

Proteinuria, Hematuria and Glomerular Disease

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**CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE**



HARVARD MEDICAL SCHOOL
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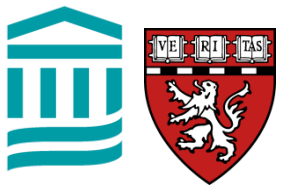
Fellowship: BWH/MGH

Clinical Interests: ICU Nephrology, Lupus Nephritis

Academic Interests:

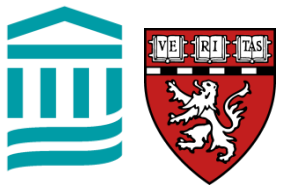
Lupus Nephritis

Post-graduate Education



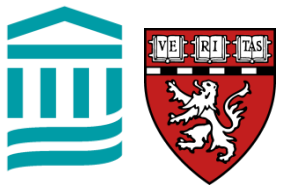
Disclosures

- Alexion Pharmaceuticals – Research Support
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- Advanced Instruments - Consultant



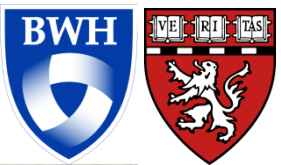
Learning Objectives:

- Learn why hematuria and proteinuria are important
- Describe the mechanisms of glomerular injury
- Discuss the causes of nephrotic and nephritic syndromes.



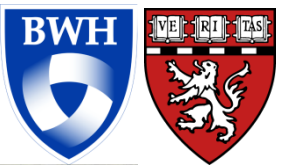
Proteinuria

- Normal excretion <150 mg/24 h
 - 60% is filtered plasma protein (20-40 mg of albumin)
 - 40% are glycoproteins -- Immunoglobulins, uromodulin
- Detected by urine dipsticks
 - Detects >10 -15 mg/dL; almost always (+) if urine alb > 30 mg/dL
- Microalbuminuria = 30-300 mg/24h
- Macroalbuminuria = >300 mg/24h
- Estimate protein (and albumin) excretion by measuring the ratio of protein to creatinine (to account for urine volume)
- Proteinuria is one of the best predictors of progression of renal disease

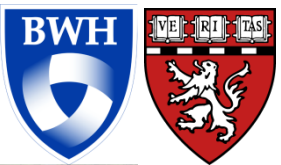
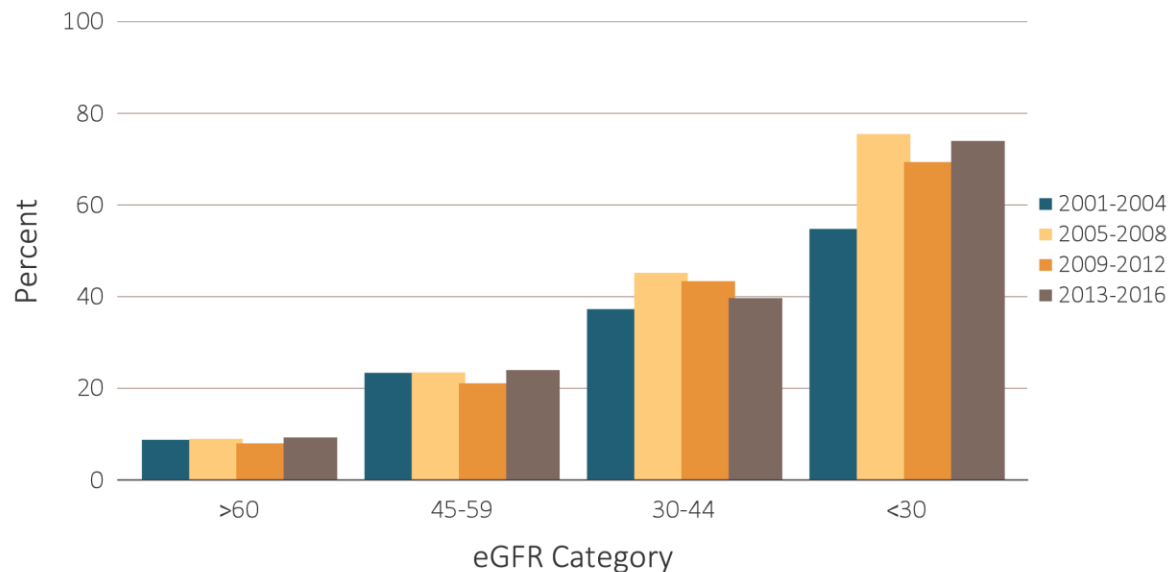
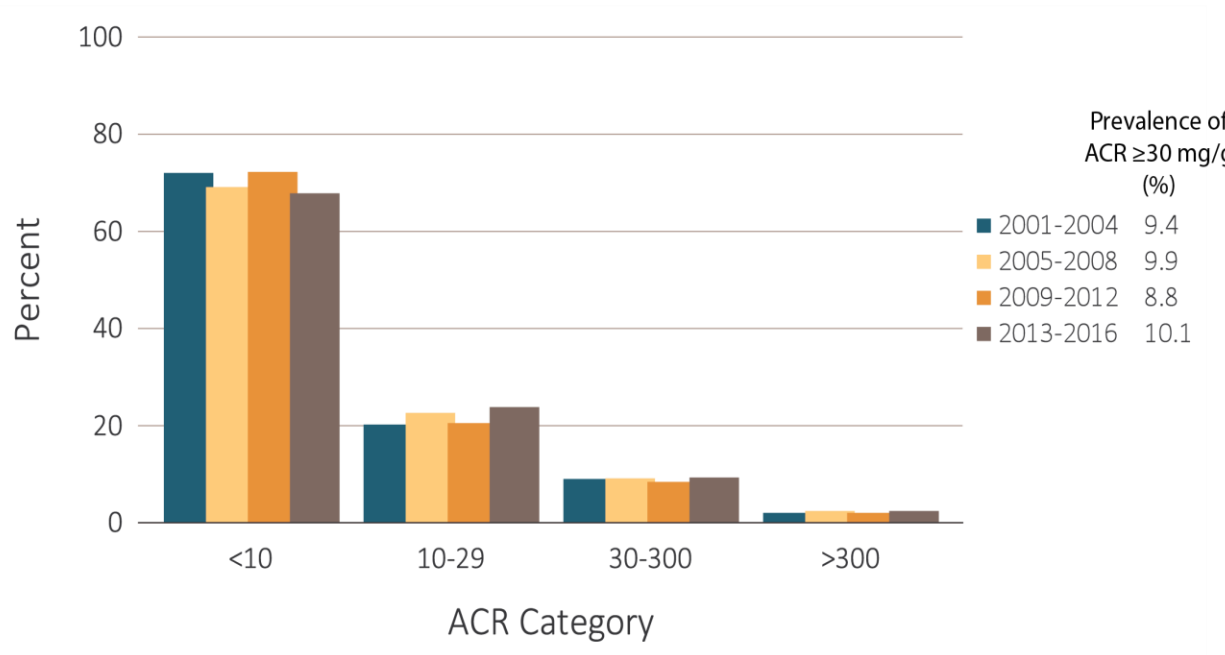


Proteinuria

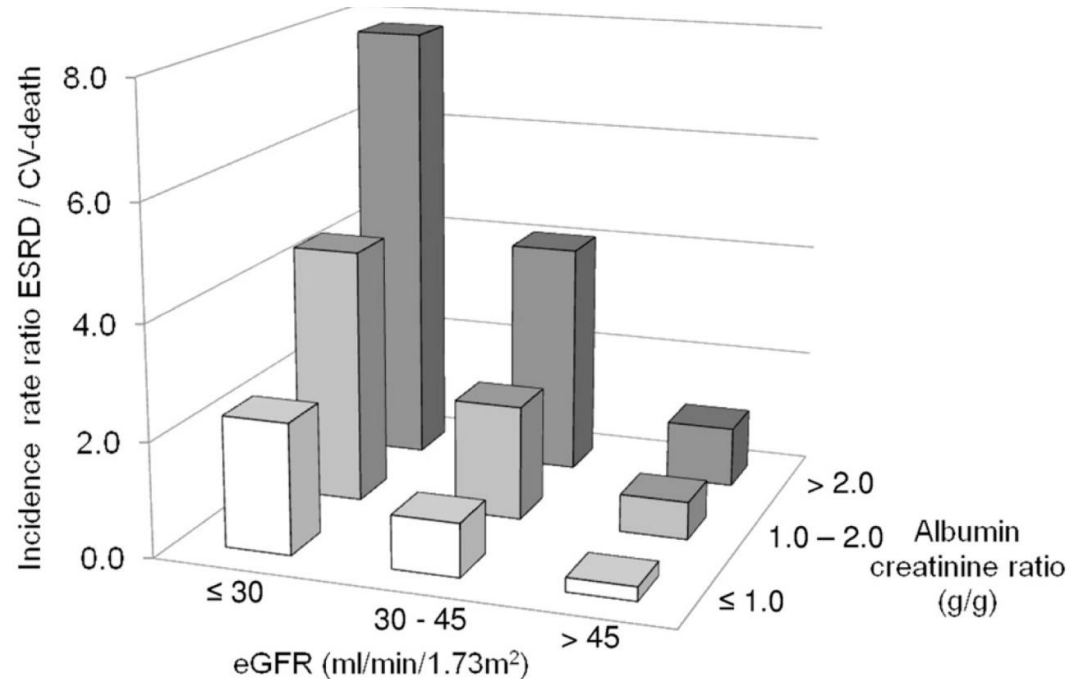
- Pearls
 - Very high (or low) creatinine production can change the protein estimation as the formula assumes 1g creatinine production daily
 - LMW proteins are usually absorbed in the proximal tubule so a high ratio of total protein to albumin may suggest either over-production of light chains (myeloma) or a proximal tubular disorder
 - There is large intra-individual variation in the albumin/creatinine ratio even in a single day



Prevalence of Albuminuria



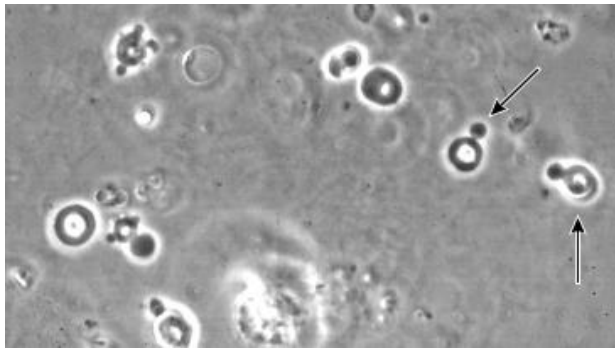
Risk for ESRD increases as proteinuria increases and GFR decreases



		eGFR (ml/min/1.73m ²)		
		≤30	30 - 45	>45
ACR (g/g)	> 2.0	12.87 (5.97-27.74)	7.46 (3.63-15.33)	7.40 (3.32-16.47)
	1.0 – 2.0	7.12 (3.16-16.04)	3.47 (1.63-7.40)	2.80 (1.18-6.64)
	≤1.0	3.61 (1.49-8.73)	1.49 (0.64-3.48)	1.00 (reference)

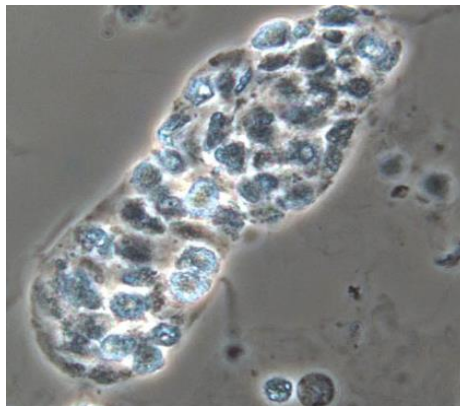
Hematuria

- Urine dipstick: Positive in the presence of RBCs, Hb or myoglobin
- Urine microscopy: >2 RBCs per hpf
- Prevalence varies with studies 0.18-16%



Glomerular Bleeding:

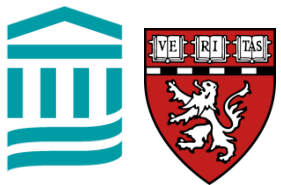
>5% acanthocytes
seen by phase
contrast



Specificity 98%
Sensitivity 52%

Hematuria Evaluation

- Confirm with microscopy
- CT urography and cystoscopy
- Urine cytology (90% sensitive for bladder cancer)
- >45 years: 20% will have an abnormality on urologic work-up, half with malignancy
- <45 years: 2% will have significant urologic disease
- If no urologic cause – proceed with glomerular work-up



Differential Diagnosis of Isolated Hematuria

Glomerular

IgA nephropathy
Thin basement
membranes
Familial
nephropathies

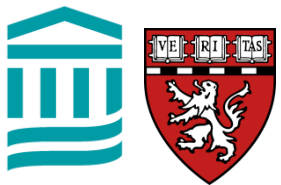
Non-glomerular

Urologic malignancy
Nephrolithiasis
Cystic renal disease
Papillary necrosis
Metabolic Abnormalities-
Hypercalcuria/Hyperuricosuria
Urinary tract infection
Cystitis including
viral/hemorrhagic

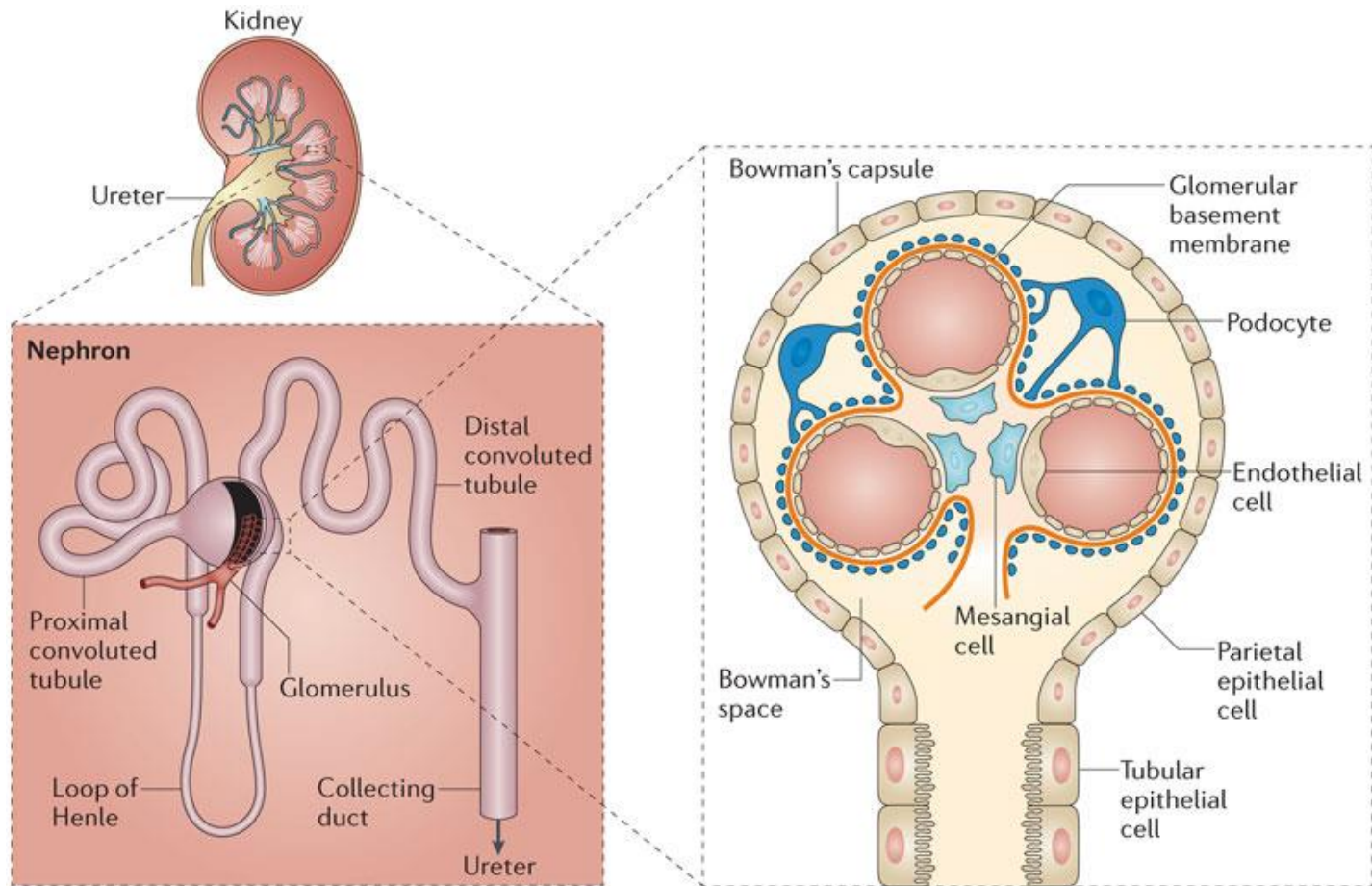
Rare causes of hematuria

Sickle cell disease
Arteriovenous
malformations/fistulas
Renal TB
Schistosomiasis
Loin pain hematuria
syndrome

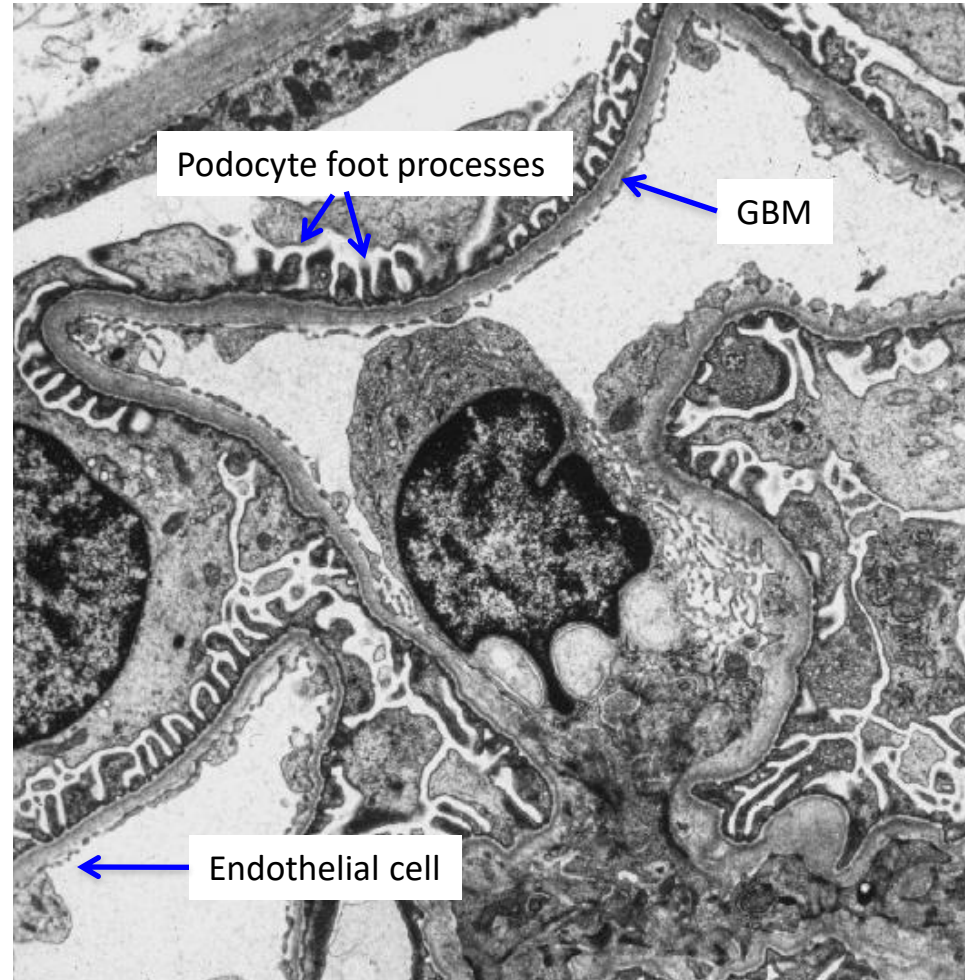
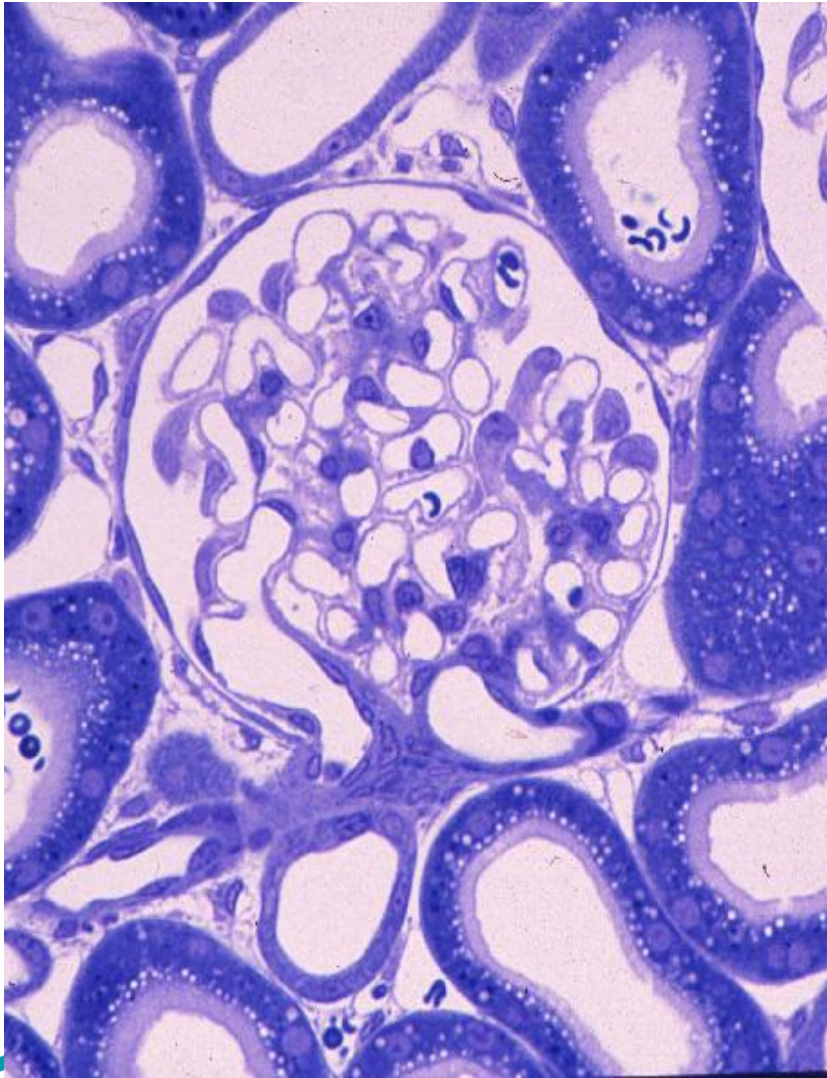
Mechanisms of Glomerular Injury



Kidney Structure



Glomerular Disease: Target of injury



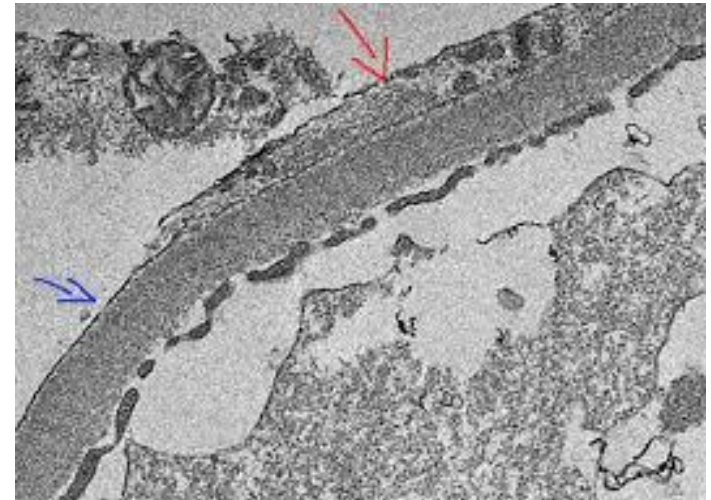
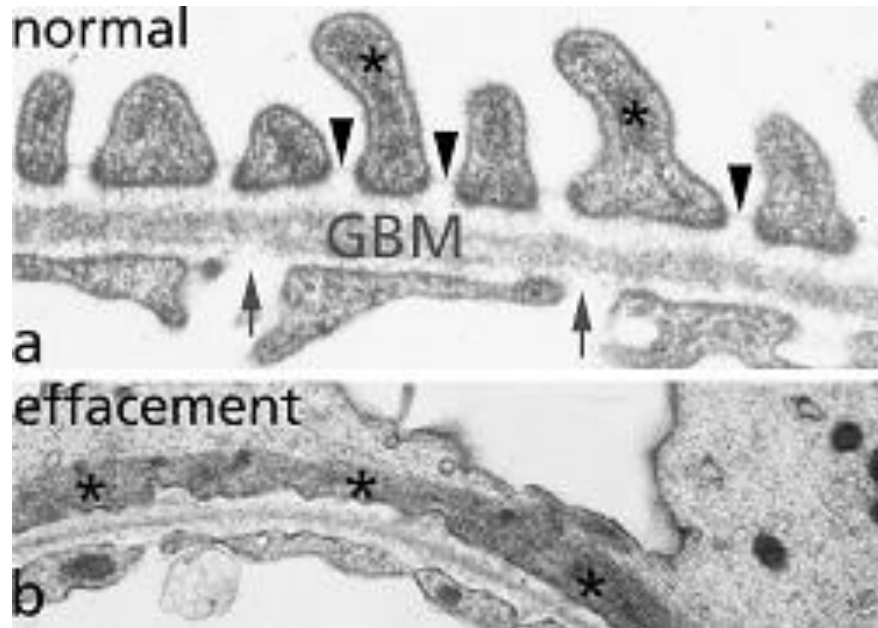
Glomerular Disease: Target of Injury

Podocyte injury:
Proteinuria &
Nephrotic syndrome

Endothelial cell injury:
Inflammation &
Nephritic syndrome



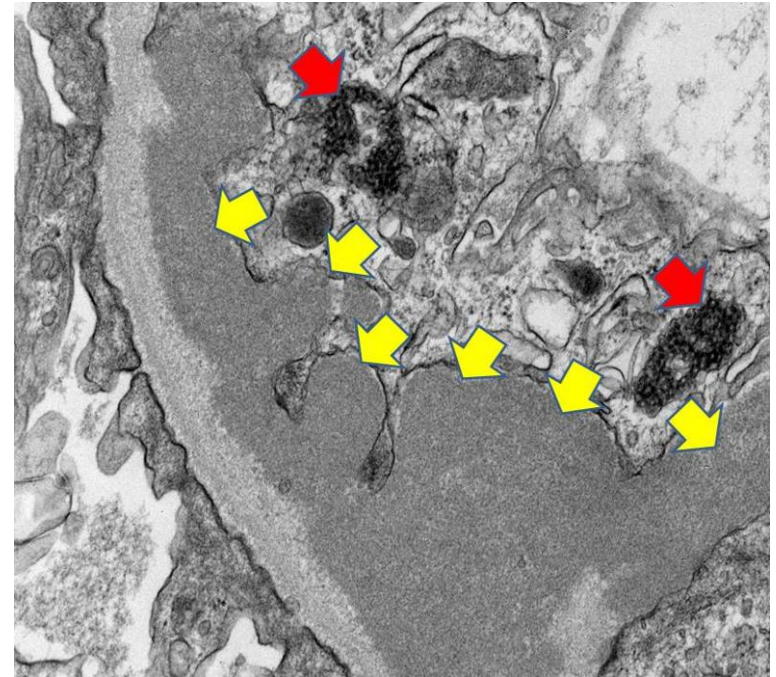
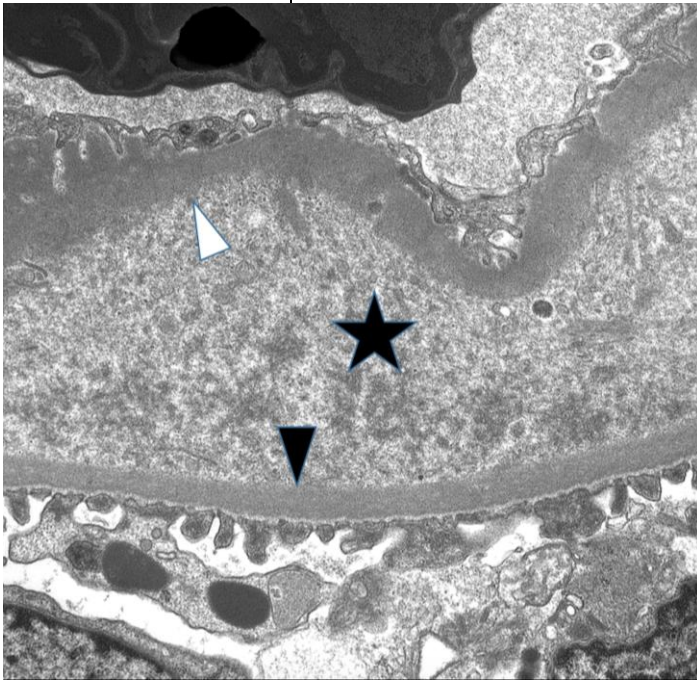
Podocyte injury: Diffuse Foot Process Effacement



Flattened foot processes, loss of slit diaphragms and disruption of glomerular barrier. Generally no inflammation

Endothelial Cell Injury

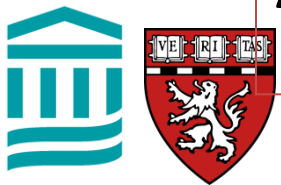
Subendothelial deposits
Activated endothelial cells
Intact foot processes
“Inflammatory Lesion”



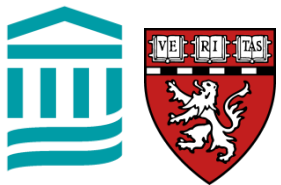
Chronic endothelial cell injury:
reduplication of basement
membrane; ‘double contour’
formation

Glomerular Disease: Clinical syndromes

	Nephrotic	Nephritic
Edema	++++	++
BP	Normal	Raised
JVP	Normal/Low	Raised
Proteinuria	++++	++
Hematuria	+/-	+++
RBC Casts	Absent	Present
Albumin	<3.0g/dL	Normal/Slight ↓

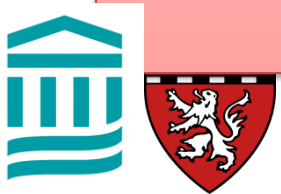


Nephrotic syndromes/Proteinuric states



Clinical Presentation of Proteinuric States

	Proteinuria	Renal dysfunction	Assoc. features
Nephrotic syndrome	>3.5g/day	Sudden onset	Edema Hypoalbuminemia Hypercholesterolemia Thrombosis risk Bland sediment
Non-nephrotic proteinuria	<3.5g/day >3.5g in later stages	Slowly progressive	No edema Normal albumin Variable sediment



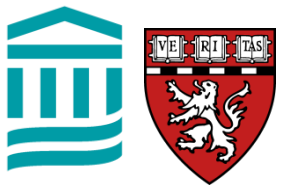
Proteinuric States

NEPHROTIC SYNDROME

Minimal Change Disease (1' or 2')
Primary FSGS
Membranous Nephropathy (1' or 2')
Amyloidosis
Collapsing Glomerulopathy

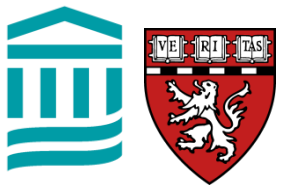
NON-NEPHROTIC *OR* NEPHROTIC-RANGE PROTEINURIA

Secondary FSGS
Autoimmune Disease
Obesity
Diabetic Nephropathy
Medications – NSAIDs, Interferon



Evaluation of proteinuria/nephrotic syndrome

- History and physical exam
- FHx, SHx, drug exposures, detailed ROS
 - Infections, age approp. malignancy screening
- Urine sediment examination
- Urine pr/cr and alb/cr ratio
- Renal U/S
- Immunoglobulins, SPEP, free light chains, UPEP
- Specific Membranous Antibodies (PLA2r, TSPD)
- HIV, Hepatitis screen
- ANA, anti-ds DNA, Complement C3 and C4
- **RENAL BIOPSY**

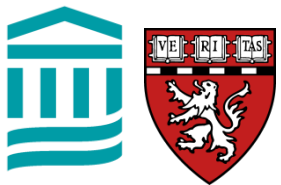


Case I

A 23-year-old woman presents with a 1-week history of lower limb edema, weight gain and decreased urine output. No PMHx, or meds of note.

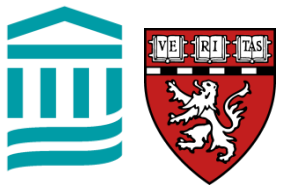
Physical Exam: BP 100/60, HR 84, no elevated JVP, clear lungs, 3+ upper and lower limb edema

- UA with negative blood, 3+ protein, no WBCs
- Urine microscopy: 2-4 RBCs/HPF, occ. granular casts
- Creatinine 0.9mg/dL, Albumin 2.1g/dL
- Spot Urine protein/creatinine ratio 9580mg/g



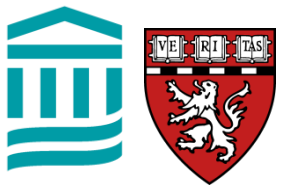
Which of the following is correct ?

- A. Renal biopsy will show immunofluorescence for IgA
- B. On light microscopy, 'spikes' will be seen on the glomerular basement membrane
- C. Antiphospholipase A2 receptor antibody is likely to be positive
- D. Electron microscopy will show patchy foot process effacement
- E. This presentation may be associated with anti-nephrin antibody deposition



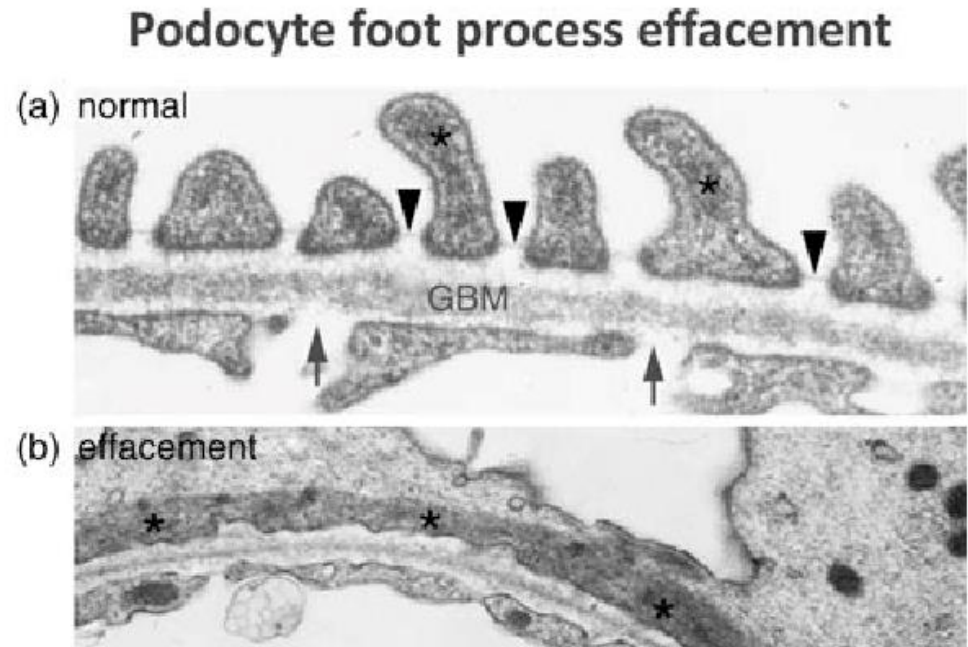
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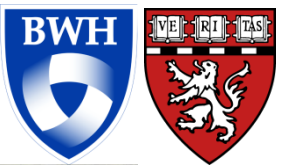
Minimal Change Disease

- Heavy proteinuria and nephrotic syndrome with rapid onset
- Hypertension, hematuria and AKI are rare
- Light and IF look normal
- Typical foot process effacement on EM

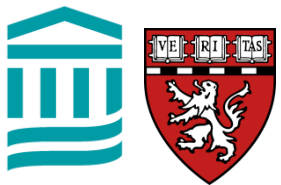


Minimal Change Disease

- Primary
 - Likely circulating permeability factor
 - Anti-Nephrin Ab in 20-30%
- Secondary
 - Infections (TB, syphilis)
 - Malignancies (NHL, Leukemia)
 - Drugs (interferon, pamidronate, ICI)
 - Allergy
- Treatment
 - Steroids was mainstay of treatment
 - Treat underlying disorder
 - Now anti-B cell therapy (rituximab) is first line in primary MN
 - Can recur after transplantation

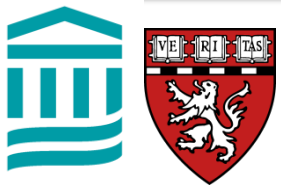


Hematuria and Nephritic syndromes



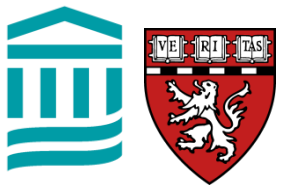
Spectrum of Clinical Presentation: Hematuria and nephritic GN

	RPGN	Acute Nephritis	Asymptomatic Hematuria
Hematuria	Y	Y	Y
Active sediment	Y	Y	N
Proteinuria	++	+	+/-
AKI	Rapid onset	Sudden onset	Rare
Hypertension	Y	Y	+/-
Edema	Y	Y	N
Oliguria	Commoner	Rare	N



Evaluation of nephritic syndrome

- History and physical exam
- FHx, SHx, drug exposures, detailed ROS
 - Infections, age-appropriate malignancy
- Urine sediment examination
- Renal U/S
- Immunoglobulins, SPEP, free light chains, UPEP
- ANCA, Anti GBM
- HIV, Hepatitis screen
- ANA, anti-ds DNA, Complement C3 and C4, cryos
- **RENAL BIOPSY**



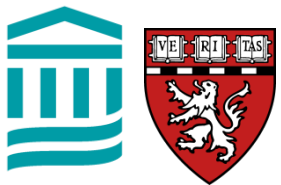
Case II: nephritic syndromes

64-year-old male presents with 1 week history of low-grade fevers, fatigue and dyspnea. Over the last few days, he has noticed a rash, increasing lower limb edema and dark colored urine.

PMHx: Hypertension, HFrEF with ICD in place, MVR

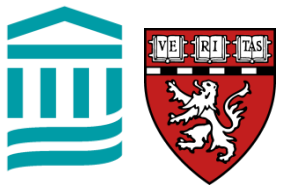
On exam: BP 170/90, HR 72, elevated JVP, basal crackles, 1+ lower limb edema. Purpuric rash on lower limbs

- Labs: Creatinine 2.5mg/dL (b/l 1.3)
- UA with 3+ blood, 2+ protein. 15-20 RBCs/hpf.
- Urine microalbumin/creatinine ratio 1240mg/g
- C3: 40 (90-180); C4 5 (10-40), ANA negative



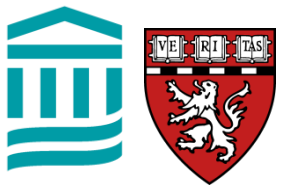
Case II: Which of the following is correct ?

- A. The patient needs a CT chest to look for pulmonary hemorrhage
- B. Renal biopsy may show negative immunofluorescence
- C. This presentation can be associated with Staph aureus bacteremia
- D. The patient should be treated with empiric steroids



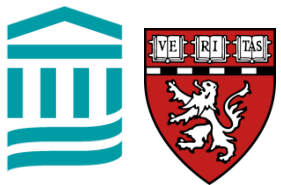
Case II: Correct Response

- A. The patient needs a CT chest to look for pulmonary hemorrhage
- B. Renal biopsy may show negative immunofluorescence
- C. This presentation can be associated with Staph aureus bacteremia**
- D. The patient should be treated with empiric steroids



Pathological classification of nephritic syndromes

- Immune complex deposition diseases
- Pauci-immune GN
- Anti-GBM disease



Pathological classification of nephritic syndromes

- **Immune complex deposition diseases**

 - IgA nephropathy

 - Infection associated GN

 - IgA-dominant SA associated GN

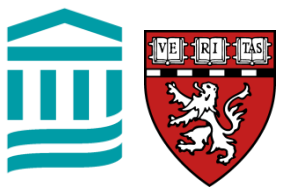
 - Lupus nephritis

 - Membranoproliferative GN (MPGN)

- **Pauci-immune GN**

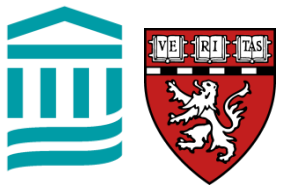
 - ANCA associated vasculitis

- **Anti-GBM disease**

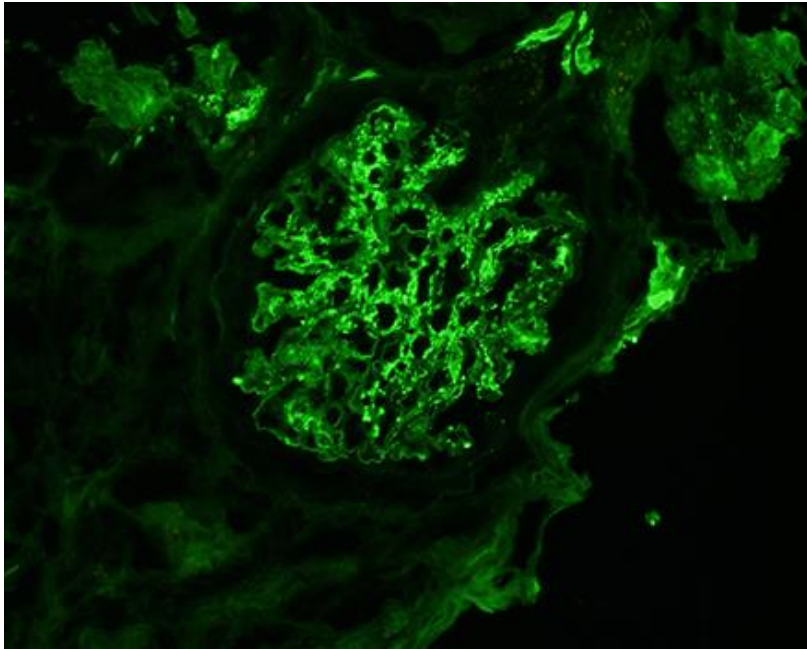


Staphylococcus associated GN

- Presentation with AKI and nephritic syndrome
- ***Concurrent*** infection with Staph aureus
- Frequently skin/soft tissue, indwelling hardware, cardiac infection
- Vasculitic rash
- Hypocomplementemia
- Renal biopsy: Diffuse endocapillary proliferative GN
- Immunofluorescence: IgA predominant, C3+



Staphylococcus associated GN

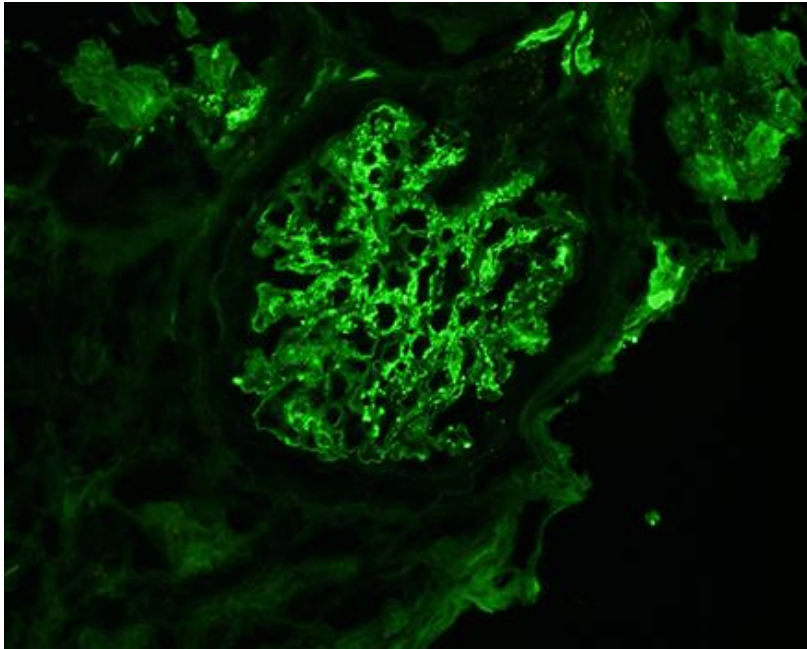


IF: Coarse, granular mesangial and capillary wall staining for IgA

Treatment is of the underlying infection

Prognosis relatively poor

Staphylococcus associated GN



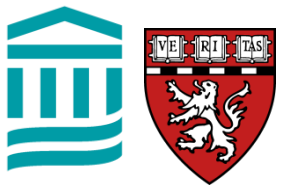
IF: Coarse, granular mesangial and capillary wall staining for **IgA**

Treatment is of the underlying infection

Prognosis relatively poor

Post infectious GN:

- Associated with Streptococcal infection
- Occurs **AFTER** infection is resolved.
- IF: **IgG** and **C3**



IgA Nephropathy

Epidemiology

Commonest cause of nephritis in the world (15-40% of primary GN in world, 20% in USA)

Males > Females (2:1)

Peak occurrence in 2nd & 3rd decades

Asian predominance (up to 40% of biopsies compared with 20% in European/U.S. registries)

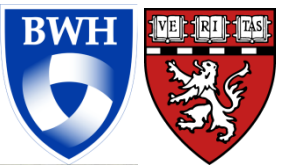
Clinical

Synpharyngitic hematuria (24 to 48 hrs after URI or GI infection -- in contrast with post-infectious nephritis 1 to 3 weeks)

Serum IgA levels elevated in ~50%

Spectrum of microscopic hematuria + low levels of albuminuria to RPGN picture

Course highly correlated with degree of proteinuria (>1g much worse prognosis)



IgA Nephropathy

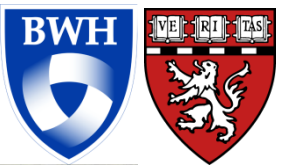
Treatment

Proteinuria <1g

- No treatment
- ACE/ARB
- SGLT2

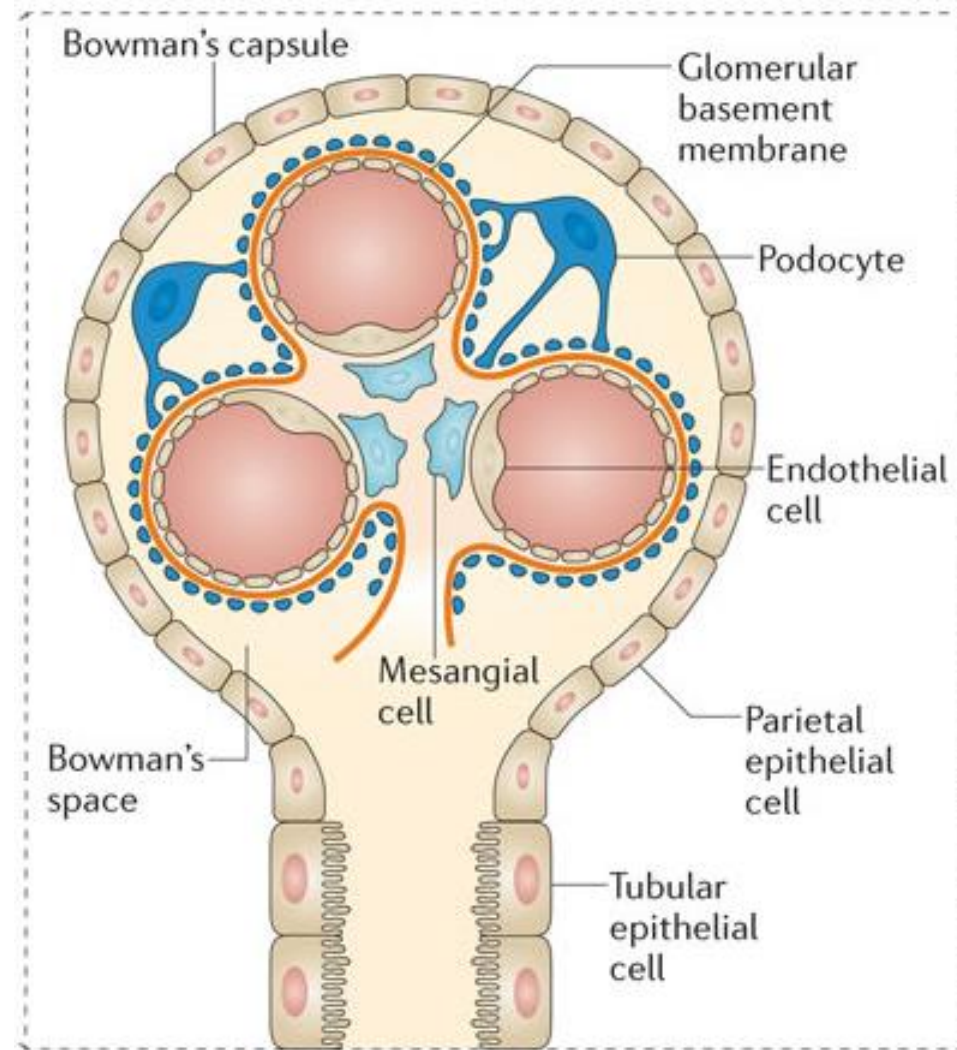
Proteinuria >1g

- Immunosuppressives (steroids, MMF, Cyclophos)
- Sparsentan
- Complement inhibitors.
- New agents in the pipeline.



Take Home Points:

- **Nephrotic** syndromes arise due to injury to the podocyte (subepithelial deposits)
- **Nephritic** syndromes arise due to injury on the endothelial side (subendothelial deposits)

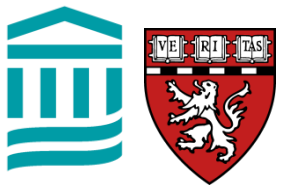


Take Home Points:

- Nephrotic range proteinuria

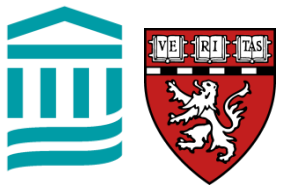
Primary nephrotic syndrome (podocyte injury)

Secondary causes of heavy proteinuria



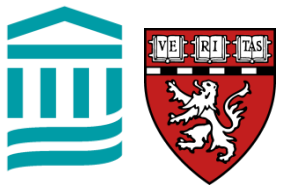
Take Home Points:

- Nephrotic range proteinuria
 - Primary nephrotic syndrome (podocyte injury)
 - Secondary causes of heavy proteinuria
- Nephritic syndrome:
 - Immune complex mediated
 - Pauci- immune
 - Anti GBM



Take Home Points:

- Nephrotic range proteinuria
 - Primary nephrotic syndrome (podocyte injury)
 - Secondary causes of heavy proteinuria
- Nephritic syndrome:
 - Immune complex mediated
 - Pauci- immune
 - Anti GBM
- Asymptomatic isolated hematuria
 - > 45yrs - Likely urological
 - < 45 yrs - Likely renal
 - Increased lifetime risk of ESKD



Take Home Points:

- Nephrotic range proteinuria
 - Primary nephrotic syndrome (podocyte injury)
 - Secondary causes of heavy proteinuria
- Nephritic syndrome:
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Thank You

