#### General

- All types of glomerulopathies are below, some cause more acute dz others more chronic dz, refer to AKI and CKD notes for a list of the common ones causing AKI and CKD
- Description based on LM/EM/IF
  - Size, Symmetry, Cellularity, Capillary Loop Morphology, Mesangium, Hilum, Origin of PCT
    - Diffuse (affecting all glomeruli) vs. Focal (affecting some but not all glomeruli)
      - Global (affecting entire glomerulus) vs. Segmental (affecting part of the glomerulus)
- Types of Disease 0
  - Isolated Hematuria (Thin BM Dz, Alport, IgA, SCD, Analgesics) to Frank Nephritic Syndromes (Glomerulonephritis-GN)
    - Mechanism: (1) Ab bind to structural component in glomerulus or to material not intrinsic to glomerulus but happens to be there or (2) Ab-Ag complex deposits in glomerulus or (3) ANCA dz or (4) genetic defect  $\rightarrow$  (1) inflammatory injury of endothelium w/ inflammatory infiltrate and (2) mesangial proliferation  $\rightarrow$  Disruption of Size Filtration  $\rightarrow$  basically you are bleeding into Bowman's space and there are inflammatory cells which necrotize the glomerulus and cause crescent formation  $\rightarrow$  pyuria with WBC casts, hematuria with the formation of RBC casts and dysmorphic RBCs, subnephrotic (<3.5mg/d) proteinuria, HTN, edema (diuretics/salt restriction), oliguria and azotemia due to the decrease in GFR
    - S/S ranges from progressive (to ESRD) to resolving, acute to chronic, asymptomatic hematuria to A/RPGN
    - Ranges from focal to diffuse infiltrate/proliferation (mild spilling to crescentic formation)
    - <50% mesangial proliferation likely asymptomatic vs >50% symptomatic
    - Bx is key!!!

#### 0 Isolated Proteinuria (refer) to Frank Nephrotic Syndrome

0

- Primary: MCD, MG, FSGS, MemPGN vs Secondary: Nodular GS 2/2 DM and Diffuse GS 2/2 Paraproteinemia Non inflammatory Injury to GBM and/or Epithelium (Podocyte) → Disruption of Size/Anionic Selection
  - Filtration → Severe Large (>150kd) Anionic Proteinuria (>3.5g/1.73m<sup>2</sup>/day) →
    - Loss of Albumin (<3.5mg/dL)
      - Decrease in Oncotic P w/ Secondary Na retention  $\rightarrow$  Generalized Pitting Edema (main reason why pts present to PCP) w/ Normal BP, Ascites, Effusions, Frothy urine
      - ? but some say Compensatory Albumin Production by Hepatocytes -> Impaired Lipid Homeostasis by Hepatocytes  $\rightarrow$  Hyperlipidemia (increased LDL & TGL but also IDL, VLDL,
      - Lp(a), etc), lipiduria, Free Fat Droplets, Fatty Casts, Oval Fat Bodies, Atherosclerotic dz!!!, NB there is resorption of fat by PCT cells seen as red droplets on Trichrome stain

Loss of AC esp antithrombin III (NB there is also loss of fibrinolytic factors, increased platelet aggregation, increased fibrinogen, etc) → DVTs but uniquely Renal Vein Thrombosis which is 90% of time asymptomatic but 10% of time can cause AKI and PEs, seen esp in pts w/ MGN, CAD (but could be all 2/2 hyperlipidemia above)

- Loss of Ab/Complement  $\rightarrow$  Infections esp bacterial (pneumococcal peritonitis) and viral (herpes)
  - Loss of VitD  $\rightarrow$  hypocalcemia (Tx give a MVI)
  - Loss of thyroid  $\rightarrow$  hypothyroidism
  - Loss of glucocorticoid  $\rightarrow$  hypoadrenalism

# Loss of epo and transferrrin $\rightarrow$ IDA Loss of Other $\rightarrow$ Fatigue, Ab pain, D

Tx: ACE-I/ARB (goal BP <125/75, NB it takes 1mo for effect on proteinuria while it takes 1d for effect on BP suggesting the RAS system on proteinuria is not due to hemodynamic mechanisms, even in the absence of BP changes RAS inhibition causes less proteinuria), protein supplementation fails to replace lost protein and now there is evidence that protein restriction is helpful in the end very controversial and most nephrologist recommend normal protein intake, there is some evidence that NSAIDs decrease proteinuria but b/c of SEs it is not recommended, sodium restriction, diuretics for edema, treat hyperlipidemia w/ Statins/Niacin, AC prophylaxis is controversial but consider in pts w/ MGN and albumin <20g/L, refer to specific type for immunotherapy, treat secondary causes

#### Type I (smooth IF, nl complement) Ig against GBM

#### Anti-GBM Dz and Goodpasture's Disease

- Epidemiology: Anti-GBM (older women) vs Goodpasture's (young men)
- Mechanism: IgG against alpha-3 chain of Type IV collagen in renal glomerular BM ± pulmonary alveolar BM (then 0 called Goodpasture's)
- 0 Etiology: autoimmune disorder
- S/S: Constitutional Symptoms (F, myalgia)  $\rightarrow$  perihilar alveolar infiltrates w/ alveolar hemorrhage ranging from 0 chronic IDA w/ hemosiderin laden macrophages in sputum to overt hemoptysis  $\rightarrow$  RPGN (ranges from severe to clinically silent), NB Types of Pulmonary-Renal Syndrome: Autoimmune (Goodpasture's, SLE), ANCA Small Vessel Vasculitis (Wegener's, MPA, CSS), Infection (Legionnaires)
- 0 Dx
- LM: crescentic & proliferative changes
- EM:

- IF: diffuse linear IgG lining GBM
- Tx: steroids, plasma exchange, cyclophosphamide, Tx for 3mo and then taper over 3mo, follow IgG titers for remission/relapse (which is rare)
- Prognosis: highly variable (hrs to yrs) but is usually fatal if untreated

#### Type II (granular IF, variable complement) Ig+Ag deposition in GBM

WHO Classes of		%	S/S	Prognosis	Тх
Lupus Nephritis (LN)					
I	Mild MesPGN	10	Normal	+	Observe
II	Mod MesPGN	15	+	++	Steroids
111	Focal MemPGN (<50% of glomueruli)	15	++	+++	Steroids + Cytotoxic Drugs
IV	Diffuse MemPGN (>50% of glomeruli)	45	+++	++++	Steroids + Cytotoxic Drugs
V	MGN	15	++	++	Steroids
VI	Advanced Sclerosing aka ESRD	5	++++	NA	RRT
Different types depending on where ICs deposit					
Ranges from slowly progressive asymptomatic proteinuria/hematuria to acute					
<ul> <li>symptomatic nephrotic/nephritic syndrome</li> <li>Low complement during flares</li> </ul>					
•	infiltration w/ tubular	(Ig BIVI damag	deposition, se and inter	stitial fibrosis	and Necrotizing Vasculitis

(acellular necrosis of vessel walls along w/ proteinaceous occlusive thrombi

presenting as rapidly accelerating HTN and ARF)

• Post-Strept GN (PSGN)

Epidemiology: (M>F, 2-10yo), Group A Beta Hemolytic Streptococcus Type 12 & 49 (Nephritogenic Strains), NB other bacteria (Mycoplasma, Strept pneumonia, Neisseria, etc) can cause a GN similar to post-strept

- Etiology:
- Mechanism: Stept exotoxins have an affinity for glomerular endothelium which attract Ab (IgG) and subsequently activate complement cascade
- S/S: sudden Sx 1-3wks following infection of skin (10-21d) or pharynx (7-10d) depending on geographic location of pt, usually presents as a RPGN
- o Dx
- LM: enlarged glomeruli w/ mesangial and endothelial proliferation
- EM: subepithelial electron dense humps and foot process fusion
- IF: granular pattern 2/2 IC (+C3 and IgG) subendothelial deposition
- Labs: decreased C3 nl C4, increased ASO titer (pharyngitis), increased anti-DNAase B and antihyaluronidase (skin dz)
- Tx/Prognosis: despite RPGN most pts spontaneously recover (80% completely vs 20% some degree of CKD) from clinical symptoms (wks) and hematuria/proteinuria (mos) w/o harm therefore no treatment just manage HTN and Tx symptoms (bed rest, salt restriction, antihypertensives, loop diuretics) NB steroids and other immunomodulators are not indicated except if Bx is severe and the older the pt b/c of higher r/o permanent renal damage

# • Focal Segmental GlomeruloSclerosis (FSGS)

- Epidemiology: Black or Hispanic
- Mechanism: unknown but thought to be 2/2 presence of a permeability factor
- S/S: mixed nephrotic > nephritic syndrome, a more indolent disease developing over time
- Etiology
  - 1° Idiopathic
    - Prior Renal Dz (progression from MCD, MesPGN, etc)
    - Familial (nephrin, podocin, actinin-4, CDAP, TRPc6, LCAT mutations aka proteins that make up podocytes)
    - Cancer (solid carcinomas and liquid tumors)
    - Oligonephronia aka low number of nephrons resulting in sustained hyperfiltration (partial nephrectomy, renal agenesis/dysplasia, variable causes of renal necrosis, variable causes of renal scarring, chronic pyelo, chronic vesico-uretic reflux, Asl-Upmark Syndrome, Radiation Nephritis)
    - Infections (HIV, HepB, Parvovirus)
    - Medicines (Analgesics, pamidronate, IFN, cyclosporine A)
    - Toxins (Heroin)

- Other (Obesity, Post Renal Transplant, SCD, Polycythemia, Autonomic Insufficiency, Sarcoid)
- Dx: Bx (changes are focal (not diffuse aka not all glomeruli) and segmental (not global aka not entire glomerulus) thus false negatives are common), focal tubule-interstitial fibrosis is also often seen
  - LM: mild increase in mesangial cell #, subendothelial/mesangial hyaline deposits (sclerosis)
  - EM: effacement, epithelial cell detachment from GBM (denuding), increase in mesangial matrix
  - IF: IgM/C3 segmental glanular
  - Pathologic Variants which have prognostic and treatment relevance
    - Typical Perihilar FSGS (hereditary and oligonephronia causes)
      - Collapsing Variant FSGS (usually young black pts, worse prognosis, harder to Tx but HAART/steroids help, seen in AA pts, drug induced, and viral induced esp HIV called HIVAN (HIV-associated nephropathy) along w/ tubular-interstitial nephritis w/ lymphocytes/plasma cells and markedly dilated tubules filled w/ numerous tubule-reticular inclusion microcysts called "interferon fingerprints" b/c due to Tx with IFN) called HIVAN when Collapsing Variant FSGS + Microcystic Tubular Disease, NB other GP occur in HIV including MemPGN
      - FSGS w/ Glomurular Tip Lesion (usually old white pts, hypertrophy and vacuolated cells at origin of PCT, best prognosis, good response to Tx)
- Tx/Prognosis: 50% partial/complete remission after 5months of Tx w/ prednisone PO 60mg QD x3mo, relapse is common and when it occurs try cytotoxic agents, steroid resistance is associated w/ 80% progression to ESRD in 6yrs and requires cytotoxic agents, 35% recurrence in renal transplant pts

### Membranous GN (MGN)

- Epidemiology: White, >65yo, 5% peds/80% adults (most common adult cause of nephrotic syndrome), Old adults (rarely seen in children)
- Mechanism: damage to size filtration (opposite of MCD)
- Etiology:
  - Idiopathic (most common in children)
    - Autoimmune (1° Class V Lupus Nephritis, RA, etc)
    - Infection (1° HepB, HepC, Syphilis, Schistosomiasis, Filiariasis, Malaria, Hydatid Infections, Leprosy)
    - Medications (1° NSAIDs, Gold, Penicillamine, Captopril, Hg, Nifedipine)
    - Cancer (1° solid carcinomas, liquid tumors)
    - Other (de novo post transplant, SCD, Kimura Dz, T2DM)
- S/S: nephrotic syndrome
- o Dx:
  - LM: thickened capillary wall (which is actually 2/2 GBM deposition), tubulo-interstitial atrophy and fibrosis
    - EM: Stage I (small subepithelial electron dense deposits w/ otherwise nl GBM), Stage II (deposits become larger and GBM thickens forming spikes b/t deposits), Stage III (GBM spikes now engulf deposits making them smaller and appear w/in GBM), Stage IV (deposits begin to fade leaving lucent gaps in GBM which now appears very thick and irregular)
  - IF: IgG/C3 diffuse granular pattern
- Tx/Prognosis: prognosis (1/3 spontaneous remission, 1/3 persistent disease, 1/3 progressive disease to ESRD)
  - dependent on degree of proteinuria, older males worse than younger females, 1/3 spontaneous complete/partial remissions after 4yrs vs 1/3 ongoing Sx vs 1/3 ESRD in 20yrs, Tx w/ steroids has NO effect on remissions or progression to ESRD BUT the addition of alkylating agents to steroids does therefore must give both x6-12mo, it is controversial when to start Tx but it is generally based on (1) symptoms (2) prognostic factors (Poor: >50yo, male, HTN, reduced GFR, proteinuria >10g/d, interstitial fibrosis) and (3) course of dz, 20% relapse, similar relapse Tx to MCD, as noted above these pts are at high risk for RVT therefore consider prophylactic AC

#### • Membrano-Proliferative GN (MemPGN)

- Epidemiology: older children and young adults, decreasing in developed countries but increasing in undeveloped countries suggesting a strong environmental influence
- o Mechanism
  - Type I mesangial proliferation, expansion of mesangial matrix, diffuse enlargement of glomerular tufts, "tram-tracking" appearance 2/2 deposition of mesangial matrix b/t GBM and endothelium, C3 deposition in mesanguim
  - Type II deposits create a ribbon-like thickening of capillary wall, on EM these deposits are in GBM, +C3 in mesangium and capillary loops, no Ig
  - Type III (sub-epithelial and sub-endothelial electron dense IgG deposits aka Burkholder Variant OR fragmented GBM aka Ander-Strife Variant)
- o Etiology
  - Idiopathic
    - Infection (1° HepC induced cryoglobulinemia, HepB, CMV, EBV, SBE, AV Shunt infection)
    - Autoimmune (1° Class III/IV Lupus Nephritis, Sjogren's)
    - Other (SCD, Partial Lipodystrophy, Renal Transplant, Complement Deficiency)
- S/S: variable from chronic asymptomatic proteinuria>hematuria to acute frank Nephrotic>Nephritic syndrome (nephritic > nephrotic syndrome)

- Dx 0
- LM: mesangial proliferation, increased mesangial matrix, capillary wall thickening, glomeruli appear "duplicated" or "split"???
- EM: thickened GBM ("tram track appearance"), ICs deposits in mesangial and subendothelial region
- IF: C3 diffuse coarse deposits (low C3)
- Tx/Prognosis: steroids helpful in children but not in adults, if HCV induced consider antivirals, spontaneous 0 remission rare, usually a chronic progressive course, prognosis depends on the degree of proteinuria and decrease in GFR, 50% develop ESRD, NB Types I and III often recur after renal transplant

## **Mesangial Proliferative GN (MesPGN)**

- Epidemiology: rare but seen in young adults 0
- Etiology (several different types, overall uncommon except Berger's) 0
  - 1° Class I/II Lupus Nephritis
- S/S: mixed nephrotic and nephritic syndrome 0
- Dx 0

0

- LM: increase in mesangial cell number
  - EM: focal/diffuse and global electron densities in the mesangium
- IF: various types of deposition C3 often
- Tx: Steroid Tx, Highly variable course with nephrotic>nephritic more likely to develop ESRD
- IgA Nephropathy (Berger's Disease) 0
  - Epidemiology: most common cause of GN, Asian/Caucasians/Hispanics>AA, males, predominance with mean age of 20yo
  - . Mechanism: URTI/GI (immediate like 3-5d not 1-3wk latency as seen in PSGN)  $\rightarrow$  increased mucosal IgA but it is abnormally glycosylated (sporadic or familial) so it is not removed by reticulo endothelial system  $\rightarrow$  IC deposition in mesangium  $\rightarrow$  inflammatory response
  - S/S: asymptomatic microscopic hematuria (35%) to episodic gross hematuria (45% most common) w/ sometimes flank pain and constitutional Sx resulting in extensive work-up for stones, infections, etc to chronic GN (10%) to RPGN (5%), also associated w/ cirrhosis, ankylosing spondylitis, gluten enteropathy, Henoch-Schonlein-Purpura
    - Dx (over time since it is a relapsing disease there can be scar tissue also)
      - LM: mesangial proliferation and mesangial matrix expansion
      - EM: electron dense deposits in mesangial matrix
      - IF: diffuse granular mesangial IgA
      - Labs: increased serum/skin IgA but normal complement C3

Tx/Prognosis: if mild then just RAS inhibition and supportive care but if S/S worsen then consider steroids and fish oil and if pt acutely worsens then add plasma exchange and other immunomodulators, consider tonsillectomy if recurrent bouts as URTI are a cause for flares, 1/3 resolve on own w/o complications, 1/3 maintain a relatively benign disease, 1/3 progress to ESRD after 20yrs of presentation, prognosis all depends on degree of proteinuria and degree of renal dysfunction and presence of crescents and normal BP, 50% recurrence in renal transplant pts but usually does not lead to loss of graft

Type III (negative IF hence "Pauci-Immune", nl complement)

Pauci Immune (ANCA) Small Vessel Vasculitis (refer) Xander Mantas MD PA

- Nodular Glomerulosclerosis 2/2 DM
  - Etiology: Diabetes only after 10yrs of DM does dz begin to occur w/ microalbuminuria which then progresses over 0 another 10yrs to macroalbuminuria which then progresses over another 10yrs to nephrotic syndrome / ESRD (initially there is hyper then eu then hypofiltration)
  - S/S: asymptomatic proteinuria to nephrotic syndrome 0
  - Dx 0
- LM: nodular, glomerular enlargement, BM thickening, mesangial expansion, foot process fusion, glomerular scelerosis, tubular atrophy, interstitial fibrosis, PAS+ Kimmelstiel Wilson Lesions (nodules that are only seen in 25% of pts but is the most specific finding)
- EM:
- IF:
- Diffuse Glomerulosclerosis 2/2 ParaProtein
  - Etiology: Paraproteinemias (MM, Amyloidosis, Cryo, etc) 0
  - S/S: nephrotic > nephritic syndrome 0
  - Dx: 0
    - IM:
      - EM: non-branching, non periodtic, extracellular microfibrils/tubules in glomeruli
    - IF:
- Minimal Change Disease (MCD)
  - Epidemiology: 80% peds (most common cause of nephrotic syndrome in children) vs 40% adults 0

- Mechanism: Dysfunctional T-cells release cytokines that injure glomerular visceral epithelial cells (podocytes) resulting in fusion of foot processes ("effacement") and inability of podocytes to make polyanions for GBM BUT interestingly size filtration is not affected ONLY charge filtration b/c no polyanions
- Etiology
  - Idiopathic (likely viral URTI)
  - Cancer (1° liquid cancers esp HL, some solid tumors esp pancreatic)
  - Meds (1° NSAID, Li, IFN, Gold, Amp, Rifampin)
  - Allergic (bee stings, atopic dermatitis, food allergens, vaccinations)
  - Infection (HIV, Mono)
  - Other (T1DM, SLE, IgA Nepropathy)
- S/S: nephrotic syndrome, rarely do pts develop CKD, typically the onset of edema is very rapid, 20% can develop nephritic syndrome
- Dx (NB given the fact that MCD is the most common cause of nephrotic syndrome in children Bx is not indicated for diagnosis rather most pediatricians Dx based on response to Tx. This is not the case in adults where Bx is needed. Some say it is a Dx of exclusion)
  - LM: normal hence "MCD" but some call it "hypernormal" b/c glomeruli sometime appear swollen
  - IFM: normal
  - EM: diffuse effacement of visceral epithelial foot processes
- Tx: address underlying cause, 40% remit spontaneously hence Tx is not necessarily mandatory however given the risk of nephrotic syndrome complications including infections and thrombosis Tx is generally always done w/ Prednisone PO 1mg/kg/d x4-6wks or until remission then taper over x6-12wks and follow urine protein to see if relapse, 10% become dependent on steroids or are resistant and thus consider cytotoxic agents or an error in diagnosis as MCD can be confused w/ FSGS, Supportive Therapy for Nephrotic Syndrome (refer) sodium restriction but NOT fluid restriction or lasix b/c pts are so edematous and thus given lots of lasix and placed on fluid restriction that they actually develop pre-renal AKI, If pt is refractory to Tx then consider FSGS as a Dx missed on Bx
- Prognosis: <5% develop ESRD, 90% (adults) 95% (children) achieve remission, early (children) late (adults), 60% will relapse during tapering or up to years later, often intercurrent illness or allergies sets off relapse, pts on average have about 3 relapses in 1 year before complete remission, b/c of the r/o steroid toxicity esp in growing children or b/c refractory to steroids other agents are used including alkylating agents, etc</li>
- Alport's Syndrome aka Hereditary Nephritis

## Epidemiology: rare

- Mechanism: X-Linked (80%), AD (10%) or AR (10%) mutation of COL4A5 gene (Xq22, 2q35-37) that codes for alpha-5 chain of Type IV collagen → collagen chains are unable to associate together thus forming a BM that is thin/thick and splits, NB Thin Basement Membrane Disease aka Benign Familial Hematuria (AR mutation of alpha-3/4 chains of Type IV collagen, unlike Alport's Syndrome this dz does not result in RF rather pts only have micro/macroscopic hematuria)
- Etiology: genetic disorder
- S/S: Renal (progressive nephritic syndrome w/ ESRD at 30yo), Ear (high frequency sensorineural hearing impairment), Eye (lens dislocation)
- o Dx
  - LM:
  - EM: "basket weave" appearance of BM
  - pyrif absent alpha-5 stain Alexander Mantas MD PA
- Tx: no TX (pts have undergo transplantation actually develop Goodpasture's Syndrome b/c the body recognizes the now normal Type IV collagen)
- Prognosis: