What’s New in Pediatric FSGS?
Annual Dialysis Conference
Long Beach, March 11, 2017

Aims
- Review glomerular podocyte biology and how it relates to FSGS
- Understand primary FSGS in childhood compared to
  - Genetic FSGS
  - Secondary FSGS in pediatrics
- Discuss current therapy and management of FSGS, including dialysis and kidney transplant

What’s a Podocyte?
Glomerular Cell around the Capillary Loop with Interdigitating Foot Processes
Normal Glomerular Podocyte
(view with electron microscope)

Foot Processes
Slit Diaphragms
Capillary Space

Glomerular Podocyte Regulatory Function:
Lots of Genes and their Gene Products
Control What Gets Filtered into the Urine

Progressive Foot Process (FP)
Disorganization and Effacement*

*Effacement = obliteration of form or features; the medical process
of becoming shorter, thinner, softer like cervix in labor

Health → Disease
Diseased Podocytes/Effaced Foot Processes Lose their Complicated Endocytosis Function → Large Amounts Albumin Escape into Urine

How Do Podocytes Relate to FSGS?
- Normal podocytes help maintain the glomerular filtration barrier through complex interactions and signaling
- Podocytes adapt to stress & pathologic stimuli
- Excessive stress may lead to transient or permanent podocyte injury with loss of cell integrity and dysregulation of metabolism
- “Sick podocytes”
  - Don’t cross-talk well with capillary endothelial cells
  - May detach from GBM and undergo death/sclerosis
  - Limited podocyte capacity to replicate & cover gaps
  - One podocyte cell death/sclerosis → potential domino effect on other podocytes

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**Pediatric FSGS**

- Much less common cause of NS (~10%) than minimal change disease (~80%) in <10 yo
- Usually not biopsied at presentation with NS
- Unless high BP, serum Cr, gross hematuria or renal tubular disease (e.g., renal glucosuria)
- Initial treatment FSGS same as for MCNS
- NS or proteinuria often poorly responsive or resistant to steroid therapy → then biopsy
- 50% of patients reach ESRD within 10 years
- Worse prognosis in adolescents, African Americans and Hispanics

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**Presentation of FSGS in Childhood-1**

- Nephrotic syndrome (NS)
  - most frequent presentation
  - occurs in all pediatric age groups
    - about 10% of all 1-10 yo with NS
    - about 20% of all adolescents with NS
- Proteinuria alone
  - detected by screening urinalysis
- Up to 50% may have hematuria

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**Presentation of FSGS in Childhood-2**

- Persistent or gross hematuria with NS suggests disease other than minimal change NS (MCNS)
  - **FSGS**
    - Membranoproliferative GN
    - Membranous GN
    - IgA nephropathy
    - Lupus nephritis
  - **TRANSIENT** microscopic hematuria occurs in up to 25% with minimal change disease
**Presentation of FSGS in Childhood-3**

- 4 criteria for diagnosis of nephrotic syndrome
  - Proteinuria
  - Hypoproteinemia
  - Edema (when serum albumin <2.5 g/dL)
  - Hyperlipidemia (serum cholesterol, triglycerides)
- Nephrotic range proteinuria, if no edema
  - random urine protein/creatinine ratio >2 mg/mg
  - 24-hour urine protein >40 mg/m2 BSA/hr
    (>1700 mg/1.73m2 BSA/day)

**Pediatric FSGS: Diagnosis**

- Suspect if poor response to initial steroids
- Resistance to 8 week course high-dose corticosteroids
- Frequently relapsing NS with taper of corticosteroids
- Renal biopsy needed for diagnosis
- Indicated before 8 weeks corticosteroid therapy, if
  - Hypertension
  - Renal failure
  - Gross hematuria + red blood cell casts
  - Presentation between 3-12 months of age
  - Presentation as adolescent
  - Positive family history for FSGS

**Normal Kidney Biopsy: Light Microscopy**
Normal Kidney Biopsy: Electron Microscopy

Pathology of FSGS Kidney Biopsy

- **Focal**: affects only some glomeruli
  - opposite = diffuse (affects all of the glomeruli)
  - glomeruli at corticomedullary junction affected first
- **Segmental**: affects only part of glomerulus
  - opposite = global (affects the whole glomerulus)
  - earliest lesions in glomeruli at corticomedullary junction
- Pathologist does serial examination of the entire renal biopsy core to look for the focal lesions
- Key lesion: segmental sclerosis or hyalinosis
- Glomerular tip lesion (earliest lesion)
  - prominent vacuolated podocytes & intracapillary foam cells at/adjacent to urinary pole of glomerulus; often with adhesion to Bowman’s capsule

Pathology of FSGS Kidney Biopsy: Columbia Classification (2004)

<table>
<thead>
<tr>
<th>Type</th>
<th>Key Histology</th>
<th>Possible Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not otherwise specified</td>
<td>Segmental sclerosis</td>
<td>Typical Course</td>
</tr>
<tr>
<td>Tip lesion</td>
<td>Sclerosis of glomerular tuft at proximal (urinary) pole</td>
<td>Better prognosis? Early lesion?</td>
</tr>
<tr>
<td>Cellular</td>
<td>Endocapillary proliferation, often podocyte hyperplasia</td>
<td>Early lesion?</td>
</tr>
<tr>
<td>Collapsing</td>
<td>Collapse of glomerular tuft, podocyte hyperplasia</td>
<td>Poor</td>
</tr>
<tr>
<td>Perihilar</td>
<td>Sclerosis and hyalinosis at glomerular vascular pole</td>
<td>Secondary FSGS?</td>
</tr>
</tbody>
</table>

Adapted from Fogo A, Nat Rev Nephrol 2015; 11:76-87
FSGS Kidney Biopsy: Light Microscopy (PAS Stain)

FSGS Kidney Biopsy-single glomerulus: Light Microscopy (PAS Stain)

FSGS Kidney Biopsy: Electron Microscopy (EM)

Effaced podocyte foot processes
FSGS Kidney Biopsy-Tip Lesion: Light Microscopy (PAS Stain)

FSGS Kidney Biopsy-Advanced with Tubular Atrophy & Fibrosis: Light Microscopy (PAS Stain)

Pediatric FSGS
- Primary FSGS
- No identifiable associated disease or toxin
- Most common cause of ESRD resulting from primary childhood NS or glomerulonephritis
- Genetic FSGS (including familial FSGS)
- Secondary NS/FSGS
- Presence of other systemic disease (like lupus, HSP), hereditary disease, infections, or drugs/toxins
**Pediatric Secondary NS/FSGS: Causes**

- **Hereditary Diseases**
  - Familial FSGS (NPHS2 podocin mutation)
  - Denys-Drash syndrome
  - Congenital NS, Finnish type
  - Congenital NS, mesangial sclerosis
  - Schimke immunoosseous dysplasia
  - Ngal-patella syndrome
  - Alport’s hereditary nephritis
  - Galloway-Mowat syndrome
  - Charcot-Marie Tooth disease
  - Jeune’s syndrome
  - Bardet-Biedl syndrome
  - Lipoprotein disorders

- **Infections**
  - HIV nephropathy
  - Malaria
  - Hepatitis B
  - Syphilis, CMV, toxoplasma

- **Drugs/Toxins**
  - Penicillamine, gold
  - NSAIDS
  - Mercury, lithium
  - Sirolimus

- **Malignancy**
  - Lymphoma, leukemia

- **Glomer hyperfiltration**
  - Morbid obesity
  - Adaptation to kidney tissue (small BW babies)

**Pediatric Genetic FSGS**

- Accounts for about 20% of FSGS in childhood
- About 70% present with NS in first 2 years of life, so genetic FSGS should always be considered in steroid-resistant NS in <3yo
- Diagnosis FSGS by kidney biopsy
- Whole blood for “early onset genetic evaluation for nephrotic syndrome”
  - 2 mL (ped, minimum 1 mL) or 8 mL (adult) sample
  - Athena Diagnostics; results turn around in 2-4 wks
  - Currently detects mutations in NPHS1, NPHS2, PLCE1, LAMB2, and WT1 genes

**Genes Associated with Pediatric NS/FSGS**

(PC=podocyte; AR=autosomal recessive; AD=autosomal dominant)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein Product</th>
<th>Function</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPHS1*</td>
<td>Nephrin</td>
<td>PC slit diaphragm</td>
<td>Congenital NS</td>
</tr>
<tr>
<td>NPHS2*</td>
<td>Podocin</td>
<td>PC slit diaphragm</td>
<td>Early onset AR-FSGS</td>
</tr>
<tr>
<td>MYO1E</td>
<td>Unconventional myosin 1E</td>
<td>Actin function</td>
<td>Early onset AR-FSGS</td>
</tr>
<tr>
<td>ARHGDIA</td>
<td>Rho GDP-dissociation inhibitor 1</td>
<td>rho GTPase signaling, actin dynamics</td>
<td>Early onset AR-FSGS</td>
</tr>
<tr>
<td>PLCE1*</td>
<td>Phospholipase Cε1</td>
<td>PC differentiation</td>
<td>Early onset AR-FSGS</td>
</tr>
<tr>
<td>CD151</td>
<td>CD151 antigen</td>
<td>PC, GABA-internalizing integron interaction</td>
<td>Early onset AR-FSGS</td>
</tr>
<tr>
<td>PTPRO</td>
<td>Receptor-type protein tyrosine phosphatase</td>
<td>PC signaling</td>
<td>Childhood AR-FSGS</td>
</tr>
<tr>
<td>SMARCA1</td>
<td>SWI/SNF-related matrix associated regulator</td>
<td>Chromatin remodeling, gene transcription</td>
<td>Childhood FSGS, AR-Shimke</td>
</tr>
<tr>
<td>LAMB2*</td>
<td>Laminin B2 chain</td>
<td>Interacts with integrin, cytoskeleton</td>
<td>FSGS, AR-Pierson syndrome</td>
</tr>
<tr>
<td>ITGB4</td>
<td>Integrin 14</td>
<td>Cell-matrix adhesion</td>
<td>Rare FSGS</td>
</tr>
<tr>
<td>WT1*</td>
<td>Wilms tumor protein</td>
<td>PC development</td>
<td>Sporadic AD-FSGS</td>
</tr>
</tbody>
</table>

*Whole blood gene mutation analysis available

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**Pediatric Primary FSGS**
- Most common type of FSGS in childhood (80%)
- Increased incidence in African-Americans
  - 2-3x higher in adult primary FSGS; **APOL1** gene-associated
- 90% present with nephrotic syndrome
- Caused by primary podocyte problem(s)
- Recurs in kidney transplant
- Search for biomarkers (examples) for diagnosis
  - **SuPAR**: Soluble urokinase plasminogen activating receptor in blood or urine proposed as biomarker, but never confirmed
  - CD80 staining of podocytes → not specific for primary FSGS vs. secondary FSGS or minimal change NS

**Primary FSGS Pathogenesis**
- Likely multifactorial
  - Podocyte injury?
    - Gene mutations of podocyte proteins of slit diaphragm disrupt interaction with glomerular basement membrane, lead to urine protein loss → fibrosis → podocyte cell death
  - Circulating “permeability” factor? NS recurs within hours of renal transplant before histologic changes on biopsy
  - Immune dysregulation?
    - Infectious agents (like HIV)
    - Abnormal T-cells (lymphoma)
  - Understanding normal structure/function of podocytes key to new insights into FSGS pathogenesis
- Understanding pathogenesis should be focus to find better therapy for FSGS

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Pediatric FSGS Therapy-1

Initial Therapy—Corticosteroids

- Trial 8 weeks high-dose corticosteroids
- Prednisone 2 mg/kg/day or 60 mg/m2/day
- Give daily for 4 weeks, then every other day for 4 weeks if no response
- Taper when urine protein negative or trace for several consecutive days
- **Rationale:** empiric; steroids also known to affect podocytes

*No clear guide to best steroid dosing or next drug therapy*

- Randomized clinical trials to date show no next drug regimen superior to others

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Pediatric FSGS Therapy-2

Historical

- **Alkylating agents** (cyclophosphamide)
  - 1984: 30% steroid unresponsive patients responded
  - 1996 (ISKD): remission rate same in steroid vs. steroid+cyclophosphamide treated (25-30%)
- **High dose IV pulse methylprednisolone**
  - With or without alkylating agent (Tune-Mendoza protocol)
  - Response in >50%; complete remission off drug in some
  - No randomized prospective clinical trials
  - Complications: severe infections, steroid side-effects
  - Mostly Caucasian patients; uncertain if as effective in African Americans and Hispanics

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Pediatric FSGS Therapy-3

Calcineurin inhibitors (CNI)

- **Cyclosporine** (common choice)
  - Efficacy: 45-75% partial or complete NS remission; high relapse rate within 6 mon or more after stoppin
- **Tacrolimus** (few studies)
  - **Rationale**
    - Calcineurin expressed in podocytes
    - CNI reduces podocyte injury by restoring some podocyte-specific proteins and decreasing intracellular calcium influx to stabilize actin cytoskeleton in stressed podocyte
    - Animal studies show effects independent of immunologic effects of CNI on activated T-cells
  - Nephrotoxic
Pediatric FSGS Therapy-4

**Mycophenolate mofetil (MMF)**
- Efficacy: 30-40%, partial or complete
- No better than CNI (NIH randomized clinical trial FSGS in children and young adults; Gipson et al, Kidney International 2011; 80:868-878)
- **Rationale:** empiric

Pediatric FSGS Therapy-5

**Renin-angiotensin system (RAS) inhibitors**
- Well known drugs to treat ped hypertension
- ACE-I = angiotensin-converting enzyme inhibitor: lisinopril, enalapril, etc
- ARB = angiotensin receptor blocker: losartan, etc
- Used historically in FSGS for supportive care to
  - Decrease proteinuria
  - Prevent glomerular fibrosis
- **New Rationale:** inhibition of injured podocyte
  - RAS signaling may reduce injury

Pediatric FSGS Therapy-6

**Newer drugs**
- IV rituximab
  - Chimeric monoclonal antibody against CD20 glycoprotein found on B-cells
  - Few studies; response in 20-30% FSGS; used after transplant
  - **Rationale:** also known to target podocyte cytoskeleton
- IV abatacept
  - Inhibitor of costimulatory modulator B7-1 found in T-cells and podocytes; used in kidney transplants
  - Few studies of primary and recurrent FSGS
  - **Rationale:** decrease in podocyte B7-1 may prevent actin cytoskeleton destabilization → decreased FP effacement and proteinuria
Pediatric FSGS Summary

- Usually presents as primary nephrotic syndrome
- Not the most common cause of NS (~10-20%), but **THE most common cause of NS leading to pediatric ESRD**
  - Usually after 5-10 years
  - ~15% all ESRD pts, 40% of all those with GN
- Worse prognosis: African-American, Hispanic, adolescent
- Transplant recurrence rate for primary FSGS up to 55%
- Better understanding of pathogenesis is key to improving therapy
- Knowledge of podocyte biology and genetic mutations is leading to new insight