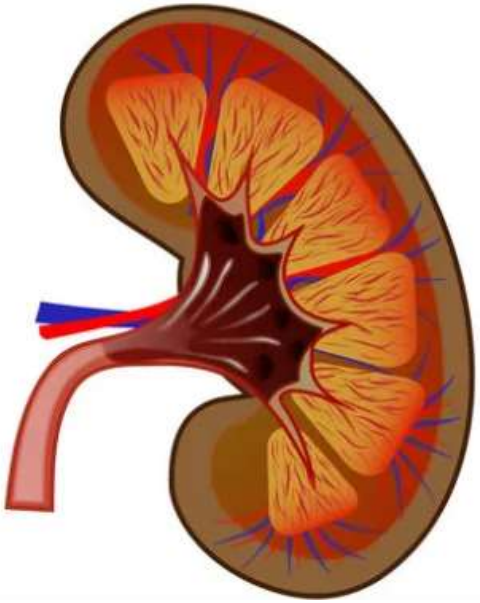
GLOMERULONEPHRITIS (GN)

MORE THAN MEETS THE EYE



DISCLOSURES

- Non-Declaration Statement: I have no relevant relationships with ineligible companies to disclose within the past 24 months. (Note: Ineligible companies are defined as those whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.)

OBJECTIVES

- Define and describe the major subtypes of GN
- Highlight the common clinical presentation of GN
- Using the KDIGO guidelines, review treatment options for GN discussing pros and cons of treatment modalities

WHAT IS GLOMERULONEPHRITIS (GN)?

Injury to the glomerulus

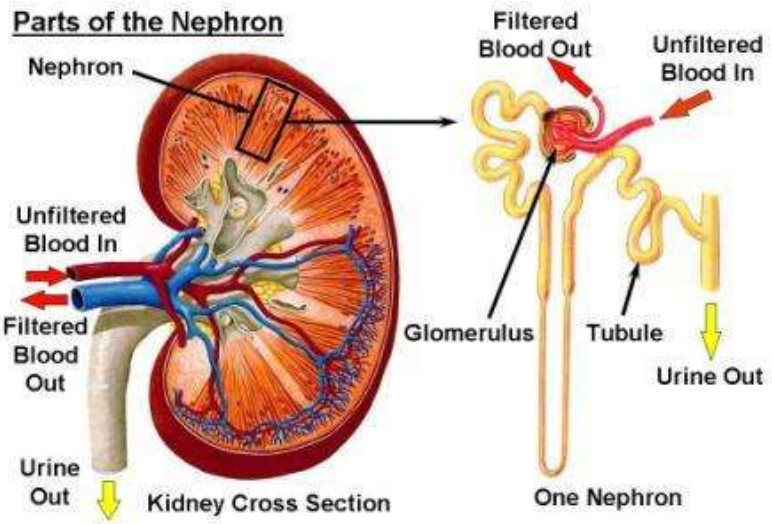
Pathological mechanisms may include:

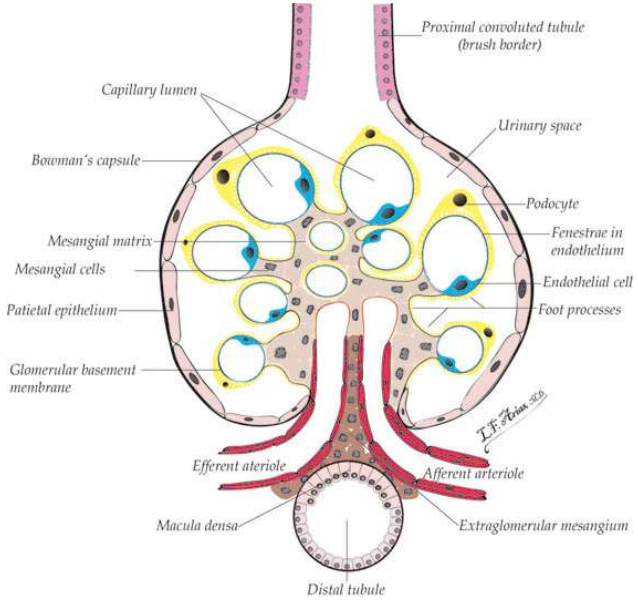
- **Immune complexes** directed at various glomerular antigens or deposited in the glomerulus from circulation
- **Complement deposition**
- **Inflammatory cell deposition**
- **Necrosis** and eventual **sclerosis** (scarring)

Glomerular injury can be

- Primary disease (IE: FSGS)
- Systemic process (IE: Lupus)

3rd most common cause of ESRD





ANATOMY REVIEW

TYPES OF GLOMERULONEPHRITIS

Primary (Problem is IN the kidney)

- Minimal Change Disease (MCD)
- Focal Segmental Glomerulosclerosis (FSGS)
- Membranous Nephropathy (MN)
- Anti-glomerular basement membrane (anti-GBM) GN
- IgA Nephropathy (IgAN)
- Membranoproliferative Glomerulonephritis (MPGN)*
- Post infectious GN

*can be considered primary or secondary

Secondary (Systemic)

- Lupus Nephritis
- Renal Vasculitis: Pauci-immune focal and segmental necrotizing GN
- Membranoproliferative Glomerulonephritis (MPGN)*
- HIVAN
- Hepatitis C
- Amyloidosis
- Multiple Myeloma (MGUS)

TYPES OF GLOMERULONEPHRITIS

Prima

Minimal Cha

Focal Segme

Membranou

Anti-glomer

IgA Nephrop

• Asian but see

Membranop

zing GN

Hepatitis C

*can be considered primary or secondary

This is **very exciting** to nephrology

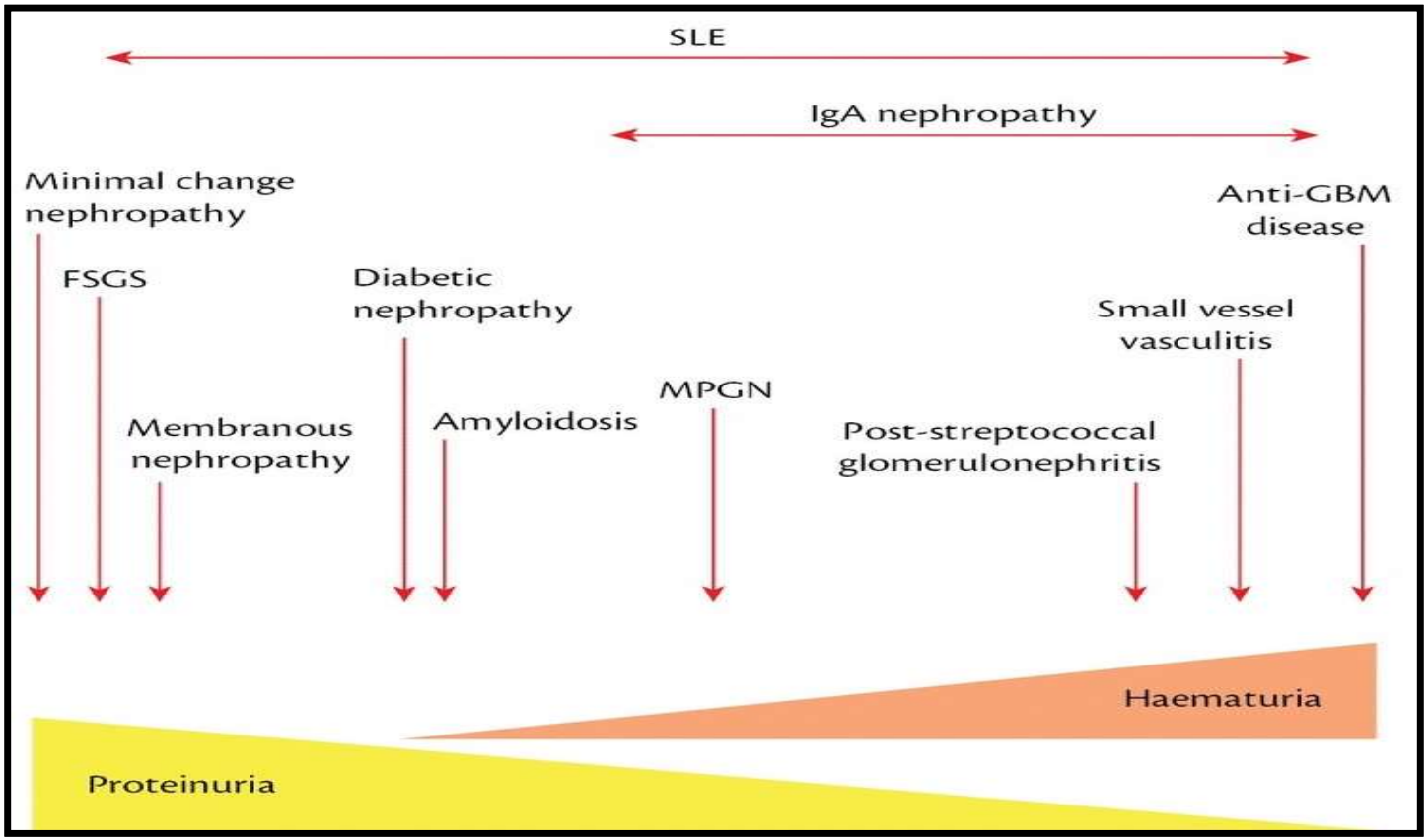
The non nephrologist needs to know:

- Causes 25-30% of ESRD
- Presentation Scenario
- Age at presentation

This is often a disease of the young….

(I consider anyone under 40 to be young)

THE SPECTRUM OF GLOMERULAR DISEASE



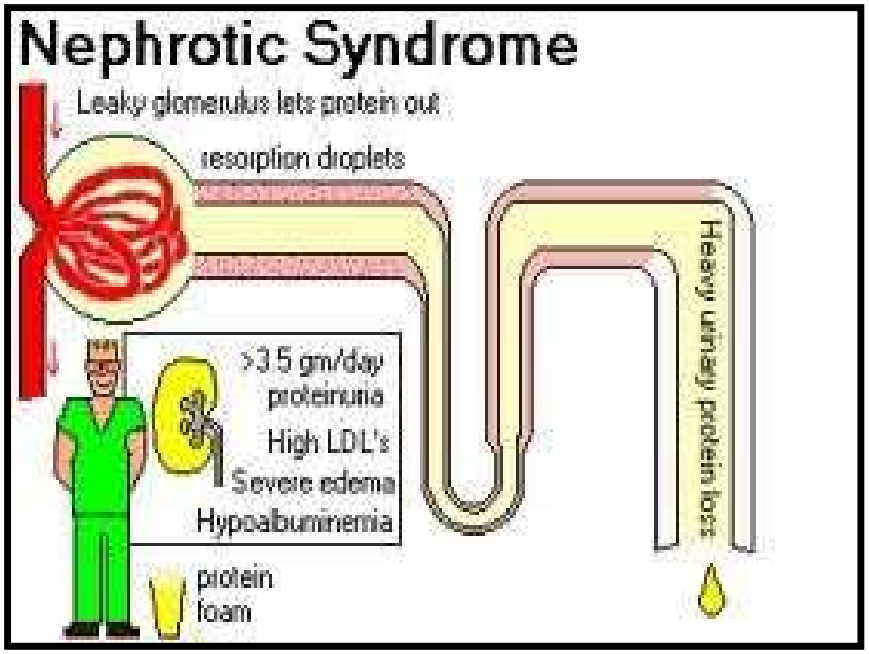
COMMON PATIENT PRESENTATIONS

Acute Nephrotic Presentation

- Proteinuria >~3.5 grams/day
- Peripheral edema
- Hypoalbuminemia
- Hyperlipidemia

Etiology of Nephrotic Syndrome

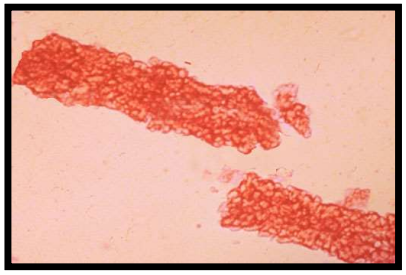
•Damage to the glomerular capillary wall → increased permeability to proteins



COMMON PATIENT PRESENTATIONS

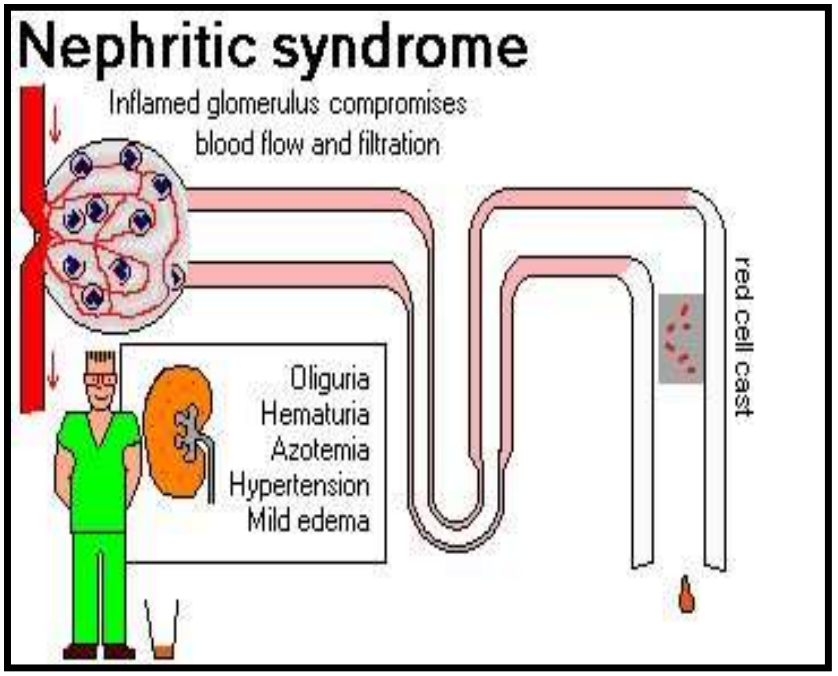
Acute Nephritic presentation

- Proteinuria
- Oliguria
- Hypertension
- Hematuria (gross or microscopic)
  - Cola-colored urine
- RBC Casts

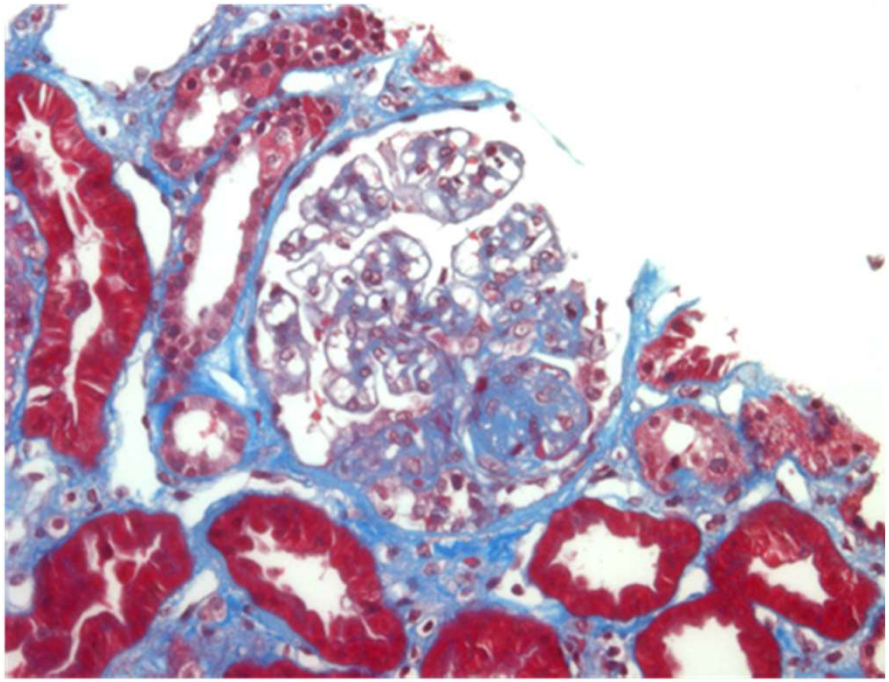


Etiology of Nephritic Syndrome

- Inflammation of the glomerulus
  - Damage to capillary wall
  - Basement membrane



GN DIAGNOSIS



Glomerulus with prominent segmental sclerosis responsible for proteinuria

(20X magnification, Masson's Trichrome Stain)

Primary GN:

- Requires histopathological diagnosis with **Kidney Biopsy**

Secondary GN:

- Serum studies can strongly support the diagnosis
- **Kidney Biopsy** often done to confirm diagnosis or refine prognosis

TREATMENT AFTER BIOPSY CONFIRMS DIAGNOSIS

Medication	Advantages	Side Effects
Corticosteroids	**MOST COMMON** Potent in inducing and maintaining remission in a variety of GNs	Psychiatric disturbances, diabetes, cataracts, fractures
CNIs Tacrolimus Cyclosporin A	Most nephrologists comfortable with medication since we use it in transplant	Long-term nephrotoxicity, HTN, may reduce proteinuria by vasoconstriction rather than directly addressing underlying disease
Cyclophosphamide		Infertility, bone marrow toxicity, secondary malignancies nausea, hemorrhagic cystitis
Mycophenolate Mofetil (MMF, Cellcept)	Steroid-sparing agent with relatively well-tolerated side effect profile	Diarrhea, cytopenias, not safe in pg
Azathioprine (AZA, Imuran)	Relatively safe in pregnancy compared with MMF	Cytopenias, hepatotoxicity, secondary malignancies, GI disturbance
Rituximab	6-month dosing reduces need for patient compliance	Infusion reaction, cytopenias, GI disturbance, immunosuppression lasting 6 months after single dose

Hyperlipidemia	Statins If resolving nephrotic syndrome, no statins needed
Immunosuppressed state	Pneumocystis prophylaxis for patients on high dose steroids TB, HBV testing prior to immunosuppressive treatment No live vaccines!
Hypercoagulable state	Anticoagulation not typically used Exception: Membranous patients with serum albumin <2.5g/dL and additional risk factors
Diet	Low Na for BP control, edema
HTN	ACEi/ARB for both HTN & proteinuria Diuretics (loop +/- amiloride) for edema
Special considerations on high-dose steroids:	Pneumocystis prophylaxis Warn of effects on glucose control, need to adjust meds/insulin if diabetic Fracture risk: ensure adequate Ca++ & Vit D Consider GI prophylaxis

WHEN TO TREAT VS WHEN TO MONITOR…

Treatment does not always guarantee cure and multiple courses often needed

Persistent, nephrotic range proteinuria or rapidly progressive GN will almost certainly result in ESRD and warrants ***an attempt*** at medical therapy

Sometimes, there are other diseases….

- Recurrent/persistent proteinuria does not always reflect relapse of the primary GN

If the risks/side effects outweigh benefit:

- Advanced CKD/ESRD (SCr>3.5mg/dL) and/or small, atrophic kidneys on ultrasound
- Relatively stable kidney function with conservative measures
- Short life expectancy (another DX)

MEMBRANOUS NEPHROPATHY

Presentation:

- Usually nephrotic range proteinuria
- Can be due to autoimmune, infectious, malignant
- High risk for PE
- More common in Caucasians

Pathology:

- Diffuse glomerular basement membrane (GBM) thickening
- Sub-epithelial immune complex deposits

Treatment:

- *Rule of thirds*
  - 1/3 spontaneously remit
  - 1/3 with persistent proteinuria
  - 1/3 progress to ESRD
- Observation (6 months) if:
  - Stable proteinuria <4g/day
  - Preserved renal function

MINIMAL CHANGE DISEASE

Presentation:	Pathology:	Treatment:
• Usually nephrotic range proteinuria • Patient feels fine but + edema • More common in kids (edema anywhere, scrotal) • HTN, hyperlipidemia	• Normal appearance by light microscopy • Diffuse foot process effacement	• Corticosteroids (high dose) X 4 weeks with slow taper • Most respond within 8 weeks • Frequent relapse • Treat hyperlipidemia, HTN

FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS)

Alonzo Mourning

Dayna Stephens

Presentation:

- No symptoms
- More common in AA males
- High SCr
- ±HTN

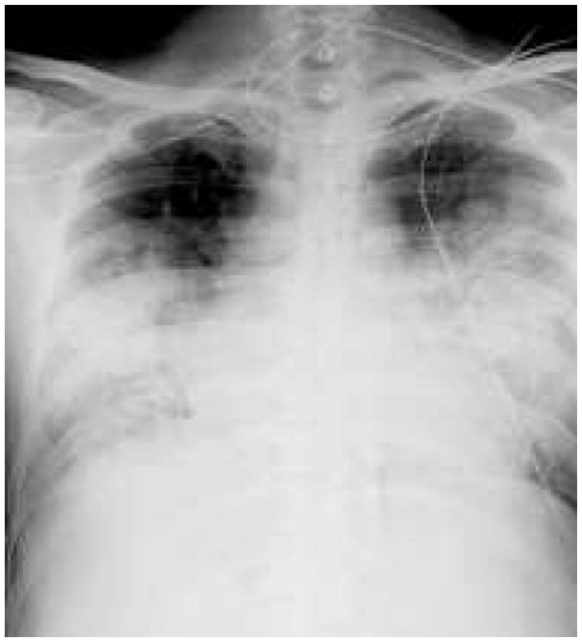
Pathology:

- Focal (% of kidney), Segmental (portion of glomeruli) Glomerular (in the glomerulus) Sclerosis (dead area)
- Biopsy can miss the 'bad area' and looks like MCD on biopsy! (*'missed FSGS'*)

Treatment:

- Blood pressure control with ACEi/ARB
- Steroids typically only employed for primary FSGS with active nephrotic syndrome
- Cyclosporine or CNIs (calcineurin inhibitors) in steroid resistant cases
- Transplant

ANTI-GLOMERULAR BASEMENT MEMBRANE (ANTI-GBM)



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Presentation:

- Usually lungs/kidney hemorrhage
- Occurs in teenage years and >50 y/o
- Previously referred to as *Goodpasture Syndrome*
- Rapidly progressive, often fatal

Pathology:

- Antibodies against the glomerular basement membrane
- Often associated with crescent formation

Treatment:

- Cyclophosphamide + corticosteroids + plasmapheresis
- Transplant deferred until anti-GBM antibodies undetectable x 6 months
- Due to high fatality rate, start RX while awaiting diagnosis!

LUPUS NEPHRITIS

Nick Cannon with Sydney the Kidney

Presentation:

- SLE more common in female AA population
- Butterfly rash
  - Can be difficult to see with darker skin tones
- Treat underlying SLE regardless of renal manifestations
- Should be co-managed with nephrology
- Typical presentation - proteinuria within 3y of diagnosis
- Bad prognostic factor - abnormal SCr in early disease

Pathology:

- 6 different subclasses based on underlying pathology
- Disease severity ranges from Class I (no light microscopy abnormalities) to Class VI (sclerosis of >90% of the glomeruli)

Treatment:

- **DEPENDENT ON BIOPSY CLASSIFICATIONS!!**
- Class I, II, VI:
  - conservative treatment
- Class III, IV, V:
  - immunosuppressive induction
  - maintenance

POST-INFECTIOUS GN

Presentation:	Pathology:	Treatment:
• Typically microscopic hematuria but it can be significant • History of infectious disease • *More common in kids*	• Often not done, with DX made b history • Diffuse, proliferative lesions or 'humps' with sub-endothelial immune deposit	• Treat underlying infection • Ex: Post-streptococcal GN with penicillin • Supportive care

IGA NEPHROPATHY

Presentation:

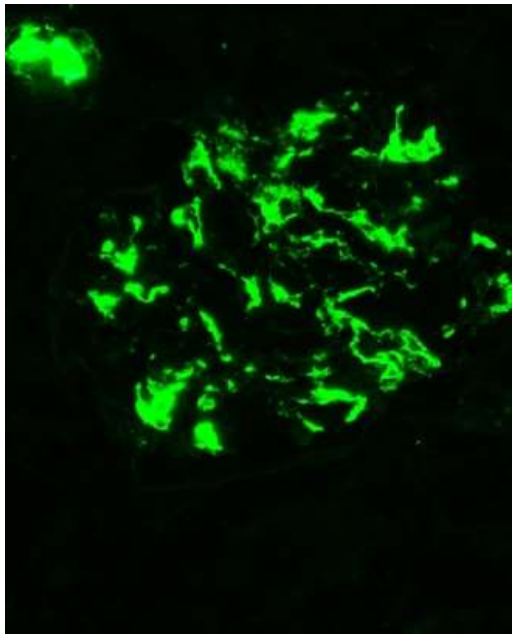
- Classically intermittent hematuria but it can be a significant amount
- More common in the Asian population but this may be a sampling bias

Pathology:

- IgA deposits in the mesagium
- Florescence on electron microscopy

Treatment:

- Risk factors for progressive disease warranting consideration of active treatment:
  - proteinuria >1g/day
  - uncontrolled HTN
  - increased serum creatinine
- Steroids can be effective, but risks usually outweigh benefits
- BP and proteinuria control with ACEi/ARB



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MEMBRANOPROLIFERATIVE

Presentation:

- Onset is insidious
- Approximately 80% of patients describe edema
- Patients may present with nonspecific complaints:
  - anorexia
  - malaise
  - fatigue
- Some patients may present with asymptomatic proteinuria

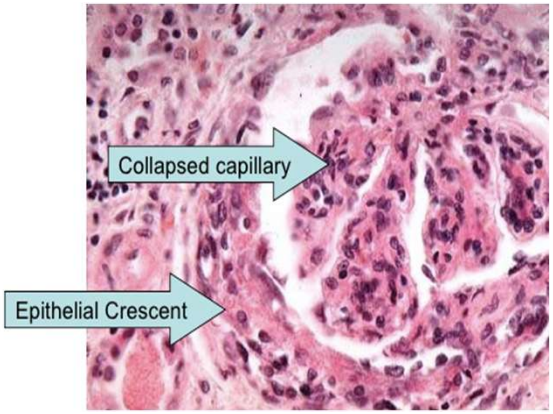
Pathology:

- Expert nephropathologist evaluation to ID specific subtype of proliferative lesions
- Location and appearance of deposits can vary depending on the cause
- Deposits can be composed of complement alone and/or immunoglobulin

Treatment:

- Limited data
- Observation reasonable in non-nephrotic patient with stable proteinuria
- Steroids + cyclophosphamide or MMF for rapidly progressive disease
- Most of us refer to expert tertiary care center (NIH, Stanford, Hopkins, Mayo)

PAUCI-IMMUNE FOCAL & SEGMENTAL



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Presentation:

- Hematuria + signs of small vessel vasculitis (diffuse skin lesions, lung hemorrhage, etc)
- Encompasses a group of diseases characterized by necrotizing inflammation of small blood vessels
- If little or no deposition of immune complexes referred to as ***pauci-immune***
- Common names: *Wegener's (granulomatosis with polyangitis - GPA)*, *microscopic polyangiitis (MPA)*, and *Churg-Strauss syndrome (eosinophilic granulomatosis with polyangitis)*; each one has slight variations but essentially are small vessel vasculitis

Pathology:

- Pauci-immune (little deposit) focal, segmental necrotizing, crescentic
- Often ANCA + (Anti-neutrophil cytoplasmic antibodies)

Treatment:

- Poor outcomes (body attacking itself) without RX
- Aggressive treatment with:
  - steroids
  - cyclophosphamide
  - rituximab
- Plasmapheresis for severe disease (rare)
- Even with GFR<10ml/min, 57% remission with RX!!!!!!

VIRAL AND BACTERIAL

Presentation:

- Disease dependent *ie*: HIV, Hep C, Hep B, *E. coli O157:H7* (food borne), Salmonella, etc
- *E.Coli 0157* - presents as bloody diarrhea that has resolved. Most children fully recover from their bowel illness without developing HUS (hemolytic uremic syndrome). However, a small percentage will become pale and have less energy, due to the progression to HUS. Their urine output may also decrease, but a loss of color in the skin is the most striking symptom

Pathology:

- Rarely done; Hep B/C may be found incidentally on biopsy
- Diagnosis often via serum assays

Treatment:

- Treat underlying disease (HIV, Hep C, Hep B)
- HUS may require dialysis, 10% death rate

AMYLOIDOSIS

Presentation

- Proteinuria
  - (AL/AA/AH)
- Can be nephrotic
  - Depends on which organs are impacted
  - Can present as kidney failure

Pathology

- Overflow proteinuria causing depositions in organs, including the kidney
- AL – most common in US
- AA more common in 3rd world countries
- Rarely genetic

- Kidney Biopsy to confirm
  - Mass spectometry to determine type

Treatment

- Supportive Care
  - Volume management
- Disease specific focus
  - AL
    - Chemotherapy
    - Bone marrow transplant
  - Secondary
    - Eradicate underlying infection
  - Hereditary
    - Liver transplant (+/- other organs)

MULTIPLE MYELOMA (MGUS/SMOLDERING)

Presentation	Pathology	Treatment

• Elevated serum calcium
• Joint pain
• More often seen in the "elderly"
	• Overflow proteinuria
	  • Cast nephropathy
	  • Monoclonal immunoglobulin deposition
	  • AL amyloidosis
	• Work up includes
	  • SPEP, UPEP
	  • Biopsy
		• Chemo
		• Plasma exchange
		• Dialysis

GLOMERULONEPHRITIS (GN)

- Seems complicated because many diagnoses are uncommon
- 3rd most common cause of ESRD after Diabetes and HTN
- Almost all will need a biopsy so involve nephrology early
- Can be primary or secondary
- Think of it as a puzzle and you

  won't tear your hair out!

REFERENCES

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THANK YOU!

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