Renal Pathology
Lecture II

Maria M. Picken MD, PhD
mpicken@lumc.edu

Goals:
1. Analyze the pathophysiology and clinical features of the glomerular diseases associated with nephrotic syndrome: immune complex-mediated
2. Analyze the pathophysiology and clinical features of the glomerular diseases associated with nephrotic syndrome: non-immune complex-mediated
3. Analyze the pathophysiology and clinical features of the glomerular diseases associated with mixed nephrotic syndrome + hematuria
4. Analyze the pathophysiology and clinical features of the glomerular diseases associated with complement dysregulation

• Robbins Pathologic Basis of Disease, 10th edition, pp 555-560 (nephrotic syndrome)
• Robbins, review pp 76-78 (complement)
• Introduction to glomerular diseases [recorded]
• Urinary tract histology – part II [recorded]

Objectives:
• analyze the pathophysiology and clinical features of membranous nephropathy
• compare and contrast minimal change disease versus focal and segmental glomerular sclerosis (FSGS)
• compare and contrast the clinical management of nephrotic syndrome in children versus adults
• utilizing the case scenarios discussed in this lecture, compare and contrast the 2 major causes of nephrotic syndrome in children versus adults
• describe the differences in glomerular morphology and laboratory findings between nephritic and nephrotic syndromes and link these to their respective pathophysiological mechanisms
• compare the pathogenesis of membranoproliferative glomerulonephritis versus dense deposit disease
# Lecture II - outline

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Disease</th>
<th>Pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute nephritic syndrome</td>
<td>Renal failure</td>
<td>IgG immune complex circulating</td>
</tr>
<tr>
<td>Recurrent hematuria</td>
<td>IgA, IgM, IgE</td>
<td>IgA immune complex circulating</td>
</tr>
<tr>
<td>Isolated hematuria</td>
<td>Type I</td>
<td>Anti-glomerular basement membrane antibodies</td>
</tr>
<tr>
<td>Acute nephritic syndrome</td>
<td>Type II</td>
<td>IgG immune complex circulating</td>
</tr>
<tr>
<td>Recurrent hematuria</td>
<td>Type III</td>
<td>IgG immune complex circulating</td>
</tr>
<tr>
<td>Isolated hematuria</td>
<td>Type II</td>
<td>IgG immune complex circulating</td>
</tr>
<tr>
<td>Acute nephritic syndrome</td>
<td>Type III</td>
<td>Anti-glomerular basement membrane antibodies</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>Membranous nephropathy</td>
<td>Anti-glomerular basement membrane antibodies</td>
</tr>
<tr>
<td>Nephrotic syndrome + hematuria</td>
<td>Membranoproliferative</td>
<td>Anti-glomerular basement membrane antibodies</td>
</tr>
<tr>
<td>Systemic diseases</td>
<td>Diabetes</td>
<td>Anti-glomerular basement membrane antibodies</td>
</tr>
<tr>
<td>Blood vessels</td>
<td>Amyloidosis</td>
<td>Anti-glomerular basement membrane antibodies</td>
</tr>
<tr>
<td></td>
<td>Systemic lupus erythematosus</td>
<td>Anti-glomerular basement membrane antibodies</td>
</tr>
<tr>
<td></td>
<td>Thrombotic microangiopathy</td>
<td>Anti-glomerular basement membrane antibodies</td>
</tr>
</tbody>
</table>

---

**Main clinical syndromes**

- Nephritic Syndrome
  - Hematuria

- Nephrotic Syndrome
  - Proteinuria

---

**Nephrotic Syndrome - Heavy Proteinuria**

Increased permeability to plasma proteins
Glomerular basement membrane – review:
- essential for maintaining serum oncotic pressure
- combination of:
  small pore size and
  negatively charged pore-forming
  molecules prevents albumin filtration

Nephrotic syndrome = a clinical syndrome:
- increased permeability to plasma proteins
- diverse causes that share a common pathophysiology
- associated with primary glomerular diseases or a part of a systemic disease

Nephrotic Syndrome – Diagnostic Criteria (must know!)
- massive proteinuria, ≥3.5 g or more daily protein loss in the urine (adults)
- hypoalbuminemia, with plasma albumin levels < 3g/dL
- generalized edema = most obvious clinical manifestation
- hyperlipidemia (increased lipids in blood) and lipiduria (lipid droplets in urine)

- Loss of protein with urine → hypoalbuminemia → drop in plasma colloid osmotic pressure → edema
- Mechanism of hyperlipidemia:
  - Hypoalbuminemia triggers increased synthesis of lipoproteins in the liver
- Lipiduria reflects the increased permeability of the glomerular basement membrane to lipoproteins
The nephrotic syndrome is characterized by severe proteinuria, decreased serum albumin level, and edema. This results from damage to one or more components of the glomerular capillary wall. In particular, the glomerular basement membrane is essential for maintaining serum oncotic pressure. In nonpathologic states, which of the following properties of the glomerular basement membrane prevent albumin from being freely filtered into the urine?

- (A) A combination of small pore size and negatively charged pore-forming molecules prevents albumin filtration
- (B) A combination of small pore size and positively charged pore-forming molecules prevents albumin filtration
- (C) Albumin is freely filtered across the basement membrane but is readily reabsorbed along the nephron
- (D) The positive charge of proteoglycans in the basement membrane repels albumin
- (E) The small size of the glomerular basement membrane pores excludes albumin molecules

Nephrotic syndrome immune complex mediated: membranous nephropathy

Membranous nephropathy - 1

1. Typical clinical presentation
   - edema, in elderly can masquerade as cardiac failure
   - thrombosis - loss of anti-thrombin III
   - infections
   - primary versus secondary, in 10% SLE patients

2. Epidemiology
   - young/middle age adults between 30 and 60 years of age
   - 30% adults, second most common cause nephrotic syndrome (children 9%)
   - 85% autoimmune ("idiopathic"), 15% secondary

3. Etiology/pathogenesis
   - in situ subepithelial immune complex formation
   - autoimmune response against renal antigen (intrinsc or planted), SLE
   - carcinomas (lung, colon, melanoma), leukemia, non-Hodgkin's lymphoma
   - infections: malaria, hepatitis B, syphilis, schistosomiasis
   - drugs: penicillin, gold, mercury

puffy eyes
Membranous nephropathy: review

The experimental model of membranous nephropathy was described by Heymann in 1959 in rats (see recorded session "Introduction to glomerular diseases"). However, it was not until recently that this model could be validated in humans:

- several families with neonatal membranous nephropathy
- mutations in neutral endopeptidase (NEP, podocyte antigen) in mothers with normal fetus
- pregnancy, mother formed antibodies to NEP which circulated across placenta to the NEP antigen of the fetus and led to the in-situ formation of sub-epithelial immune complexes in the glomeruli of the fetus, and clinically with nephrotic syndrome in the newborn.
- these observations validated the in situ paradigm in human membranous nephropathy
- in "idiopathic" cases of human membranous nephropathy – proteomic analysis of the target antigen
  identified it as phospholipase A2 receptor (PLA2R)
  - another target: thrombospondin type-1 domain containing 7A (THSD7A)
  - PLA2R and THSD7A in 80%
  - 20%

Membranous nephropathy - pathology

- NO inflammation, no proliferation, thickened "membrane"
- granular deposits of IgG and C3 (fluorescein-conjugated)
- "spike and dome" or "holey" on silver stain
- immune complex deposits = silver negative
- basement membrane = silver positive (black)

...
Membranous nephropathy – to rule out cancer!

Membranous nephropathy -2

4. Pathology
- no inflammation, no proliferation, capillary wall thickening
- IgG=Complement granular deposits
- subepithelial electron dense deposits
- loss of foot processes

5. Laboratory tests
- nephrotic syndrome (hypoalbuminemia, hyperlipidemia and lipiduria)
- secondary hyperlipidemia, total cholesterol,
- low density lipoproteins (LDL) cholesterol, accelerated atherogenesis
- NO complement drop - chronic, relatively slowly progressing
- antibody testing for PLA2R, THSD7A (for idiopathic membranous)

6. Prognosis
- ⅓ of patients have spontaneous remission
- ⅓ progress to require dialysis
- ⅓ third continue to have proteinuria, without progression of renal failure

7. Treatment
- difficult, immunosuppressive drugs (Prednisone)
- non-specific anti-proteinuric
- secondary: treatment of the underlying disease
- recurrence after transplantation
Membranous nephropathy – typical case:
- Male, young (20-40 yo)
- deep vein thrombosis (air trip, pulmonary embolus)
- edema, eye puffiness, shortness of breath, “tight shoes”
- Urine “foamy”
- UA: proteinuria 12 GM/24hrs
- Cholesterol 320 MG/DL
- Serum creatinine: 1.5 MG/DL [n=0.7-1.5]
  • Clinical diagnosis = nephrotic syndrome

A 50-year-old man with a history of large bowel obstruction is diagnosed with colon cancer and undergoes resection of his colon. He returns to his physician for his regular checkup and complains that in the past 3 weeks he has not been feeling well and has noticed significant swelling of his legs. On physical examination, the physician notes 2+ pitting edema and a blood pressure of 155/94 mm Hg. Urinalysis shows 4+ protein with no RBCs or casts. The patient has otherwise been healthy. Which of the following would most likely be present on a kidney biopsy from this patient?
  • (A) A spike-and-dome pattern of deposition on silver stain
  • (B) proliferative glomerulonephritis
  • (C) hump-like subepithelial deposits on light microscopy
  • (D) Nonlinear mesangial staining with IgA immunofluorescence
  • (E) “Splitting” of the lamina densa

Membranous nephropathy – to rule out cancer!

A 44-year-old Caucasian man complains of swelling of his legs and puffiness around his eyes. His abdomen has become protuberant and he feels short of breath. Physical examination reveals generalized edema and ascites. Total serum protein is 5.2 g/dl (reference = 5.5-8.0 g/dl), and albumin is 1.9 g/dl (reference = 3.5-5.1 g/dl). Serum cholesterol is elevated at 530 mg/dL. There are 5 g of protein in a 24-hour urine collection. The urinary sediment contains many hyaline casts but no RBCs or inflammatory cells. A renal biopsy stained by direct immunofluorescence for IgG is shown. Which of the following is the most likely diagnosis?
  • (A) anti-glomerular basement membrane glomerulonephritis
  • (B) IgA nephropathy
  • (C) hereditary nephritis
  • (D) Membranous glomerulopathy
  • (E) postinfectious glomerulonephritis
**Immunofluorescence patterns**

- Granular along basement membrane: THINK MEMBRANOUS
- Granular in mesangium: THINK IgA nephropathy
- Linear along basement membrane: THINK ANTI-GLomerular BAsement MEMBRANE GLOMerULONEPHRITIS aka type I RPGN (rapidly progressive glomerulonephritis)

---

**“lumpy-bumpy” on immunofluorescence**

**“hump-like” by electron microscopy**

Think postinfectious glomerulonephritis

---

**Hereditary nephritis - pathology:**
- Paraffin sections: normal, non-diagnostic
- Immunofluorescence: **negative**
- Electron microscopy diagnostic: **lamina densa splitting & lamination, “basket weave”**

---

**Normal**

**Aport syndrome**
Nephrotic syndrome
non immune complex mediated

Minimal Change Disease
Focal and Segmental Glomerulosclerosis (FSGS)

<table>
<thead>
<tr>
<th>Nephrotic syndrome</th>
<th>Membranous nephropathy</th>
<th>Minimal Change Disease Focal &amp; segmental glomerular sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ immune complex formation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Nephrotic syndrome + hematuria | Membranoproliferative glomerulonephritis | Dense Deposit Disease |

Minimal Change Disease - 1

1. Typical clinical presentation:
   - edema (periorbital, generalized)
2. Epidemiology:
   - children 2-6 yo, most common cause of nephrotic syndrome
   - adults only 10%
   - no biopsy if uncomplicated clinical course, presumed minimal change disease
3. Etiology/pathogenesis:
   - reversible podocyte injury
   - T cell derived? cytokines
   - depression of immunity (viral infections, Hodgkin disease)
   - NSAIDs (non-steroidal anti-inflammatory drugs)

Minimal change disease – REVERSIBLE podocyte injury

Podocyte injury:
- podocyte foot processes effacement, loss of slit diaphragm, reversal upon treatment
- no-immune complex deposition, “non-inflammatory”

Clinical: NPHROTIC syndrome
Relapses, but NO KIDNEY FAILURE
Minimal Change Disease – 2

4. Pathology:
- normal glomeruli in paraffin sections
- no immune complex deposits
- foot processes effacement by electron microscopy

5. Laboratory tests:
- nephrotic syndrome

6. Prognosis:
- several episodes of nephrotic syndrome (relapses), normal renal function (!)
- resolution @ puberty

7. Treatment:
- steroid sensitive

Minimal Change Disease – typical case

3 yo boy with periorbital and generalized edema

UA: proteinuria, 2.5 gm/24 hr

Clinical diagnosis:
nephrotic syndrome

minimal change disease:
95% of nephrotic children 1-4 years
75% of children aged 7-8 years

children overall 65% of nephrotic syndrome
Focal and Segmental Glomerular Sclerosis (FSGS) – 1

1. Typical clinical presentation:
   - nephrotic syndrome
   - higher incidence of hematuria, reduced GFR (glomerular filtration rate), HTN,
   - non-selective proteinuria more often

2. Epidemiology:
   - adults 35%, most frequent diagnosis in human kidney biopsy
   - children 10%, older children
   - African American, Hispanic patients

3. Etiology/pathogenesis:
   - irreversible injury to podocytes

Focal and Segmental glomerular sclerosis [FSGS]: irreversible and progressing podocyte injury, despite treatment. Mature podocytes have limited capacity to replicate, hence irreversible podocyte injury leads to podocyte depletion with scarring (sclerosis) clinically: NEPHROTIC SYNDROME ultimately progressing to renal failure

Glomerular sclerosis:
increased collagenous extracellular matrix that is expanding the mesangium, and subsequently obliterating the capillary lumen, or forming adhesions with the Bowman’s capsule

Segmental sclerosis (left) versus global sclerosis (right)
Minimal change disease and FSGS: one disease at opposite ends of a spectrum OR two different diseases?

FSGS:
- focal = only some glomeruli involved
- segmental = only a portion (a segment) of a tuft is involved
  - several glomeruli normal in paraffin sections
  - some (focal) glomeruli show segmental obliteration (sclerosis) of glomerular capillaries (collapse of capillary loops, increase in mesangial matrix)
  - immunofluorescence - negative
  - electron microscopy: effacement of the epithelial foot processes in ALL glomeruli

FSGS: disease progression
- initially only rare glomeruli involved (i.e. focal)
- preferentially juxtamедullary glomeruli involved (sampling)
  - with disease progression more glomeruli become sclerosed
  - segmental sclerosis gradually becomes more advanced & progressing to global sclerosis
  - secondary tubular atrophy, interstitial fibrosis, and stage kidney
FSGS = a common phenotype with diverse etiologies:
- 3 most common forms: primary FSGS, adaptive FSGS, APOL1 FSGS
- 3 less common forms: genetic FSGS (high penetrance), medication-associated FSGS, and viral FSGS

Adaptive FSGS – adaptive response to
- obesity, renal ablation, reflux nephropathy,
- hypertension, body-building….
- low birth weight/premature birth
- sickle cell disease
- scarring of previously active lesions

Genetic high-penetrance mutations
in genes encoding slit diaphragm proteins,
other HIV, parvovirus B19

“idiopathic”: circulating factor? cytokine

APOL1 FSGS “risk alleles” – genetic risk
alleles in apolipoprotein L1 (APOL1) in African Americans; 70% of idiopathic FSGS cases in AA relate to APOL1

Genetic variants in the APOL1 gene account for a large fraction of the high rates of nondiabetic kidney disease in African Americans

APOL1 risk variants have large effects on several different types of kidney disease previously thought to be distinct entities: FSGS, HIV-associated nephropathy, severe lupus nephritis, sickle cell nephropathy and unspecified CKD (Chronic Kidney Disease), often previously labelled as “hypertensive nephropathy in African Americans”

These variants, found only in individuals with recent African ancestry, (<10,000 years) confer enhanced innate immunity against African trypanosomes. These alleles are nearly absent in populations of European and Asian ancestry

Trypanosomiasis
- Heterozygous advantage
- Homozygous disadvantage

Trypanolysis, kidney disease

Sickle cell trait confers protection against malaria caused by Plasmodium falciparum

0 risk allele
1 risk allele
2 risk allele

APOL1 Nephropathy

People who have at least 1 copy of either the G1 or G2 APOL1 variant alleles are resistant to infection by trypanosomes (protozoans). But people who have 2 copies of either variant are at an increased risk of developing kidney disease.

Genotypes may be G1/G1, G2/G2, or the compound heterozygous state of G1/G2
The presence of the alleles is not enough to have the phenotype = risk alleles rather than a single-gene disorder and additional "hits" are necessary, which may be genetic, environmental, or both

Development of preventive measures to those at risk

Lessons learned:
• genetic differences substantially influence an individual's lifetime risk for kidney disease
• evolution of genes related to host defense against pathogens may limit kidney longevity
• expanding our understanding of renal development and function helpful to design novel therapeutics for kidney disease as well as preventive measures for those at risk

The variants have proven to be useful for genetic screening in African Americans and in the selection of kidney donors


Focal and Segmental Glomerular Sclerosis (FSGS) – 2

4. Pathology:
   - segmental obliteration (sclerosis) of capillaries (collapse of capillary loops, ↑ mesangial matrix)
   - initially only rare glomeruli involved (i.e. focal)
   - collapsing glomerulopathy (collapse of the glomerular tuft and epithelial cell hyperplasia)
   - idiopathic, HIV, drug-induced... very poor prognosis

5. Laboratory tests:
   - nephrotic syndrome
   - genetic testing

6. Prognosis:
   - progression to renal failure, at least 50% end-stage kidney disease within 10 years

7. Treatment:
   - initially may be steroid responsive (mimicking minimal change disease)
   - progressively steroid dependent/resistant
   - recurrence in transplants
Nephrotic syndrome - prevalence

<table>
<thead>
<tr>
<th>PRIMARY GLOMERULAR DISEASES</th>
<th>CHILDREN %</th>
<th>ADULTS %</th>
</tr>
</thead>
<tbody>
<tr>
<td>membranous</td>
<td>~5</td>
<td>30</td>
</tr>
<tr>
<td>Minimal change disease</td>
<td>65</td>
<td>10</td>
</tr>
<tr>
<td>FSGS</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>MPGN</td>
<td>~10</td>
<td>10</td>
</tr>
<tr>
<td>other</td>
<td>10</td>
<td>15</td>
</tr>
</tbody>
</table>

FSGS typical presentation:
- 10 yo boy with nephrotic syndrome
- 5 year history of relapsing nephrotic syndrome, initially responding to steroids, subsequently became steroid-dependent and steroid-resistant
- rising serum creatinine
- clinical diagnosis: nephrotic syndrome, clinically recurrent with renal failure
- children 10%, older children
- adults 35%

FSGS - Focal and Segmental Glomerular Sclerosis
- the most frequent morphologic manifestation of glomerular injury seen in human biopsy material
- continues to increase
- leads to renal failure
Nephron loss

Once renal disease, glomerular or otherwise, destroys sufficient nephrons to reduce the glomerular filtration rate to 30-50% of normal, progression to end stage renal disease proceeds at varying rates via scarring, i.e. glomerulosclerosis.

Adaptive changes in response to the loss of nephrons at this stage are ultimately maladaptive and exacerbate progressive sclerosis.

Nearly all forms of acute glomerulonephritis have a tendency to progress to chronic glomerulonephritis.

Chronic glomerulonephritis: irreversible and progressive glomerular and tubulointerstitial fibrosis, ultimately leading to a reduction in the glomerular filtration rate (GFR) and retention of uremic toxins.

Chronic glomerulonephritis is the 3rd leading cause of chronic kidney disease, ~10% of all patients on dialysis.

A 30-year-old man with a history of drug addiction presents with a 6-month history of progressive swelling in his ankles and abdomen. Urinalysis shows heavy proteinuria (>4g/24 hours) but no evidence of inflammatory cells or RBCs. Laboratory studies reveal hyperlipidemia and hypoalbuminemia. Serum creatinine level is normal. The blood test for ANCA is negative. The patient responds well to treatment with corticosteroids, but edema and proteinuria recur the following year. The steroid treatment is repeated with the same results. Upon the third recurrence of edema and proteinuria, the patient becomes steroid resistant. A renal biopsy is shown.

Which of the following is the most likely diagnosis for this patient's glomerulopathy?

- (A) Acute glomerulonephritis
- (B) Amyloidosis
- (C) Crescentic glomerulonephritis
- (D) Diffuse proliferative glomerulonephritis
- (E) Focal and segmental glomerulosclerosis

Nephrotic syndrome - summary

Pathogenesis: podocyte injury:
- immune complex (membranous)
- non-immune complex (minimal change disease, FSGS)

Membranous nephropathy:
- idiopathic
- second most common nephrotic syndrome in adults,
- resistant to steroids, variable outcome

Minimal Change Disease:
- pathogenesis?
- most common nephrotic syndrome in children,
- responds to steroids, excellent prognosis

FSGS:
- idiopathic (pathogenesis?) or secondary (diverse),
- most common biopsy diagnosis in adults,
- resistant to therapy, progression to end stage kidney disease
- risk alleles, mutations
Nephrotic syndrome + hematuria
Membranoproliferative glomerulonephritis
Dense Deposit Disease/C3 glomerulopathy

Membranoproliferative glomerulonephritis (MPGN) - 1
formerly MPGN type I
1. Typical clinical presentation
   • nephrotic syndrome and hematuria
2. Epidemiology
   • older children 10%
   • adults 10%
3. Etiology/pathogenesis
   • primary immune complex formation with classical complement activation, antigen
   • 2nd chronic autoimmune disorders, hepatitis, endocarditis, chronic bacterial infections
   • other

Membranoproliferative glomerulonephritis (MPGN)
formerly MPGN type I
-thick glomerular basement membrane
"double contour" or "tram track" on silver stain
- electron dense deposits, subepithelial
Membranoproliferative glomerulonephritis (MPGN) - formerly MPGN type I

- Pathology:
  - lobular tufts
  - thick glomerular basement with double contour
  - IgG + complement
- Laboratory tests:
  - low complement
- Prognosis:
  - progression to renal failure
- Treatment:
  - treatment of underlying disease

Pathogenesis of glomerular diseases

<table>
<thead>
<tr>
<th>IMMUNE MECHANISMA-MEDIATED GLOMERULAR INJURY</th>
<th>OTHER MECHANISMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circulating immune complex deposition</td>
<td>No immune complexes and no antibodies detectable by current methods</td>
</tr>
<tr>
<td>In situ binding of antibodies without immune complex formation</td>
<td>Nephron loss</td>
</tr>
<tr>
<td>Abnormal activation of complement</td>
<td>Structural abnormalities</td>
</tr>
</tbody>
</table>

Complement system

- Classical trigger: Ab-Ag adaptive immunity
- MBL (mannose-binding Lectin) trigger: lectin to mannose of bacteria innate immunity
- Alternative, begins @ C3 constitutively active innate immunity
- C3b convertase
- C3 convertase
- Terminal complement cascade
- MAC (membrane attack complex)
Alternative Complement pathway

C3 convertase activity must be tightly controlled in order to prevent excessive activation of complement.

Alternative pathway low-grade physiologic activity (“tick-over”)

C3\(\rightarrow\)C3b C5
↑↑↑ C3 convertase
↓↓↓ H factor
stabilize degrade

C3NeF (C3 nephritic factor)
an autoantibody against C3 convertase, limits C3 convertase & prevents its degradation (stabilizes C3 convertase, prevents sustained complement activation)

Glomerular diseases caused by complement activation in the absence of antibody:

unregulated/excessive activation of the alternative complement pathway leading to complement-mediated injury - transformation from low-grade physiologic activity (“tick-over”) to unrestrained hyperactivity

Triggers: excessive complement activation after minor vascular injuries
- acquired autoantibodies against complement components
- inherited abnormalities of complement regulatory proteins

Human diseases

Glomerular: dense deposit disease/C3 glomerulonephritis
Systemic (with significant renal manifestations): thrombotic microangiopaties (lecture III)

Dense Deposit Disease (DDD) - 1

formerly MPGN type II

1. Typical clinical presentation:
   - nephrotic syndrome with hematuria
2. Epidemiology:
   - rare
   - older children
3. Etiology/pathogenesis
   - sustained activation of complement via alternative pathway (non-antibody mediated), no antigen-antibody formation

Despite strong associations between C3 dysregulation and DDD, the evidence in humans is predominantly circumstantial and it is still not clear how the complement abnormality induces the glomerular changes
Dense Deposit Disease (DDD) - excessive complement activation

Immunofluorescence: Complement (C3), NO immunoglobulins
Electron microscopy: dense deposits in lamina densa

Note: in patients who show C3 only by immunofluorescence but NO dense deposits by electron microscopy – “C3 glomerulopathy”

Dense Deposit Disease (DDD) - 2
formerly MPGN type II
4. Pathology:
   - complement alone (C3), NO immunoglobin by immunofluorescence
   - dense deposits within lamina densa by electron microscopy
5. Laboratory tests:
   - complement levels
   - molecular studies
6. Prognosis:
   - poor, progression to renal failure
   - recurrence in transplants
7. Treatment:
   - new therapies controlling complement activation [Eculizumab, humanized monoclonal antibody functioning as a terminal complement inhibitor]
Glomerular diseases - summary comments:

- pathogenesis - evidence partial/circumstantial
- not uncommonly more than one mechanism involved
- pathology not static but evolving - a movie rather than a still picture!!!
- role of genetics/risk alleles/epigenetics – personalized medicine
- shift from morphologic to pathogenetic classification

Differential diagnosis:
- nephrotic versus nephritic syndrome
- age: adult versus child (toddler versus older child)

Questions? mpicken@lumc.edu