Focal & Segmental Glomerulo-Sclerosis

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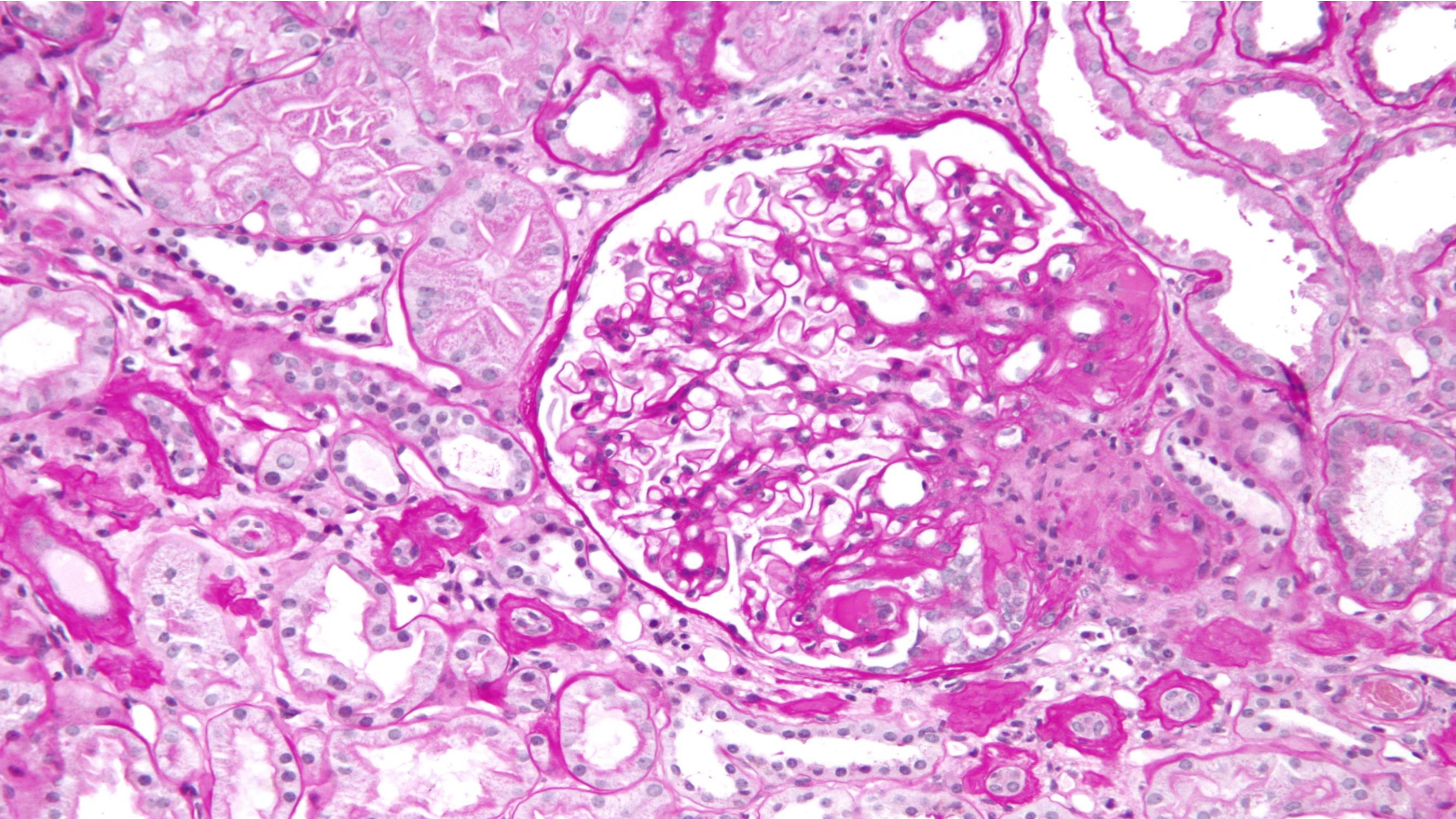
SBUMS

2019

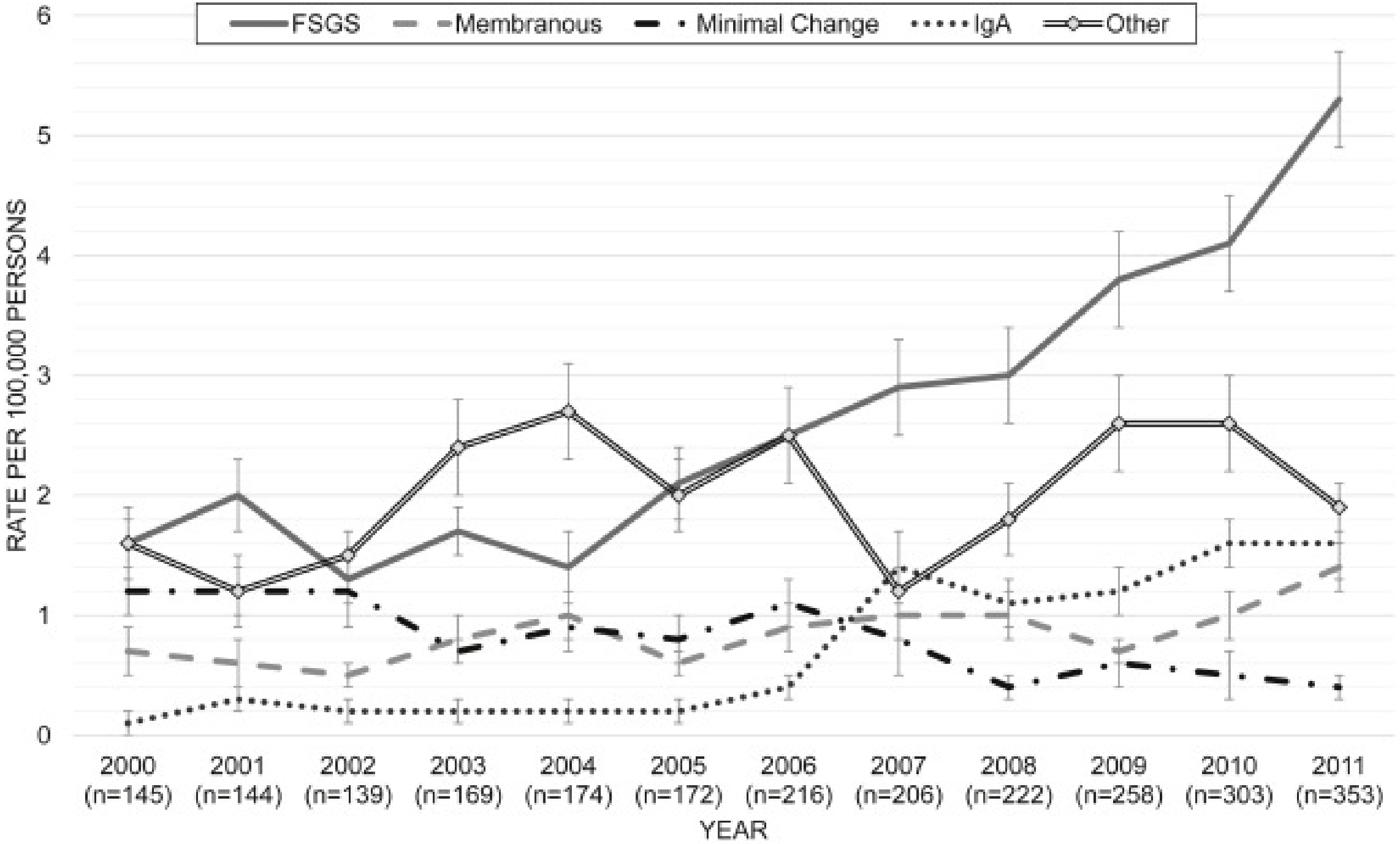


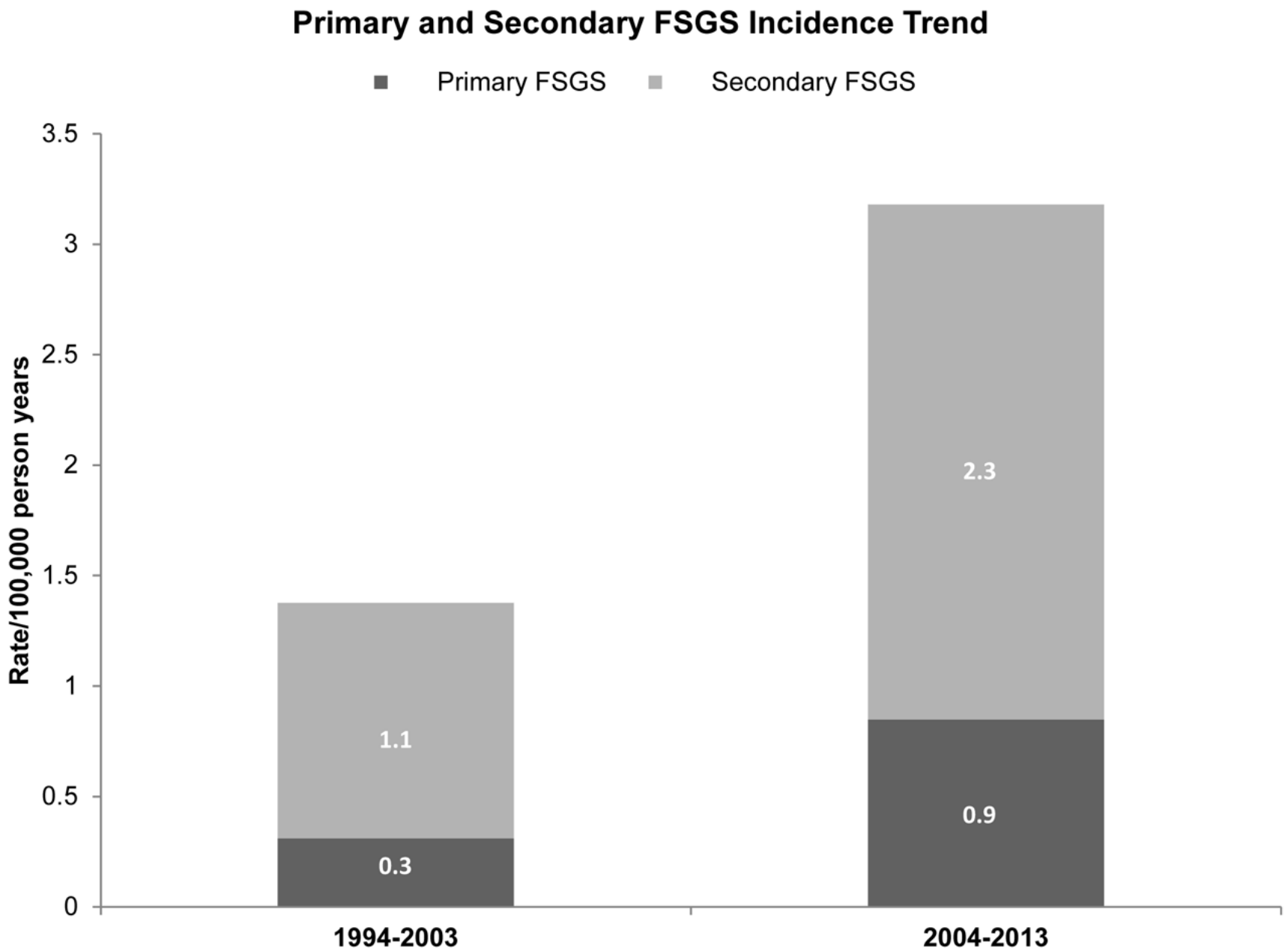
FSGS

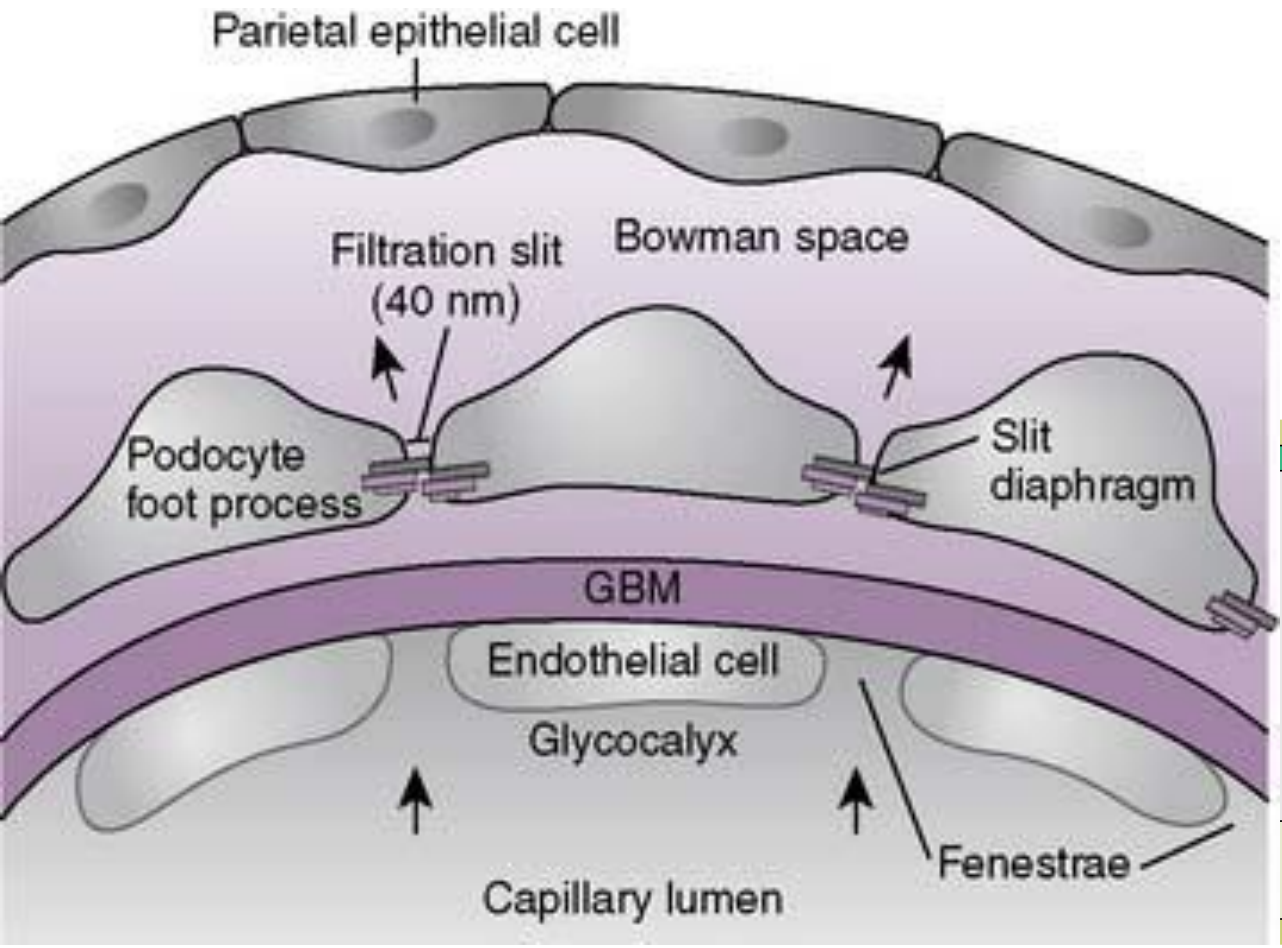
“a pattern of histologic injury rather than a disease”

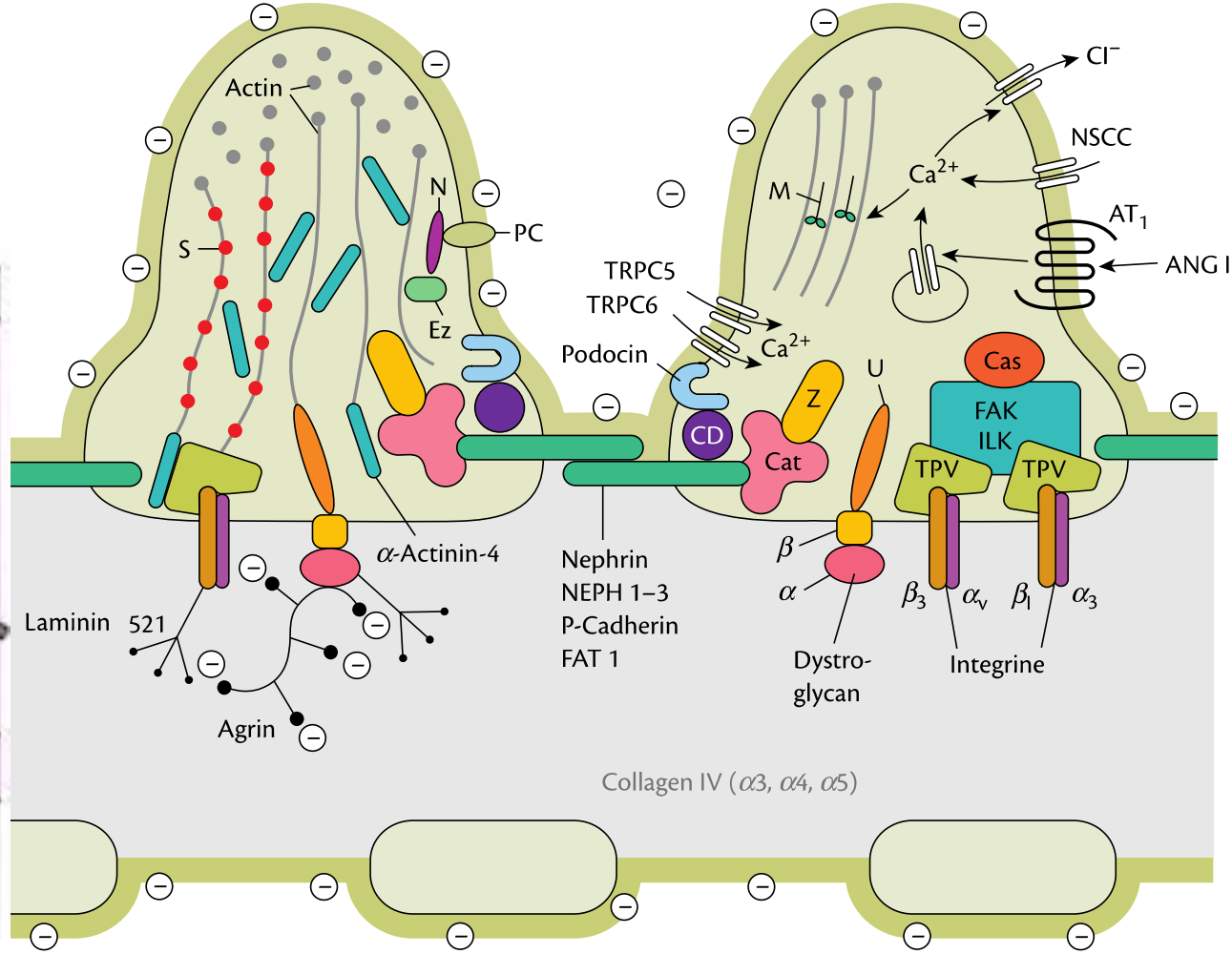
Causes

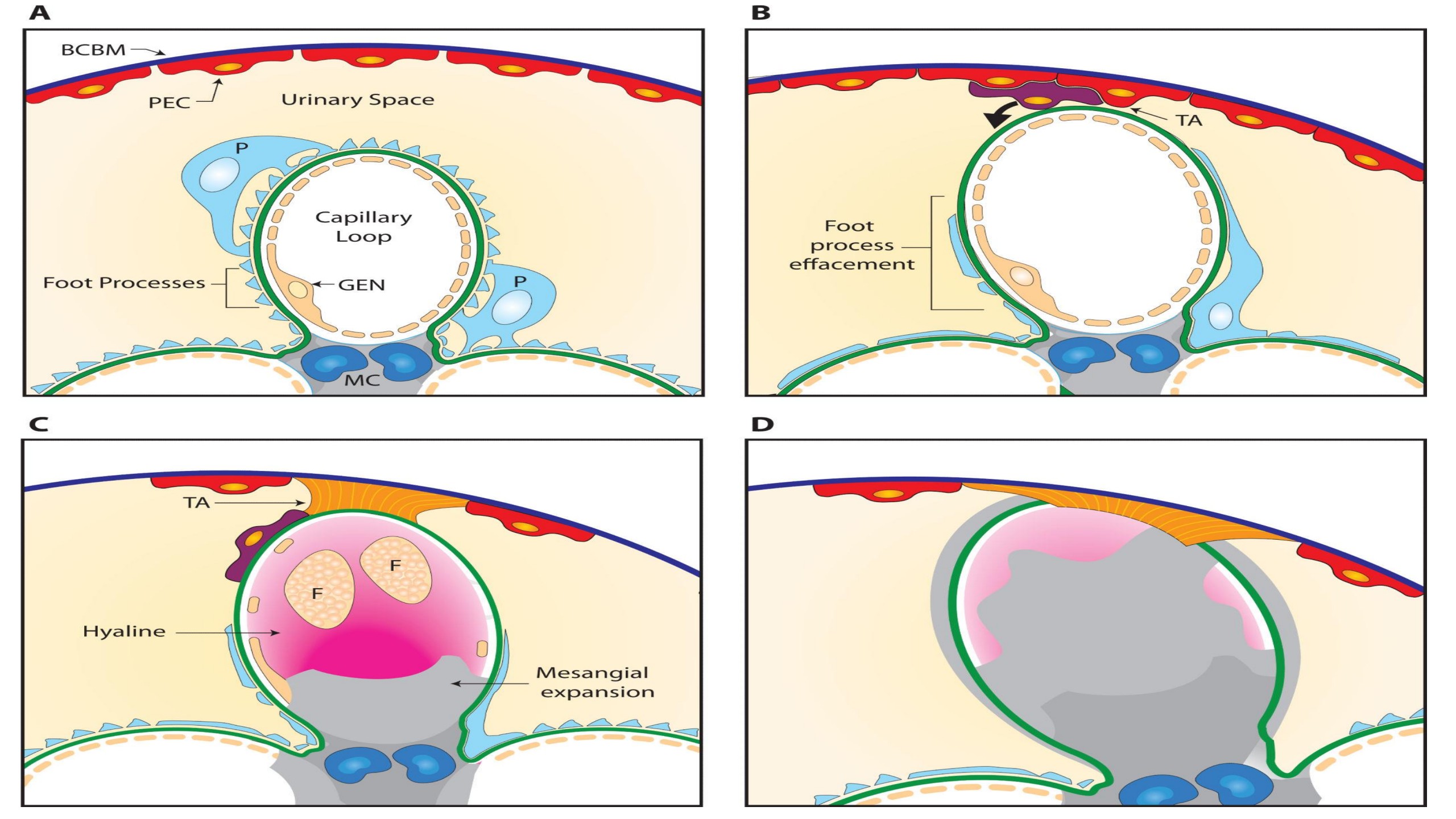
Classification	Etiology	Causes
Primary	? Circulating permeability factor	• Idiopathic
Secondary	Glomerular Hyperfiltration	• Reduced nephron mass ○ Congenital (low birth weight, renal dysplasia) ○ Acquired nephron loss (e.g. reflux nephropathy, diabetic kidney disease) • Adaptive response (obesity, sickle cell disease, cyanotic congenital heart disease)
	Viral infection	• HIV, parvovirus B19, CMV
	Drugs & Toxins	• heroin, pamidronate, lithium, anabolic steroids
Familial	Podocyte gene disorders	• Nephrin, podocin, IFN2, α-actinin-4, CD2AP, WT1; TRPC6; phospholipase Cε1

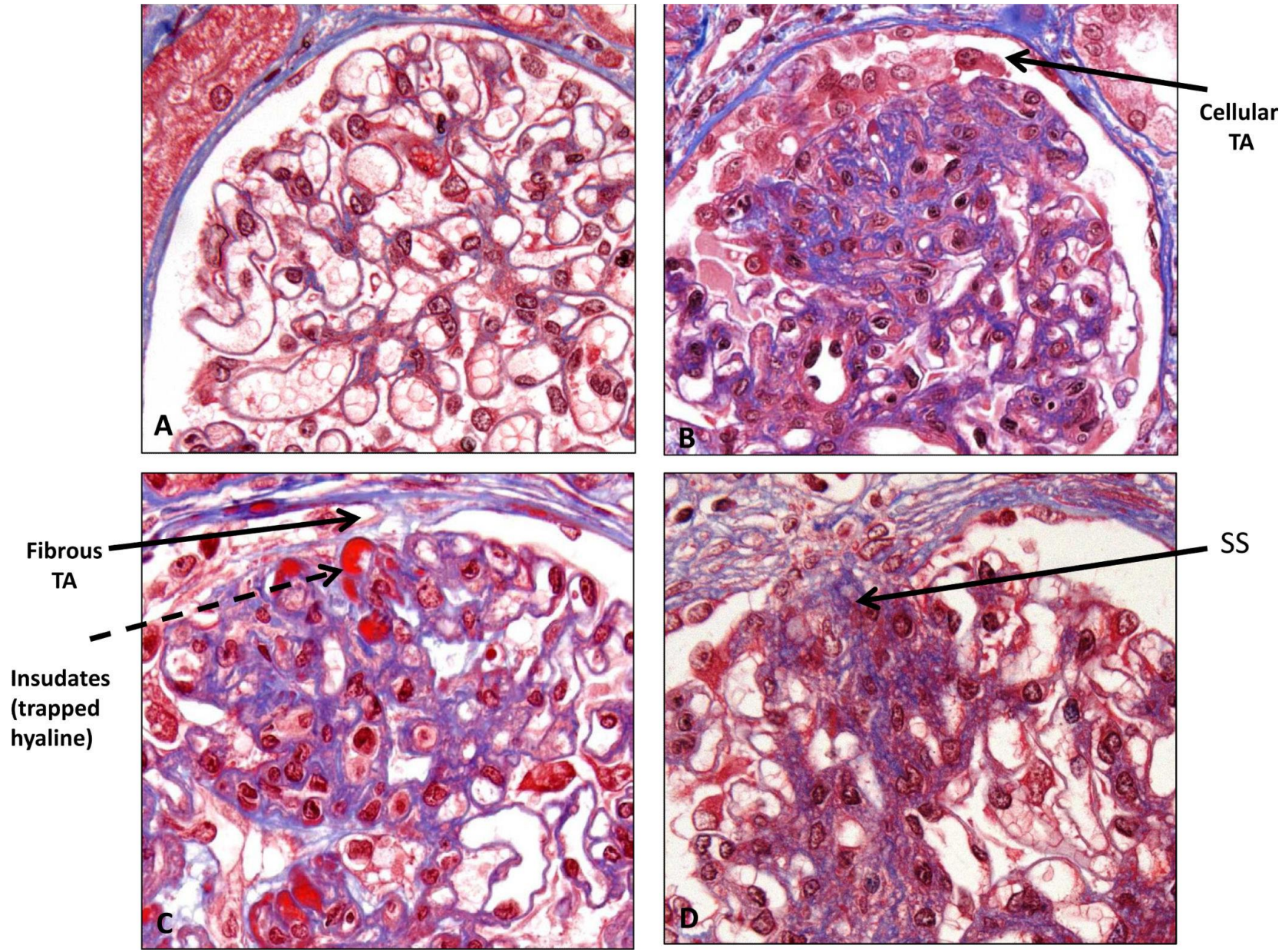

FSGS
Membranous
Minimal Change
IgA
Other
RATE PER 100,000 PERSONS
0
1
2
3
4
5
6
2000 (n=145)
2001 (n=144)
2002 (n=139)
2003 (n=169)
2004 (n=174)
2005 (n=172)
2006 (n=216)
2007 (n=206)
2008 (n=222)
2009 (n=258)
2010 (n=303)
2011 (n=353)
YEAR

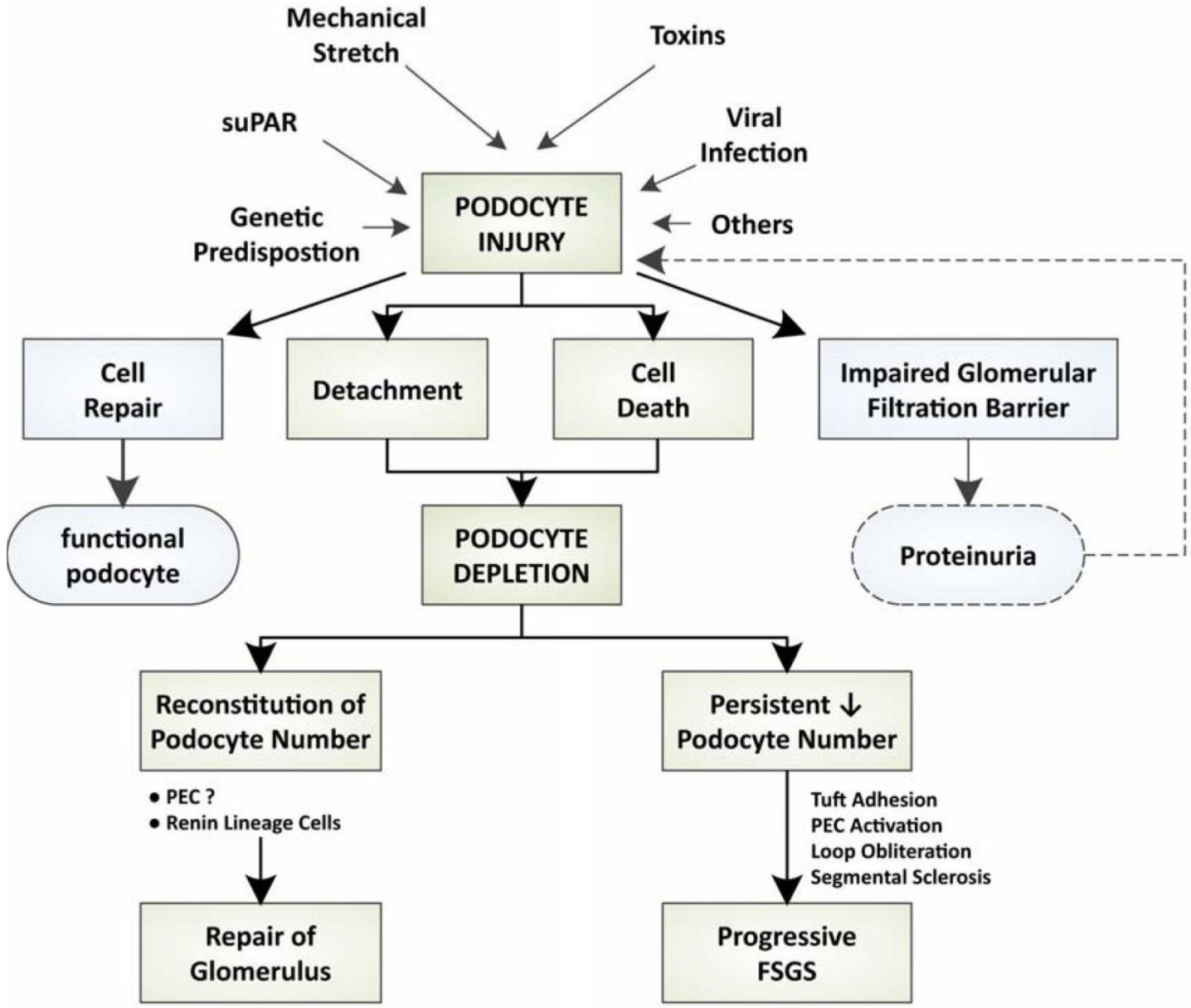

Primary and Secondary FSGS Incidence Trend
Primary FSGS
Secondary FSGS
Rate/100,000 person years
3.5
3
2.5
2
1.5
1
0.5
0
1.1
0.3
2.3
0.9
1994-2003
2004-2013

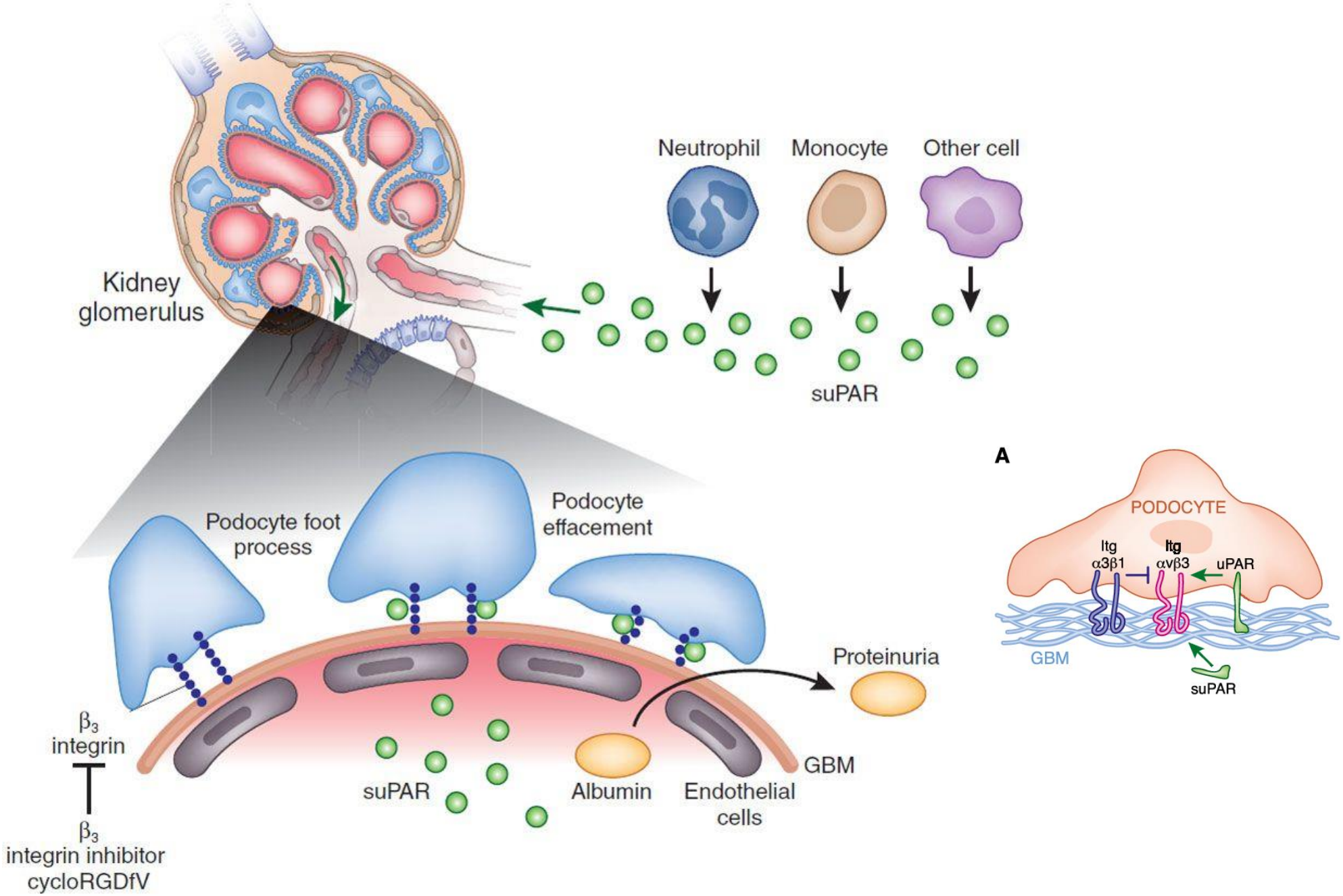

Parietal epithelial cell
Filtration slit
(40 nm)
Bowman space
Podocyte
foot process
Slit
diaphragm
GBM
Endothelial cell
Glycocalyx
Capillary lumen
Fenestrae


Actin
N
PC
S
Ez
α-Actinin-4
Laminin
521
Agrin
Nephrin
NEPH 1–3
P-Cadherin
FAT 1
Cl⁻
NSCC
Ca2+
M
AT1
ANG I
TRPC5
TRPC6
Ca2+
Podocin
CD
Z
Cat
U
Cas
FAK
ILK
TPV
TPV
β
α
β3
αv
β1
α3
Dystro-
glycan
Integrine
Collagen IV (α3, α4, α5)

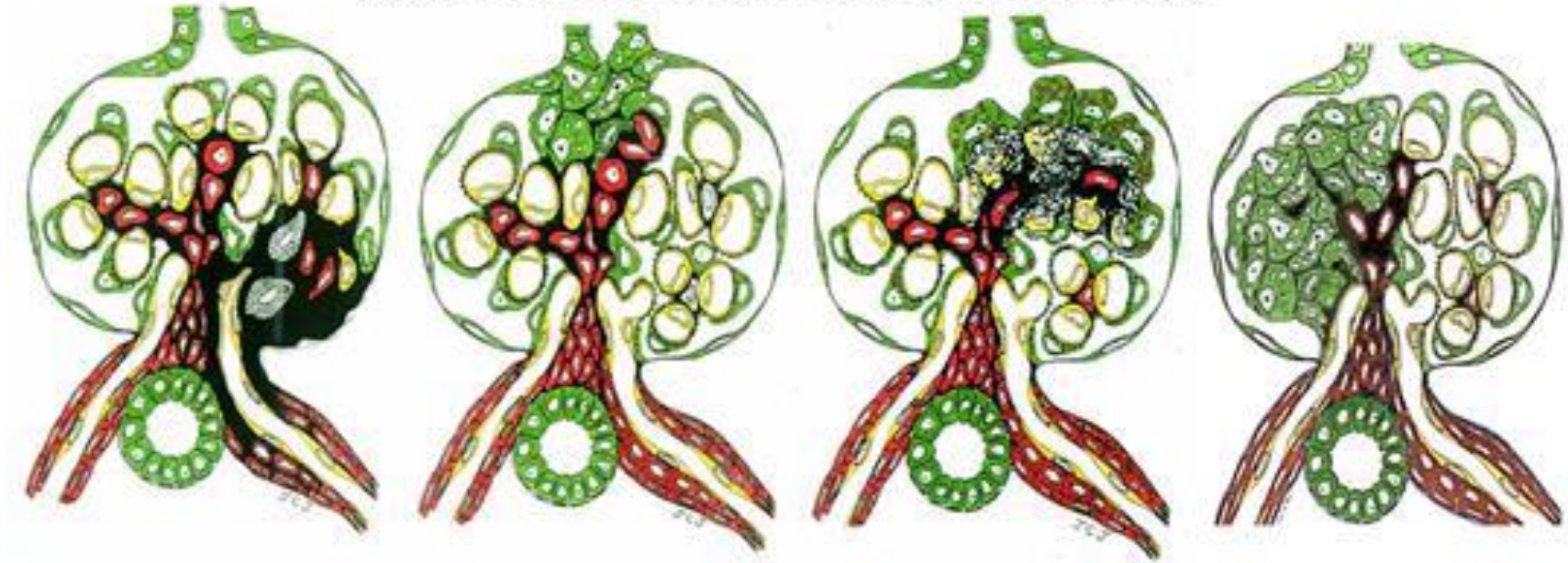

A
BCBM
PEC
Urinary Space
P
Capillary Loop
Foot Processes
GEN
P
MC
B
TA
Foot process effacement
C
TA
F
F
Hyaline
Mesangial expansion
D

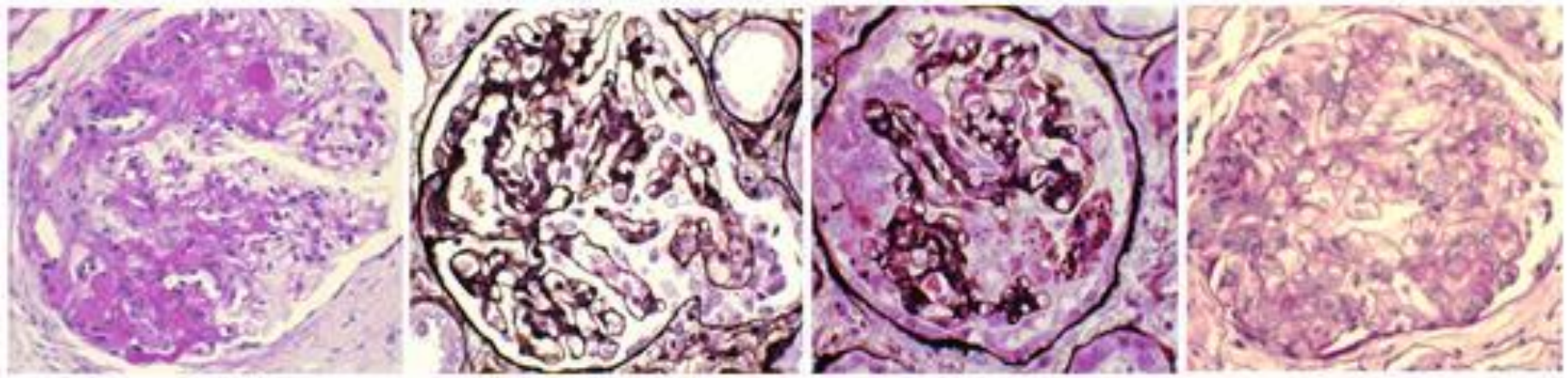

A
B
Cellular
TA
Fibrous
TA
Insudates
(trapped
hyaline)
C
D
SS


Mechanical Stretch
Toxins
suPAR
Viral Infection
Genetic Predispostion
PODOCYTE INJURY
Others
Cell Repair
Detachment
Cell Death
Impaired Glomerular Filtration Barrier
functional podocyte
PODOCYTE DEPLETION
Proteinuria
Reconstitution of Podocyte Number
Persistent ↓ Podocyte Number
• PEC ?
• Renin Lineage Cells
Tuft Adhesion
PEC Activation
Loop Obliteration
Segmental Sclerosis
Repair of Glomerulus
Progressive FSGS


Kidney glomerulus
Neutrophil
Monocyte
Other cell
suPAR
Podocyte foot process
Podocyte effacement
Proteinuria
β3 integrin
β3 integrin inhibitor cycloRGDfV
suPAR
Albumin
Endothelial cells
GBM
A
PODOCYTE
Itg α3β1
Itg αvβ3
uPAR
GBM
suPAR

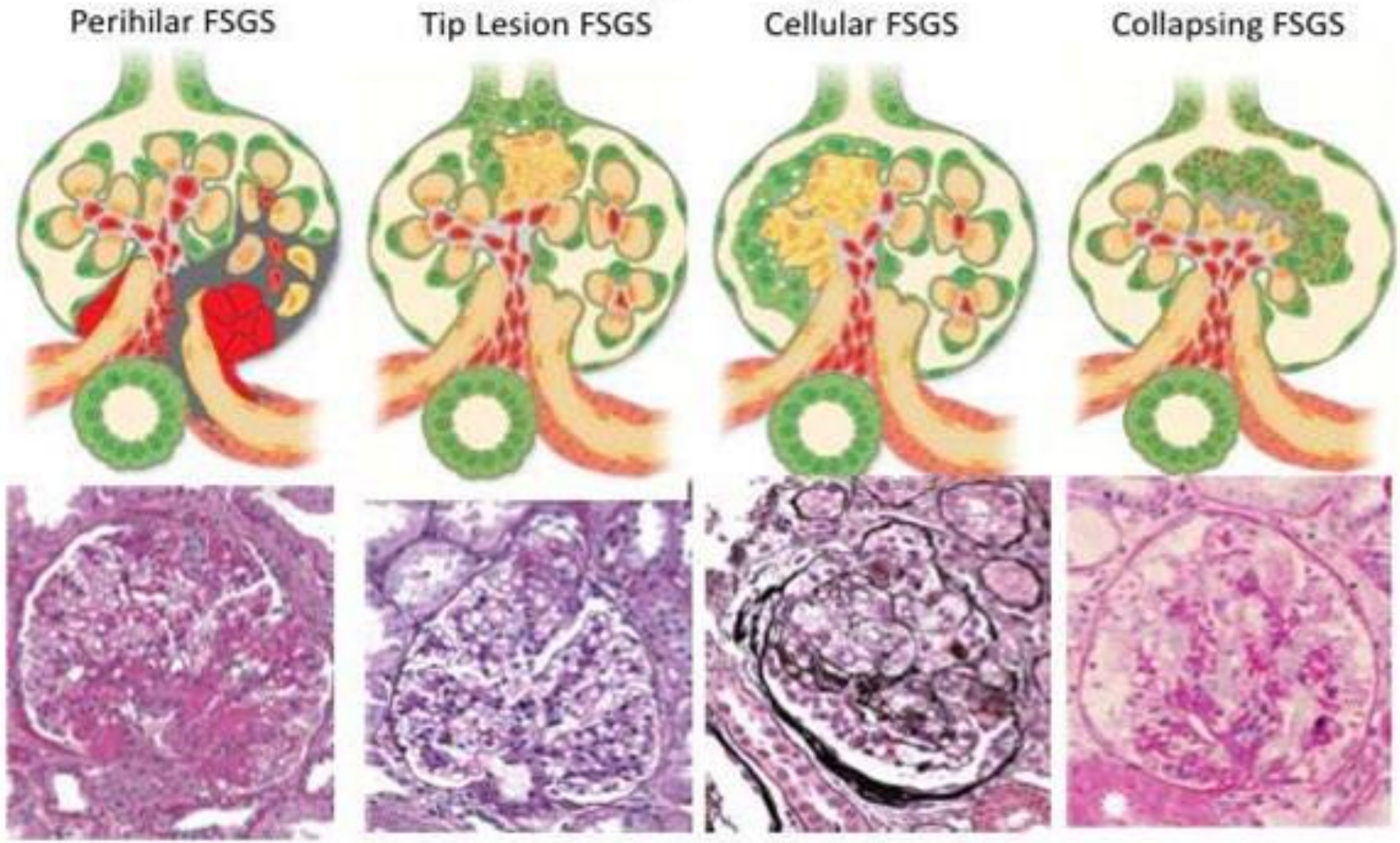
Different patterns of FSGS have different presentations and outcomes, and different causes





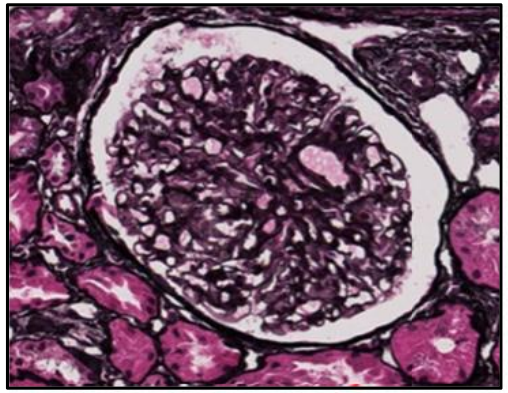
Perihilar **Tip Lesion** **Collapsing** **Cellular**

Histopathologic subtypes of FSGS

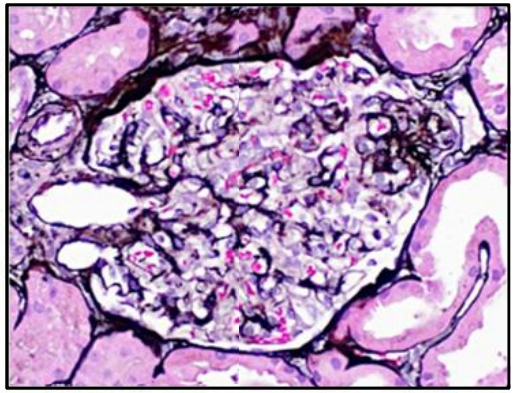


From Heptinstall's Pathology of the Kidney, 7th ed, 2014

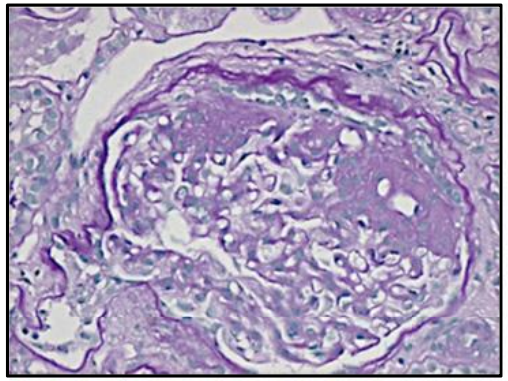
Minimal Change Disease



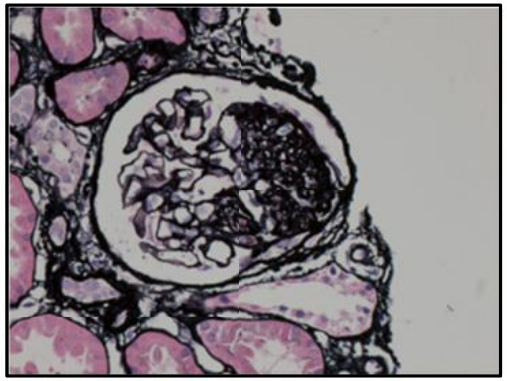
FSGS - Tip lesion variant



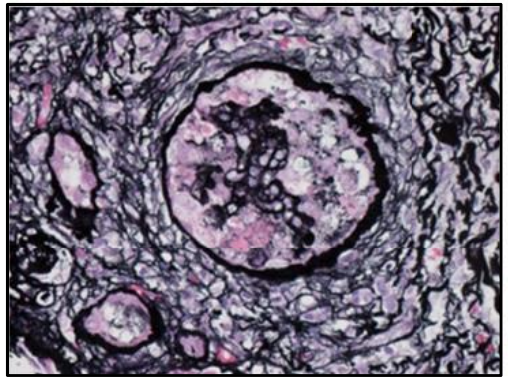
FSGS – Perihilar variant



FSGS – Not otherwise specified



FSGS – Collapsing variant



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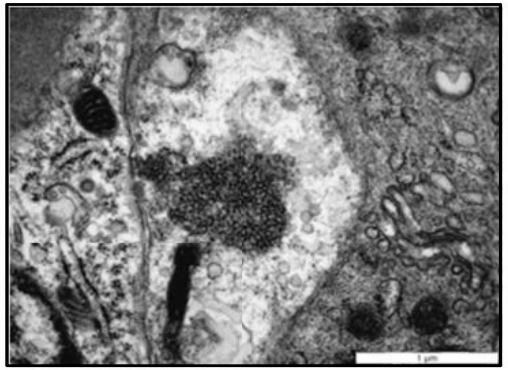
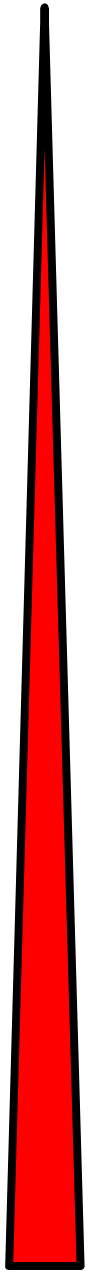
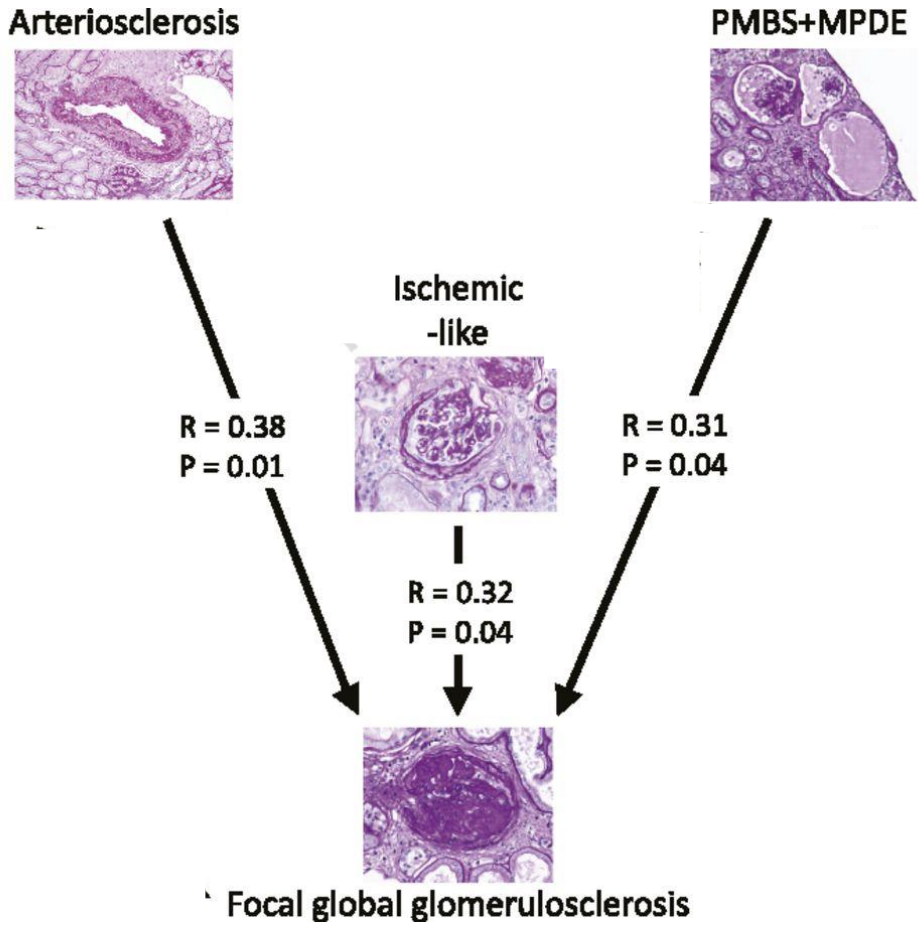
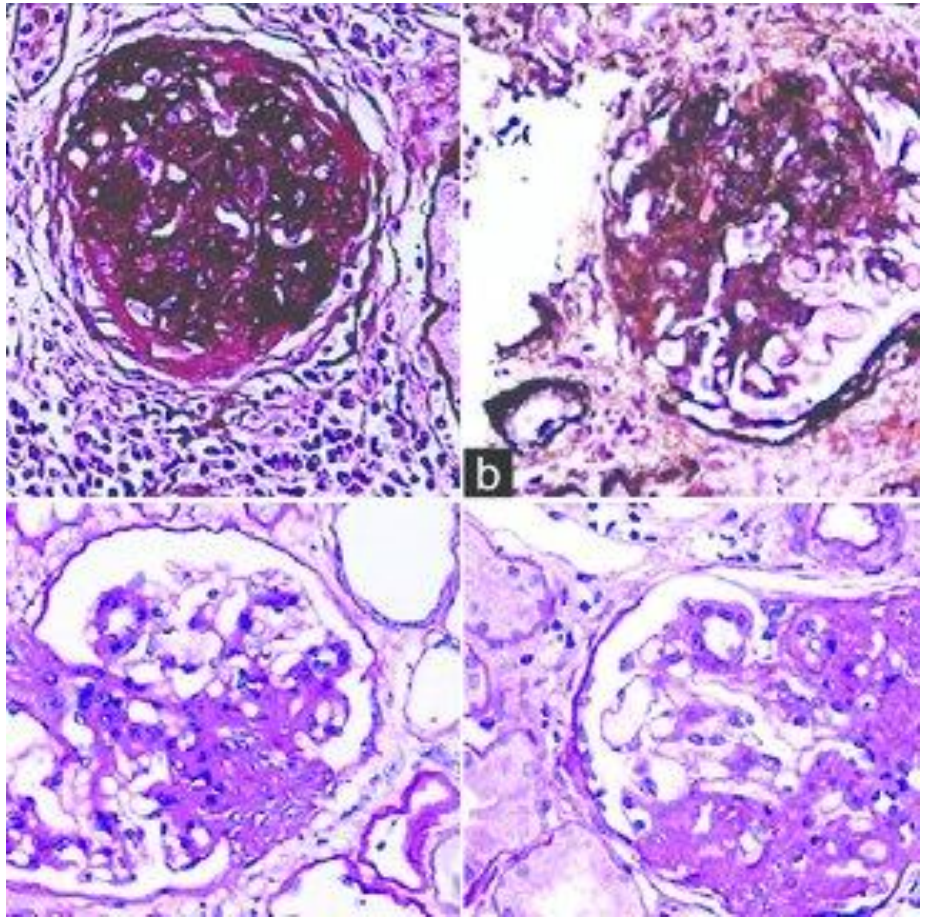




Focal & Global Glomerulo-Sclerosis





Differential Diagnostic Evaluation

- Proteinuria is the cardinal presenting clinical feature of FSGS.
- **nephrotic syndrome**
- **nephrotic-range proteinuria**
- **Sub-nephrotic proteinuria**

Primary FSGS	Secondary FSGS
Usually abrupt onset of nephrotic syndrome	Less proteinuria; slow onset
Normal-sized glomeruli, less parenchymal atrophy	Glomerular hypertrophy in unaffected glomeruli Focal interstitial fibrosis/ tubular atrophy and global glomerulosclerosis
Diffuse global podocyte foot process effacement	Less prominent and segmental podocyte foot process
No IC, TRI, or other causes	Evidence of a secondary cause (IC, crescents, TRI, DM, Fabry, Alport, HTN) effacement

Proteins other than Alb >>> think for 2nd FSGS

- compare a **urinary protein/creatinine ratio** to a **urinary albumin/creatinine ratio**.

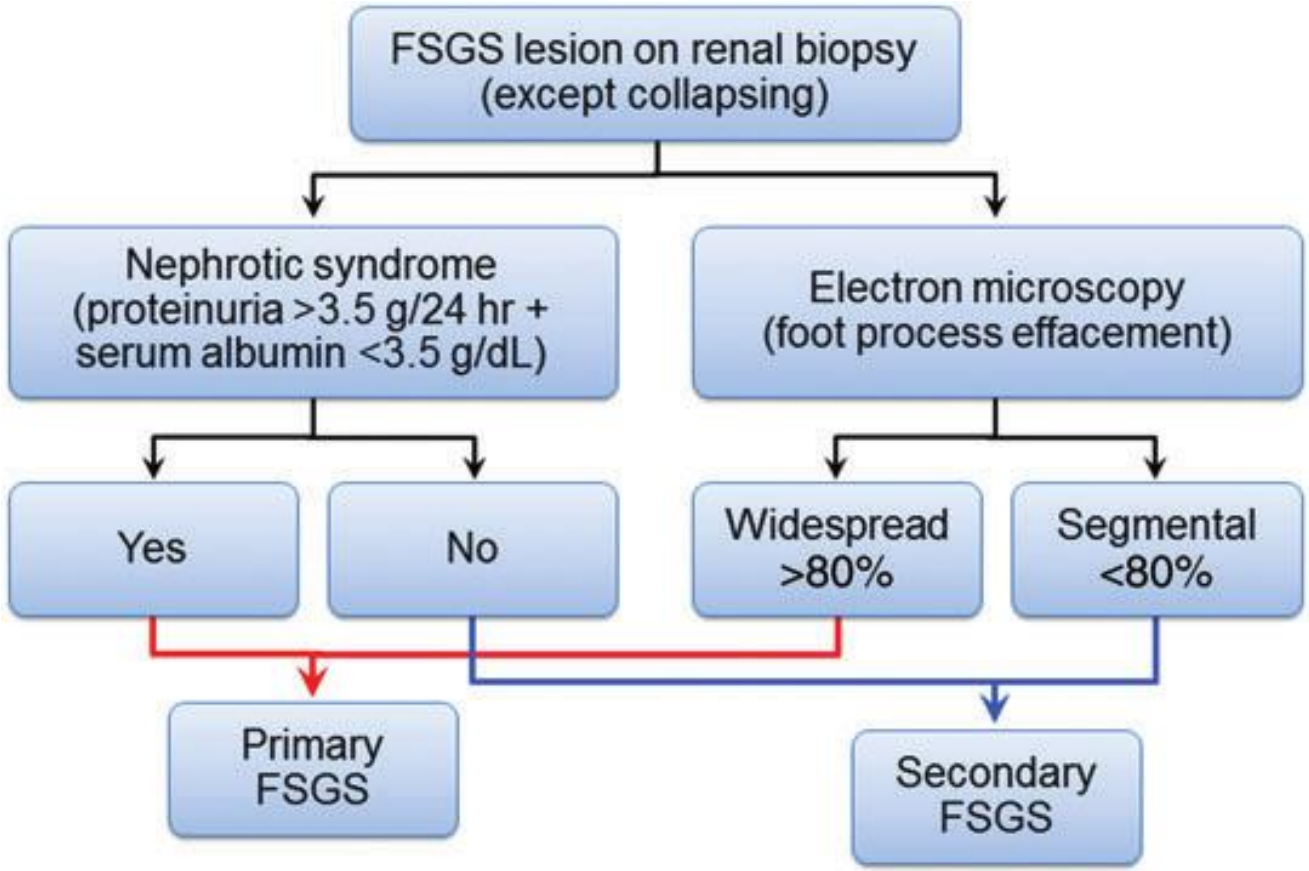
- If **<40–50% of total proteinuria are due to albumin**, then the possibility of tubular proteinuria or the presence of light chains should be considered.

- **dipstick proteinuria of trace/1+** in a patient with a **quantified urinary protein >1 g/24 h**.

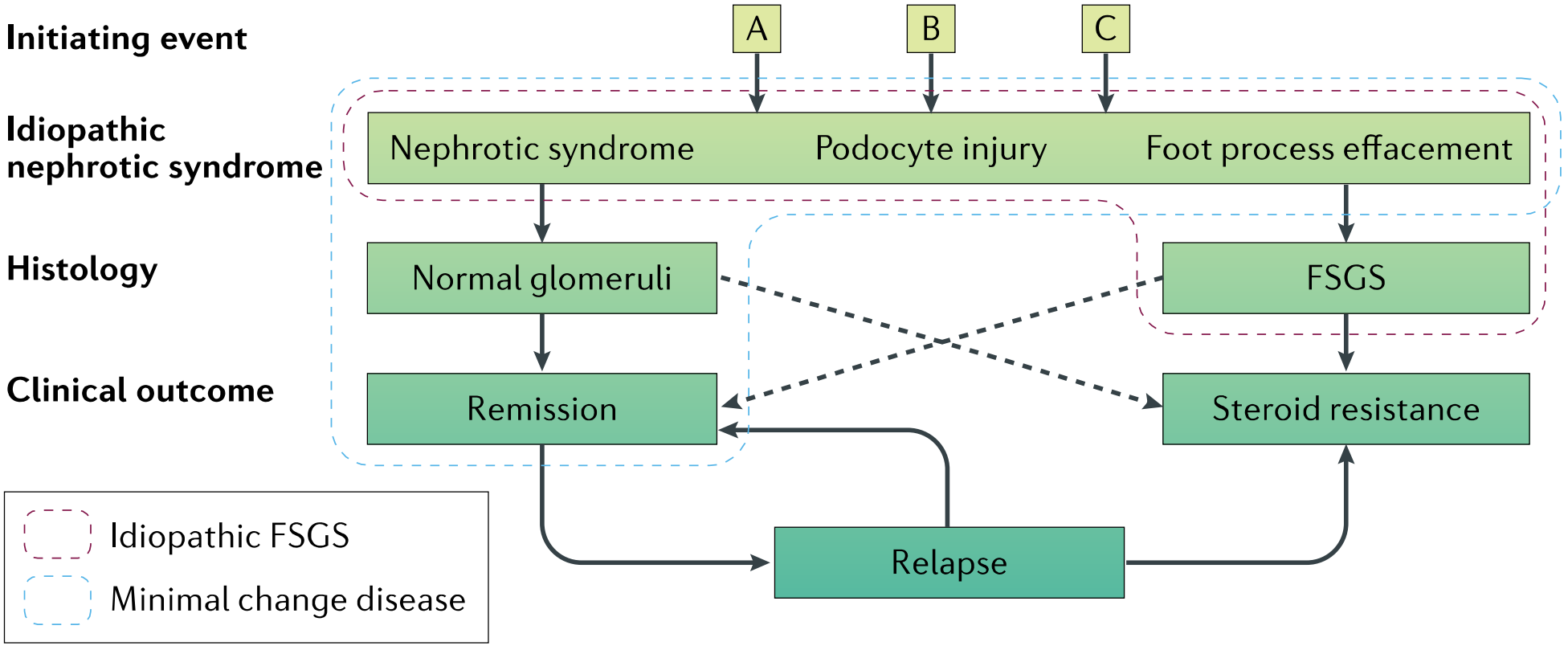
DDx of FSGS & FGGS

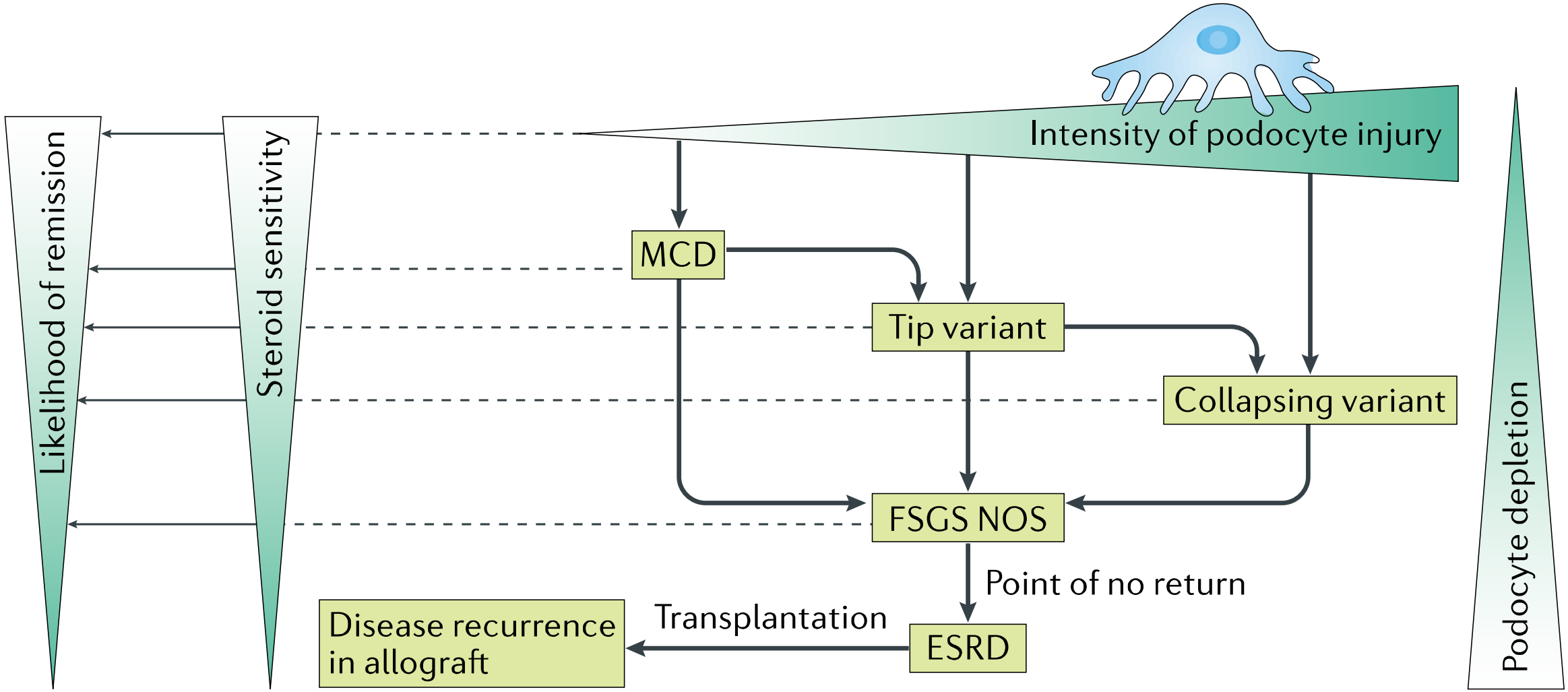
	Primary FSGS	Genetic FSGS	Maladaptive FSGS	FGGS
Clinical	NS	NS common in childhood, less common in adults	Nephrotic- or subnephrotic-range proteinuria without NS	Variable proteinuria, usually subnephrotic
LM	FSGS Often no other damage (unless late in disease course) Glomerulomegaly uncommon	FSGS FGGS common in adult-onset, uncommon in juvenile forms	FSGS Often perihilar Other signs of scarring FGGS in many glomeruli Glomerulomegaly common	FGGS No FSGS No glomerulomegaly Ischemic glomeruli[a] Associated with tubulointerstitial fibrosis, vascular sclerosis
EM	Diffuse FPE (>80%)	Variable (diffuse or segmental) FPE, characteristic features in some mutations	Segmental FPE	Minimal or no FPE in unaffected glomeruli

FSGS
primary *vs* secondary



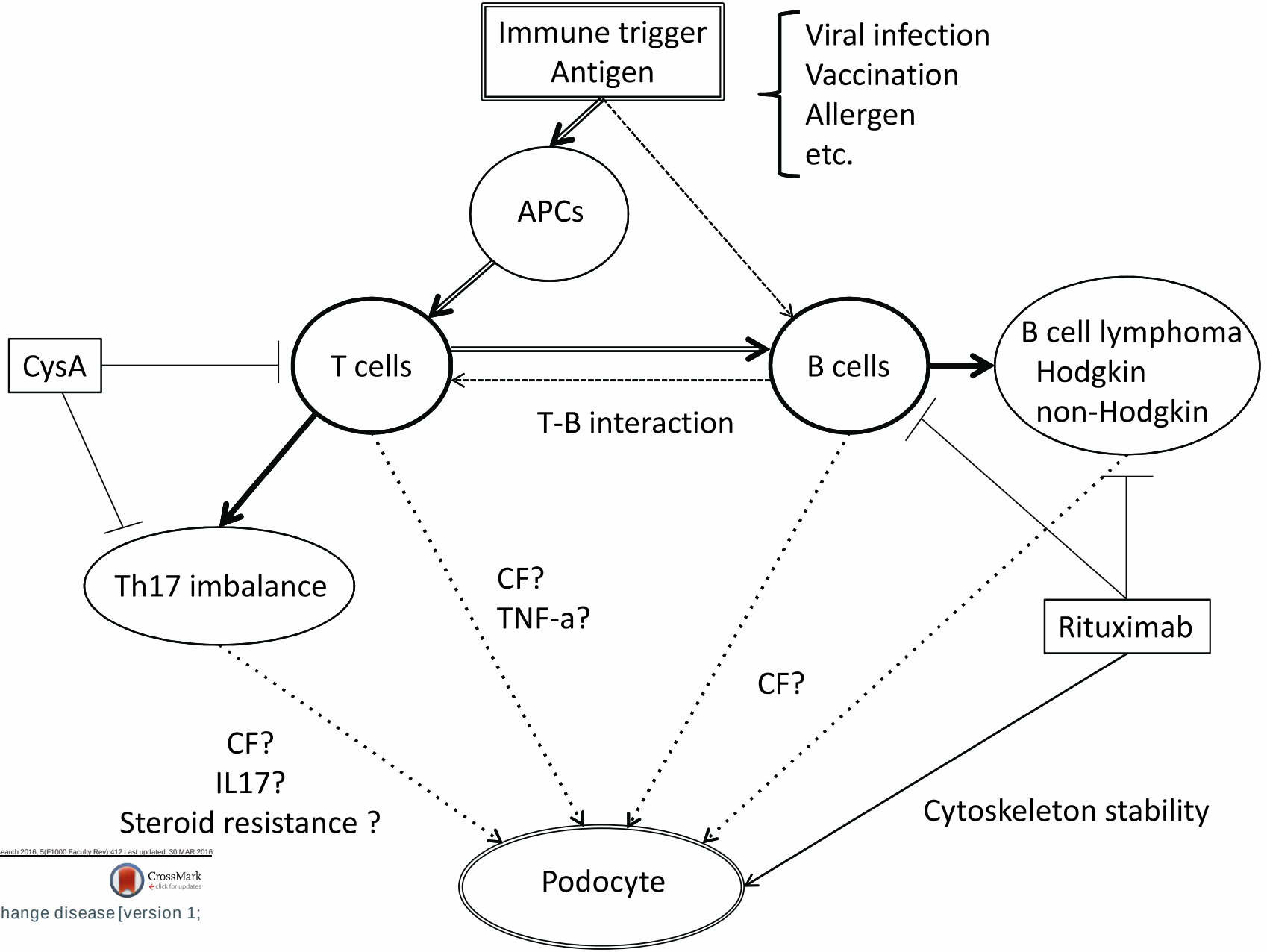
MCD *vs* FSGS


Initiating event
A
B
C
Idiopathic nephrotic syndrome
Nephrotic syndrome
Podocyte injury
Foot process effacement
Histology
Normal glomeruli
FSGS
Clinical outcome
Remission
Steroid resistance
Relapse
Idiopathic FSGS
Minimal change disease


Intensity of podocyte injury
Likelihood of remission
Steroid sensitivity
MCD
Tip variant
Collapsing variant
FSGS NOS
Point of no return
ESRD
Transplantation
Disease recurrence in allograft
Podocyte depletion

Immunosuppressive Treatment of Primary FSGS

- As the presumed origin of primary FSGS is a dysregulated autoimmune response, the use of immunosuppressive agents is advocated in its treatment.
- Recently**, direct effects of some of these agents on the podocyte** have been determined that potentially augments or supplements their immunosuppressive action.
- **Calcineurin inhibitors (CNIs)** have been shown to stabilize the podocyte actin cytoskeleton by blocking the calcineurin-mediated dephosphorylation of synaptopodin, a protein critical for **actin filament reformation**.
- **Rituximab**, a chimeric mAb against CD20 on the surface of B cells and a well established B cell– depleting immunosuppressive agent, may have a **direct antiproteinuric** effect by **preventing actin cytoskeleton disruption**

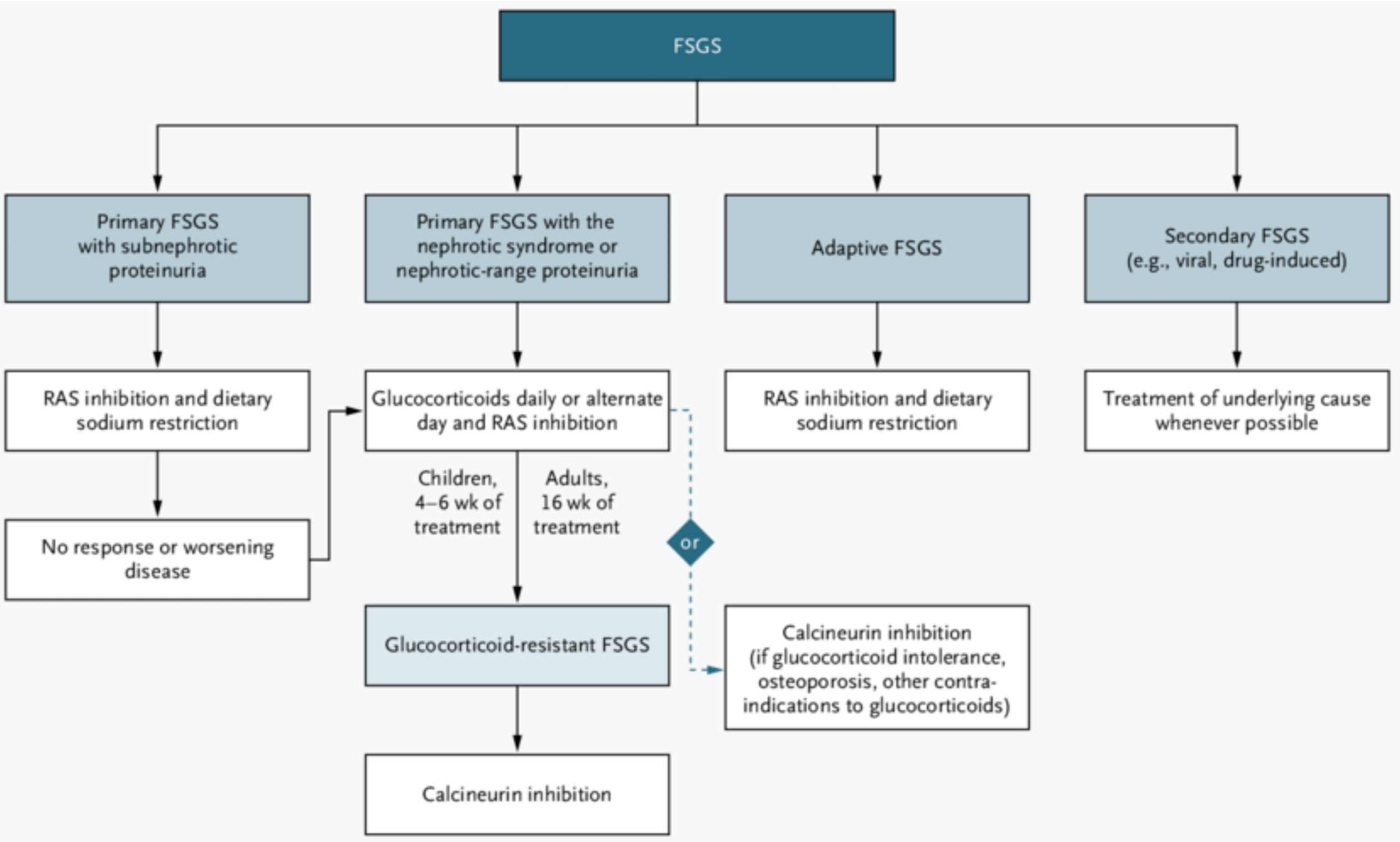


F1000Research F1000Research 2016, 5(F1000 Faculty Rev):412 Last updated: 30 MAR 2016

REVIEW

Cell biology and genetics of minimal change disease [version 1; referees: 2 approved]

Moin A. Saleem[1,2], Yasuko Kobayashi[1,3]


FSGS
Primary FSGS with subnephrotic proteinuria
Primary FSGS with the nephrotic syndrome or nephrotic-range proteinuria
Adaptive FSGS
Secondary FSGS (e.g., viral, drug-induced)
RAS inhibition and dietary sodium restriction
Glucocorticoids daily or alternate day and RAS inhibition
RAS inhibition and dietary sodium restriction
Treatment of underlying cause whenever possible
No response or worsening disease
Children, 4–6 wk of treatment
Adults, 16 wk of treatment
or
Glucocorticoid-resistant FSGS
Calcineurin inhibition (if glucocorticoid intolerance, osteoporosis, other contra-indications to glucocorticoids)
Calcineurin inhibition

If there would be “any” benefit >>> we should see the results “early” !

- *“if a patient is going to respond to therapy, proteinuria will start to decrease early in the treatment course“*
- A patient whose proteinuria does not decrease by >20% from baseline values after 2 months of high-dose corticosteroids is unlikely to respond and early steroid-taper and discontinuation should be considered, especially if steroid-related complications are a cause for concern to the physician or burdensome to the pt.
- Pt on high-dose steroid >>> should routinely receive Prophylaxis for Pneumocystis Jirovecii

CNIs

- CNI (CsA or TAC), can be used for pts who are steroid-resistant or have relapsing diseases or as 1st ttt in pts that would benefit from avoidance or have contra-indication to high-dose steroid ttt (DM)
- Failure to reduce proteinuria **after 6 months** of **CNI** treatment in adequate doses equals **resistance** to **this therapy** regimen and the drug should be discontinued

Resistance to CSA does not equal resistance to TAC

- Both **CSA and TAC** should **not** be regarded as **'curative'** agents for FSGS, as re-lapses are quite common when they are discontinued, even after prolonged usage.

- In patients with **primary FSGS** who are intolerant of CNI, the use of **Mycophenolate mofetil and (+) high-dose steroids** may be a satisfactory alternative

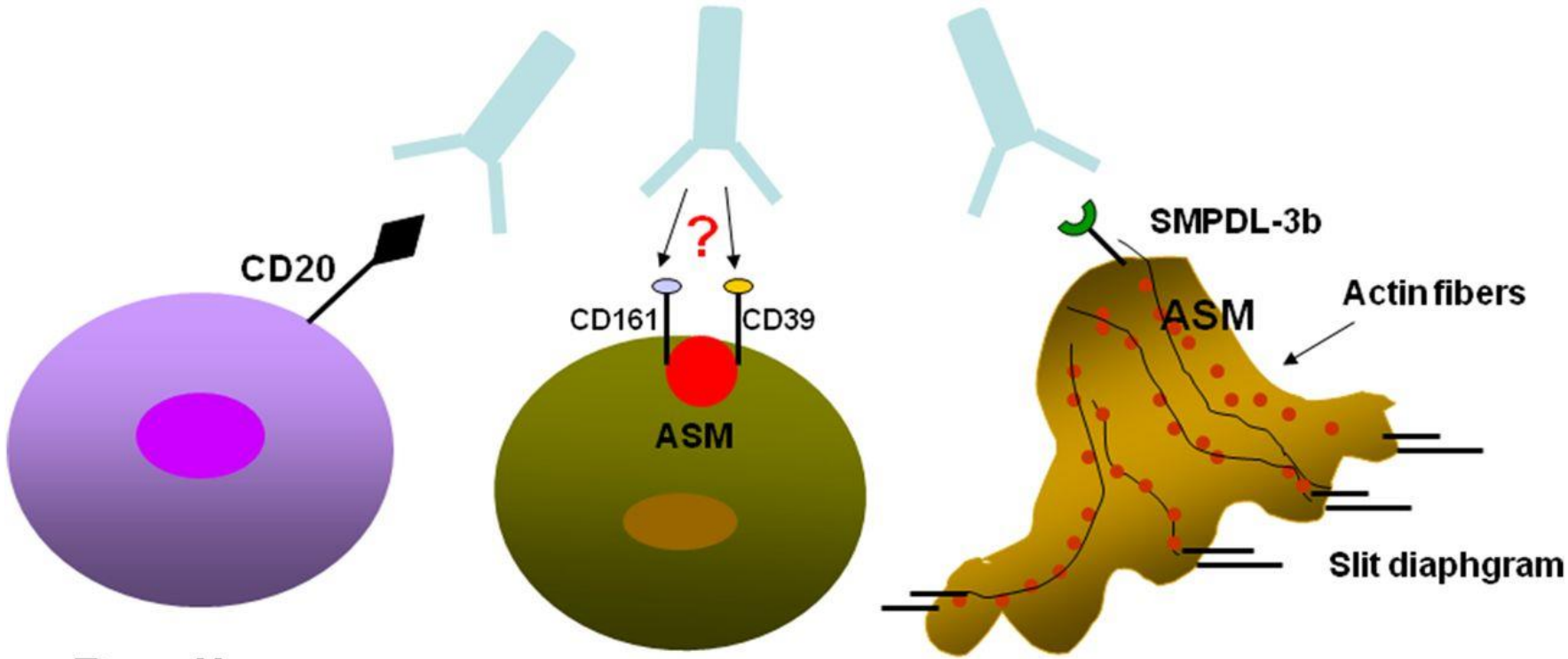
- FSGS secondary to a **genetic** mutation may respond to **CNI**

- Primary FSGS who are **steroid-sensitive** and pursue a **steroid-dependent** or **frequent relapsing** course can respond to cyclophosphamide or to **rituximab**

Novel Therapies for FSGS

Mechanism of Action	Agents
Modulation of immune system/inflammation	Rituximab ACTH Abatacept Adalimumab
Antagonism of circulating factors	Galactose Inhibitors of suPAR
Antifibrotic	TGF-β inhibitors Direct: fresolimumab Indirect: microRNAs
Stem cells	Human umbilical mesenchymal stem cells

Rituximab



B cells

CD80/CTLA4

↓

T Cells

Th17

~~↓~~

IL-17

↓

podocytes

Podocytes

SMPDL-3b

↓

ASM

↓

Actin remodelling

RTX in FSGS

Table 3 Characteristics of discussed studies of rituximab in FSGS

Study	Study design	Population	Rituximab protocol	Selected outcomes	Results
Fernandez-Fresnedo et al[26]	Retrospective case series	Eight patients with FSGS resistant to steroids and other treatments, all patients had nephrotic range proteinuria at baseline with a mean of 14±4.4 g/24 h	Variable: five patients received 4 weekly doses at 375 mg/m^2 One patient received 4 weekly doses at 375 mg/m^2 initially and again at month 12 One patient received 4 weekly doses at 375 mg/m^2 initially and 2 weekly infusions at month 6 One patient received 8 weekly doses at 375 mg/m^2	24-hour proteinuria Serum creatinine Adverse events	Two patients had significant decrease in proteinuria to 3.2 and 3.9 g/day One patient had transient decrease in proteinuria Five patients failed to respond to rituximab therapy with no significant decrease in proteinuria Serum creatinine increased from 1.4±0.5 to 2.2±1.8 mg/dL No adverse events during follow-up
Ochi et al[27]	Case series	Two patients with steroid-resistant FSGS, and two patients with steroid-dependent FSGS	Single dose at 375 mg/m^2	Complete remission (not defined in the manuscript)	CR achieved in the two patients with steroid-dependent FSGS The two patients with steroid-resistant FSGS did not respond to therapy
Ruggenenti et al[28]	Prospective, open-label, longitudinal, within-patient controlled study	30 patients (ten children, 20 adults) with steroid-dependent or frequently relapsing nephrotic syndrome (included eight patients with FSGS, five adults, three children)	Single dose at 375 mg/m^2 (28 patients) Or two doses of rituximab (two patients)	Number of relapse of nephrotic syndrome in the year after rituximab therapy vs the year before rituximab therapy Side effects	Fivefold decrease in number of relapse in all patients and in patients with FSGS No treatment-related adverse events

Study	Patients (n)	Age (y); Duration Disease (y)*	375 mg/m² Once Weekly	FU (mo)	Remission (%)	Relapse (%)	Time to Relapse (mo)*	Remarks
Retrospective studies								
Prytula 2010[31]	28	NA; NA	1-4 doses 2° course: n = 5	1-10	36	46	6 (1-16)	• No data available about indication and timepoint of repeated course rituximab. • 5 patients without response to rituximab.
Ito 2011[32]	7	13.8 ± 5.2; 6.3 ± 3.3	1 dose 2° course: n = 3	12	14	86	NA	• 2° course because of relapse (timepoint not available). • Steroid-induced remission before rituximab administration.
Gulati 2010[33]	24	11.7 ± 2.9; 8.9 ± 2.9	2° course: n = 1	12	83	17	11.2 (8-14)	• At end FU at 12-38 mo: sustained remission in 17 patients. • Steroid-induced remission before rituximab administration.
Kemper 2012[34]	37	13.4 (6.4-18.2); 2.0-14.8	1-4 doses ≥2 course: n = 19	12 24	70 32	30 68	– –	• No data available about indication of repeated courses rituximab. • Overall time to relapse after initial course rituximab: 9.6 mo (5.2-64.1).
Ito 2013[35]	55	4.5 (0.9-16.3); 4.8 (0.2-14.7)	1.8 ± 1.4 doses (range 1-7)	7-31	49	51	5 (1-24)	• Including ≥15 patients from other studies.[32,40,41] • Steroid-induced remission before rituximab administration.
Tellier 2013[36]	18	13.5 (5.9-18); 10.4 (3.5-16)	1-4 doses ≥2 courses: n = 15	24	44	56	13 (5-22)	• Repeated courses when relapse or CD19 >1% • Steroid-induced remission before rituximab administration.
Kronbichler 2013[37]	5	29.2 ± 3.9; 18.3 ± 10.2	1-4 doses	14	100	0	NA	• Childhood onset: 3; adult onset: 2. • After total FU (range 14-55 mo) 1 relapse after 23 mo. • Steroid-induced remission before rituximab administration in 2 patients, 3 patients with proteinuria.

2013[38]		(1.8-30.5)					(range 4.8-16.3)	onset: 5. • Steroid-induced remis before rituximab administration in 10 pa 7 patients with protein
Prospective studies								
Ravani 2013[43]	46	9.9 ± 4.3; 6.3 ± 4.1	1-5 doses	12	20	80	NA	• Including long-term FU of 27 children from previous study.[46] • Inclusion criteria: neve a remission without IS therapy. • Relapse: presence of proteinuria or restart of IS after complete withdrawal of IS thera • Steroid-induced remis before rituximab administration.
Sellier-Leclerc 2012[44]	30	12.9 (3.7-19.7); 9.5 (0.3-17.5)	1-4 doses ≥2 courses: n = 30	26-52	60	40	NA	• Repeated courses to maintain B cell depleti for at least 15 mo. • Steroid-induced remis before rituximab administration.
Kamei 2009[40]	12	12.7 (5-19); 7.2 (1.5-10.6)	1 dose	12	25	75	4 (0.3-12)	• Relapse rate in 6 mo before/after rituximab: 2.83 (SD 1.19) vs 1.08 (SD 1.08) ($P = .016$). • Steroid-induced remis before rituximab administration.
Fujinaga 2010[41]	10	11.1 ± 4.5; 4.6 (2.8-10.8)	1-2 doses	12	70	30	NA	• At end FU at 16.8 ± 5.! sustained remission ir patients; 5 patients ha a relapse and these pa discontinued the CsA a rituximab infusion. • Relapse rate in 12 mo before/after: 4.1 ± 1.7 vs 0.6 ± 0.6 ($P < .01$). • Steroid-induced remis before rituximab administration.

(Co

Study	Patients (n)	Age (y); Duration Disease (y)*	Rituximab 375 mg/m^2 Once Weekly	FU (mo)	Outcome: Remission (%)	Outcome: Relapse (%)	Outcome: Time to Relapse (mo)*	Remarks
Guigonis 2008[56]	22	14.3 (6.3-22.1) 11.0 (3.6-16.5)	2-4 doses ≥2 courses (n = 12)	6-39	73	14	7-17	• Including 2 steroid-resistant, CsA-sensitive patients. • Steroid-induced remission before rituximab administration in 15 patients, 7 patients with proteinuria. • Indication repeated courses: when response on first course (defined as no relapse of proteinuria before reappearance of CD19 cells despite IS tapering below the usual threshold of relapse). • 3 patients without response to rituximab.
Hoxha 2011[61]	6	24.8 ± 6.3; 7.9 ± 4.9	1 dose >2 course: n = 5	12	50	50	4-12	• Additional courses rituximab when B cells increased or when proteinuria increased. • At end of FU (17.2 ± 4.8 mo), 5 patients attained complete remission and 1 patient a partial remission after repeated infusions of rituximab. • Proteinuria 0.2-9.4 g/d at moment of rituximab administration.
Takei 2013[45]	25	30 ± 12; 10 ± 8	1 dose 2° course at 6 mo	6 12	88 96	12 4	5-6 12	• In total, 4 different patients with a relapse. • Steroid-induced remission before rituximab administration in 9 patients; 16 patients with proteinuria.
Comparative studies								
Sinha 2012[39]	23	Group 1 (n = 10): 12.2 ± 2.3; 3.6 ± 1.5 (age at onset) Group 2 (n = 13): 12.3 ± 3.0; 3.6 ± 2.2 (age at onset)	2-3 doses in Group 1	12	50 (Group 1) 46 (Group 2)	50 (Group 1) 54 (Group 2)	8.5 ± 5.1 (Group 1) 9.8 ± 5.6 (Group 2)	• Retrospective study. • Group 1 received rituximab treatment; Group 2 received tacrolimus 0.1-0.2 mg/kg/d. • Including 3 patients from another study.[33]

Study	Patients (n)	Age (y); Duration Disease (y)*	Rituximab 375 mg/m^2 Once Weekly	FU (mo)	Outcome			Remarks
					Remission (%)	No Response (%)	Time to Remission (mo)*	
Retrospective studies								
Gulati 2010[33]	33	12.7 ± 9.1; 6.4 ± 4.7	1-4	6	48: CR :27 PR: 21	52	32 d (8-60 d)	• Definition SRNS: lack of remission despite therapy with prednisone for 4 wk. • Primary resistance: 24; secondary resistance: 9. • No significant difference in response between primary or late resistance.
Prytula 2010[31]	27	NA	1-5	NA	44:CR:22PR:22	56	NA	• Definition SRNS: lack of remission despite therapy with prednisone for 4 wk. • Primary resistance: 13; secondary resistance: 13. • FU after initial response (6-12 mo) : sustained remission: 2/12; relapse: 9/12 (time to relapse: 5 mo (1-16)) (data only available of 11 patients).
Ito 2013[35]	19	NA	2.3 ± 1.4	12	63: CR:31.5 PR:31.5	37	NA	• Definition SRNS: lack of remission despite therapy with prednisone for 4 wk. • Including 1 patient with a mutation in *WT1* (no response to rituximab).
Kari 2011[47]	4	9.7 ± 1.5; 2.3 (0.5-5)	1	3	25 (CR)	75	NA	• Definition SRNS: lack of remission despite therapy with prednisone for 4 wk. • Primary resistance: 2; secondary resistance: 2. • FU after initial response: relapse: 1/1 (time to relapse: 4 mo).
Fernandez 2009[50]	8	31 ± 14; 50 ± 35 (mo)	4 doses 2° course (n = 3): • at 6 mo: 2 doses (n = 1) • at 12 mo: 4 doses (n = 2)	1-12	0	100	–	• Definition SRNS: nephrotic syndrome despite prednisone therapy (1 mg/kg per day) for ≥4 mo. At 1 mo: • Proteinuria >50% diminished: 3. At 6 mo: • Sustained >50% decrease of proteinuria: 1 • Relapse: 2. At 12 mo • Proteinuria >50% diminished: 2 (these patients

								rituximab).
Prospective study								
Bagga 2007[51]	5	10.5 y ± 5.3; 8.3 ± 5	4	10 wk	100: CR:60 PR:40	0	NA	• Definition SRNS: resistance to high-dose steroids, alkylating agents, and CNI.
Randomized controlled trial								
Magnasco 2012[49]	31	8 (2-16); 1.5	Group 1 (n = 16): 2 doses + standard therapy Group 2 (n = 15): standard therapy	3	No difference in reduction of proteinuria between the 2 groups ($P = .77$)			• Definition SRNS: primary and delayed resistance to corticosteroids and CNIs for at least 6 mo. • Standard therapy of PSL + CNI 30 d after rituximab reduction of IS if proteinuria is <1 g/d/m^2

Rituximab in Steroid-Dependent or Frequently Relapsing Idiopathic Nephrotic Syndrome

Piero Ruggenenti,*† Barbara Ruggiero,* Paolo Cravedi,* Marina Vivarelli,‡ Laura Massella,‡ Maddalena Marasà,† Antonietta Chianca,* Nadia Rubis,* Bogdan Ene-Iordache,* Michael Rudnicki,§ Rosa Maria Pollastro,‖ Giovambattista Capasso,‖ Antonio Pisani,¶ Marco Pennesi,** Francesco Emma,‡ and Giuseppe Remuzzi,*† for the Rituximab in Nephrotic Syndrome of Steroid-Dependent or Frequently Relapsing Minimal Change Disease Or Focal Segmental Glomerulosclerosis (NEMO) Study Group

*IRCCS - Istituto di Ricerche Farmacologiche "Mario Negri," Clinical Research Center for Rare Diseases "Aldo e Cele Daccò," Ranica, Bergamo, Italy; †Unit of Nephrology and Dialysis, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy; ‡Division of Nephrology and Dialysis, Children's Hospital Bambino Gesù, IRCCS, Rome, Italy; §Department of Nephrology and Hypertension, Medical University, Innsbruck, Austria; ‖Department of Nephrology, Second University of Naples, Naples, Italy; ¶Department of Nephrology, Federico II University, Naples, Italy; and **Institute for Maternal and Child Health - IRCCS "Burlo Garofolo," Trieste, Italy

ABSTRACT

The outcome of steroid-dependent or frequently relapsing nephrotic syndrome of minimal change disease (MCD), mesangial proliferative GN (MesGN), or FSGS may be poor and with major treatment toxicity. This academic, multicenter, off-on trial (ClinicalTrials.gov #NCT00981838) primarily evaluated the effects of rituximab therapy followed by immunosuppression withdrawal on disease recurrence in 10 children and 20 adults with MCD/MesGN (n=22) or FSGS who had suffered ≥2 recurrences over the previous year and were in steroid-induced remission for ≥1 month. Participants received one dose (n=28) or two doses of rituximab (375 mg/m^2 intravenously). At 1 year, all patients were in remission: 18 were treatment-free and 15 never relapsed. Compared with the year before rituximab treatment, total relapses decreased from 88 to 22 and the per-patient median number of relapses decreased from 2.5 (interquartile range [IQR], 2–4) to 0.5 (IQR, 0–1; $P<0.001$) during 1 year of follow-up. Reduction was significant across subgroups (children, adults, MCD/MesGN, and FSGS; $P<0.01$). After rituximab, the per-patient steroid maintenance median dose decreased from 0.27 mg/kg (IQR, 0.19–0.60) to 0 mg/kg (IQR, 0–0.23) ($P<0.001$), and the median cumulative dose to achieve relapse remission decreased from 19.5 mg/kg (IQR, 13.0–29.2) to 0.5 mg/kg (IQR, 0–9.4) ($P<0.001$). Furthermore, the mean estimated GFR increased from 111.3±25.7 to 121.8±29.2 ml/min per 1.73 m^2 (P=0.01), with the largest increases in children and in FSGS subgroups. The mean height z score slope stabilized in children ($P<0.01$). Treatment was well tolerated. Rituximab effectively and safely prevented recurrences and reduced the need for immunosuppression in steroid-dependent or frequently relapsing nephrotic syndrome, and halted disease-associated growth deficit in children.

Treatment of Idiopathic FSGS with Adrenocorticotropic Hormone Gel

Jonathan Hogan, Andrew S. Bomback,* Kshama Mehta,† Pietro A. Canetta,* Maya K. Rao,* Gerald B. Appel,* Jai Radhakrishnan,* and Richard A. Lafayette†*

Summary

Background and objectives Adrenocorticotropic hormone (ACTH) has shown efficacy as primary and secondary therapy for nephrotic syndrome due to membranous nephropathy. The data on using ACTH to treat idiopathic FSGS are limited. This report describes our experience using ACTH for nephrotic syndrome due to idiopathic FSGS in the United States.

Design, setting, participants, & measurements Twenty-four patients with nephrotic syndrome from idiopathic FSGS were treated with ACTH gel at two academic medical centers between 2009 and 2012, either as part of investigator-initiated pilot studies (n=16) or by prescription for treatment-resistant FSGS (n=8). The primary outcome was remission of proteinuria. The median dose of ACTH was 80 units injected subcutaneously twice weekly. Treatment durations were not uniform.

Results Twenty-two patients had received immunosuppression (mean, 2.2 medications) before ACTH therapy. Six patients had steroid-dependent and 15 had steroid-resistant FSGS. At the time of ACTH initiation, the median serum creatinine (interquartile range) was 2.0 (1.1–2.7) mg/dl, estimated GFR was 36 (28–78) ml/min per 1.73 m^2, and urine protein-to-creatinine ratio was 4595 (2200–8020) mg/g. At the end of ACTH therapy, 7 of 24 patients (29%) experienced remission (n=2 complete remissions, n=5 partial remissions). All remitters had steroid-resistant (n=5) or steroid-dependent (n=2) FSGS. Two responders relapsed during the follow-up period (mean ± SD, 70±31 weeks). Adverse events occurred in 21 of 24 patients, including one episode of new-onset diabetes that resolved after stopping ACTH and two episodes of AKI.

Conclusions Response to ACTH treatment among steroid-resistant or steroid-dependent patients with FSGS is low, but ACTH gel may be a viable treatment option for some patients with resistant nephrotic syndrome due to idiopathic FSGS. Further research is necessary to determine which patients will respond to therapy.

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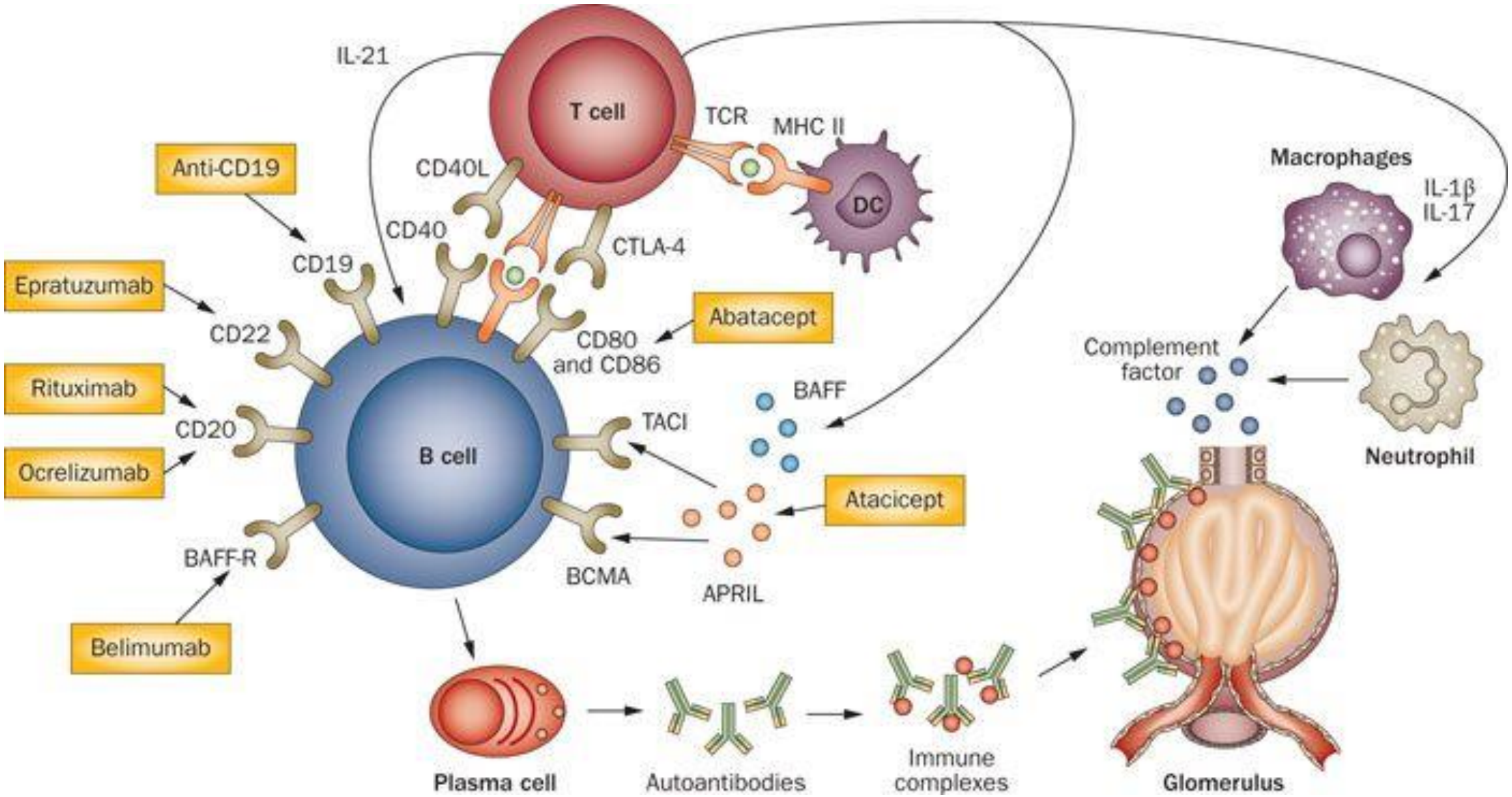
Introduction

FSGS, one of the leading causes of the nephrotic syndrome, is categorized as idiopathic (primary) or secondary to another disease process or a genetic mutation. FSGS is more common in black and Hispanic patients, but its incidence has increased in all racial groups over time (1–5). Untreated, it carries a high risk of ESRD. High-dose corticosteroid treatment is considered first-line therapy for idiopathic FSGS (6), leading to complete remission of proteinuria in approximately 30%–50% of patients and partial remission in approximately 20%–30% of patients. The achievement of remission in proteinuria is associated with improved long-term renal outcomes, even if relapse occurs (7,8).

In patients who have not responded to or have relapsed after steroid treatment, immunosuppressive treatment with calcineurin inhibitors (9–16), mycophenolate mofetil (MMF) (12,17–19), cyclophosphamide (20,21), rituximab (22), and plasma exchange therapy (23) have all been used with varying success. Overall, response rates are lower in patients who relapse, and many of these patients progress to ESRD. Therefore, the demand exists for novel therapies for FSGS.

ACTH injections were one of the first therapies used for the nephrotic syndrome in children (24,25) but fell out of favor when oral prednisone became an inexpensive and easy-to-use alternative. There has been recent interest in the role of ACTH in treating the nephrotic syndrome and in the noncorticosteroid actions of this drug (26). A synthetic ACTH analogue (tetracosactide, Synacthen R, Novartis Pharmaceuticals, Basel, Switzerland) and a highly purified ACTH gel (H.P. Acthar Gel, Questcor Pharmaceuticals, Inc., Union City, CA) have been used for patients with nephrotic syndrome (26–32), predominantly in those with membranous nephropathy. To date, the literature describes only five patients (one patient in Europe and four patients in the United States) with nephrotic syndrome due to idiopathic FSGS who have been treated with ACTH; one patient achieved complete response and two patients achieved partial


NDC 63004-7731-1
H.P.* Acthar®
Gel
(repository corticotropin injection) in 16% gelatin
5 mL multiple-dose vial
80 USP UNITS PER mL
Rx only
*HIGHLY PURIFIED
Each mL contains:
80 USP units corticotropin, 16% gelatin, 0.5% phenol, not more than 0.1% cysteine (added), sodium hydroxide and/or acetic acid to adjust pH, and water for injection, q.s.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T cell
TCR
MHC II
DC
Anti-CD19
CD40L
CD40
CTLA-4
CD19
Epratuzumab
CD22
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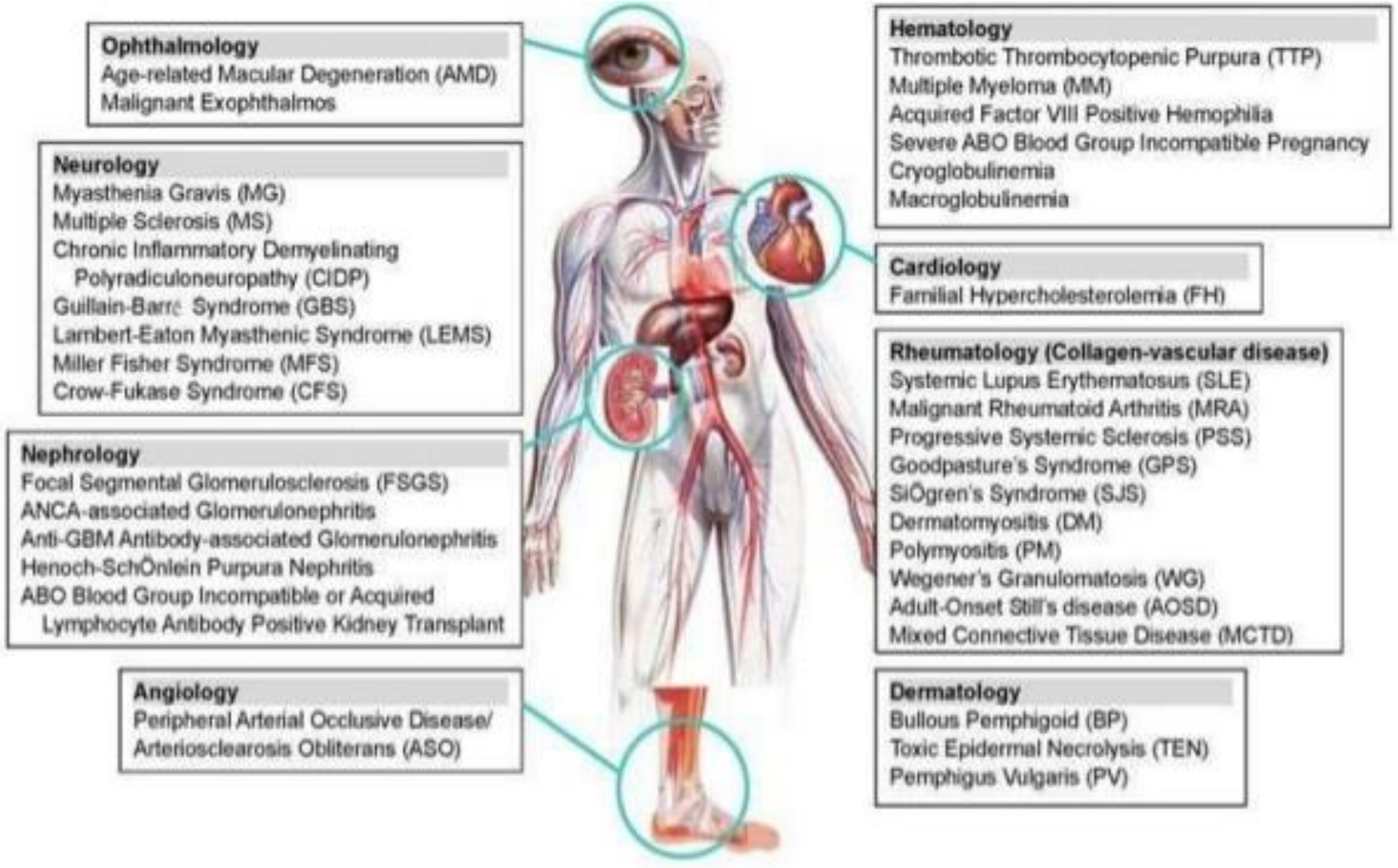
CD80
and CD86
Rituximab
CD20
Ocrelizumab
B cell
BAFF
TACI
Atacicept
BAFF-R
BCMA
APRIL
Belimumab
Macrophages
IL-1β
IL-17
Complement
factor
Neutrophil
Plasma cell
Autoantibodies
Immune
complexes
Glomerulus

TPE Applications



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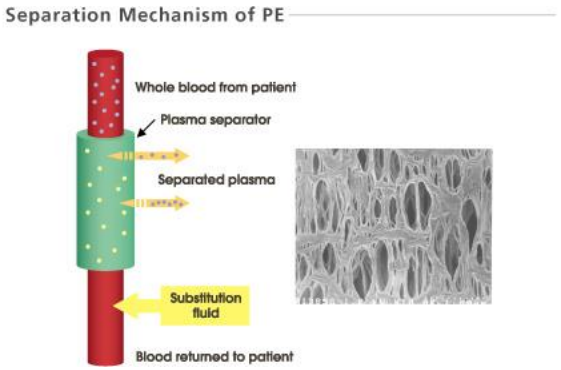
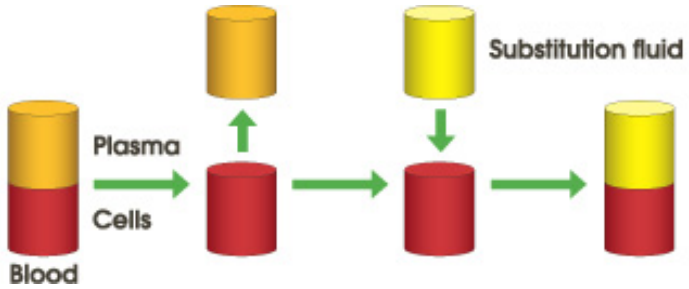
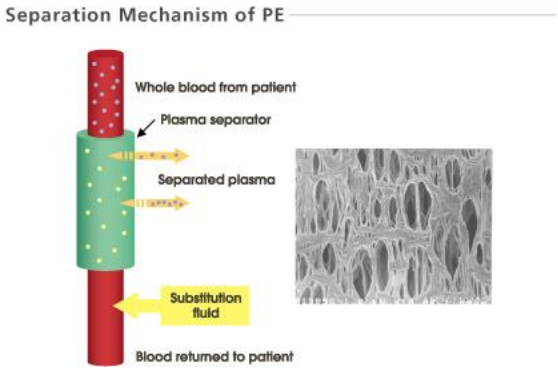
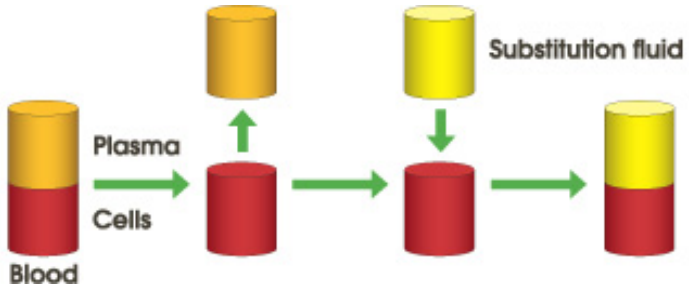
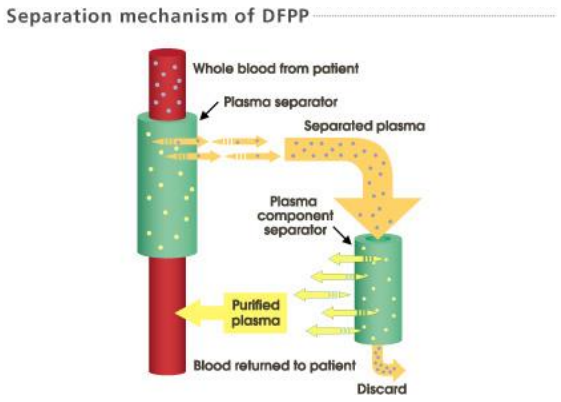

Separation Mechanism of PE
Whole blood from patient
Plasma separator
Separated plasma
Substitution fluid
Blood returned to patient


Substitution fluid
Plasma
Cells
Blood

TPE


Separation Mechanism of PE
Whole blood from patient
Plasma separator
Separated plasma
Substitution fluid
Blood returned to patient


Substitution fluid
Plasma
Cells
Blood


Separation mechanism of DFPP
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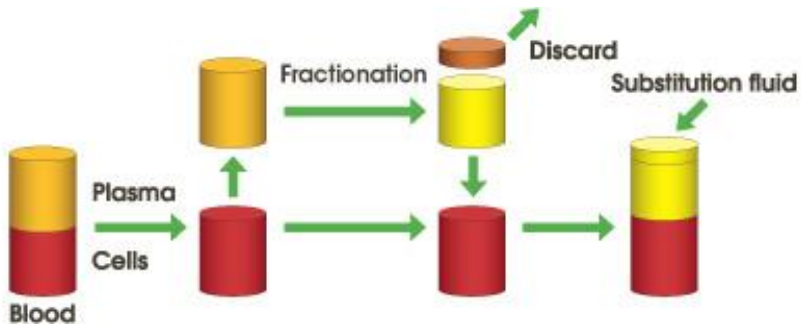
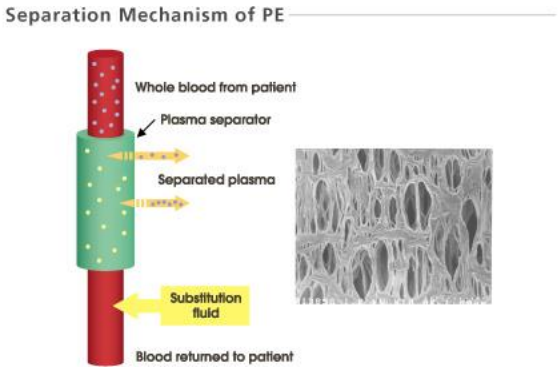
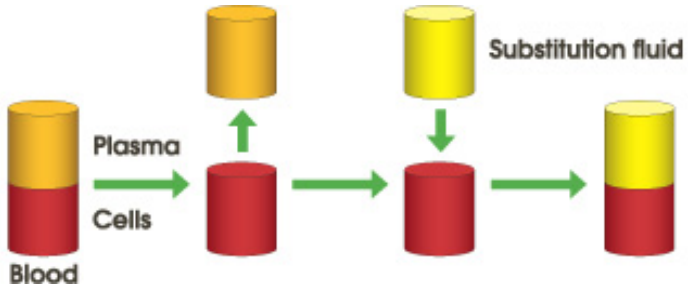
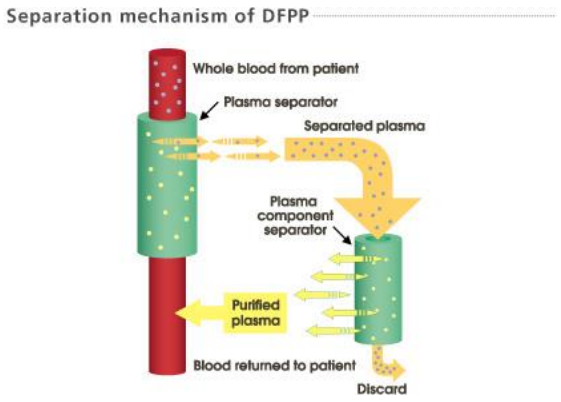
Plasma separator
Separated plasma
Plasma component separator
Purified plasma
Blood returned to patient
Discard

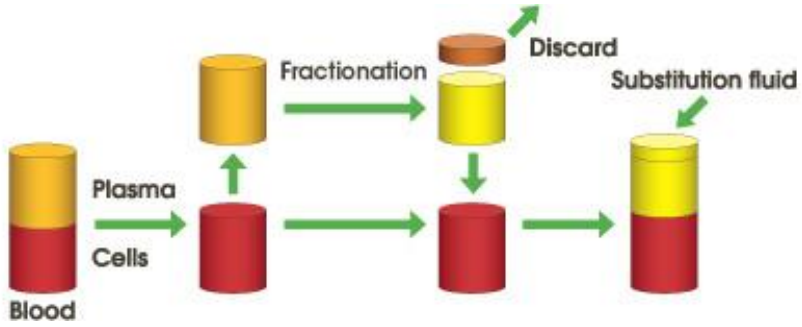

Fractionation
Discard
Substitution fluid
Plasma
Cells
Blood

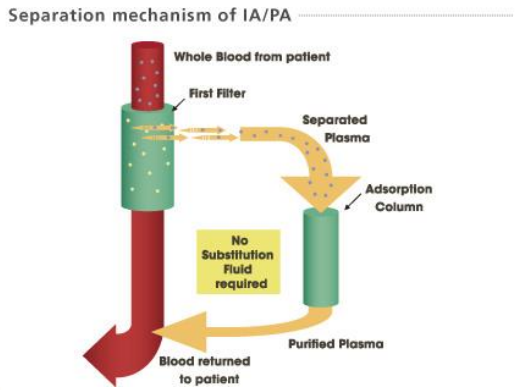
TPE


Separation Mechanism of PE
Whole blood from patient
Plasma separator
Separated plasma
Substitution fluid
Blood returned to patient

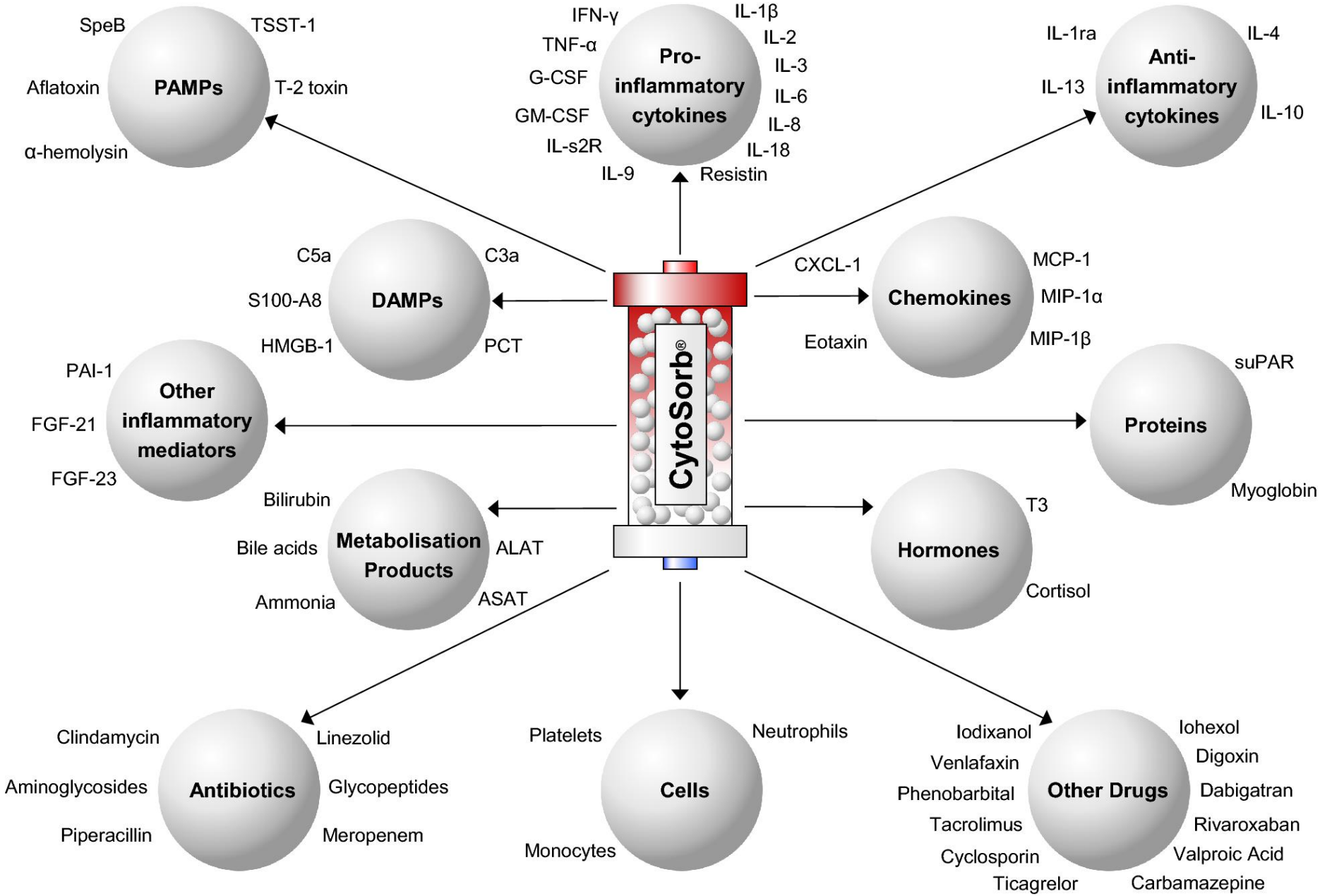

Substitution fluid
Plasma
Cells
Blood


Separation mechanism of DFPP
Whole blood from patient
Plasma separator
Separated plasma
Plasma component separator
Purified plasma
Blood returned to patient
Discard


Discard
Fractionation
Substitution fluid
Plasma
Cells
Blood


Separation mechanism of IA/PA
Whole Blood from patient
First Filter
Separated Plasma
Adsorption Column
No Substitution Fluid required
Purified Plasma
Blood returned to patient


Adsorption
Plasma
Cells
Blood


SpeB
TSST-1
Aflatoxin
PAMPs
T-2 toxin
α-hemolysin
IFN-γ
IL-1β
TNF-α
IL-2
G-CSF
Pro-inflammatory cytokines
IL-3
IL-6
GM-CSF
IL-8
IL-s2R
IL-18
IL-9
Resistin
IL-1ra
IL-4
IL-13
Anti-inflammatory cytokines
IL-10
C5a
C3a
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DAMPs
HMGB-1
PCT
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MCP-1
Chemokines
MIP-1α
Eotaxin
MIP-1β
PAI-1
Other inflammatory mediators
FGF-21
FGF-23
CytoSorb®
suPAR
Proteins
Myoglobin
Bilirubin
Bile acids
Metabolisation Products
ALAT
Ammonia
ASAT
T3
Hormones
Cortisol
Clindamycin
Linezolid
Aminoglycosides
Antibiotics
Glycopeptides
Piperacillin
Meropenem
Platelets
Neutrophils
Cells
Monocytes
Iodixanol
Iohexol
Venlafaxin
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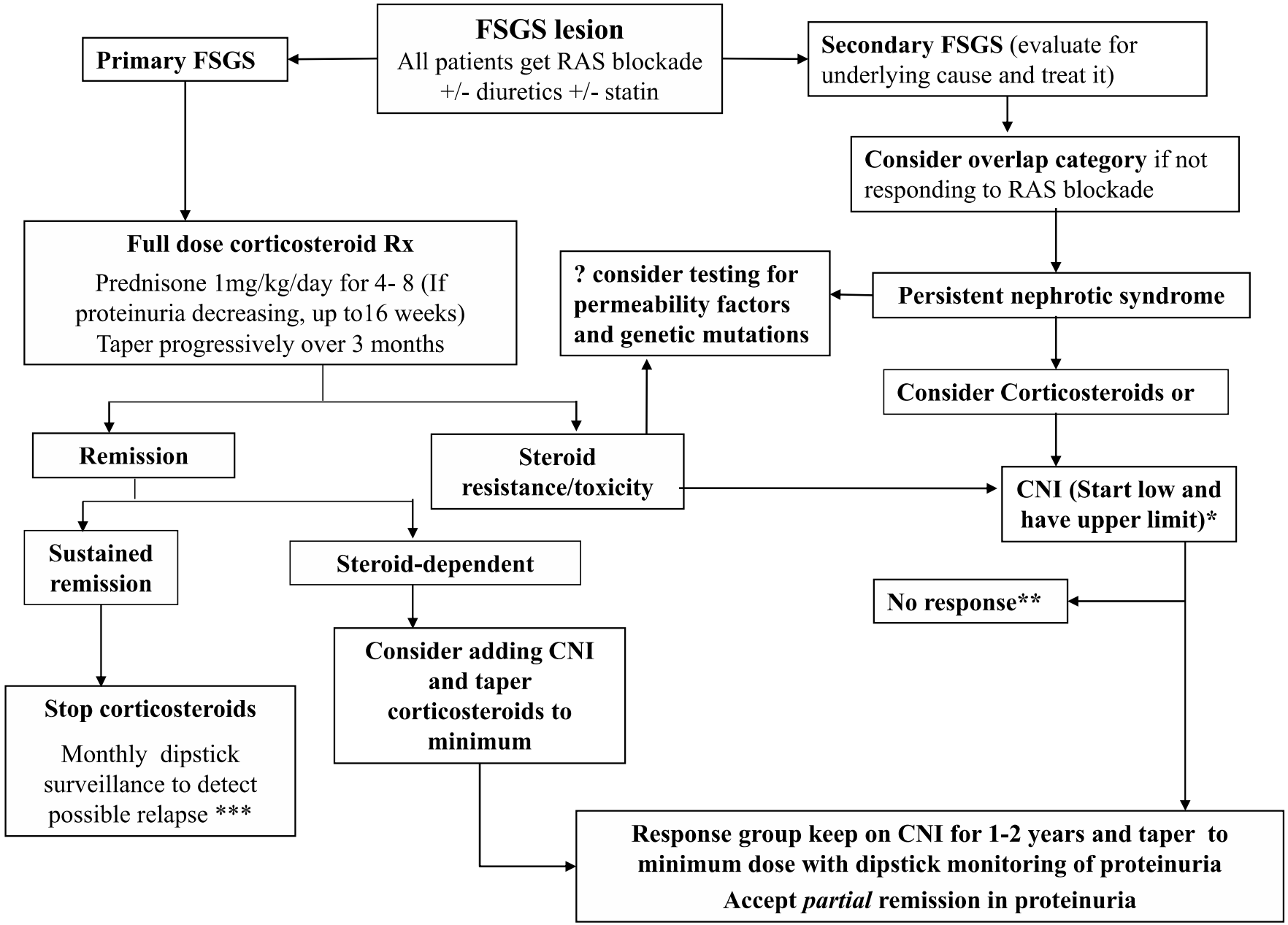
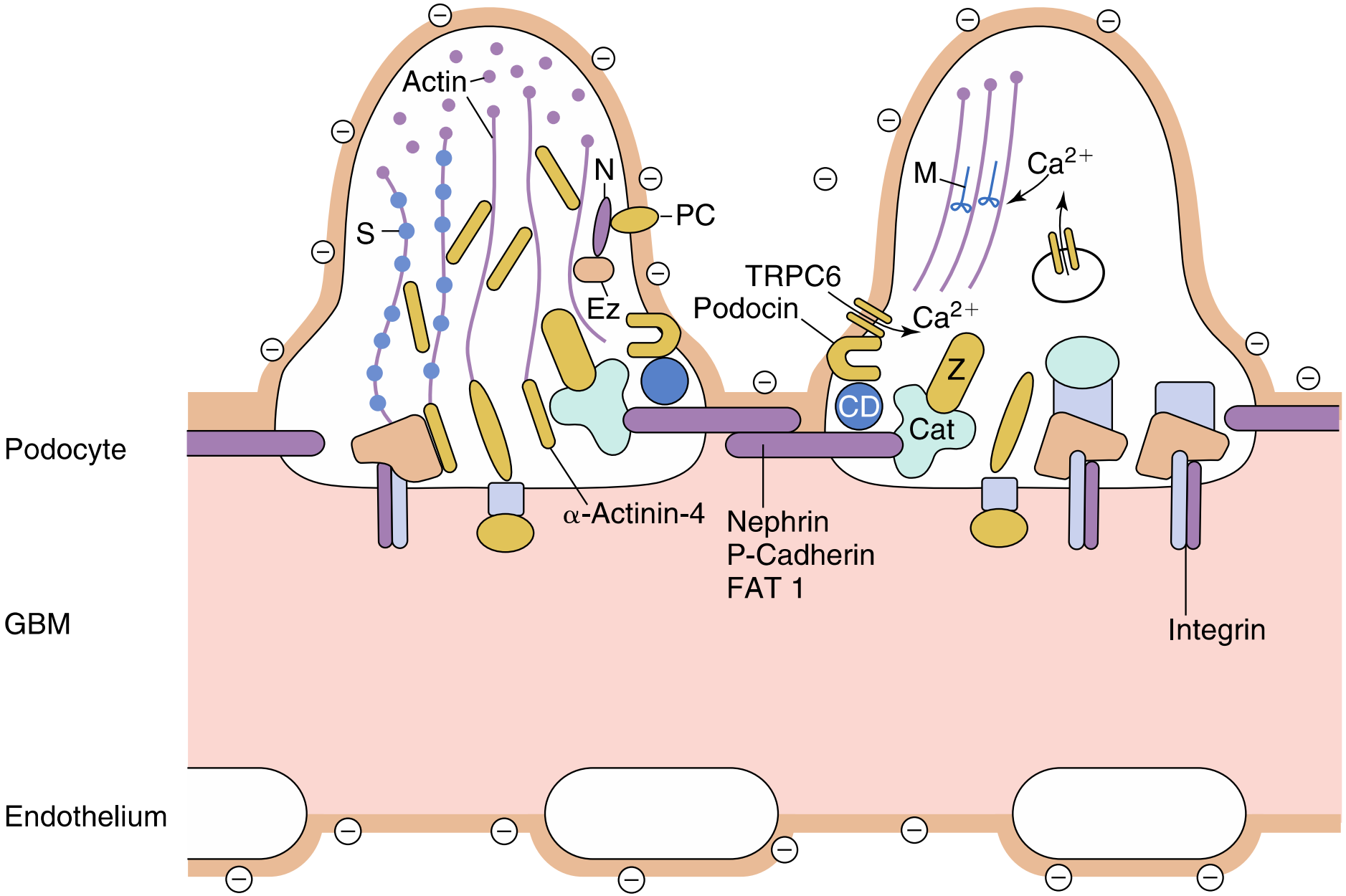

FSGS lesion
All patients get RAS blockade
+/- diuretics +/- statin
Primary FSGS
Secondary FSGS (evaluate for underlying cause and treat it)
Consider overlap category if not responding to RAS blockade
Full dose corticosteroid Rx
Prednisone 1mg/kg/day for 4- 8 (If proteinuria decreasing, up to16 weeks)
Taper progressively over 3 months
? consider testing for permeability factors and genetic mutations
Persistent nephrotic syndrome
Consider Corticosteroids or
Remission
Steroid resistance/toxicity
CNI (Start low and have upper limit)*
Sustained remission
Steroid-dependent
No response**
Stop corticosteroids
Monthly dipstick surveillance to detect possible relapse ***
Consider adding CNI and taper corticosteroids to minimum
Response group keep on CNI for 1-2 years and taper to minimum dose with dipstick monitoring of proteinuria
Accept *partial* remission in proteinuria

Things to Remember

- FSGS is a lesion, not a disease.
- The separation into primary FSGS (a result of immunologic-mediated injury) versus secondary FSGS (related to a variety of causes) is often difficult.
- MCD & Idiopathic FSGS: manifestation of the same disease.
- The etiopathogenesis of FSGS cannot be reliably determined by LM alone

MERCI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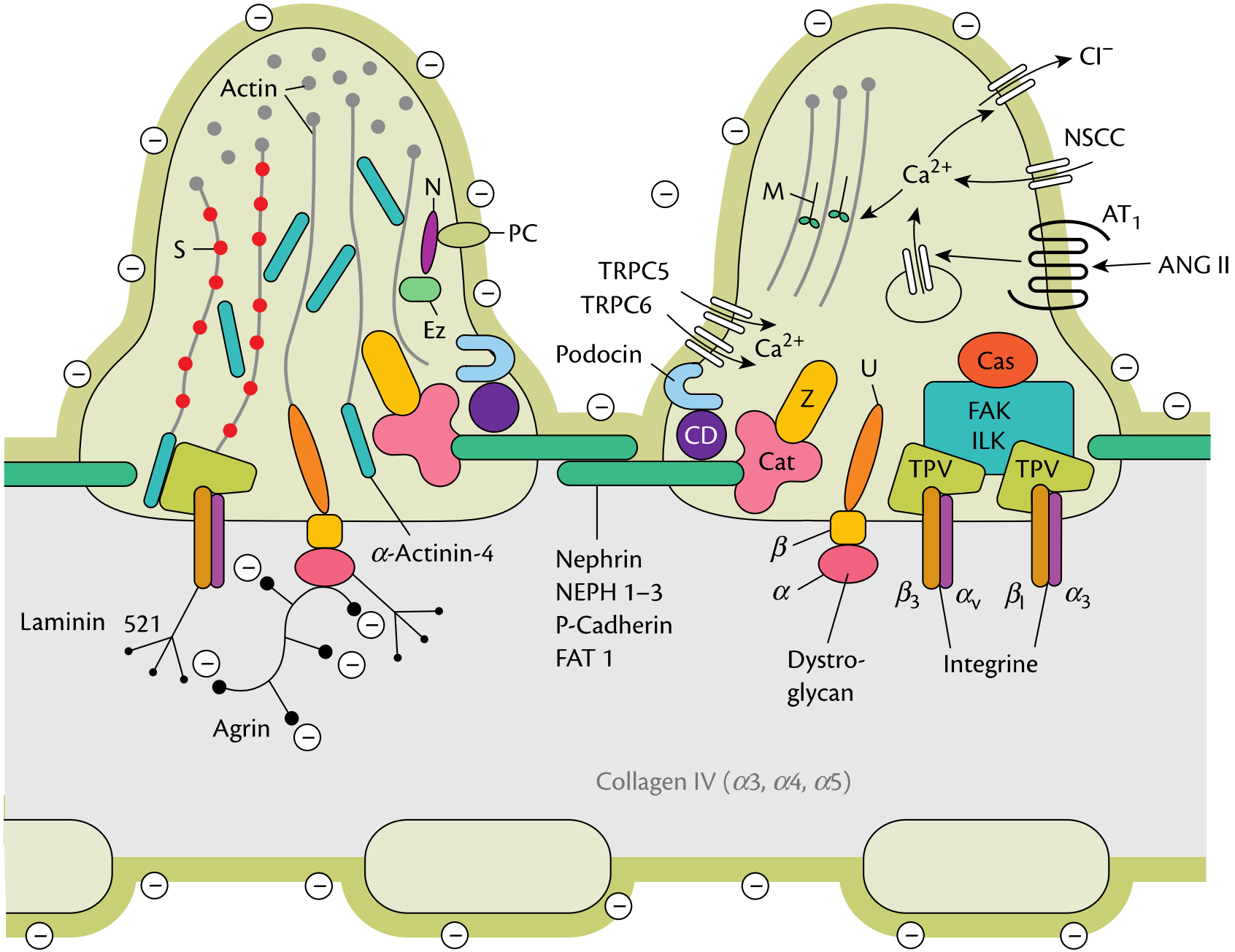
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TRPC6
Podocin
Ca2+
CD
Z
Cat
U
M
Cl−
NSCC
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ANG II
Cas
FAK
ILK
TPV
TPV
β
α
β3
αv
β1
α3
Dystro-
glycan
Integrine
Collagen IV (α3, α4, α5)