Preserve Those Nephrons

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Objectives

• Identify risk factors for developing chronic renal insufficiency

• Understand treatment approaches to preserve renal function

• Responsible prescribing practices for patients with renal insufficiency

Introduction

Epidemiology

• 30 million adults
• Estimated millions more undiagnosed
• Prevalence of 14%
• ½ have diabetes and/or CVD
• Kills more people annually than breast or prostate cancer
• > 600,000 Americans have End Stage Renal Disease (ESRD)
• Approximately 2/3 are on dialysis
• Approximately 21,000 new cases of ESRD annually

Prevalence

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>CKD</th>
<th>ESRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>African Americans</td>
<td>3.7</td>
<td>3.5</td>
</tr>
<tr>
<td>Asian Americans</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Native Americans</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Mexican Americans</td>
<td>1.1</td>
<td>1.5</td>
</tr>
</tbody>
</table>

• Increased hospitalizations and readmissions as CKD advances
  • In 2013, 10% of patients with CKD were readmitted within 30 days
• Mortality rates more than double with CKD
  • Higher in men
  • Higher with diabetes
• In 2013, Medicare spending exceeded $50 billion (20% of total)
  • Diabetes and CHF doubles spending
• Mortality rates decreasing for dialysis and transplant
• > 50% deaths in ESRD patient from CVD
  • Arrhythmia and cardiac arrest
What we know

• Most kidney diseases attack the nephron
• "disease multiplier"
• Diabetes and HTN are the top two leading causes of CKD in adults
• Lose approximately 1 mL/min/1.73 m² per year after age 40 due to aging
• "silent disease": Patient awareness is < 10% for stages 1-3
• Screening and Early Detection
• Heart Disease is major cause of death

Kidney Transplant

• Median wait time 3.5 years
• Less than 1/3 are from living donors
• 1 year post transplant survival rates > 95%

Leading Causes of ESRD in Pediatrics

<table>
<thead>
<tr>
<th>Cause</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic/Hereditary/Congenital Diseases</td>
<td>33%</td>
</tr>
<tr>
<td>Glomerular Disease</td>
<td>25%</td>
</tr>
<tr>
<td>Secondary causes of Glomerulonephritis</td>
<td>13%</td>
</tr>
</tbody>
</table>

Stages

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt; 90 mL/min</td>
</tr>
<tr>
<td>2</td>
<td>60 – 89 mL/min</td>
</tr>
<tr>
<td>3</td>
<td>30-59 mL/min</td>
</tr>
<tr>
<td>4</td>
<td>15-29 mL/min</td>
</tr>
<tr>
<td>5</td>
<td>&lt; 15 mL/min</td>
</tr>
</tbody>
</table>

Risk Factors and Screening
### Risk Factors
- Diabetes
- HTN
- Glomerulonephritis and other systemic diseases
- Family History
- Congenital malformations
- African Americans, Hispanics, Pacific Islanders, American Indians, and the Elderly

### Diabetic Nephropathy
- Type 1, Type 2, secondary diabetes
- Glomerular Sclerosis
- Albuminuria ("microalbuminuria")
  - 30 – 300 mg/day
  - Predicts future nephropathy
  - 20-30% at 15 years
  - <50% develop overt nephropathy
- Hematuria
  - May indicate severity

### Hypertension
- Nephrosclerosis
- 24-hour ambulatory blood pressure
- May be stronger predictor of:
  - CVD
  - Death

### Causes of Hypertension
- Sodium Retention
- Renin Secretion
  - Stimulated by renal ischemia
- Sympathetic Nervous System
- Secondary HPT
  - Increased intracellular calcium causes vasoconstriction
- Erythropoietin treatment for anemia

### Glomerulonephritis and systemic diseases
- Autoimmune
  - SLE
- Medication/Drugs
  - NSAIDs, heavy metals
- Infection associated
  - HIV, Strep, HCV

### Familial and Congenital
- Diabetic Nephropathy
- Autosomal Dominant Polycystic Kidney disease
- IgA Nephropathy (Eastern Kentucky)
- Renal hypoplasia or dysplasia
Screening
• Screening everyone has no clear benefit at this time
• Who to screen:
  • Type 1 diabetics 5 years after dx and then annually
  • Type 2 diabetics at dx and then annually (albuminuria)
• Consider Screening
  • Family Hx of diabetic nephropathy

Screening Tests
• Spot urine to creatinine ratio
• Serum creatinine
• Estimated Glomerular Filtration Rate
  • Modification of Diet in Renal Disease Study (MDRD)
  • Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)

Screening Cautions
• Albuminuria
• Creatinine

Evaluation and Diagnosis

Initial Evaluation Labs
<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Urinalysis</td>
<td>Glucose</td>
</tr>
<tr>
<td>Urine Album to Creatinine</td>
<td>Calcium</td>
</tr>
<tr>
<td>Serum Creatinine with sGFR</td>
<td>Phosphorus</td>
</tr>
<tr>
<td>BUN</td>
<td>Albumin</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>CBC</td>
</tr>
</tbody>
</table>

Further Evaluation Labs
<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B Serology</td>
<td>Complement 4</td>
</tr>
<tr>
<td>Hepatitis C Serology</td>
<td>Serum Protein Electrophoresis</td>
</tr>
<tr>
<td>Antinuclear antibody test</td>
<td>Urine Protein Electrophoresis</td>
</tr>
<tr>
<td>Rheumatoid Factor</td>
<td>Renal Ultrasound</td>
</tr>
<tr>
<td>Complement 3</td>
<td>Dilated Retinal Exam</td>
</tr>
</tbody>
</table>
CKD Diagnosis

- All of the following are true:
  - > 3 months of urine albumin > 30 mg/g creatinine
  - Other clinical findings (hematuria)
  - Decreased function as measured by eGFR < 60 mL/min/1.73 m²

- Tip: Include patient's baseline eGFR in your note with diagnosis

Diabetic Kidney Disease

- Can be diagnosed clinically if patient has:
  - Diabetes
  - Retinopathy
  - Albuminuria

  and further evaluation tests are negative

Inflammation and Infection

- Stages
  - Stage 1: Damage with normal function > 89 mL/min
  - Stage 2: Damage with mild loss 60 – 89 mL/min
  - Stage 3: Mild to severe loss 30 - 59 mL/min
  - Stage 4: Severe loss of function 15 - 29 mL/min
  - Stage 5: Failure < 15 mL/min Requires dialysis or transplant

Managing patient with CKD

- Monitor UACR
- Monitor eGFR
- Control Blood Pressure
- Control Blood Glucose
- Lower Urine Albumin Levels
- Dietician
- Social Worker
- Pharmacist
- Nephrologist
Diabetes

- Tight glucose control
  - Help prevent mesangial injury
  - Reduce microvascular complications (reducing AGE)
  - Reduce proteinuria (prevent GBM permeability)
  - Reduce inflammation and fibrosis
- Ace inhibitor or ARBs
  - Reduce blood pressure
  - Blocks renin-angiotensin system
  - Antagonizes profibrotic effects of angiotensin II
  - Reduce serum concentrations of TGF-beta
  - Reduced progression in Type 1 DM by about 50%
- Diet and Weight loss
  - Reduce albuminuria
  - Increase eGFR

Type 2 Diabetes Treatment

- Diet
- Exercise
- Metformin
- Sulfonylurea, thiazolidinedione, SGLT-2 inhibitor, or DPP-4 inhibitor
- Insulin

Hypertension

- HTN can Cause CKD
- CKD can Cause HTN
- How high is too high?
  - AAFP treat if BP is ≥ 150 / ≥ 90 in pts 60 yoa or older
  - AAFP treat if BP is ≥ 140 / ≥ 90 in pts less than 60 yoa
  - AAFP treat if BP is ≥ 140 / ≥ 90 in pts ≥ 18 yoa with DM (thiazide, CCB, ACEi, or ARB)
  - AAFP treat if BP is ≥ 140 / ≥ 90 in pts ≥ 18 yoa with CKD (ACEi or ARB)
- Low Sodium Diet
- Tip: treat BP per patients ability to safely tolerate

Proteinuria

- ≥ 500 mg/day
  - ACE inhibitor or ARB
  - Diuretics
  - Non-dihydropyridine CCBs
- Goal
  - < 1000 mg/day
  - < 3.5 g/day

Immunization

- Influenza annually
- Hepatitis B for stages 4 and 5
- Pneumonia PCV13 followed by PPSV23 at least 8 weeks apart
- PPSV23 revaccination every 5+ years
- Shingrix 2 dose series 2-6 months apart

Complications
Complications

- Cardiovascular Disease
- Anemia
- Malnutrition
- Mineral and Bone Disorders
- Hyperkalemia
- Sexual Dysfunction

Cardiovascular Disease

- CKD is an independent risk factor
- Risk is increased two fold in those with CKD
- Most frequent is atherosclerotic disease
- Increased cardiovascular procedures

Anemia of CKD

- Normocytic, normochromic
- Screen annually for eGFR $\geq 45$ mL/min
- Screen twice yearly for eGFR $< 45$ mL/min
- CBC, RBC indices, Reticulocyte count, serum Fe, TIBC, Tsat, Ferritin, folate, B12, occult blood in stool
- Treatment
  - If Fe deficient, Tx first (goal of Tsat $> 25\%$ and ferritin $> 200$ ng/mL)
  - Erythropoiesis-stimulating agents for CKD and Hb $< 10$ g/dL

Malnutrition

- Late to ESRD
- Decreased food intake
- Decreased intestinal absorption and digestion
- Metabolic acidosis
- Low protein diets
- Serum albumin and body weight q3 mos if eGFR $< 20$ mL/min
- Albumin level correlates with RRT tolerance

Mineral and Bone Disorders

- Hyperphosphatemia
- Hyperparathyroidism

Hyperkalemia

- Frequency up to 50% in patients with CKD compared with 2-3% in general population
- Increased risk: pts with DM, advanced CKD, kidney transplant recipient, taking RAAS inhibitors
- An episode of hyperkalemia with CKD increases mortality within one day of the event
Hyperkalemia
• Increased if:
  • Oliguria
  • High-potassium diet
  • Increased tissue breakdown
  • Hypoaldosteronism

• Prevention and Treatment:
  • Low potassium diet (<1500 to 2700 mg/day)
  • Avoid NSAIDs
  • Emergent Tx if K>7 mEq/L or if symptomatic
    • Calcium
    • Insulin with glucose
    • Lasix
    • Kayexalate
    • Dialysis

Sexual Dysfunction
• >50% of men with uremia have:
  • ED
  • Decreased libido
  • Decreased frequency of intercourse

• Treatment
  • Sildenafil
  • Tadalafil

When to Refer
• eGFR < 30 mL/min
• Difficult to control hypertension
• Interprofessional Resources
• Patient's wishes
• Up to 50% saw Nephrologist within 1 month of starting RRT
  • Dialysis initiated in the hospital
• Late referral increases:
  • Acidosis, anemia, hypercalcemia, hypoalbuminemia, hyperphosphatemia

Cardiovascular Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>CrCl Threshold (mL/min)</th>
<th>Recommendation</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiloride</td>
<td>&lt;30</td>
<td>Avoid use</td>
<td>Hyperkalemia, hyponatremia</td>
</tr>
<tr>
<td>Enalapril</td>
<td>&gt;30</td>
<td>Avoid use</td>
<td>Hyperkalemia, hyponatremia</td>
</tr>
<tr>
<td>Esmolol</td>
<td>&gt;30</td>
<td>Avoid use</td>
<td>Hyperkalemia, hyponatremia</td>
</tr>
<tr>
<td>Furosemide</td>
<td>&gt;30</td>
<td>May need higher dose</td>
<td>Reduced renal function</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>&lt;10</td>
<td>Avoid use</td>
<td>Fluid leaving the loop of Henle is reabsorbed in the distal tubule</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>&lt;30</td>
<td>Avoid use</td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td>Triamterene</td>
<td>&lt;30</td>
<td>Avoid use</td>
<td>Hyperkalemia, hyponatremia</td>
</tr>
</tbody>
</table>

Antihypertension Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>CrCl Threshold (mL/min)</th>
<th>Recommendation</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lisinopril</td>
<td>&lt;30</td>
<td>Initial 2.5 mg qd</td>
<td>Possible deterioration of renal function</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Use with caution, consider additional ECG monitoring</td>
<td>Increased risk of adverse events, atrioventricular block</td>
<td></td>
</tr>
</tbody>
</table>

Medications
CNS and Analgesics Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>CrCl Threshold (mL/min)</th>
<th>Recommendation</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine</td>
<td>&lt; 30</td>
<td>Avoid use</td>
<td>Increased nausea, diarrhea</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>&lt; 60</td>
<td>Reduce Dose</td>
<td>Increased CNS AE</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>≤ 80</td>
<td>Reduce Dose</td>
<td>Increased CNS AE</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>&lt; 60</td>
<td>Reduce Dose</td>
<td>Increased CNS AE</td>
</tr>
<tr>
<td>Tramadol</td>
<td>&lt; 30</td>
<td>Immediate Release dose reduction</td>
<td>Avoid using extended release increased CNS AE</td>
</tr>
</tbody>
</table>

Diabetes Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>CrCl Threshold (mL/min)</th>
<th>Recommendation</th>
</tr>
</thead>
</table>

Diabetes Medications: DPP-4 Inhibitors

<table>
<thead>
<tr>
<th>Medication</th>
<th>CrCl Threshold (mL/min)</th>
<th>Recommendation</th>
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Diabetes Medications: SGLT2 Inhibitors

<table>
<thead>
<tr>
<th>Medication</th>
<th>CrCl Threshold (mL/min)</th>
<th>Recommendation</th>
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GI Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>CrCl Threshold (mL/min)</th>
<th>Recommendation</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine</td>
<td>&lt; 50</td>
<td>Reduce Dose</td>
<td>Mental status changes</td>
</tr>
<tr>
<td>Famotidine</td>
<td>&lt; 50</td>
<td>Reduce Dose</td>
<td>Mental status changes</td>
</tr>
<tr>
<td>Nizatidine</td>
<td>&lt; 50</td>
<td>Reduce Dose</td>
<td>Mental status changes</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>&lt; 50</td>
<td>Reduce Dose</td>
<td>Mental status changes</td>
</tr>
</tbody>
</table>

Erectile Dysfunction Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>CrCl Threshold (mL/min)</th>
<th>Recommendation</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil (PRN)</td>
<td>&lt; 30</td>
<td>Initial 25 mg</td>
<td>Increased risk of adverse events</td>
</tr>
<tr>
<td>Tadalafil (PRN)</td>
<td>30 – 50</td>
<td>&lt; 30</td>
<td>Increased risk of adverse events</td>
</tr>
<tr>
<td>Tadalafil (once daily)</td>
<td>&lt; 30</td>
<td>Initial 5 mg qd, max 10 mg q48 hours</td>
<td>Increased risk of adverse events</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Max 5 mg q72 hours</td>
<td></td>
</tr>
</tbody>
</table>

Context is King with CKD

- Know patient baseline, risks, goals
- Inform the patient and the treatment plan.
- Normalize what you can
- Get help from an interprofessional team

References

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- https://www.nih.gov/
- https://www.cdc.gov/nchs/nhanes/index.htm

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