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](chart.png)

**Prognosis of CKD by GFR and Albuminuria Categories**

<table>
<thead>
<tr>
<th>Albuminuria categories</th>
<th>Description and range</th>
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<tbody>
<tr>
<td><strong>GFR categories (mL/min/1.73 m²)</strong></td>
<td><strong>A1</strong></td>
</tr>
<tr>
<td>Normal to mildly increased</td>
<td>&lt;30 mg/g</td>
</tr>
<tr>
<td>Moderately increased</td>
<td>30-299 mg/g</td>
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<tr>
<td>Severely increased</td>
<td>≥300 mg/g</td>
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**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:
      - Phospholipase A2 receptor antibodies (PLA2R-Ab)

[Diagram of podocyte foot processes showing abnormalities in composition:
- Thickening
- Immune deposits
- Loss of structural integrity]
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 YEAR
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
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)
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 buttocks 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;

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

*subacute cutaneous lupus erythematous
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
Jackie has a kidney biopsy done showing class IV lupus nephritis

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