Glomerular Diseases

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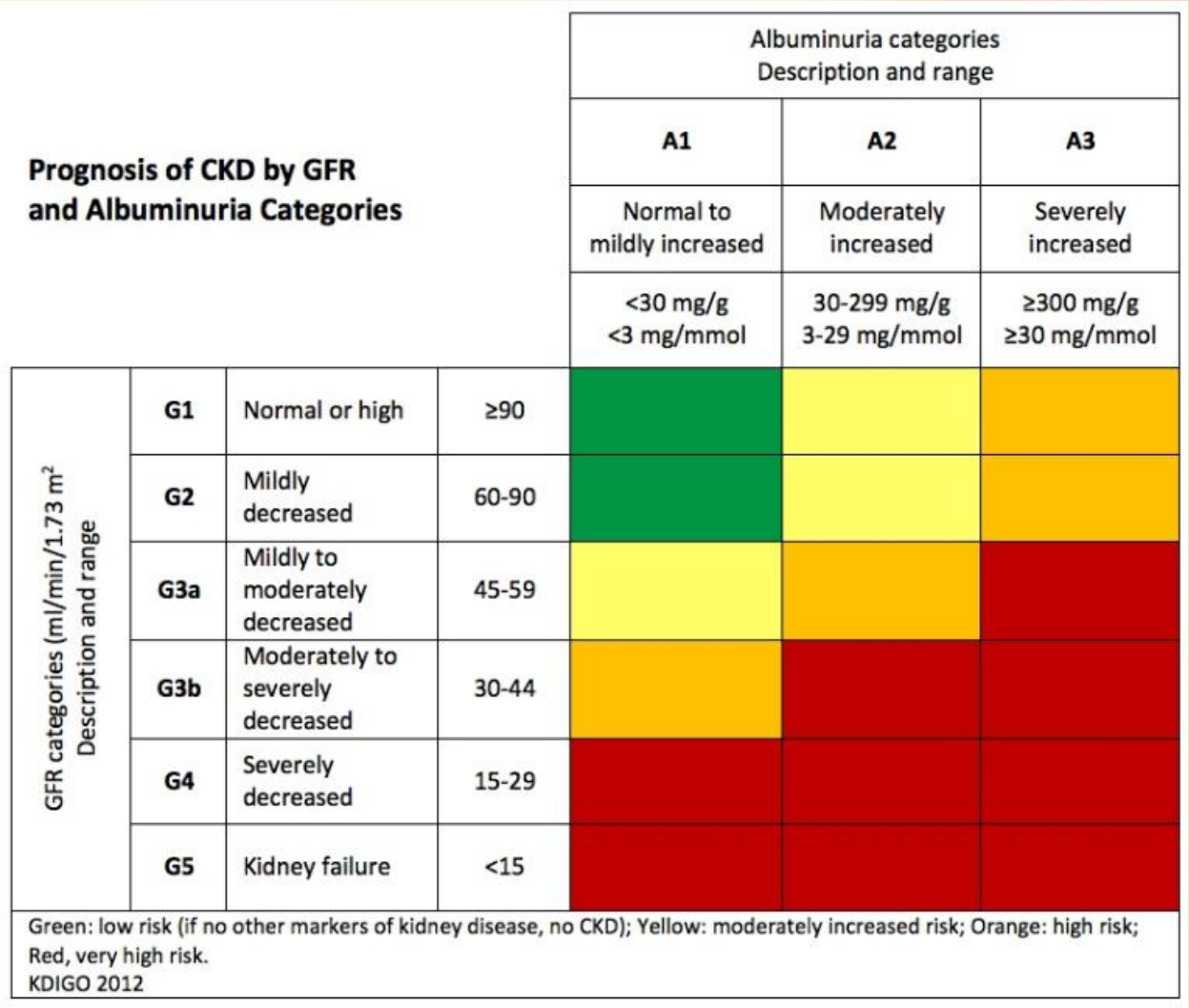
CKD 101

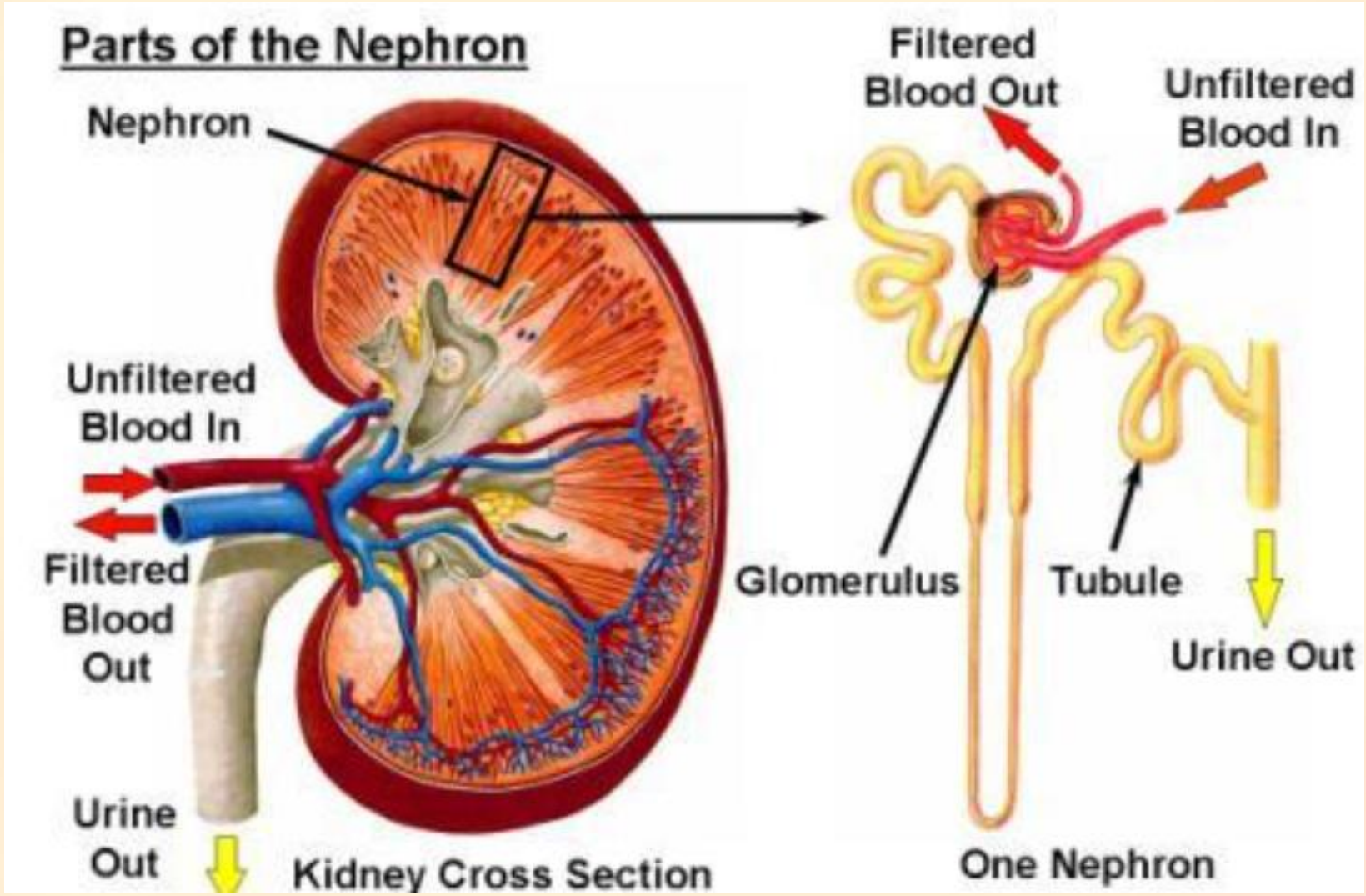
- Important Labs
  - Creatinine versus eGFR
  - Urine protein versus albumin
  - Methods of measuring urine protein/albumin
    - 24 hr urine collection for protein or albumin
    - UPCR (urine protein creatinine ratio)
    - UACR (urine albumin creatinine ratio)



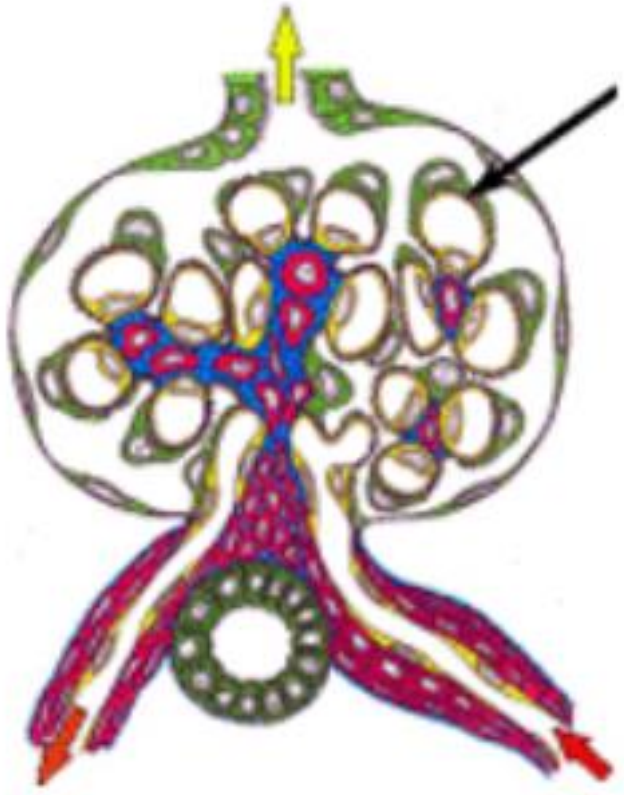
Prognosis of CKD by GFR and Albuminuria Categories				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (ml/min/1.73 m²) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60-90			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.
KDIGO 2012

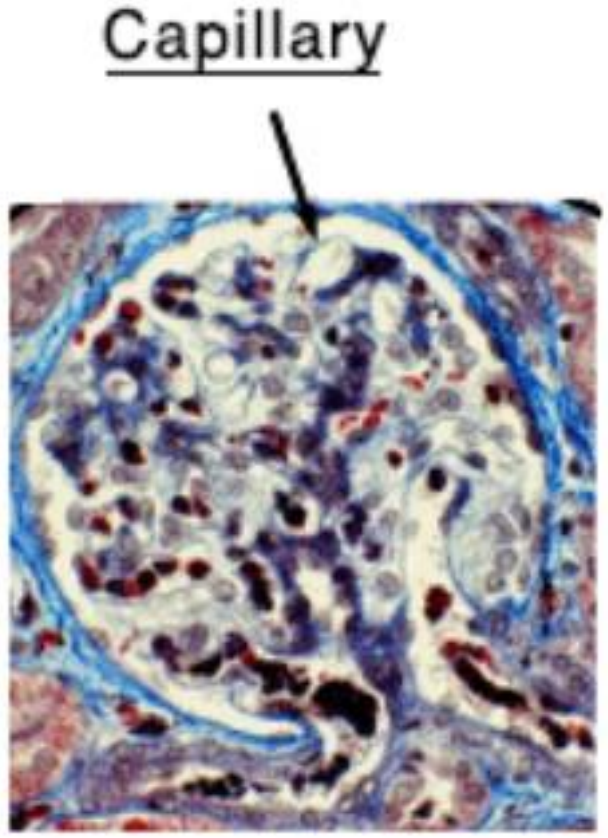
Microscopic structural/functional components of the kidney



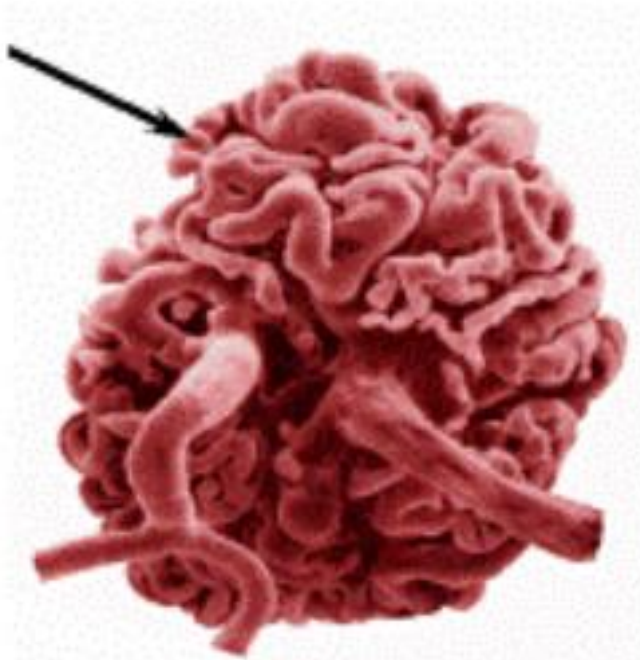
Glomerular Diseases



Schematic of a cross section of a glomerulus



Light micrograph of a cross section of a glomerulus



Electron micrograph of a whole section of a glomerulus

Glomerular Diseases: 10% of ESKD

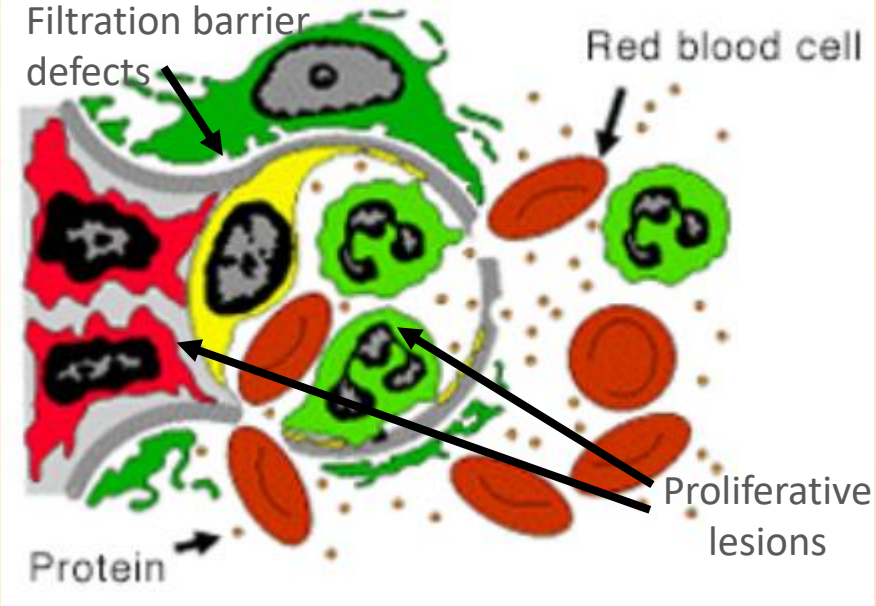
Nephritic Syndromes

- Hematuria
- Proliferative Glomerular Lesions

Nephrotic Syndromes

- Proteinuria and Edema
- Filtration barrier defects

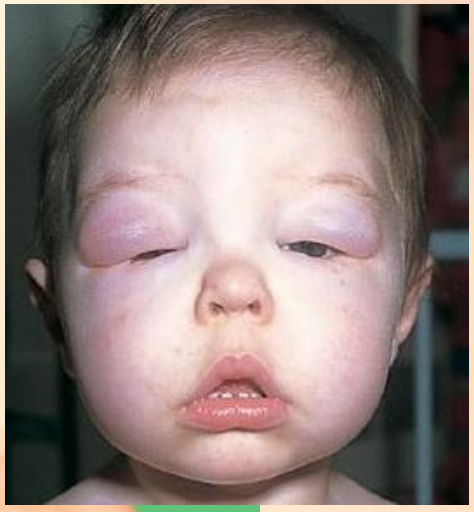
Normal glomerulus

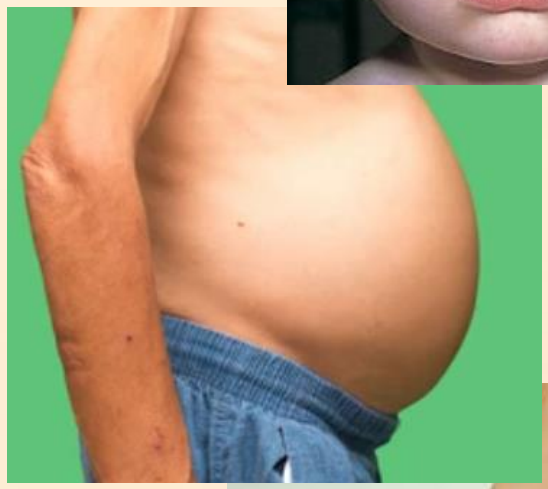


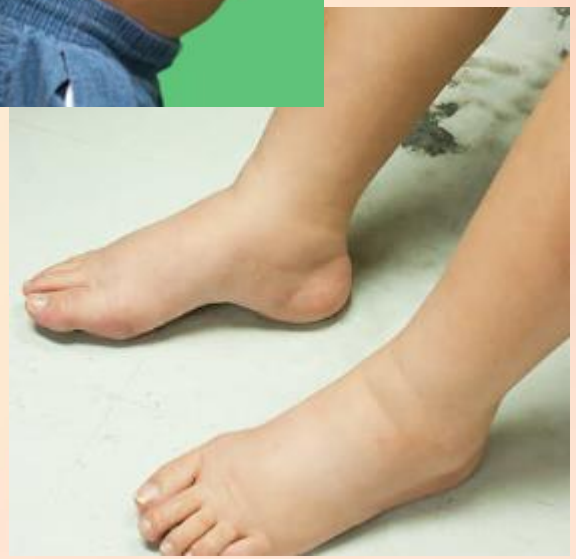
Glomerular Disease

Nephrotic Syndrome

- Definition:
  - Proteinuria (>3g/g per day on urine protein:creatinine ratio)
  - Hypoalbuminemia (<3g/dl, often <2g/dl)
  - Edema
  - Hyperlipidemia
- Presenting complaint is usually impressive edema
  - Periorbital edema, pedal edema, and ascites
- Complications:
  - Immunosuppression due to immunoglobulin loss in urine
  - Loss of mobility and skin integrity (blistering, ulceration)
  - DVT/PE due to loss of anticoagulant proteins
  - Spontaneous bacterial peritonitis (kids)

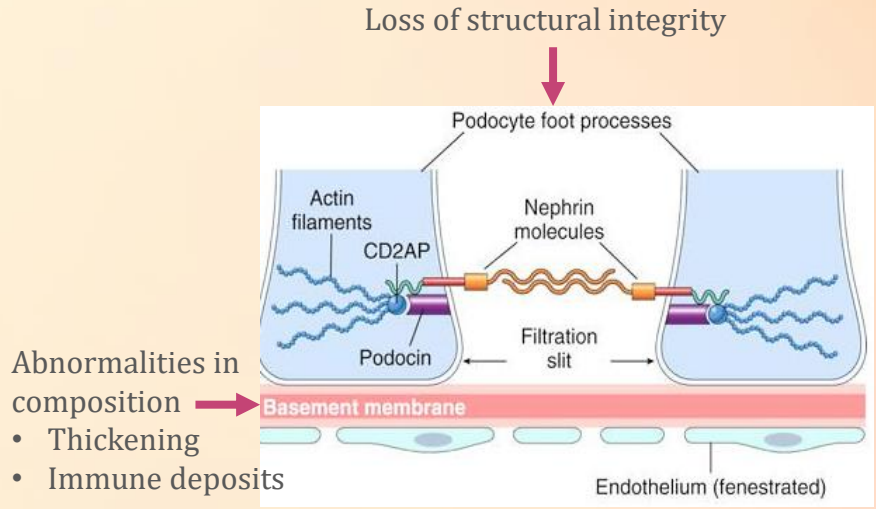






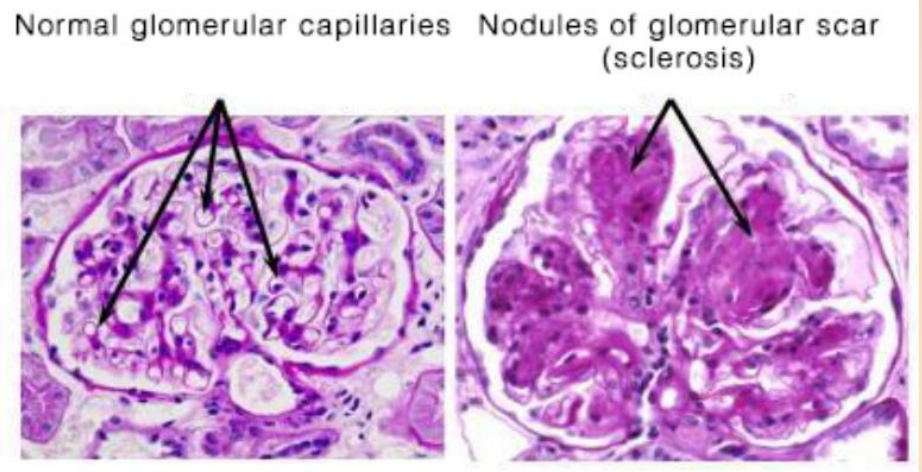
Nephrotic Syndrome

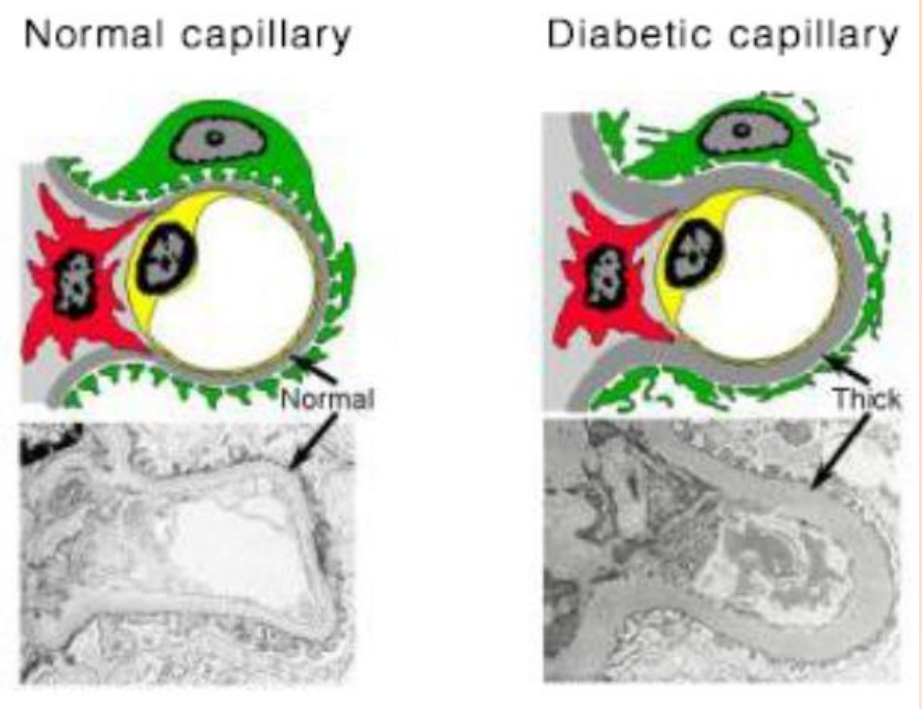
- Aberrations in the glomerular basement membrane and/or cytoskeleton of the podocyte foot processes
- Most common diseases:
  - Type 1 or Type 2 Diabetes: Most common cause in adults
  - Minimal Change Disease: Most common cause in children
  - Focal Segmental Glomerulosclerosis
    - Most common cause of *primary* nephrotic syndrome in adults
  - Membranous Nephropathy
    - Almost exclusive to adults
    - Often secondary to cancers or malignancy
    - Primary forms being elucidated:
      - Phopholipase A2 receptor antibodies (PLA2R-Ab)



Diabetic Glomerulosclerosis

- Sometimes referred to as: diabetic nephropathy, diabetic kidney disease
- Most people with diabetic kidney disease do not develop nephrotic syndrome
- Sclerosis = scarring
  - Due to expansion of mesangial matrix (collagen)
- Worse proteinuria, particularly nephrotic syndrome associated with extremely rapid loss of kidney function
  - Loss of >5-10ml/min/1.73m2 per <u>YEAR</u>



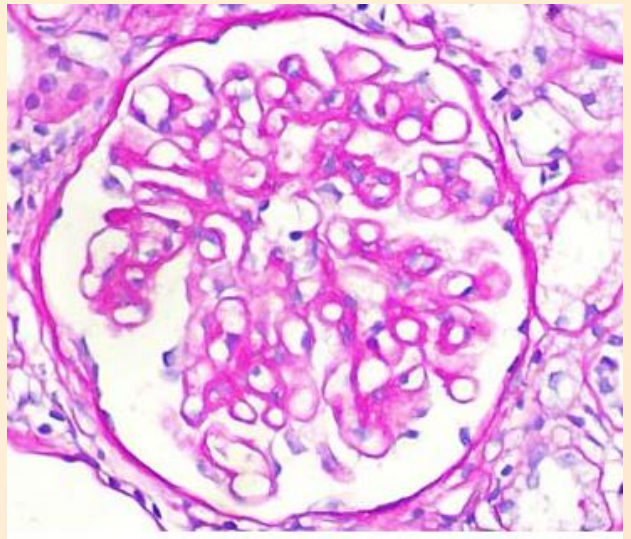


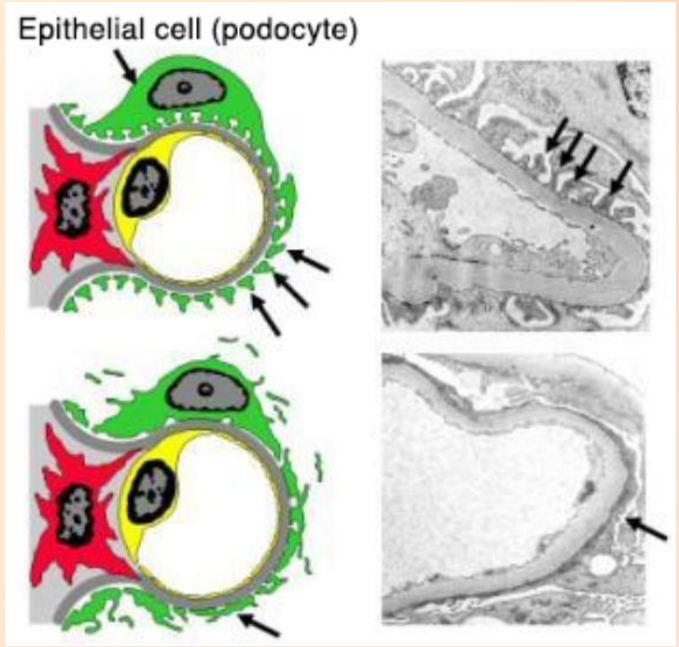
Treatment of Diabetes and CKD

- Diabetes Control: A1c < 8.0% in everyone; lower in some
- HTN Control: BP <130/80
- Renin-Angiotensin System Inhibitors
  - Angiotensin Converting Enzyme Inhibitors (ACEIs): lisinopril, enalapril, ramipril, etc.
  - Angiotensin Receptor Blockers (ARBs): losartan, valsartan, irbesartan, etc.
- Sodium glucose cotransporter 2 inhibitors (SGLT2 inhibitors)
  - The 'Flozins': empagliflozin, dapagliflozin, canagliflozin
- Nonsteroidal mineralocorticoid receptor blockers (finerenone)

Case Discussion: Mary

- 38 yo woman with history of hypothyroidism
- Sudden onset edema, frothy urine; no other symptoms
- Sees her PCP – found to have a creatinine of 0.5mg/dl; UPC 5.2g/g; serum albumin 2.4; total cholesterol 420; LDL 205
- BP 152/86; weight 84kg (up from 74kg)
- Undergoes kidney biopsy:
  - Light microscopy: normal glomeruli
  - Electron microscopy: normal GBM but global foot process effacement

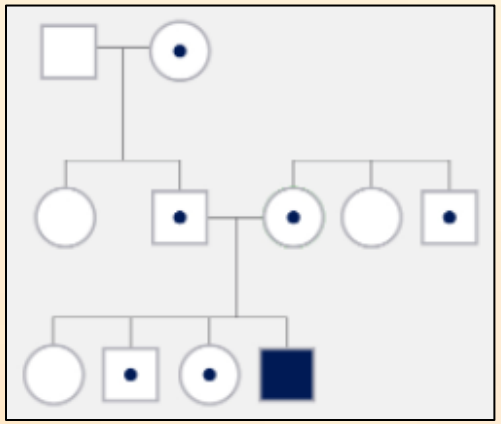




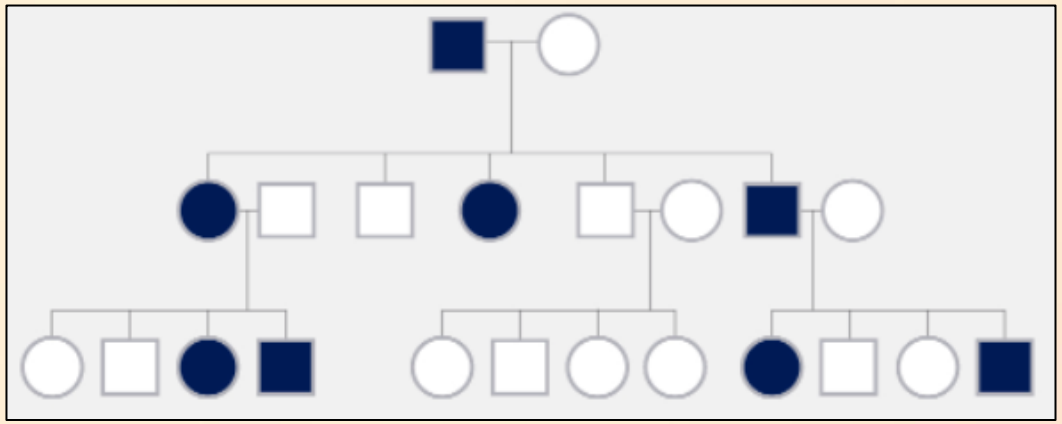
Minimal Change Disease

- Most common cause of nephrotic syndrome in children
- Rare genetic forms are congenital and/or familial (Finnish: founder effect)
  - Autosomal recessive > autosomal dominant
- Among adults, often older people, but can occur at any age

Autosomal Recessive



Autosomal Dominant



Anna sees a nephrologist

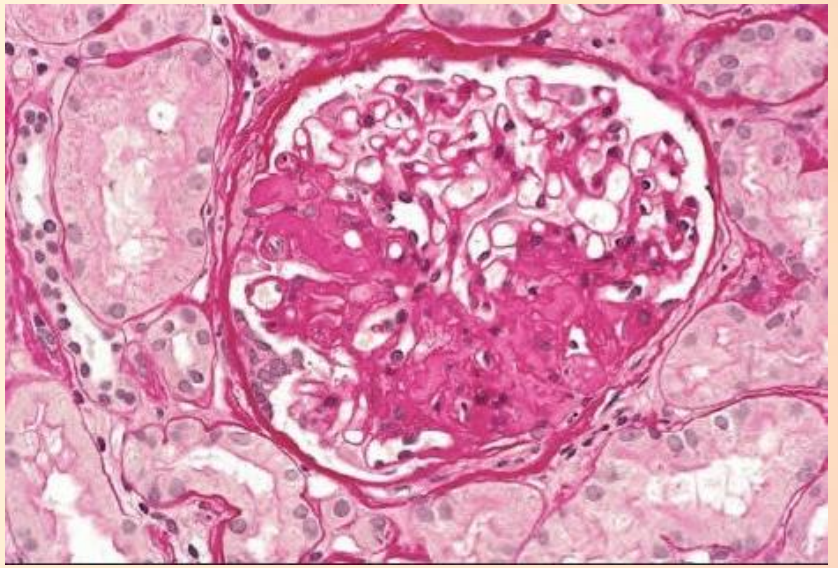
- Treatments : starts valsartan (ARB), prednisone 1mg/kg: 60mg daily, Lasix 40mg twice daily
  - Discuss side effects: weight gain, diabetes, infection, GERD/ gastritis, osteopenia, irritability, insomnia
- Prophylaxis against steroidal side effects
  - Prophylaxis against PJP with trimethoprim sulfamethoxazole TIW
  - GI prophylaxis with omeprazole
  - Vitamin D, calcium

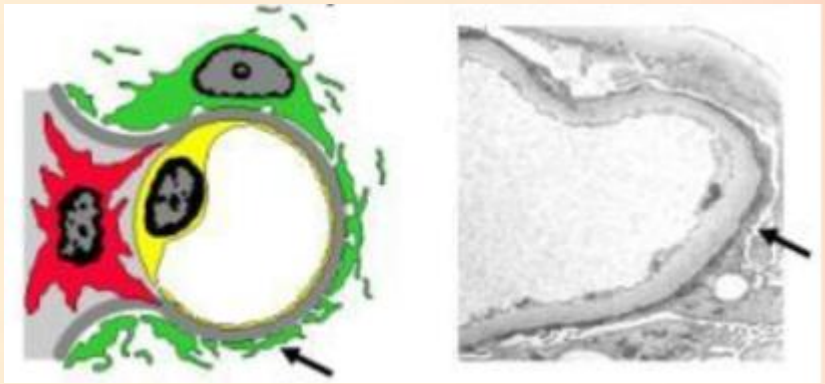
Anna 6 weeks later…

- Anna feels better, weight back to 74kg; edema mostly gone; BP 132/84; creatinine 0.7mg/dl; UPCR 540mg/gm
- Steroid sensitivity versus resistant is important for prognosis and management
  - Resistant may indicate need for rebiopsy to ensure this isn't FSGS
  - Resistant disease treated with calcineurin inhibitors: tacrolimus or cyclosporine
- 3 months later… Anna returns on 10mg prednisone
  - Creatinine 0.8mg/dl; UPCR 2800mg/gm
  - Steroid dependent minimal change disease
    - Requires 'steroid sparing' agent: rituximab, cyclophosphamide

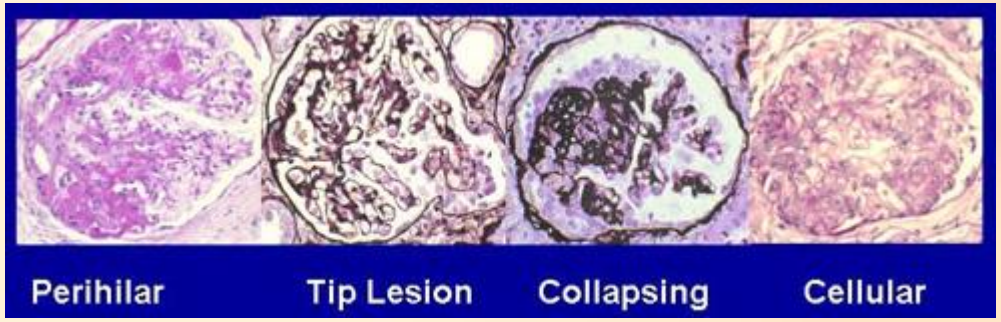
Focal Segmental Glomerulosclerosis

- Most common cause of nephrotic syndrome in adults
- Second most common cause of nephrotic syndrome in childhood
- African Americans disproportionately affected
  - APOL1: 2 gene variants
- Secondary forms common
  - Obesity, obstructive sleep apnea, hypertension
  - Viral infections; HIV, COVID-19, Parvovirus





Focal Segmental Glomerulosclerosis

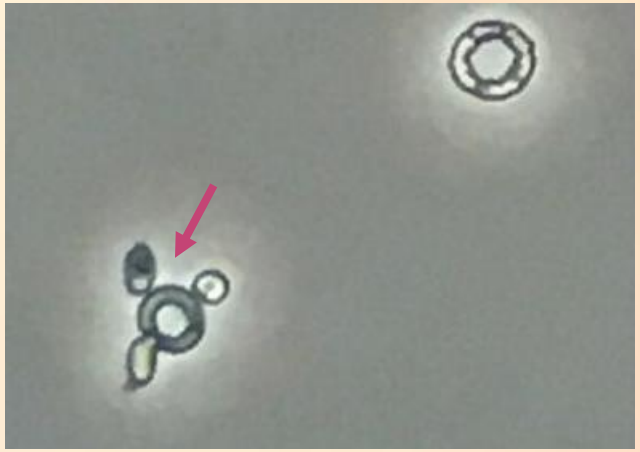


- Different ‘subtypes’ depending on the pattern of FSGS
  - Perihilar: often seen in obesity “Obesity related glomerulopathy”
  - Tip Lesion: clinically behaves more like MCD in response to steroid, rituximab
  - Collapsing: Worst prognosis: progresses to ESKD within several years
- Less likely to be responsive to steroids (10%) than MCD
- Few treatments that work other than calcineurin inhibitors (tacrolimus and cyclosporine)
  - Many clinical trials ongoing – important to encourage patients to participate
- Progresses to end stage kidney disease much more often and quickly than other forms of nephrotic syndrome

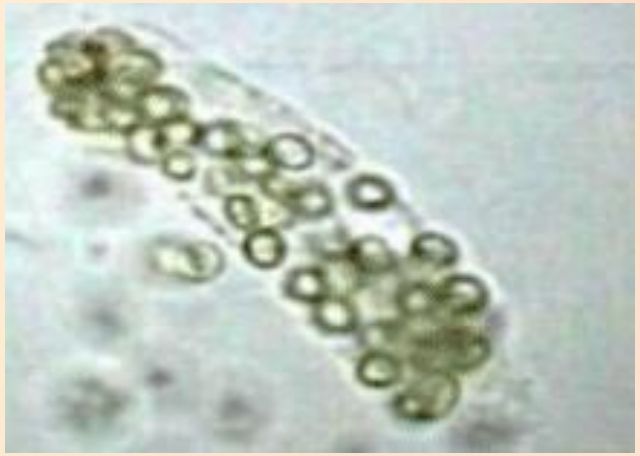
Nephritic Syndromes

- Characterized by inflammatory (cellular infiltrates) within the glomerulus
  - Dysmorphic hematuria, RBC casts on urine microscopy
  - +/- proteinuria (usually less severe than in nephrosis)
  - +/- acute kidney injury
  - +/- hypertension
- Most common diseases include:
  - IgA nephropathy – most common GN worldwide
  - Lupus nephritis
  - Post infectious (children; young adults)
  - ANCA Vasculitis (AntiNeutrophil Cytoplasmic Antibodies)

Dysmorphic RBC = 'acanthocyte'



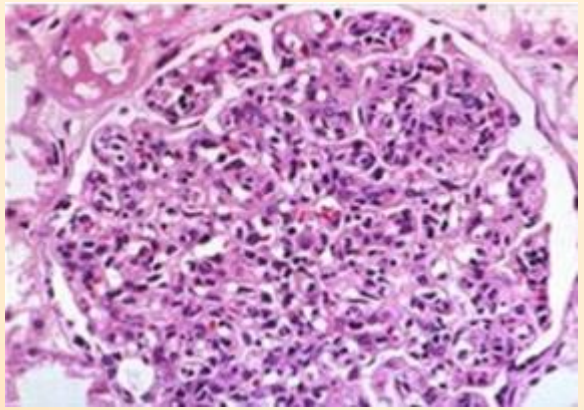
Red blood cell cast



Aspects of two most common causes of nephritis

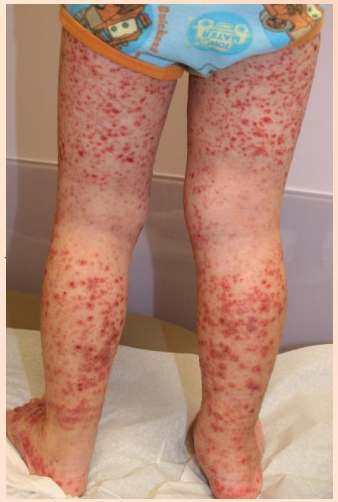
Post-infectious GN

- Three to four weeks AFTER strep throat or impetigo (strep) or a URI or pneumonia
- Self-resolves with supportive therapy, never comes back
- Complement levels important to discern from other nephritides:
  - Low C3, normal C4

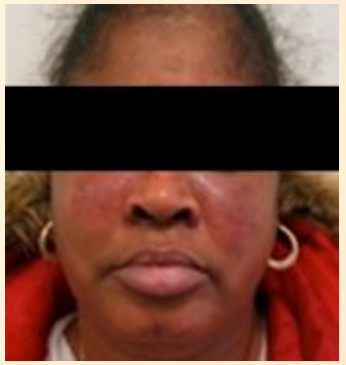


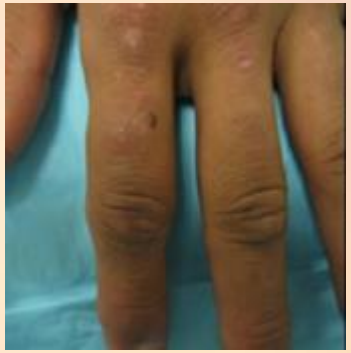
IgA nephritis

- Synpharyngitic (at same time as a sore throat or URI) – often gross hematuria
- Chronic, relapsing/remitting disease
- Normal C3, normal C4
- Treatment based on activity on kidney biopsy, degree of proteinuria (>1000mg/gm)
  - SGLT2 inhibitors
  - Budesonide versus Prednisone
- IgA Vasculitis
  - Formerly Henoch Schoenlein Purpura (HSP)
  - Leukocytoclastic vasculitis: petechial rash of and lower extremities
  - Gut involvement can be seen



Case Discussion: Jackie





- Jackie is a 20 yo woman with no PMH seen in the ER with diffuse joint swelling in her B/L hands and swelling in her legs over the last two weeks
- Exam: Appears nontoxic; BP 146/90 HR 80 afebrile
  - Diffuse, erythematous rash over her cheeks and involving the bridge of her nose
  - Finger (PIP) and hand (MCP) joints are warm, erythematous, swollen and tender
  - 2+ pitting edema B/L ankles
- Labs: Creatinine 1.3; UPCR 1400mg/gm; UA 2+ blood/3+ protein
- Serologies pending and d/c'd to follow-up with nephrology 2 days later

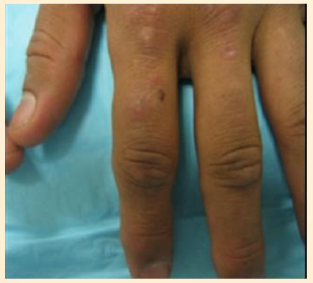
Jackie sees nephrology:
C3 & C4 low; +++ANA/Anti-dsDNA;

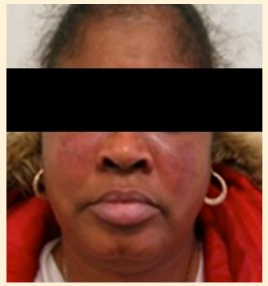
Antibodies	Lupus Specificity	Clinical Associations
ANA	Low	Nonspecific
Anti-dsDNA	High	Nephritis
Anti-Sm	High	Nephritis, CNS, Hemolytic anemia
Anti-RNP	Low	Arthritis, myositis, lung disease
Anti-SSA	Low	Dry eyes/mouth, photosensitivity, SCLE*, neonatal lupus
Anti-SSB	Low	Same as above
Anti-phospholipid	Intermediate	Clotting diathesis
Anti-histone Ab	High	Drug induced Lupus
Anti-ribosomal P	Low	CNS Lupus & Hepatitis

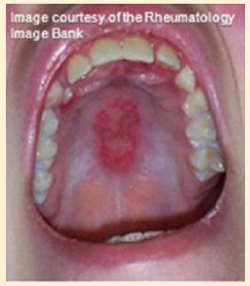
*subacute cutaneous lupus erythematosus

Systemic Lupus Erythematosis

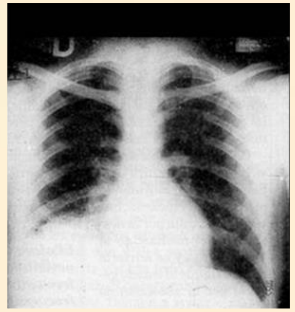
- 1.5 million Americans; AA and LatinX disproportionately affected
  - Diagnosed age 15-40 yrs
  - 9:1 ratio of women:men
- 40% develop clinical lupus nephritis
  - 22% develop ESKD over a mean of 15 years


Synovitis

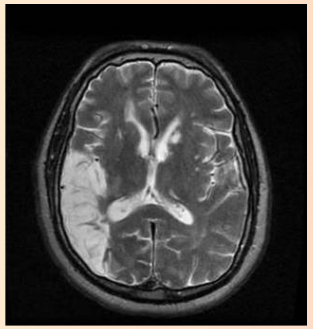

Malar rash

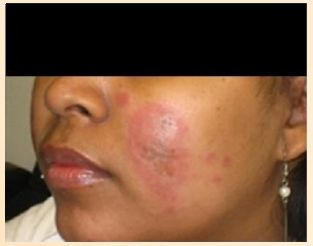


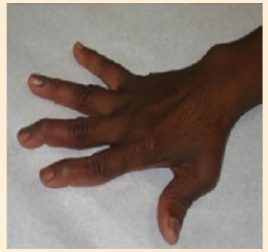
Painless oral ulcer

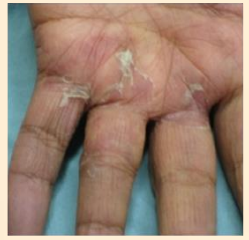

Serositis

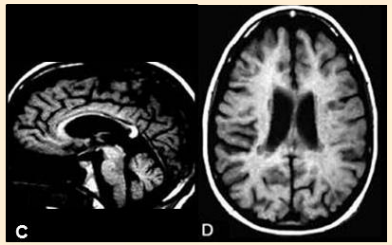
Pericardial effusion


Cerebral infarct

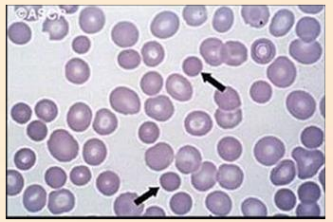

Discoid rash

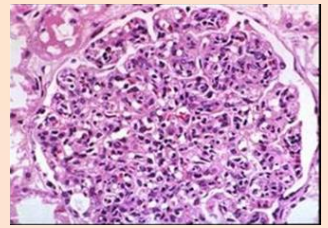

Jaccoud's arthropathy


Vasculitis

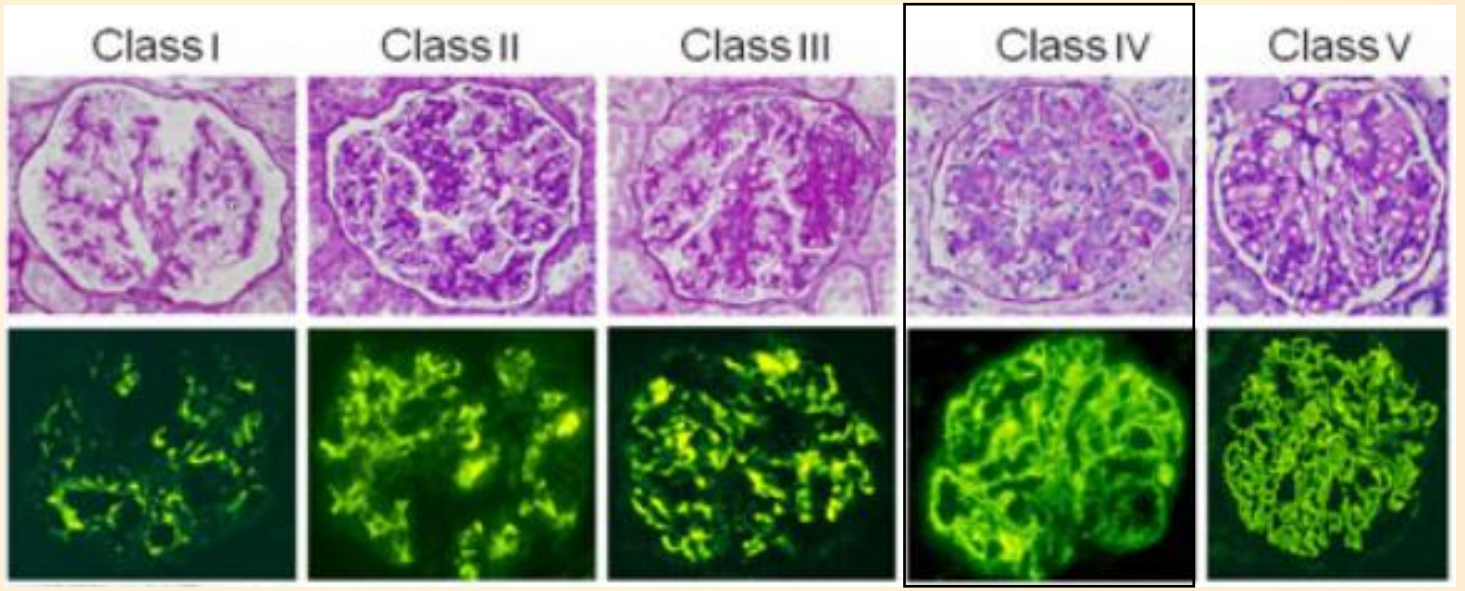


Brain atrophy


Spherocytes


Glomerulonephritis

Jackie has a kidney biopsy done showing class IV lupus nephritis



Minimal Mesangial LN

Mesangial Proliferative LN

Focal Proliferative LN

Diffuse Proliferative LN

Membranous LN

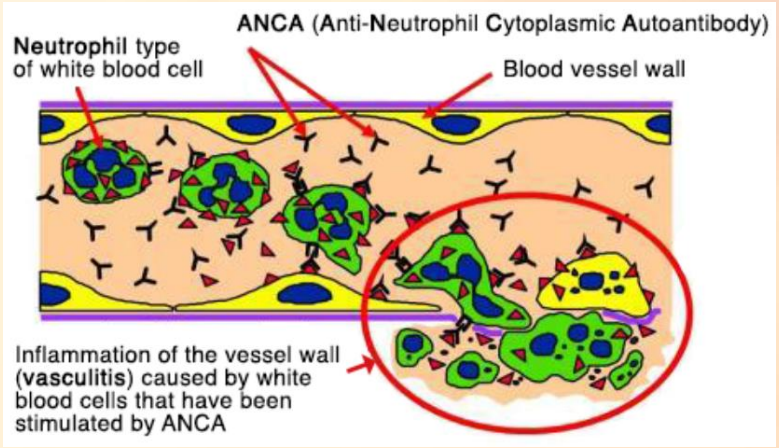
These are usually subclinical and rarely biopsied

These require therapy

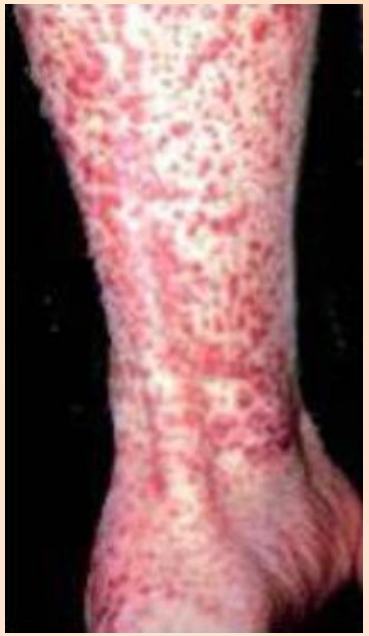
Jackie needs treatment

- Hydroxychloroquine (aka Plaquenil) – Used in almost all patients
- Prednisone: Pulse IV methylprednisolone (500mg/d x 3d then 1mg/kg)
- Steroid sparing therapies to start along with prednisone:
  - Mycophenolate versus Azathioprine
    - MMF: outcomes slightly better than with AZA but can cause spontaneous abortions and severe birth defects
    - Azathioprine has proven safe during pregnancy
  - Cyclophosphamide (IV or oral): potent; used for most severe organ threatening disease
    - Can cause infertility – higher cumulative doses = higher risk
      - Sperm banking; oocyte cryofreezing; GnRH antagonist (e.g. leuprolide)
  - Adjunct therapies: Voclosporine (oral) and Belimumab (IV or SQ) improve response rates
    - Tacrolimus and Cyclosporine (both oral) can also be used; less trial data but less expensive

ANCA-associated Vasculitis

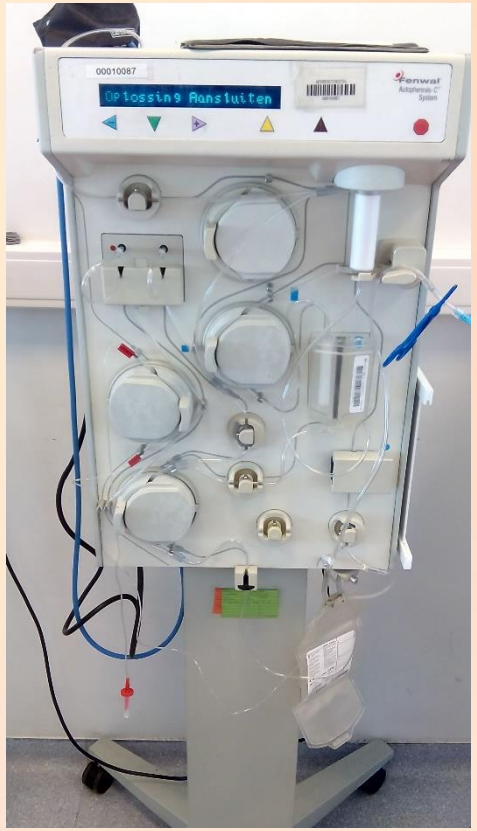


- Vasculitis: Inflammation of blood vessels
  - Large – Medium – Small vessels can be involved
- ANCA vasculitis is a small-vessel vasculitis
  - Anti-Neutrophilic Cytoplasmic Antibodies attach to neutrophils causing them to 'attack' the small blood vessels
  - Systemic disease: fatigue, night sweats, weight loss, leukocytoclastic vasculitis (skin)
- Different diseases based on clinical characteristics
  - Granulomatosis with Polyangiitis (GPA) – formerly known as 'Wegener's
    - Nephritis
    - Lung infiltrates, nodules, hemoptysis
    - Destructive sinusitis – nose bleeds, congestion/nasal discharge, vocal cord paralysis
  - Microscopic Polyangiitis (MPA)
    - Nephritis
    - Lung infiltrates, nodules, hemoptysis
  - Eosinophilic granulomatosis with polyangiitis (EGPA) – formerly known as Churg-Strauss
    - Similar to GPA – granulomas, lung sinus involvement; kidney is less frequent
    - Eosinophilia, asthma



ANCA Vasculitis Treatments

- Induction Therapy:
  - Steroids: IV pulse methylprednisolone (500mg IV QD x 3) then prednisone 1mg/kg
  - Cyclophosphamide (IV) or Rituximab (IV) or combination thereof
  - Plasmapharesis (Diffuse alveolar hemorrhage or severe AKI)
    - Looks like dialysis, but different – centrifugation to separate plasma and remove ‘evil humors
- Maintenance Therapy:
  - Rituximab
  - Azathioprine or Mycophenolate
  - Nobody knows how long continue but most agree 18-24 mos



Wrap up