- founding the medical discipline of nephrology
- having performed the first renal transplantation in France in 1952
- Il est le créateur du concept de réanimation médicale en 1953 et de la discipline qu'il a proposé de nommer néphrologie,

- A nephrologist is a physician who specializes in the care and treatment of kidney disease. Nephrology requires additional training to become an expert with advanced skills. Nephrologists may provide care to people without kidney problems and may work in general/internal medicine, transplant medicine, immunosuppression management, intensive care medicine, clinical pharmacology, perioperative medicine, or pediatric nephrology.
- Nephrologists may further sub-specialise in dialysis, kidney transplantation, chronic kidney disease, cancer-related kidney diseases (Onconephrology), procedural nephrology or other non-nephrology areas as described above.
- Procedures a nephrologist may perform include native kidney and transplant kidney biopsy, dialysis access insertion (temporary vascular access lines, tunnelled vascular access lines, peritoneal dialysis access lines), fistula management (angiographic or surgical fistulogram and plasty), and bone biopsy

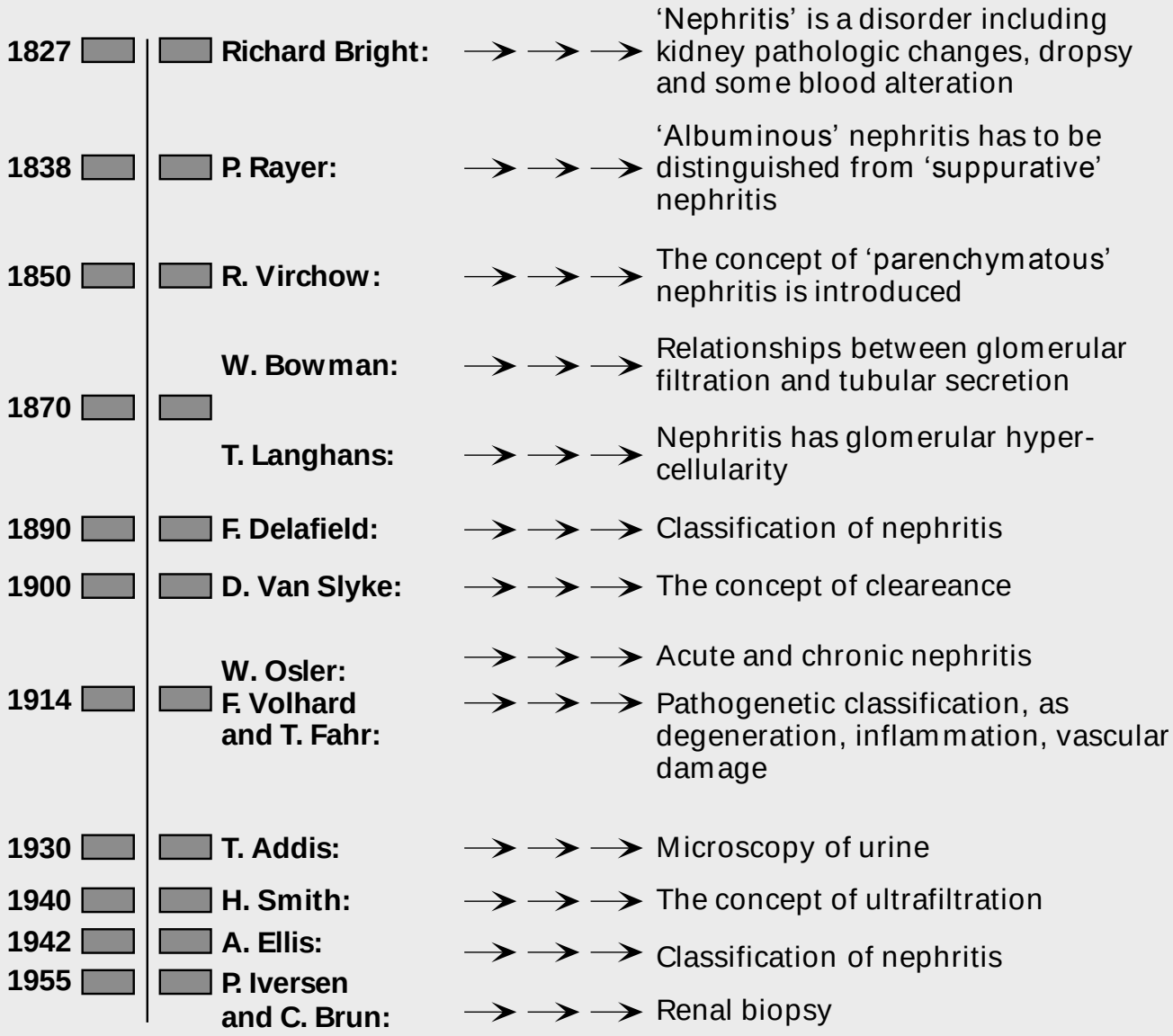
Glomerular Disease

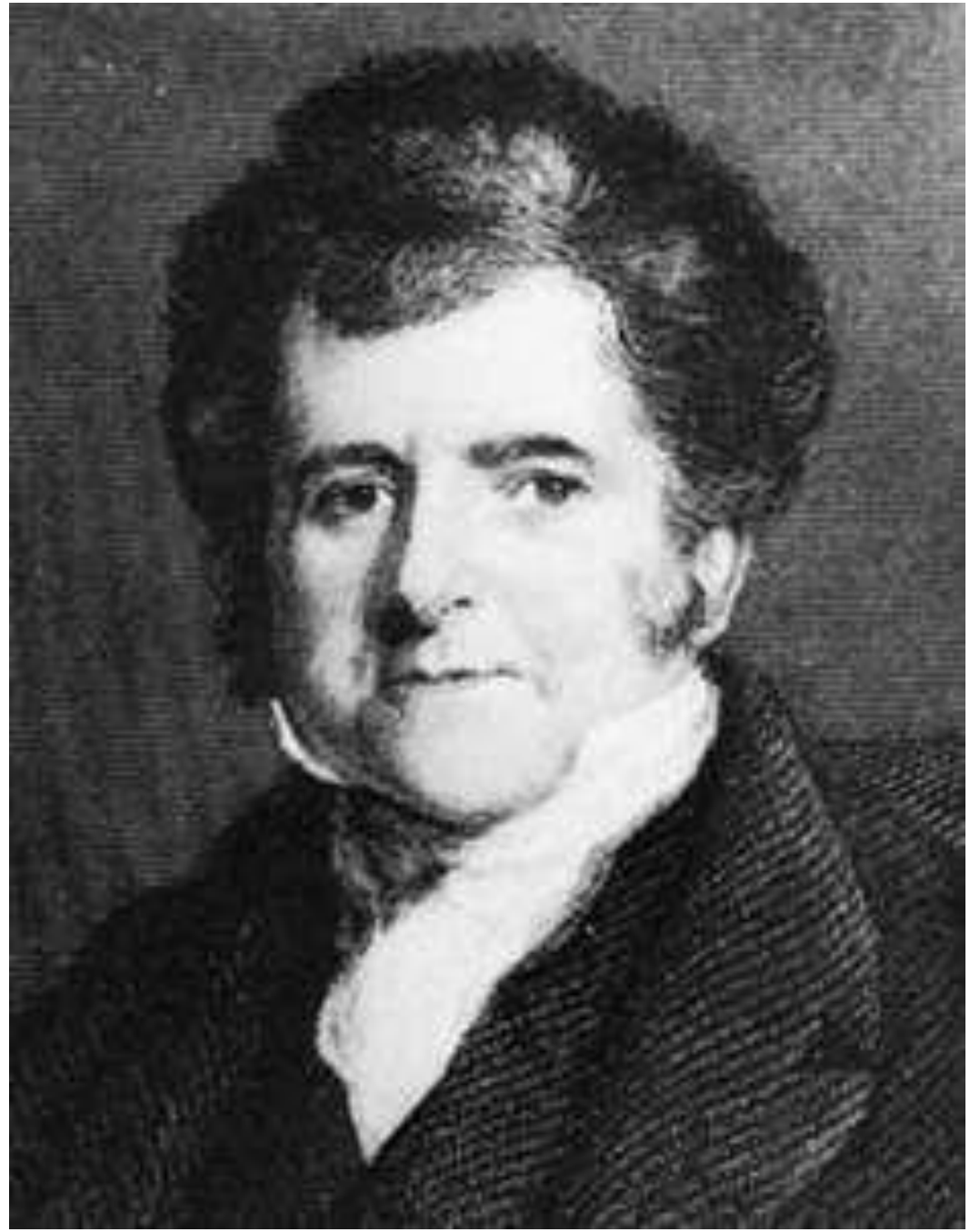
135th seminar

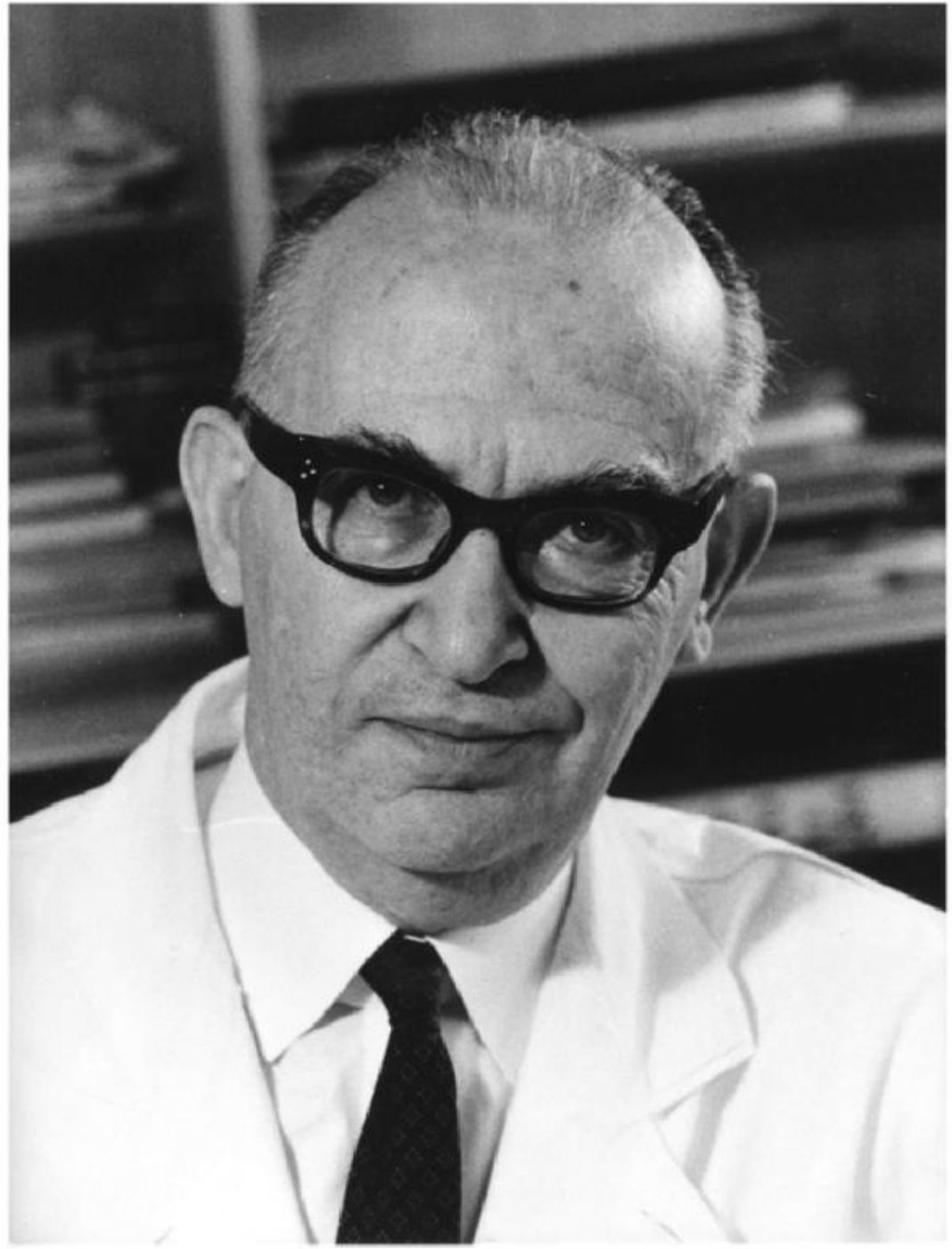
Iranian Society of Nephrology

July 2019

The line of the time







Renal Pathology

- Societe de Pathologie Renale founded; first nephrology society; first president Jean Hamburger; first meeting February 1949, Paris

- Jean Hamburger (Paris); founded the Société de Néphrologie, as a continuation of the older society, the Société de Pathologie Rénale 1959
- - Founding of ISN 1960 'Premier Congrès International de Néphrologie' in Evian and Geneva; first meeting of the ISN; where the word 'nephrology' appeared for the first time at a conference (2-4th September)

Glomerulonephritis

- In the second half of the 19th century, the term ‘glomerulonephritis’ was coined by Edwin T. Klebs (1834– 1913, Germany), and first appeared in the title of a scien- tific publication concerning a pathologic study.

- However, the concept of glomerulonephritis, in the sense of an inflammatory process, mainly confined to the glomerulus, gained evidence even in other works where the term ‘nephritis’ was still employed.

Nephrologist

- A nephrologist is a physician who specializes in the care and treatment of kidney disease. Nephrology requires additional training to become an expert with advanced skills. Nephrologists may provide care to people without kidney problems and may work in general/internal medicine, transplant medicine, immunosuppression management, intensive care medicine, clinical pharmacology, perioperative medicine, or pediatric nephrology.
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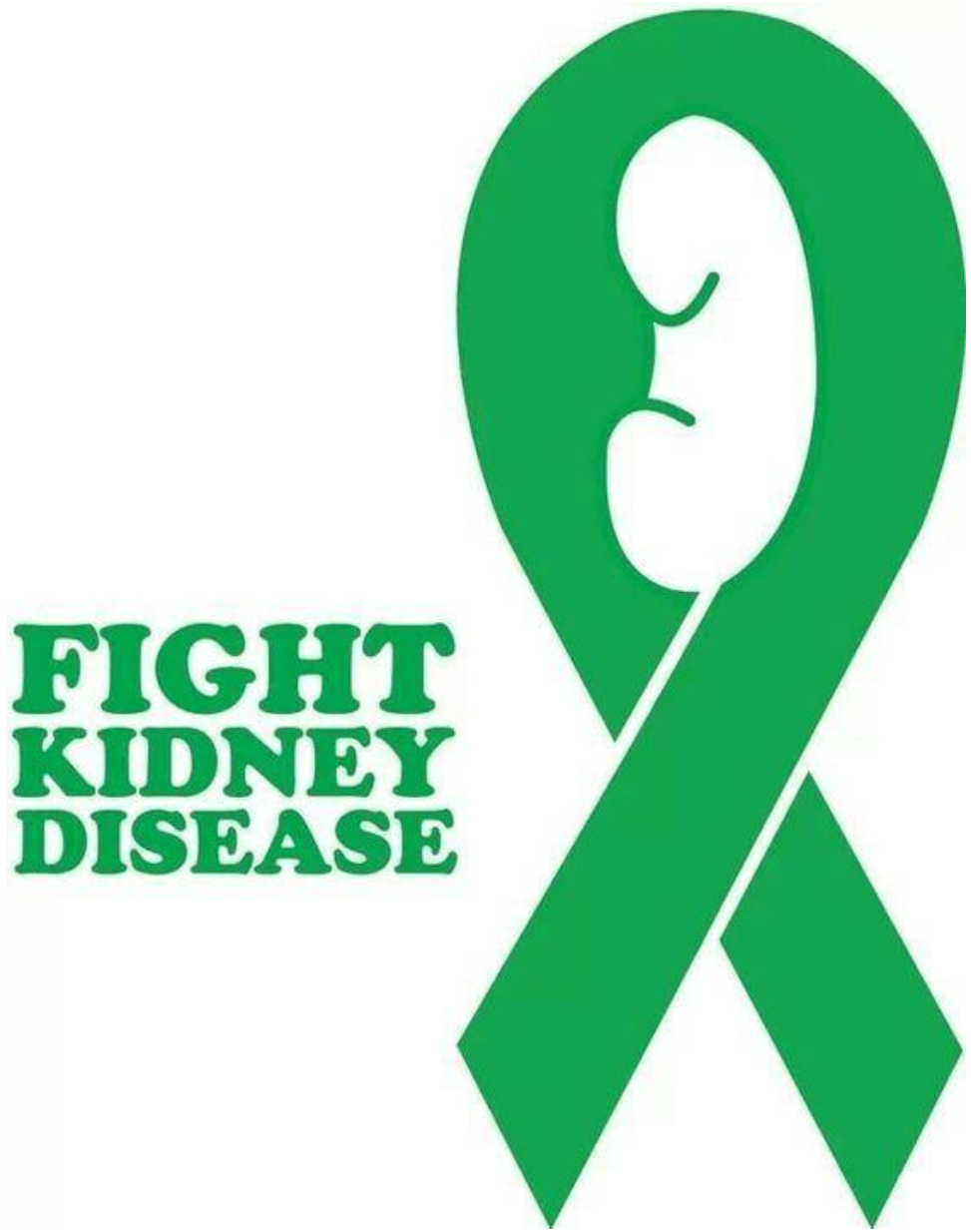

FIGHT
KIDNEY
DISEASE

- The first half of 19th century saw the advent of many brilliant protagonists of studies on kidney diseases (the word ‘nephrology’ having yet to be coined), shaped by a dominant interest in metabolic problems and pathophysi- ology.


Kidney
Disease
Awareness

Focal & Segmental Glomerulo-Sclerosis

Amir A. Nassiri, M.D, D.I.U

SBUMS

2019

FSGS

- FSGS is a common “histologic” lesion (not in the elderly – vs FGGS)
- FSGS is either primary or adaptive (2nd to nephron mass reduction)
- FSGS is primarily a visceral epithelial cell (podocyte) injury (Focal & segmental by LM)
- FSGS is a “misleading name” (neither focal & nor segmental) >>> podocytes injury in the **entire** glomerular population by EM >>> the lesions are not really segmental & only rarely tuly focal
- FSGS >>> not focal >>> the entire glom population, so not focal & >90% 0f a glomeruli is involved, and so not segmental
- LM & single sections >>> underestimates the % of abnormal sclerotic injury >>> <15 glom cannot exclude FSGS & lesions are initially JXM and not cortical
- Glom is a sphere >>>3-D glom morphologic analysis >>> after subtotal Nx >90% abnormal
- EM required for the proper Dx
- EM evaluation of the “non-sclerosed glom” >>> confer a primary podocytothopathy >>> and if + widespread foot process effacement >>> support for IS ttt
- FSGS is not a “disease” >>> represent a process, leading ultimately to identification of a specific etiology & its ttt

Primary vs Secondary

- Primary: widespread effacement of foot process >>> Pr-uria like MCD

- Secondary (post-adaptive): glomerular tuft hyper-trophy & the number of podocyte do not increase >>> stretched podocyte >>> to cover a larger surface area >>> podocyte ”attenuation” >>> foot processes are largely preserved >>> areas of podocyte detachment & attachement to Bowman’s caps >>> synechia (sclerosis)

- FSGS accounts for nearly 5% to 10% of pediatric and adult patients who progress to end-stage kidney disease (ESKD).

Molecular Markers

WHAT HAS RECURRENT PRIMARY FSGS POST-TRANSPLANT TAUGHT US?

- In recurrent FSGS post-Tx >>> diffuse FPE within minutes after reperfusion !
- Diffuse FPE >>> followed by massive Pr-uria (hrs to days after Tx) & with time, FSGS lesions develops !
- Thus >>> **FPE** is the **"earliest" structural change** & **KEY initial event** in the development of FSGS
- A putative "**circulating permeability factor**" proposed >>> to play a role in the pathogenesis of primary FSGS >>> supported by clinical and experimental evidence >>> rapid appearance of Pr-uria following KTx & the efficacy of TPE (or IA) in reducing Pr-uria following recurrence & serum of FSGS into rats to causes Pr-uris,…

- A variety of permeability factors of different biochemical nature !
- the soluble form of the urokinase-plasminogen activator receptor (suPAR) has been proposed as the missing permeability factor.
- The uPAR has important functions in **cell migration** and in the **maintenance of the slit diaphragm** through its ability to form signaling complexes with other transmembrane proteins, including αvβ3 integrin.
- It can be **released from the plasma membrane of many cells** including **leukocytes and podocytes** **in the form of suPAR** and has also been found to be **up-regulated in FSGS**

- Activation of podocyte beta-3 integrin by high levels of suPAR >>> podocyte effacement , Pr-uria, glom damage & loss of renal function.

- Patients with FSGS have elevated levels of suPAR with high levels seen in patients with post-transplant recurrent disease

- Increased activation of β3-integrin has been reported in the native glomeruli of patients with primary FSGS as well as in the transplanted kidney, compared with controls with MCD or membranous nephropathy.

- A decrease of serum suPAR and β3-integrin activation after plasmapheresis has been associated with remission of proteinuria.

- Although the results from in vitro and animal studies are highly suggestive of a role for suPAR in the pathogenesis of FSGS, a number of **recent studies** have added **skepticism** to the specific pathogenic role of suPAR in ‘primary’ FSGS (reviewed in [38])
- Maas RJ, Deegens JK, Wetzels JF. Serum suPAR in patients with FSGS: trash or treasure? Pediatr Nephrol 2013; 28: 1041–1048

- Briefly, the data need to be reconciled with the fact that:
- (i) suPAR levels (at least the isoforms measured by conventional assays) are very much determined by the prevailing glomerular filtration rate (GFR) level [39];
- (ii) the exact source of the suPAR found in the plasma of some subjects with primary FSGS is unknown;
- (iii) elevated suPAR levels (even higher than patients with biopsy- proven FSGS) have been reported in other glomerular diseases [40, 41] as well as a number of diseases in the absence of pro- teinuria [42–46];
- (iv) pretransplant suPAR levels do not predict the recurrence of FSGS following transplantation [47, 48];
- (v) serum suPAR levels are higher in FSGS secondary to genetic mutations compared with primary FSGS [48];
- (vi) a significant number of patients with FSGS have normal suPAR levels;
- (vii) the specificity of elevated serum suPAR levels for primary versus secondary forms of FSGS and other primary glomerular diseases is debated

suPAR ?

- At the present time, it seems **doubtful** that measurement of **plasma suPAR levels** (with available assays) will be able to **accurately distinguish primary from secondary forms of FSGS** [40], but additional work in this area may ultimately yield a biochemical marker that is unique to primary FSGS.

PRIMARY VERSUS SECONDARY FSGS:
CAN MOLECULAR MARKERS HELP TO DIFFERENTIATE ?

- Podocyte expression of CD-80 may help to diff between primary vs 2nd FSGS
- CD-80 >>> a co-stimulatory molecule, associated with an increased glom permselectivity
- Enhanced podocyte CD-80 expression (animal model) >>> Pr-uria
- CD-80 >>> not commonly expressed in normal human podocyte & **up-regulated** in some pts with certain glom disease like **MCD** and to a **lesser degree in primary FSGS**
- CD-80 >>> +ve stain in primary FSGS & absent in 2nd FSGS (despite extensive podocyte damage) & in recurrent FSGS post-Tx

- Increased urinary CD-80 in MCD with relapse BUT NOT in MCD in remission or FSGS
- At present time: CD-80 in urine or IHC in Bx specimens >>> could not be useful to diff between MCD & FSGS or to distinguish primary vs 2bd FSGS

PRIMARY VERSUS SECONDARY FSGS: WHAT IS THE ROLE OF EM EXAMINATION?

Role of EM

- An important consideration in the evaluation of renal Bx showing FSGS pattern on LM >>> the degree of FP effacement – FPE (on EM)
- The degree of FPE on EM >>> correlated with the amount of Pr-uira
- The degree of FPE on EM >>> determined by the “nature” of the pathogenic process affecting the podocyte
- 2nd FSGS >>> % glom area affected by FPE is less (vs primary FSGS) & FP are relatively “preserved; in 2nd cases of FSGS
- FPE is more severe in primary FSGS

- Variants of primary FSGS (tip, cellular, collapsing) >>> have widespread FPE
- NOS (not otherwise specified) variant >>> FPE is variable
- Peri-hilar >>> FPE may be relatively mild & segmental
- 2nd FSGS (because they are commonly adaptive) >>> FPE is mild + sub-nephrotic range Pr-uria
- Primary FSGS >>> more likely resemble MCD on EM (wide FPE & Nephrotic Pr-ria)
- Toxic drug or viral-induced forms of secondary FSGS may show extensive foot process effacement.

- the degree of foot process effacement by EM is a crucial clue to a primary versus secondary form of FSGS,
- with some exceptions, such as cases of ‘collapsing’ FSGS, secondary to HIV [56], interferon [57] or pamidronate [58] therapy that are characterized by widespread foot process effacement on EM.

- In addition, some patients can exhibit widespread foot process effacement while presenting with subnephrotic-range proteinuria. Typically, these latter patients have primary forms of FSGS

- It is critically important to select relatively intact and not segmentally sclerosed glomeruli for ultrastructural studies.
- Segmentally sclerosed or scarred glomeruli in the setting of either primary or secondary FSGS may show extensive foot process effacement.
- On the other hand, nonsclerosed glomeruli in primary FSGS show widespread foot process effacement, while there is only segmental effacement in secondary FSGS
- Sclerosed area >>> wide FPE
- If non-sclerosed area show (wide) FPE >>> think for primary FSGS

- **Rarely**, however, a patient may present with **widespread foot process effacement** without nephrotic syndrome >>> crucial that a nonsclerotic glomerulus is selected for EM

- If a nonsclerotic glomerulus is selected and the patient is non-nephrotic, we would recommend conservative treatment only, with a close follow-up (because it may represent early phase primary FSGS) and
- only consider immunosuppres- sive therapy if there is progression to full nephrotic syndrome (see section on treatment below).

- rarer scenario is a patient with a full nephrotic syndrome with segmental foot process effacement on EM of a nonsclerosed glomerulus.
- In this case, it is important to rule out the (Hx of) use of immunosuppressive therapy prior to or concomitantly at the time of the renal biopsy, because the EM findings may represent a resolving process.

- If true segmental foot process effacement is present on EM as well as nephrotic syndrome, we would recommend maxi- mizing conservative therapy and, if the nephrotic syndrome persists, then commence on a trial of corticosteroid therapy.

THE IMPORTANCE OF DISTINGUISHING NEPHROTIC-RANGE PROTEINURIA FROM NEPHROTIC SYNDROME

Primary FSGS >>> Nephrotic Syndrome
Secondary FSGS >>> Nephrotic Range Pr-uria

- It should also be recognized that **nephrotic-range proteinuria** (>3.5 g/24 h) and **nephrotic syndrome** (>3.5 g/24 h and serum albumin <3.5 g/dL) are not necessarily synonymous
- Important clinical distinction particularly in patients with ne- phrotic-range proteinuria in which a kidney biopsy shows FSGS, but who do not have full-blown nephrotic syndrome
- These patients are more likely to have FSGS due to a sec- ondary process while patients with **primary FSGS** are more likely to present with nephrotic syndrome and marked edema and hyperlipidemia.
- patients with **secondary FSGS** are less likely to have edema or hyperlipidemia

- Primary FSGS >>> Nephrotic Syndrome
- Secondary FSGS >>> Nephrotic Range Pr-uria

- Patients with obesity-related FSGS, reflux nephropathy or renal mass reduction do not develop complete nephrotic syndrome even in the presence of massive proteinuria (>10–15 g/day)
- The reason why patients with secondary FSGS do not develop hypoalbuminemia is unknown
- the **very slow appearance of proteinuria** observed in **secondary** FSGS may allow for compensatory mechanisms to **counterba-lance the loss** of protein, while in patients with **primary FSGS** the onset is **sudden**.

Sudden Pr-uria >>> Primary
Slowly progressive Pr-ruia >>> Secondary

- The sudden onset of severe proteinuria and edema is another clue that the physician is dealing with a patient with primary FSGS, which is in contrast to secondary FSGS where edema is usually absent or develops gradually

- In- terestingly, a significant number of patients with **collapsing FSGS** do not present with edema despite massive proteinuria perhaps due to the **rapid loss in GFR**

True, Primary FSGS >>> more NS

- It has been often stated that nephrotic syndrome occurs in only 50–60% of patients with FSGS, but in our opinion this is due to failure of past studies to recognize the differences between primary and secondary FSGS.
- The inclusion of such patients, as well as African-Americans labeled as FSGS (see below) in previous studies has given the impression that nephrotic syndrome is less common in FSGS than in MCD.

- it is important to verify the identity of the proteinuria:
- is it due mainly to albumin? or is it due to other proteins?

- it is important to rule out proteinuria due to low-molecular-weight (LMW) proteins (retinol-binding protein, beta-2-microglobulin and alpha-1-microglobulin) or light chain proteins in patients presenting with a focal glomer- ular lesion (FSGS or FGGS).

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

- Tubulopathies can give rise to focal glomerular lesions, predominantly of the FGGS category
- A simple approach is to 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.
- A similar clue that **proteins other than albumin account** for the proteinuria is the finding of a **dipstick proteinuria of trace/1+** in a patient with a **quantified urinary protein >1 g/24 h**.

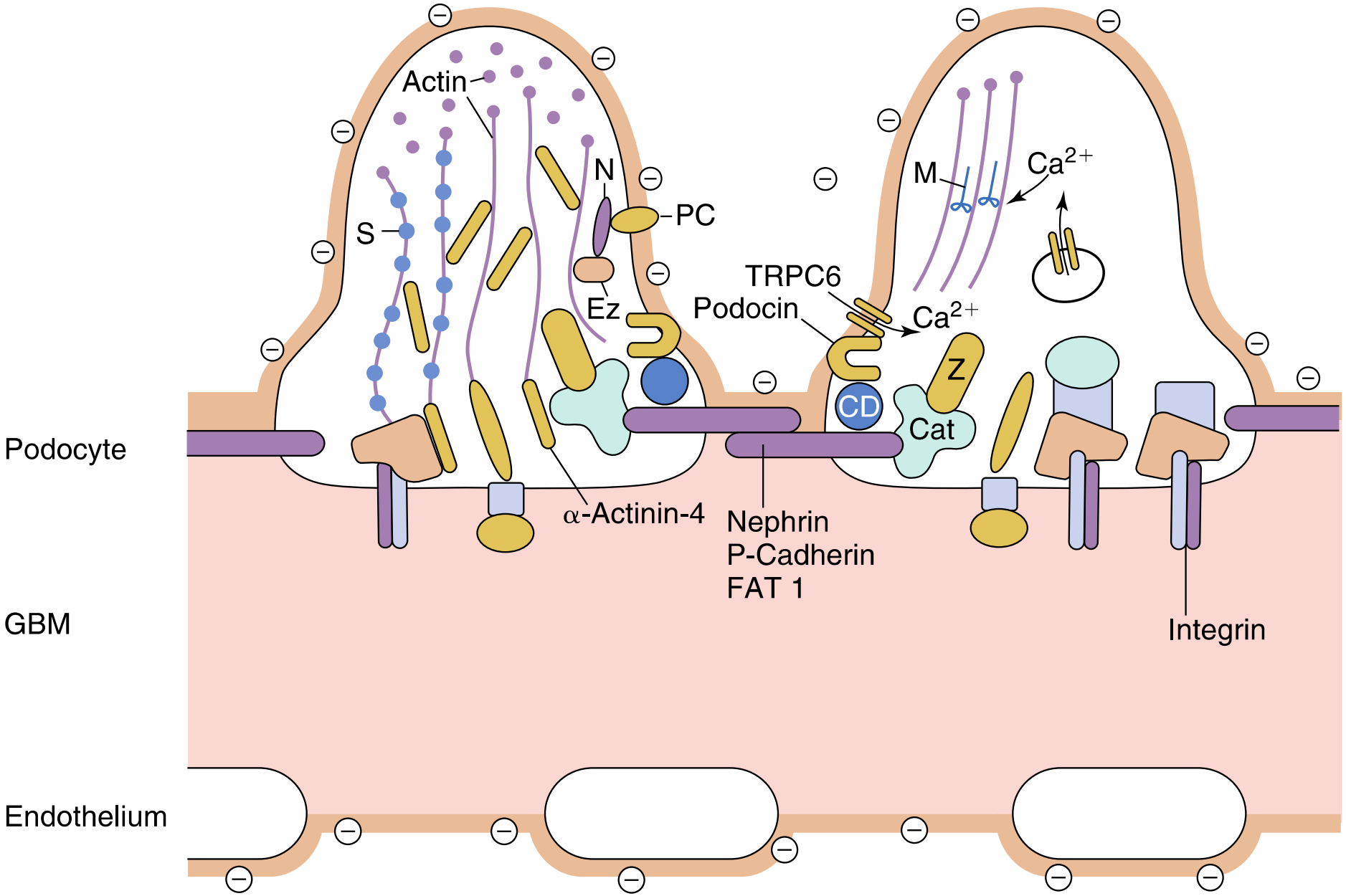
FSGS in AA >>> different from primary FSGS in Caucasians

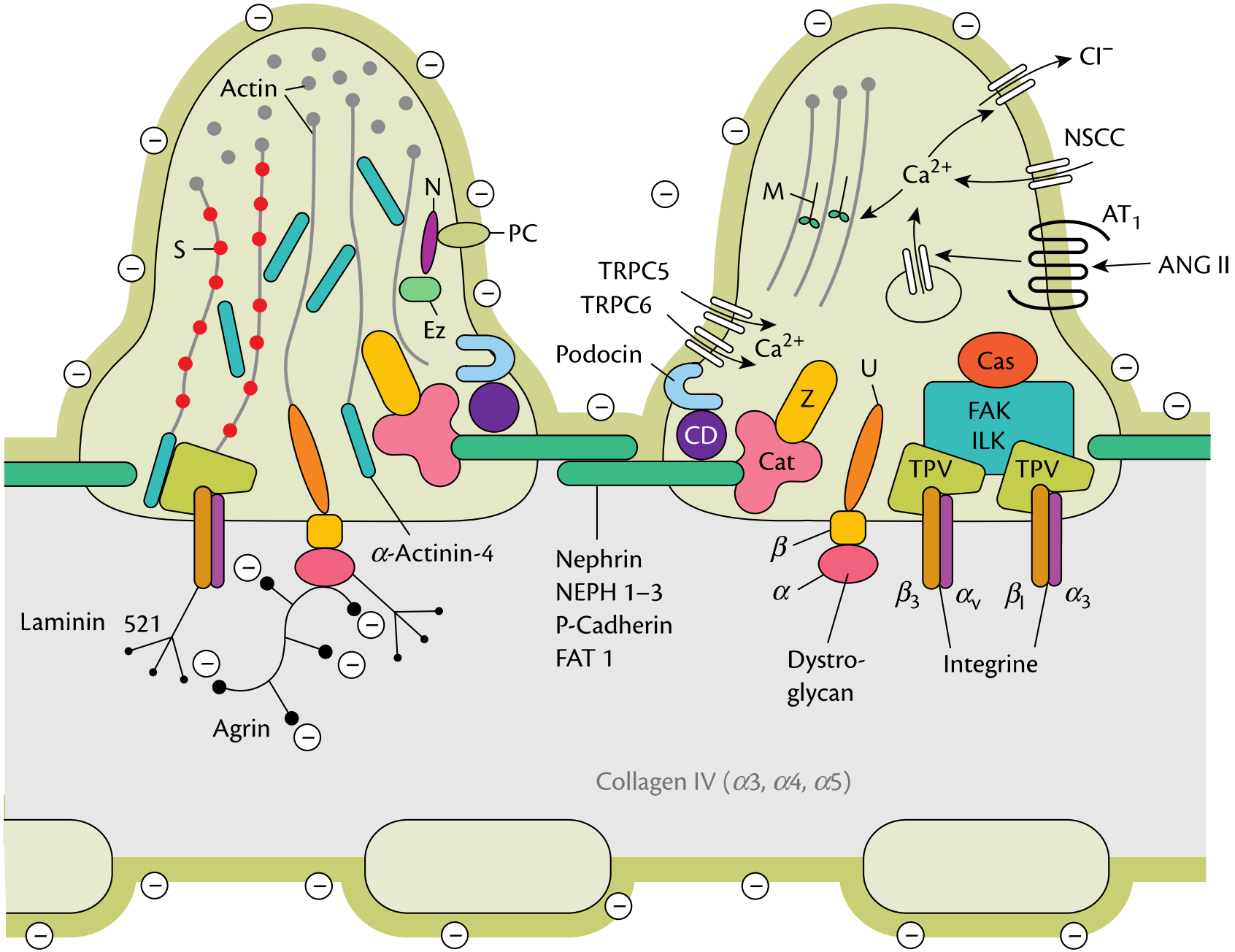
- The confusion between primary and secondary FSGS also applies to the diagnosis of **FSGS in African-Americans**,
- which we think is an altogether **different disease from primary FSGS seen in Caucasians.**

- In **African-American** patients **without nephrotic syndrome**, with an **FGGS** lesion on renal biopsy that reveals only segmental foot process effacement on EM and who also have the APOL1 gene risk variants, the diagnosis should be '**APOL1-associated nephropathy**' (the term nephropathy to reflect the fact that ***it is more than pure glomerulosclerosis***).
- Abnorm- alities in APOL1 expression in the arterial beds may alter cellular physiology as to promote vascular sclerosis
- APOL1 overexpression results in an increase in the rate of cell death from autophagy or apoptosis, which may be the main pathogenic mechanism leading to the development of APOL1-associated nephropathy

GENETIC CAUSES OF FSGS:
DO THEY ALL CAUSE NEPHROTIC SYNDROME?

- It is clear that a number of genetic mutations varying from genes coding for proteins of the slit diaphragm [NPHS1 (nephrin), NPHS2 (podocin) and CD2AP], podocyte membrane (β4-integrin, CD151, PTPRO, TRPC6 and laminin β2), cytosol (PLCE1), actin cytoskeleton (inverted formin, myosin IIA, α-actinin-4 and MYO1E), lysosomes (SCARB2/LIMP-2), mitochondria [COQ2, tRNA(Leu) and COQ6] and cellular nucleus (WT1) result in proteinuria and a FSGS lesion on renal biopsy


Actin
N
PC
S
Ez
TRPC6
Podocin
M
Ca2+
Ca2+
Z
CD
Cat
α-Actinin-4
Nephrin
P-Cadherin
FAT 1
Integrin
Podocyte
GBM
Endothelium


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

- The majority of the genetic causes of FSGS follow an **autosomal recessive** pattern of inheritance and are manifested in the first year of life with mutations in **nephrin and podocin genes** (NPHS1 and NPHS2, respectively) being the most common.
- **Autosomal dominant** forms (e.g. mutations in α-actinin-4, TRPC6) more commonly present during adolescence or later in adulthood
- FSGS presenting in **adulthood is rarely attributed to a specific mutation** (<15% of all adult cases)
-

Genetic FSGS:
Nephrotic Syndrome or Nephrotic-range Pr-uria

- while full nephrotic syndrome has been clearly documented among infantile and adolescent cases of FSGS caused by genetic mutations, in the **majority of adults with genetic forms of FSGS proteinuria is not massive** (usually <5 g/24) and they do not frequently develop a full-blown nephrotic syndrome.
- In fact, reviewing the literature, it is surprising that documentation regarding the full phenotype in these patients (i.e. presence of nephrotic syndrome versus nephrotic-range proteinuria alone) is not reported in the great majority of studies

FSGS due to Genetic Mutation:
relatively benign (low IS ttt needed & Low recurrence rate)

- The understanding of these differences is important, because adult patients with **FSGS secondary to a genetic mutation**:
- 1- should **not** be treated with **prolonged steroid therapy** and
- 2- have a **low** propensity for a **recurrence** of FSGS in a **transplanted** kidney.

TREATMENT OF FSGS IN A NUTSHELL

- Patients with **primary FSGS** very rarely develop spontaneous remissions of the disorder
- Initial therapy with an **angiotensin- converting enzyme inhibitor or an AII receptor blocker** is often recommended, but such treatments have ***no impact in the degree of foot process effacement*** and are unlikely to **greatly** reduce proteinuria or preserve renal function, unless moderate to severe **hypertensio**n is also present and is well controlled (<140/90 mmHg) on these medications

- Primary FSGS (possibly excluding advanced forms of collap- sing FSGS or the rare primary forms of the perihilar variant of FSGS) can respond to **high-dose corticosteroids** although at a lower rate than MCD and requires a **more prolonged course** of therapy

- **Oral prednisone** or prednisolone, at a dose of **1 mg/kg/day** orally (not to exceed 80 mg/day) for **at least 4 months**, is the traditional therapeutic regimen, although there are very few randomized controlled studies to support its use !
- **Steroid resistance** is considered for a patient who **fails** to respond with a **partial or complete** remission of proteinuria **after 4 months** of **high-dose** corticosteroids

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 (The UK National Comprehensive Cancer Network >>> Pneumocystis prophylaxis if pts receive >20 mg/day PRD over 4 w) & American thoracis Society >>> IS pts without HIV >>> Pneumo prophylaxis if PRD >20 mg/d for 1 mo

- 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)
- In our opinion, CNI can also be used as monotherapy, when concomitant use of corticosteroids is of concern.
- 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.

- **Long-duration** (e.g. >1 year), **low-dose CNI** therapy may be considered in patients with CNI-dependency, but the prospect of **cumulative nephrotoxicity** of these agents looms on the horizon and requires very careful attention, and **re-biopsy** in some cases

- The **CNI agents** as a class are best regarded as **anti-proteinuric agents** **rather than immuno-suppressive** agents in the context of treating **primary FSGS**.

- They have **little or no effect on the putative circulating factors** likely responsible for primary FSGS and do **not prevent its re-currence in renal allografts**

-

- Mycophenolate mofetil [98], adre-nocorticotropic hormone (native ACTH) and rituximab, have all been tried with various degrees of success, mostly in patients **refractory to corticosteroids and/or CNI treatment.**

- Patients with primary FSGS who are **steroid and CNI-resistant** are **unlikely** to respond to **rituximab** or cyclophos-phamide

- There has been one report of successful use of **sirolimus** in patients with FSGS, but the use of this medication in patients with **high-degree proteinuria** carries the **risk of acute renal failure**

- 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**

- **Plasmapheresis and rituximab** are important therapeutic options in the prevention and/or treatment of **recurrent FSGS after kidney transplantation**
- A recent study reported on the beneficial effect with the use of **Abatacept** [cytotoxic T-lymphocyte-associated antigen 4-immunoglobulin fusion protein (CTLA-4-Ig)], a co-stimulatory inhibitor that **targets CD80**, in five patients with recurrent FSGS after transplantation and in one patient with primary FSGS with all patients showing positive podocyte CD80 staining on renal biopsy.
- In patients with recurrent FSGS, a single dose of Abatacept induced partial or complete remissions of proteinuria, suggesting that Abatacept may stabilize β1-**integrin activation in podocytes** and reduce proteinuria in patients **with CD80-positive glomerular disease**
-

- Patients with secondary FSGS should be treated conservatively aiming to maximize blood pressure control with the use of AII blockade, low salt diet (<4 g/day), moderate protein diets (0.8–1 g/kg/day), lipid control with the use of a statin, smoking cessation, weight control and avoidance of nephrotoxic medications.
- Blood pressure should be strictly controlled to values <140/90 mmHg.

Conclusion

- The most important lesson is that “FSGS is a lesion” and “not a disease”.
- The finding of FSGS lesion in a renal Bx of a pt with Pr-uria >>> is the start of an exploratory process (hopefully) leading to a “specific disease Dx” and not an end in itself
- Primary FSGS >>> more likely to have “full-blown NS” & “very extensive FPE” on EM
- Secondary FSGS >>> more likely to have sub-nephrotic or only nephrotic-range Pr-uria (& not NS) and in EM >>> more likely to show segmental FPE

Diagram helping the practicing clinician to differentiate/classify between primary vs secondary FSGS, according to clinical presentation

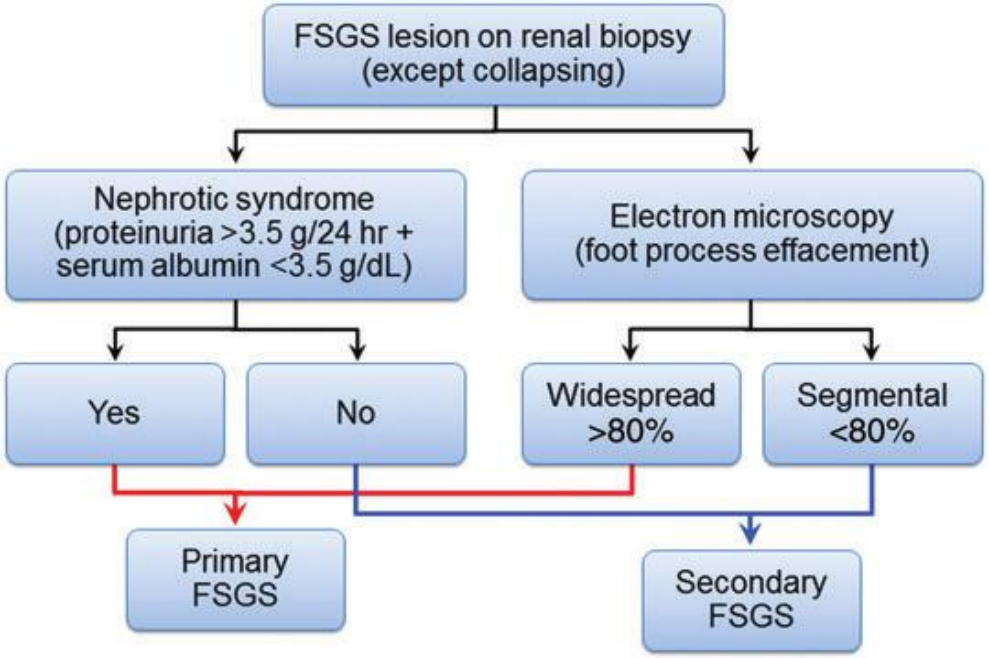
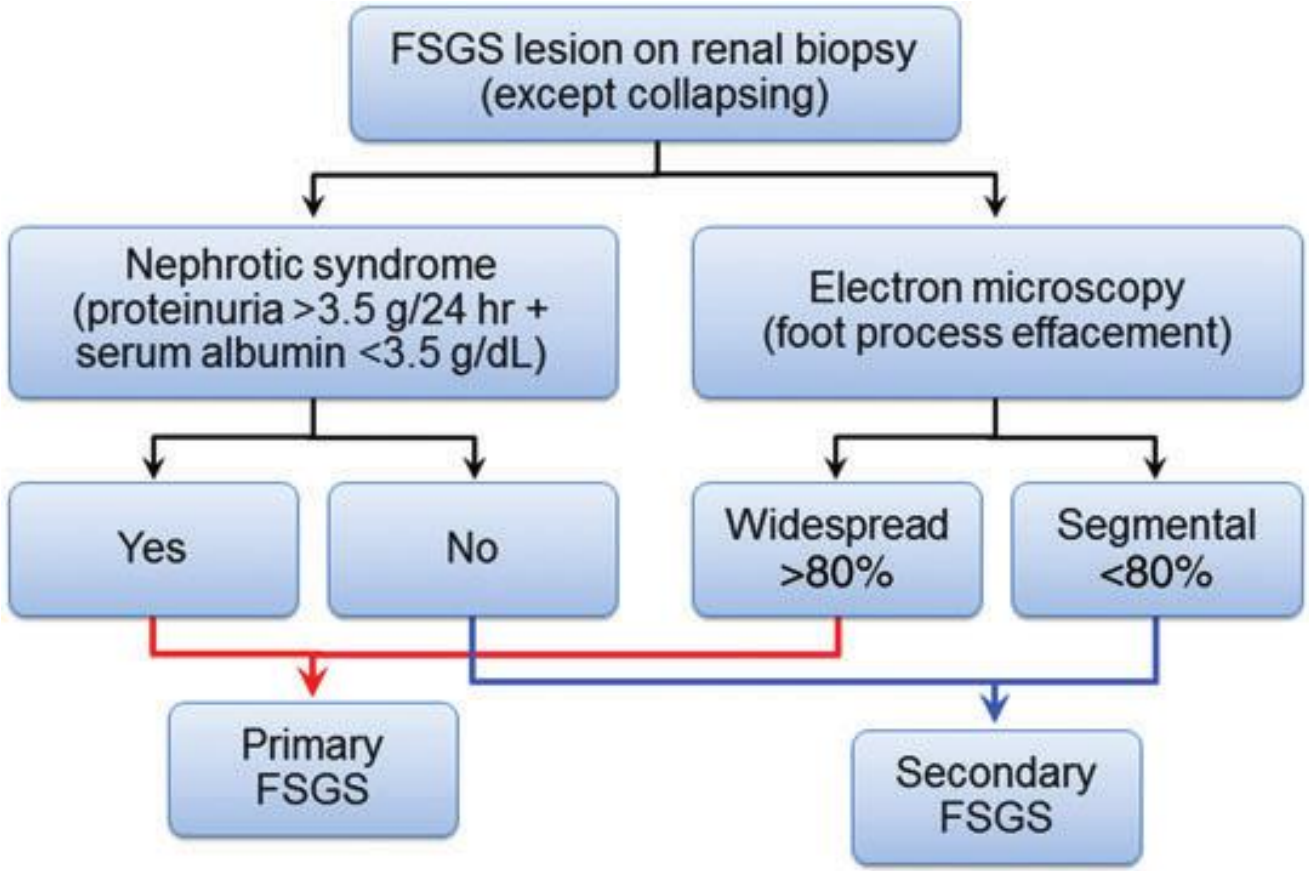


FIGURE 3: Proposed diagram to differentiate between primary and secondary FSGS based on clinical presentation and EM examination (collapsing FSGS is excluded).

FSGS
primary *vs* secondary



- A conerted effort to diff primary from secondary FSGS is crucial at the time of discovery of the lesion >>> because primary FSGS may respond to steroid &/or CNI, while those with 2nd FSGS should be managed conservatively aiming to control BP & non-specific reduction of Pr-uria.
- The clinical presentation (NS vs non-nephrotic sdrm) + EM findings >>> offers ”the most practical way to differentiate between the two”

Failure to diff primary vs 2nd FSGS >>> may result in un-necessary & potentially hazardous ttt !

Summary

- 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.

FSGS is a “histologic pattern”

- FSGS is the **most common primary glomerular histologic lesion** associated with high-grade proteinuria and with ESRD

- FSGS is a pattern of histologic injury rather than a disease and can be either **primary or secondary** to a variety of underlying processes.

- Separation into these two categories of FSGS is **not always easy**.

- There is a significant overlap of clinical and histologic features making the assignment of each patient to a single specific category difficult
- Some FSGS patients are known to have significant genetic mutations but still respond to immunosuppres- sive treatment
- This conundrum of primary versus secondary FSGS is critical not only for diagnos- tic but also therapeutic purposes because this decision virtually drives all subsequent aspects of patient man- agement.

- Currently, **the best method of separation** is based on pathology (**electron microscopy** that demon- strates **> 80% diffuse foot process effacement** is classically associated **with primary FSGS**) but the correlation with the clinical and laboratory parameters, response to therapy and eventual outcome is imprecise.

- Primary FSGS is:
- 1- usually a progressive disorder with ,
- 2- 5% spontaneous remission and
- 3- a 50% ESRD rate over a period of 5–8 years from the time of biopsy in patients that are either unresponsive to treatment or not treated
- Nephrotic-range proteinuria with or without other features of the nephrotic syndrome is the classic pattern of presentation of primary FSGS and is seen in 75%–90% of children and 50%–60% of adults.

Histologic Variants

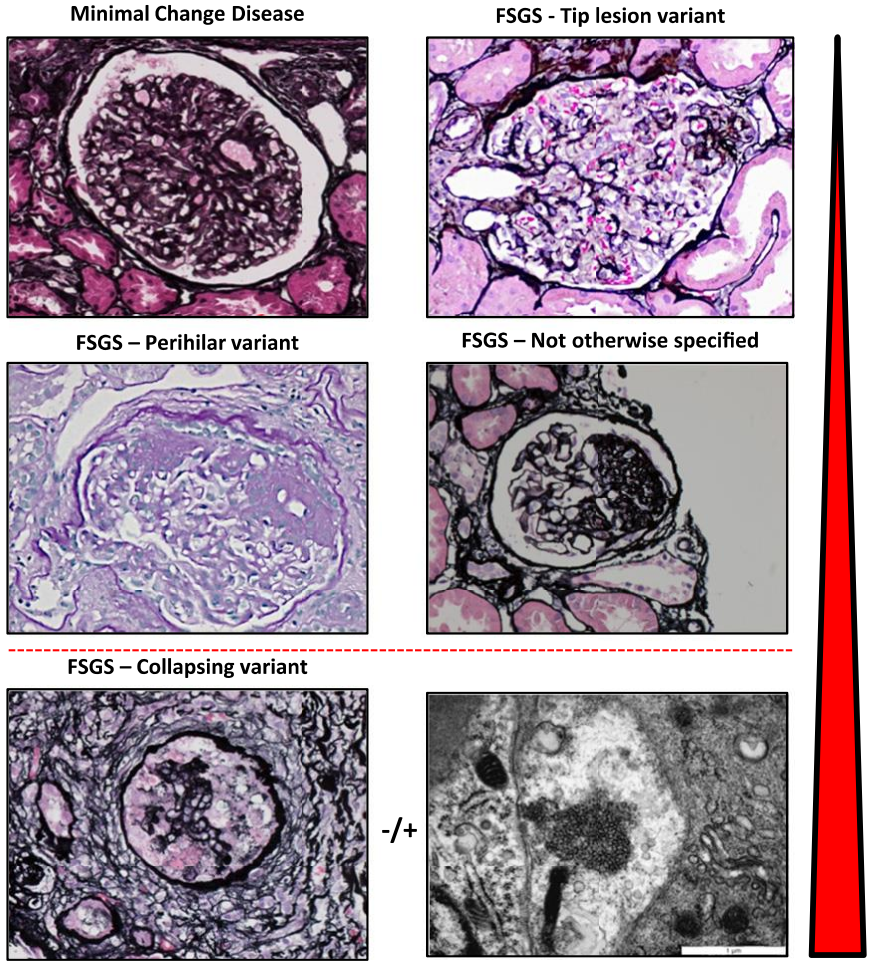
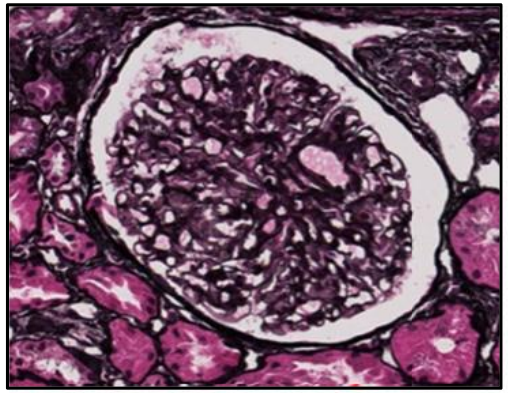
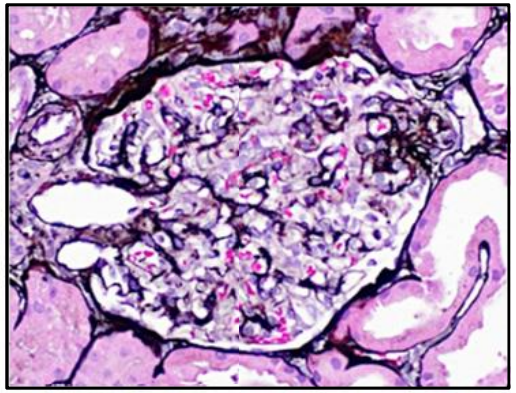


Figure 1. | Histopathology of minimal change disease and focal segmental glomerulosclerosis. Minimal change disease shows patent glomeruli in the absence of tubulointersitial scarring (silver stain, ×40). The tip lesion represents a focal adhesion of the glomerular tuft to Bowman's capsule near the proximal tubule takeoff (silver stain, ×400). The most common forms of FSGS seen in adaptive FSGS and across all etiologies of FSGS are the perihilar variant (periodic acid–Schiff stain, ×40) and not otherwise specified pattern (silver stain, ×400). The most distinctive variant is the collapsing variant (collapsing glomerulopathy; silver stain, ×40). A specific instance of collapsing variant can be appreciated in the setting of endothelial tubuloreticular inclusions seen on ultrastructural analysis. These may be observed in high IFN states, including viral infection and exogenous IFN. The red arrowhead indicates the relative response to therapy and propensity of progression of these various forms, with minimal change disease and tip lesion being most responsive and least progressive and collapsing glomerulopathy being most therapy resistant and rapidly progressing.

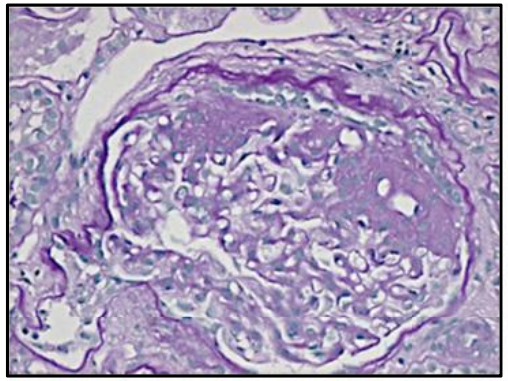
Minimal Change Disease



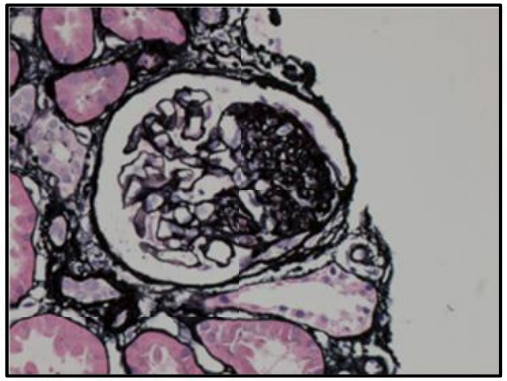
FSGS - Tip lesion variant



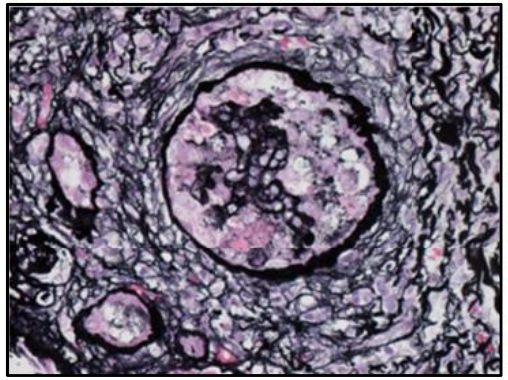
FSGS – Perihilar variant



FSGS – Not otherwise specified



FSGS – Collapsing variant



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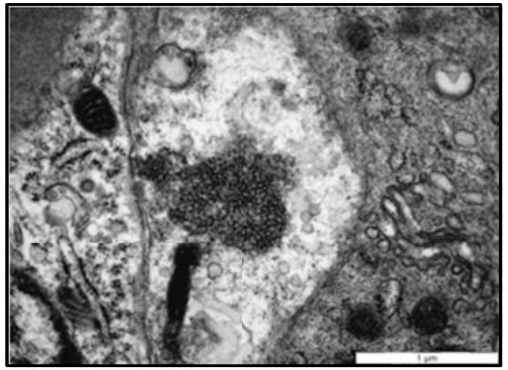
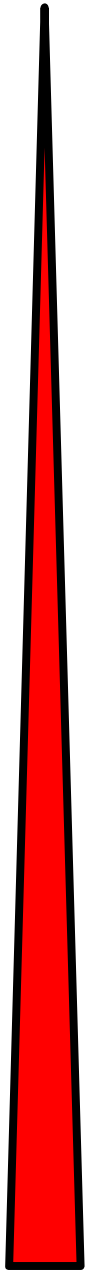




- In 2004 a group of renal pathologists proposed a standardized pathological classification system for FSGS, which was **based entirely** on **light microscopic evaluation**.
- In this classification, non-sclerotic lesions — termed the ‘tip’ and ‘collapsing’ variants — are considered to be forms of FSGS.
- Although the classification system was intended to enable greater insight into the pathogenesis of FSGS, it may have unintentionally contributed to the notion that FSGS is an individual disease, or even that several forms of idiopathic FSGS exist.
- As outlined below, **the majority of the existing data do not support this view.**

- The most current histologic classification includes the following variants:
- 1- classic FSGS (also called FSGS not otherwise specified [FSGS NOS]),
- 2- collapsing,
- 3- tip,
- 4- perihilar, and
- 5- cellular types

Columbia classification

- this approach, designated the Columbia classification, has had a **variable and at times poor correlation** with both the **natural history and therapeutic responsiveness** of FSGS patients

- **Classic FSGS** (**NOS** variant) is the most common variant observed.
- Prognosis of the **cellular variant** is intermediate between collapsing and a classic FSGS.
- Although the **collapsing variant** of FSGS is most often associated with HIV infection, other causes (including idiopathic causes) exist. Of all of the variants, it still carries the worse prognosis.
- Patients with the **tip lesion** have the most favorable prognosis and may be more responsive to corticosteroid therapy than the other types.
- The **perihilar variant** is more commonly associated with secondary FSGS and is considered to be mediated by an adaptive response to increased glomerular capillary pressures and flow rates.

- a change from no light microscopic abnormalities to the presence of FSGS variants has been observed in sequential biopsy samples, with the ‘not otherwise specified’ variant as a final stage.
- A change from FSGS variants to no light microscopic abnormalities has not been reported.

OPINION

Minimal change disease and idiopathic FSGS: manifestations of the same disease

Rutger J. Maas[1], Jeroen K. Deegens[1], Bart Smeets[2], Marcus J. Moeller[3] and Jack F. Wetzels[1]

- In most textbooks, MCD and idiopathic FSGS are described as separate entities

- they are in fact different histological manifestations of the same disease processes.

- Minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) both underlie idiopathic nephrotic syndrome (INS)

Idiopathic Nephrotic Syndrome

- INS is a primary podocytopathy, and the underlying abnormality is extensive podocyte foot process effacement on electron microscopy.
- **MCD** is currently considered to be **a single disease entity**, which is characterized by nephrotic syndrome, the absence of any glomerular abnormality on light microscopy, complete remission of proteinuria on corticosteroid treatment, and maintenance of kidney function.
- By contrast, **FSGS** is **not** considered to be a **single disease entity**, but **a *"histologic" description* of glomerular damage**.

- The morphology and underlying causes of FSGS are heterogeneous.
- Originally, the **histological diagnosis of FSGS** required the identification of **segmental sclerotic lesions** in at least one glomerulus.
- More recently, **non-sclerotic glomerular lesions** became **part of the FSGS spectrum.**
- Of note, the current morphological classification was defined for all forms of FSGS and does not reflect the underlying aetiology.
- The term idiopathic FSGS (also known as primary FSGS) was coined to differentiate FSGS with no known cause from secondary forms of FSGS, which are caused by pathogenic events, such as structural and/or functional adaptations owing to nephron loss or mutations in podocyte-associated genes.

- **Many secondary** forms of FSGS, are **not** accompanied by **complete <u>podocyte foot process effacement</u>** so can be easily differentiated from idiopathic FSGS

MCD vs FSGS

- Compared with MCD, idiopathic FSGS is associated with a higher likelihood of **steroid resistance** and **progression to renal failure**.
- In patients with steroid-resistant INS who initially have normal appearing glomeruli on light microscopy but later progress to FSGS, some researchers have suggested that an **initial diagnosis of FSGS could have been missed** owing to the focal and segmental nature of the FSGS lesion.
- Although we agree that **sampling error** might occur, convincing evidence indicates that **FSGS lesions might be absent in the early phase** of steroid-resistant INS and the finding of **FSGS lesions in repeat biopsy** samples reflects disease progression.

- The initial podocyte injury is the critical step; the extent of this injury, the vulnerability of the podocytes, additional factors (such as comorbid hypertension) and the response to therapy determine whether FSGS lesions will develop.
- In our view, MCD and idiopathic FSGS have the same underlying causes
- Importantly, we do not suggest that a single cause of the initial podocyte injury exists.
- Moreover, as the development of podocyte injury could be the result of more than one podocytotoxic factor, INS might not represent a single disease entity.
-

- the entity that is currently referred to as idiopathic FSGS, is the result of extensive podocyte injury in patients with INS.

Minimal change disease and **idiopathic FSGS**:

*manifestations of the **same disease***

MCD and FSGS: a continuum

- Fahr described the presence of sclerotic glomeruli in patients with persistent **lipoid nephrosis**
- in 1957, Rich described his careful studies of autopsy samples from patients with lipoid nephrosis, the **majority** of whom **died** as a result of complications of nephrotic syndrome.
- From his description, it is clear that Rich linked the course of pathological abnormalities in these patients “with ***the gradual clinical transition from the pure nephrotic stage to the one with increasing damage***”. The extent of the lesions increased with time, as illustrated by the relationship between the extent of the histological changes and the duration of disease.
- Thus, both Fahr and Rich considered FSGS to be the consequence of non-remitting INS.

- In the 1970s, the observation of FSGS lesions in patients with recent-onset nephrotic syndrome, and the association of this nephrotic syndrome with prednisone resistance, led researchers to conclude that MCD and idiopathic FSGS are separate diseases, and that the term lipoid nephrosis is outdated

Table 1 | **Evidence for and against the hypothesis that MCD and idiopathic FSGS are separate entities**

	For	Against
Biopsy findings	In steroid-resistant INS with normal appearing glomeruli, FSGS is likely missed owing to sampling error[9,10,7]	Recurrent FSGS is characterized by an initial phase with diffuse podocyte foot process effacement and normal appearing glomeruli on light microscopy, even in biopsy samples with many glomeruli[23,24]
	Later biopsy samples always show FSGS[18,19]	Findings in later biopsy samples are compatible with the concept that FSGS develops over time[18,19]
Animal models	NA	Following an initial phase with only diffuse podocyte foot process effacement, all of the available animal models of persistent proteinuria develop FSGS[33,35–37]; in models of toxic damage to podocytes, FSGS development is dose-dependent[34,37,39]
Circulating factors	FSGS is caused by a circulating permeability factor that is associated with progressive decline in renal function and recurrence of proteinuria after transplantation[56]; MCD is not associated with loss of renal function[118–120]	Circulating factors have been implicated in both MCD and FSGS[55]; they have not been identified but might be identical in MCD and FSGS — this hypothesis is supported by the observation that post-transplantation recurrence of FSGS occurs in patients with initially steroid-sensitive INS who develop secondary steroid resistance[125]
	Serum suPAR concentration is elevated in FSGS compared with MCD; high levels of suPAR were associated with post-transplantation FSGS recurrence[56]	Elevated serum suPAR concentration has not been validated as a biomarker of FSGS; suPAR levels were not elevated in patients with FSGS after correction for renal function[63–66]
	Angptl4 expression was upregulated in the glomeruli of patients with MCD; these patients had a distinctive pattern of Angptl4 oligomers in their urine, which was not seen in patients with FSGS[51]	Glomerular Angptl4 expression was not investigated in patients with FSGS; urinary tests were performed in a small group of patients, and two of the four patients with FSGS were not nephrotic[51]; the results have not yet been validated
Histological markers	Patients with MCD can be differentiated from those with FSGS by urinary B7-1 excretion[90,91]	Elevated urinary B7-1 excretion in MCD has not been validated; patients with FSGS may also have strong B7-1 expression[93]
	Decreased glomerular α-dystroglycan staining has been documented in MCD; expression of α-dystroglycan was normal in idiopathic FSGS[98,99]	Among patients with INS, dystroglycan staining did not predict proteinuria remission in response to therapy[99]; differential expression of α-dystroglycan between MCD and idiopathic FSGS was not confirmed in a subsequent study[100]
	The ratio of podocin to synaptopodin mRNA expression distinguished patients with MCD from those with early-stage idiopathic FSGS and a steroid-resistant disease course[101]	Differences in the ratio of podocin to synaptopodin mRNA expression in patients with MCD and idiopathic FSGS have not been validated; studies of glomerular mRNA expression profiles in idiopathic FSGS[104,102] and MCD[102] confirm that podocyte stress and parietal epithelial cell activation are involved in the development of FSGS lesions[103,105]
	Many genes are differentially expressed in the glomeruli of patients with MCD versus those with idiopathic FSGS[102,104]	The reported gene profiles are compatible with different stages of disease progression rather than differences in the aetiology of MCD and idiopathic FSGS[102,104]
Immune pathogenesis	Evidence suggests that abnormal T-cell function underlies MCD[68,71]; this mechanism has not been reported in FSGS	T-cell function in MCD and idiopathic FSGS has not been systematically compared; data from a humanized mouse model suggest that $CD34^+$ peripheral blood mononuclear cells are involved in the pathogenesis of both MCD and idiopathic FSGS[74]
Genetic causes	FSGS often has genetic causes[75,77–80]; no genetic causes of MCD have been identified	Genetic FSGS often has clear features of secondary FSGS with a gradual increase in proteinuria and incomplete podocyte foot process effacement[77,79]; no genetic causes of idiopathic steroid-sensitive FSGS have been reported
Steroid responses	MCD is steroid sensitive, whereas FSGS is steroid resistant	Some patients with MCD might have relapsing or secondary steroid-resistant disease resulting in FSGS, whereas some patients with FSGS might have complete remission on corticosteroid treatment[120,122,123]

FSGS lesions evolve over time

- Hayslett *et al.* were among the first authors to note progression from apparently normal glomeruli to sclerotic lesions in a small case series of patients with lipoid nephrosis published in 1969
- Further evidence supporting a transition from MCD to FSGS was reported by Tejani *et al.* in 1985 (REF. 19).
- These researchers analysed renal biopsy samples from 48 children with a typical disease course of steroid-sensitive INS.
- The first renal biopsies, which were performed because of frequent relapses 1.5 years after disease onset, showed MCD only.
- Approximately 4.5 years after the first biopsy, a second biopsy was performed in 33 patients who had a continued relapsing disease course.
- Typical FSGS lesions were reported in 15 (55%) of these patients, most of whom later developed end-stage renal disease.

Recurrent FSGS

- The concept that FSGS always occurs secondary to an underlying glomerular injury, and is thus preceded by a period of INS that is characterized by podocyte foot process effacement only on kidney biopsy, is nicely illustrated by the post-transplantation recurrence of FSGS
- Canaud *et al.* noted that in early post-transplantation biopsy samples no glomerular abnormalities were visible
  on light microscopy, whereas electron microscopy showed extensive foot process effacement.
- Post-transplantation FSGS recurrence is characterized by early-onset proteinuria despite treatment with high-dose corticosteroids and other immunosuppressive drugs.

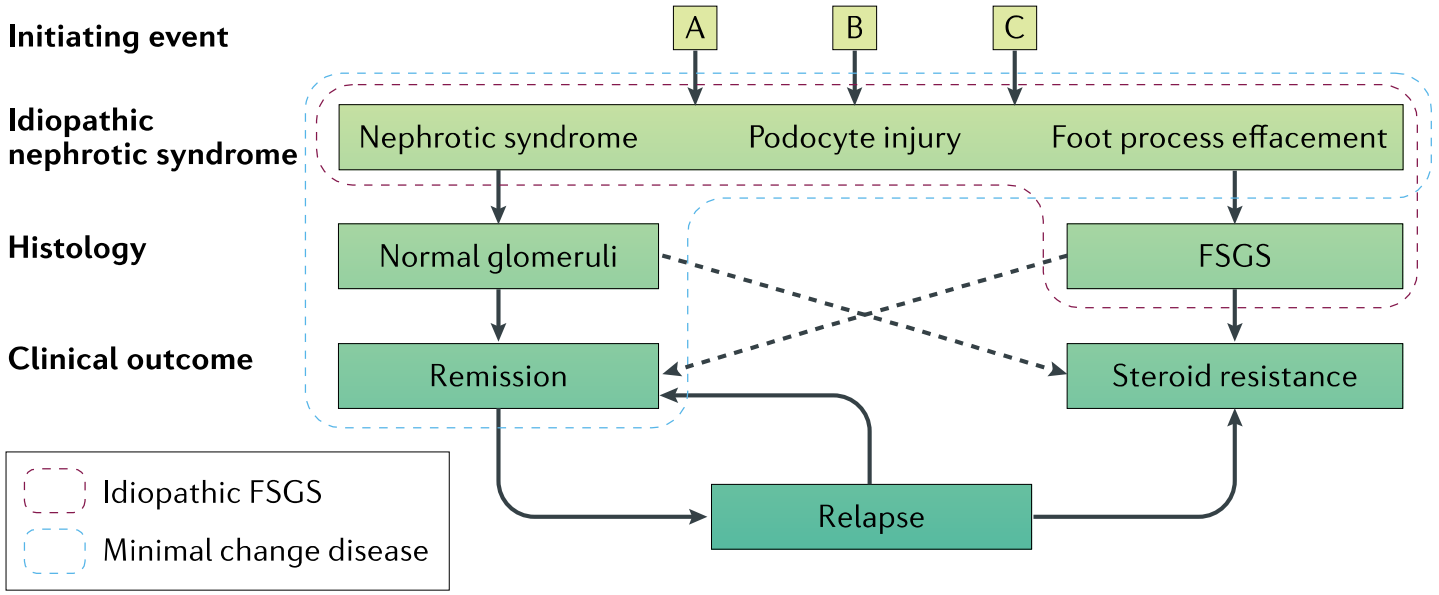
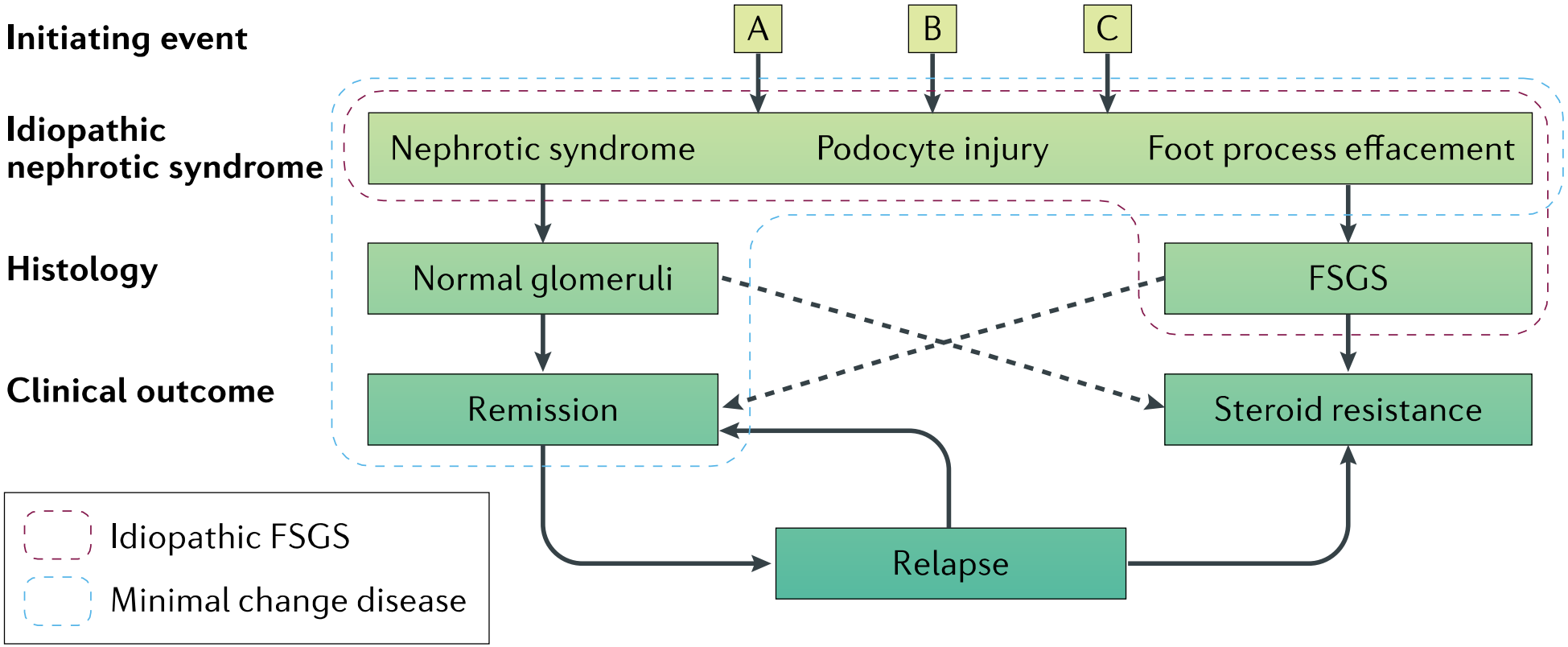


Figure 1 | **Schematic representation of idiopathic nephrotic syndrome, minimal change disease and idiopathic focal segmental glomerulosclerosis (FSGS).** Idiopathic nephrotic syndrome is caused by unknown initiating events (A, B and C) that lead to podocyte damage. Clinical features include gross proteinuria and hypoalbuminaemia, often accompanied by oedema and dyslipidaemia. The disease is histologically defined by complete podocyte foot process effacement with no immune deposits and no glomerular basement alterations. On light microscopy, either normal appearing glomeruli or FSGS might be visible. Disease outcomes are unpredictable at diagnosis, and might include steroid-induced proteinuria remission, potentially followed by relapse, or (primary or secondary) corticosteroid resistance. Patients with persistent proteinuria ultimately develop FSGS. Minimal change disease and idiopathic FSGS are manifestations of idiopathic nephrotic syndrome that are defined by histology and/or clinical outcomes; minimal change disease is characterized by foot process effacement, normal glomeruli and steroid sensitivity, whereas idiopathic FSGS is characterized by foot process effacement and FSGS lesions.


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

- The available data suggest that MCD and idiopathic FSGS are **different phenotypes** of the same disease, which is best described as INS
- MCD and idiopathic FSGS represent **a gradual overlap** in clinical characteristics, treatment responses and outcomes.
- Clinicopathological studies and experimental models support our hypothesis that **idiopathic FSGS is the consequence of extensive podocyte injury in patients with INS**, and that **the same initiating factors are responsible for both MCD and idiopathic FSGS.**

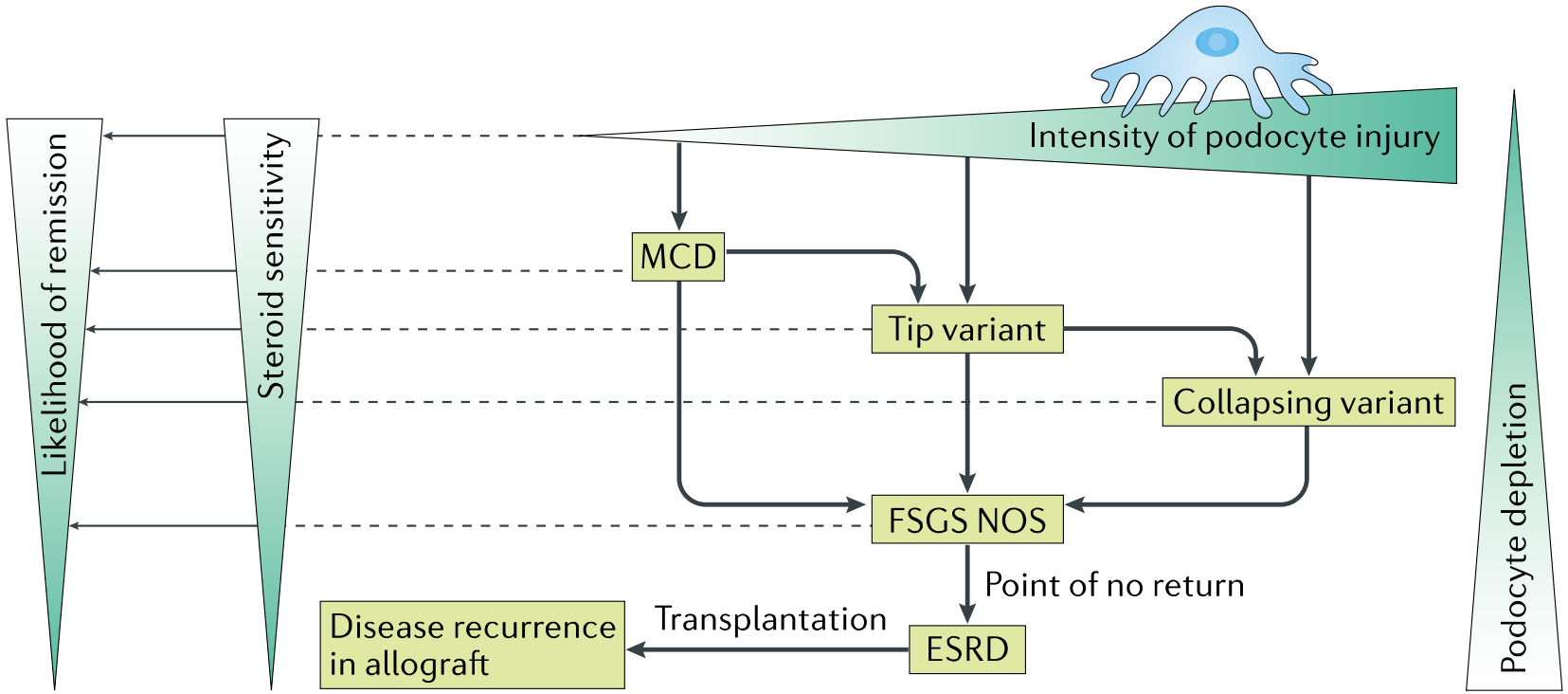
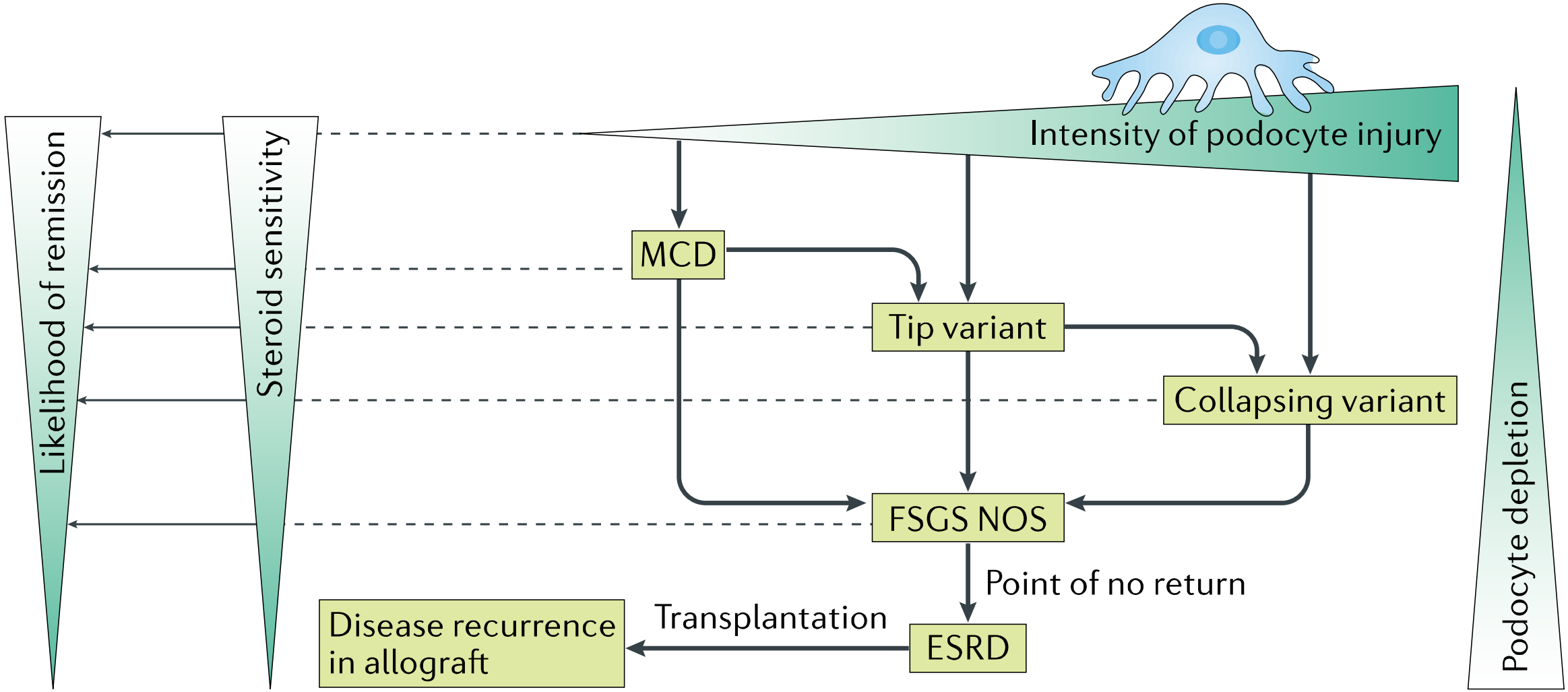


Figure 2 | **Minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) are manifestations of the same disease.** MCD is characterized by podocyte injury, which results in foot process effacement and proteinuria. If the initial injury is severe, focal segmental glomerulosclerosis (FSGS) lesions might develop. These lesions are characterized by parietal epithelial cell proliferation (resulting in the tip and collapsing FSGS variants). In the initial phase, the disease is steroid sensitive apart from in patients with the most severe injury. With longer duration of proteinuria or multiple relapses, ongoing loss of podocytes occurs. This process contributes to loss of steroid sensitivity and reduced likelihood of remission. When more than 30–40% of podocytes are lost, a point of no return is reached and progression to end-stage renal disease (ESRD) is inevitable. After transplantation, disease recurrence in the allograft manifests with proteinuria, podocyte foot process effacement and ultimately the development of FSGS lesions. NOS, not otherwise specified variant.


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

Important

In clinical trials, idiopathic FSGS

***should be considered** to be*

*an **advanced stage of MCD***

Response to treatment *is, therefore,*
less likely *in patients with* ***idiopathic FSGS***
than in those with ***MCD***

Pathogenesis of FSGS

The traditional view of the pathogenesis of most forms of FSGS is that the initial injury is at the level of podocytes

Morphological studies place podocytes at the center of FSGS

- podocyte injury exemplified by cell body attenuation,
- foot process effacement,
- pseudocyst formation and
- microvillous transformation, is the earliest feature of FSGS.

- In human FSGS, these electron microscopic findings may be seen weeks to months prior to the development of visible lesions by light microscopy.

- If the podocyte does not recover from this initial/early injury, the resultant cell death and/or detachment leads to a reduction in podocyte number and a **mismatch between podocyte coverage and the underlying glomerular basement membrane (GBM) surface area**, leading to **“uncovered” bare areas of GBM**
- Possibly due to loss of structural support by overlying podocytes at these sites, the capillary loop may bulge toward Bowman's capsule (**ballooning**) and an early connection (**cell bridge**) forms between the cells lining Bowman's capsule (the parietal epithelial cells, abbreviated herein as PECs) and the podocyte deprived areas of GBM.
- Taken together, these studies highlight that the initiating events in classic FSGS are in podocytes.
- Their contribution to the evolution of the FSGS lesion is well known (and will be discussed below), but other resident glomerular cells participate in the underlying pathogenesis of this lesion.

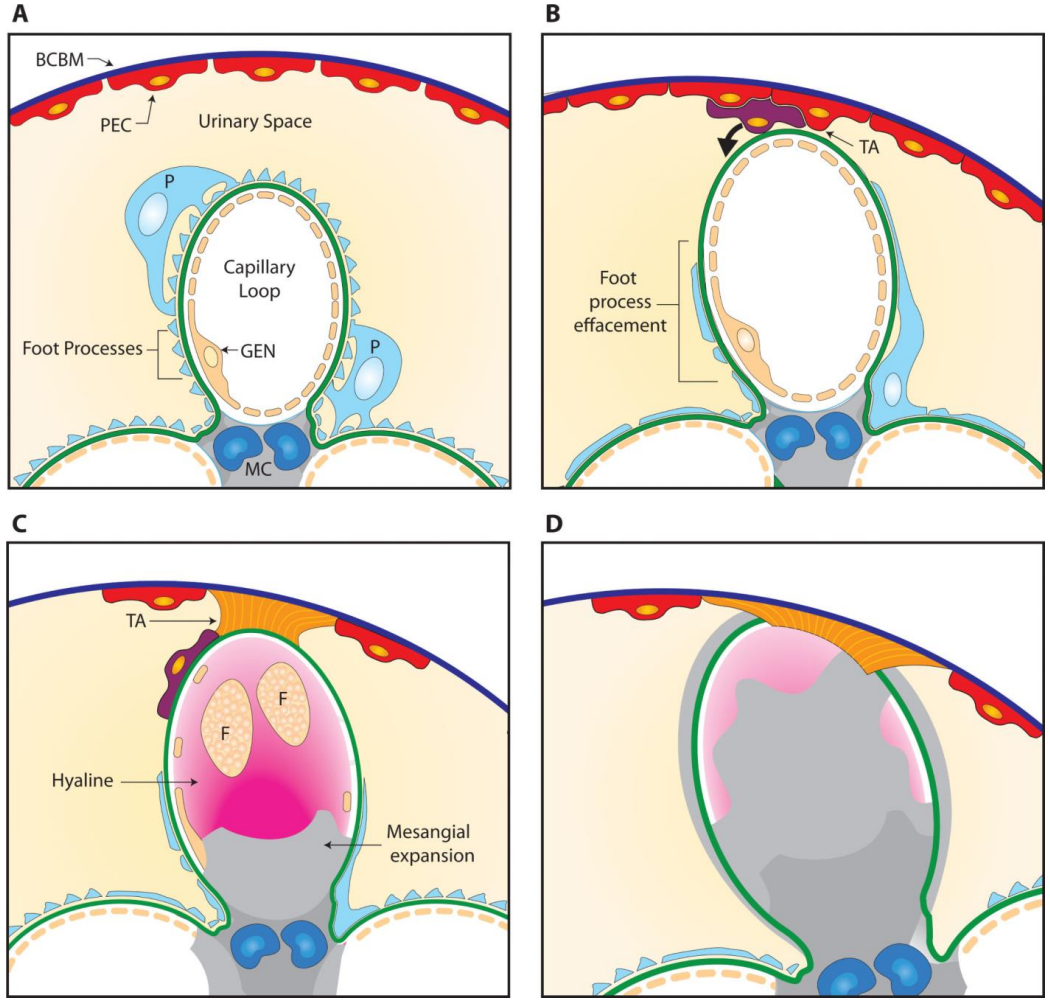
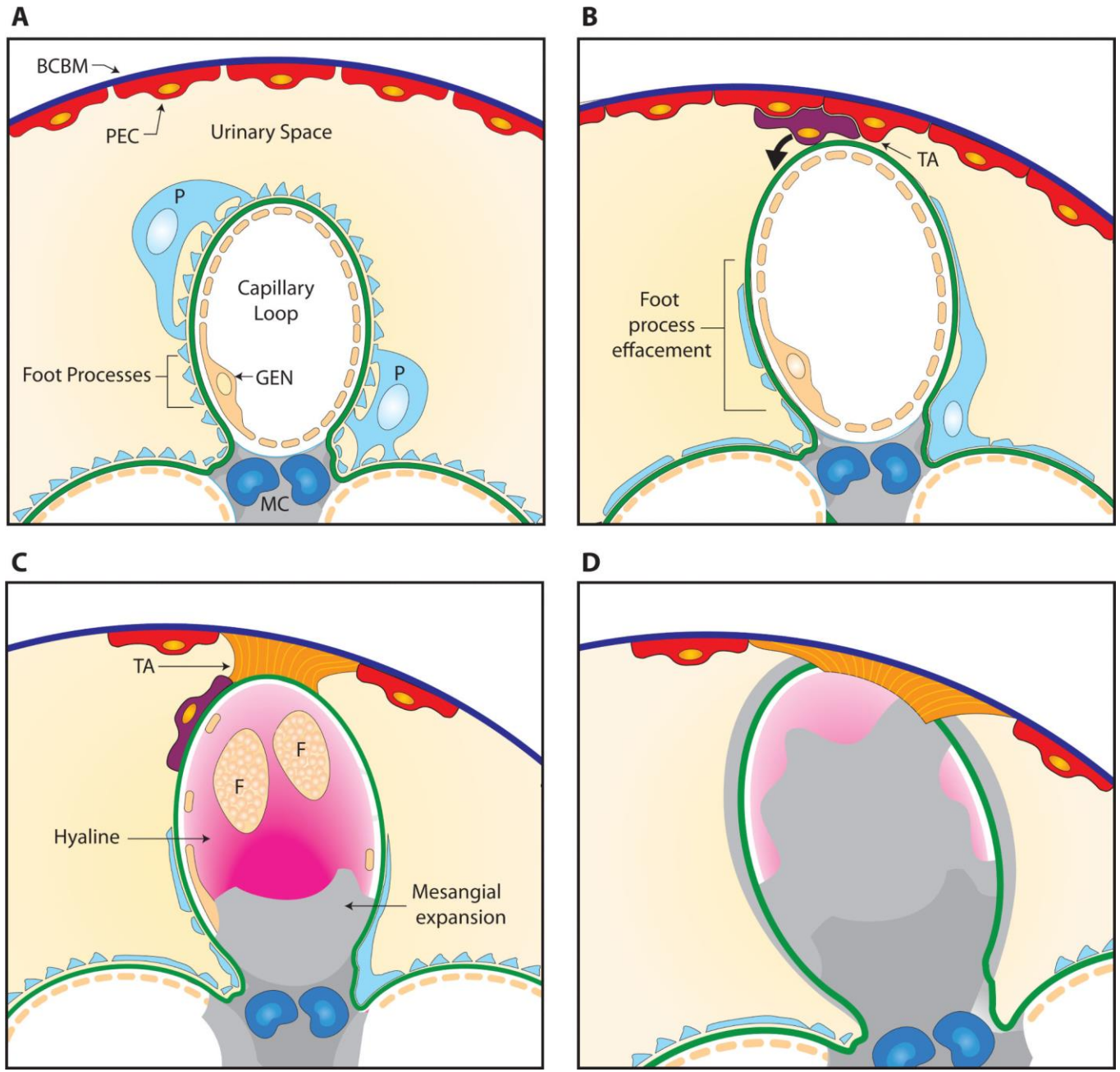


Figure 1. Pathogenesis of FSGS

Panel A: Normal capillary loop (segment) within a glomerulus showing glomerular basement membrane (GBM) lined by the fenestrated endothelium (GEN) and covered by a podocyte (P) with intact foot processes. Mesangial cells (MC) support capillary loop. Bowman's capsule basement membrane (BCBM) is covered with parietal epithelial cells (PECs). Panel B: Podocyte injury with foot process effacement (FPE) leads to loss of podocyte coverage (cell death or detachment) and an area of uncovered GBM. A tuft adhesion (TA) forms between PECs and the uncovered GBM. Panel C: PECs deposit matrix leading to a broad fibrous tuft attachment (TA). Some PECs migrate onto the glomerular tuft via the attachment and deposit matrix on the glomerular segment on the outside of the GBM.

Deposition of fibrillar collagen leads to mesangial expansion reducing capillary lumen. Hyalinosis (trapped plasma proteins) and foam cells (F) obliterate capillary lumen. Panel D: Fully formed segmental sclerosis (fibrosis) with collapse of capillary lumen and areas of trapped hyaline.

- The glomerular parietal epithelial cells (PECs) forming the cell bridge can deposit matrix between these bridging cells to form a fibrous attachment (tuft adhesion) between the glomerular tuft and Bowman's capsule (**Figures 2 & 3**).
- The tuft adhesion is considered the earliest feature of FSGS seen on light microscopy in human biopsies.


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

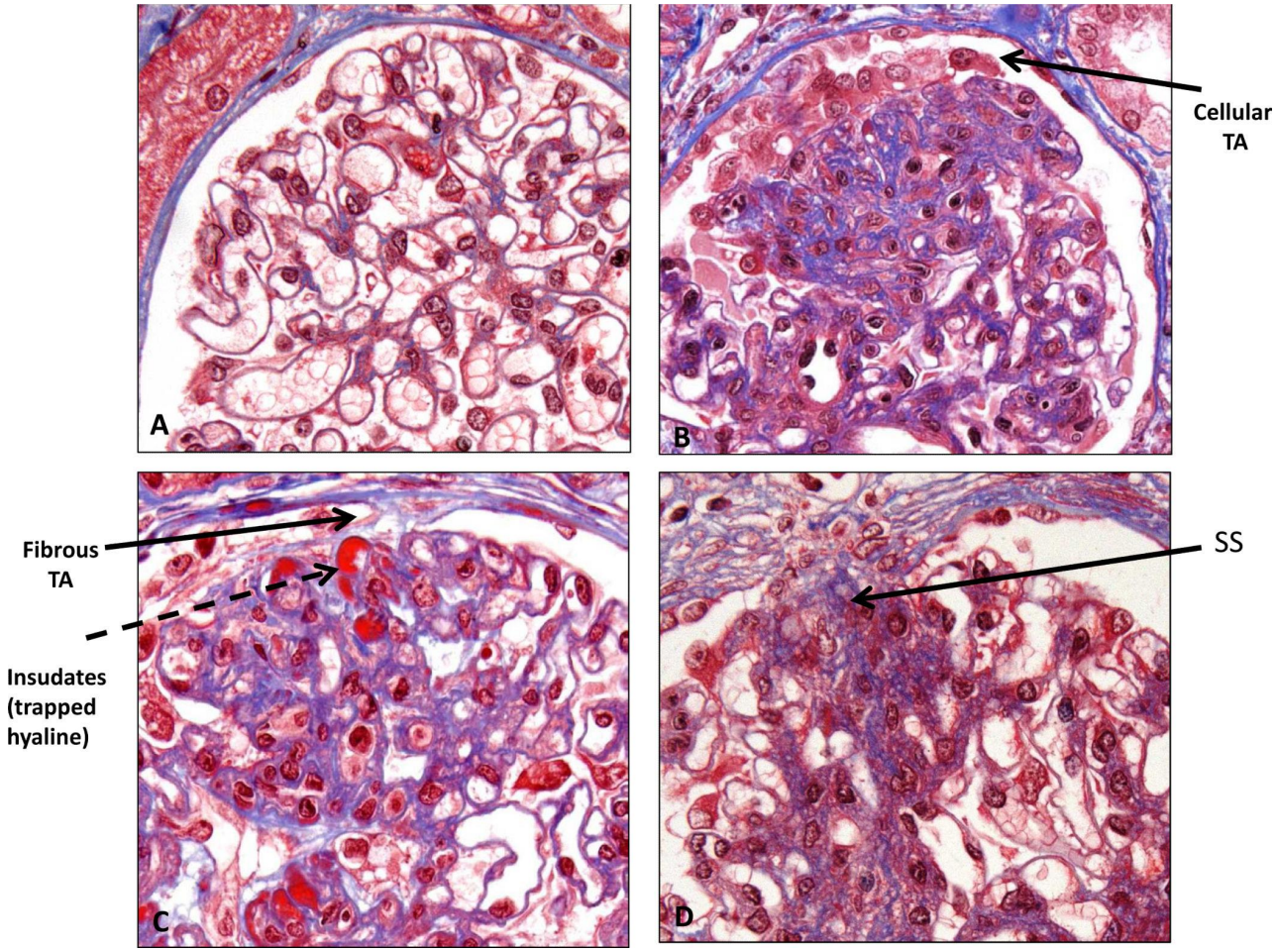
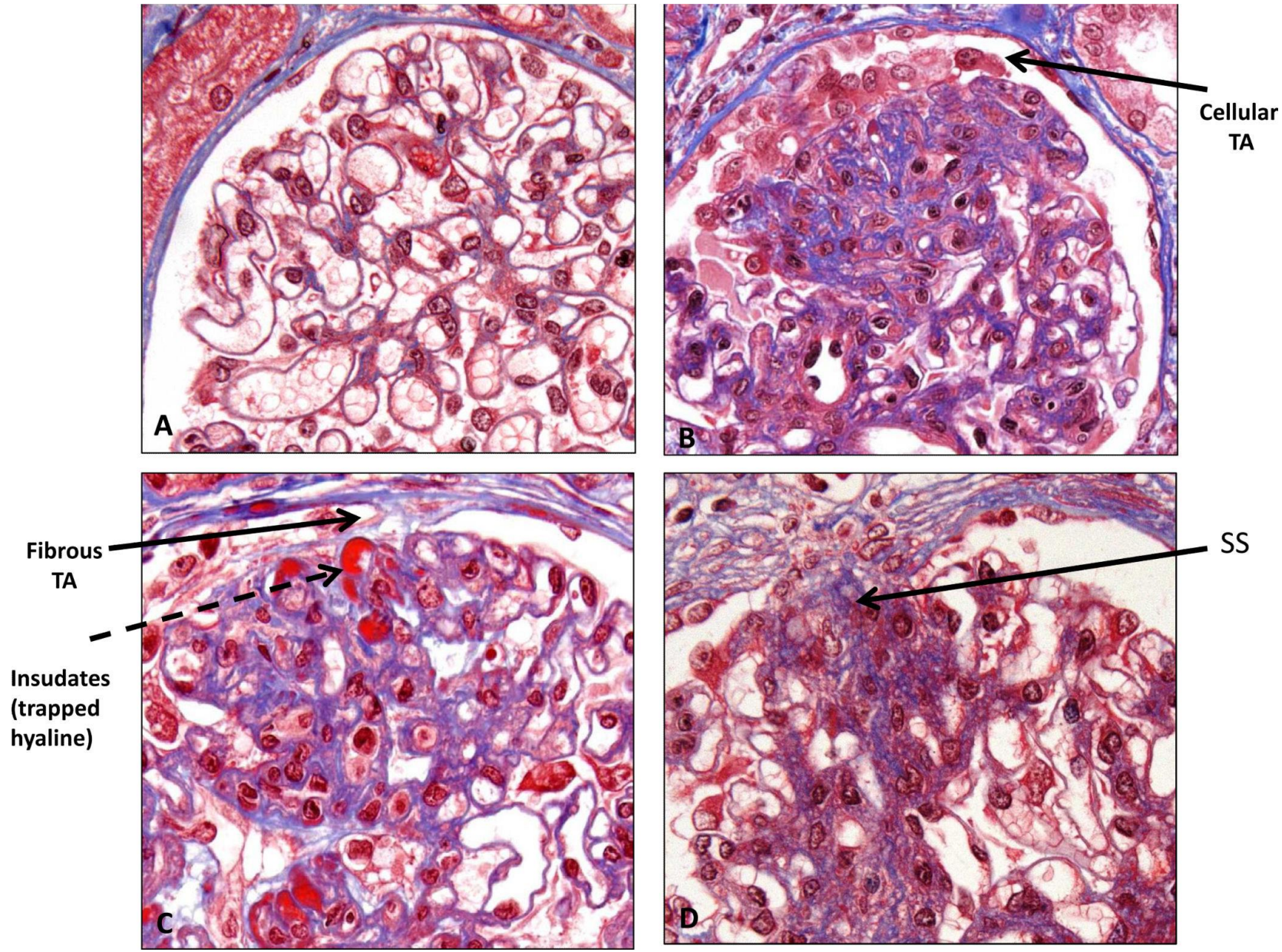


Figure 2. Formation of FSGS lesion

Light microscopy (Trichrome stain). Panel A: Normal glomerulus showing multiple open capillary loops (compare with single loop in Figure 1). Panel B: A cellular tuft adhesion (TA) forms between parietal epithelial cells (PECs) and capillary loop(s) with early matrix deposition. Panel C: Further deposition of matrix by PECs leads to formation of fibrous tuft adhesion, with underlying insudates of trapped hyaline. Panel D: Area of segmental sclerosis (SS) within glomerulus, with adherence to Bowman's capsule.


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

- A suggested consequence of the adherence PEC's to the naked areas of GBM, is the formation of **gaps in the parietal epithelium** into which glomerular filtrate from attached capillary loops can traverse (misdirected filtration).
- This leads to stripping of PEC's off the Bowman's basement membrane, the formation of proteinaceous pseudo-crescents, and the spreading of filtrate along the tubular basement membrane (peritubular filtrate spreading) resulting in tubular atrophy.
- Accumulation of proteinaceous material in the adherent capillary loop (hyalinosis), the deposition of extracellular matrix, and the accumulation of intracapillary foam cells (lipid-laden macrophages) leads to obliteration of capillary loops, the characteristic lesion of segmental sclerosis.
- Mesangial expansion due to increased matrix is commonly noted.
- In FSGS, the sclerosis is by definition segmental and other portions of the glomerular tuft appear normal, although this lesion may progress to global glomerulosclerosis over time.
- Taken together, FSGS involves several glomerular cell types and other structures, all which will be considered in the overall pathogenesis of this glomerular lesion in this review.

- Podocyte injury is the earliest morphological feature of FSGS, which has led to the current paradigm that classic FSGS is primarily a podocyte disorder, at least initially.
- A wide range of genetic and acquired cellular causative insults have been identified (**Table 1**)
- Hyperglycemia and insulin signaling, mechanical stress, angiotensin II, calcium signaling, viral infection, toxins, oxidants, and immunological injury are all well described.
- A wide range of disease states can therefore lead to the development of the FSGS pattern of injury reflecting the difficulties of classification of this group of disparate conditions.

Classification of FSGS by Underlying Cause

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

Genetic causes of FSGS: defects in constitutive podocyte proteins

Genetic studies of familial FSGS have identified multiple disease causing genes that are primarily expressed in the podocyte.

Many of these **gene products** encode **critical structural podocyte elements** including the slit diaphragm (nephrin, podocin, CD2AP, TRPC6, GLEPP1, MYO1E), actin cytoskeleton (α-actinin 4, formin, myosin IIA, ARHGAP24, ARHGDIA), or foot process-GBM interaction (LAMB2, ITGA3).

Notably, the clinical presentation in each of these disorders is variable.

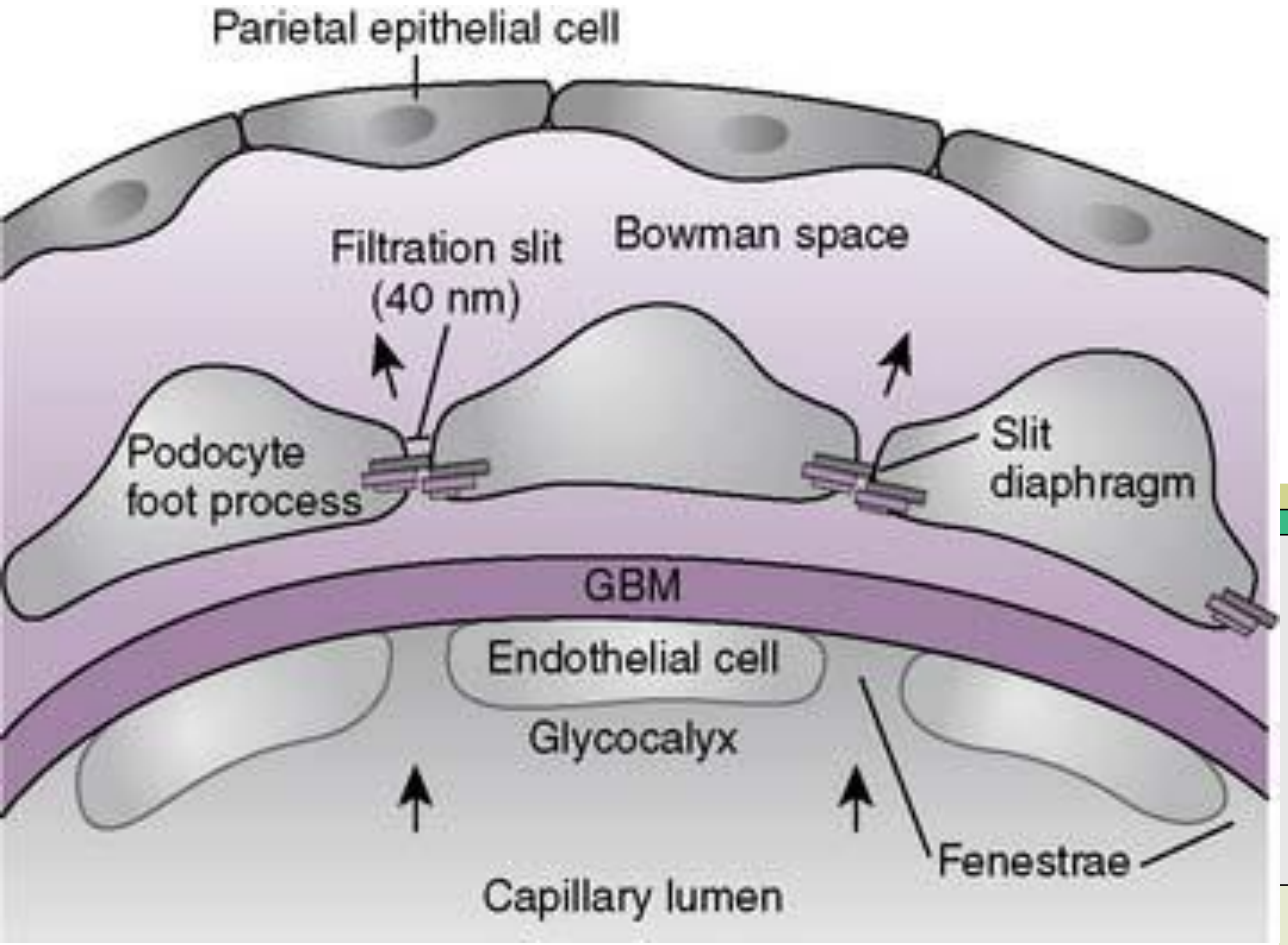
For example, mutations in genes encoding proteins of the **slit diaphragm** often lead to **early onset disease**, whereas gene disorders of the **actin cytoskeleton more commonly lead to disease onset in adulthood**, suggesting the requirement of additional podocyte insults to generate this condition.

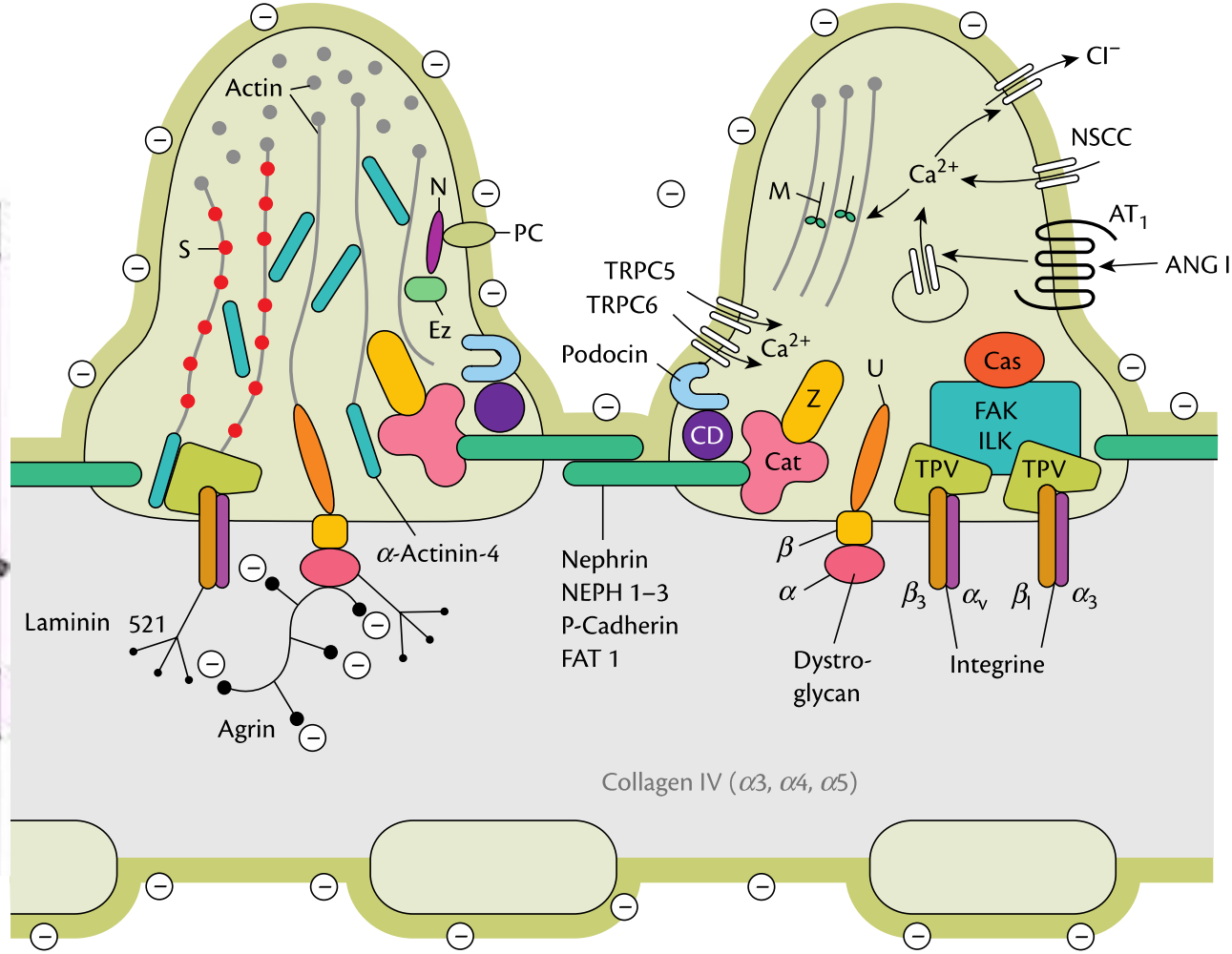
Notably, the majority of these **hereditary podocytopathies** are ***resistant to immunosuppression.***

Circulating Permeability Factors

- A circulating permeability factor has long been implicated in primary FSGS.
- The major pieces of evidence supporting this include:
- (1) primary FSGS can recur very rapidly after kidney transplantation,
- (2) injection of plasma or plasma fractions from patients with FSGS into rats causes proteinuria,
- (3) sera from patients with FSGS increase albumin permeability in an isolated glomerulus model ex vivo, and
- (4) a transient nephrotic syndrome has been transmitted to a newborn from a mother with FSGS.
- The soluble urokinase plasminogen-activator receptor (suPAR) is a recent candidate.

- Podocytes adhere tightly to the glomerular basement membrane (GBM) via interactions between the actin cytoskeleton, integrins α3β1 and αvβ3, and the GBM components laminin 521 and type IV collagen.
- enhanced αvβ3 integrin signaling within podocytes is associated with foot process effacement and the development of proteinuria.
- They showed that ß3 integrin signaling may be activated by both membrane bound urokinase-type plasminogen activator receptor (uPAR) on podocytes and circulating (soluble) uPAR fragments (suPAR).


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)

- In uPAR null mice, chronic suPAR overexpression or administration resulted in a glomerulopathy with foot process effacement, proteinuria and other features of FSGS, which could be ameliorated with a uPAR-specific monoclonal antibody.

- Although there are questions over the suPAR bioassay, several, but not all, studies have confirmed high levels of suPAR in patients with FSGS

Glomerulomegaly and Mechanical Stretch: Podocyte and GBM mismatch

- Human conditions typically associated with **glomerulomegaly** include obesity, hypertension and the reduced nephron number (oligonephronia) seen in low birth weight subjects.
- The combination of glomerulomegaly and mechanical stretch from **glomerular hyperfiltration** may play important pathogenic roles in the development of what has been described as secondary FSGS.

- The podocyte with its contractile **actin** cytoskeleton plays a critical role in counteracting the hemodynamic forces encountered by the glomerular capillary.
- According to the Brenner hypothesis of **glomerular hyperfiltration**, **chronic glomerular hypertension** leads to progressive glomerular injury that can be ameliorated with blockade of the renin angiotensin system.
- In experimental models, **chronic hypertension** can lead to FSGS, possibly due to **mechanical stretch of podocytes**.

Mechanical stretch >>> local AT1 receptor within the podocytes >>> Local RAS activity >>> injury

- **mechanical stretch** has been shown to lead to >>> **podocyte injury** with activation of a **local renin angiotensin system >>>** and **overexpression of the AT1 receptor** within the podocyte causes glomerulosclerosis

- **angiotensin inhibition** is still **renoprotective** in models of FSGS where the **AT1 receptor** has been specifically deleted from **podocytes** suggesting other beneficial effects of angiotensin blockade.

- When an increase in glomerular tuft size (**glomerulomegaly**) occurs, the resultant **increase in GBM surface** area provides **a challenge to the resident podocyte** population **to ensure adequate GBM coverage**.
- As ***podocyte proliferation is limited***, **cell hypertrophy** becomes an **important protective response**, at least initially (later hypertrophy is maladaptive).
- **In order to hypertrophy**, >>> the **cell must re-enter the cell cycle**, >>> but instead of progressing to mitosis, the **cell arrests at the G1 or G2/M restriction point**.
- This **entry into the cell cycle** is associated with **re-organization of the actin cytoskeleton** with the associated **risks of detachment** or **mitotic catastrophe leading to cell death**.

- By **inhibiting this protective podocyte hypertrophic response** using a podocyte targeted inhibitor of the mammalian target of rapamycin complex 1 (**mTORC1**), Fukuda *et al* demonstrated the elaboration of **albuminuria and FSGS** developing along the classic pathways of bare GBM, formation of tuft adhesions and segmental sclerosis.
-
- Slowing glomerular enlargement with calorie restriction in these transgenic rats leads to abrogation of glomerulosclerosis.

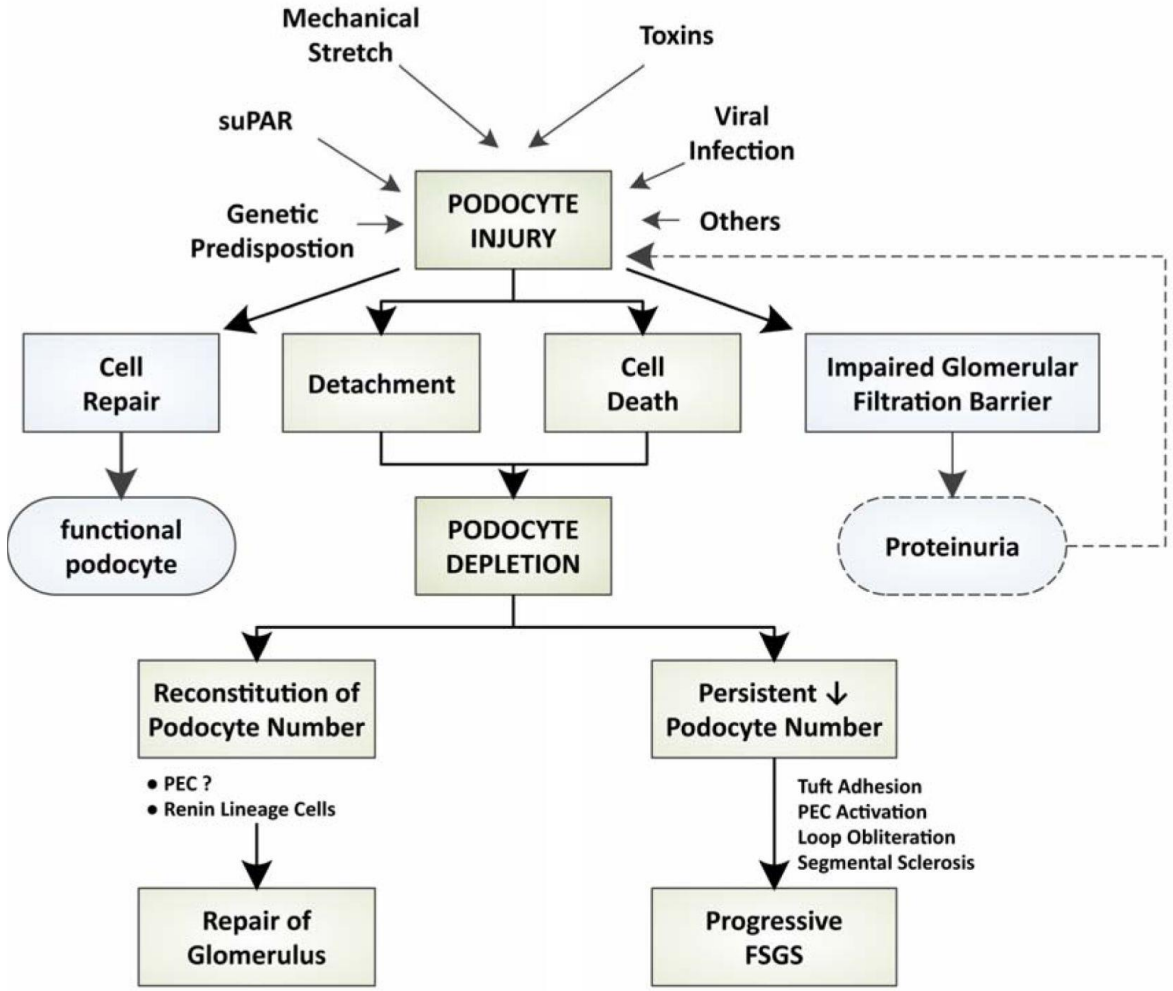
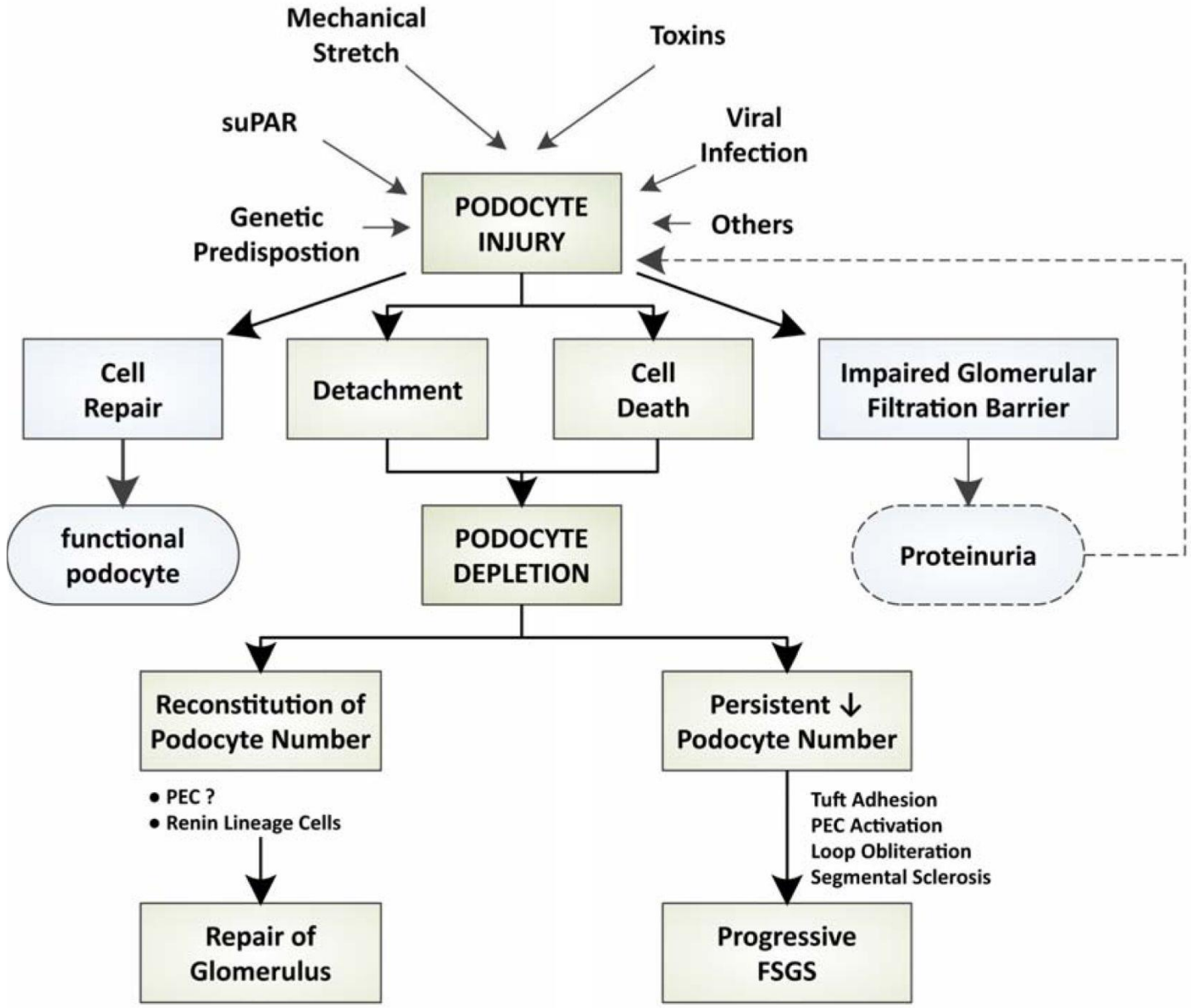


Figure 4. Persistent podocyte depletion results in FSGS

Multiple etiologies may cause podocyte injury resulting in podocyte depletion. Alterations in the glomerular filtration barrier lead to proteinuria which can further podocyte injury. Reconstitution of podocyte number may lead to recovery of glomerular architecture and function, whereas persistent podocyte depletion produces a cascade of steps leading to an FSGS lesion (see Figure 1).

- In the adult human kidney, there are approximately 500-600 podocytes per glomerular tuft, and the **turnover of adult podocytes has never been demonstrated** under physiological conditions.
- As **adult podocytes are terminally differentiated epithelial cells** with a very limited ability to proliferate, ***podocyte loss following injury can result in a reduction in podocyte number***.
- Following podocyte injury from a diverse range of causes, a stereotypical podocyte response is often seen


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

- The adult podocyte is considered a terminally differentiated cell with a very limited ability to proliferate partly associated with constitutive expression of certain cyclin dependent kinase inhibitors.
- Although podocytes may enter the cell cycle, and rarely undergo mitosis (nuclear division), they cannot complete cytokinesis (cell division), sometimes resulting in binucleated cells and/or mitotic catastrophe.
- Given the critical role of the podocyte it may be considered surprising that the cell is unable to efficiently replicate.

- If the podocyte number can be restored, the glomerulus may recover, however, in progressive FSGS, podocytes are not replenished, indeed, further injury may spread to other podocytes with progression of chronic kidney disease.
- Recent evidence has confirmed that in experimental models, a **decrease in podocyte number can be restored despite the absence of podocyte proliferation**.
- This raises the question of how the podocyte number is reconstituted?

- It has been suggested that there may be. **reservoirs of cells outside the glomerular tuft which can relocate to the GBM surface and differentiate into mature podocytes.**
- Bone marrow derived stem cells are not podocyte progenitors in two experimental models.
- Some studies in humans have suggested that **PECs may serve this podocyte progenitor role** and repopulate the glomerulus following podocyte loss, although this remains controversial, as similar paradigms do not exist in adult mice.
- Cells of renin lineage have also been postulated to act as both podocyte and PEC progenitor cells.
- Using genetic fate mapping studies, Pippin *et al* detected labeled cells of renin lineage which also expressed podocyte markers on the glomerular tuft after podocyte injury, suggesting that some juxtaglomerular cells may fulfill a podocyte progenitor role.
- Taken together, a literature is emerging that adult podocyte progenitors may exist, and their role will likely be better understood in the near future.

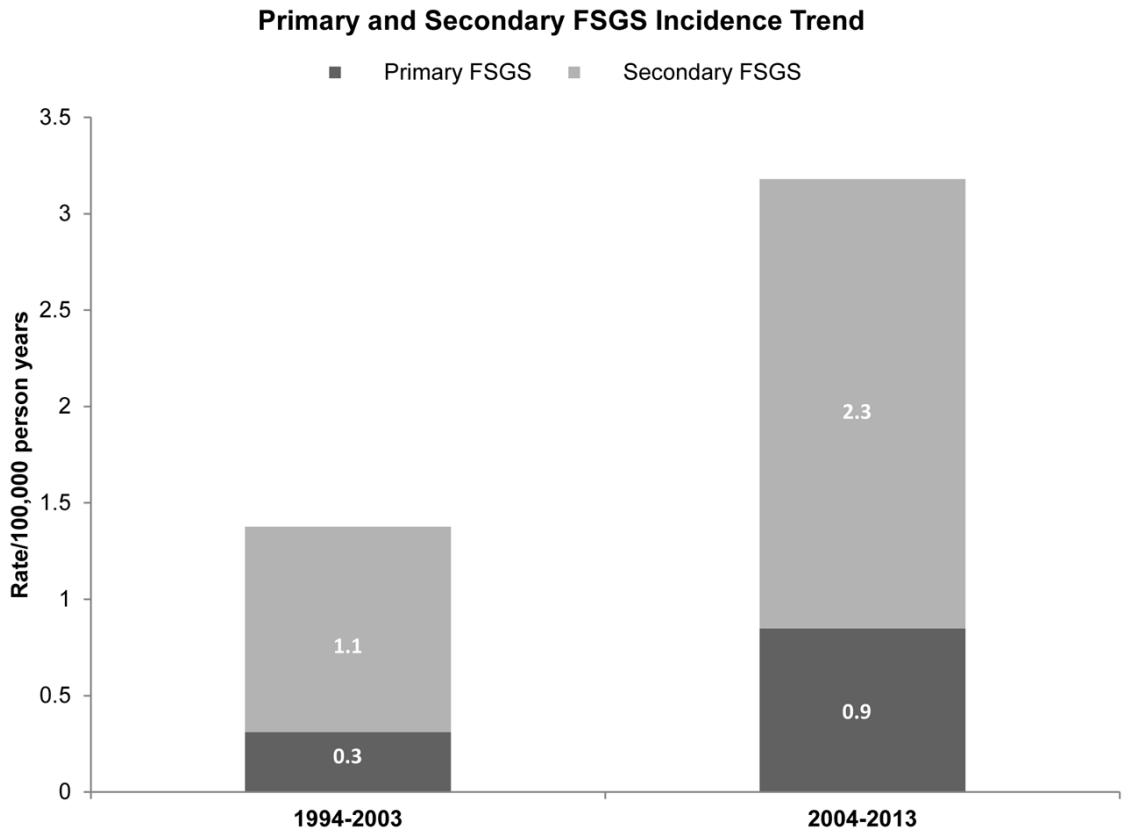


Figure 1. Trend in the incidence rates of primary and secondary focal segmental glomerulosclerosis (FSGS) over the period of 1994–2013

In the first decade of 1994–2003, out of the 12 cases of FSGS, 3 (25%) were primary FSGS.

In the second decade of 2004–2013, out of 34 cases of FSGS, 9 (26%) were primary FSGS.

- In conclusion, while the incidence rate of FSGS is increasing, the ratio of primary and secondary FSGS has remained stable over the last two decades.
- The increasing rate of kidney biopsy may contribute to this observed increase in the incidence of FSGS, but does not explain the whole picture.
- Distinguishing primary from secondary FSGS remains a challenge in the absence of a serological marker.
- Until a specific gold standard biomarker test for diagnosing primary FSGS is developed, using a combination of clinical features (nephrotic syndrome) and pathological features (diffuse FPE), in the absence of any identifiable cause, provides the best approach to distinguishing primary from secondary FSGS.

WHAT IS FSGS?

- FSGS describes a renal histologic lesion with diverse causes and pathogenicities that are linked by podocyte injury and depletion.
- The lesion of FSGS represents a segmental increase in glomerular matrix with obliteration of the capillary lumina in at least one glomerulus in the entire kidney biopsy.
- This histologic lesion is caused by diverse etiologies and pathogenic mechanisms, sharing the initiating and defining feature of podocyte alterations and depletion (podocyt- opathy).
- The lesion of FSGS can be broadly subdivided into primary (“idio-pathic”), genetic, and secondary forms.

- Primary FSGS is presumably caused by a circulating factor, possibly a cytokine elaborated from extrarenal sources, which causes generalized injury to podocytes.
- Primary FSGS may respond to corticosteroids, immunomodulatory agents, plasmapheresis, or immunoad- sorption and is prone to recur post-transplantation.
- Maladaptive forms of secondary FSGS ensue from a reduction in the number of functioning nephrons or from a normal nephron population subjected to abnormal stress, and should primarily be treated with renin-angiotensin-aldosteron system inhibi- tion.
- Other forms of secondary FSGS include virus-associated FSGS5 and drug-induced FSGS, which typically improve on resolution of the infection or cessation of the drug.

- The genetic causes of FSGS may present as sporadic or familial disease, with autosomal dominant, autosomal recessive, X-linked, or mitochondrial (matrilineal) inheritance patterns.
- The age of onset of genetic FSGS is usually early childhood, but as additional mutations associated with FSGS are identified, adult- onset genetic FSGS assumes increasing significance.
- Genetic FSGS may be either limited to the kidney or part of a broader syndrome with extrarenal involvement .
- Genetic FSGS is typically resistant to corticosteroids.
- Calcineurin in-hibitors may be effective in few patients, possibly reflecting direct stabilization of the podocyte actin cytoskeleton rather than an immunosuppressive effect.

Table 1. Causes of FSGS

Primary	Circulating podocyte-toxic factor
Secondary: Maladaptive	Reduced number of functioning nephrons (*e.g.*, unilateral renal agenesis, renal dysplasia, oligomeganephronia, glycogen storage disease, low birth weight)
	Abnormal stress on an initially normal nephron population (*e.g.*, morbid obesity, surgical reduction of renal mass [usually >75%], reflux nephropathy, high-protein diet, sickle cell disease, any advanced kidney disease with substantial loss of nephrons)
	Other causes: sleep apnea, cyanotic congenital heart disease, renal artery stenosis, malignant hypertension, cholesterol emboli
Secondary: Viral	HIV (established), CMV (probably), parvovirus B19 (possibly), EBV (possibly), HCV (possibly), hemophagocytic syndrome (possibly)
Secondary: Drug induced	Direct-acting antiviral therapy (ledipasvir, sofosbuvir), mTOR inhibitors, calcineurin inhibitors, anthracyclines, heroin(adulterants), lithium, IFN, anabolic steroids
Genetic	Renal limited (Table 2)
	Syndromic (Table 3)
Unknown	

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HCV, Hepatitis C virus; mTOR, mammalian target of rapamycin. IFN, interferon

- Many patients with FSGS cannot be readily classified, because an underlying cause or genetic mutation is not identified (the “un-known” forms of FSGS).
- At least some of these are likely genetic in origin.

- Despite the heterogeneous etiology and pathogenesis of FSGS, the clinical and pathologic presentations may be similar (Figure 1).
- In the absence of a serum or urine nongenetic biomarker that reliably discriminates primary from secondary and genetic forms, correctly classifying the type of FSGS is often challenging.
- Importantly, a mis-classification may lead to inappropriate and potentially harmful therapy.

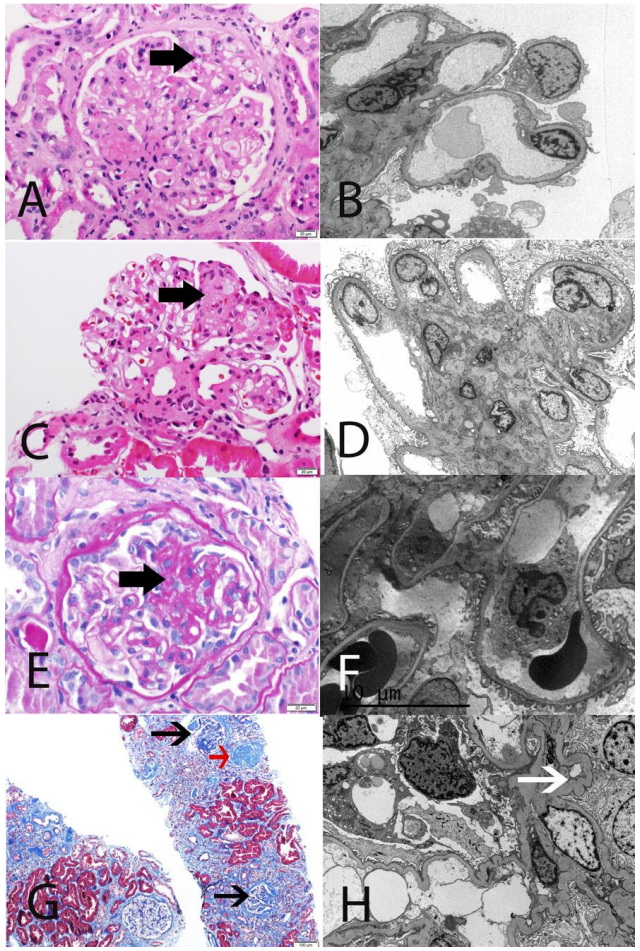


Figure 1. Representative LM and EM findings in FSGS and FGGS. (A and B) Primary FSGS in a 61-year-old white man with serum creatinine 1.5 mg/dl, proteinuria 14.2 g/24 h, and serum albumin 2.5 mg/dl. LM shows segmental sclerosis, and EM highlights diffuse FPE. (C and D) Maladaptive FSGS in a 53-year-old white man with serum creatinine 1.9 mg/dl, proteinuria 5.8 g/24 h, and serum albumin 4.1 mg/dl. LM shows segmental sclerosis, and EM reveals well preserved foot processes. (E and F) Genetic FSGS in a 39-year-old white man with familial history of *PLCE1* mutation, serum creatinine 1.3 mg/dl, proteinuria 2.0 g/24 h, and serum albumin 4 g/dl. LM shows segmental sclerosis, and EM features only minimal FPE. (G and H) FGGS in a 38-year-old black man with a long history of uncontrolled hypertension, serum creatinine 5.1 mg/dl, proteinuria 2.8 g/24 h, and serum albumin 4.3 g/dl. LM shows ischemic changes, as well as a globally sclerosed glomerulus (red arrow), and EM shows relatively well preserved foot processes. Note ischemic capillary loops (white arrow). (A, C, E) Thick black arrow points to segmental sclerosis, and (G) thin black arrow points to ischemic glomeruli. (A and C) Hematoxylin and eosin. (E) Periodic acid–Schiff. (G) Masson trichrome stain. Original magnification, ×40 in A, C, and E; ×2500 in B; ×3000 in D; ×3500 in F; ×10 in G; ×5000 in H.

Table 4. Differential diagnostic characteristics of primary FSGS, genetic FSGS, maladaptive FSGS, and 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

- WHAT IS FSGS?
- Glomerulosclerosis
- Focal
- Segmental

Glomerulosclerosis

- The glomerular visceral epithelial cells (podocytes) are anchored to the under- lying glomerular basement membrane (GBM) by their foot processes.
- This lim- ited attachment to the GBM, along with their continuous exposure to the flow of the primary filtrate, render podocytes prone to detachment and loss in the urine.
- Podocytes are terminally differen- tiated, postmitotic cells unable to prolif- erate to compensate for lost cells.
- The ability of neighboring podocytes to hy- pertrophy and cover denuded areas of the GBM is limited.
- The stress caused by the process of hypertrophy and extend- ing over bare areas of the GBM weakens the attachment to the GBM in the remain- ing podocytes that, in turn, detach.
- In this way, podocyte detachment and GBM de- nudation become self-perpetuating processes.
- The GBM tends to bulge outward in these bare areas, because the intraglomerular capillary hydrostatic pressure is no longer opposed by the po- docytes, and synechial attachments with the parietal epithelial cells and Bowman's capsule occur.
- After podocyte loss has reached a critical point, the capillary loop collapses, and extracellular matrix accumulates, thus creating the character- istic segmental obliteration of the glo- merular capillary tuft.
- In an animal model, glomerular growth exceeding the capacity of podocytes to adapt and adequately cover the filtration surface also resulted in a FSGS lesion, without a detectable reduction in average podocyte number per glomerulus.14

Focal

- The term “focal” denotes a heterogeneous involvement of the glomerular population in the renal cortex.
- However, the segmental sclerotic lesion has only a small volume (on average, 12% of the entire glomerular volume) and can thus be easily missed on a single section.
- Serial morphologic analysis in the various forms of FSGS shows that the sclerotic lesions involve the **great majority of the glomeruli**, revealing that **FSGS is not as focal as the name implies**.

Segmental

- The segmental pattern (affecting only a portion of the glomerular tuft) characteristic of the lesion of FSGS must be distinguished from nonspecific focal global glomerulosclerosis (FGGS; affecting the entire glomerular tuft) observed in aging and hypertensive nephropathy .
- FGGS seen in the aging kidney usually occurs without FSGS.
- The likely driving process for age-related FGGS is arteriosclerosis and glomerular ischemia, resulting in podocyte stress and depletion.
- An alternative and more podocyte-centered viewpoint suggests that progressive podocyte loss with aging is the primary event, resulting in an ever-increasing hypertrophic stress on remaining podocytes.
- Whatever the initiating event, after a critical number of podocytes are lost, catastrophic podocyte detachment leads to glomerular tuft collapse and rapid obsolescence of the entire glomerulus.
- Global glomerulosclerosis exceeding the threshold expected for a given age is indicative of CKD as a consequence of hypertensive damage.

Not Nonspecific Scarring

- FSGS should also be differentiated from **focal segmental "scarring"** that develops in **immune-mediated GN** (e.g., IgA ne- phropathy, ANCA-associated GN, and lupus nephritis) as a result of **postin-flammatory scarring** of necrotizing or proliferative lesions.
- In addition to non- specific scarring, a significant proportion of segmental sclerotic lesions in **IgA nephropathy** may represent podocyte injury with mechanisms similar to those seen in FSGS.

- Podocytes can be damaged by a spectrum of mechanisms that encompass nonmechanical insults (immunologic, toxic, viral), mechanical stress, and genetic mutations, which compromise specific cellular components.
- Whatever the type of stress, the podocyte initially responds with loss of the interdigitating foot process pattern, termed foot process effacement (FPE).
- FPE starts with sealing of the filtration slits between neighboring cells through replacement of the slit diaphragm with occluding junctions.
- It proceeds with retraction, shortening, and widening of the foot processes, ultimately resulting in a continuous and flattened cytoplasmic sheet covering the GBM.
- Whether FPE is merely a sign of derangement of a highly organized system or rather, a co-ordinated process to promote cell sur-vival remains controversial. However, substantive evidence supports the latter view, i.e. that **FPE may be a protective** response, whereby **podocytes attempt to secure adhesion to the GBM and thus escape detachment.**
- Indeed, FP**E is potentially reversible**.
- When local conditions improve, podocytes resume their original shape, and the functionality of the filtration barrier steadily improves. In contrast, the persistence of stress of whatever cause may overwhelm the ca-pacity of FPE to enable podocyte adherence to the GBM, thereby leading to irreversible podocyte detachment.

- Maladaptive FSGS results from a mis-match between glomerular load and glomerular capacity in conditions associated with hyperfiltration, glomerular capillary hypertension, and glomerular hypertrophy.
- Hyperfiltration and glomerular capillary hypertension represent a major mechanical strain to the podocytes.
- Podocytes are extremely sensitive to shear stress generated by the increased filtrate flow through the filtration slits and over their apical surface.
- Glomerular hypertrophy challenges the podocytes to cover an increased filtration surface.
- However, the ability of the foot processes to display hypertrophic growth is limited.
- The podocytes may be unable to maintain a normal foot process pattern, leading to a further increase in local shear stress.
- When the rheologic stress becomes untenable, **the process of FPE is set in motion to redistribute the mechanical forces and decrease the local shear stress.**
- Although glomerular capillary hyper- tension affects all capillaries to comparable degrees, shear stress is unevenly distributed along the glomerular capillaries, decreasing toward the end of the capillary network.

- **FPE** as a response to increased fluid shear stress is, therefore, ***typically a segmental phenomenon***, encountered only in the parts of the podocyte that are affected by the rheologic disturbances, whereas the other parts display an intact foot process pattern.
- This crucial new insight explains why **FPE develops slowly** and has a **hetero-geneous distribution** in maladaptive FSGS.
- The mean percentage of the glomerular surface area affected by FPE was reported to be 40% in obesity-related FSGS and 25% in reflux nephropathy.
- In a mixed cohort of patients with **secondary FSGS** (that also included some patients with genetic FSGS), the median degree of FPE was **30%.**

- In primary FSGS, however, a putative circulating factor capable of crossing the GBM barrier causes generalized podo- cyte dysfunction, ensuing in sudden and widespread FPE
- patients with primary FSGS, median FPE was 100%

- The mechanism of **virus**-associated FSGS, epitomized by HIV-associated nephropathy, involves **direct infection of the podocytes**, resulting in dysregulation of the cellular phenotype and apoptosis.
- In accordance, **diffuse FPE** (referring to the entire population of glomeruli) (mean, 89%) was reported in patients with **HIV**- associated nephropathy, although in another cohort, only 57% of patients had FPE covering > 80% of the glomerular capillary surface.
- **Direct podocyte toxicity** resulting in dysregulation of the cytoskeleton has also been described in **drug-induced FSGS**.
- As an example, biopsies of patients with collapsing FSGS caused by high-dose **pamidronate** featured **extensive FPE** (mean, 84%; range, 60%–100%) associated with loss of expression of the cytoskeletal protein synaptopodin.

Nephrotic Syndrome, Nephrotic- Range Proteinuria, and Subnephrotic Proteinuria

- Proteinuria is the cardinal presenting clinical feature of FSGS.
- The distinction between **nephrotic syndrome** (defined as urinary protein excretion $3.5 g/24 h, serum albumin concentration of #3.5 g/dl, often but not necessarily accompanied by hyperlipidemia, lipiduria, and/ or edema), **nephrotic-range proteinuria** (defined as urinary protein excretion $3.5 g/24 h in the absence of low serum albumin), and **subnephrotic proteinuria** (defined as urinary protein excretion .0.2 and ,3.5 g/24 h) is helpful in the **differential diagnostic evaluation** of patients with an FSGS lesion.

- Patients with **primary FSGS** typically present with **abrupt-onset marked protein-uria** (sometimes as much as 20 g/24 h or greater) and severe nephrotic syndrome.
- The prevalence of nephrotic syndrome in primary FSGS has been reported to vary from 54%28 to 58%41 to 70%42 to 90%.
- Such variability may be due to the inclusion of unrecognized sporadic genetic FSGS, because primary FSGS has historically been defined as FSGS with absence of conditions typically associated with secondary FSGS.

- More consistently, patients with well- defined forms of **maladaptive FSGS** (such as obesity, vesicoureteral reflux, and renal mass reduction) present with **sub-nephrotic-range to nephrotic-range proteinuria** and rarely, if ever, develop nephrotic syndrome, despite often marked proteinuria well above 3.5 g/24 h.

- Most patients with **childhood-onset genetic FSGS** have **autosomal recessive** mutations that almost always convey full penetrance and present with or progress to severe nephrotic syndrome.
- However, **adult-onset genetic FSGS** is generally inherited as **autosomal dominant** disease with variable penetrance, and it exhibits proteinuria of usually ,5 g/24 h and more slowly progressive CKD.

PROPOSAL FOR A CLINICOPATHOLOGIC APPROACH TO A LESION OF FSGS

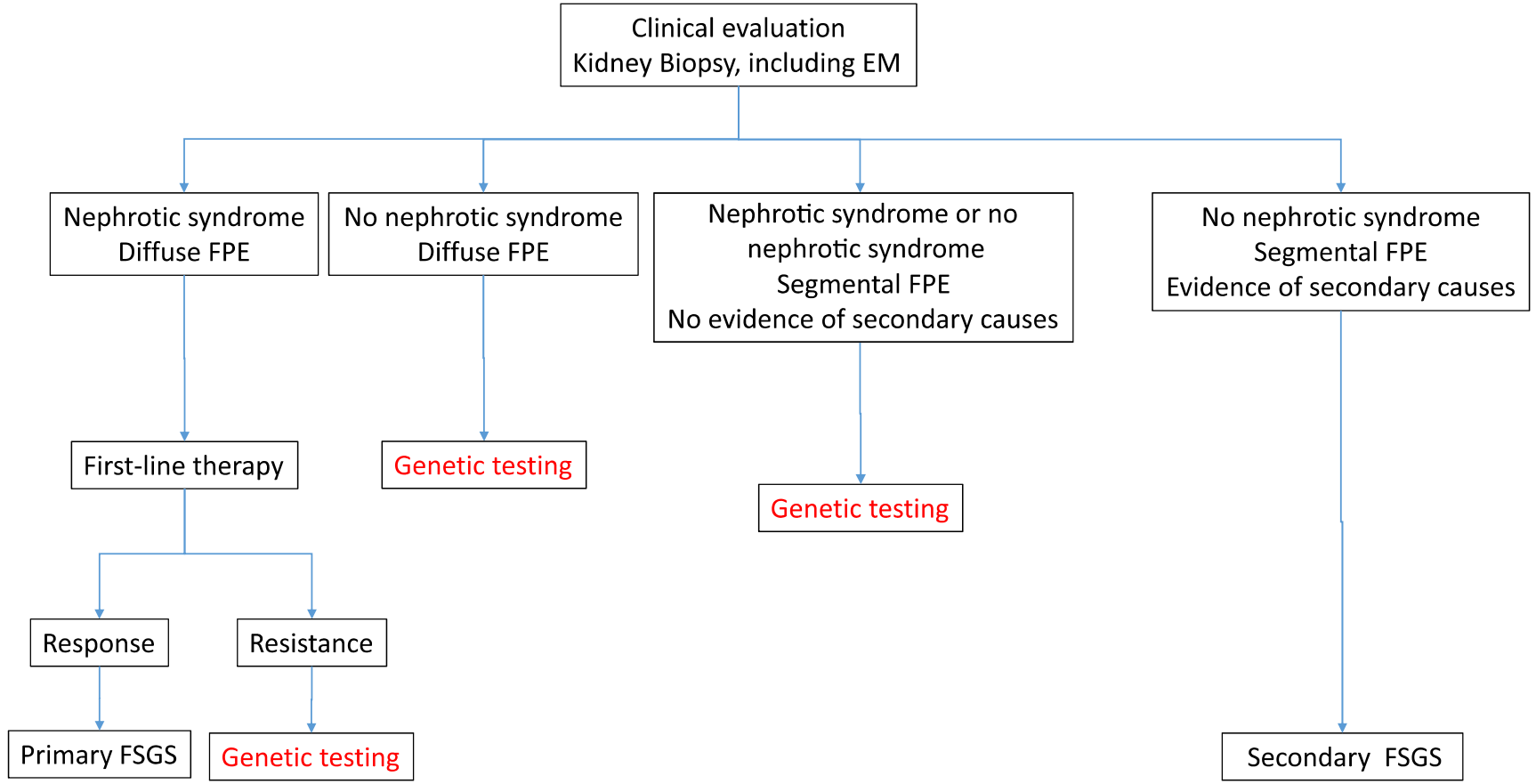


Figure 4. Opinion-based approach to genetic testing in adult-onset FSGS. Note that viral- and drug-associated forms of FSGS are usually excluded by clinical and serologic evaluation.

- Clinical Evaluation
- Detailed documentation of the clinical phenotype remains of unassailable importance, even when a kidney biopsy is the next diagnostic step.
- Medical, medication and family history, body mass index, birth weight, and viral serology should be documented.
- Clinical evidence of a syndromic presentation should also be sought (e.g., hearing loss, skin or eye abnormalities, cardiac dysfunction or anatomic distur- bances, hepatosplenomegaly, etc.).
- Measurement of serum albumin concentration and quantitation of urinary proteins are the required first steps in patient stratification.
- It is also important to determine the **identity of the urinary proteins**.
- Initially, a **urinary protein-to-creatinine ratio** can be **compared with** a **urinary albumin-to-creatinine ratio**.
- **If ,50% of total proteinuria is due to albumin**, >>> then the possibility of **tubular proteinuria or presence of light chains should be considered.**

Pathologic Evaluation

- Light Microscopy
- The Columbia classification subdivides the lesion of FSGS irrespective of under- lying etiology or pathogenesis by its appearance on LM into collapsing, tip lesion, cellular, perihilar lesion, and not otherwise specified variants

- Not otherwise specified (NOS) is the most common variant, and it is equally distributed among primary and secondary forms.
- Perihilar lesions are more usual in maladaptive FSGS, although they can also occur in primary FSGS and genetic FSGS.
- Tip lesion, cellular, and collapsing variants usually share the pre-senting features of **heavy proteinuria** and the nephrotic syndrome, but they may also present with subnephrotic-range proteinuria.
- Tip lesions tend to occur more frequently in white patients, are more likely to respond to therapy, and have overall the best prognosis.

- Conversely, the **collapsing variant** affects predominantly patients from African heritage and is particularly **malignant** in its course.
- The clinical course and morphologic characteristics of the collapsing variant are different from the other FSGS variants, such that ***some believe that it is a different entity altogether.***
- The collapsing pattern of injury occurs in patients with **primary FSGS**, but it is also the characteristic lesion seen **in HIV-associated** nephropathy, **parvo B19 virus** infection, and **pamidronate toxicity**.

- **Glomerulomegaly** is very common in FSGS caused by **obesity, reflux nephrop- athy, or surgical- or disease-related re- ductions in nephron mass or in low-birth weight individuals**, but it is also observed in **10%–30%** of patients with presumed **primary FSGS**

- Because primary FSGS presents with an abrupt onset of nephrotic syndrome, kidney biopsy is often done early in the course and generally shows a relatively well preserved parenchyma with few glo- meruli featuring the characteristic FSGS lesion.
- In contrast, maladaptive FSGS of- ten presents with progressive protein- uria, and the kidney biopsy is done later in the course. As such, varying degrees of parenchymal scarring are often associ- ated with maladaptive FSGS

IMPORTANT

- Taken together, none of the LM features are pathognomonic for a particular type of FSGS.
- **Thus, the etiopathogenesis of FSGS cannot be reliably determined by LM alone.**

- With the current state of knowledge, empirical treatment of FSGS with corticosteroids or immunosuppressive agents is no longer defensible: such treatment is often ineffective and may impose considerably toxicity.
- A central consideration in the management of patients with FSGS is the identification of those patients who would likely benefit from such therapies and the delineation of those patients for whom renin-angiotensin-aldosteron system blockade remains the prudent therapeutic approach.

- FSGS should be differentiated from FGGS and nonspecific segmental scar- ring.
- When a typical FSGS lesion is identified on LM, careful interpretation of clinical and electron microscopic characteristics may point to one of the main subtypes.
- Patients with primary disease or high-penetrance mutations disruptive to podocyte function present with sudden onset of nephrotic syndrome and with diffuse FPE.
- Patients with maladaptive FSGS are characterized by slow development of subnephrotic or nephrotic-range proteinuria without nephrotic syndrome and by segmental FPE.
- In contrast to these two phenotypes, there is a significant subset of patients lacking clear causative factors and exhibiting variable degrees of proteinuria and FPE.
- Many of these patients may have an undiagnosed genetic basis of FSGS

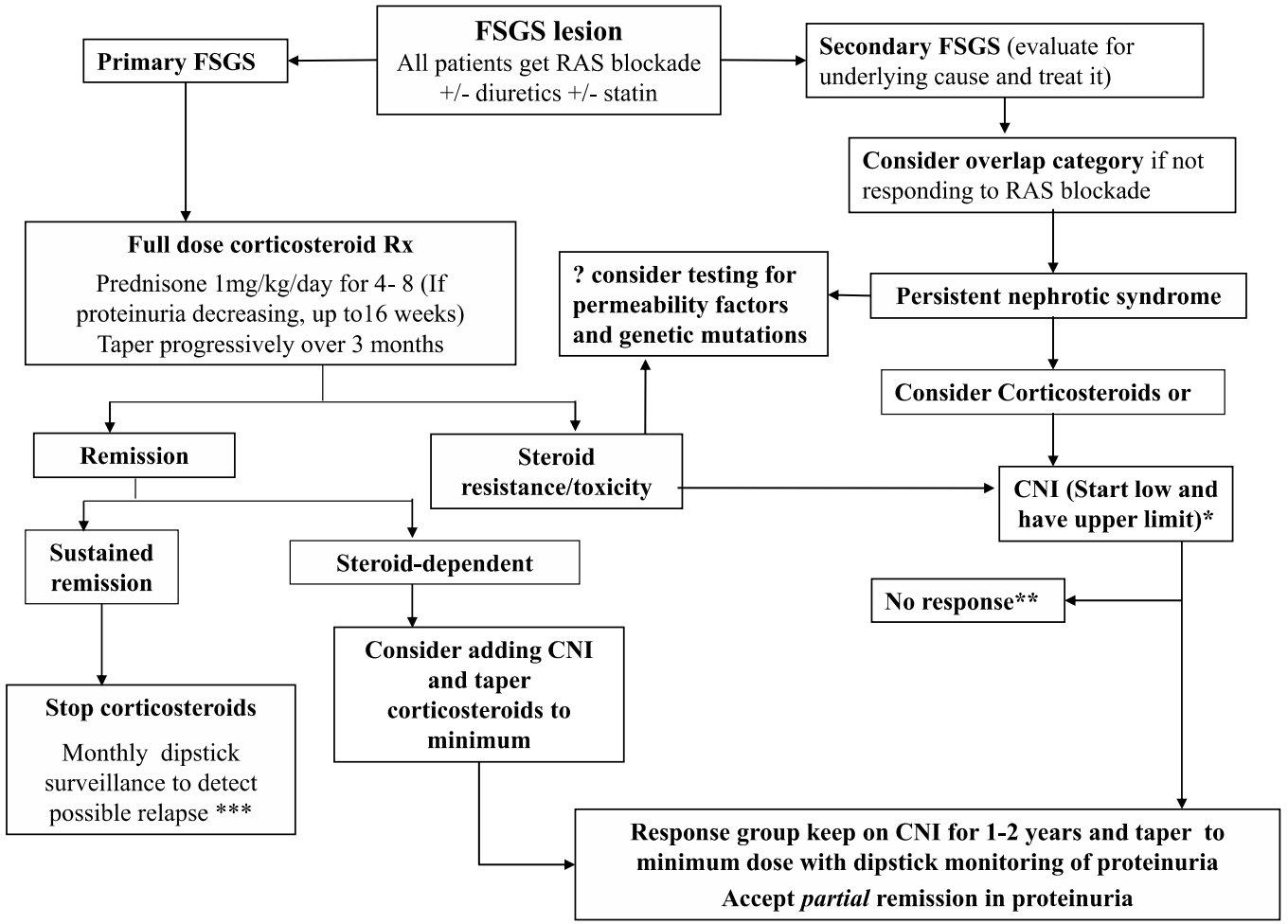


Figure 2. | Treatment algorithm for FSGS. *CNI dose as per the KDIGO guidelines on GN. **See the text on options to consider in the management of nonresponders. ***See the text on how to manage relapse. RAS, renin-angiotensin system; CNI, calcineurin inhibitor; MMF, mycophenolate mofetil.

- Current therapy, consisting of corticosteroids and calcineurin inhibitors, fails to achieve a sustained remission in most patients.
- Therefore, there is a pressing need to develop new treatments for this glomerulopathy.

- The goal of treatment in patients with FSGS is normaliza- tion of urinary protein excretion and preservation of kid- ney function. However, even partial reduction in proteinuria is beneficial

- The **standard of care** for patients with primary FSGS includes initial treatment with a course of corticosteroids.
- Up to 25% of patients will respond to this therapy, and their prognosis is more favorable.
- For those who are steroid resistant, the next option is a calcineurin inhibitor with an expected complete or partial remission rate in 40% to 50% of patients.
- If these drugs are ineffective, then there is no proven therapy that can consistently achieve a significant and sustained reduction in proteinuria.

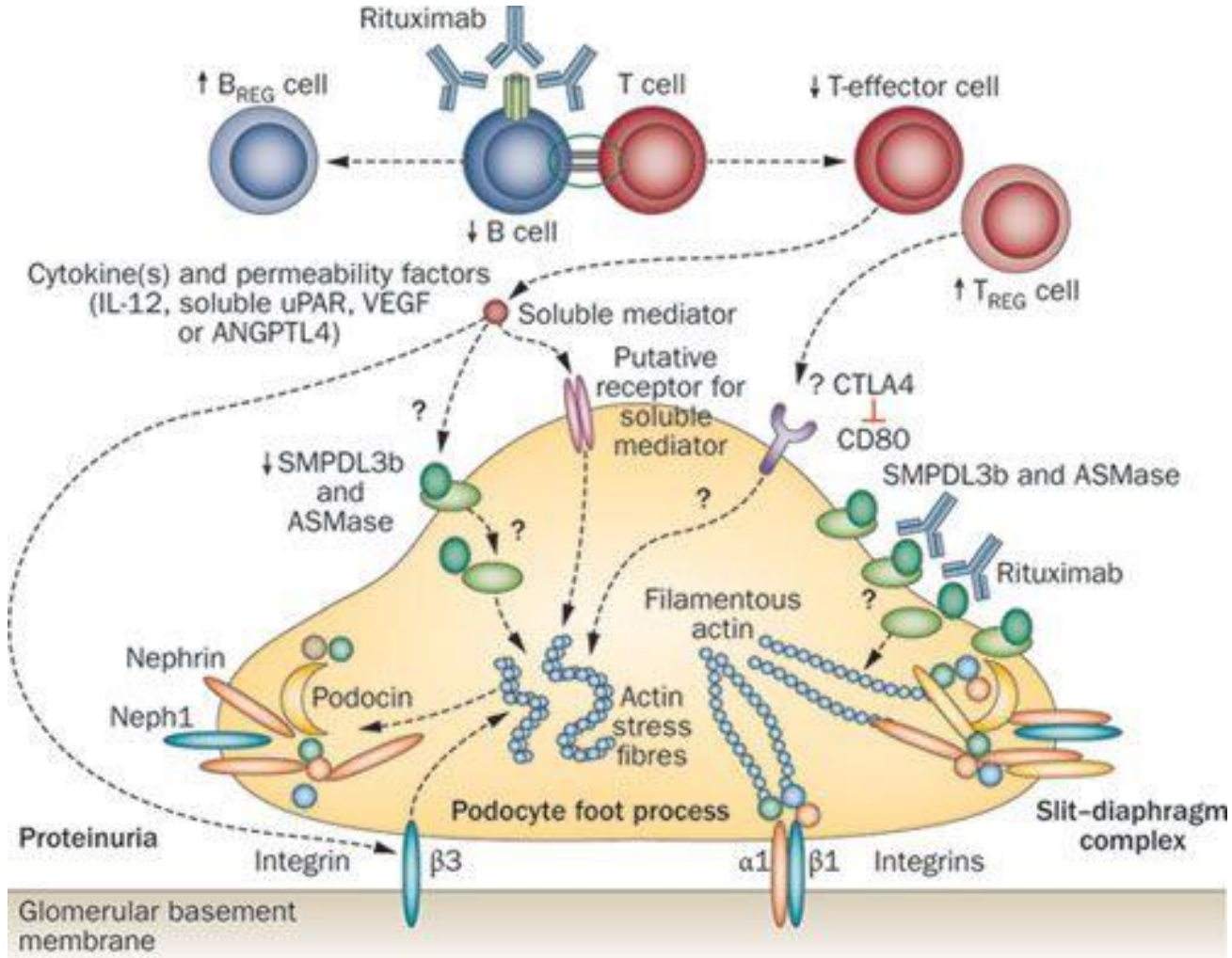
- Current therapy of focal segmental glomerulosclerosis is generally ineffective and cannot prevent progression to end-stage kidney disease in most patients.

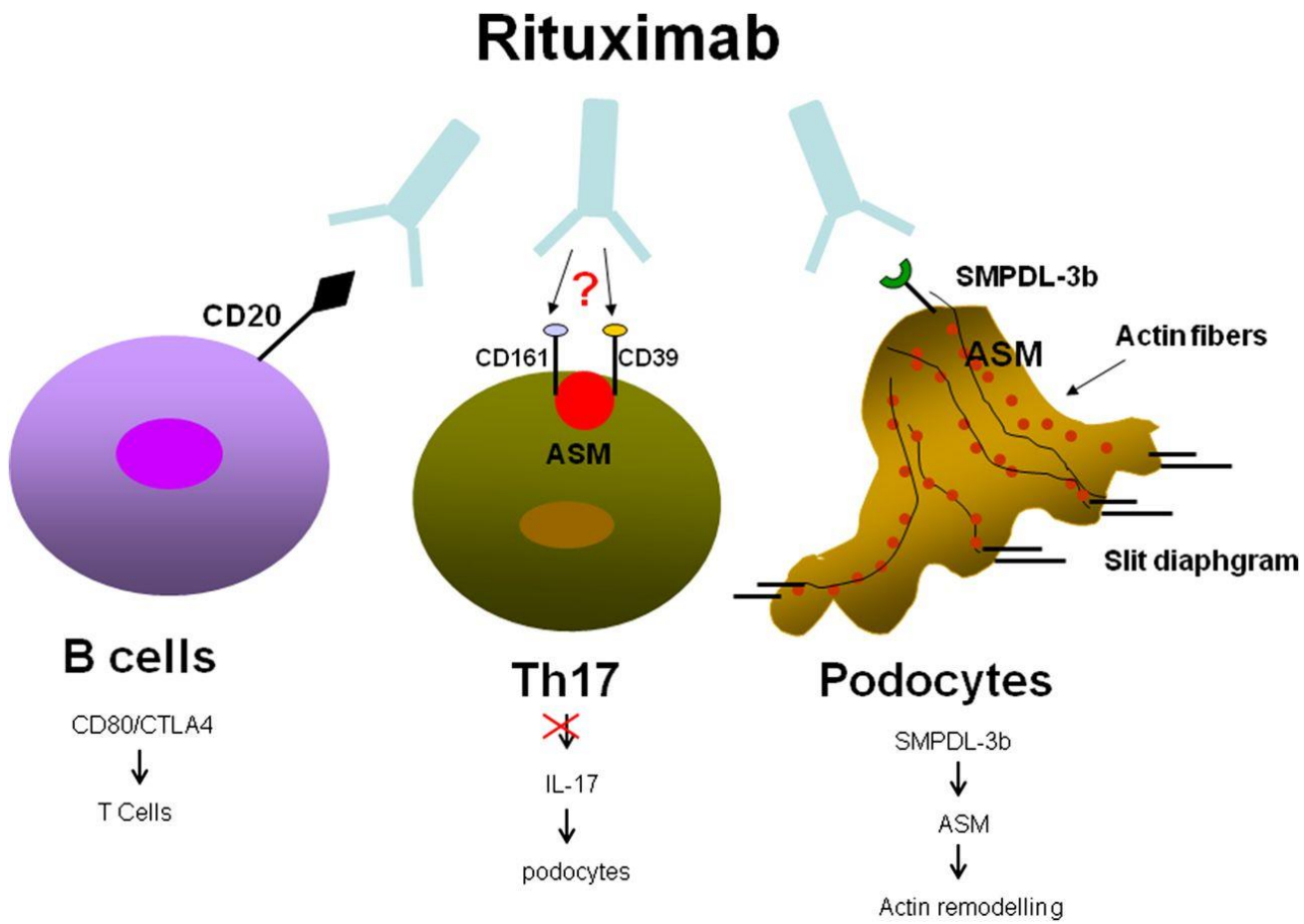
- Treatments that can consis- tently achieve a durable remission in proteinuria and pres- ervation of kidney function are sorely lacking
- Despite decades of intensive basic science and clinical research, no therapeutic target has been identified that is applicable to all patients.
- This suggests that FSGS is a heterogeneous disease **-like cancer** and that **multiple approaches will be needed to achieve a "cure" for affected patients**

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
- Rituximab, a monoclonal antibody against CD20 on B cells, was first demonstrated to induce remission of proteinuria in a single patient with a **transplant-related lymphoma and recurrent FSGS after kidney transplanta- tion.**
- Subsequent reports have evaluated the effect of rituximab in case series of patients with primary FSGS.
- Overall, the response has been low, in the range of **20% to 30%,** suggesting that this therapy may have a role in **selected patients** with primary FSGS.
- There is evidence that rituximab may have **off-target effects** on **lipid metabolism in podocytes** by binding to **sphingo- myelin phosphodiesterase acid-like 3b protein** and **regulating acid sphingomyelinase activity**.
- This action may contribute to the efficacy of rituximab in post- transplant FSGS. Further research is required to place rituximab into a rational framework for the treatment of FSGS.


Rituximab
↑ B_{REG} cell
T cell
↓ T-effector cell
↓ B cell
↑ T_{REG} cell
Cytokine(s) and permeability factors (IL-12, soluble uPAR, VEGF or ANGPTL4)
Soluble mediator
Putative receptor for soluble mediator
? CTLA4
CD80
↓ SMPDL3b and ASMase
SMPDL3b and ASMase
Rituximab
Filamentous actin
Nephrin
Podocin
Neph1
Actin stress fibres
Podocyte foot process
Proteinuria
Integrin
β3
α1
β1
Integrins
Slit-diaphragm complex
Glomerular basement membrane


Rituximab
CD20
?
CD161
CD39
ASM
SMPDL-3b
ASM
Actin fibers
Slit diaphgram
B cells
CD80/CTLA4
T Cells
Th17
IL-17
podocytes
Podocytes
SMPDL-3b
ASM
Actin remodelling

ACTH

- Injections with adrenocorti-cotropic hormone (ACTH),a pituitary neuroimmunoen-docrine polypeptide, were one of the first therapies used for childhood nephrotic syndrome.
- Broad clinical and experimental evidences had long suggested that ACTH has antiproteinuric,
  lipid-lowering, and renopro-tective properties, and the drug was reintroduced as a treatment alternative for nephrotic syndrome, initially in Europe with a synthetic ACTH depot and then in the United States with natural ACTH gel.
- Hogan and colleagues treated 24 adult patients with steroid-resistant or steroid-dependent FSGS with ACTH and achieved remission in 7 (29%), indicating that this drug may represent an alternative in patients who do not respond to steroids and other common second-line agents.
- It is suggested that ACTH may have actions beyond those attributable to corticosteroids, possibly acting via anti- inflammatory mechanisms or directly on podocytes via the melanocortin 1 receptor.

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.

Clin J Am Soc Nephrol 8: 2072–2081, 2013. doi: 10.2215/CJN.02840313

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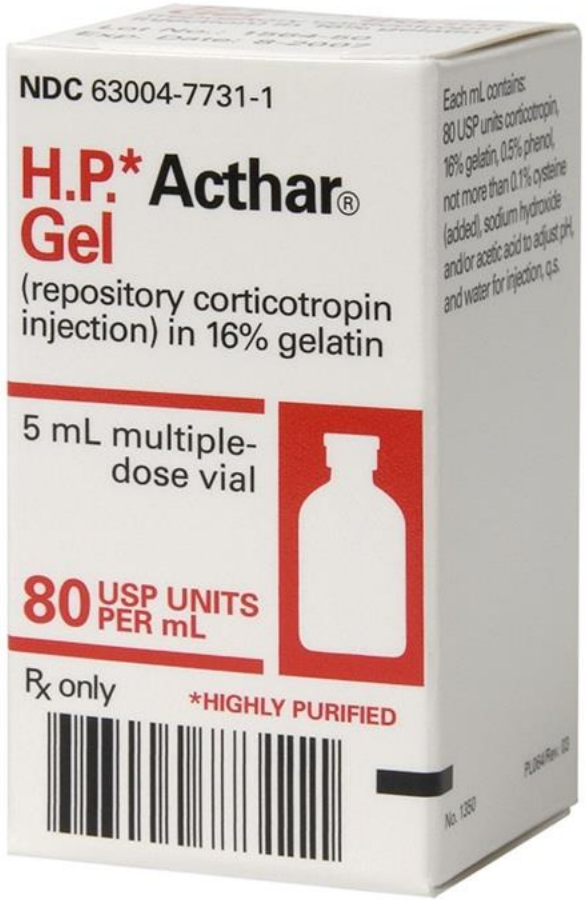
Introduction

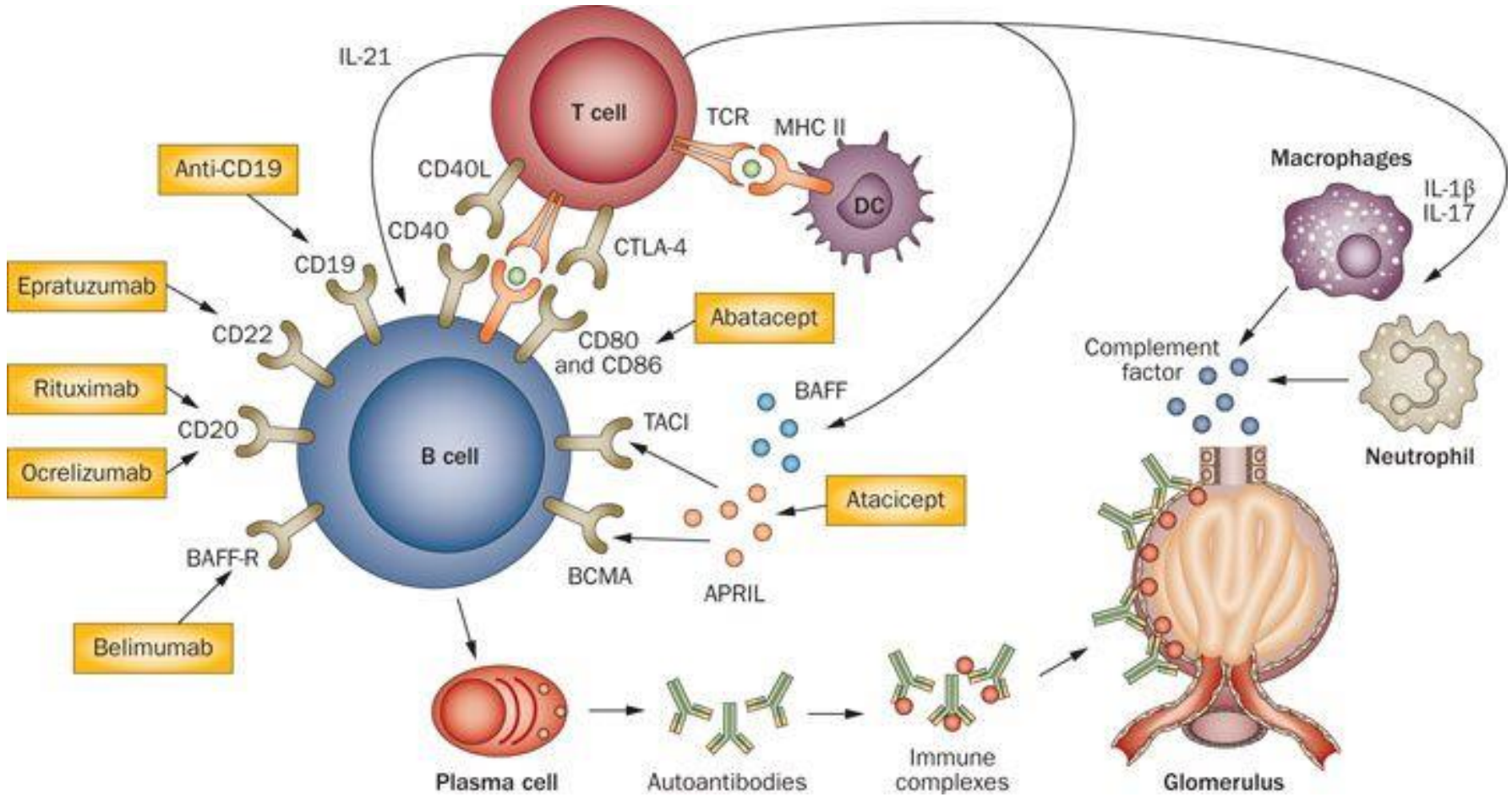
FSGS, one of the leading causes of the nephrotic syndrome, is categorized as idiopathic (primary) or secondary to another disease process or a genetic mutation. FSGS is more common in black and Hispanic patients, but its incidence has increased in all racial groups over time (1–5). Untreated, it carries 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

- this medicine is for injection into a muscle or under the skin




IL-21
T cell
TCR
MHC II
DC
CD40L
CD40
CTLA-4
Anti-CD19
CD19
Epratuzumab
CD22
Rituximab
CD20
Ocrelizumab
Abatacept
CD80
and CD86
BAFF
TACI
Atacicept
BCMA
APRIL
BAFF-R
Belimumab
B cell
Macrophages
IL-1β
IL-17
Complement
factor
Neutrophil
Plasma cell
Autoantibodies
Immune
complexes
Glomerulus

Abatacept

- Abatacept (CTLA-4-Ig) is a costimulatory inhibitor that targets B7-1 and is currently approved for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis.
- Reiser and others17 have shown that induction of the T-cell costimulatory molecule B7-1 in podocytes is associated with nephrotic syndrome.
- Yu and colleagues randomly selected biopsy specimens of native human kidneys and identified a subpopulation of patients with minimal change disease or primary FSGS who had B7-1 immunostaining of podocytes
- If validated, abatacept may be a new therapeutic tool for the subgroup of patients with FSGS who exhibit B7-1 immunostaining in the kidney biopsy specimens.
- This drug may stabilize b1-integrin activation in podocytes and reduce proteinuria in patients with B7-1-positive glomerular disease.

- The goal of therapy is to induce a complete remission of proteinuria that in turn will lead to better long-term preservation of renal function.
- Achieving partial remission, although not optimal, does slow the progression of kidney disease and substantially improve renal survival .
- Regardless of the underlying causative process, the signs and symptoms of nephrotic syndrome should be managed with renin-angiotensin system inhibitors, statins, a low-salt diet, and diuretics, because even low-level persistent proteinuria has been associated with an increased risk of cardiovascular disease and the potential for long-term organic kidney damage

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**

- The current KDIGO guideline on GN recommends initial treatment of primary FSGS with **high-dose prednisone** given for between **4 and 16 weeks or until complete remission.**
- **CNIs** are recommended for patients with FSGS who are **resistant or intolerant to glucocorticoids** and are continued for a minimum of 1 year if the patient is responsive.
- The above treatments are effective but side effects are significant, and rates of treatment failure and relapse are high.
- **Steroid resistance can be seen in up to 50%** of patients and a prolonged course is associated with significant side effects, including diabetes, increased infection rates, osteoporosis, and weight gain.

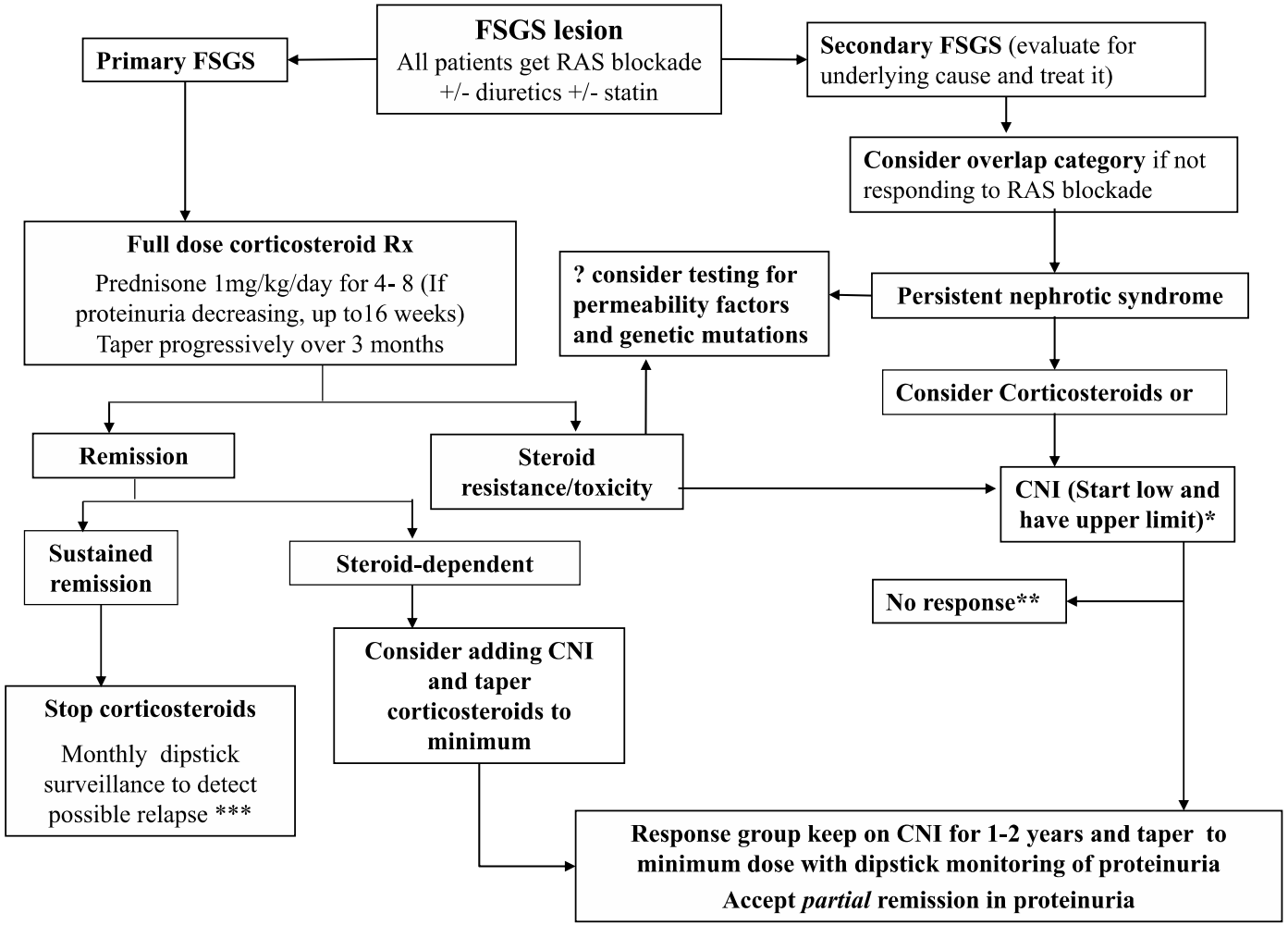
Relapse

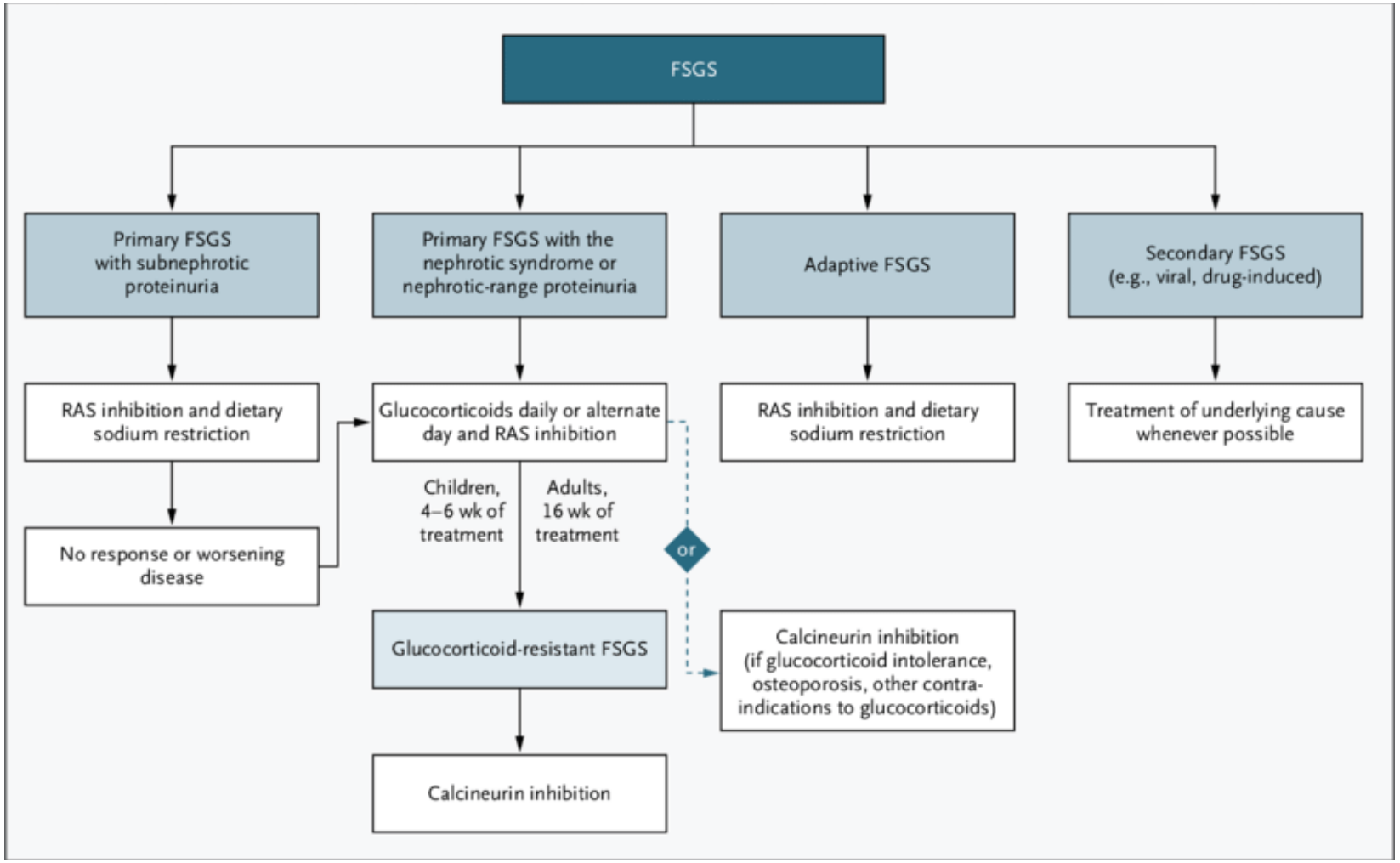
- The current guideline suggests that patients who relapse should be treated with the same agent and duration that resulted in their initial remission.

- The current available data do not support the general use of alkylating agents in the treatment of FSGS in adults

- Pilot studies in resistant patients using mycophenolate mofetil (MMF) alone showed a low but significant response rate of approximately15%–20%

- Although the KDIGO guideline on GN indicates that there is insufficient evidence to support the use of alkylat- ing agents, MMF, or rituximab in the treatment of FSGS, these drugs may have a role in patients who are resistant or intolerant to conventional treatment. A practical algorithm for consideration in the treatment of FSGS is provided


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**
Consider adding CNI and taper corticosteroids to minimum
Stop corticosteroids
Monthly dipstick surveillance to detect possible relapse ***
Response group keep on CNI for 1-2 years and taper to minimum dose with dipstick monitoring of proteinuria
Accept *partial* remission in proteinuria


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
Children, 4–6 wk of treatment
Adults, 16 wk of treatment
No response or worsening disease
or
Glucocorticoid-resistant FSGS
Calcineurin inhibition (if glucocorticoid intolerance, osteoporosis, other contra-indications to glucocorticoids)
Calcineurin inhibition

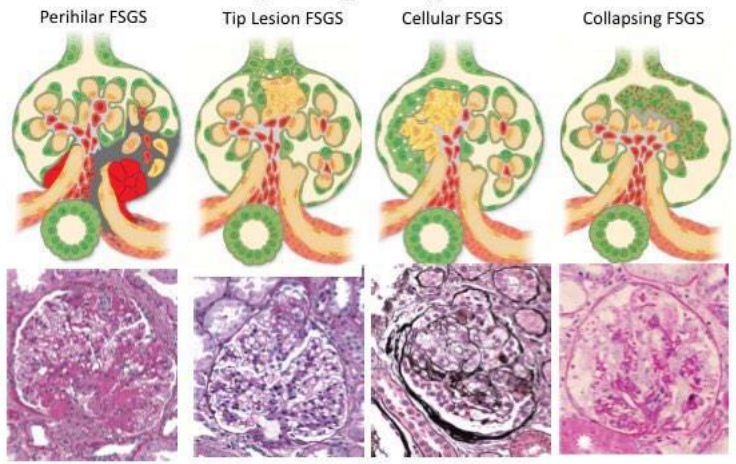
KDIGO Guideline
(Level of Evidence Classification)

Grade*	Implications		
	Patients	Clinicians	Policy
Level 1 "We recommend"	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

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

KDIGO Clinical Practice Guideline for Glomerulonephritis 2012

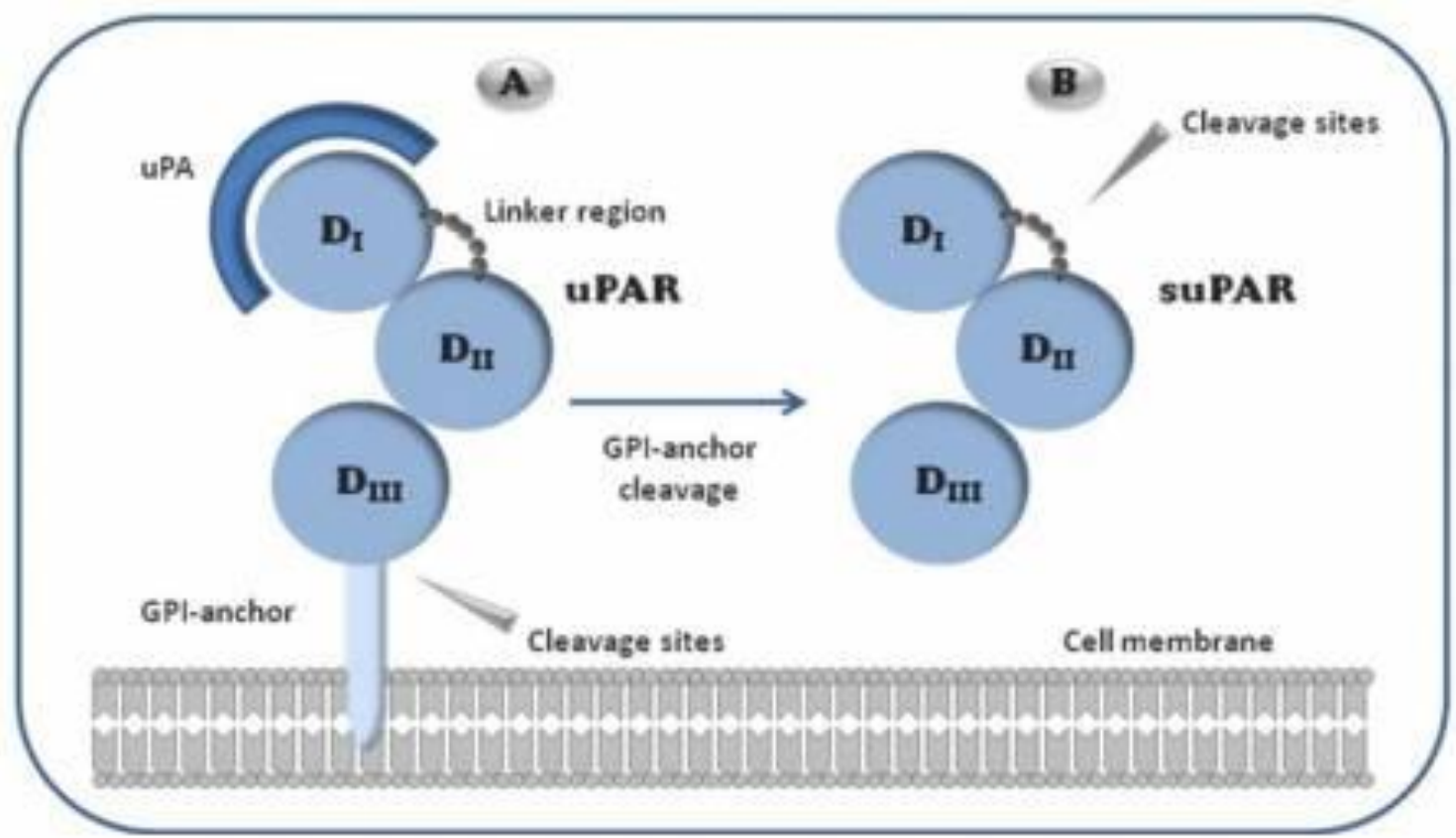
Histopathologic subtypes of FSGS

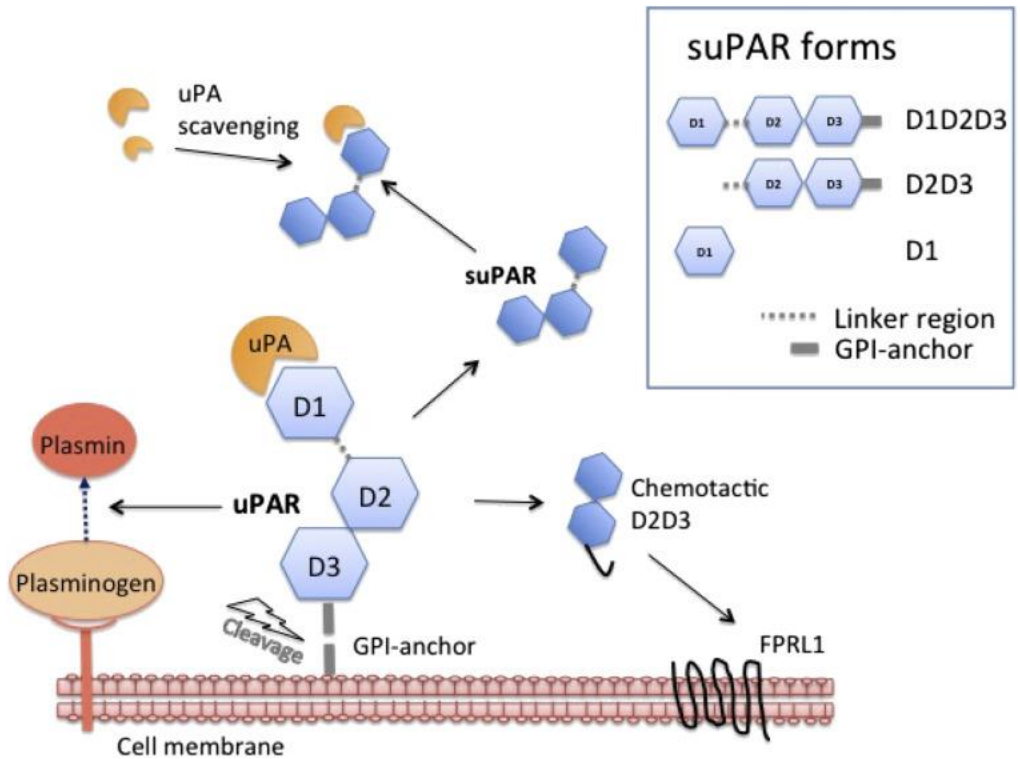


From Heptinstall's Pathology of the Kidney, 7th ed, 2014

- suPAR (soluble urokinase plasminogen activator receptor) is a protein in the blood.
  The plasma level of suPAR reflects **immune activation** and is increased in several **infectious diseases**, such as **HIV-1**-infection, **malaria**, **tuberculosis**, **Streptococcus pneumonia bacteraemia**, **sepsis**, **pneumococcal pneumonia** and bacterial and viral **CNS infection**.
- Furthermore, high suPAR levels are associated with **increased inflammation**, disease progression and risk of mortality.
- **Measuring suPAR levels can thus serve as a marker to determine chances for survival upon hospital admission as well as for monitoring for prevention of disease progression and earlier intervention time point.**

- suPAR is the soluble form of the urokinase-type plasminogen activator receptor (uPAR), a three domain receptor [12] mainly expressed on immune cells, including neutrophils, activated T-cells, and macrophages.


A
B
uPA
Linker region
D_I
D_{II}
D_{III}
uPAR
GPI-anchor
cleavage
Cleavage sites
suPAR
GPI-anchor
Cleavage sites
Cell membrane


suPAR forms
D1D2D3
D2D3
D1
Linker region
GPI-anchor
uPA
scavenging
suPAR
uPA
D1
D2
D3
uPAR
Plasmin
Plasminogen
Cleavage
GPI-anchor
Chemotactic
D2D3
FPRL1
Cell membrane