Chronic Kidney Disease (CKD) and End Stage Renal Disease (ESRD)

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CKD: Definition and Epidemiology

Presence of either kidney damage or decreased renal function
- Duration for > 3 months irrespective of cause
- +/- Albuminuria

HTN, Diabetes Mellitus make up 72% of all cases

More common in African Americans

Prevalence overall on the rise
- Aging populations
- Increased prevalence of HTN, DM, obesity

CKD: Definition and Epidemiology

CKD risk factor for cardiovascular disease
- Angina pectoris
- ACS
- Heart Failure
- Stroke
- AKI
- Peripheral Vascular Disease
- Arrhythmias/Sudden Cardiac Death

< 2% of patients ultimately require RRT
- Most die from CV causes before ESRD
KDIGO CLASSIFICATION - 2012
(Don’t need to remember this table)

 CALCULATION OF eGFR
(estimated GFR)

MDRD (Modified Diet in Renal Disease) formula: widely used.

Current staging of CKD based on MDRD classification.

Some important considerations of MDRD:
1. Can’t be used in AKI, has to be in steady state
2. Underestimates GFR in the healthy
3. Not tested in pregnancy and the very elderly
4. Relies on creatinine and so all the pitfalls associated with it.

CKD EPI equation thought to be more accurate than MDRD

Prevalence of CKD by stage among NHANES participants, 1999-2014

**Etiology of CKD**

<table>
<thead>
<tr>
<th>Cause</th>
<th>% of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Mellitus</td>
<td>44.9%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>27.2%</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>8.2%</td>
</tr>
<tr>
<td>Chronic Interstitial Nephritis or Obstruction</td>
<td>3.6%</td>
</tr>
<tr>
<td>Hereditary or Cystic Disease</td>
<td>3.1%</td>
</tr>
<tr>
<td>Secondary Glomerulonephritis or Vasculitis</td>
<td>2.1%</td>
</tr>
<tr>
<td>Neoplasms or Plasma-Cell Dyscrasias</td>
<td>2.1%</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>4.6%</td>
</tr>
<tr>
<td>Uncertain Cause</td>
<td>5.2%</td>
</tr>
</tbody>
</table>

*U.S. Renal Data System 2018*
CKD Snapshots

Diabetic Nephropathy

Most common cause of CKD/ESRD in US
Pathogenesis: hyperglycemia and glycation of tissue proteins leads to mesangial expansion; glomerular basement membrane thickening; podocyte injury; and hyaline deposition in the glomerular arterioles (nodular glomerulosclerosis or Kimmelstiel-Wilson lesions)

<table>
<thead>
<tr>
<th>Diabetic Nephropathy</th>
<th>Type I DM</th>
<th>Type II DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>15 years</td>
<td>5-10 years</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>Precedes nephropathy</td>
<td>Not always the case</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hematuria</td>
<td>Can be present</td>
<td>Can be present</td>
</tr>
<tr>
<td>Treatment</td>
<td>Tight control of DM early in the diagnosis and ACEI/ARB for BP control</td>
<td></td>
</tr>
</tbody>
</table>

Progression of Diabetic Nephropathy

Not always the case and albuminuria can improve with tight DM and BP control.
Hypertensive Nephropathy

2nd most common cause of CKD/ESRD in US.
Also known as "hypertensive nephrosclerosis" or "benign nephrosclerosis".
African Americans at 8 fold increased risk even if good BP control is achieved.
Possible role of apolipoprotein -1 (APOL-1) gene variation.
Generally seen in patients with long standing history of HTN with slow gradual decline in renal function.
Pathogenesis: Hyaline arteriosclerosis of small arteries and arterioles in the kidney along with focal and segmental sclerosis and interstitial fibrosis.
Proteinuria is present but generally less than a gm/24 hours.
Small to normal size kidneys on ultrasound imaging.
Treatment is control of BP.

Glomerular Diseases: Glomerulonephritis

CLINICO-PATHOLOGICAL DIAGNOSES: based on biopsy findings in appropriate clinical settings
IgA nephropathy
Post-infectious glomerulonephritis
Membranoproliferative glomerulonephritis
Lupus nephritis
Rapidly progressive glomerulonephritis

IgA Nephropathy

Most common glomerulonephritis worldwide
IgA deposits in glomeruli
Progresses to CKD over several decades in 25-30% of cases
Typically presents as hematuria 1-2 days after URI
Less common presentations:
- MCD, membranous/proteinuria (older patients)
- AKI, nephrotic range proteinuria (rare)
Many associated systemic diseases (RA, HIV, HSP)
Post-infectious GN

Most often a complication of streptococcal skin infections (impetigo) or streptococcal pharyngitis

Immune complexes become lodged in the glomerular basement membrane (GBM)

Complement activation leads to GBM destruction

Onset of disease usually 2-4 weeks after initial infection

High ASO titre, low serum complement usual findings

Membranoproliferative Glomerulonephritis - MPGN

Occurs most commonly in children and young adults

Seen with Hepatitis – C infection

Caused by deposits in the GBM and the mesangium

Complement activation leads to glomerular destruction

Not to be confused with membranous glomerulonephritis (does not affect mesangium)

Lupus Nephritis

Auto-immune disease with anti-nuclear antibodies and complement activation leading to multi-system organ involvement.

Kidney involvement seen in up to 50% at some point in time.

Six histologic subtypes of disease described

I: minimal mesangial nephritis

II: mesangial proliferative nephritis

III: focal lupus nephritis

IV: diffuse proliferative nephritis

V: membranous nephritis

VI: advanced sclerosing lupus nephritis
Lupus Nephritis

Lupus nephritis staging does NOT imply a chronological progression from stages I-VI.

- Can see stage V with other stages
- Stage IV is most common and most severe

Clinical sequelae
- HTN, hematuria, proteinuria/nephrosis
- Progressive CKD, thrombophilia

Rapidly Progressive Glomerulonephritis- RPGN

A.K.A. “crescentic glomerulonephritis”
- High numbers of crescents seen on renal biopsy histology
- Rapid decline in renal function (in days/weeks/months)

Common causes
- Goodpasture’s syndrome
- Immune complex GN – Lupus, Ig A
- Pauci-immune as in ANCA Vasculitis

Glomerular Diseases: Nephrotic Syndrome

- Minimal change disease
- Focal segmental glomerulosclerosis
- Membranous nephropathy
- Amyloidosis
Minimal Change Disease

Most common cause of nephrotic syndrome in young children
- Can also occur in older children and adults

More common in those with history of autoimmunity

Bland light microscopy findings
- Hence the name of the disease

Usually treatable with steroids and ACE-I therapy

Focal Segmental Glomerulosclerosis - FSGS

Occurs in children and adolescents more often than in adults
- Most common cause of nephrotic syndrome in adults, though

Can be primary disease or secondary to other conditions
- HIV, heroin use, familial forms

Less responsive to treatment compared to minimal change disease

Can be misdiagnosed as Minimal Change Disease as focal sclerosis can be missed.
Membranous Nephropathy

- 2nd most common cause of nephrotic syndrome in adults
- Tendency to affect Caucasians
- Most cases are primary
- Increased risk of thromboses compared to other nephrotic syndromes
- Secondary causes:
  - SLE, infections (hepatitis B), drugs, tumors
- Treatment: immunosuppression (mixed results)

Amyloidosis

- Variety of disorders in which amyloid proteins deposit in tissues/organs and cause damage
- Primary disease: AL amyloidosis
- Secondary disease: AA amyloidosis
- Clinical features: CKD, heart disease, skin lesions, macroglossia, GI disease, polyneuropathy

Miscellaneous: Cholesterol Atheroembolic Disease

- Seen in the presence of severe atherosclerotic disease.
- Occurs when cholesterol is released from an atheromatous plaque into the bloodstream.
- Generally occurs after an intervention (angiogram, vascular surgery) but can occur spontaneously as well (hemodynamic stress).
- Clinical manifestations: Fever, malaise, digital gangrene, characteristic rash (livedo reticularis), renal failure.
- Low complements and peripheral eosinophilia can be present.
- Definitive diagnosis is by tissue biopsy.
- Treatment: Supportive medical management.
Polycystic Kidney Disease

Two types: ADPKD – Autosomal Dominant Polycystic Kidney Disease and ARPKD – Autosomal Recessive Polycystic Kidney Disease
ADPKD more common than ARPKD, approximately 1 in every 400 to 1000 live births
Mutations in PKD1 (85% cases, chromosome 16) or PKD2 (15% cases, chromosome 4) genes account for most cases of ADPKD.
Clinical presentation: Hematuria, flank pain, kidney stones, Concomitant liver cysts, diverticulosis of the colon, mitral valve prolapse and intracranial aneurysms can be seen.
Diagnosis: Genetic testing available and presence of multiple cysts on imaging studies.

CKD Management

CONSEQUENCES OF RENAL FAILURE
MAD HUNGER - PNEUMONIC
• Metabolic Acidosis
• Dyslipidemia (especially high triglycerides)
• Hyperkalemia
• Uremia – clinical syndrome marked by ↑ BUN leading to nausea, anorexia, asteraxis, encephalopathy, pericarditis, platelet dysfunction.
• Na+/H2O retention – HTN, Volume Overload, Heart failure
• Growth retardation and developmental delay
• Erythropoietin deficiency
• Renal Osteodystrophy
CKD: Stage II/III Management:
“Conservative Renoprotection”

Promote healthy living
- Smoking cessation
- Normal body weight, exercise

BP, lipid control

Glycemic control (diabetics)

CKD: Stage II/III Management:
“Conservative Renoprotection”

Optimize coexistent liver, cardiac disease

ACE-I/ARB therapy
- Especially with proteinuria

Medication dosage adjustment per eGFR

Avoid nephrotoxic agents (NSAIDs, e.g.)

CKD Stage III-V Management

Step One:

Nephrology Referral
CKD Stage III-V Management:

**Hypertension Control**

Pathophysiology: Sodium retention due to decreased GFR
  - High renin state

Lifestyle changes play a huge role: 2 gm sodium diet
  - Weight loss, smoking cessation

Just as an example: One slice of bread can contain anywhere from 80 to 230 mg of sodium, and a slice of frozen pizza can contain between 370 and 730 mg.

CKD Stage III-IV Management:

**Proteinuria Reduction**

Goal is < 300mg – 500mg/day

- Slows CKD progression
- Usually through ACE-I +/-ARB

Reduce dietary protein intake
  - 0.8 – 1.0g/kg/day
CKD Stage IV-V Management: Mineral/Bone Disorders

- Reduced renal phosphorus clearance
- Hyperphosphatemia
- Increased FGF-23

Vitamin D resistance
- Reduced 1,25 (OH), vitamin D
- Calcitriol deficiency

Secondary Hyperparathyroidism

High Phosphorus Diet

- All Dairy Products
- Dried Beans and Lentils
- Processed meat
- Chocolate
- Cold, Diet, and Beer
- Muffins, Biscuits, or Pancakes from Mix
- Liver or Organ Meats
- Nuts and Seeds
CKD Stage IV-V Management: Anemia

Many contributing factors:
- ↓ Erythropoietin synthesis
- ↓ Erythrocyte half-life
- Blood loss in dialysis patients

Treatment goals:
- Target hemoglobin 9-11 g/dL
- Target transferrin saturation > 20%

Treatment options:
- Exogenous erythropoietin – subcutaneous or IV routes
- Iron supplementation – oral or IV

CKD Stage IV-V Management: Metabolic acidosis

Early CKD: normal anion gap metabolic acidosis
- Due to defective tubular hydrogen ion secretion

Advanced CKD: increased anion gap acidosis
- Due to defective sulfate acid secretion

Long term effects if metabolic acidosis in CKD:
- Progression of CKD by accelerating interstitial fibrosis
- Bone resorption and osteopenia

Treatment options:
- Sodium bicarbonate or sodium citrate.
- Aim to keep serum bicarbonate in the normal range (22-24).
- Would avoid in volume overloaded patients.

ESRD – End Stage Renal Disease

Renal Replacement Therapy Options

1. Kidney Transplantation: Living or deceased donor
2. Hemodialysis: In-center or home HD
3. Peritoneal dialysis

Kidney transplantation is the best option but not everyone is a candidate and not enough kidneys available.
DIALYSIS

- Dialysis is a process by which the solute composition in one compartment (blood) is altered by exposing it to a solution in a second compartment (dialysate) through a semipermeable membrane.
- It is a process of removing toxins and fluid from the extravascular compartment.
- The goal of dialysis is to remove accumulated fluid and toxins to maintain their concentrations below the levels at which they produce uremic symptoms.
PRINCIPLE MECHANISMS IN PD

<table>
<thead>
<tr>
<th>SIMPLE DIFFUSION</th>
<th>OSMOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Removal of toxins and waste products</td>
<td>Volume removal by osmotic gradient using dextrose</td>
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</tbody>
</table>

Sequelae of ESRD

Uremic cardiovascular disease
- Medial vascular calcification
- Arterial stiffness
- LV hypertrophy
- Higher risk of cardiac arrest and heart failure