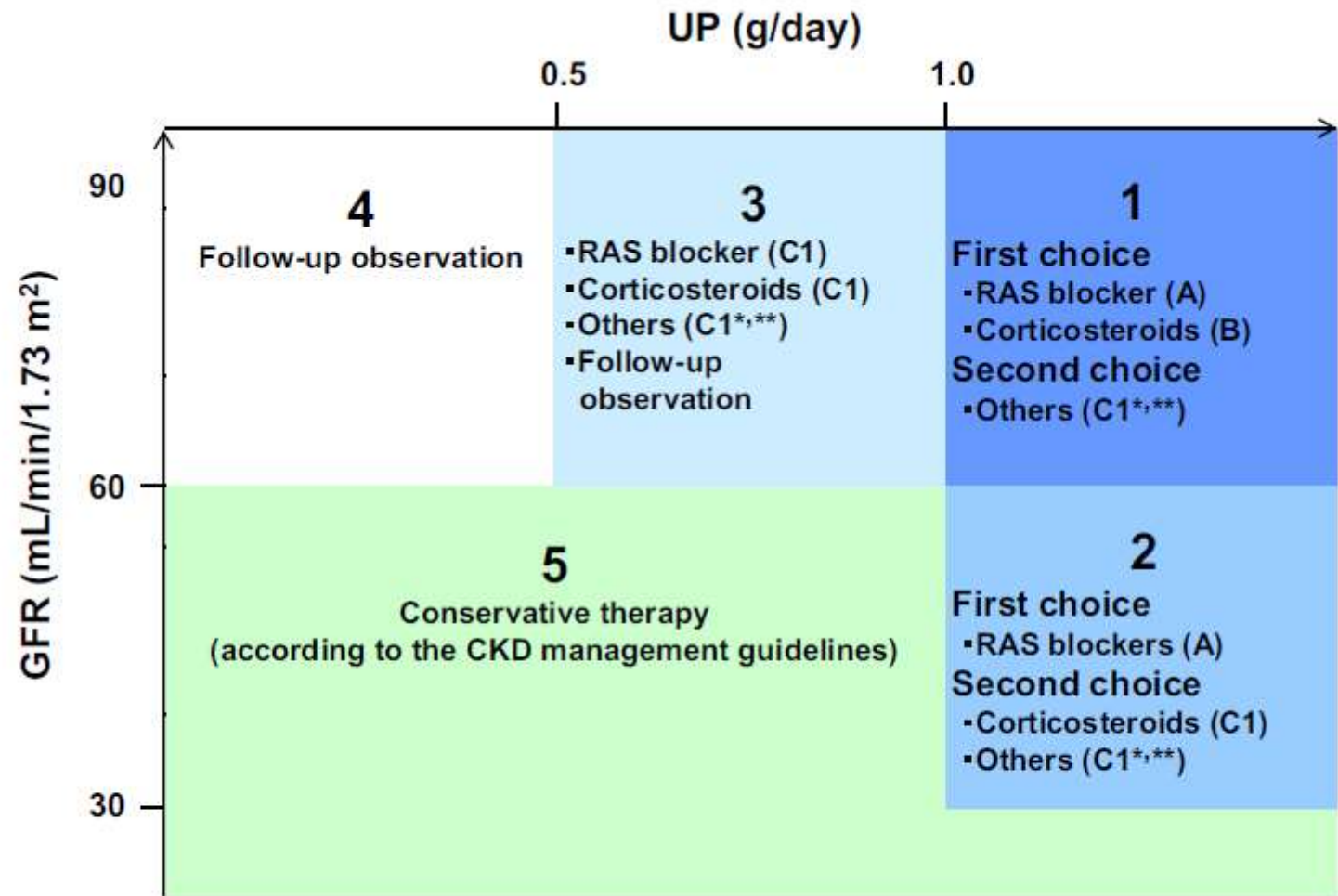


# IgAN elméleti terápiás lehetőségei



# IgAN EBM terápiája

[Recommendation C]  
 Grade A: Strongly in favor of treatment on the basis of strong scientific basis.  
 Grade B: Recommendation in favor of treatment on the basis of moderate scientific basis.  
 Grade C1: Recommendation in favor of treatment on the basis of weak scientific basis.  
 Grade C2: Not recommended on the basis of weak scientific basis.  
 Grade D: Not recommended on the basis of weak scientific basis. Shows treatment to be harmful.



**Fig. 3** An outline of treatment of IgAN in adults with a focus on prevention of renal dysfunction (based on randomized controlled

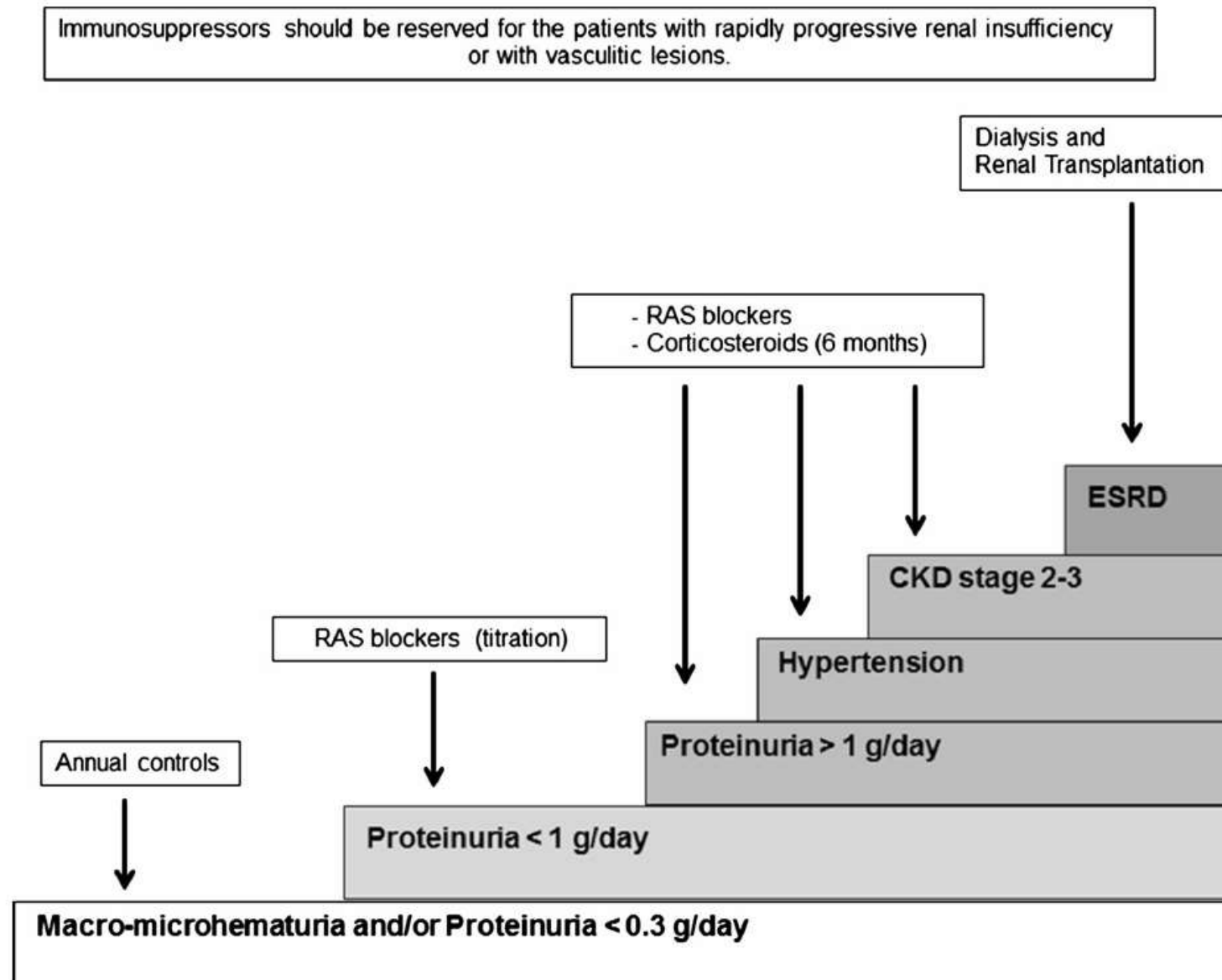
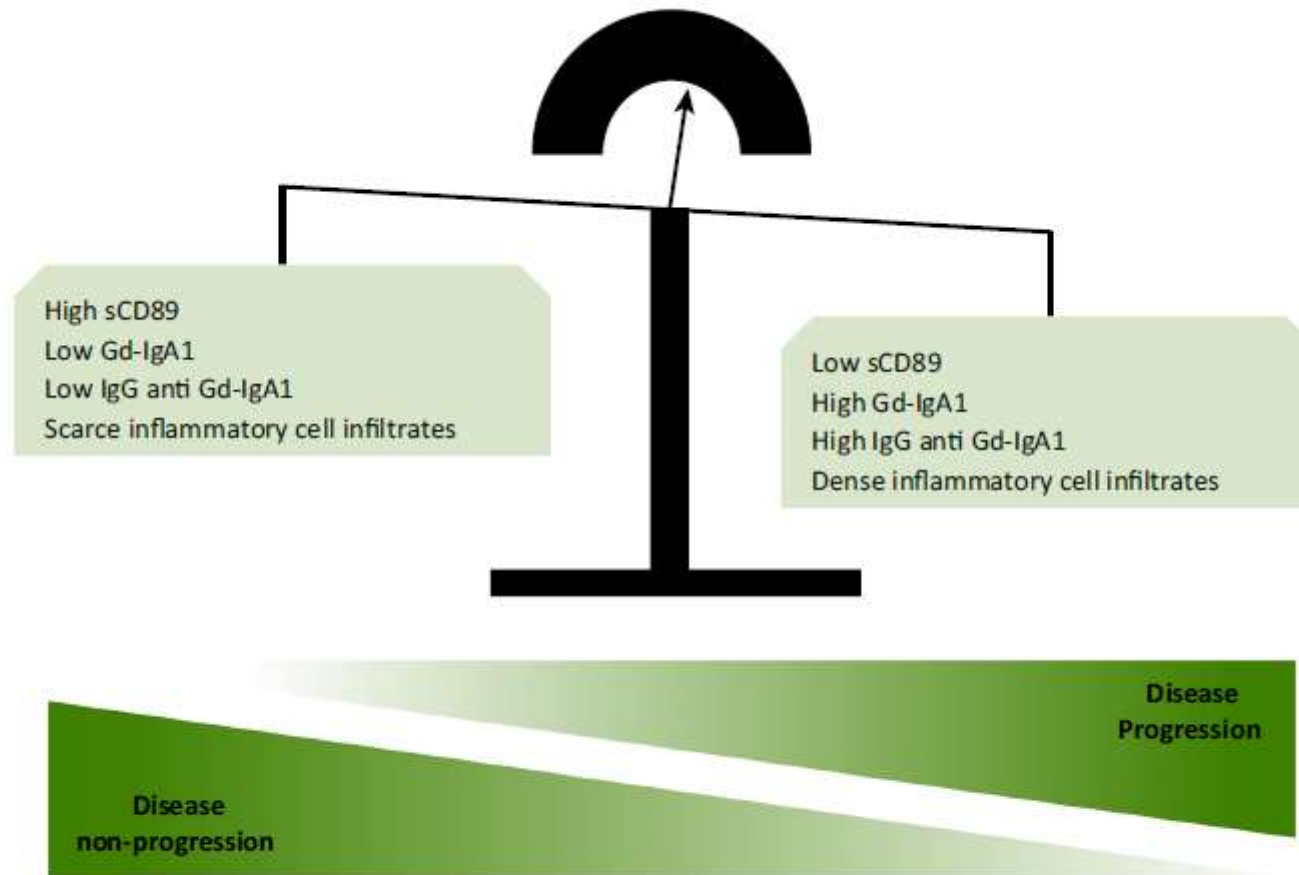


Fig. 1 Progressive therapy for IgAN patients

# IgA nephropathia progressziója



Trends in Molecular Medicine

Figure 2. IgA Nephropathy and Severity of Disease: An Equilibrium between the Different Immunological Players. High sCD89, low Gd-IgA1, IgG antibody anti-Gd-IgA1 inflammatory cells might represent predictive factors of non-renal failure. Low sCD89, high IgA1, IgG antibody anti-Gd-IgA1 might represent predictive factors of disease progression.

T. Robert <http://dx.doi.org/10.1016/j.molmed.2015.10.003>

**sCD89: solubilis IgA Fc receptor**



# IgA nephropathia progressziója

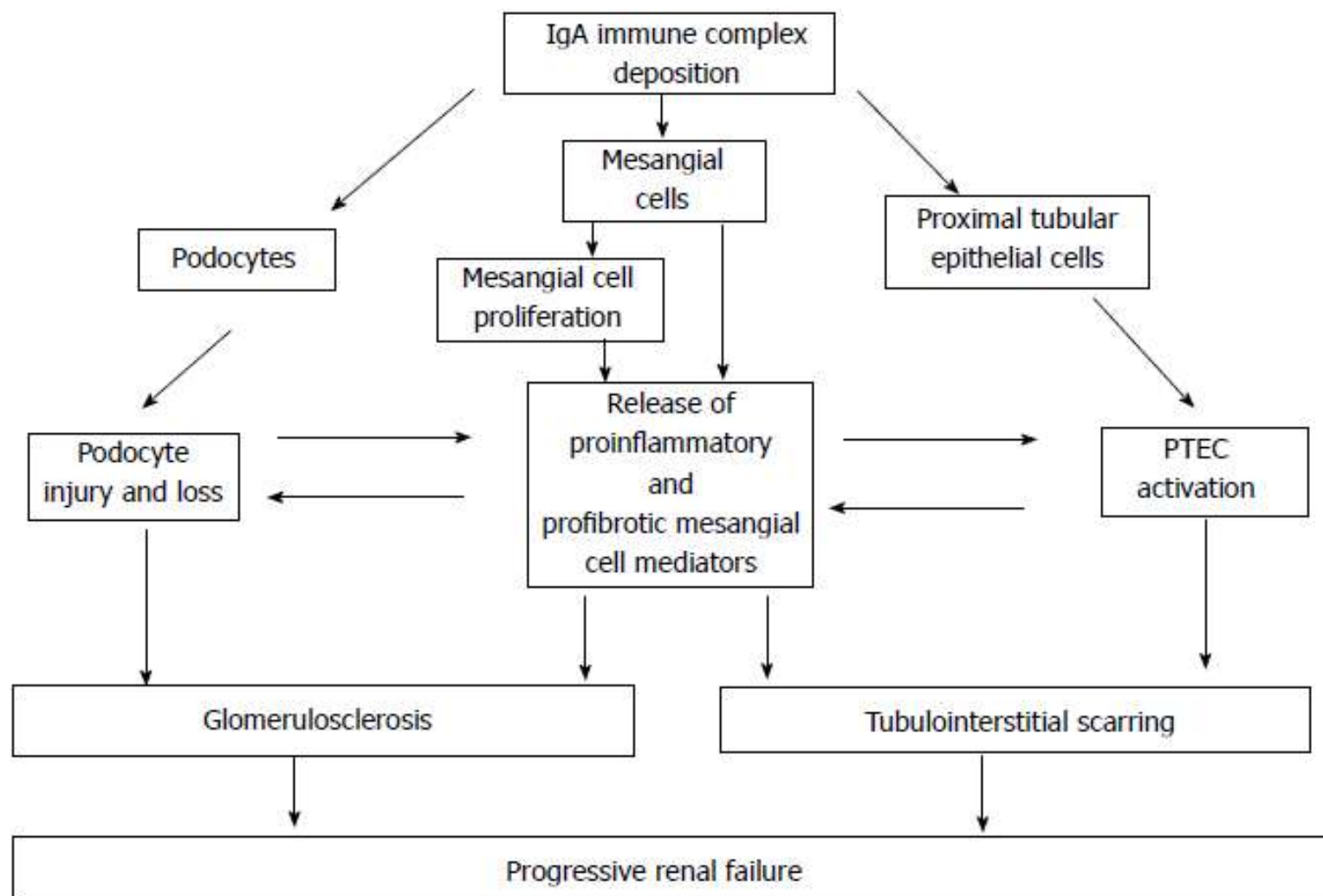


Figure 4 Pathways to glomerular damage and tubulointerstitial injury in Immunoglobulin A nephropathy.

# **Az IgAN természetes lefolyása**

20 évvel a kezdet (vesebiopszia) után

20-30% ESRF

40-50% lassan csökkenő vesefunkció

30-35% a vesefunkció megtartott



# ROSSZ PROGNÓZISRA UTALÓ JELEK

International IgAN Prediction Tool

([International IgAN Prediction Tool - Adults | QxMD](#))

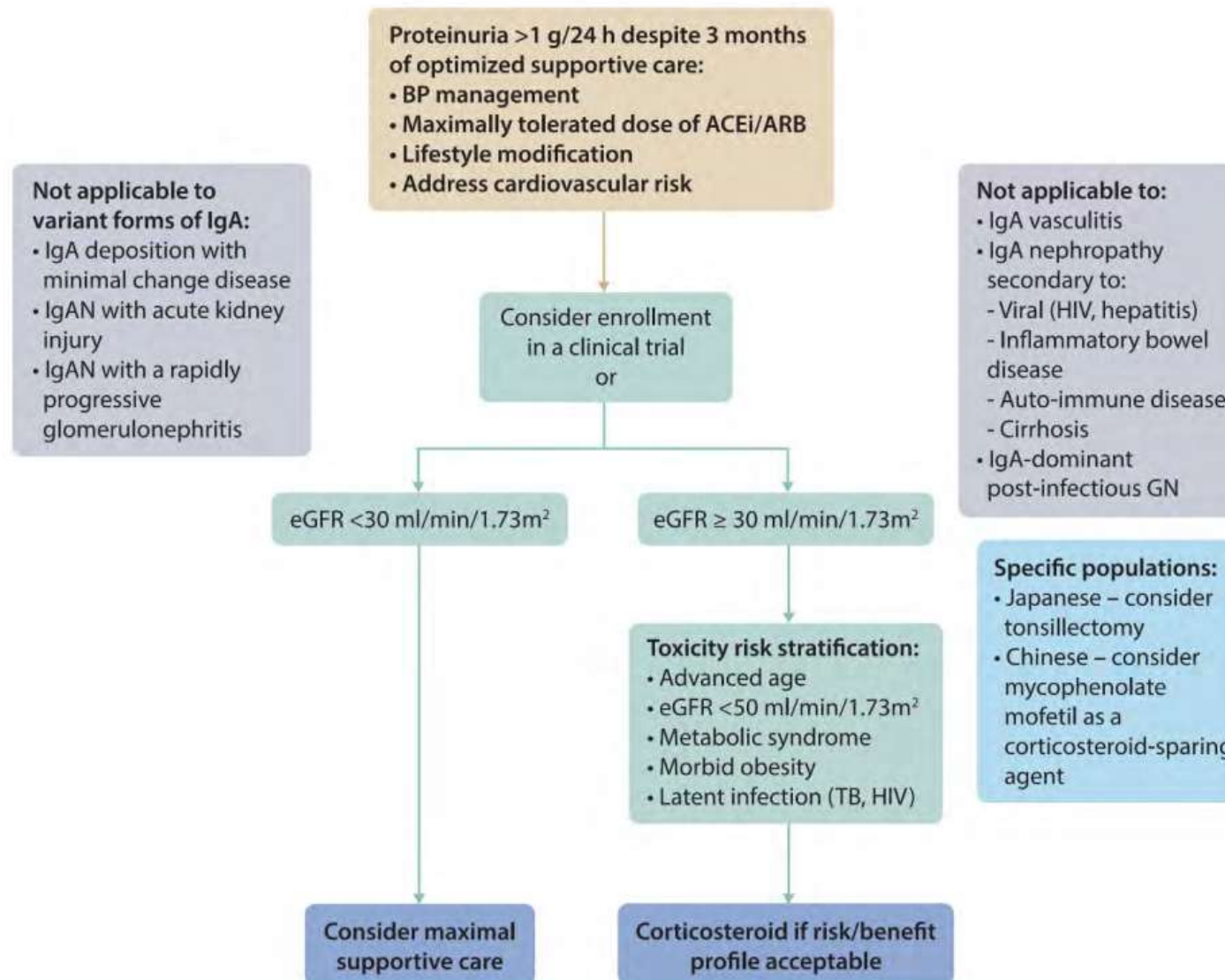
## Klinikailag

- férfi
- se creat > 150  $\mu$ mol/l már a diagnózisnál
- nincsenek macrohaematuriás epizódok
- PU > 1 g/die
- hypertonia
- hyperuricaemia, obesitas, dyslipidaemia
- dohányzás

## Szövettanilag

- kiterjedt glomerulosclerosis
- félholdak > 50%-ban
- interstitiális fibrosis

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



# TERÁPIA

## Specifikus kezelés

**sec. esetekben**

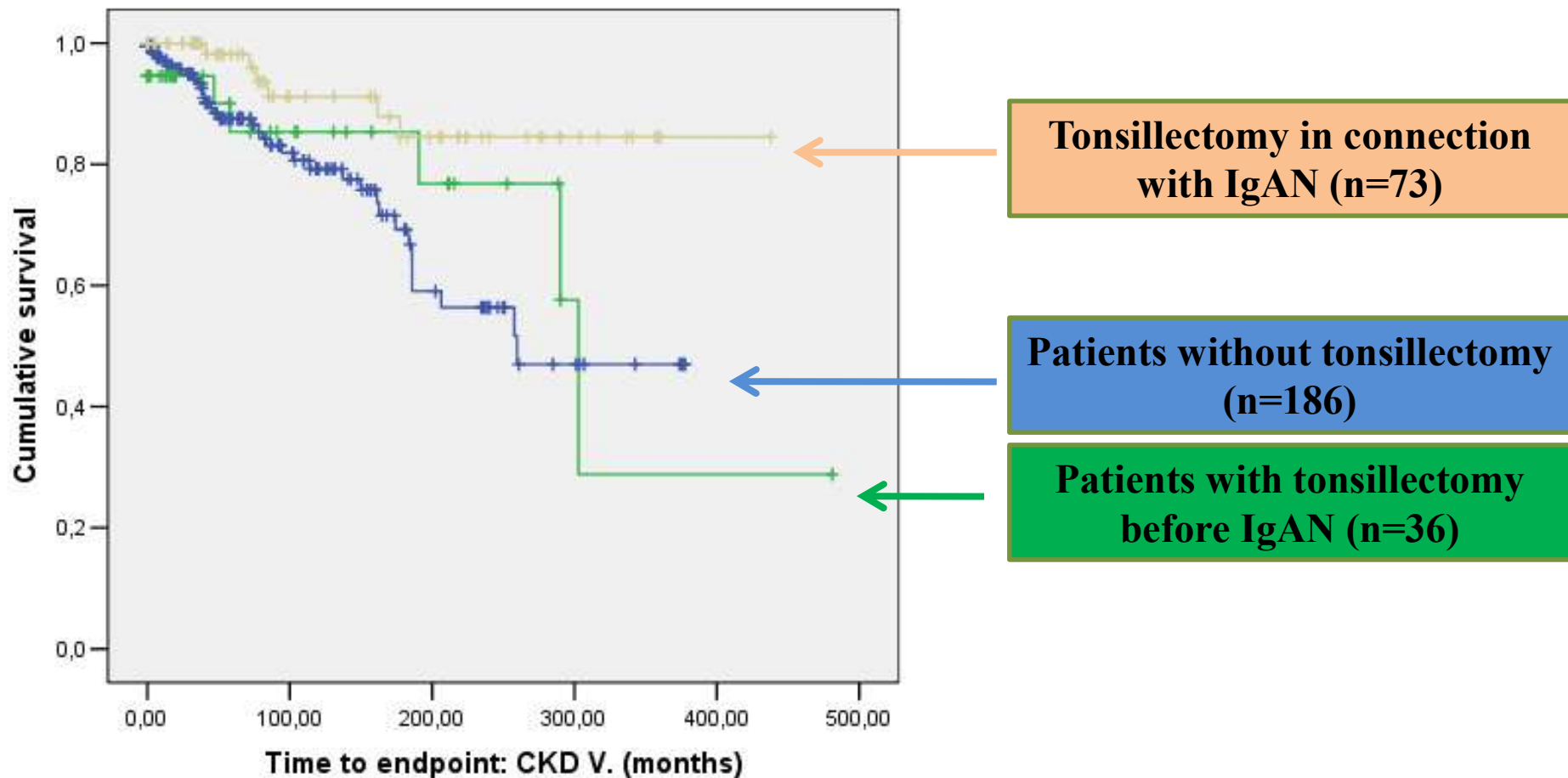
**aktív súlyos formában : ISU (steroid+CPH) - ???**

**Nem-specifikus kezelés (általános): mindenkinél alkalmazandó!**

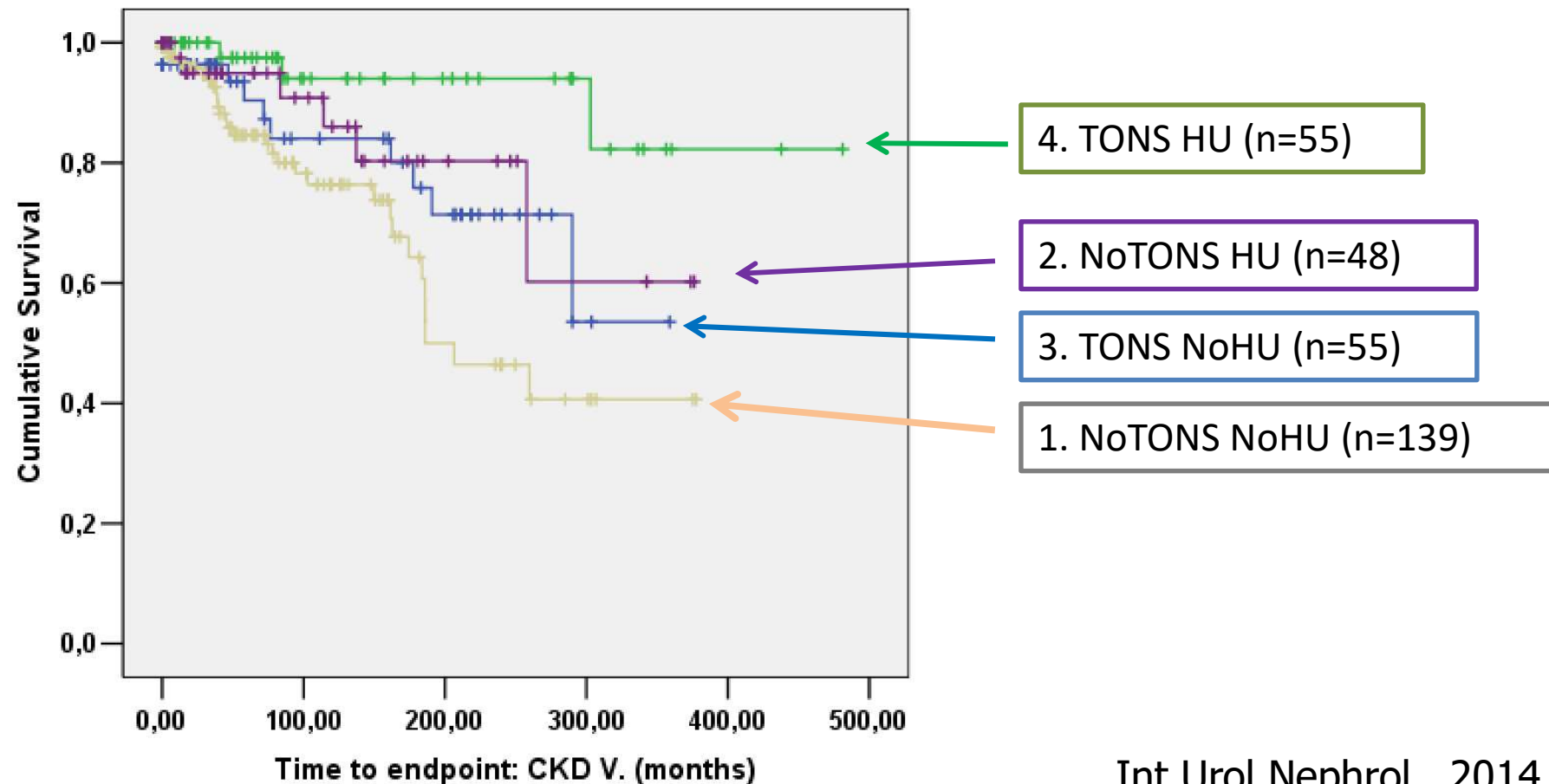
- **ACEI és(?)/vagy ARB**
- **Étrend: fehérjeszegény, sószegény, atherogén lipidszegény**
- **Testsúly normalizálása**
- **Lipidek normalizálására statinok sz.sz.**
- **Dohányzás abbahagyása**
- **Vérnyomás „szupernormalizálása”**
- **Egyéb: halolaj, tonsillectomia?**

# Vese túlélés IgA nephropathiában

(**Tonsillectomia a betegség kapcsán;** **Nem tonsillectomizált;**  
**Korábban tonsillectomizált csop.)** Kaplan-Meier teszt



# Renal survival rate by Kaplan-Meier test in the different IgAN groups



# Minimal change nephropathia

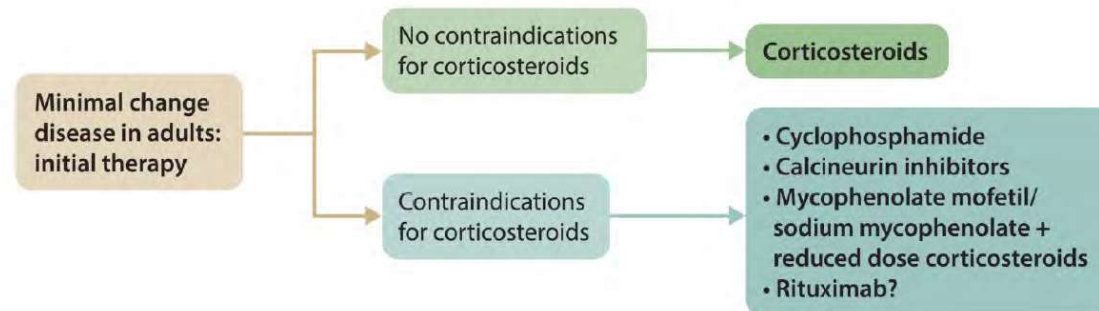
- Ok: ismeretlen (típusosan gyermekkorban)  
Secunder: gyógyszer (NSAID, interferon-a) allergia;  
tumor: Hodgkin kór, CLL, mycosis fungoides
- Pathogenesis: sejt közvetítette immunválasz zavara  
(limphokinek károsító hatása az epithelsejtekre?)
  - keringő permeabilitást fokozó faktorok
- Pathologia: EM: állábfúzió
- Klinikai kép: nephrosis sy (szelektív pu), normális vesefunkció



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

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

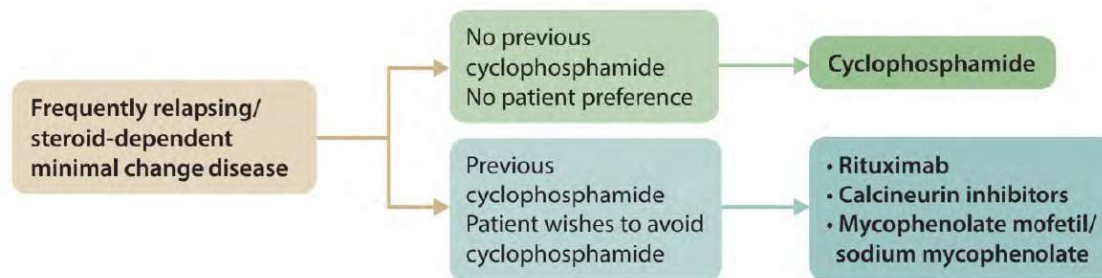
*Figure MCD1. Initial treatment of MCD in adults\**



\*The optimal corticosteroid regimen is not well-defined; however, suggested doses are outlined in Table MCD1

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

*Figure MCD2. Treatment of FR/SD MCD in adults*



**Practice Point 5.3.1.2.** Treat infrequent relapses with corticosteroids (Table MCD2).

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

# Idiopathic NS

Spectrum: from MCD to FSGS



80-90 % MCD



Non  
Relapsing

Infrequently  
Relapsing

Frequently  
Relapsing

Steroid  
Dependent

Steroid  
Resistant

**~90 % Steroid Sensitive - PROGNOSTIC**

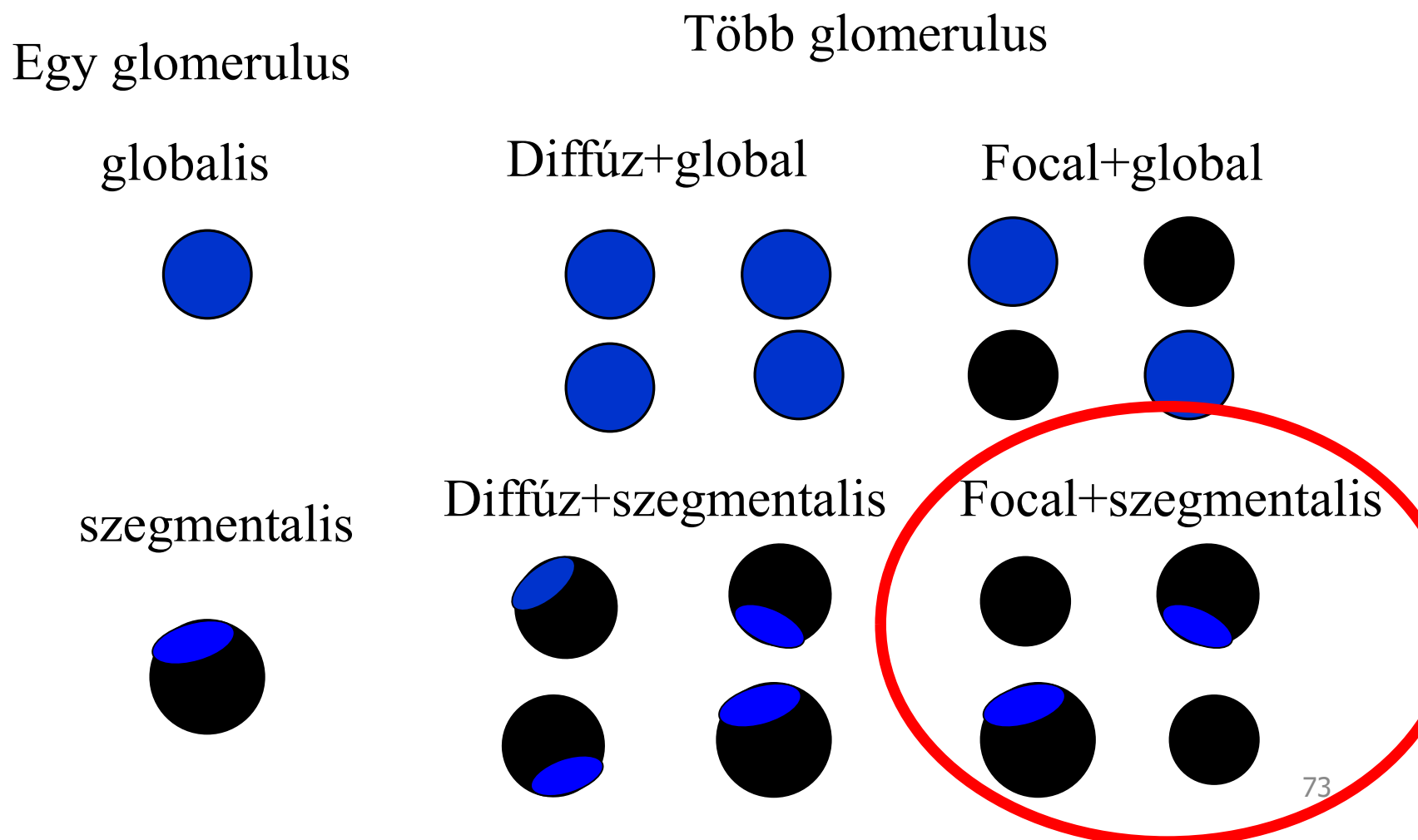
**Multiple aetiologies**

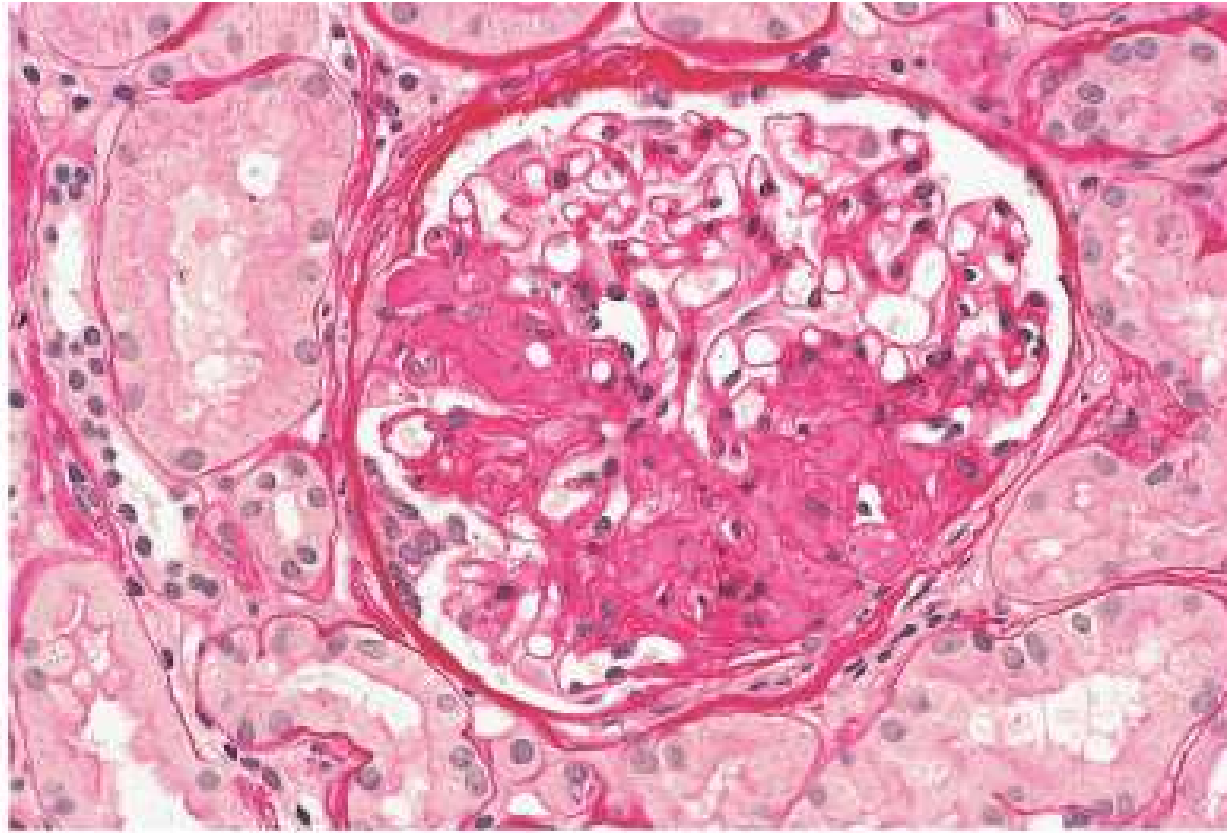
# Focalis segmentalis glomerulosclerosis (FSGS)

- FM: segmentalis capillaris obliteratio, mesangialis matrix felszaporodás
- IH: gócos IgM, C3
- Pathogenezis: keringő permeabilitást fokozó faktor(ok), hemodinamikai tényezők
  - Primer
  - Secunder: vírus: HIV, parvovirus B19); gyógyszer (heroin); csökkent nephron szám (koraszülöttek, CAN); normál nephron szám (HT, obezitás); VUR
- Klinikai kép: nephrosis sy (esetleg HU is!) + HT
- Prognózis: rossz (esetek 1/3-a 3-10 év után ESRD)

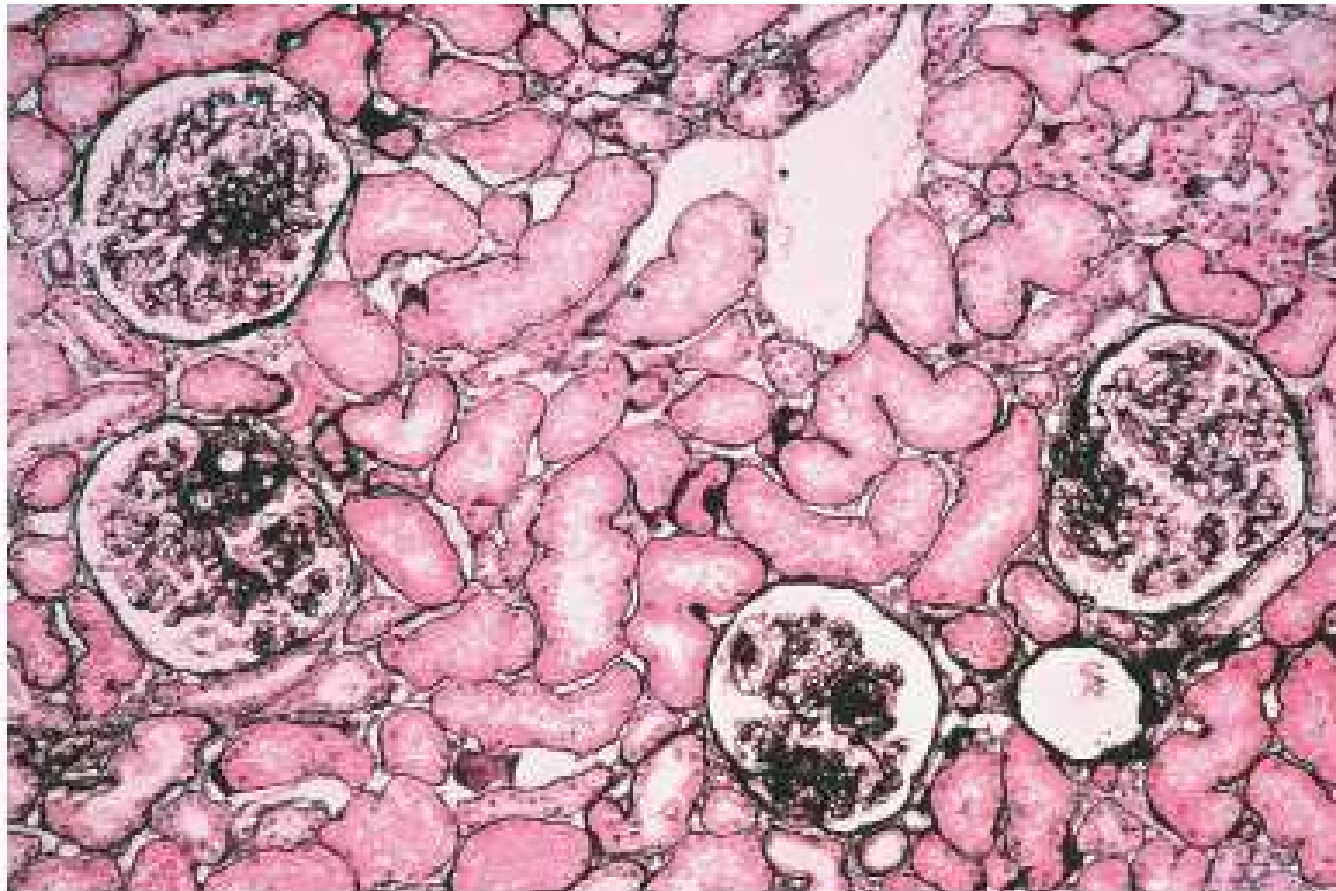
# Szöveti elváltozások a vesében

## a. glomerulus





**Figure 18.4 Focal segmental glomerulosclerosis not otherwise specified.** The lesions of segmental sclerosis display increased extracellular matrix and hyalinosis. There is adhesion to Bowman's capsule without significant podocyte hypertrophy. The nonsclerotic capillaries have glomerular basement membranes of normal thickness and mild podocyte swelling (periodic acid–Schiff; magnification  $\times 400$ ).



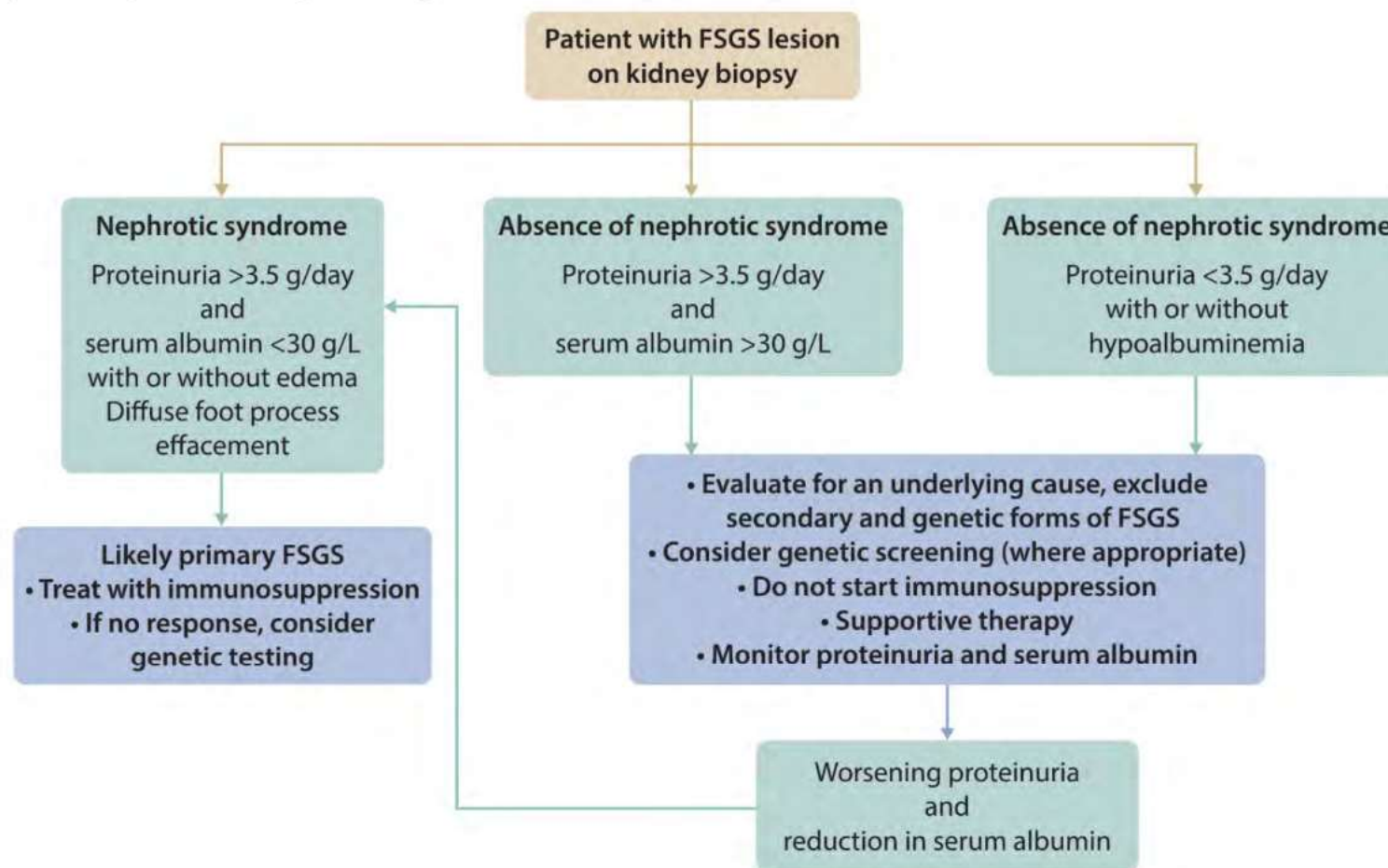
**Figure 18.3 Focal segmental glomerulosclerosis not otherwise specified.** A low-power view shows four glomeruli with discrete lesions of segmental sclerosis involving a portion of the tuft. The adjacent nonsclerotic capillaries are unremarkable. In this example, there is no evidence of tubulointerstitial injury (Jones methenamine silver; magnification  $\times 100$ ).



# FSGS-ben progresszióra hajlamosító tényezők

- **Klinikai jelek a biopsziakor:**
  - Nephrosis vagy masszív proteinuria
  - Csökkent GFR
  - Fekete rassz
- **Szövettani jelek:**
  - Collapsing variáns
  - Tubulointerstitialis fibrosis
- **Klinikai jelek a követés során:**
  - Partialis vagy komplett remisszió hiánya

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



FSGS, focal segmental glomerulosclerosis

## Therapeutic Options in FSGS

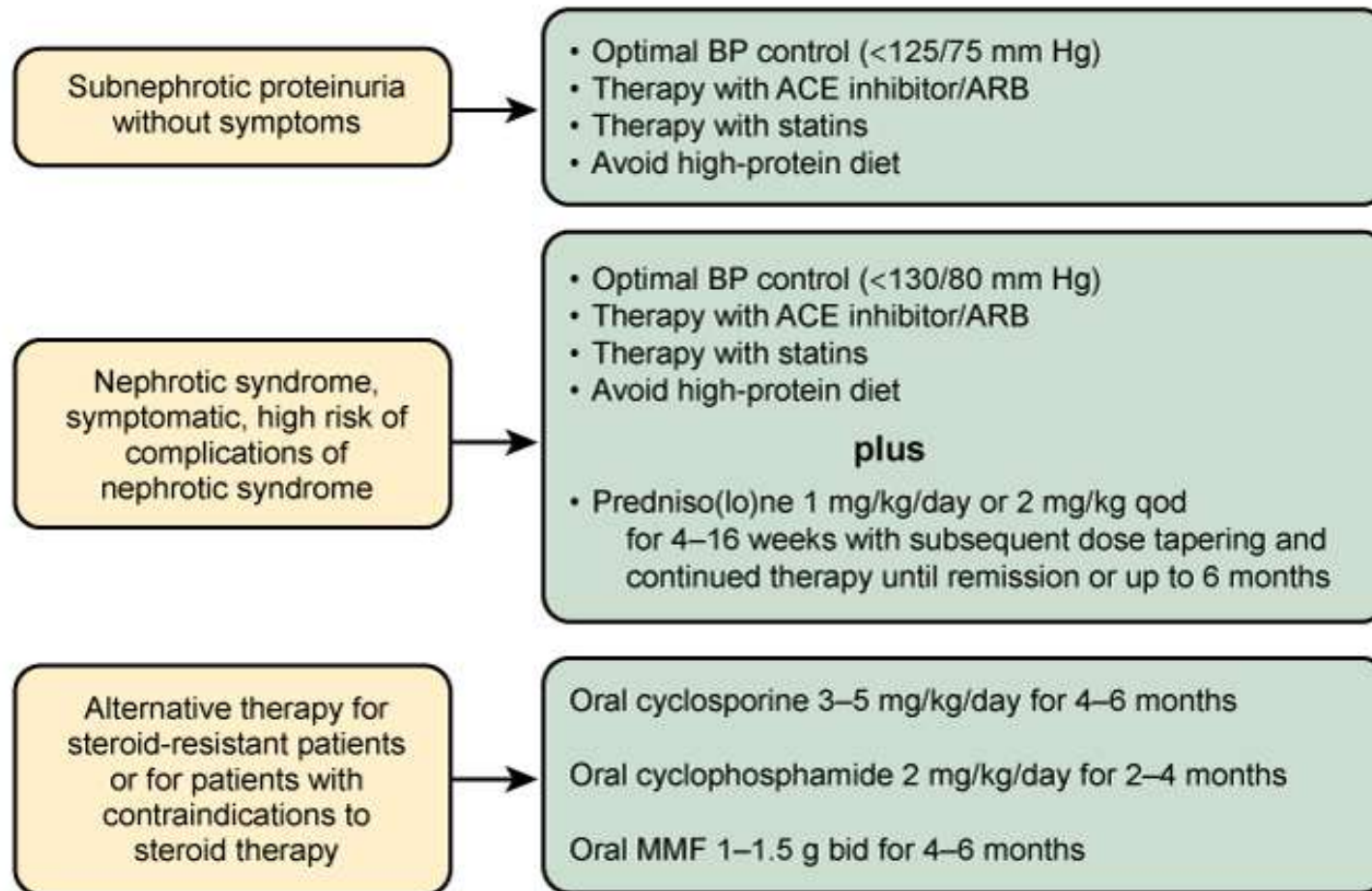


Fig. 18-19. **Therapeutic options in focal segmental glomerulosclerosis.** Treatment of secondary FSGS should be directed at the underlying cause whenever possible. For HIV-associated nephropathy, treatment with highly active antiretroviral therapy (HAART); for pamidronate nephrotoxicity, discontinue the medication; and for obesity-related glomerulopathy, weight loss. ACE, Angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; MMF, mycophenolate.

**? Biológiai terápia: vizsgálatok Abatacept (CD80), Ofatumumab (CD20)  
Fresolimumab (anti TGF- $\beta$ )**

# Membranosus glomerulonephritis

- **Dg:** FM ezüst festéssel megvastagodott glomeruláris kapilláris fal
- IF: granularis IgG és C3 EM: subepithelialis depositumok

**Klinikai kép:** felnőtt korban, idősekben  
nephrosis sy (25%-ban nincs!)

HT: 20-40%

vesevéna thrombózis: 20-30%

**Prognózis:** jó, spontán remisszió is gyakori (kb 30%)

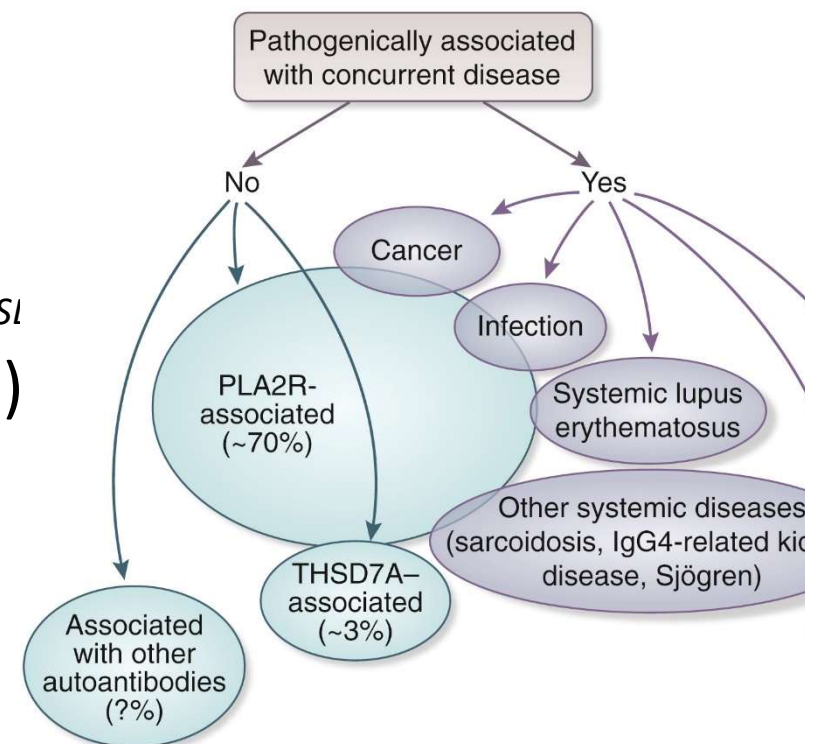
# Membranous glomerulonephritis etiológiája

- **Primer (75%)**

- Foszfolipáz A2 receptor ellenes AT – *PLA2R*  
(podocytákon, subepitheliális IC-ben)
- ~~Thrombospondin type 1 domain containing 7A ell.  
AT *THSD7A*~~

- **Secunder (25%)**

- Immunbetegségek (SLE, RA)
- Vírus fertőzések (Hepatitis B, C, )
- Tumorok (tüdő, prostata, hematológiai, colo-rectalis)
- Thrombospondin type 1 domain containing 7A ell. AT *THSD7A*
- Gyógyszer indukálta (arany, penicilamin, NSAID, captopril)





# Phospholipase A<sub>2</sub> receptor

**Role in:  
Eicosanoids,  
Reactive oxygen species productions  
& DNA damage**

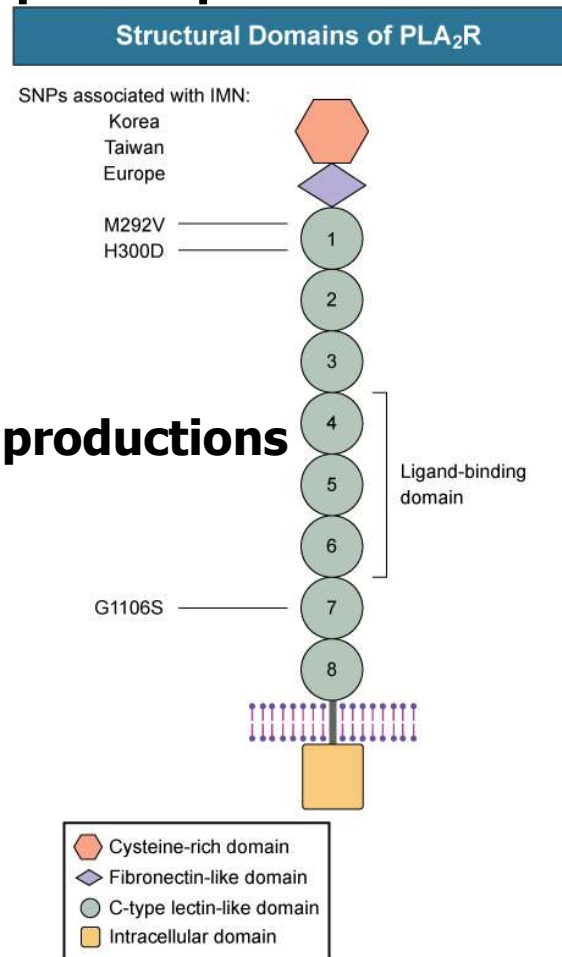


Fig. 20-3. **Structural domains of phospholipase A<sub>2</sub> receptor (PLA<sub>2</sub>R).** The M-type phospholipase A<sub>2</sub> receptor is a transmembrane protein and receptor for secretory PLA<sub>2</sub> (CTLD5). The N-terminal region from the cysteine-rich domain through CTLD4 of other members of the mannose receptor family is known to exist in extended or folded configurations. PLA<sub>2</sub>R is involved in the production of eicosanoids, reactive oxygen species, DNA damage and cellular senescence. Its role in podocytes is unknown. *SNPs*, Single-nucleotide polymorphisms.

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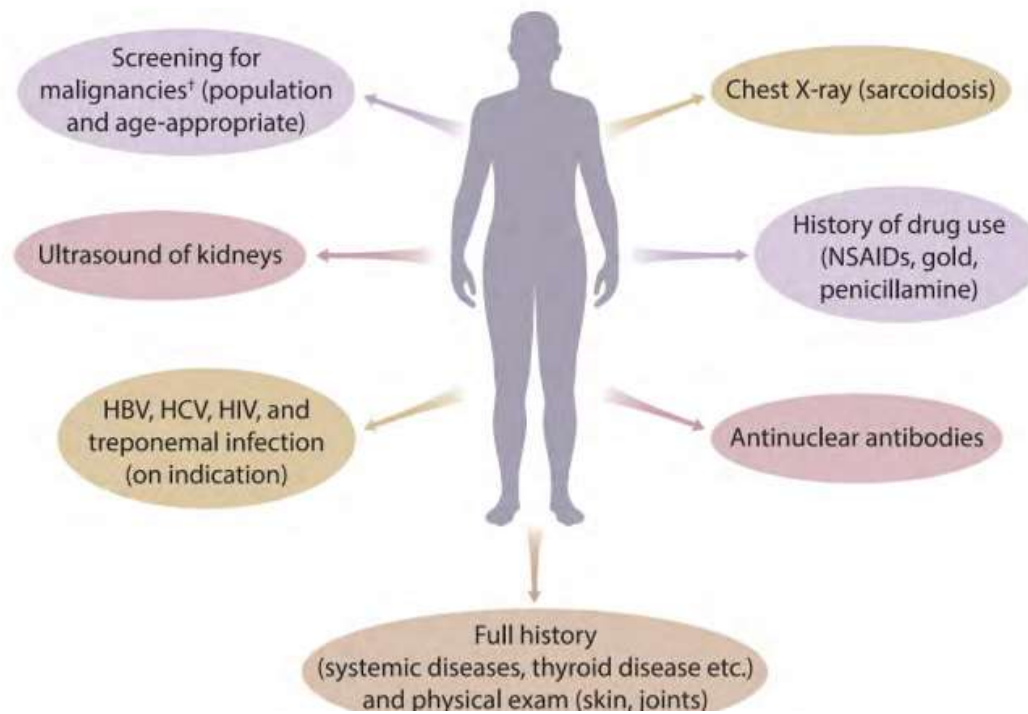
## CHAPTER 3. MEMBRANOUS NEPHROPATHY

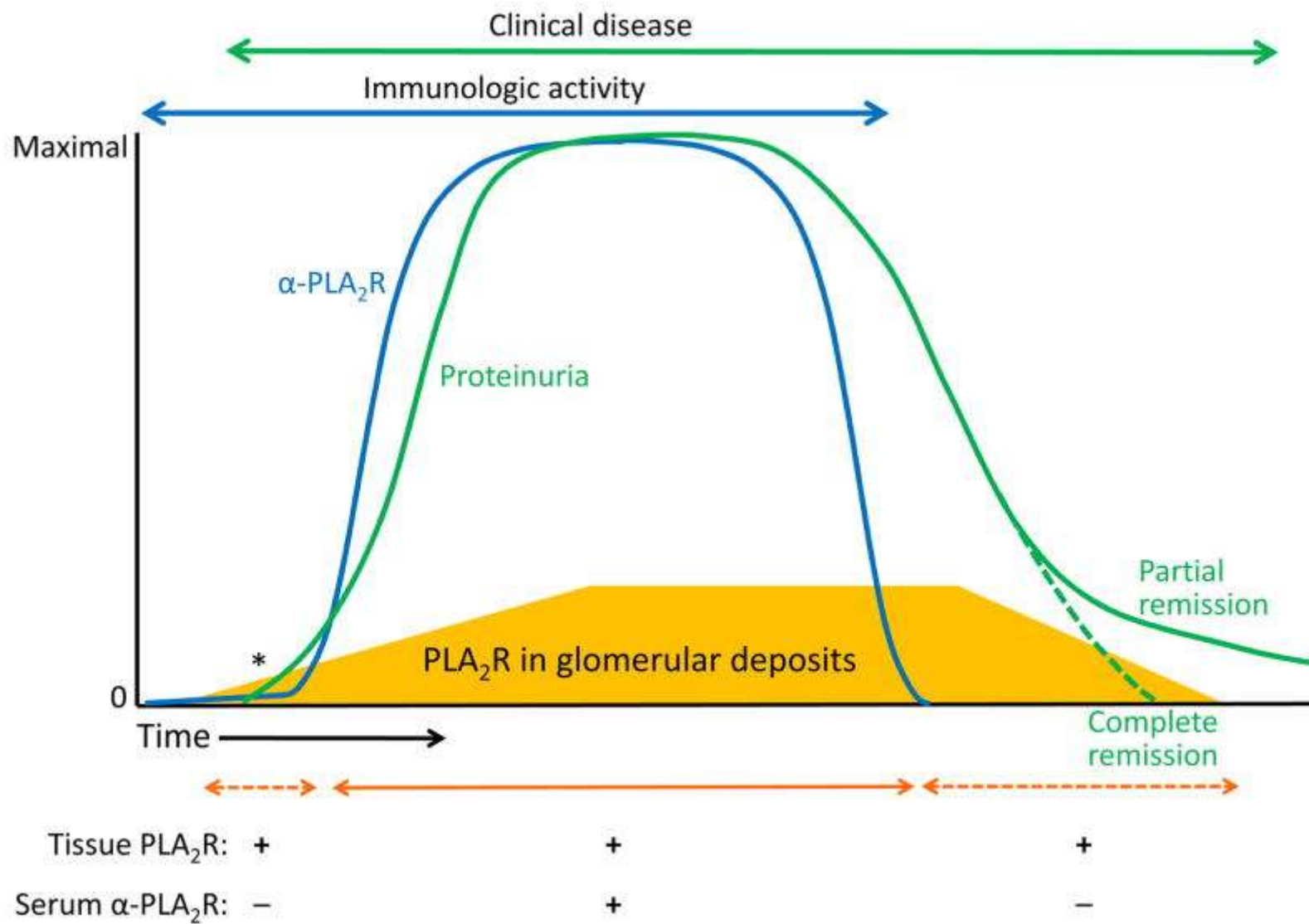
### 3.1. Diagnosis

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

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

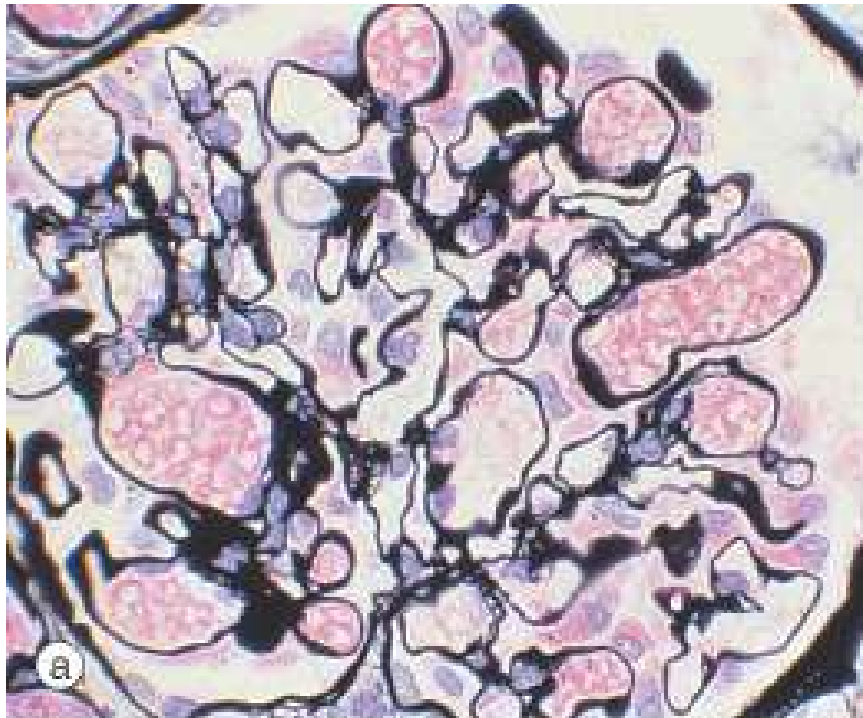
*Figure MN3. Evaluation of patients with MN for associated conditions\**



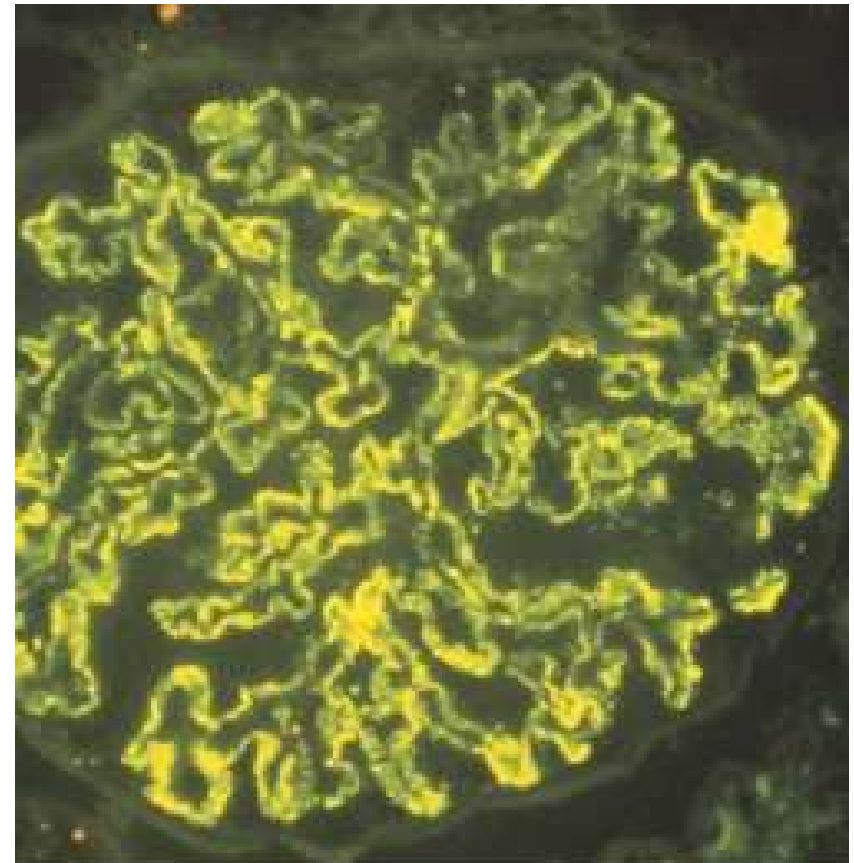


# Membranous GN

(ezüst ill. immunhisztologia)



**Figure 19.5A** Light microscopy in membranous nephropathy (MN). *a*, Early MN: a glomerulus from a patient with severe nephrotic syndrome and early MN, exhibiting normal architecture and peripheral capillary basement membranes of normal thickness (methenamine silver  $\times 400$ ). *b*, Morphologically advanced MN: uniform increase in the thickness of the

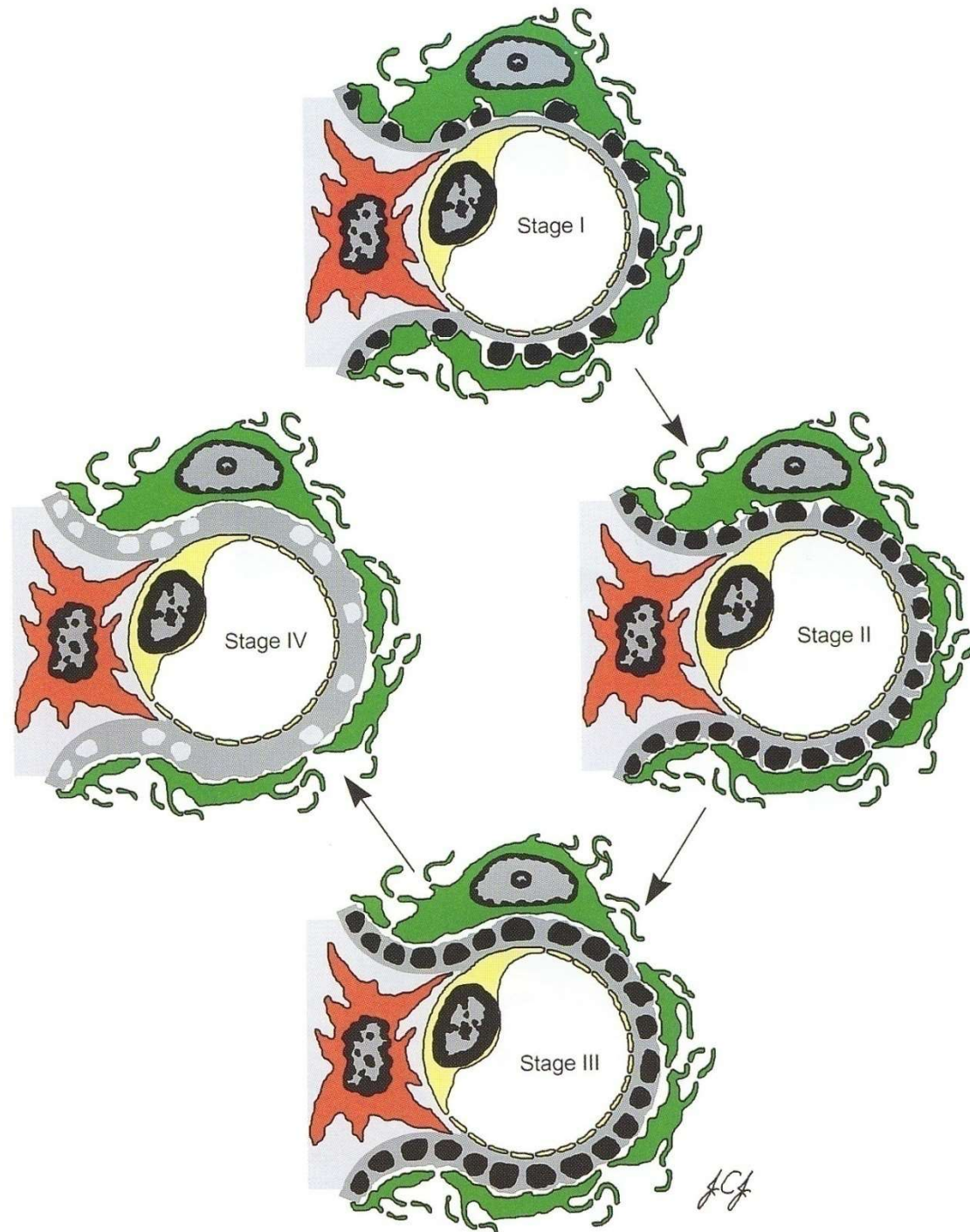


**Figure 19.6** Immunofluorescence in membranous nephropathy. A glomerulus with diffuse, finely granular deposition of IgG along the outer surface

# Pathogenesis

- Exogen ag (kisméretű, kation) - in situ IC képződés
- Ag-At IC komplex disszociál a GBM-n átjutva ismét egymáshoz kötődik





## **Membranous nephropathia terápiája I.**

### **Nondisease-specific therapy: in all patients**

Blood pressure control (130/85mmHg): sodium restriction; drug therapy, angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers preferred

Reduction in lipid levels

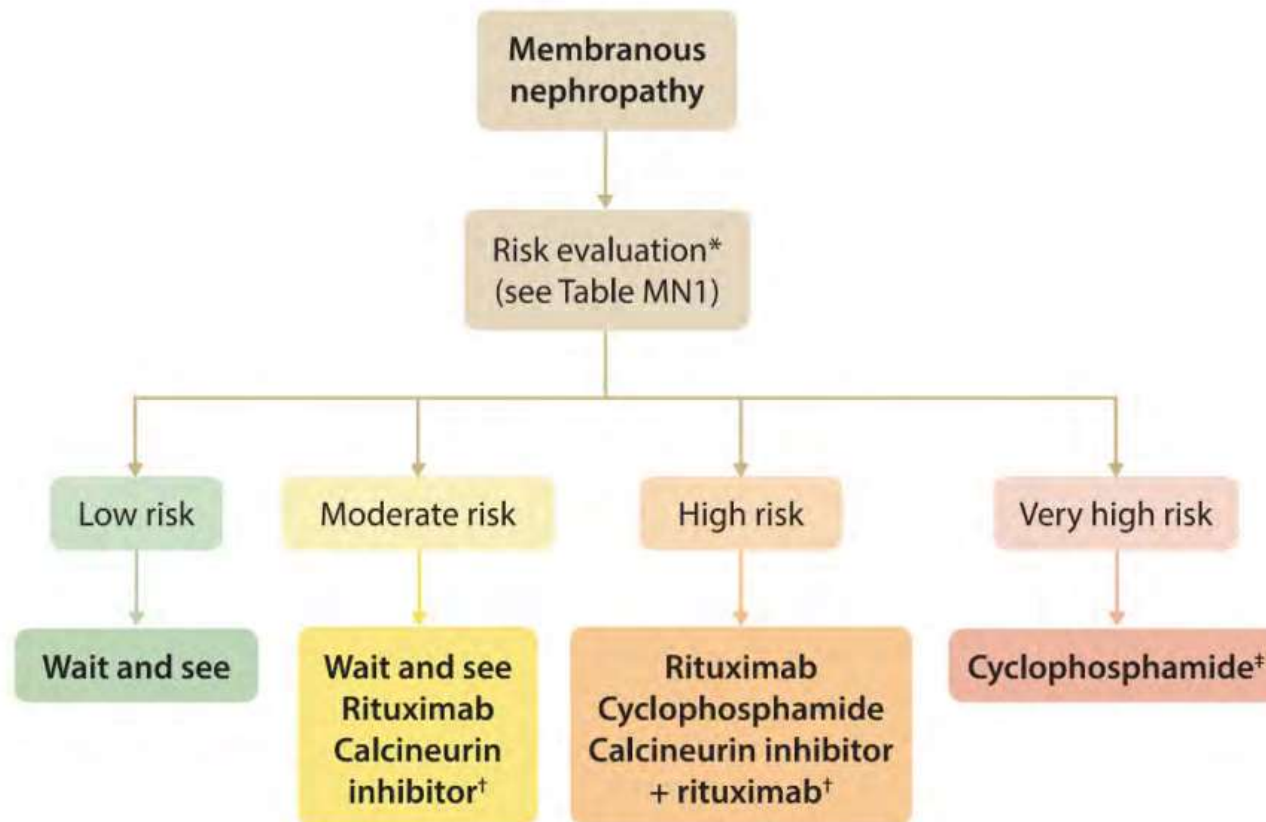
Reduction in urine protein excretion

Dietary protein restriction (0.8g/kg daily): ACE inhibitors or angiotensin II receptor blockers, nonsteroidal anti-inflammatory agents (selected patients), anticoagulation (selected patients)

### **Disease-specific therapy: in selected patients**

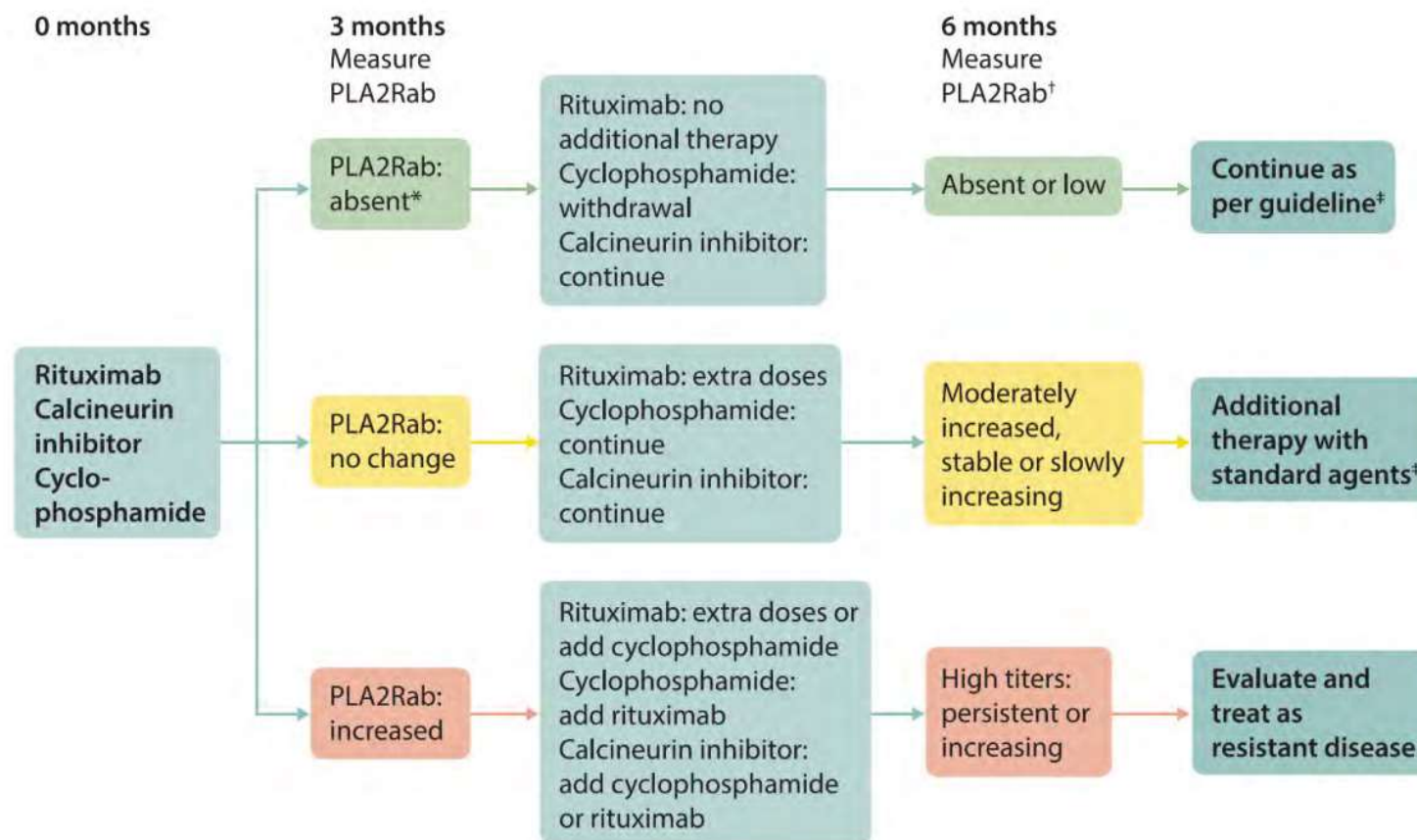


## Membranous nephropathia terápiája II.



Low risk	Moderate risk	High risk	Very high risk
<ul style="list-style-type: none"> <li>• Normal eGFR, proteinuria &lt;3.5 g/d and/or serum albumin &gt;30 g/L</li> </ul>	<ul style="list-style-type: none"> <li>• Normal eGFR, proteinuria &gt;4 g/d and no decrease &gt;50% after 6 months of conservative therapy with ACEi/ARB</li> <li>• PLA2Rab &lt;50 RU/ml<sup>†</sup></li> <li>• Mild low molecular weight proteinuria</li> <li>• Selectivity index &lt;0.15</li> <li>• U IgG &lt;250 mg/d</li> </ul>	<ul style="list-style-type: none"> <li>• eGFR &lt;60 ml/min/1.73m<sup>2*</sup></li> <li>• Proteinuria &gt;8 g/d for &gt;6 months</li> <li>• PLA2Rab &gt;150 RU/ml<sup>†</sup></li> <li>• High low molecular weight proteinuria</li> <li>• U IgG &gt;250 mg/d</li> <li>• Selectivity index &gt;0.20</li> </ul>	<ul style="list-style-type: none"> <li>• Life-threatening nephrotic syndrome</li> <li>• Rapid deterioration of kidney function not otherwise explained</li> <li>• High low molecular weight proteinuria in two urine samples collected with interval of 6–12 months</li> </ul>

## Antibody-guided diagnosis and treatment algorithm for primary membranous nephropathy (PMN).



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

\*A large decrease in PLA2Rab levels may indicate a good clinical response. Although there are no defined cut-off values,

## **Gyors progressziójú ("félholdas") GN**

### **Rapidan progresszív GN (RPGN)**

**Gyorsan kialakuló nephritis sy. képe, ami kezelés nélkül, hetek-hónapok alatt veseelégtelenségbe torkollik.**

**Dg. csak vesebiopsziával ?? !!**

#### **Etiológia:**

**1) idiopathiás**

**2) szekunder**

**vírusos és bact. infekciók**

**szénhidrogén belégzés**

**szisztémás betegségek: SLE stb.**



## **Pathológia:**

## **Gyakoriság**

**FM: glom. >50%-ában félholdak**

**IH: I. típus: anti-GBM At - linearis IgG + C3**

**5 - 20%**

**II. típus: IC - granulált Ig + C3**

**25 - 45%**

**III. típus: IC és anti- GBM At negatív**

**= ANCA pozitív vasculitisek**

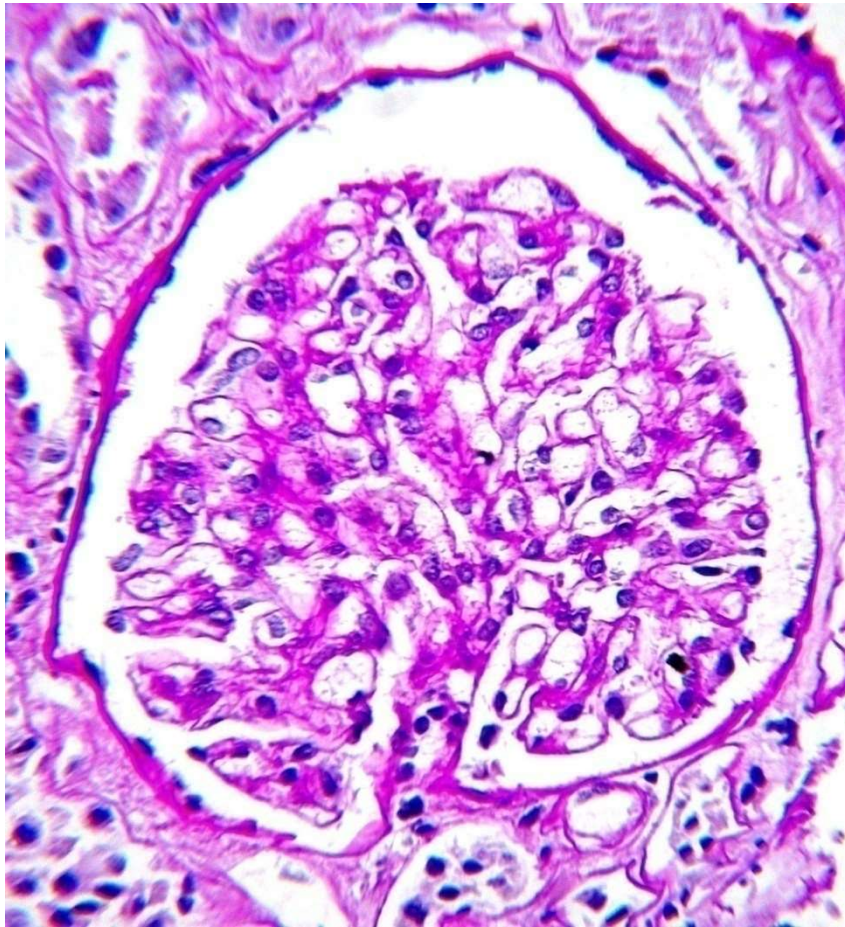
**34 - 65%**

**fibrin a Bowmann Üregben mindhárom típusban**

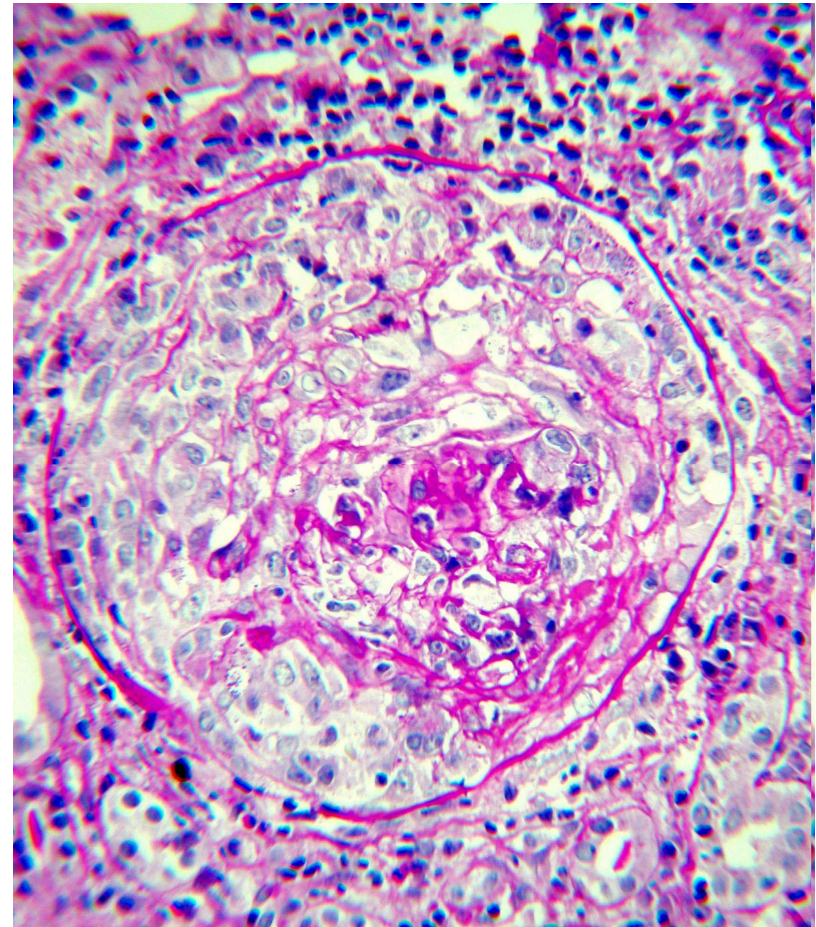
**EM: GBM rupturak**

**IC = immun complex, At = antitest**

Normál glomerulus

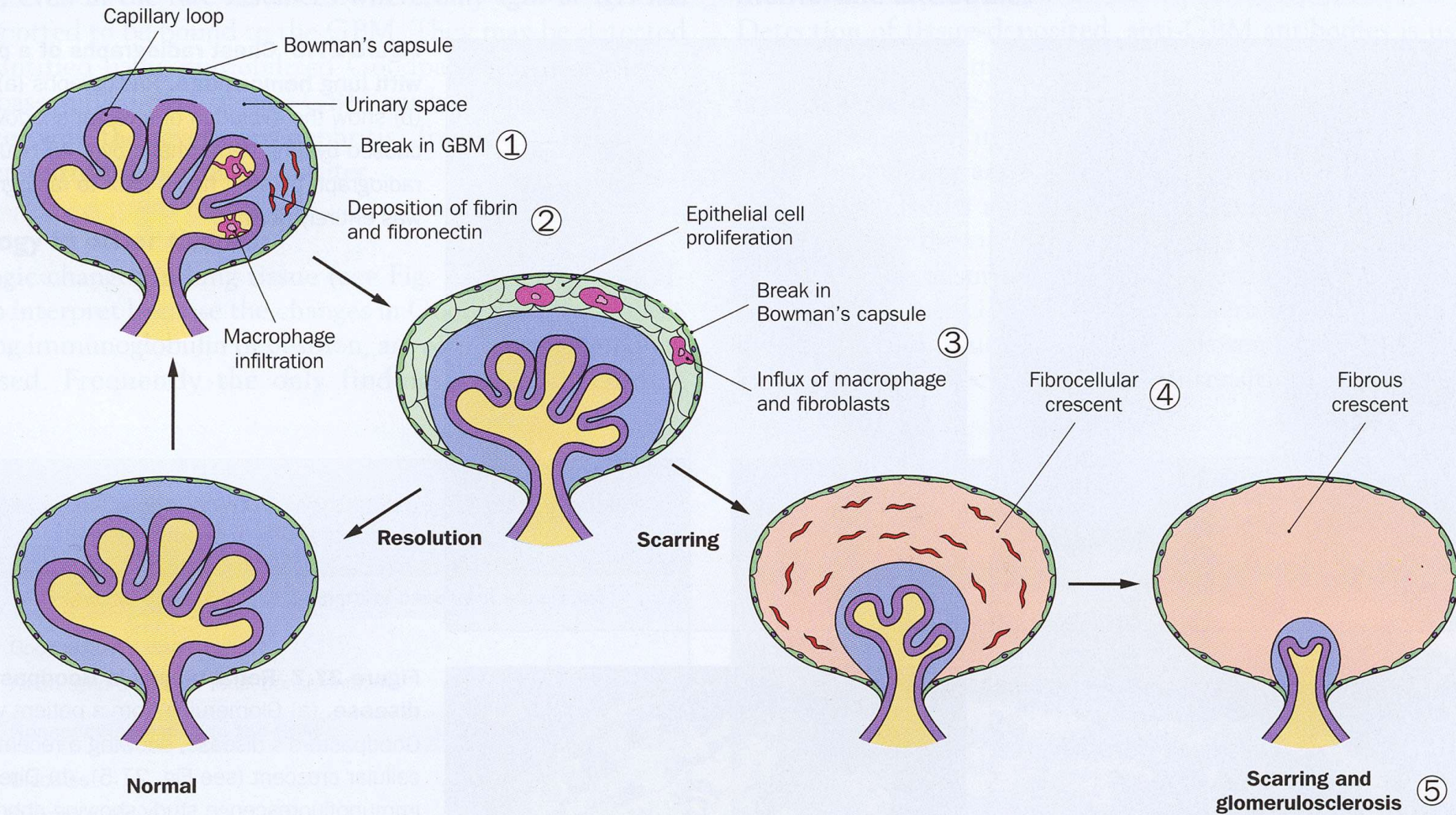


Félholdas glomerulus (RPGN)





## Crescent formation



**Figure 27.5 Crescent formation.** Following fractures and perforations of the glomerular basement membrane [GBM] (1), deposition of fibrin and serum proteins (2) stimulates proliferation of epithelial cells to form a cellular crescent. Macrophages contribute to this to a variable degree; this may in part depend on whether the disease process also causes perforations of Bowman's capsule (3). Such perforations also permit influx of fibroblasts, and this may influence whether or not there is resolution of the crescent, or formation of fibrocellular crescents (4) and glomerulosclerosis (5). In experimental models crescent formation can be inhibited by defibrination or anticoagulation, although these have not so far proved to be practical therapies in man. Formation of crescents is also T-lymphocyte dependent, and is blocked by T cell depletion or by inhibition of their activation. It is not clear whether this effect is mediated through reduction of initial tissue damage (and thus of GBM or Bowman's capsule fractures) or by inhibition of some secondary step.

## **Pathológia:**

## **Gyakoriság**

**FM: glom. >50%-ában félholdak**

**IH: I. típus: anti-GBM At - linearis IgG + C3**

**5 - 20%**

**II. típus: IC - granulált Ig + C3**

**25 - 45%**

**III. típus: IC és anti- GBM At negatív**

**= ANCA pozitív vasculitisek**

**34 - 65%**

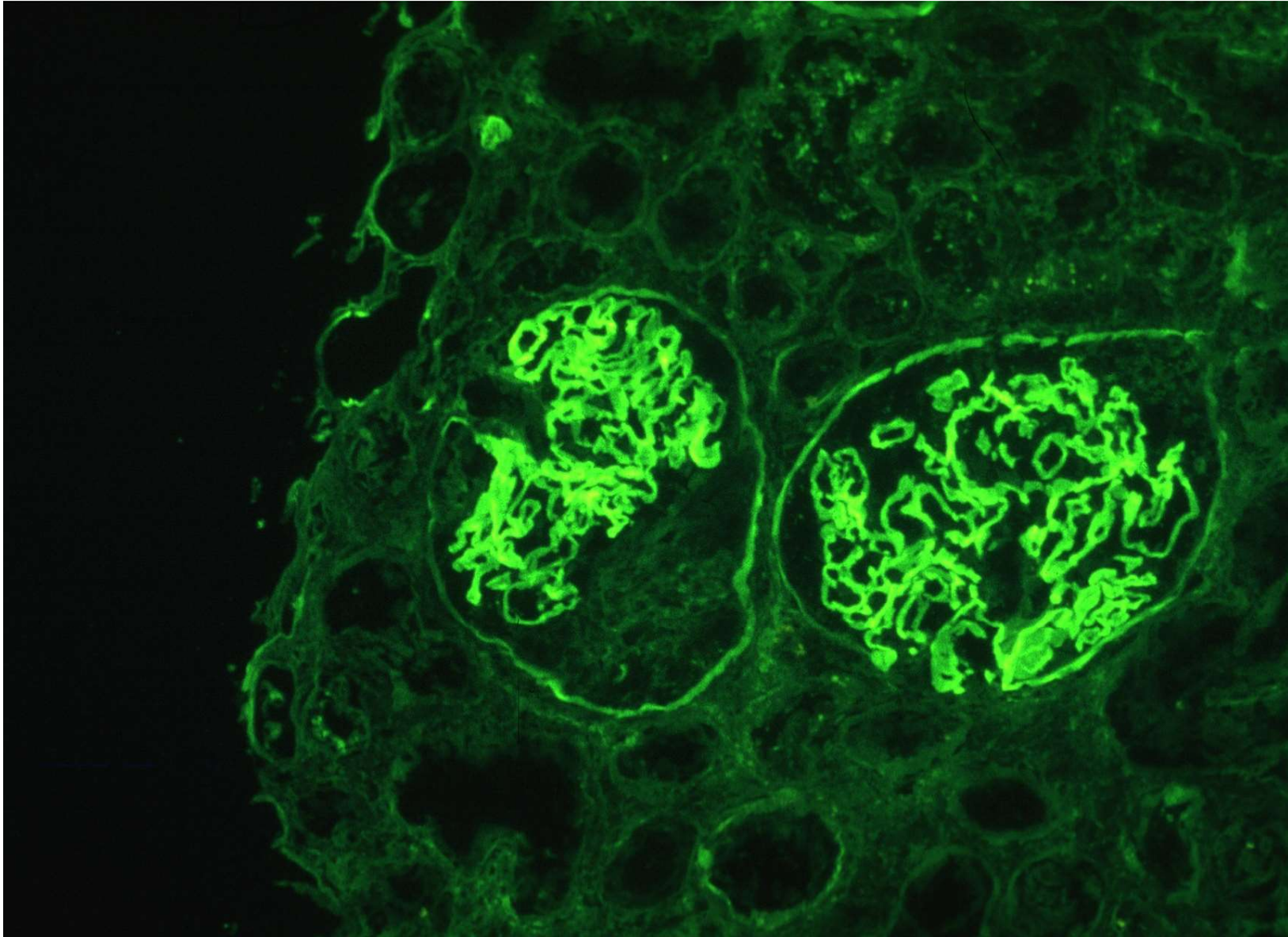
**fibrin a Bowmann Üregben mindhárom típusban**

**EM: GBM rupturak**

**IC = immun complex, At = antitest**



# **I. típus: Anti GBM antitest betegség**





## Common glomerular diseases presenting as rapidly progressive glomerulonephritis

Disease	Association	Serologic tests helpful in diagnosis
Goodpasture's disease	Lung hemorrhage	Antiglomerular basement membrane (anti-GBM) antibody [occasionally antineutrophil cytoplasmic antibodies (ANCA) present]
Vasculitis		
Wegener's granulomatosis	Upper and lower respiratory involvement	cANCA (cytoplasmic)
Microscopic polyangiitis	Multisystem involvement	pANCA (perinuclear)
Pauci-immune crescentic glomerulonephritis	Renal involvement only	pANCA
'Immune complex'		
Systemic lupus	Other multisystem features of lupus	Antinuclear antibody, anti-doublestranded DNA antibody, C3 ↓, C4 ↓
Poststreptococcal glomerulonephritis	Pharyngitis, impetigo	Asotiter, streptozyme antibody, C3 ↓, C4 normal
IgA nephropathy/ Henoch-Schönlein purpura (HSP)	Characteristic rash ± abdominal pain in HSP	Serum IgA ↑ (30%), C3 and C4 normal
Endocarditis	Cardiac murmur; other systemic features of bacteremia	Blood cultures, ANCA (occasionally), C3 ↓, C4 normal

# **Klinikai tünetek:**

- bizonytalan kezdet, vírus infekció ált. tünetei  
(myalgia, arthralgia stb.)
- uraemia tünetei (gyengeség, hányinger, anaemia, olygo-anuria)
- gyorsan romló általános állapot!

# Laboratóriumi vizsgálatok:

1. szérum: creat<sup>↑</sup> K<sup>↑</sup> anaemia

I. típusban: anti-GBM At

II. típusban: complement ↓

III. típusban: ANCA

2. vizeletben: vvt, fehérje

3. vesefunkció: creat clear ↓

UH: mko. nagyobb vesék

# Terápia I.

- Aggresszív terapia **javasolt**:
  - se-creat <600  $\mu\text{mol/l}$
  - ANCA pozitív
  - tüdővérzés
  - döntően friss sejtes crescentek
- Aggresszív terapia **NEM javasolt**:
  - se-creat >600  $\mu\text{mol/l}$
  - oliguria
  - fibrotikus crescentek
  - ISU kezelés kockázatos

# Terápia II.

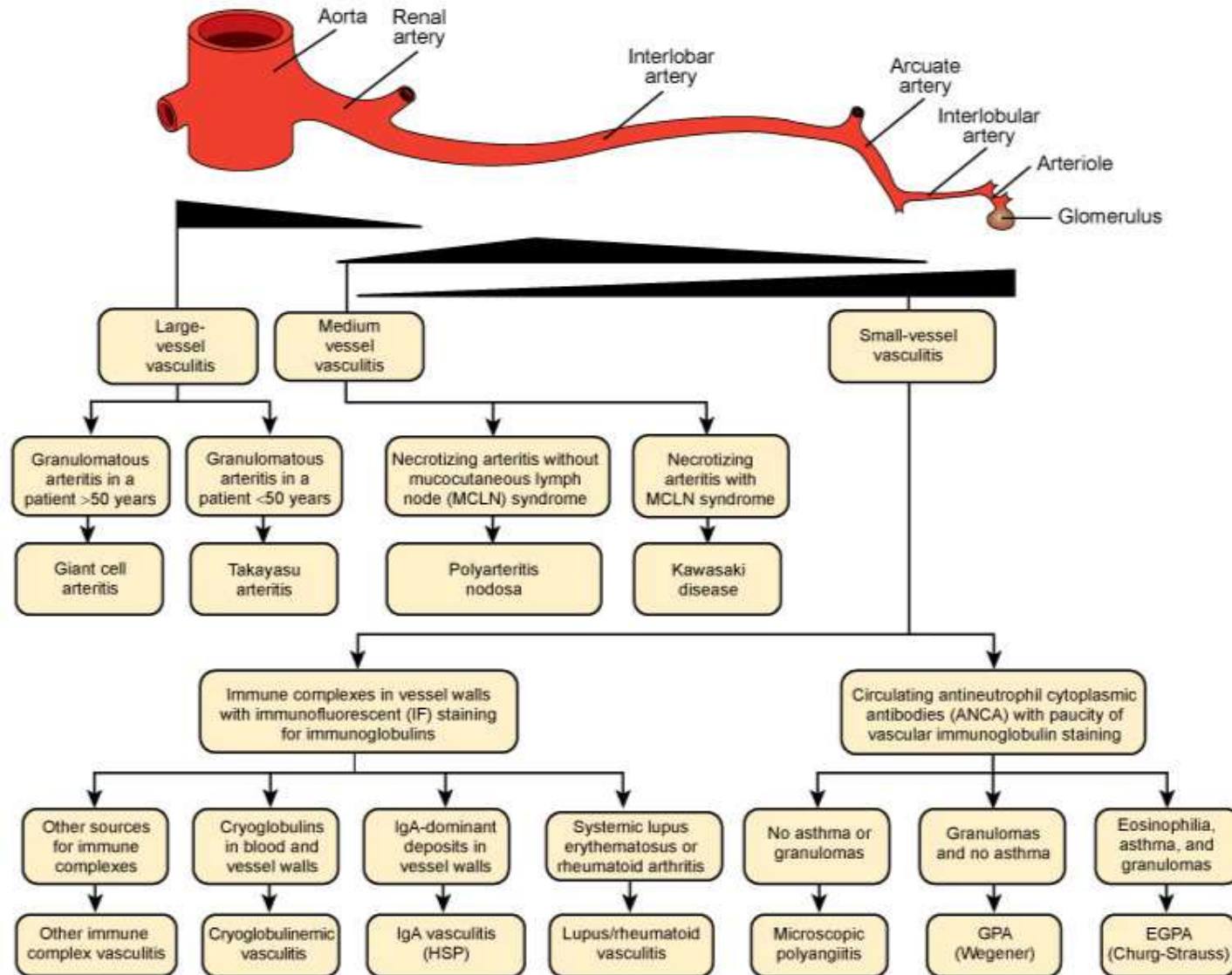
- **steroid** (metylprednisolon lökés th., 1 gr/nap másnaponta, 3x, utána per os 1 mg/kg/nap)
- **immunsuppressio** (Cyclophosphamid 10 mg/kg infúzióban 1x havonta, összesen 6x  
vagy per os 2-3 mg/kg/nap)
- **plasmapheresis** (elsősorban I. típusban 8-14 alkalommal, naponta, de III. típusban is)
- **anticoagulálás szóba jöhet**
- **haemodialysis**
- **transzplantáció**  
anti-GBM antitestet monitorozzuk előtte



# Autoimmun kórképek vesemanifestációi

- Gyors progressziójú glomerulonephritisek
- **Vasculitisek renalis manifestatioi**
- Lupus nephritis
- Collagén betegségek veseszövődményei

## Renal Vascular Involvement in Vasculitides



Modified from reference 3.

Fig. 25-1. **Renal vasculitis.** Predominant distribution of renal vascular involvement by a variety of vasculitides. The heights of the trapezoids represent the relative frequency of involvement of different portions of the renal vasculature by the three major categories of vasculitis. *EGPA*, Eosinophilic granulomatous polyangiitis; *GPA*, granulomatous polyangiitis; *HSP*, Henoch-Schönlein purpura.

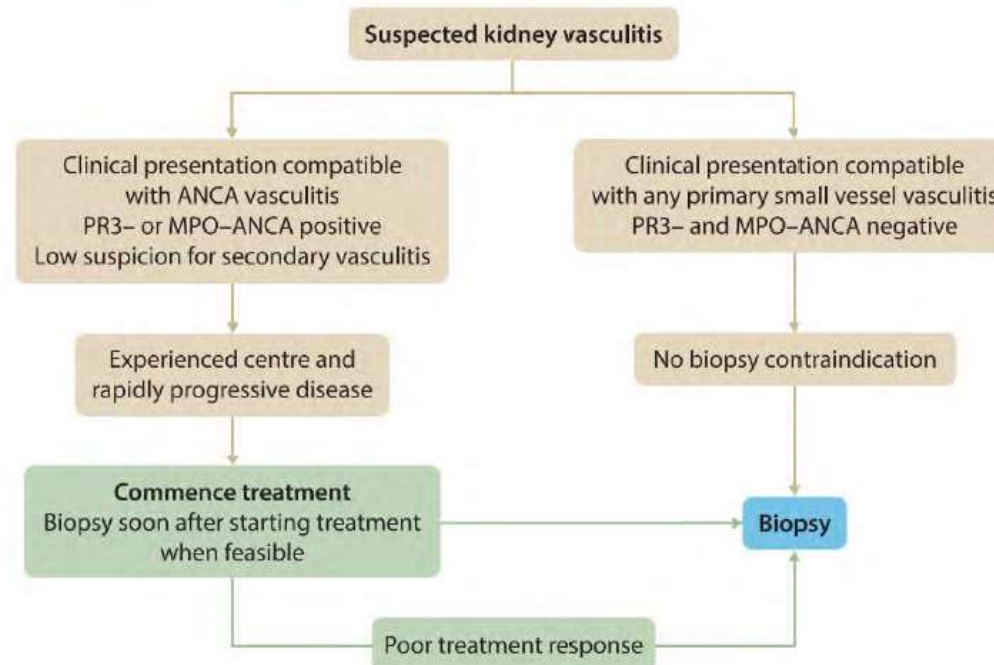
# ANCA asszociált vasculitisek (AAV) csoportjába tartozó kórképek:

- GPA (granulomatosis polyangitis; Wegener granulomatosis)
- MPA (mikroszkópikus polyangitis)
- EGPA (eosinophil granulomatosis polyangitis; Churg-Strauss syndrome)

### **9.1. Diagnosis**

**Practice Point 9.1.1.** In case of a clinical presentation compatible with small-vessel vasculitis in combination with positive MPO- or PR3-ANCA serology, waiting for a kidney biopsy to be performed or reported should not delay starting immunosuppressive therapy, especially in patients who are rapidly deteriorating (Figure ANCA1).

*Figure ANCA1. Biopsy strategy in suspected kidney vasculitis*



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

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

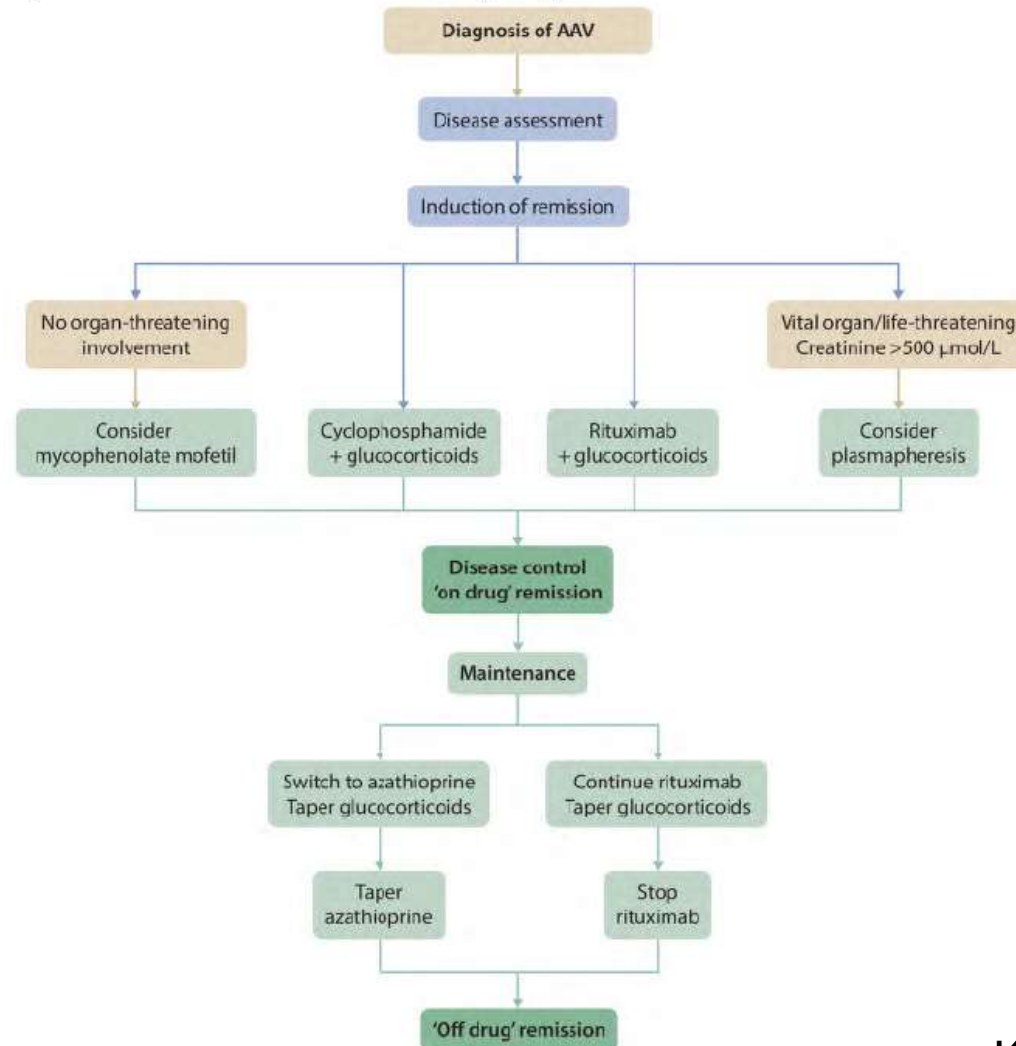
### 9.3. Treatment

#### 9.3.1. Induction

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

**Practice Point 9.3.1.1.** A recommended treatment algorithm for AAV is given in Figure ANCA4.

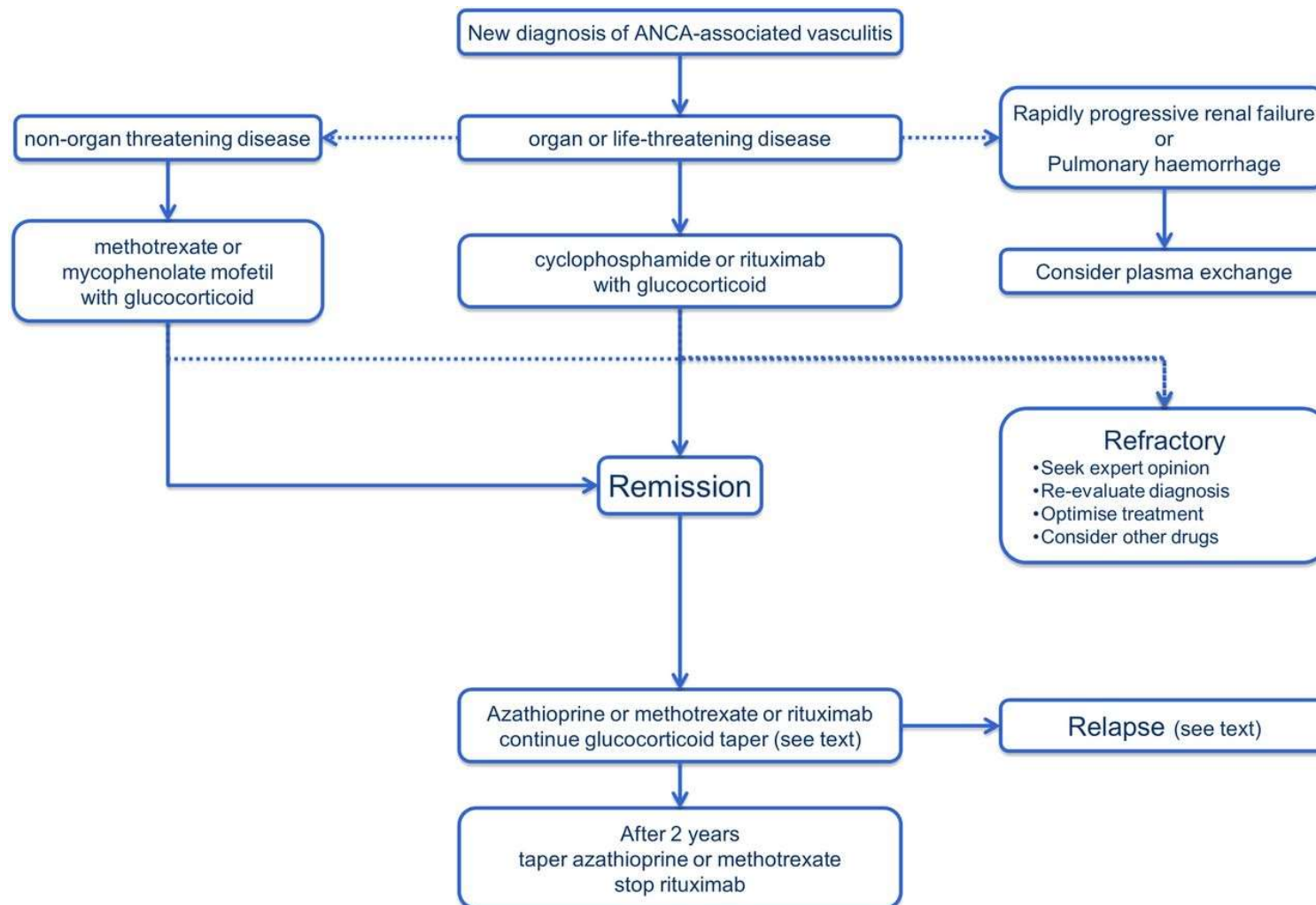
Figure ANCA4. Recommended treatment regimen for AAV





# Összefoglalás

## ANCA asszociált vasculitis kezelésének



M Yates et al. Ann Rheum Dis doi:10.1136/annrheumdis-2016-209133

# EULAR ajánlás

## Rituximab vs. cyclophosphamid

- Non-inferior
  - Rituximab/iv. CPH vs iv. CPH/AZA
  - Rituximab vs. p.o. CPH
    - Relapsusokban hatékonyabb volt a rituximab
    - Kevesebb lesz a kumulatív CPH dózis
- Rituximab lehetséges előnye
  - Nem okoz infertilitást vs. CPH
- CPH refrakter esetben váltsunk Rituximabra
- Rituximab refrakter esetben váltsunk CPH-ra

Köszönöm a megtisztelő figyelmet!

