Knowledge of the structure and function of the glomerulus aids in understanding the clinical manifestations of glomerular diseases. Glomerular capillaries are efficient filters that selectively retard the permeation of macromolecular plasma proteins but allow the free filtration of water (at the rate of 150 to 180 L/day), electrolytes, and other small solutes such as urea and creatinine. This is attributable to certain characteristics of glomerular capillaries, including a high transmembrane pressure gradient that serves as the driving force for filtration and a capillary wall that is highly porous to water and small solutes, but that restricts the passage of large molecules on the basis of their molecular size and charge.

Composition of the Capillary Wall

- Fenestrated endothelial cells coated with podoclyxin, a polyanionic glycoprotein rich in sialic acid, surround glomerular capillaries; they normally form a nonthrombogenic surface and express von Willebrand’s factor and receptors for vascular endothelial growth factor (VEGF); can be induced to express leukocyte adhesion molecules;
- Visceral epithelial cells (podocytes) have prominent foot processes that are attached to the glomerular basement membrane (GBM) by α3β1 integrins and dystroglycans and are also coated with podoclyxin. Adjacent foot processes are separated by gaps that form the filtration pathway (filtration slits) and are bridged by a zipper-like slit-diaphragm. The slit-diaphragms constitute the final barrier to macromolecular permeation and contain nephrin, the immunoglobulin (Ig)-like transmembrane protein that is mutated in congenital nephrotic syndrome. Additional proteins anchor the slit-diaphragms to the podocyte cytoskeleton and in the plasma membrane. Among these are podocin, the protein mutated in steroid resistant nephrotic syndrome, and α-actinin, the protein mutated in a form of hereditary focal glomerulosclerosis.
- Mesangial cells occupy the axial region between glomerular capillary loops; they synthesize the mesangial matrix and share several features with smooth muscle cells and macrophages. They also elaborate and have receptors for inflammatory mediators and growth factors and contract in response to vasoactive stimuli, thereby regulating glomerular capillary surface area. A small population of tissue monocytes/macrophages also occupies the normal mesangium.
- The GBM comprises a meshwork of α3, α4, and α5 type IV collagen fibrils that provide tensile strength embedded in a glycoprotein matrix of laminin, entactin/nidogen, and heparan-sulfate proteoglycans. Lamnin serves as the predominant cell attachment ligand for podocyte and endothelial integrins, and the heparan-sulfate proteoglycans confer an overall anionic charge.
- The mesangial matrix is made up of α1 and α2 type IV collagen fibrils, laminin, tenascin, and chondroitin sulfate proteoglycans. The result of this composition is that the capillary wall is rich in negatively charged residues and the permeation of plasma proteins from capillary lumen to urinary space is restricted on
the basis of molecular charge as well as molecular size. In effect, negatively charged macromolecules encounter narrower “pores” than do positively charged molecules of the same size. Thus albumin, which would be freely filtered on the basis of its size (69,000 daltons), is retarded by virtue of its overall negative charge.

**Determinants of Glomerular Filtration Rate**
- Transmembrane hydrostatic pressure ($\Delta P$)
- Filtration surface area ($S$)
- Hydraulic conductivity of the capillary wall ($K$)
  - inversely proportional to “pore” length (GBM thickness)
  - proportional to “pore” density (filtration slit frequency)

Thus, glomerular diseases that cause occlusion or obliteration of glomerular capillary loops or reduce hydraulic conductivity of the glomerular capillary wall will cause a fall in glomerular filtration rate ($\text{GFR}$), whereas alterations in size- and/or charge-selectivity will cause proteinuria.

**Clinical Syndromes Associated With Glomerular Diseases**
- Isolated hematuria—Microscopic or macroscopic (red blood cell [RBC] casts)
- Acute nephritic syndrome
- Rapidly progressive glomerulonephritis (RPGN)
- Asymptomatic proteinuria
- Nephrotic syndrome
- Combinations of above

**Definition of Clinical Syndromes**
See Table 1.

**Clinical-Pathological Correlations**
See Table 2.

**Diseases Presenting With Proteinuria or Nephrotic Syndrome**
Exclude transient or “benign” causes of proteinuria—eg, exercise-induced, febrile, congestive heart failure, orthostatic (postural) proteinuria.

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**Table 1. Definition of Clinical Syndromes**

<table>
<thead>
<tr>
<th>Acute Nephritic Syndrome (ANS)</th>
<th>Nephrotic Syndrome (NS)</th>
<th>Rapidly Progressive Glomerulonephritis (RPGN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute onset of:</td>
<td>Insidious onset of:</td>
<td>Rapidly progressive renal failure</td>
</tr>
<tr>
<td>● Hematuria—macroscopic or</td>
<td>● Proteinuria—severe</td>
<td>● Hematuria with RBC casts</td>
</tr>
<tr>
<td>microscopic (RBC casts)</td>
<td>● Edema—severe (anasarca)</td>
<td>● Oliguria—variable</td>
</tr>
<tr>
<td>● Hypertension</td>
<td>● Hypoalbuminemia</td>
<td>● Hypertension—variable</td>
</tr>
<tr>
<td>● Oliguria</td>
<td>● Hyperlipidemia</td>
<td>● Proteinuria—variable</td>
</tr>
<tr>
<td>● Edema—moderate</td>
<td>● Lipiduria</td>
<td></td>
</tr>
<tr>
<td>● Proteinuria—mild to moderate</td>
<td>● Hypercoagulability</td>
<td></td>
</tr>
<tr>
<td>● Azotemia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Table 2. Clinical-Pathological Correlations**

<table>
<thead>
<tr>
<th>Histological Lesions Associated With Hematuric Syndromes (Isolated Hematuria, ANS, or RPGN)</th>
<th>Histological Lesions Associated With Proteinuric Syndromes (Isolated Proteinuria NS)</th>
<th>Histological Lesions Associated With Both Nephritic and Nephrotic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Mesangial proliferative GN (eg, IgA nephropathy)</td>
<td>● Minimal change disease</td>
<td>● Membranoproliferative GN</td>
</tr>
<tr>
<td>● Focal and segmental GN (eg, lupus nephritis WHO III, infective endocarditis)</td>
<td>● Focal and segmental glomerulosclerosis</td>
<td>● Fibrillary glomerulopathies</td>
</tr>
<tr>
<td>● Diffuse proliferative GN (eg, post-streptococcal GN, lupus nephritis WHO IV)</td>
<td>● Collapsing glomerulopathy</td>
<td>● Hereditary nephritis (Alport syndrome)</td>
</tr>
<tr>
<td>● Crescentic GN (eg, anti-GBM nephritis, pauci-immune nephritis)</td>
<td>● Membranous nephropathy</td>
<td>● Some cases of mesangial, focal, and diffuse proliferative GN</td>
</tr>
</tbody>
</table>
Pathophysiology of Nephrotic Syndrome

- Hypoalbuminemia from urinary loss and increased tubular catabolism of albumin
- Edema from avid sodium and water retention by the kidney and decreased plasma oncotic pressure in systemic capillaries due to hypoalbuminemia
- Hyperlipidemia from increased hepatic synthesis of lipoproteins
- Hypercoagulability from increased hepatic synthesis of coagulation factors and loss of regulatory factors (anti-thrombin III, protein C and protein S) in the urine

Clinical Consequences of Nephrotic Syndrome

- Predisposition to infection (especially gram positive) from low serum IgG levels
- Increased risk of thromboembolism and renal vein thrombosis
- Predisposition to hypovolemic shock
- Possible predisposition to atherosclerotic vascular disease
- Urinary loss of hormone-binding proteins (eg, thyroid, vitamin D, cortisol)—effects uncertain

General Principles of Management of Proteinuria and Nephrotic Syndrome

- Salt restriction
- Angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) to reduce proteinuria and retard progression
- Judicious use of diuretics to control edema and for synergistic action with ACE inhibitors or ARBs
- Lipid lowering agent—Benefit as yet unproven in clinical studies, but statins are safe in nephrotic syndrome with monitoring of muscle and liver enzymes and use is prudent given increased rate of coronary artery disease in nephrotic patients
- Hormone replacement is generally unnecessary because free hormone levels are normal—calcitriol is occasionally indicated if ionized calcium is reduced
- Patients on extended corticosteroid therapy—monitor bone density and supplementation with calcium carbonate and calcitriol. Bisphosphonates prevent steroid-induced bone loss in other settings but their efficacy and safety in nephrotic syndrome are not established

Principal Secondary Causes of Nephrotic Syndrome

Nephrotic syndrome may be due to a primary (idiopathic) glomerular disease or secondary to one of several other diseases or toxic agents. Some of the secondary causes of nephrotic syndrome have the same clinical and histological features as the primary renal diseases (see Table 3).
REFERENCES


Minimal Change Disease

Pathogenesis
- Unknown; appears to be a primary disorder of podocytes; may be linked to T-cell-mediated immunity

Clinical and Laboratory Features
- Steroid-sensitive nephrotic syndrome
- Main cause of nephrotic syndrome in children
- Renal function and blood pressure (BP) usually normal
- No known serological abnormalities

Course and Treatment
- >80% respond to corticosteroid or immunosuppressive treatment
- Relapse is common (>50%)
- Cyclophosphamide or cyclosporin is effective in steroid-dependent and frequently relapsing cases
- Does not progress to chronic renal failure

Secondary Causes
- Hodgkin’s lymphoma, NSAIDs, other drugs

- Light microscopy (LM): Glomeruli normal
- Immunofluorescence (IF): Negative

REFERENCES


Focal and Segmental Glomerulosclerosis (FSGS)

Pathogenesis
- Unknown in idiopathic FSGS; hereditary cases point to the podocyte as the primary site of injury; a soluble circulating “permeability-inducing” factor seems to account for cases that recur after transplantation
- By analogy to experimental models, glomerular hypertension appears to underlie focal podocyte injury in secondary FSGS

Clinical and Laboratory Features
- Idiopathic FSGS—Common cause of adult nephrotic syndrome, especially among Blacks; steroid-resistant NS; may be familial; often progressive and accompanied by hypertension; and may recur after renal transplantation
- Secondary FSGS—Tends to occur after loss of nephron mass from other diseases, eg, vesico-ureteric reflux, sickle cell and analgesic nephropathies, renal ablation in early childhood, or “healed” proliferative GN; also in morbid obesity; often presents as asymptomatic proteinuria

Course and Treatment
- Idiopathic FSGS—Up to 40% respond to prolonged treatment with corticosteroids; studies of cyclosporin and other agents are ongoing; plasmapheresis is often effective for recurrent FSGS posttransplant
- Secondary FSGS—Proteinuria often improves with ACE inhibitors or ARBs.

- LM: Because of the focal nature, glomeruli may appear normal in early disease; later lesions show segmental areas of sclerosis
and hyalinosis of the glomerular tuft, expansion of mesangial matrix, and interstitial fibrosis with tubular atrophy

- **IF**: Negative except for IgM and C3 in sclerotic lesions
- **EM**: Idiopathic FSGS: diffuse effacement of foot processes and degeneration of podocytes; secondary FSGS—patchy effacement of podocyte foot processes

**REFERENCES**

**Collapsing Glomerulopathy (CG)**

**Pathogenesis**
- Most cases are associated with human immunodeficiency virus (HIV) infection; a similar lesion in a murine transgenic model of HIV-associated nephropathy (HIVAN) and viral detection studies suggest that HIV infects and injures glomerular epithelial cells despite the lack of known HIV receptors
- The cause of idiopathic CG is unknown, but its similarity to HIVAN suggests the possibility of other viral infections such as parvovirus; there may be an association with pamidronate therapy

- **Clinical and Laboratory Features**
  - Presents with explosive onset of massive proteinuria, severe hypoalbuminemia, and rapidly deteriorating renal function; BP may be normal
  - Most prevalent in black patients
  - CD4 count is frequently low on presentation of HIVAN
  - Clues to diagnosis include large echogenic kidneys and very broad waxy urinary casts

**Course and Treatment**
- The majority of patients progress to end-stage renal failure within 13 months; treatment with steroids and immunosuppressives is generally ineffective, although rare cases of idiopathic CG may undergo spontaneous remission and there are some reported cases of steroid-associated remission; ACE inhibitors may reduce proteinuria and slow progression
- The incidence of HIVAN may have declined since introduction of highly active antiretroviral treatment (HAART) and HAART plus prednisone may slow the progression of established HIVAN

**Histopathology**

- LM: Focal and segmental glomerulosclerosis with collapse of the glomerular tufts, wrinkling of the GBM, and visceral epithelial cell hyperplasia and severe microcystic changes of the tubules with interstitial fibrosis
- **IF**: Negative except for IgM and C3 in sclerotic lesions
- **EM**: Effacement of podocyte foot processes and degeneration of podocytes; tubuloreticular structures in glomerular endothelial cells (especially in HIVAN)

**REFERENCES**
Membranous Nephropathy (MN)

Pathogenesis
- Autoimmune disease due to antibodies directed at an unknown podocyte protein; a rare case of neonatal MN due to allosensitization of the mother to neutral endopeptidase indicates that antigen(s) on the soles of podocyte foot processes is a likely target in human MN, as in Heymann nephritis in rats.
- By analogy to experimental models, antibody-induced assembly of the membrane attack complex of complement causes podocyte injury and production of new GBM material around immune deposits shed from the podocyte cell surface.

Clinical and Laboratory Features
- Commonest cause of idiopathic NS in adult Caucasians (FSGS is more common in African Americans).
- Peak incidence 4th to 6th decades; male: female 2-3:1.
- Most present with nephrotic syndrome, the rest with asymptomatic proteinuria.
- Glomerular filtration rate (GFR) and blood pressure (BP) are often normal on initial presentation but hypertension develops in about 30% cases; microscopic hematuria may be present.
- No serological abnormalities.
- Some cases present with thromboembolic complications.

Course and Treatment
- Spontaneous remission (40%); progressive renal failure (30%); persistent proteinuria with variable renal dysfunction (30%).
- Risk factors for progression: male gender, severe proteinuria (>10 g/24 h), hypertension, and azotemia, tubulointerstitial fibrosis, and glomerulosclerosis.
- ACE inhibitor or ARB as tolerated to lower BP to 125/75 and reduce proteinuria, lipid-lowering agent, and diuretic as tolerated for control of anasarca.
- Cytotoxic agents and prednisone are indicated for progressive cases and those with symptomatic nephrotic syndrome at risk for progression; other immunosuppressive agents are under investigation.
- May recur or occur de novo posttransplant.

- **LM:** The cortex and glomeruli may be normal in early MN; later, the GBM is thickened and the capillary wall appears more rigid than normal; in advanced cases, the capillary wall is with spikes of GBM extending between and around subepithelial deposits. Advanced glomerular lesions are associated with tubular atrophy and interstitial fibrosis.
- **IF:** Granular glomerular capillary wall deposits of IgG ± C3 are characteristic even if light microscopy is normal.
- **EM:** Subepithelial electron dense deposits along the capillary loops with effacement of overlying foot processes. With advancing disease, new GBM material is laid down at the sides of and around the deposits. Clues to a secondary form of MN include endothelial cell tubulo-reticular structures (lupus MN) and mesangial deposits (hepatitis B-associated, lupus MN).

REFERENCES

Dysproteinemias

Amyloid Nephropathy

Pathogenesis
- Glomerular, renal vascular, and interstitial deposition of beta-pleated sheets of amyloid fibrils occurs in both primary (AL) and secondary (AA) forms of amyloidosis.
- AL amyloid—Monoclonal Ig light chains (usually λ) produced by an abnormal clone of plasma cells.
• AA amyloid—Overproduction and proteolysis of serum AA protein, an acute-phase reactant, in chronic inflammatory states (eg, rheumatoid arthritis, juvenile rheumatoid arthritis, inflammatory bowel disease, familial Mediterranean fever [FMF], tuberculosis, chronic sepsis)

**Clinical and Laboratory Features**

- Renal manifestations are the same in AL and AA amyloidosis
- Severe nephrotic syndrome with progressive renal failure
- Multiorgan involvement is common, including cardiac, gastrointestinal, cutaneous, autonomic and peripheral nerve disease
- Diagnosis is made by finding Congo red-positive material in affected tissues including abdominal fat pad aspirates (especially useful in AL amyloidosis)
- Monoclonal light chains are found in the urine in AL amyloidosis

**Course and Treatment**

- Five-year survival is <20% even with dialysis; cardiac disease confers the gravest prognosis
- Intensive treatment of AL amyloidosis with melphalan and prednisone ± autologous stem cell replacement may induce hematological remission and halt progression in some cases
- Treatment of AA amyloidosis is limited to controlling inflammation or chronic infection, including colchicine for FMF; experimental therapies are directed at disrupting fibril formation


- **LM:** Pale acellular eosinophilic material infiltrates mesangial areas and peripheral capillary loops; arterioles, small arteries, and peritubular interstitium may also be involved; apple green birefringence of Congo red-stained sections under polarized light is diagnostic of amyloid
- **EM:** Randomly oriented fibrils of 10- to 12-nm diameter replace the mesangium and GBM

**Light Chain Deposition Disease (LCDD)**

**Pathogenesis**

- Systemic disease due to tissue deposition of monoclonal Ig light chains (most often κ or occasionally heavy chains)
- Overt myeloma may be present or develop over time, but the absence of a monoclonal spike on serum or urine electrophoresis or an increase in bone marrow plasma cells is still consistent with LCDD
- It is unclear why some light chains have a predilection for tissue deposition rather than filtration and tubular cast formation as in myeloma kidney

**Clinical and Laboratory Features**

- May present with asymptomatic albuminuria ± renal insufficiency or with nephrotic syndrome
- Albuminuria in a patient with myeloma indicates either LCDD or development of amyloidosis
- Other organs may be affected as in AL amyloidosis

**Course and Treatment**

- Progressive renal failure is the rule
- Treatment as for myeloma with melphalan and prednisone may prevent deterioration in renal function in some patients with mild azotemia but is associated with high morbidity

**REFERENCES**


- **LM**: Nodular glomerulosclerosis indistinguishable from diabetic nephropathy; Congo red stain is negative
- **IF**: Glomerular capillary wall ± mesangial staining for a monoclonal λ or λ light chain is key to the diagnosis
- **EM**: Amorphous, granular subendothelial, mesangial and tubular basement membrane deposits without fibrils

**REFERENCES**


**Fibrillary and Immunotactoid Glomerulopathies**

**Pathogenesis**

- Fibrillary glomerulopathy (FGN) is due to the deposition of polyclonal Ig that forms organized, Congo red-negative fibrils; the cause is unknown
- Immunotactoid glomerulopathy (ITGN) is most often due to the deposition of monoclonal Ig that forms Congo red-negative microtubular structures and may be associated with a monoclonal gammopathy or lymphoproliferative disease

**Clinical and Laboratory Features**

- The clinical presentation of FGN and ITGN is the same with variable amounts of proteinuria, hematuria, hypertension, and more or less rapidly progressive renal failure
- Most patients have heavy proteinuria with nephrotic syndrome in about 60%; some have a more nephritic presentation
- There are no consistent abnormalities in serum complement, autoantibodies, antiviral titers, or cryoglobulins in either FGN or ITGN
- ITGN may be associated with chronic lymphocytic leukemia or non-Hodgkin’s lymphoma; IgG or IgM paraproteins of the same isotype are found in the serum and renal tissue in most cases of ITGN but not in FGN

**Course and Treatment**

- FGN and ITGN cause progressive renal failure; however, those cases of ITGN with a lymphoproliferative disease may respond to chemotherapy


- **LM**: The morphology is similar in FGN and ITGN, with mild to severe mesangial proliferation and a membranoproliferative pattern being most common; crescents are present in some cases; Congo red stain is negative
- **IF**: Strongly positive granular mesangial and capillary wall staining for IgG (especially IgG4 in FGN); monoclonality is documented in ITGN by positive staining for λ or λ light chains
- **EM**: Randomly arranged fibrils in mesangial, intramembranous, subepithelial, and/or subendothelial locations; the size of the fibrils in FGN resemble those in amyloid but are generally larger (12 to 15 nm); however, the distinction is made by the negative Congo red staining. In ITGN the fibrils assume a microtubular structure

**REFERENCES**


**Hereditary Nephropathies**

**Alport Syndrome and Thin Basement Membrane Disease**

**Pathogenesis**

- Alport syndrome (AS) is X-linked in approximately 80% of cases; mutations of the gene for α5 type IV collagen (COL4A5) lead to defective assembly of the GBM in
males (including lack of incorporation of α3 and α4 type IV collagen); eventually the fragile GBM degenerates; female carriers have thin GBMs

- Homozygous autosomal recessive mutations of the genes for α3 (COL4A3) or α4 (COL4A4) type IV collagen on chromosome 2 cause AS in males and females equally; mutation of the gene on one allele causes thin basement membrane disease
- Benign familial hematuria most often is due to thin basement membrane disease resulting from the heterozygous mutation of one allele of COL4A3 or COL4A4

**Clinical and Laboratory Features**

- In X-linked AS, microscopic hematuria is usually present in affected males and female carriers at or shortly after birth; severe proteinuria ± nephrotic syndrome, hypertension, and progressive renal failure develop during adolescence in males but may be delayed into adulthood; most females retain normal renal function despite persistent hematuria
- The clinical features in autosomal recessive AS are the same as in X-linked disease, except that females are equally affected
- Extrarenal manifestations including sensorineural hearing loss and/or ocular abnormalities may be present in either X-linked or autosomal AS; rarely, esophageal leiomyomas are found in X-linked AS
- Diagnosis depends on clinical features, family history, screening family members for hematuria, or classical renal biopsy findings; immunofluorescence of skin biopsy for α5 type IV collagen may be helpful
- Genetic testing is presently in limited use due to the variability in genetic mutations, but may be indicated in certain circumstances, eg, to exclude the carrier state in an asymptomatic potential kidney donor
- Most patients with thin basement membrane disease remain asymptomatic except for microscopic and occasional episodes of gross hematuria; however, as with female carriers of X-linked AS, proteinuria, hypertension, and renal insufficiency may occur

**Course and Treatment**

- End-stage renal disease (ESRD) usually occurs in males with AS in their late teens to mid-30s but may be delayed into middle age
- There is no proven benefit of any therapy in AS, but treatment with an ACE inhibitor or ARB would seem prudent. A small proportion of patients develop severe anti-GBM nephritis after renal transplantation due to allosensitization to the type IV collagen isoform missing from their own tissues and present in the allograft; plasmapheresis and cytotoxic agents are variably effective in such cases


- LM: Focal and segmental or global glomerulosclerosis with interstitial fibrosis and foam cells is present in advanced cases
- IF: No deposits are present; the absence of GBM staining with antibody to α5 type IV collagen is characteristic of X-linked AS
- EM: Irregular thinning and thickening of the GBM with a lamellated basket-weave appearance; podocyte foot processes are focally effaced

**Histopathology of Thin Basement Membrane Disease (Am J Kidney Dis Vol. 34, No. 6, December 1999, Atlas)**

- LM: Normal glomeruli
- IF: Negative
- EM: Width of the GBM is uniformly reduced by comparison with age-matched normal controls but otherwise appears normal; the podocytes and endothelial cells are normal

**REFERENCES**

Congenital Nephrotic Syndrome (of the Finnish Type)

- Autosomal recessive disease presenting with severe proteinuria and nephrotic syndrome in utero and at birth due to mutation of Nephrotic syndrome 1 (NPHS1) on chromosome 19
- NPHS1 encodes nephrin, an Ig-like transmembrane protein and a major constituent of the podocyte slit-diaphragm
- Histology shows sclerosis of glomeruli, microcystic dilatation of tubules and interstitial fibrosis on light microscopy, and podocyte abnormalities and absence of slit-diaphragms on electron microscopy
- Early nephrectomy, dialysis and renal transplantation may be life saving
- Recurrent nephrotic syndrome develops after transplantation in some cases and may be due to allosensitization to nephrin in the allograft

Steroid-Resistant Nephrotic Syndrome

- Autosomal recessive, steroid-resistant nephrotic syndrome (SRNS) in early childhood due to mutation of NPHS2 on chromosome 1
- NPHS2 encodes a hairpin-like protein of the stomatin family called podocin that may anchor nephrin and the slit-diaphragm in the plasma membrane
- SRNS presents with proteinuria several months to years after birth and progresses to end-stage renal failure
- NPHS2 mutations have been found in apparently idiopathic cases of steroid-resistant focal glomerulosclerosis
- Histology shows focal and segmental glomerulosclerosis with podocyte abnormalities on electron microscopy

Familial Focal Glomerulosclerosis

- Autosomal dominant disease in which several members of affected families have asymptomatic proteinuria, nephrotic syndrome, and/or renal insufficiency in adult life due to mutations of ACTN4 on chromosome 19
- Alpha actinin 4 (ACTN4) encodes α-actinin-4, a podocyte-specific actin-bundling protein
- Other forms of familial focal glomerulosclerosis exist in which the affected gene has not been identified

Congenital Syndromes Associated With Glomerular Abnormalities

- Nail-patella syndrome is an autosomal dominant disease with dysplastic finger nails, skeletal anomalies, and proteinuric renal disease due to mutation of LMX1B, a podocyte-specific transcription factor that regulates the coordinated expression of α3 and α4 type IV collagen and podocin genes and is characterized by GBM and podocyte abnormalities
- Two syndromes are caused by different mutations of the Wilms tumor suppressor gene 1 (WT1):
  - Denys-Drash syndrome—Ambiguous or female genitalia, XY karyotype and dysgenetic gonads, Wilms tumor, and proteinuria from diffuse mesangial sclerosis during the first year of life
  - Frazier syndrome—Male pseudo-hermaphroditism with female external genitalia, streak gonads and XY karyotype, gonadoblastoma, and nephrotic syndrome due to focal and segmental glomerulosclerosis, progressing to end-stage renal failure in adolescence or early adulthood

REFERENCES


Diabetic Nephropathy

Pathogenesis

- Magnitude of pathogenetic features effects is likely modulated by genetic factors
- Numerous risk genes have been reported, but these require confirmation
• Risk factors include parental hypertension and diabetes, sibling with diabetic nephropathy, poor glycemic control, minority ethnicity.


- **LM:** Diffuse or nodular mesangial expansion with thickened GBMs
- **IF:** Pseudolinear deposition of albumin and IgG along GBM; non-specific IgM and complement may be present in segments of glomerulosclerosis
- **EM:** Diffuse or nodular mesangial expansion; thickened GBMs

**Clinical and Laboratory Features**

- **Normoalbuminuria**
  - After initial presentation, diagnosis, and stabilization on insulin, Type 1 diabetic patients are normoalbuminuric
  - Type 2 diabetics may not be normoalbuminuric on initial diagnosis
- **Microalbuminuria**
  - Earliest manifestation of nephropathy; predates overt disease
  - Defined as 20 to 300 μg/min albumin excretion or a spot albumin/creatinine ratio of 0.03 to 0.3
  - In microalbuminuric Type 1 diabetics, particularly of long duration (>10 years), significant renal morphological changes are present
  - Affects 25% to 30% of diabetics within 5 to 15 years of diagnosis
  - Microalbuminuria occurs at a higher frequency in ethnic minorities
  - Progression from microalbuminuria to overt proteinuria in the pre-ACE inhibitor era was estimated to be approximately 80% for patients with Type 1 diabetes and approximately 20% for those with Type 2 diabetes. In recent years, progression, particularly for those with Type 1 diabetes has declined to approximately 40% to 50%
  - Microalbuminuria is a cardiovascular morbidity/mortality risk factor
- **Overt Proteinuria**
  - Defined as ≥500 mg proteinuria/24 h, occurs approximately 15 to 20 years after developing Type 1 diabetes or ≥5 to 10 years after diagnosis of Type 2 diabetes
  - Most have concomitant diabetic retinopathy (concordance of retinopathy is higher for Type 1 than Type 2 diabetics)
  - Progression to overt nephropathy occurs more frequently in ethnic minorities compared to European-Americans
  - Urinalysis generally bland, although microscopic hematuria may be seen in approximately 15% of patients
  - Azotemia follows the onset of overt nephropathy
  - Average decline in renal function was approximately 1 mL/min/mo in the pre-ACE inhibitor era; now approximately 0.3 mL/min/mo in the best-controlled patients
  - Renal biopsy not usually necessary to diagnose diabetic nephropathy
  - Renal biopsy is rarely indicated in patients with: renal function declining more rapidly than anticipated; active urinary sediment; or in the setting of a history, physical exam, or serologies suggestive of an alternative systemic disease or primary glomerulopathy

**Therapy**

- Glycemic control prevents/delays progression from normoalbuminuria to microalbuminuria and from microalbuminuria to overt nephropathy, Goal HbA1c ≤7%
- Blood pressure control diminishes the risk of developing nephropathy and slows progressive loss of renal function. Goal BP <130/80
- ACE inhibitors/ARBs slow progression from normoalbuminuria to microalbuminuria
- JNC 7 recommendations for ACE inhibitors or ARBs along with diuretics to BP <130/80 mm Hg
- High protein diets should be avoided

**Course and Prognosis**

- Patients with overt nephropathy generally progress to ESRD
- Major mortality for these patients is cardiovascular and cerebrovascular
- Renal transplantation appears to confer a survival advantage
REFERENCES

INDUCTION OF GLOMERULONEPHRITIS

Immunologically mediated glomerulonephritis results from the generation of glomerular immune complexes or the dysregulation of T-cell-mediated immunity in the absence of immune complexes (“pauci-immune”). Secondary mediators then modulate the local inflammatory response.

Immune-Complex Mediated Glomerulonephritis

Immune complexes (IC) are macromolecules of antigen, antibody, and any fixed complement components. The antigen can be exogenous (ie, bacterial, viral, chemical) or endogenous (ie, deoxyribonucleic acid [DNA], thyroglobulin, tumor antigen, etc). The level and persistence of immune complexes is dependent upon the source and amount of antigen, the potency and duration of antibody response, and the level of function of the mononuclear phagocyte system for clearing IC from the circulation.

There are two mechanisms for glomerular IC deposition
1. Deposition of IC from the circulation (CIC)
2. In situ complex formation: Antigen and antibody are independently trapped to form an IC

The major clinical examples are membranous nephropathy and anti-GBM nephritis

Pauci-Immune Glomerulonephritis

- Characterized by the absence of immune deposits (negative immunofluorescence) with cellular infiltration of lymphocytes and monocytes in Bowman’s space (crescent)
- Initiators unknown
- Abnormal immunoregulatory mechanisms (perhaps genetically defined) permit the dysregulation of autoreactive T- and/or B-cell clones
- Vast majority of these patients have antibodies to neutrophil lysosomal antigens (c-antineutrophil cytoplasmic antibody [ANCA] or p-ANCA, see below)
- Clinical examples include: Wegener granulomatosis, microscopic polyangiitis (microscopic polyarteritis nodosa), Churg-Strauss disease, and idiopathic crescentic glomerulonephritis

Secondary Mediators of Inflammation

Complement
- Complement functions: Cell lysis or injury, chemotaxis, opsonization, immune complex solubilization, enhanced vascular permeability
- C5b-9 membrane attack complex (MAC) induces cell membrane lysis and injury; urinary MAC may reflect degree of glomerular injury, particularly in membranous nephropathy

Cytokines
- Regulate cell proliferation, differentiation, phenotype, secretion, and/or migration
- Cytokine families include:
  — Interleukins
  — Colony-stimulating factors
— Interferons
— Chemokines
— Growth factors

A description of a few cytokines/growth factors that are important in the kidney follows:

- **Transforming growth factor-β**
  - Master regulator of matrix synthesis and degradation; promotes fibrosis
  - Regulates cell proliferation and differentiation, wound healing, angiogenesis
  - Pathogenetically implicated in most experimental forms of glomerulonephritis
  - Increased in human diabetic nephropathy
- **Platelet-derived growth factor**
  - Increases mitogenesis, chemotaxis, mesangial cell contraction
  - Implicated in the pathogenesis of IgA nephropathy, diabetic nephropathy
- **Insulin-like growth factor-1/growth hormone**
  - Implicated in the pathogenesis of renal hypertrophy and glomerulosclerosis
- **Adhesion molecules/integrins/selectins**
  - Regulate cell-cell and cell-matrix interactions
  - Coordinates (in concert with cytokines and chemokines) the development of immune and inflammatory reactions
  - Facilitates signaling from inside the cell to the outside matrix and from outside the cell to the nucleus via the cytoskeleton

**Reactive Oxygen Species**
- Potential injurious agents—primarily $\text{O}^-$, $\text{H}_2\text{O}_2$, $\text{OH}^-$, $\text{HCl}$
  - Detoxification: enzymes (superoxide dismutase, catalase); $\text{O}_2$ scavengers

**Signal Transduction Molecules**
- Exogenous molecules such as cytokines, chemokines, growth factors, and hyperglycemia induce activation of intracellular signaling molecules within cells
- Signaling pathways such as the mitogen-activated protein kinases and the protein kinase C pathway mediate actions of the extracellular signals by inducing the formation of nuclear transcription factors, which bind to regions on genes and activate them
- These mediate change in experimental models of glomerular disease

**REFERENCES**

**DISORDERS ASSOCIATED WITH NEPHRITIS**

**Membranoproliferative Glomerulonephritis (MPGN)**

**Pathogenesis**

Three distinct entities defined by histopathology.
- **Type I**: The most common form; immune-complex mediated
- **Type II (dense deposit disease)**: Less common; in animal models and some families, there is a deficiency or absence of complement Factor H
- **Type III**: Rare; immune-complex mediated

**Pathology**
- **Type II**: Deposition of electron dense material within capillary wall; complement C3c is present (Am J Kidney Dis Vol. 31, No. 2, February 1998, Atlas)
- **Type III**: Subepithelial and subendothelial deposits associated with GBM disruption and lamina densa layering
  - All 3 types have double-contoured GBM

**Clinical Associations**
- Histological features of Type 1 MPGN may be seen in patients (particularly adults) with
underlying neoplasms, infections, and collagen-vascular diseases
● Partial lipodystrophy associated with Type 2, less commonly other types

This Section Focuses on the Primary Forms of MPGN
● May present as...
  — Asymptomatic with microhematuria or nonnephrotic proteinuria
  — Nephrotic syndrome
  — Acute nephritic syndrome
  — Crescentic rapidly progressive glomerulonephritis
● Hypertension and diminished GFR may be present at diagnosis
● ≥80% of patients with Type 1 MPGN have underlying hepatitis C; less commonly, hepatitis B
● Cryoglobulinemic vasculitis (Am J Kidney Dis Vol. 32, No. 6, December 1998, Atlas) may complicate hepatitis C-associated MPGN and present with low C3 and/or C4, rheumatoid factor, positive ANA (approximately 20%), arthritis, and skin leukocytoclastic vasculitis
● Low C3 is found in approximately 70% to 90% of patients
  — In idiopathic MPGN, C3 nephritic factor stabilizes C3 convertase
  — In some families, complement factor H deficiency induces continued C3 activation
● Usually sporadic, but some hereditary, particularly Types II and III
● Slow progression to end-stage renal disease (ESRD) in Types I and II, more frequently than Type III
● Spontaneous remission occurs rarely
● All may recur in renal allografts, particularly with a live-related donor

Therapy
● No consensus. All of the following have been used:
  — Steroids/immunosuppressives may enhance viral replication in hepatitis-associated MPGN; may be necessary with complicating cryoglobulinemic vasculitis
  — Cyclosporine, mycophenolate mofetil, and intravenous (IV) Igs used anecdotally
  — ACE inhibitor/ARB for their antiproteinuric effects
  — Pegylated interferon and ribavirin have not been studied systematically for effects on nephritis
  — Ribavirin is contraindicated with GFR <50%

REFERENCES

IgA Nephropathy (Berger’s Disease)

Pathogenesis
● Mesangial deposition of undergalactosylated polyclonal IgA1
● Origin of IgA1 controversial, but may derive from bone marrow or mucosa
● Posited to be due to binding of IgA to mesangial cell Fc receptors, resulting in mesangial cell growth factor, cytokine, and chemokine elaboration inducing mesangial proliferation, infiltrating monocytes, and matrix expansion

Clinical Associations
● Primary idiopathic form
● Secondary forms: Henoch-Schönlein purpura, alcoholic cirrhosis, gluten enteropathy, HLA-B27 arthritides, IgA monoclonal gammopathies, dermatitis herpetiformis, psoriasis
● Some familial forms

- **LM:** global or segmental mesangial hypercellularity; mesangial deposits may be seen with trichrome stain
- **IF:** microscopy: mesangial IgA and C3. Co-deposition of mesangial IgG or IgM frequent. Deposits may occasionally extend to involve the GBM
- **EM:** mesangial deposits often with clustering at the paramesangial basement membrane.

Clinical and Laboratory Features

- Most common primary glomerulonephritis in the world
- Varied clinical presentation
  - Asymptomatic; microscopic hematuria; intermittent gross hematuria; synpharyngitic hematuria; nephrotic (<15%) or nonnephrotic proteinuria; acute glomerulonephritis; rapidly progressive glomerulonephritis
- Often associated with hypertension
- Approximately 50% of patients have increased serum IgA levels

Course and Prognosis

- 20-year renal survival approximately 50% to 70%
- Risk factors for progression: heavy proteinuria, diminished GFR at onset, older age at onset, uncontrolled hypertension, crescents, tubulointerstitial fibrosis/atrophy, familial forms
- Prognostic value of gross hematuria is controversial
- Certain genotypes may be associated with progression
- Recurrent IgA deposits in renal allografts rarely induce clinical disease

Therapy: Controversial; Varies Substantially According to Local Practices

- ACE inhibitor/ARB for their antiproteinuric effects. GFR benefit mostly inferential
- Eicosapentaenoic acid/docosahexaenoic acid slowed progression in some but not all studies
- Mycophenolate mofetil under study in randomized trials

REFERENCES


Henoch-Schönlein Purpura Nephritis (HSP)

Pathogenesis

- Similar to IgA nephropathy (above), but with widespread systemic involvement, particularly in the kidneys, skin and gastrointestinal tract

Histopathology: Highly Variable

- **LM:**
  - Minimal changes (2%)
  - Mild mesangial hypercellularity, few leukocytes (10% to 32%)
  - Focal/segmental mesangial hypercellularity, more WBCs (20% to 45%)
  - Diffuse mesangial hypercellularity, up to 50% crescents (15%)
- **IF:** Granular mesangial IgA with C3, fibrinogen, both light chains, lesser amounts of IgG/IgM
- **EM:** Mesangial electron dense deposits; occasional involvement of capillary loops; variable foot process effacement; occasional GBM thickening, thickening, and lamellation

Clinical and Laboratory Features

- Classical clinical triad is purpura, abdominal pain, and hematuria
- Affects children predominantly; M:F ratio 2:1 in children
- More prevalent in winter
- Approximately 1 in 3 patients experience a precipitant event
- Spectrum of symptoms from mild to severe petechial rash, gastrointestinal, renal, neuro-
logic, urologic, pulmonary, and rheumatologic disease

- Predominance of renal involvement in adults, skin in children
- Susceptibility may be genetic; uncommon in those of African descent
- May recur in renal allografts, particularly living-related kidneys

**Course**

- Average renal disease duration approximately 1 month
- Extrarenal involvement often lasts \( > 1 \) month
- Overall good renal outcome; complete recovery in approximately 90% adults
- Protracted courses and relapse may occur
- Prognosis poorer in acute nephritic syndrome or proteinuria \( > 1 \) g/d
- Persistent proteinuria should be treated with ACE inhibitors and/or ARBs

**Therapy**

- Symptomatic for mild cases
- For severe nephritis, treatment is controversial and is based on experience from small series and case reports. All of the following have been tried:
  - Steroids as monotherapy
  - Multidrug therapy with various combinations of steroids, cyclophosphamide, di-pyridamole, heparin, and/or warfarin
  - IV Ig


- World Health Organization (WHO) classification of 1982 (currently undergoing revision): I—Normal; II—Mesangial proliferation with immune complexes limited to mesangium; III—Focal proliferative (FPGN); IV—Diffuse proliferative (DPGN); V—Membranous; VI—Sclerosing
- Activity/chronicity indices score severity of inflammation/sclerosis
- Immune deposits often characterized by “full-house” IF, with IgG, IgA, IgM, C1q, C3, fibrin, \( \kappa \) and \( \lambda \) light chains
- Electron microscopy shows dense deposits (II—mesangial; III and IV—mesangial, subendothelial, occasional subepithelial; V—subepithelial) and frequently endothelial tubuloreticular structures
- “Non-WHO” lesions may also occur:
  - Combinations of WHO lesions
  - Superimposed acute tubular necrosis or acute interstitial nephritis
  - Thrombotic microangiopathy

**Clinical and Laboratory Features**

- Nonnephrotic or nephrotic range proteinuria, usually with hematuria, often with some pyuria
- Red cell casts may be present, especially in patients with FPGN and DPGN with or without crescents, so-called “telescopic urine”
  - Renal presentation occasionally precedes systemic lupus erythematosus (SLE) diagnosis
- Hypertension (\( > 50\% \))
- Hypocomplementemia (particularly direct pathway components C2, C3, C4) approximately 90% in DPGN/FPGN
- Systemic: Arthralgias, nondeforming arthritis, malar or discoid rash, photosensitivity, oral ulcers, alopecia, myalgias, serositis, cerebritis, myocarditis

**Course and Prognosis**

- Good prognosis for patients with mesangial proliferation only

**Reference**


**Lupus Nephritis**

**Pathogenesis**

- Loss of self-tolerance, followed by autoantibody production
- Leads to immune complex deposition
- The latter induces activation of complement and elaboration of chemokines and cytokines, resulting in leukocyte chemotaxis, mesangial hypercellularity and matrix expansion, occasionally fibrinoid necrosis and/or crescentic GN, and glomerulosclerosis
• Progression to renal failure is more common in FPGN and DPGN
  — Improved prognosis for DPGN; progression to ESRD in 5 years now approximately 10% reflecting success of current therapies
• Membranous SLE prognosis is similar to idiopathic membranous
• Conversion from less to more proliferation occurs in approximately 35% of patients
• Risk factors for progression, apart from WHO class, include African-American race, hematocrit <25%, elevated serum creatinine, and heavy proteinuria at presentation
• SLE activity usually becomes quiescent at ESRD, but exceptions occur
• Clinically significant lupus nephritis rarely recurs in renal allografts

_Therapy: Highly Controversial_

• General principles
  — Most aggressive therapy is directed toward treating DPGN because of its serious prognosis if inadequately treated
  — The more sclerosis and tubulointerstitial fibrosis on biopsy the greater the likelihood of progression
• Treatment of mesangial proliferation
  — Treat extrarenal manifestations only
• Treatment of FPGN/DPGN
  — Current regimens of prednisone, methylprednisolone pulsing, and IV cyclophosphamide improved prognosis
  — Optimal duration of treatment course controversial
  — Concerns regarding toxicity, including sepsis, hemorrhagic cystitis, bladder cancer, and ovarian failure spurred assessment of alternative regimens
  — Continued interest in the use of azathioprine to induce and/or consolidate remission
  — Recent reports suggest results with mycophenolate mofetil equivalent to cyclophosphamide to induce or consolidate remission
  — Fewer side-effects with mycophenolate mofetil
  — Long-term renal survival is currently unknown with mycophenolate mofetil
  — Azathioprine may be best choice during pregnancy
  — Plasmapheresis has no proven benefit
  — Total lymphoid irradiation, IV Ig, and stem cell infusions have been used as salvage therapy in selected patients
  — New immunomodulatory agents are under investigation
• Treatment of membranous lupus nephritis
  — ACE inhibitor/ARB initially to minimize proteinuria
  — Steroids for extrarenal manifestations
  — If proteinuria remains nephrotic and/or serum creatinine is rising, consider cyclosporine or IV cyclophosphamide and steroids
  — Preliminary studies from NIH suggest benefit with these beyond steroids alone
  — Relapse after achievement of complete remission is common, occurring in 45% of patients at a median time of 36 months, emphasizing the need for continued follow-up

_References_


_ANCA-Associated/ANCA-Generated Glomerulonephritis (Pauci-Immune)_

_Pathogenesis_

• Infection, drug exposure, or other inflammatory processes activate polymorphonuclear leukocytes and endothelial cells, leading to:
  — Local generation of cytokines
— Translocation of ANCA lysosomal antigens proteinase-3 (PR3) or myeloperoxidase (MPO) to the cell membrane
— Specific anti-PR3 or anti-MPO antibodies bind and further activate target neutrophils to secrete damaging reactive oxygen species and other mediators of inflammation

- Crescentic glomerulonephritis and systemic vasculitis can be transferred by infusion of MPO ANCA antibody or by activated splenocytes synthesizing anti-MPO ANCA antibody, supporting a pathogenetic role for MPO ANCA

**Laboratory Diagnosis**

Tests are performed by indirect immunofluorescence (IIF) for the pattern of antigen expression or by enzyme-linked immunosorbent assay (ELISA) for specific antigen identification

- **Indirect IF**: Ethanol-permeabilized WBCs are incubated with patients' sera and then with fluorescein-conjugated antihuman IgG. A cytoplasmic pattern (cANCA) indicates that the target antigen is PR3. A perinuclear pattern (pANCA) usually indicates that the antigen is MPO. Other antigens can also uncommonly confer a perinuclear pattern
- **ELISA**: Identifies the antigen to which the ANCA antibody is directed in a positive IIF test

**Wegener Granulomatosis**


- **LM**: Granulomatous vasculitis of medium sized to small arterioles and venules. Renal biopsy may disclose any of the following: normal; mesangial proliferative glomerulonephritis; segmental necrotizing glomerulonephritis; crescents
- **IF**: Pauci-immune glomerulonephritis; fibrin may be present in crescents; tubulointerstitial granulomas
- **EM**: No immune deposits are seen

**Laboratory Diagnosis**

- cANCA is specific and sensitive for diagnosing untreated patients
- Some patients (approximately 20% to 30%) have pANCA and a few may be ANCA negative, particularly in the setting of partial or full treatment
- Titers may be useful to follow therapeutic response or predict relapse (controversial)

**Clinical Presentation**

- Presenting symptoms most often involve upper respiratory tract including rhinorrhea, sinusitis, nasopharyngeal mucosal ulceration
- Lung involvement in >80% of patients, most often cough, dyspnea, hemoptysis; transient infiltrates or nodular densities may be seen on chest x-ray (CXR)
- Renal involvement characterized by proteinuria, hematuria, red cell casts
- Approximately 10% of patients have azotemia on presentation
- Other signs/symptoms: fever, weight loss, malaise, arthralgias, nondeforming arthritis, mononeuritis multiplex, skin papules, vesicles, purpura

**Treatment**

- Oral cyclophosphamide dramatically improved survival in uncontrolled trials
- High incidence of bladder cancer the decade following prolonged treatment with daily oral cyclophosphamide
- IV cyclophosphamide advocated to diminish side effects
- Oral and IV cyclophosphamide protocols are roughly equivalent in remission induction efficacy, but oral may be marginally better than IV in preventing relapse
- Steroids useful adjunctive therapy, particularly in patients with severe renal or pulmonary disease, skin or cerebral vasculitis, eye involvement, or pericarditis
- In situations with severe pulmonary hemorrhage and fulminant renal disease, pulse methylprednisolone and/or plasmapheresis may confer additional benefit
- Studies of short course cyclophosphamide followed by azathioprine claim equivalent short-term efficacy compared to more intensive cyclophosphamide-based regimens; long-term efficacy and relapse rates not yet known
- Sulfamethoxazole/trimethaprim may dimin-
ish relapse rates, particularly respiratory, but drug intolerance is common.

- In refractory patients, the following have been tried with limited success: mycophenolate mofetil, IV Ig, anti–tumor necrosis factor (TNF) drugs (etanercept; infliximab); antithymocyte globulin, deoxyspergualin, leflunomide.

**Course and Prognosis**

- >80% to 90% 1-year mortality if left untreated.
- Relapse occurs in 25% to 50% of patients followed up for 3 to 5 years.

**Microscopic Polyangiitis (Polyarteritis)**


Vasculitis of small to medium sized arteries and venules, without granulomatous changes typical of Wegener granulomatosis. Glomeruli with pauci-immune glomerulonephritis.

**Laboratory Diagnosis**

- Both pANCA and cANCA positivity is seen, with a slight preponderance of pANCA.

**Clinical Presentation**

- Similar to Wegener granulomatosis, but with less emphasis on pulmonary and upper respiratory tract involvement, although alveolar capillaritis without granulomatous change causing hemoptysis can occur.
- The following medications have been associated with the development of microscopic polyangiitis: propylthiouracil, hydralazine, penicillamine, and silica.

**Treatment and Course**

- Similar to Wegener granulomatosis.

**Churg-Strauss Vasculitis**

**Histopathology**

Similar to other ANCA-positive vasculitides, but characteristic feature is eosinophilic pulmonary infiltrates.

**Laboratory Diagnosis**

- Usually pANCA (MPO) positive.

**Clinical Presentation**

- Eosinophilia and necrotizing vasculitis in the presence of asthma.
- Vasculitis can affect lung, skin, peripheral nerves, muscles, intestine, and kidneys, although glomerulonephritis is usually (but not always) mild.
- Associated with leukotriene antagonist therapy, but causation not proven.

**Treatment and Course**

- Glomerular involvement usually mild; severe crescentic glomerulonephritis is rare.
- Progression to ESRD is uncommon.
- Therapy is similar to other forms of vasculitis and is dependent upon the severity of organ involvement in the major systems involved.

**Idiopathic Crescentic Glomerulonephritis**

**Histopathology**

Pauci-immune crescentic glomerulonephritis.

**Laboratory Diagnosis**

- Both pANCA and cANCA positivity is seen, mostly pANCA.

**Clinical Presentation**

- Renal-limited glomerular capillaritis, characterized by gross or microscopic hematuria, nonnephrotic proteinuria, red cell urinary casts, and rapidly rising serum creatinine.
- Extra-renal signs/symptoms absent except nonspecific constitutional symptoms.

**Treatment and Course**

- Similar to Wegener granulomatosis.

**REFERENCES**


**Goodpasture Syndrome (Anti-GBM Nephritis)**

**Pathogenesis**

Inflammatory sequelae due to antibodies to an epitope on the noncollagenous domain of the α3.
chain of Type IV collagen. Expression of the antigen is restricted predominantly to glomerular and alveolar basement membranes.

**Clinical Associations**

- Pulmonary hemorrhage exacerbated by volatile hydrocarbon exposure, smoking, influenza
- Rarely occurs superimposed on nail-patella syndrome or membranous nephropathy
- Anti-GBM antibodies may deposit in renal allografts of patients with Alport syndrome


- **LM:** Glomerulonephritis without tuft hypercellularity, crescents frequent
- **IF:** Continuous linear IgG and C3 along GBM. Rarely other Iggs
- **EM:** No deposits

**Clinical and Laboratory Features**

- Once thought to occur primarily in young adult males; now M:F sexual predilection closer to 55:45
- Presentations
  - Pulmonary symptoms (cough, dyspnea, rales, hemoptysis) precede or are coincident with renal symptoms ≥70% of cases
  - Azotemia in 50% to 70% of cases at initial presentation
  - Arthritis/arthralgia common
  - Anemia is out of proportion to degree of azotemia and presents with iron deficiency characteristics due to pulmonary hemorrhage
  - Hypertension uncommon (<20%)
  - Urinalysis shows hematuria, red cell casts, non-nephrotic proteinuria
  - Serology usually negative/normal except for the anti-GBM antibody
  - Antibody titer does not correlate with severity of illness
  - Approximately 20% to 30% of patients are also pANCA positive

**Therapy**

- Remissions have been achieved with plasmapheresis, glucocorticoids, and cytotoxic agents in patients with serum creatinine <5 mg/dL (<=442 μmol/L)
- Renal recovery less likely with oligoanuria and serum creatinine >6 mg/dL (>530 μmol/L)

**Course**

- Majority of untreated patients progress to ESRD, although rare spontaneous remissions reported
- Smoking and volatile hydrocarbon exposure exacerbates pulmonary hemorrhage and may precipitate recurrence
- Recurrence in renal allografts is rare if antibody titers are negative

**REFERENCES**


**Infection-Associated Glomerulonephritis**

**Post-Streptococcal Glomerulonephritis (PSGN)**

**Pathogenesis**

- Due to an immune response to infection with nephritogenic Group A (rarely Groups C or G) β-hemolytic streptococcus
- Deposited antibodies may be directed at streptococcal antigens and/or intrinsic glomerular epitopes such as extracellular matrix
- Local activation of the complement cascade, interleukin-6 (IL-6), intercellular adhesion molecule-1 (ICAM-1), and the plasmin-plasminogen system contribute to local inflammation


- **LM:** Glomerular tufts are enlarged, hypercellular, with leukocytes in glomerular capillaries; rarely crescents. Hypercellularity may be global or segmental
- **IF:** Large, irregular subepithelial, and some mesangial and/or subendothelial deposits, usually with IgG, IgM, and complement. Deposition of C3 may precede Ig. Three patterns of deposits reported:
  - Starry sky describes presence of fine granular capillary wall and mesangial
deposits. Has been associated with chronicity
— Mesangial describes a mesangial-predominant pattern of immune deposits
— Garland describes predominantly capillary wall deposits
- **EM:** Subepithelial “hump” shaped deposits; some mesangial and subendothelial deposits

**Clinical and Laboratory Manifestations**
- Typically a preceding throat or skin infection with a latent period of approximately 1 to 3 weeks or 3 to 6 weeks, respectively, for the appearance of renal symptoms
- Infection often inapparent when glomerulonephritic symptoms present
- Occurs epidemically and sporadically
- Most frequent in school-age children with M:F ratio 2:1
- **Presentation**
  — Gross hematuria (50%)
  — Nephrotic/nonnephrotic proteinuria (96%)
  — Edema (85%)
  — Hypertension (60%)
  — Lethargy, confusion, seizures (20%)
  — Oligoanuria (35%)
  — Azotemia (74%)
  — Pulmonary symptoms (23%)
  — Gastrointestinal complaints (29%)
  — Ascites (particularly in children) (26%)
- Hypocomplementemia (low C3 but normal C4 demonstrating alternate complement pathway activation), present in almost all patients, usually resolves within 2 months
- Low level cryoglobulinemia is frequent
- Anti-streptolysin O titers are usually elevated with a preceding throat infection. Antihyaluronidase and anti-DNAse B titers are more common with preceding skin infections

**Therapy**
- No specific therapy; treatment of underlying infection as appropriate
- Gentle diuresis may be required for comfort
- Hypertension should be aggressively treated, especially in children, in whom hypertensive seizures may occur
- Supportive dialysis as necessary

**Course and Prognosis**
- Complete resolution of hematuria/proteinuria may take months to years
- Renal prognosis favorable in children except with severe acute disease
- Up to 40% of adults develop chronic azotemia

**REFERENCE**

**Acute and Subacute Bacterial Endocarditis (ABE, SBE)**

**Pathogenesis**
Immune-complex mediated

**Histopathology**
- **LM:** ABE—Glomerular hypercellularity with or without segmental necrosis; SBE—Focal segmental proliferation, often with fibrinoid necrosis or capillary thrombi; rarely crescents
- **IF:** IgG, IgM, and complement deposits in mesangium and GBM
- **EM:** ABE—Dense deposits in the mesangium and GBM; SBE—Mostly mesangial deposits, with relative sparing of GBM

**Clinical and Laboratory Features**
- In industrialized nations, mostly seen in patients with prosthetic heart valves or in IV drug abusers
- In developing nations, mostly seen in patients with a history of rheumatic heart disease
- May also complicate aortic sclerosis/mitral valve prolapse

**Presentation**
- Fever, myalgias, malaise, arthralgias, anemia, purpura
- Gross or microscopic hematuria
- Usually nonnephrotic proteinuria
- Often azotemia, but rapid progression is uncommon
- Fewer extrarenal clinical manifestations in right-sided endocarditis, but renal involvement more common
- Hypocomplementemia (low C3 and C4),
normochromic normocytic anemia, leukocytosis, elevated sedimentation rate, and elevated C-reactive protein are characteristic

• Low-level cryoglobulinemia is frequent

**Therapy**

• Supportive care in conjunction with treatment of the underlying infection

• In patients with crescentic glomerulonephritis, anecdotal reports suggest benefit from steroids, immunosuppression, and/or plasmapheresis after or in conjunction with antibiotics

**Course and Prognosis**

• Overall prognosis determined by therapy for the valvular disease

• Most renal disease resolves within weeks with antibiotic treatment

• In patients with severe renal disease on presentation, there may be residual proteinuria, hypertension, and/or azotemia

**Other Infection-Related Syndromes**

• Chronic visceral abscess

• Shunt nephritis

• Pneumonia

**REFERENCE**


**Thrombotic Microangiopathies (TMA)**

**Thrombotic Thrombocytopenic Purpura (TTP)**

**Pathogenesis**

• Diminished activity of von Willebrand factor (vWF) cleaving protein, due to either an inherited mutation or to the presence of an Ig interfering with the function of the vWF cleaving protein, results in abnormal amount and/or size of vWF

• Unusually large vWF binds to extracellular matrix and platelets, induces platelet activation and aggregation, and leads to intravascular platelet thrombi, organ ischemia, and necrosis

• Defective vWF cleavage typifies active TTP and distinguishes it from other causes of hemolysis, thrombosis, or thrombocytopenia

• vWF cleaving protein is a zinc metalloproteinase named “a disintegrin and metalloproteinase with thrombospondin type 1 repeat” (ADAMTS)

• Patients with familial and recurrent TTP have ADAMTS13 mutations


• LM: Glomerular capillary and sometimes arteriolar fibrin thrombi

• IF: Fibrin in capillaries and arterioles; no immune complexes

• EM: Endothelial cell swelling, capillary and arteriolar fibrin, and lamina rara externa expansion due to fibrin deposition

**Clinical and Laboratory Features**

• Presentation

  — Classic pentad of fever, microangiopathic hemolytic anemia, thrombocytopenic purpura, renal disease, central nervous system symptoms

  — Occurs as acquired acute disease or in a chronic relapsing form

  — Continued hemolysis best followed by serum LDH levels

• Clinical associations

  — Medications: quinine, mitomycin-C, cyclophilin inhibitors, ticlopidine

  — Collagen-vascular disorders: SLE, scleroderma

  — Malignancy

  — Infections: HIV

**Therapy**

• Plasma infusion provides missing enzyme activity

• Plasma exchange removes any circulating vWF cleaving protein inhibitor and facilitates infusion of large amounts of fresh frozen plasma (FFP) (average course of FFP is approximately 21 L)

• Steroids may be useful adjunctive therapy

• Supportive dialysis therapy as needed

• Rituximab used with some success in a few refractory patients
Splenectomy and platelet inhibitors are not of proven value. Platelet infusions are contraindicated.

Course and Prognosis
- Untreated, mortality approaches 90%
- 60% to 90% patient survival with plasma infusion ± plasma exchange
- Most who go into remission have excellent long-term prognoses
- A subset develop chronic TTP and require long-term treatment.

Hemolytic-Uremic Syndrome (HUS)

Pathogenesis
- Biochemical and genetic data regarding defective vWF cleaving protein and ADAMTS 13 in TTP (above) challenge the assumption that HUS and TTP represent different clinical expressions of a single disease process.
- In HUS with a diarrheal prodrome (D+HUS), it is postulated that Shiga-like toxin binds to colonic epithelium and induces elaboration of chemokines and cytokines, causing polymorphonuclear (PMN) influx and abrogation of barrier function, permitting Shiga-like toxin to enter the circulation free or bound to PMNs.
- Toxin binds to glomerular/renal arteriolar and proximal tubular epithelial cell receptors, resulting in local inflammation, endothelial injury, thrombosis, and acute renal failure.

Histopathology
All TMAs are histologically identical (see TTP).

Clinical and Laboratory Features
Classic triad of microangiopathic hemolytic anemia, thrombocytopenia, and renal disease, with peak incidence in summer.
- D+HUS induced by organisms producing a Shiga-like toxin (predominantly *Escherichia coli* O157:H7) or other enteric infections (Shigella, Salmonella, Campylobacter, Yersinia).
- Epidemics associated with ingestion of undercooked hamburger.
- May also occur in a nondiarrheal form (D-HUS).
  - Inherited form (complement factor H mutation).
  - Medications: calcineurin inhibitors, rapamycin, mitomycin-C, ciprofloxacin, oral contraceptives, gencrytine.
  - Other infections: *S. pneumoniae*.
  - Pregnancy.
  - Neoplasms.
  - Collagen-vascular disease.
  - Systemic vasculitis.
  - Bone marrow transplantation.
- Leukocytosis and fever common.
- Diarrhea ranges from watery to hemorrhagic.
- Other manifestations: fluid/electrolyte disturbances, hypertension, cerebral edema/seizures, congestive heart failure, pulmonary edema, arrhythmias.

Therapy
- Supportive.
- Of questionable or no value: anticoagulants, fibrinolytics, IV Ig, plasma infusion, plasmapheresis, antiplatelet agents.

Course and Prognosis
- Poor outcome associated with marked leukocytosis, older age at onset, D-HUS, pregnancy, Shigella or pneumococcal infection, anuria, persistent proteinuria, hypertension, cortical necrosis.

Antiphospholipid Syndrome

Pathogenesis
Induced by antibodies to phospholipid moieties and/or to the phospholipid binding protein β2-glycoprotein I, resulting in TMA.

Histopathology
All TMAs are histologically identical (see TTP).

Clinical and Laboratory Features
- Diagnosis requires ≥1 clinical and ≥1 laboratory manifestation.
- Obstetrical: frequent first trimester spontaneous abortions; fetal death; prematurity.
- Also may involve arterial/venous, central...
nervous system, kidney, gastrointestinal tract, lung, skin, skeletal, cerebrovascular, and cardiovascular systems

- Diagnostic laboratory studies involve a demonstration of antibodies to phospholipid moieties and includes any of the following: prolonged prothrombin time or partial thromboplastin time, abnormal Russell viper venom test, antiphospholipid antibody, or false positive VDRL test
- Antibody to the phospholipid binding protein β2-glycoprotein 1 is frequent, but not yet included in the diagnostic classification
- Thrombocytopenia is frequent
- May occur as a primary syndrome or associated with SLE
- May occur in a “catastrophic” form (presence of 3 organ systems)

Renal presentations
- Acute renal failure
- Hypertension: mild to malignant
- Cortical necrosis
- Thrombotic microangiopathy
- Progressive chronic renal insufficiency to failure
- Thrombosed renal allografts

Therapy
- Anticoagulation for the primary syndrome and those with SLE (INR >3)
- Avoid prothrombotic drugs (calcineurin antagonists, oral contraceptives, hydralazine, procainamide, chlorpromazine)
- ASA in women with prior pregnancy complications
- Hydroxychloroquine/chloroquine in SLE
- Role in prevention of thrombosis is controversial
- Pregnancy management
- Addition of steroids, plasmapheresis, IV Ig implemented as salvage therapy in patients with severe and/or multiple organ involvement

Course and Prognosis
- Long-term anticoagulation required
- Mortality of “catastrophic” syndrome approximately 50%

REFERENCES