## Differential Diagnosis of Glomerular Diseases

Glomerulonephritis can be classified as: Nephrotic or Nephritic (mild or moderate-to-severe)

<table>
<thead>
<tr>
<th>Nephrotic Syndrome</th>
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<tr>
<td>Proteinuria &gt;3.5 g/day, Hypoalbuminemia, edema, hyperlipidemia + bland urinary sediment (few cells or casts)</td>
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### Minimal change disease
- Most common cause of nephrotic syndrome in children (Children age <10)
- Idiopathic → T-cell injury to podocytes → increased permeability to albumin.
- Associations → Hodgkin’s lymphoma / NSAID
- Children age <10 with isolated nephrotic syndrome do not require biopsy for diagnosis as MCD is highly likely → next step: prednisone.
  - **LM:** Normal finding (MCQ).
  - **EM:** foot processes fusion of podocytes
  - Immunofluorescence: negative.

### Focal segmental glomerulosclerosis
- Most common cause of nephrotic syndrome in adults.
- African American
- Associations → HIV / Heroin use / Obesity (HHO)
  - **LM:** focal and segmental glomerulosclerosis.
  - **EM:** foot processes fusion of podocytes.
- Other forms of HIV-related glomerulopathies that can present with nephrotic-range proteinuria (less common than FSGN):
  1. Membranous glomerulonephritis → if they also have hepatitis-B infection.
  2. Membranoproliferative glomerulonephritis → see below.
  3. Diffuse proliferative glomerulonephritis → In lupus nephritis type IV

### Membranous nephropathy
- It is a common cause of nephrotic syndrome in adults + adolescents (14 yrs) especially if associated with HBV infection "hepatitis B virus-associated membranous nephropathy (HBVMN)"
- Associations → Adenocarcinoma (lung & breast) / Hepatitis B / SLE / NSAID (ABSD)
  1. **HBVMN:** serum C3 is low.
  2. **Lupus nephritis:** antinuclear antibody is elevated
  - **LM:** Thickened GBM and subepithelial "spikes".
  - **EM:** Subepithelial deposits.
  - **Immunofluorescence:** Granular IgG, C3.

### Membranoproliferative glomerulonephritis
- Membranoproliferative glomerulonephritis can be Nephrotic or Nephritic.
- Associations → **Hepatitis B (less common than membranous nephropathy)**
  - **Hepatitis C** → mixed cryoglobulinemia (test for viral markers):
    - The immune complexes are IgM antibodies (similar to RF) that form complexes with IgG anti-hepatitis C virus antibodies → Immune complex deposition in small blood vessels (vasculitis).
      - Skin (eg, palpable purpura doesn't blanch with pressure)
      - Kidney (eg, MPGN)
      - Nervous system (eg, motor sensory axonopathy),
      - Musculoskeletal system (eg, arthralgias).
    - Serologically (serum cryoglobulins + low complement levels + increased RF + increased liver enzymes) + Biopsy.

<table>
<thead>
<tr>
<th>D.D. of Low complement levels with glomerulonephritis</th>
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<tbody>
<tr>
<td>Postinfectious GN</td>
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<tr>
<td>Lupus nephritis</td>
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<tr>
<td>Mixed cryoglobulinemia with hepatitis C</td>
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</tbody>
</table>
  - **LM:** Mesangial hypercellularity
  - **EM:** Type I: Mesangial and subendothelial deposits.
    - **Type II:** Dense deposits Disease (DDD) in GBM
      - Immunofluorescence: Granular IgG, C3 (in type I)
Diabetic Nephropathy

Diabetes mellitus is the leading cause of end-stage renal disease in the United States.

- Patient with diabetes for long time ( > 10 years) + poor glycemic control.
- Diabetic nephropathy is characterized by proteinuria & progressive decline in GFR.

**Glomerular hyperfiltration (MCQ)** is the earliest renal abnormality seen.

**Histology:**
- First change that quantitated: *Thickening of the glomerular basement membrane.*
- Pathognomonic hallmark: nodular glomerulosclerosis (Kimmelstie-Wilson nodules).
- The most common histologic lesion is *diffuse glomerulosclerosis.*

Amyloidosis

- **Rheumatoid arthritis is the most common cause of AA amyloidosis in the United States.**

- Amyloidosis is a group of diseases in which amyloid fibrils, builds up in tissue.
- Deposits consist of light chains (AL amyloidosis) or abnormal proteins (AA amyloidosis).

<table>
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<tr>
<th>AL amyloidosis</th>
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<tbody>
<tr>
<td>Associated condition</td>
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<td>Composition of amyloid</td>
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<th>AA amyloidosis (Inflammatory amyloidosis)</th>
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<tr>
<td>Chronic inflammatory conditions:</td>
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<tr>
<td>- Rheumatoid arthritis</td>
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<tr>
<td>- Inflammatory bowel disease</td>
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**History:**
- Patient with *Rheumatoid arthritis,* presented with nephrotic manifestations + Hepatomegaly. + U/S: bilateral kidneys enlargement.

**Renal biopsy:**
- Amyloid deposits are seen in GBM, blood vessels, and interstitium of the kidneys.
- Immunofluorescence: Deposits that stain with Congo red and demonstrate a characteristic apple-green birefringence under polarized light.
- EM: randomly arranged thin fibrils.

Nephritic Syndrome

RBCs (dysmorphic), WBCs, casts (red blood cell and/or white blood cell), and variable degrees of proteinuria

IgA nephropathy (Berger’s disease)

- IgA nephropathy can present with nephrotic syndrome (<10%), but more commonly (40%) presents with hematuria following an URT infection.
- **Associations** → *Upper respiratory tract infection (within 5 days)*
- **Symptoms:**
  - More common in young adult men (age 20-30)
  - Presents as: *episodes of gross hematuria*
- **Diagnosis:**
  - Serum complements: Normal
  - Kidney biopsy: *Mesangial IgA deposits seen in*

Poststreptococcal Glomerulonephritis

- Acute post-streptococcal glomerulonephritis after throat or skin infections with B-hemolytic streptococcal infection.
- **Associations** → *Upper respiratory tract infection (10-21 days postpharyngitic)*
- **Symptoms:**
  - More common in children (age 6-10), but can occur in adults.
  - Presents as: gross hematuria.
- **Diagnosis:**
  - Serum complements: Low
  - Kidney biopsy: subepithelial humps consisting of C3 complement.
  - *Elevated anti-streptolysin O &/or anti-DNAse B*

Lupus nephritis

- Immune complexes composed of dsDNA (and) anti-dsDNA antibodies deposit in:
  1) *Mesangium and/or subendothelial space* → inflammatory reaction with activation of complement system, lowering C3 & C4 [Diffuse membranoproliferative GN].
  2) Subepithelial space → presenting with nephrotic syndrome without normal complement levels (membranous GN)
- **Laboratory:**
  - Anemia, leukopenia, thrombocytopenia
  - Positive ANA, anti-dsDNA, anti-Sm
  - Low complement levels, increased immune complexes