AJKD
Core Curriculum in Nephrology

Podocyte Disorders: Core Curriculum 2011

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INTRODUCTION

There are approximately 1 million glomeruli in each human kidney. Each glomerulus is composed of a tuft of capillary loops supported by the mesangium and enclosed in a pouch-like extension of the renal tubule of the nephron known as Bowman capsule. The glomerulus consists of 4 resident cell types: the mesangial cell, glomerular endothelial cell, visceral epithelial cell (podocyte), and parietal epithelial cell lining Bowman basement membrane. Recent experimental and clinical advances have identified the podocyte as the predominant cell of injury in glomerular diseases typified by heavy proteinuria, which is the focus of this article.

STRUCTURE, FUNCTION, AND INJURY OF THE PODOCYTE

Normal Structure of the Podocyte

- The podocyte is a highly differentiated epithelial cell sitting on the outside of the glomerular capillary loop
  - Consists of a large cell body (soma) in the urinary space
  - Connects to the underlying glomerular basement membrane (GBM) of the capillary loop by major cellular extensions from the soma
  - Extensions terminate as foot processes on the GBM that interdigitate with those from adjacent podocytes (Fig 1)
  - Podocyte foot processes are anchored to the GBM by $\alpha_3\beta_1$ integrins and α- and β-dystroglycans
  - Between foot processes, the filtration slit is bridged by a 40-nm wide zipper-like slit diaphragm
    - Slit diaphragm is highly permeable to water and small solutes
    - Small pore size (5-15 nm) of the slit diaphragm limits the passage of larger proteins, including albumin
    - Nephrin is the major component of the slit diaphragm and is linked to the actin cytoskeleton by CD2AP (CD2-associated protein), podocin, and others
- Approximately 500-600 podocytes/glomerular tuft in adult human kidney
  - Rate of turnover is very slow
  - Very limited ability to proliferate
- An extensive actin cytoskeleton
  - Allows dynamic contraction to support the glomerular capillary
  - Counteracts glomerular capillary hydrostatic pressure (~60 mm Hg), which is much greater in than other capillary beds

Major Functions of the Podocyte

- Structural support of the capillary loop
- Major component of glomerular filtration barrier (GFB) to proteins
- Synthesis and repair of the GBM
- Production of growth factors
  - Vascular endothelial growth factor (VEGF) traverses the GBM against the flow of glomerular filtration
    - Acts on VEGF receptors on glomerular endothelial cells
    - Effect is to maintain a healthy fenestrated endothelium
  - Platelet-derived growth factors (PDGFs) critical for the development and migration of mesangial cells into the mesangium
- Immunologic function
  - Podocytes may be a component of the innate immune system
  - Possibly have a surveillance role for pathogens or abnormal proteins in Bowman space

Glomerular Filtration Barrier

Glomerular Filtration of Plasma Water

- Occurs across glomerular capillary walls into the urinary (Bowman) space
  - Approximately 180 L/d filtered
  - A portion of glomerular ultrafiltrate is not filtered directly into the urinary space

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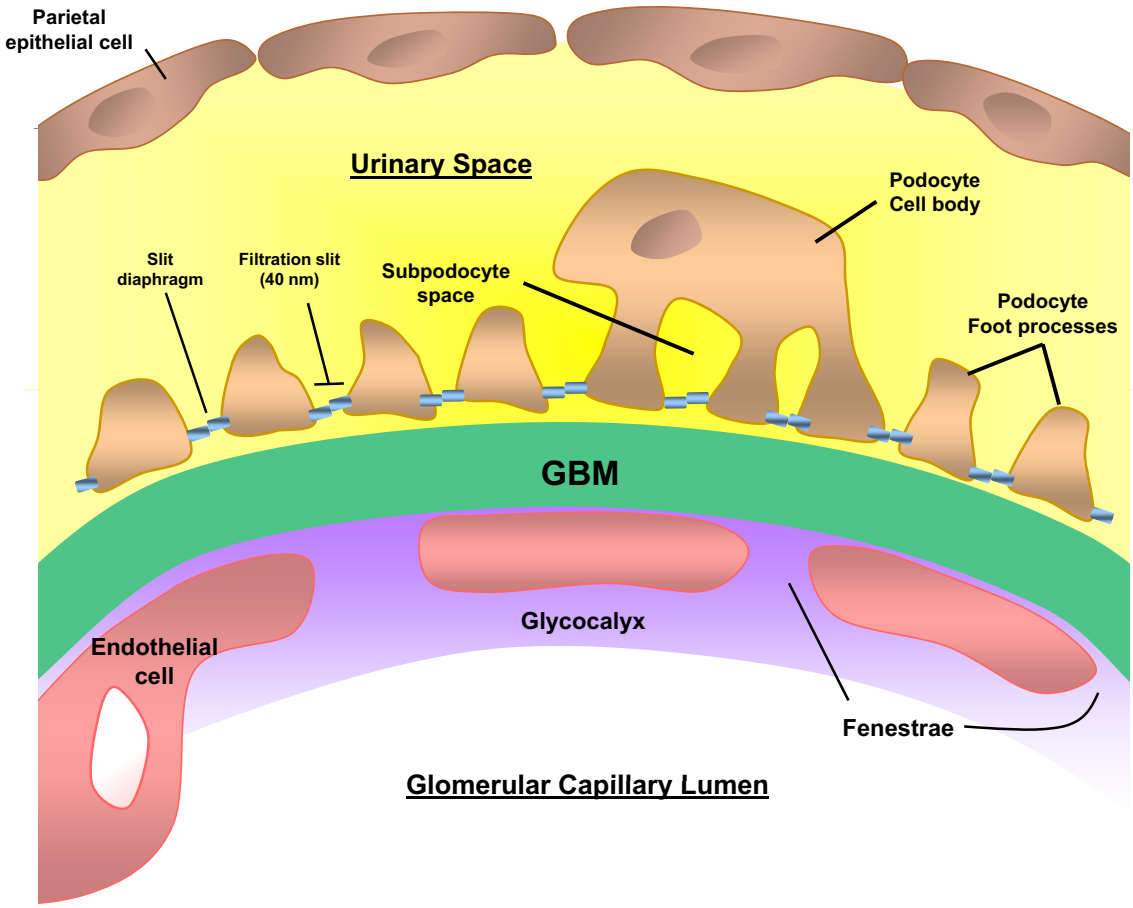

Figure 1. Glomerular capillary wall. The 3 layers of the capillary wall (glomerular endothelial cell, glomerular basement membrane [GBM], and podocyte) act as the glomerular filtration barrier (GFB), preventing proteins and large molecules from passing from the capillary lumen into the urinary space. The podocyte cell body lies with the urinary space, and the cell is attached to the GBM through foot processes. Adjacent foot processes are separated by the filtration slit, bridged by the slit diaphragm. Disruption of the GFB leads the passage of protein across the capillary wall, leading to proteinuria.

    - Instead, it goes first to a space underneath the podocyte cell body (subpodocyte space)
    - Subpodocyte space may have a role in restricting hydraulic permeability
- GFB limits the passage of larger molecules, such as albumin
    - Small amounts of protein (~4 g/d) normally are filtered across the GFB into the urinary (Bowman) space
    - Most protein is reabsorbed in the proximal tubule through the megalin/cubulin coreceptor

Structure of GFB

- Composed of 3 layers (Fig 1); damage to one or more layers leads to proteinuria
- Layer closest to lumen: fenestrated endothelial cells coated with glycocalyx
    - Fenestrations facilitate hydraulic permeability
    - Overlying glycocalyx (composed of a network of proteoglycans with negatively charged glycosaminoglycan side chains) limits the passage of albumin and larger molecules
- Middle layer: GBM
    - Major component is type IV collagen
        - Early $\alpha_1\alpha_2\alpha_1$ collagen network secreted by the glomerular endothelial cell during fetal development is replaced by the more robust $\alpha_3\alpha_4\alpha_5$ collagen network secreted by the podocyte
        - Failure to secrete this network results in a range of hereditary nephropathies, the type IV collagenopathies
        - Type IV collagenopathies include Alport syndrome, nail patella syndrome, and thin basement membrane disease; all can be considered podocyte disorders
    - Other GBM components include the glycoproteins laminin, entactin, and nidogen and heparan-sulfate proteoglycans

    - Laminin serves as the predominant cell attachment ligand for podocyte and endothelial integrins
    - Heparan-sulfate proteoglycans confer an overall anionic charge
- Layer closest to urinary space: podocytes
  - Multiple examples of both inherited and acquired podocyte injury, especially to proteins making up the slit diaphragm domain, show the critical role of the podocyte in the prevention of proteinuria
  - Podocytes also maintain the GFB by removing protein and immunoglobulins that may clog the filter
- Although injury to any layer may lead to proteinuria, nephrotic-range proteinuria most typically is due to diseases of podocytes

Podocyte Responses to Injury in Disease

Overview

- Glomerular diseases include a wide range of immune and nonimmune insults that may target and thus injure the podocyte
- In many of these conditions, podocytes respond to injury along defined pathways, which may explain the resultant clinical and histologic changes

Decrease in Podocyte Number (Podocytopenia)

- Potential causes (can occur in combination)
  - Detachment: podocytes may lose their ability to anchor to the GBM, detach into Bowman space, and shed into urine
  - Apoptosis: podocytes may undergo programmed cell death
  - Inability to proliferate
    - Characteristic response of differentiated podocytes to most insults
    - Podocytes lost by detachment or apoptosis are not replaced by adjacent viable podocytes, leading to podocytopenia
    - Ultimate result is leaky GFB
- Consequences of podocytopenia
  - Glomerular capillaries denuded of podocytes balloon and form synechial attachments to Bowman capsule
  - Kriz hypothesis: these attachments can lead to the development of focal segmental glomerulosclerosis (FSGS)
  - Recent evidence suggests that parietal epithelial cell precursors on Bowman basement membrane may serve as a source for podocyte replacement
  - Clinical studies in diabetic kidney disease have suggested that the degree of podocytopenia predicts progression of kidney disease

Podocyte Proliferation

- May be seen rarely in dedifferentiated podocytes
- Feature of collapsing glomerulopathy

Foot-Process Effacement

- Characteristic feature of proteinuric diseases
  - Readily seen on electron microscopy as flattening of foot processes
  - The only pathologic abnormality seen in minimal change disease (MCD)
- An active process induced by changes in the actin cytoskeleton
- The flattened foot processes, which should not be considered as cells adherent to one another, severely disrupt the normal shape and integrity of these cells
- Other morphologic changes characteristic of podocyte injury include microvillus transformation and the presence of protein reabsorption droplets
- It is unclear whether effacement alone may cause proteinuria or effacement is simply a manifestation of podocyte injury

Altered Slit Diaphragm Integrity

- The slit diaphragm between adjacent podocyte foot processes is one of the major impediments to protein permeability across the glomerular capillary wall
- Alterations in cytoskeletal architecture and/or expression of slit diaphragm proteins can be shown in most nephrotic disorders

Production of Inflammatory Mediators

- Podocytes may respond to immune complex–mediated injury by producing inflammatory mediators
  - Examples are oxidative radicals, proteases, eicosanoids, chemokines, and growth factors
  - Inflammatory mediators may amplify the initial podocyte injury
- Oxidative injury is a prominent feature in membranous nephropathy (MN)

SUGGESTED READING

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NEPHROTIC SYNDROME

Classic Features of Nephrotic Syndrome

- Heavy proteinuria (protein excretion >3.5 g/24 h; also called nephrotic-range proteinuria)
- Hypoalbuminemia (albumin <3 g/dL)
- Peripheral edema
- Hyperlipidemia (elevated total and low-density lipoprotein cholesterol levels)
- Lipiduria

Pathophysiology of Nephrotic Syndrome

- Proteinuria and nephrotic syndrome are the clinical signatures of podocyte injury
  - Podocytes lie on the outside of the glomerular capillary and therefore are separated from the circulation by the GBM
  - Subepithelial immune complexes (as in MN) or podocyte injury usually do not lead to leukocyte recruitment and inflammation, but rather disrupt the GFB
    - Typically, urine sediment is devoid of leukocytes and erythrocytes
    - Disruption of GFB leads to proteinuria
- In contrast, injury to mesangial or endothelial cells, which are in direct contact with blood (containing leukocytes, complement, and inflammatory proteins), typically leads to inflammatory kidney disease (nephritis) with active urine sediment

Clinical Manifestations and Complications of Nephrotic Syndrome

Hypoalbuminemia and Edema

- Hypoalbuminemia may decrease plasma oncotic pressure, resulting in a decrease in effective circulating volume and activation of the renin-angiotensin system, leading to sodium retention (underfill theory)
- However, in most cases, edema appears to result from a primary defect in sodium excretion (ie, glomerular disease inhibits sodium excretion)
  - Leads to expanded plasma volume
  - Followed by transudation of fluid in the setting of low oncotic pressure (overfill theory)

Hyperlipidemia

- Hepatic cholesterol and lipoprotein synthesis are increased in nephrotic patients, probably in response to decreased oncotic pressure
- There also is decreased catabolism, partly explaining the increase in levels of very low-density lipoprotein cholesterol

Lipiduria

- After glomerular filtration of lipoproteins, lipids may be taken up by proximal epithelial tubular cells
- Desquamated proximal epithelial tubular cells containing lipid may be seen in urine as oval fat bodies or lipid-containing granular casts (fatty casts)

Thrombosis

- Hypercoagulability from increased hepatic synthesis of coagulation factors (eg, fibrinogen) and loss of regulatory factors (antithrombin III, protein C, and protein S) in urine
- Kidney vein thrombosis complicates all forms of nephrotic syndrome (especially MN)
  - May be asymptomatic
  - May present acutely as a sudden decrease in kidney function, loin pain, hematuria, or even systemic emboli

Infection

- Increased susceptibility to infection
  - Particular vulnerability to Gram-positive bacteria
  - Caused by urinary losses of immunoglobulin G (IgG) and complement, plus impaired cellular immunity

Bone Disease

- Loss of vitamin D binding protein in urine may lead to vitamin D deficiency
- Also, treatment with steroids may exacerbate bone loss

Common Causes of Nephrotic Syndrome

- Two categories of nephrotic syndrome etiology
  - Major pathology limited to or predominantly in the glomerulus
  - Systemic disorders, in which glomerular disease is a component of systemic manifestations (Box 1)
    - Systemic disorders do not manifest an idiopathic form limited to the glomerulus
    - Diabetic kidney disease is the most common systemic cause of nephrotic syndrome
    - Although mesangial cell injury is prominent in diabetic kidney disease, the proteinuria likely is a manifestation of podocyte injury
- Each glomerular disorder may be idiopathic or associated with other secondary causes (eg, MN secondary to lupus)

Box 1. Common Causes of Nephrotic Syndrome

Predominant Glomerular Disease
- Minimal change disease (see Box 2 for secondary causes)
- FSGS (see Table 3 for secondary causes)
- Collapsing glomerulopathy (see Box 4 for secondary causes)
- Membranous nephropathy (see Box 5 for secondary causes)
- MPGN

Systemic Disorders With Glomerular Component
- Diabetic kidney disease
- Amyloidosis

Note: Podocyte injury is prominent in each of these conditions. Nephritic glomerular disorders (eg, IgA nephropathy) may also present with nephrotic-range proteinuria. Rare causes of nephrotic syndrome include fibrillary glomerulopathy, immunotactoid glomerulopathy, collagen III glomerulopathy, lipoprotein glomerulopathy, fibronectin glomerulopathy.

Abbreviations: FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis.

General Therapeutic Strategies for Nephrotic Syndrome

- Decrease proteinuria (to protein excretion <1 g/24 h)
  - Use combination therapy with angiotensin-converting enzyme inhibitors and diuretics (± the angiotensin receptor blocker spironolactone)
  - Proteinuria reduction may slow the progression of kidney disease by ameliorating the tubular toxicity of filtered proteins
- Treat any complications
  - Volume overload: salt restriction, diuretics
  - Hypertension: blood pressure goal <125/75 mm Hg
  - Hyperlipidemia: statins
  - Thromboembolism: aspirin; anticoagulation therapy for patients at high risk of venous thrombosis (eg, with serum albumin level <2.0 g/dL)
  - Bone disease: calcium and vitamin D supplementation
- Treat any underlying secondary cause (eg, hepatitis B in MN)
- Provide disease-specific therapy (typically immunosuppression)

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CLINICAL PODOCYTE DISORDERS

Minimal Change Disease

Epidemiology

- Most common cause of nephrotic syndrome in children
- Most (90%) cases occur in children younger than 10 years

Box 2. Secondary Causes of Minimal Change Disease

Tumors (often T-cell related)
- Hodgkin's lymphoma
- Thymoma

Drugs and toxins
- NSAIDs
- Lithium
- Bisphosphonate
- Rarely: tiopronin, ampicillin, rifampicin, interferon

Other
- Atopy/eczema
- Chronic graft-versus-host disease

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

- Therefore, most young children with nephrotic syndrome are treated empirically with steroids without kidney biopsy
- Causes 10%-15% of adult nephrotic syndrome

Cause and Pathogenesis

- Podocyte injury typified by diffuse foot-process effacement on electron microscopy
- Evidence for a possible T-cell–mediated cytokine leading to podocyte injury (Box 2)
  - Interleukin 13 (IL-13) is a recent candidate
    - Serum IL-13 levels are increased in patients with MCD
    - Rats overexpressing IL-13 develop minimal change–type lesions
  - Angiopoietin-like 4 (ANGPTL4): overexpression in rat podocytes leads to steroid-sensitive nephrotic syndrome
- Proteinuria likely secondary to loss of slit diaphragm integrity and podocyte effacement; some evidence for decrease in glomerular charge barrier

Pathology

- Light microscopy: unremarkable (Fig 2A)
- Immunofluorescence: unremarkable (rarely, C1q or IgM staining, which may herald a worse prognosis)
- Electron microscopy shows characteristic diffuse effacement of podocyte foot processes (Fig 2C)

Clinical Features

- Presents with acute-onset nephrotic syndrome (may be very heavy proteinuria [protein excretion >10 g/24 h])
- Associated features in adults
  - Include hematuria (~30%), hypertension (~40%), thrombosis (5%)
  - Acute kidney injury (AKI) occurs in 10%-25% (mostly older, severe nephrotic syndrome)
- In children, hypertension is less common, AKI may occur

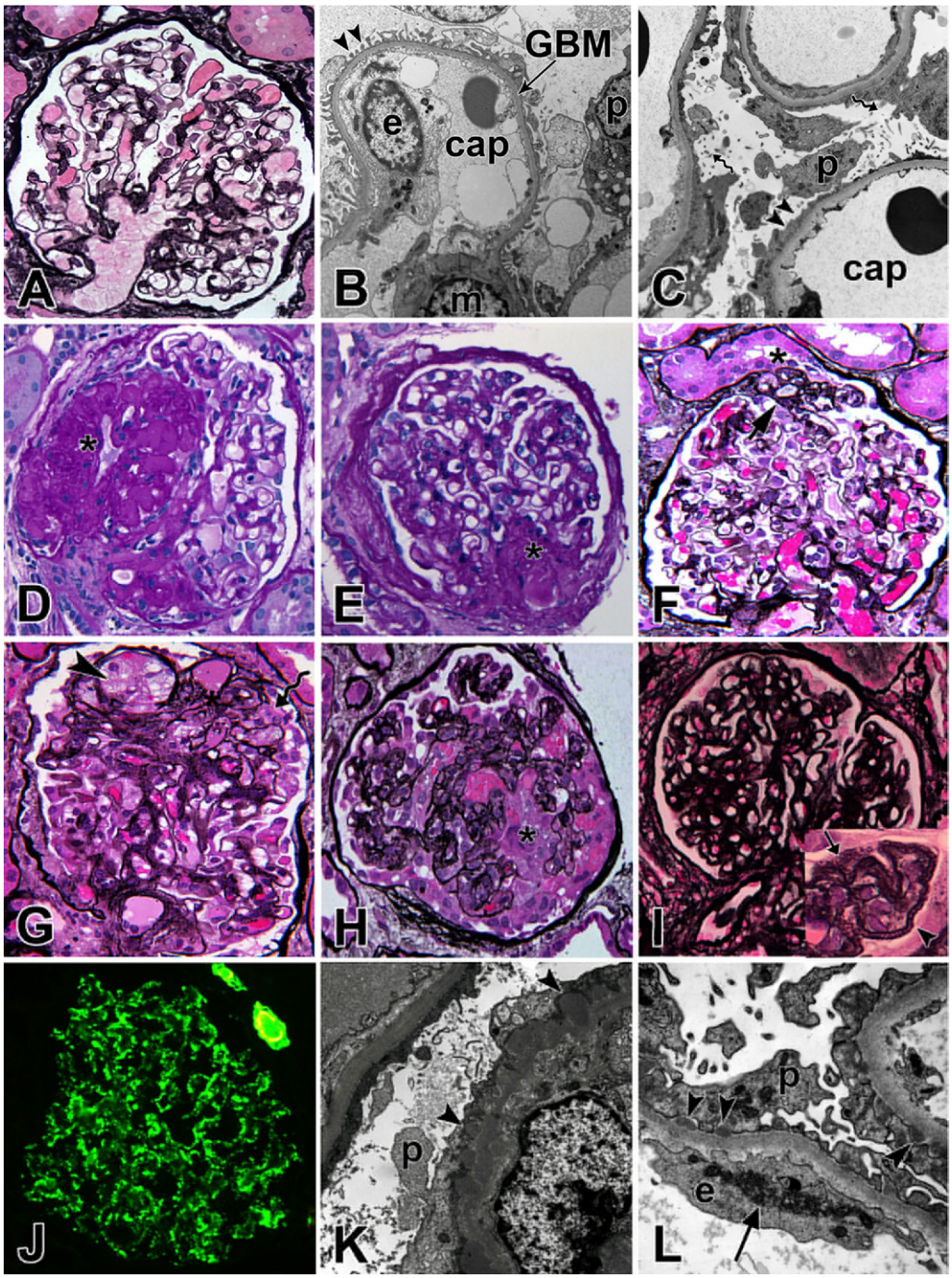

Figure 2. Renal pathology of clinical podocyte disorders. (A) Light microscopy image of a normal glomerulus, Jones methenamine silver (JMS) stain. (B) Electron micrograph of a capillary loop from a normal glomerulus. Arrowheads point to regularly arranged intact foot processes. Abbreviations: cap, capillary lumen; GBM, glomerular basement membrane; p, podocyte; e, endothelial cell. (C) Extensive effacement of foot processes (arrowheads) in minimal change disease. Spiral arrows point to microvillus transformation of podocytes. (D) Focal segmental glomerulosclerosis (FSGS), not otherwise specified (NOS), with obliterated capillary loops (*), hyalin deposition, and adhesion of tuft to Bowman capsule; periodic acid–Schiff (PAS) stain. (E) FSGS, perihilar variant with segmental sclerosis at the vascular pole (*); PAS. (F) FSGS, tip variant with segmental sclerosis (arrow) located at the glomerulotubular junction (*); JMS. (G) FSGS, cellular variant with foam cells (arrowhead) infiltrating capillary loops of sclerotic segment and prominent overlying podocytes (spiral arrow), but no collapse of capillary loops; JMS. (H) FSGS, collapsing variant with collapse of capillary loops and podocyte proliferation (*); JMS. (I) Membranous nephropathy with thickened GBM. The inset shows a magnified view of capillary loops with frequent GBM holes (arrow) and spikes (arrowhead). (J) Immunofluorescent staining for immunoglobulin G (IgG) in membranous nephropathy shows global fine granular peripheral capillary wall staining pattern. (K) Electron micrograph of membranous nephropathy with subepithelial immune complex deposits (arrowhead) and extensive effacement of foot processes. (L) Electron micrograph of a case of membranous nephropathy secondary to lupus erythematosus. Arrowheads show subepithelial deposits and arrow shows an endothelial tubuloreticular inclusion, a common finding in lupus nephritis.

Table 1. Etiologic Classification of FSGS

Classification/Etiology	Causes
Primary	
? Circulating permeability factor	• Idiopathic
Secondary	
Glomerular hyperfiltration	• Reduced nephron mass ◦ Congenital (low birth weight, renal dysplasia) ◦ Acquired nephron loss (eg, 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, interferon
Familial	
Podocyte gene disorder	• Nephrin, podocin, INF2, α-actinin 4, CD2AP, WT1; TRPC6; phospholipase Cε1

Abbreviations: CD2AP, CD2-associated protein; CMV, cytomegalovirus; FSGS, focal segmental glomerulosclerosis; HIV, human immunodeficiency virus; INF2, inverted formin 2; TRPC6, transient receptor potential cation channel 6; WT1, Wilms tumor 1.

Treatment

- For adults, prednisone, 1 mg/kg/d (or 2 mg/kg on alternate days)
  - High dose until 2 weeks after complete remission (minimum, 8 weeks)
  - Then taper over 2-4 months
  - Relapse rate is ~50%
  - Steroid-dependent/multiply relapsing: each flare responds to steroid
    - Prolonged remission may be achieved with 3-month course of cyclophosphamide (60%-70%) or prolonged course of mycophenolate
  - Steroid-resistant form occurs in 25%
    - Failure to enter remission after 16 weeks of high-dose steroid
    - May respond to cyclosporin or mycophenolate
    - Steroid resistance suggests the possibility of not having identified FSGS on the biopsy specimen due to sampling phenomenon
- Children typically are more steroid sensitive, but have a high relapse rate (~70%) and 30%-40% will have multiple relapses

Focal Segmental Glomerulosclerosis

Overview

- FSGS describes a histologic pattern rather than a specific disease
- Can be idiopathic or due to secondary causes from a variety of underlying disorders (Table 1)
- "Focal" defines that <50% of glomeruli in the sample are affected
- "Segmental" defines that only a portion of the affected glomerulus is sclerosed (scarred), whereas other portions of the glomerular tuft look normal by light microscopy

Epidemiology

- Increasing in prevalence
  - Has become the most common cause of nephrotic syndrome in adults
  - Higher prevalence in black and Hispanic races
  - Most common cause of primary glomerular disease leading to end-stage renal disease (ESRD) in the United States
- Although often considered a more advanced manifestation of MCD, many clinicopathologic features suggest that FSGS is a completely separate group of diseases
- FSGS often responds poorly to steroid therapy and commonly progresses to kidney failure

Pathology

Light Microscopy

- Lesion is defined by the early presence of an adhesion between a peripheral capillary loop and Bowman capsule
  - Progressive obliteration of the glomerular capillary lumen by acellular matrix-like material (Fig 2D)
  - Leads to segmental scarring of glomerular tuft
- Uninvolved areas of glomerular tuft are relatively normal
- In addition to the clinical/etiologic classification (Table 1), FSGS may be classified by histologic features (Box 3)

Immunofluorescence

- C3, IgM, and fibrin staining in sclerotic regions; otherwise unremarkable

Electron Microscopy

- Diffuse effacement of podocyte foot processes even in glomeruli seemingly uninvolved on light microscopy

Box 3. Columbia Pathologic Classification of FSGS

NOS
- Classic FSGS

Perihilar variant
- Exemplified in Fig 2E
- More common in FSGS secondary to hyperfiltration as glomerular pressure highest closer to afferent arteriole (ie, perihilar)

Tip variant
- Exemplified in Fig 2F
- Tuft adhesion at glomerular tip (the area adjacent to the origin of the proximal tubule, opposite the vascular pole)
- Usually idiopathic, may be more steroid responsive

Cellular variant
- Exemplified in Fig 2G
- Segmental endocapillary hypercellularity
- Intermediate prognosis between NOS and collapsing

Collapsing variant
- Exemplified in Fig 2H
- Tuft collapse with proliferation of overlying epithelial cells
- Worst prognosis
- Many consider this a separate disorder (collapsing glomerulopathy)

Abbreviations: FSGS, focal segmental glomerulosclerosis; NOS, not otherwise specified.

Pathogenesis

- Proteinuria due to alteration in glomerular permselectivity in a manner similar to MCD (may be glomeruli that appear normal on light microscopy that are mostly responsible for the proteinuria)
- Ultrastructural examination of the podocyte shows evidence of cell injury with foot-process effacement, cell hypertrophy, and pseudocyst formation
- Decrease in podocyte number
  - Due to podocyte detachment and apoptosis
  - Loss of structural support to the capillary loop
  - Areas of denuded GBM, which can attach to the overlying parietal epithelial cells on Bowman basement membrane, forming synechiae
- Capillary loops within the adhesion may deliver filtrate into interstitial areas rather than Bowman space, but ultimately collapse with thrombosis and hyalinosis

Primary FSGS

- Immunologic injury to the podocyte; exact mechanisms are unclear
- Circulating permeability factor
  - The rapid recurrence of primary FSGS after kidney transplant, sometimes as early as the first week, suggests that a circulating host factor leads to podocyte injury
  - Soluble urokinase receptor is a recently proposed candidate

Secondary FSGS

- Glomerular hyperfiltration: loss of nephrons (decreased nephron mass) or dilation of the afferent arteriole (eg, obesity) may lead to glomerular hypertension and hyperfiltration
- Chronic glomerular hypertension promotes podocyte injury and distension of the glomerular capillary
- Glomerulomegaly (larger glomeruli may be more vulnerable to hyperfiltration injury and often the larger juxtamedullary glomeruli develop glomerulosclerosis)
- Black individuals have fewer and larger glomeruli than whites, which may partly explain the greater prevalence of FSGS
- Nephron endowment
  - New nephrons continue to develop in the third trimester
  - Children born prematurely may have decreased nephron number
  - Could predispose to glomerular hyperfiltration, with increased kidney disease and hypertension in later life

Clinical Features

Primary FSGS

- Typically presents with severe nephrotic syndrome, which may be of acute onset
- Associated with hematuria (~50%), hypertension (~60%), and decreased kidney function (25%-50%)
- Prognosis heavily dependent on achievement of partial/complete remission with immunosuppression
- Nonresponders have only 40% chance of 10-year kidney survival

Secondary FSGS

- Typically slower onset, less proteinuria
- Serum albumin often preserved, less edema
- Does not respond to immunosuppression, but overall prognosis much better

Treatment

- Differentiate primary from secondary FSGS because the latter typically are not steroid responsive
  - Clinical: assess for secondary causes, acuteness, and severity of nephrotic syndrome
  - Pathologic: secondary FSGS suggested by glomerulomegaly, perihilar variant, and focal (<50%) effacement of foot processes
- General therapy for nephrotic syndrome
- Immunosuppression (for primary FSGS only; Table 2)
  - Prednisone, 1 mg/kg/d (or 2 mg/kg on alternate days); prolonged course (up to 4 months) may be required before taper

Table 2. Immunosuppressive Treatment for Adult MCD and Primary FSGS

	Initial Approach	Prednisone Duration	Second-line Agents
Minimal Change Disease			
Initial therapy	Prednisone (1 mg/kg; max, 80 mg/d)	Until 2 wk after complete remission (min, 8 wk; taper over 2-4 mo	NA
Steroid resistant	Prolonged high-dose steroid course	Discontinue after 4-6 mo if no response	MMF; cyclosporine; tacrolimus
Relapsing/steroid dependent	Try to detect early; repeat prednisone (1 mg/kg); consider MMF or cyclosporine for induction	Shorter steroid course (4 wk high dose, taper 1-2 mo), then second-line agent	Oral cyclophosphamide (2 mg/kg for 12 wk); MMF; calcineurin inhibitors; rituximab
Focal Segmental Glomerulosclerosis			
Initial therapy	Prednisone (1 mg/kg; max, 80 mg/d)	Until 2 wk after complete remission (min, 8 wk), then taper 2-4 mo	NA
Partial remission	Prolonged steroid course, as late complete remissions seen	High-dose steroid for 3-4 mo, then slow taper over 6-9 mo	Calcineurin inhibitors; MMF
Steroid resistant	Prolonged steroid course	High dose for 4 mo; add second-line agent with taper	Calcineurin inhibitors; MMF
Relapsing/steroid dependent	Treat as relapsing/dependent MCD (above)	Treat as relapsing/dependent MCD (above)	Treat as relapsing/dependent MCD (above)

Abbreviations: FSGS, focal segmental glomerulosclerosis; max, maximum; MCD, minimal change disease; min, minimum; MMF, mycophenolate mofetil; NA, not applicable.

Box 4. Causes of Collapsing Glomerulopathy

Infection
- HIV
- CMV
- Parvovirus B19
- Tuberculosis

Malignancy
- Myeloma
- Hemophagocytic syndrome
- Acute leukemia

Drugs
- Bisphosphonates
- Interferons
- Anabolic steroids

Autoimmune
- Adult Still disease
- Lupus
- Mixed connective tissue disease

Abbreviations: CMV, cytomegalovirus; HIV, human immunodeficiency virus.

  - Steroid resistant (50%): consider cyclosporin, 3-6 mg/kg/d, or mycophenolate mofetil, 1-1.5 g, twice daily

Special Considerations

Collapsing Glomerulopathy

- Classified as a pathologic variant of FSGS, but many consider this a separate disease entity
- Most commonly described secondary to human immunodeficiency virus (HIV) infection, but other secondary causes noted (Box 4)
- Characteristic feature is extracapillary proliferation of glomerular epithelial cells with collapse of glomerular tuft
- Recent evidence suggests that podocyte injury results in dedifferentiation and renewed ability to proliferate and/or induction of aberrant hyperplastic repair by parietal epithelial cells
- HIV-associated nephropathy (HIVAN)
  - Almost exclusively in patients of African descent; associated with low CD4 counts and more advanced HIV infection
  - Typically presents with severe nephrotic syndrome, often progresses rapidly to ESRD (<12 months)
  - Surprisingly, patients often are normotensive
  - Evidence for direct infection of podocytes by HIV; tubular cell infection may account for the prominent tubular microcystic changes often found
  - Treatment with highly active antiretroviral therapy has dramatically changed the prevalence and prognosis for this condition
- Non-HIV collapsing glomerulopathy
  - Predominately in patients of African descent, but more whites noted than for HIVAN

Table 3. Common Forms of Familial FSGS

Gene (protein affected)	Inheritance	Typical Age of Onset	Distinguishing Clinical Features
NPHS1 (nephrin)	AR	Infancy	Congenital nephrotic syndrome (Finnish type); severe nephrosis leading to ESRD
NPHS2 (podocin)	AR	3 mo-5 y	10%-20% of SRNS in children
WT1 (Wilms tumor 1)	AD	Child	Diffuse mesangial sclerosis/FSGS ± Wilms tumor or urogenital lesions
PLCε1 (phospholipase Cε1)	AR	4 mo-12 y	Diffuse mesangial sclerosis/FSGS
CD2AP (CD2-associated protein)	AR	<6 y	Rare, progresses to ESRD
INF2 (inverted formin 2)	AD	Teen/young adult	Mild nephrotic syndrome, but progressive CKD
ACTN4 (α-actinin 4)	AD	Any age	Mild nephrotic syndrome, may develop progressive CKD
TRPC6	AD	Adult (age 20-35 y)	Nephrotic, progressive CKD
$tRNA^{Leu(UUR)}$ gene	Mitochondrial DNA	Adult	May be associated deafness, diabetes, muscle problems, retinopathy (maternal inheritance)

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CKD, chronic kidney disease; ESRD, end-stage renal disease; FSGS, focal segmental glomerulosclerosis; Leu, leucine; SRNS, steroid-resistant nephrotic syndrome; tRNA, transfer RNA; TRPC6, transient receptor potential cation channel 6.

- Clinical features and pathology similar to HIVAN; tubuloreticular structures typically are not found in non-HIV collapsing glomerulopathy

Familial FSGS

- Presents at different ages with different modes of inheritance (Table 3)
- Genetic testing is clinically available for most of these conditions
- Establishing diagnosis may alter therapy because these disorders typically are resistant to immunosuppression
- Familial FSGS is less likely to recur posttransplant
- Sequence variants in the *APOL1* (apolipoprotein L-I) gene have been identified in African American patients with sporadic FSGS and hypertensive nephrosclerosis, which partly accounts for the increased prevalence in this group

Recurrent FSGS Posttransplant

- Primary FSGS recurs in 20%-30% of patients
  - Typically within the first month, but can occur later
  - Early recurrence supports theory of circulating permeability factor
- Transplant loss is 40%-50% without plasmapheresis
- Treatment: plasmapheresis for 2-3 weeks, longer in some; cyclophosphamide may be appropriate
- Risk factors for recurrence
  - Young age (<15 years)
  - Aggressive course (<3 years from diagnosis to ESRD)
  - Race (less common in African Americans)
  - Living donor (some recommend avoiding living donors in those at high risk of recurrence, but data not clear)

Membranous Nephropathy

Epidemiology

- MN is most common cause of nephrotic syndrome in whites and older adults
- Seen more often in males, rare in children
- Mostly primary (idiopathic), although ~20% of cases are associated with clinical conditions, such as cancer, infections, autoimmune disease, and drugs (Box 5)

Box 5. Secondary Causes of Membranous Nephropathy

Tumors
Carcinoma (lung, colon, rectum, stomach, breast, kidney), melanoma, leukemia/lymphoma
Infections
Hepatitis B, hepatitis C, syphilis, quartan malaria, schistosomiasis, filariasis, hydatid disease, leprosy, scabies, tuberculosis
Drugs and Toxins
Gold, penicillamine, bucillamine, captopril, probenecid, NSAIDs, tiopronin, lithium, mercury, formaldehyde, hydrocarbons
Autoimmune diseases
Systemic lupus erythematosus, rheumatoid arthritis, mixed connective tissue disease, Sjögren syndrome, Graves disease, Hashimoto thyroiditis, dermatomyositis, primary biliary cirrhosis, bullous pemphigoid, dermatitis herpetiformis, ankylosing spondylitis, Guillain-Barre syndrome, myasthenia gravis
Miscellaneous
Diabetes mellitus, sarcoidosis, sickle cell anemia, Kimura disease, sclerosing cholangitis, systemic mastocytosis, Gardner-Diamond syndrome

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

- Familial MN has been described, but is rare

Cause and Pathogenesis

- Characterized by the development of immune complexes in the subepithelial (subpodocyte) space
- In primary MN, immune deposits likely develop in situ due to the passage of preformed antibodies across the capillary wall targeting a specific podocyte antigen
- Immune deposits consist of immunoglobulin (IgG, predominantly IgG4), complement components (C3 and C5b-9), and antigen
  - Leads to podocyte damage, which causes increased production of extracellular matrix proteins along the GBM
  - Results in characteristic thickening of the GBM, from which the name of the disease derives
- Antigens in MN
  - M-Type phospholipase A2 receptor (PLA2R)
    - Antibodies to PLA2R have been identified in 70% of patients with idiopathic MN
    - Antibody levels may correlate with disease activity and help identify patients suitable for immunosuppression
    - Anti-PLA2R antibodies usually not found in secondary forms of MN
  - Neutral endopeptidase: identified as the antigen in alloimmune neonatal MN occurring in newborns from neutral endopeptidase–deficient mothers
  - Subepithelial deposits of secondary MN
    - Believed to derive from circulating preformed immune complexes that dissociate and reform in the subepithelial space or by deposition of antigen alone (planted antigen), followed by antibody response
    - Range of antigens has been detected, including tumor antigens (carcinoembryonic antigen and prostate-specific antigen), thyroglobulin, infection antigens (hepatitis B, hepatitis C, *Helicobacter pylori*, and syphilis), and DNA-associated antigens (double-stranded DNA, histones, and nucleosomes)
    - Unclear if antigens are causal or epiphenomena
  - Heymann nephritis model
    - A rat model of MN that has had a key role in identifying many pathogenic mechanisms in MN
    - Pathogenic antigen is megalin, but this is not expressed by human podocytes
- Complement activation occurs, likely through the alternate pathway
  - C5b-9 is generated and inserts into podocyte membrane
  - Instead of cell lysis, a series of signaling events result in cell activation (release of reactive oxygen species, proteases, and eicosanoids) and changes in podocyte structure

Pathology

Light Microscopy

- At early stages, glomeruli and interstitium look essentially normal
- With disease progression, pathognomonic thickening of capillary loops becomes evident
  - Accumulation of subepithelial immune complexes
  - Deposition of new basement membrane material by the podocyte
- Staining with silver methenamine may reveal spikes representing new basement membrane material projecting between immune deposits (Fig 2I)
- Glomerular cellularity typically is normal

Immunofluorescence

- Granular deposits of IgG in a subepithelial distribution (Fig 2J)
- C1q, IgA, and IgM usually undetectable
- Complement C3 present in ~50% of adult patients

Electron Microscopy

- Characteristic subepithelial immune deposits
  - Initially small without a prominent basement membrane response
  - With time, basement membrane material projects around and encloses the immune deposits (Fig 2K)
- Effacement of podocyte foot processes is found overlying areas of electron-dense deposits
- Biopsy features suggestive of secondary MN include mesangial hypercellularity; leukocyte infiltration; the presence of C1q, IgA, or IgM by immunofluorescence; or the presence of mesangial/subendothelial immune deposits or tubuloreticular structures by electron microscopy (Fig 2L)

Clinical Features of Idiopathic MN

- Typically presents as nephrotic syndrome (80%), onset more gradual than for MCD or primary FSGS
- Associated features
  - Microhematuria is common (50%)
  - Blood pressure and kidney function typically are normal at presentation.
- Less severe disease in younger females and Asian race
- Risk of kidney vein thrombosis higher than for other forms of nephrotic syndrome

Table 4. Treatment of Membranous Nephropathy

Risk Level	Approach	Immunosuppression
Low risk (proteinuria <4 g/d, normal kidney function)	General measures[a]	None
Moderate risk (proteinuria = 4-8 g/d, normal kidney function)	General measures; observe for 6 mo	Cyclophosphamide + steroid (alternative is cyclosporine/tacrolimus)
High risk (proteinuria >8 g/d ± reduced kidney function)	General measures; consider early immunosuppression	Cyclophosphamide + steroid (alternative is cyclosporin/tacrolimus)

[a] See general measures for treatment of nephrotic syndrome.

Natural History and Prognosis of Idiopathic MN

- Course in adults is variable, but 30%-40% develop progressive disease
- 30% undergo spontaneous remission (especially in younger females)
- Prognostic risk factors for progression include:
  - Greater degree and duration of proteinuria
  - Impaired kidney function at presentation
  - Hypertension
  - Male sex and age older than 50 years
  - Non-Asian race
  - Biopsy features
    - Glomerulosclerosis, FSGS, stage III/IV disease, tubulointerstitial fibrosis
    - Has been argued that pathologic features on kidney biopsy do not give further prognostic risk stratification independent of clinical variables
  - Urinary excretion of biomarkers such as β_2-microglobulin and/or IgG may be more accurate prognostic indicators than total urinary protein excretion, although these assays are not widely available

Treatment of Idiopathic MN

- Exclusion of secondary causes
  - Thorough history and examination
  - Check of antinuclear antibody, complement levels, hepatitis B and C
  - Malignancy screen
    - In general, risk of malignancy is greatest in males and increases with age
    - Rare in those younger than 40 years
  - Investigations may include stool guaiac, colonoscopy, chest radiography, mammography, and prostate-specific antigen measurements
  - Screening recommendations are similar to age-appropriate cancer screening investigations for the general population
- Assessment of prognosis
  - Treatment is individualized based on prognostic risk factors
  - Almost all patients are treated with general measures outlined in the section on treatment of nephrotic syndrome
- Immunosuppression is considered for patients at higher risk of progression (Table 4)
  - If nephrotic syndrome is not too severe, 6 months' close observation often is used to determine whether there is evidence of spontaneous remission (occurs in ~30% of patients)
  - Cyclophosphamide or calcineurin inhibitor with steroid is usual first-line therapy
  - Steroids alone typically are ineffective
  - Emerging data for rituximab are promising

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