Introduction to Glomerular Disease

Anna Vinnikova, MD
Glomerular Disease Basics

I. Ultrastructure and function of healthy and damaged glomerular barrier
II. Glomerular pathology terms
III. Mechanisms of glomerular injury
IV. Manifestations of glomerular injury
V. Classification of glomerular diseases
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Glomerulus
Capillary loops are covered with podocytes from outside and lined with fenestrated endothelium from inside.
Podocytes
Permeability barrier
Filtration Slit
Slit Diaphragm

Quaggin, JCI, 2009
Glomerular Filtration
Albumin is negatively charged and is not filtered due to charge barrier
Podocyte Injury

Diagram showing the urinary filtrate and the processes involved in podocyte injury. The diagram highlights the actin cytoskeleton, filtration slit, podocyte foot process, SD, GBM, endothelial cell, and endothelial glycocalyx. It also shows the flow of molecules, rbc, albumin, and the reorganization of actin cytoskeleton with CatL dynK44A p40 and dynL356Q dynR725A.
Podocytes with normal foot processes
Podocytes with effaced foot processes
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Kidney biopsy

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Kidney biopsy

Light microscopy (LM)

Electron microscopy (EM)

Immunofluorescence microscopy (IF)
Pathology Terms for Glomerular Disease

- **Focal**: <50% glomeruli involved
- **Diffuse**: >50% glomeruli involved
Is this process focal or diffuse?
Pathology Terms for Glomerular Disease

**Segmental**: involving only segment of the glomerular tuft

**Global**: involving the entire glomerulus
Is this process segmental or global?
Pathology Terms for Glomerular Disease

• **Primary** glomerulonephritis: idiopathic disease

• **Secondary**: associated with systemic disease
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Mechanisms of glomerular injury

• Immune
• Non-immune
Immune mechanisms of glomerular injury: immune deposits
Immune mechanisms of glomerular injury

- Antibody to a resident glomerular antigen
- Antibody to a planted glomerular antigen
- Circulating immune complexes
- Cell-mediated injury/Cytotoxic antibody
- Thrombotic injury and complement dysregulation
Resident glomerular antigen

Ex: Anti-GBM (Goodpasture) disease - unmasked antigen within GBM (and sometimes alveolar BM)
Anti-GBM disease
Planted antigen

Ex: Post-strep GN - streptococcal proteins with affinity for GBM form *in situ* immune complexes, which activate complement.
Circulating immune complexes

Ex: Lupus - subendothelial deposits disrupt glomerular barrier
Iii.

Cell-mediated injury

Ex: Minimal Change Disease, FSGS
Immune cells produce toxic factor against podocytes
III.

Thrombotic injury

Ex: Thrombotic Microangiopathy, Hemolytic Uremic Syndrome, Preeclampsia

Abnormal platelet aggregation causes endothelial injury and damages microcirculation
Immune mechanisms of glomerular injury

• Antibody to a resident glomerular antigen
• Antibody to a planted glomerular antigen
• Circulating immune complexes
• Cell-mediated injury/cytotoxic antibody
• Thrombotic injury and complement dysregulation
Mechanisms of glomerular injury

- Immune
- Non-immune
  - Deposition Diseases
  - Genetic Diseases
Deposition diseases

Ex: Amyloidosis, Diabetes
Genetic diseases

Ex: Alport’s syndrome

Fabry’s disease
Glomerular Disease Basics

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Manifestations of Glomerular Injury

- Proteinuria
- Hematuria
- Decreased GFR
Manifestations of Glomerular Injury

• Proteinuria
• Hematuria
• Decreased GFR
Proteinuria
Proteinuria
Proteinuria

• Definition: $>150 \text{ mg}$ protein/24 hour collection in adults

• Abnormal proteinuria is often the first indication of renal disease
Proteinuria: Detection

Dipstick: detects **albumin** only
Proteinuria: Detection

Sulfosalicylic acid: can detect urine proteins other than albumin, like Bence Jones proteins
Proteinuria: Quantitation

24 hour urine is the most accurate method; can also do a random urine protein/creatinine ratio.
Proteinuria: Classification

• Isolated
• Nephrotic range
• Nephrotic syndrome
Isolated Proteinuria

• Subnephrotic, <=3.5 gm/day
• No other associated abnormalities of urine or renal function
• Has a “benign prognosis”
  – Can be associated with acute illness, strenuous exercise, orthostatic proteinuria
Nephrotic Range Proteinurina

• > 3.5 gm/24 hours by definition
• In general GFR is maintained until late in the disease
• Urinalysis characterized by “bland” sediment
Nephrotic range proteinuria
>3.5 g albumin (1 egg)

Nephrotic Syndrome

1. Nephrotic-range proteinuria
2. Hypoalbuminemia
3. Edema
4. Hyperlipidemia (lipiduria)
Nephrotic syndrome

• **Hypoalbuminemia**
  - **protein** lost in the urine
  - **signal** (? circulating factor) sent to liver to make up for lost albumin
  - **counter signal** (? inhibitory cytokine) prevents liver from making enough albumin
  - this only happens in nephrotic syndrome – in nephrotic range proteinuria liver does compensate and serum albumin remains normal
Nephrotic syndrome

• Hyperlipidemia
  – protein lost in the urine
  – signal (? circulating factor) sent to liver to make up for lost albumin
  – since albumin synthesis in the liver is inhibited, liver makes lipoproteins instead
Nephrotic syndrome

• **Edema:** 2 factors
  – intravascular “underfilling” due to low oncotic pressure
  – total body salt/water “overfilling” due to renal sodium retention

http://ahmed-sadawi.blogspot.com/2012/05/2-nephrotic-syndrome.html
Nephrotic Syndrome: additional signs & symptoms

• Due to loss of proteins in the urine
  – Hypocalcemia: loss of Vitatim D binding protein
  – Hypercoagulability: loss of Protein C, S and antithrombin III
  – Hypogammaglobulinemia: increased infections
Nephrotic Syndrome: additional signs & symptoms

• Due to loss of lipids in the urine
  – Lipiduria with oval fat bodies or fatty casts

![Image showing fatty casts and oval fat bodies (OFB) with copyright notice: Nobuko IMAI, Central Laboratory for Clinical Investigation, Osaka University Hospital.]
Manifestations of Glomerular Injury

• Proteinuria
• Hematuria
• Decreased GFR
Hematuria
Hematuria

www.unckidneycenter.org
Hematuria
Hematuria

RBC cast
IV.
Manifestations of Glomerular Injury

• Proteinuria
• Hematuria
• Decreased GFR
Decreased GFR

- Plugging of capillary with inflammatory cells
- Decreased ultrafiltration coefficient of the glomerulus (mesangial function)
- Hemodynamic alterations
Nephritic syndrome

1. Decreased GFR
2. Hematuria (RBC casts are diagnostic)
3. Proteinuria (<3.5 gm/day)
4. Salt & water retention
   - Hypertension
   - Weight gain
   - Edema (late finding)
<table>
<thead>
<tr>
<th></th>
<th>Nephrotic</th>
<th>Nephritic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria</td>
<td>&gt; 3.5 gm/day</td>
<td>&lt; 3.5 gm/day</td>
</tr>
<tr>
<td>Hypertension</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>GFR</td>
<td>Normal or mildly decreased on presentation</td>
<td>Decreased</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>“Bland” sediment; Oval Fat Bodies</td>
<td>“Active” sediment. Dysmorphic RBC, RBC casts</td>
</tr>
<tr>
<td>Edema</td>
<td>Yes</td>
<td>Generally mild</td>
</tr>
</tbody>
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Clinical Classification of Glomerular Diseases

Isolated Proteinuria
Nephrotic Range Proteinuria
Nephrotic Syndrome (Glomerulonephropathy)
Nephritic Syndrome (Glomerulonephritis)
Rapidly Progressive Glomerulonephritis (RPGN)
RPGN

• Acute nephritic syndrome characterized by marked and progressive drop in GFR

• Pathologically: extensive crescent formation (crescentic GN)

• Can be caused by anything that causes Nephritic Syndrome gone severe, but especially vasculitis
The purpose of classifying things into Nephrotic vs Nephritic?

• To help with differential diagnosis and tests you would order

Ultimately a biopsy is usually required for diagnosis and prognosis
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Interrelationship of pathologic and clinical manifestations of glomerular injury

- minimal change disease
- focal segmental glomerulosclerosis
- membranous glomerulopathy
- membranoproliferative glomerulonephritis
- mesangioproliferative glomerulonephritis
- proliferative glomerulonephritis
- crescentic glomerulonephritis

Nephrotic syndrome

Nephritic syndrome
Classification of pathologic and clinical manifestations of glomerular injury

**Histopathologic name**
- Minimal Change Disease
- Focal Segmental Glomerulosclerosis
- Nodular Glomerulosclerosis
- Membranous Nephropathy
- Membranoproliferative Glomerulonephritis (MPGN)
- Mesangioproliferative Glomerulonephritis (MPGN)
- Proliferative Glomerulonephritis
- Crescentic Glomerulonephritis

**Clinical name**
- Minimal Change Disease
- FSGS, HIV nephropathy
- Diabetic Nephropathy, Amyloidosis
- Membranous Nephropathy
- MPGN
- IgA Nephropathy
- Post-infections (Post-Strep) GN
- Rapidly Progressive Glomerulonephritis (RPGN)

**Clinical presentation**
- Nephrotic
- Nephritic
Classification of Glomerular Diseases

• Primary Glomerulopathy:
  – Minimal Change Disease (MCD)
  – Focal Segmental Glomerulosclerosis (FSGS)
  – Membranous GN (MGN)

• Secondary Glomerulopathy
  – Diabetes
  – Amyloidosis
  – Autoimmune: Membranous Nephropathy from SLE
  – Infections: FSGS from HIV
  – Malignancies: MCD from lymphoma
Classification of Glomerular Diseases

• Possible tests you might do:
  – Serum and urine electrophoresis
  – Routine screens for colon, prostate, breast, lung cancer when indicated
  – Antinuclear antibody (ANA)
  – Hepatitis panel and HIV
Classification of Glomerular Diseases

• Primary Glomerulonephritis
  – Crescentic GN (RPGN)
  – Membranoproliferative GN (MPGN)
  – IgA nephropathy (really is “nephritis”)

• Secondary Glomerulonephritis
  – Autoimmune: Lupus
  – Infections: Post-strep GN, Hepatitis C
Classification of Glomerular Diseases

• Evaluation similar to Nephrotic Syndrome with the addition of the following:
  – Serum complements (total, $C_3$, $C_4$)
  – Antistreptolysin O antibody (ASO)
  – Cryoglobulins
  – Anti-GBM antibody
  – Antineutrophil cytoplasmic antibodies (ANCA)
Treatment of Glomerular Disorders

• Often involves modulation of the immune system with a combination of steroids, chemotherapeutic agents (eg Cytoxan), and agents that are primarily used to prevent transplant rejection (eg. Cyclosporine or Mycophenolate)

• Other Treatment: dietary changes, ACE inhibitors
Now let’s see if you’ve been paying attention...
What is normal urine protein excretion:

A. <1g/24 hrs
B. <500 mg/24 hrs
C. <150 mg/24 hrs
D. >3.5 g/24 hrs
E. Any amount of protein in the urine is abnormal
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A. <1g/24 hrs
B. <500 mg/24 hrs
C. <150 mg/24 hrs
D. >3.5 g/24 hrs
E. Any amount of protein in the urine is abnormal
Which statement regarding Bence-Jones proteinuria is NOT correct:

A. It is not detected by urine dipstick
B. It can be detected by sulfosalicylic acid test
C. It can be detected by urine protein electrophoresis
D. It is a feature of nephrotic syndrome
Which statement regarding Bence-Jones proteinuria is NOT correct:

A. It is not detected by urine dipstick
B. It can be detected by sulfosalicylic acid test
C. It can be detected by urine protein electrophoresis
D. It is a feature of nephrotic syndrome
Which is NOT a required feature of Nephrotic Syndrome:

A. Proteinuria
B. Hypoalbuminemia
C. Hypertension
D. Edema
E. Hyperlipidemia
Which is NOT a required feature of Nephrotic Syndrome:

A. Proteinuria
B. Hypoalbuminemia
C. Hypertension
D. Edema
E. Hyperlipidemia
Which is NOT a typical feature of Nephritic Syndrome:

A. Decreased GFR
B. Proteinuria
C. Hematuria
D. Bland urinary sediment
E. Hypertension
Which is NOT a typical feature of Nephritic Syndrome:

A. Decreased GFR
B. Proteinuria
C. Hematuria
D. Bland urinary sediment
E. Hypertension
Which is the primary mechanism of nephrotic edema:

A. Decreased GFR
B. Hypoalbuminemia with low oncotic pressure
C. Renal sodium retention and impaired oncotic gradient if hypoalbuminemia is acute or very severe
D. Edema is not a feature of nephrotic syndrome
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