PATHOLOGY OF GLOMERULAR DISEASES

Disease	Etiology	Pathophysiology and Clinical Presentation	Lab Findings and Diagnosis	Treatment
NEPHROTIC SYNDROME				
Urinalysis in Nephrotic Syndrome NML excretion: 150 mg/d : < 0.15 g total protein/g urine creatinine Nephrosis : > 3.5 g/d OR > 3.5 g/g urine creatinine Lipiduria and fatty casts (Maltese cross appearance when illuminated by polarized light) 2+/3+ on dipstick without microhematuria				
MINIMAL CHANGE NEPHROTIC SYNDROME	Typically a pediatric disease Loss of anionic epithelial layer (podocyte processes) of the filtration barrier Typically diffuse and global	Presents with the classic tetrad of **nephrotic syndrome** Massive proteinuria (>3. 5 g/d) Hypoalbuminemia Edema Hyperlipidemia	LM: no changes IF: no changes EM: podocyte foot process effacement Bx is usually not necessary	Prednisone Usually controls disease if onset and treatment is early in life With age, recurrence is more likely
FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS)	**Inherited** Mutations in the Nephrin gene product result in dysfunctional slit diaphragms (Finnish Congenital Nephritic Syndrome) **Infective** HIV infection (collapsing glomerulopathy) **Loss of Renal Mass** Unilateral renal agenesis SCD Vesicoureteral Reflux Some evidence for circulating toxins, since Dz recurs after transplantation	Nephrotic Syndrome Results in progressive kidney failure Can be thought of as a more severe variant of MCNS The **primary injury is podocyte foot process obliteration**	LM: focal segmental fibroplasia and obliteration of the capillary lumen + hyaline deposits EM: widespread effacement of foot processes IF: Minimal IgM and C3 deposits; no immune complexes	Transplantation ACE inhibitors Predisone

MEMBRANOUS GLOMERULOPATHY	**Autoimmune** Deposition of immune complexes in the subepithelial space IgG and complement form complexes with cryptic GBM antigens + allergens, pathogens, and drugs	Nephrotic Syndrome Results in renal failure with increasing serum BUN and creatinine	LM: thickening of the GBM with spiking into the urinary space IF: granular deposits (immune complexes, IgG, C3) along the GBM	ACE inhibitors Predisone
DIABETIC NEPHROPATHY	A frequent sequela of DMI and DMII Glycosylation of surface proteins → conformational changes → hyperfiltration The disease is exacerbated by systemic hypertension	Microalbuminuria progressing to nephrotic syndrome and renal failure NML urinary albumin: < 30 mg/g creatinine Microalbuminemia: 30 – 300 mg/g creatinine *These ranges are not detectable by dipstick*	LM: diffuse nodular mesangial matrix expansion (Kimmelstiel-Wilson Nodules) + capillary thickening + hyaline casts in efferent and afferent arterioles IF: Linear deposition of IgG and albumin is due to greatly increased endothelial permeability	ACE inhibitors ARBs Dual kidney and pancreas transplantation in ESRD
AMYLOIDOSIS	**Deposition of Immunoglobulin** Light chain infiltration secondary to multiple myeloma **AL amyloidosis** **Chronic Inflammation** Deposition of **Protein AA** secondary to RA and chronic osteomyelitis	Proteinuria in nephrotic range Systemic disease Progresses to ESRD	LM: stain with CR and illumination with polarized light reveals green birefringence. Deposits are typically amorphous and eosinophilic. EM: Fibrillar deposits	
SECONDARY HYPERTENSION				
HYPERTENSIVE NEPHROSCLEROSIS	Culpable for 25 – 40% of all ESRD **Sequela of longstanding HTN** Vascular injury → atherosclerosis of large vessels + arteriolosclerosis of smaller vessels → ischemia and necrosis of renal parenchyma		Gross: Nodular and fibrosed surface; loss of parenchymal volume; cortical denuding, fibrosed renal pyramids LM: intimal proliferation, hyperplasia of tunica media, reduplication of elastic lamina, luminal obliteration Glomerular sclerosis, hypertrophy of	

			the medial SM	
MALIGNANT HYPERTENSION		Severe HTN Typically requires DBP > 130 mmHg The disease is systemic		

NEPHRITIC SYNDROME

Urinalysis in Nephritic Syndrome
Active urine sediment (dysmorphic RBCs + RBC casts)
Hematuria on dipstick (measures heme; thus can be elevated with muscle damage and intravascular hemolysis)

Characteristics of Nephritic Syndrome: discolored (darkened) urine, HTN, AKI with oliguria

IMMUNOGLOBLULIN A NEPHROPATHY BERGER DISEASE	Most common primary glomerular disease Usually correlated with URIs and other bacterial infections	Striking presentation: visible hematuria following soon after respiratory infection (typically 1 – 3 d). Typical presentation is hematuria and subnephrotic proteinuria May convert to nephrotic syndrome	Dx requires Bx + r/o infection LM: hypercellularity of the mesangium EM: electron-dense deposits within mesangium IF: detection of IgA deposition within the mesangium	May progress to renal failure: requires dialysis or transplant
ANTI-GBM DISEASE (RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS)	These are diseases with rapid progression to renal failure **Autoimmune Mechanism** Circulating Abs against Type IV collagen within the GMB → binding → elicit Type II hypersensitivity → activation of complement + cytokine release + plasma clotting cascade → glomerular damage and **sclerosis** → renal failure	The presentation is hematuria progressing to acute renal failure Rapid rise in serum BUN and creatinine **Goodpasture Syndrome** Circulating antibodies are avid against GBM and the pulmonary basal laminae Presentation is hematuria + hemoptysis	LM: focal capillary necrosis, crescentic masses within Bowman's space (parietal epithelium + macrophages + fibrin) IF: linear deposits of IgG EM: NO electron-dense deposits Serum: Anti-GMB Ab (this is diagnostic)	Immunosuppression Plasmapheresis Response occurs only if Tx is initiated early. Transplant after decline in Anti-GMB titre.
THIN BASEMENT MEMBRANE NEPHROPATHY BENIGN FAMILIAL HEMATURIA	**Inherited** AD pattern Prevalence ~ 10% ; typically asymptomatic	ECF volume is NML Renal function is typically NML Presentation is microhematuria wth a relatively benign course	LM: NML glomerular morphology EM: thinned GBM Dx: FH + clinical Hx + Bx	

ALPORT SYNDROME	Mutations involve the Collagen IV gene. Alport demonstrates X-linked inheritance	Microhematuria **progressing** to renal failure Extrarenal pathology: sensorineural hearing loss, cataracts, lens dislocation	EM: thickened, split, and laminated GBM Dx: FH + clinical Hx + Bx	
LUPUS NEPHRITIS	**Immune Complexes** ANA + DNA complexes are deposited throughout the glomerulus (subepithelial, subendothelial, mesangial) → activation of complement	Renal involvement of SLE ranges from microhematuria to neprhotic syndrome A common finding in advanced disease s hematuria + nephrotic syndrome There are six clinical stages of LN 1. Minimal Mesangial 2. Mesangial Proliferative 3. Focal Lupus Nephritis 4. Diffuse Lupus Nephritis 5. Membranous Changes 6. Advanced Sclerosing Nephritis Most patients present in Stage IV Note that renal disease occurs within the clinical spectrum of SLE: Malar rash, hematologic abnormalities (anemia, leucopenia), serositis, neurologic deficits, arthralgia, complement depletion, elevated ESR	LM: diffuse proliferation of all cell types, capillary thickening into **wire-loop lesions** (immune complex deposits), hypercelullar mesangium, increased mesangial matrix IF: IgG, IgA, IgM + complement (C3, C4, C1q) in granular pattern Full-House staining! EM: electron-dense deposits in mesangium, **subendothelium**, and GMB; tuboreticular inclusions (microtubule concretion formed in a background of IFN-γ) Serum: ANA, anti-dsDNA Ab	Prednisone Cyclophosphamide Mycophenolate Mofetil
MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS (MPGN)	**Immune Complexes** Idiopathic MPGN (Types I – III) Autoimmune Dx: SLE, RA, Sjogren's Chronic Infection: HepC with cryoglobulins, HepB, endocarditis, malaria, schistosomiasis **Resolving Thrombotic Microangiopathy** Convalescent HUS or TTP Antiphospholipid Antibody Syndrome **Dense Deposit Disease**	Hematuria + Nephrotic Syndrome (Similar to Lupus Nephritis) NH: gradual decline in renal function with progression to ESRD within 10 yrs in 50% of patients	LM: large and lobular glomeruli with increased cellularity, split capillary walls (tram-track appearance) due to interposed mesangium IF: C3 without immunoglobulin. GBM may be replaced with continuous electron-dense deposits Dense Deposit Disease (MPGN Type II) EM: hypercellular mesangium, mensangial interposition into the GBM, split GBM, subendothelial and	Steroids and immuosuppression NOT EFFECTIVE Recurs after kidney transplant

			mesangial deposits	
POSTSTREOPTOCOCCAL GLOMERULONEPHRITIS	**Infection with Nephritogenic Group A Streptococci** Typically seen only in developing countries Inflammation can occur via two mechanisms Bacterial nephritis-associated streptococcal plasmin receptor (NAP1r) → binds to glomerular subepithelium → local inflammation Circulating immune complexes (M protein:IgG or serine proteinase:IgG) → deposit into subepithelium → activation of complement	Edema Hematuria Hypertension Manifest approximately 10 d. following streptococcal pharyngitis	LM: enlarged glomerular tufts, endothelial proliferation, PMN infiltrates IF: granular deposits of IgG (complexed to Strep Ags) and C3 EM: semilunar densities located in the subepithelium Serum: ASO +ve, depleted C3 (involved in classical pathway of Ab binding)	Tx edema and HTN Prophylaxis with ABx
VASCULITIS PAUCI-IMMUNE CRESCENTIC GLOMERULONEPHRITIS Wegner's Granulomatosis Microscopic Polyangiitis Churg-Strauss Syndrome	**Renal Arteries** are affected in **Polyarteritis Nodosa** **Vasculitis of Small Vessels** Viral infection or cytokine release → expression of intracellular protein on neutrophil plasmalemma (Proteinase 3 or myeloperoxidase) → reaction with circulating ANCA → degranulation and tissue injury	These diseases are typically systemic (**except renal-specific MPA**) Thus, a Pulmonary-Renal syndrome is typically seen It is not mediated by immune complex deposition! NH: diseases are typically classified as RPGN, along with anti-GBM disease	**Wegener's Granulomatosis** LM: Focal necrosis of glomerular capillaries, cellular crescents in Bowman's space, renal and pulmonary granulomas Serum: cANCA against Proteinase 3 IF: diffuse granular signal (cANCA), fibrin, NO immunoglobulin or complement EM: no protein deposits **Microscopic Polyangiitis** LM: focal capillary necrosis, glomerular crescents IF: perinuclear enhancement of granular deposits within neutrophils (pANCA), fibrin, NO immunoglobulin or complement EM: no protein deposits	Prednisone Cyclophosphamide Mycophenolate Mofetil Treatment must be initiated early in the disease history

THROMBOTIC MICROANGIOPATHY	**Pediatric Hemolytic Uremia Syndrome (HUS)** Intravasation of EHEC or Shigella toxin → renal intravascular coagulation → renal failure **Adult HUS** (without GI illness) May be secondary to BLEO, cisplatin, and cyclosporine Antiphospholipid Antibody Syndrome Scleroderma Complication of pregnancy **Familial HUS** **Thrombotic Thrombocytopenic Purpura (TTP)** Defective vWF cleaving protease → oligomerization of vWF → hypercoagulatability → platelet activation → microthrombi May also be caused by a cryptic circulating immunoglobulin → inhibit vWF protease	Endovascular injury → loss of thromboresistance → platelet activation → fibrin deposition → formation of microthrombi The clinical presentation is Hematuria Mircoangiopathic Hemolytic Anemia Intravascular RBC fragmentation seen on peripheral blood smear Thrombocytopenia (diathesis) Rapidly progressive renal failure (uremia)	LM: extensive deposition of fibrin in glomerular capillaries and larger renal vessels, endothelial swelling and proliferation, fibrin thrombi IF: fibrin	**TTP:** TX with plasmaphoresis + antiplatelet therapy