Chronic Kidney Disease: A Silent Epidemic (Part 1)

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Objectives

- Define CKD: prevalence, epidemiology, and risk factors
- Discuss occurrence of complications and co-morbid conditions of CKD
- Describe treatment guidelines
Kidney Anatomy

- Normal adult kidney is 11–12 cm long; Wt: 125–170 g
- Left kidney > Right kidney in size, male > female; located at T12 to L3
- The kidney (a bean-shaped structure) is composed of: parenchyma and the collecting system. Parenchyma consists of the renal cortex and inner medulla. The collecting system includes the calyces that form the renal pelvis that drains into the ureters
- Kidneys are usually perfused by a single renal branching artery
Physical Location of Human Kidney

- LEFT KIDNEY
- URETER
- BLADDER
Anatomy of the Kidney

- FIBROUS CAPSULE
- CORTEX
- PYRAMID
- PAPILA
- RENAL CALYX
- RENAL PELVIS
- RENAL ARTERY
- RENAL VEIN
- URETER
Microscopic Anatomy

- There are 300,000 to 1,200,000 nephrons (basic structure and functional unit of the kidney) in a single kidney
- Glomeruli, loop of Henle, proximal and distal tubule compose the nephron
A MICROSCOPIC LOOK AT THE RENAL CORTEX

- Bowman's capsule
- Afferent arteriole
- Capsule
- Proximal tubule
- Distal tubule
- Cortex
- Collecting tubule
- Pyramid
- Loop of Henle
- Papillary duct
- Renal calyx
- Glomerulus
Glomerulus Anatomy
Basic Concepts of the Kidney

- Regulatory function: Controls composition and volume of the body fluids
- Maintains acid-base balance by varying the excretion of water and solutes
- Endocrine function: producing several hormones:
  - renin
  - erythropoietin
  - active vitamin D3
  - prostaglandins, adenosine, etc
Basic concepts of the Kidney

- Excretory function: removes various nitrogenous metabolic end products in urine. For example, the kidneys filter blood through the glomerulus forming an ultrafiltrate.

- As the ultrafiltrate passes through the kidney, reabsorption of essential products and secretion of unwanted products occur.
DYSFunction of the Kidney

- **Disrupts “HOMEOSTASIS”**.
  - Excretion of waste products of metabolism.
  - Water electrolyte and acid base balance.

- **Disrupts HORMONAL FUNCTION**.
  - Erythropoietin.
  - Vitamin D3
  - Renin, prostaglandins, angiotensinogen 2, nitric oxide, endothelin and bradykinin
  - Miscellaneous:
    - Gluconeogenesis
**CKD: Background**

- Common disorder
  - Less common than HTN
  - More common than diabetes

- Progressive disorder
  - Underdiagnosed
  - Undertreated ... due to lack of agreement of its definition and staging

Chronic Kidney Disease (CKD)

- Includes **all** types and **levels** of kidney dysfunction
  - Avoid usage of “CRI” and “CRF,” which do not indicate severity of dysfunction
- CKD is not etiology-specific and causation must always be pursued
  - CKD from “diabetic nephropathy”
  - CKD from “hypertensive nephrosclerosis”
  - Membranous nephropathy

Overview of CKD

Epidemiology of CKD

- 20 million adults in the United States
- Millions more at risk:
  - Aging population
  - Increasing prevalence of diabetes mellitus
  - Increasing prevalence of hypertension
CKD: Care is Costly

- CKD Care: $19.3 Billion/Yr
- Total NIH Budget: $17.8 Billion/Yr
- CKD Accounts for 6% of Medicare Payments
- Lost Income for pts is $2–4 Billion/Yr

CKD: Prevalence by NHANES III

Endstage Renal Disease (ESRD)

- ESRD
  - Medicare term — permits federal reimbursement
  - Pt requires renal replacement therapy for survival
    - Hemodialysis
    - Peritoneal dialysis
    - Kidney transplantation

ESRD: Increasing Problem

- **ESRD incidence, prevalence, cost**
  - Pts living longer
  - Increased prevalence of diabetes
  - Prevalence in 2003, 300,000+ pts
  - Projection for 2010, 600,000 pts

- Wayne Co., MI — highest prevalence of ESRD *per capita* of all U.S. counties*
  - 1079 of 3093 new starts in MI, 2001
  - 3913 of 9913 prevalent pts in MI, 2001

**ESRD: Disease of the Elderly**

United States Renal Data System (USRDS) 1997 Annual Data Report.
ESRD: ↑ Risk by Ethnicity
Racial Differences in ESRD in U.S. from 1990–1998

*P < 0.0001
### ESRD: Prevalence by Ethnicity

<table>
<thead>
<tr>
<th>Abbrev</th>
<th>Percent (%) of Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA</td>
<td>0.9</td>
</tr>
<tr>
<td>Asian</td>
<td>3.8</td>
</tr>
<tr>
<td>AA</td>
<td>31</td>
</tr>
<tr>
<td>C</td>
<td>32.6</td>
</tr>
</tbody>
</table>

**Abbrev:** NA, Native American; AA, African-American; C, Caucasian.

**n = 361,031**

United States Renal Data System (USRDS) 1997 Annual Data Report.
**ESRD**: Incidence by Ethnicity
Racial Differences in ESRD in U.S. from 1990–1998

United States Renal Data System (USRDS). 2000 Annual Data Report • WWW.USRDS.ORG.
ESRD: ↑ Incidence and Prevalence

Diabetes is the most common cause in Caucasians, Hispanics, Asians, and overall. Among African-Americans, hypertension is the most common cause of ESRD.

ESRD: Racial Distribution for Comorbidities in Dialysis (1999)

§ Diabetes mellitus as a primary diagnosis or contributing diagnosis.
‡ Diabetes mellitus that requires insulin treatment, which is a subset of the diabetes category.

United States Renal Data System (USRDS) 2000
Annual Data Report • WWW.USRDS.ORG
Inpatient Days among Elderly Medicare Pts with CKD in the United States.

GFR and Hospitalization

Age-Standardized Rates of Hospitalization


Change in

CKD

2

3

4

ESRD
CKD Becomes the Focus

• **Rationale** for Initiative

1. CKD is a public health problem.

2. Economical, effective testing methods and therapies exist.

3. Testing and therapy are inadequately applied.


Timely Referral Keeps pts Out of the Red Zone

NKF CKD Stage by MDRD GFR Equation

Refer in Stage 1 or 2:
- Uncontrolled HTN
- Hematuria
- Proteinuria
- Structural lesion

NORMAL AGE DECLINE

GFR (mL / min / 1.73 m²)

CKD: Early CKD Treatment Preserves Kidney Function

CKD Complications
Evolution and Acceleration by Stage

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>Affected pts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hypertension</td>
</tr>
<tr>
<td>2</td>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>3</td>
<td>Anemia (Hgb &lt; 12 g/dl)</td>
</tr>
<tr>
<td>4</td>
<td>Phosphorus &gt; 4.5 mEq/L</td>
</tr>
</tbody>
</table>

DM, ARF: CKD complications may occur earlier
Death Is Recognized To Be a More Common Event Than Dialysis in CKD

5-Year Follow-Up

Patient population: health plan patients with estimated GFR $^\dagger$ <90 followed up until RRT, death, or disenrollment from health plan. N=27,998.

*RRT=renal replacement therapy; $^\dagger$GFR=mL/min/1.73 m$^2$

**CKD: Three-Fold Initiative**

1. Screen and prevent CKD in pts who are **at-risk**
2. Develop an early CKD identification process
3. Establish a collaborative disease management model for internists, family practitioners, **and** nephrologists
### Detection of pts at Risk

**Measures of Kidney Function**
- Serum creatinine
- BUN
- Creatinine clearance
- GFR

**Markers of Kidney Damage**
- Microalbuminuria
- Overt proteinuria

**Other Physiologic Markers**
- Hemoglobin/hematocrit
- Total cholesterol
- Triglycerides
- Calcium/phosphorus
- Intact parathyroid hormone
- Serum bicarbonate
- Serum electrolytes
- Albumin

BUN = blood urea nitrogen; GFR = glomerular filtration rate.
Pereira. Personal communication.
**CKD: Screening and Prevention**

- **Identify at-risk medical populations**
  - Hypertension
  - Diabetes
  - Metabolic syndrome
  - 1\textsuperscript{st} degree relatives of ESRD pts

- **CKD history often neglected during Hx**

- **Identify at-risk ethnic groups**
  - Hispanics
  - African-Americans
  - American Indians (Native Americans)

United States Renal Data System (USRDS) 2000 Annual Data Report • WWW.USRDS.ORG.
**CKD:** High-Risk Groups

- Diabetics with urine Alb:Cr ratios >30 mg Alb/1 g Cr
- Non-diabetics with urine Alb:Cr ratios >300 mg Alb/1 g Cr
- Non-diabetics with MDRD GFR <60 mL/min/1.73 m²

CKD: Screening and Prevention

- Screening at-risk pts
  - Biochemical profile
  - Urinalysis with microscopic exam
  - Urine protein (albumin) determinations
  - MDRD GFR estimation
**CKD: Three-Fold Initiative**

- Screening of pts at-risk for CKD

2. Development of an early CKD identification process

- Establishment of a disease management protocol between internists and family practitioners and nephrologists
**CKD: Evolution of GFR Estimating Methods**

- **BUN**
  - S\_Cr
  - Highly Insensitive For CKD Detection

- **24-h CrCl**
  - Overestimates GFR
  - Unnecessary test

- **Cockroft Gault Eqn**
  - Estimates raw CrCl, not GFR

- **MDRD GFR Eqn**
  - Validated
  - Best choice

CKD: MDRD GFR

- Multi-variable equation
  - Demographics: Age, Gender, Ethnicity
  - Biochemical: Albumin, $S_{Cr}$, BUN
- Validated in 577 pts
  - By iothalamate clearance
  - For GFRs 30–90 mL/min/1.73 m²
- MDRD GFR Eqn. 7 (mL/min/1.73 m²)
  \[
  = 170 \times S_{Cr}^{-0.999} \times Age^{-0.176} \times BUN^{-0.17} \times Alb^{0.318} \times 0.762 \quad \text{(female)} \quad \times 1.18 \quad \text{(African-American)}
  \]

CKD: Classification by MDRD GFR

- **Rationale** for use
  - GFR — direct measurement of kidney function
  - GFR — best index of kidney function in health and disease
  - GFR — correlates with pathologic severity of disease
  - GFR — correlates functional level with risks of CKD progression and development of CV disease

**CKD: NKF Definition**

- Disorder must be >3 mo duration
  - MDRD GFR <90 mL/min/1.73 m² or
  - GFR >90 mL/min/1.73 m² with either
    - Parenchymal abnormality (cyst, scar) or
    - Hematuria (>4 RBCs/hpf) confirmed by microscopical examination on 2 occasions or
    - Proteinuria (2 occasions, 1 mo apart)
      - Dipstick ≥2+ or 100 mg/dL
      - Pro:Cr ratio ≥1.0 (Pro and Cr in mg/dL)
      - Alb:Cr ratio ≥500 mg/g
      - 24-h collection ≥1.0 g/24-h/1.73 m²

CKD: Normal Kidney Function

- MDRD GFR >90 mL/min/1.73 m² and all of the following
  - No hematuria
  - No proteinuria
  - No parenchymal or structural abnormality (cyst, scar, hydronephrosis)

CKD: Age-Related Decline in GFR

- Age-related declines in GFR occur
  - Should not be considered “disease”
  - GFR 60–89 mL/min/1.73 m²
  - Do not refer pt to nephrologist if GFR is stable and all of the following
    - No proteinuria
    - No hematuria
    - No structural lesion(s)

# NKF CKD Stages 1–5

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chronic kidney damage with normal or ↑ GFR</td>
<td>&gt; 90</td>
</tr>
<tr>
<td>2</td>
<td>Mild ↓ GFR</td>
<td>60–89*</td>
</tr>
<tr>
<td>3</td>
<td>Moderate ↓ GFR</td>
<td>30–59</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓ GFR</td>
<td>15–29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15 or dialysis</td>
</tr>
</tbody>
</table>

CKD: Screening and Prevention Summary

- Use MDRD GFR not $S_{Cr}$
- “Spot” urine Alb:Cr ratio
  - Collect specimen at 0600–1200 hours
  - 24-h urine collection, no longer required
- Screenees?
  - GFR <90 mL/min/1.73 m²
    - Not from age-related decline
  - Hypertension
  - Diabetes — annual testing
  - FH of CKD — less frequently, if normal
  - Hematuria
  - Edema of unknown cause

CKD: Three-Fold Initiative

• Screening for and prevention of CKD in pts at-risk for CKD

• Development of an early CKD identification process

3. Establishment of a collaborative disease management model between internists and family practitioners and nephrologists
CKD: Under-recognized Problem

- Patients unaware
  - Only 13% of pts with CrCl <60 mL/min or +1 dipstick proteinuria aware of their CKD
  - Only 8% of pts with “known CKD” aware of their CKD, despite recent physician visit

- Implications
  - Physicians require more CKD knowledge
  - “Late” referral of pts with advanced CKD to nephrologists, e.g., African-American men

**CKD: Under-recognized Problem**

- Only 10% of Medicare beneficiaries with diabetes receive annual urine albumin tests.
- Less than 1/3 of hospitalized CKD pts with proteinuria are prescribed an ACEI at discharge.

## CKD: Survey of PCPs

### Table 2. Reasons Given by PCPs for Delaying Referral to Nephrologists

<table>
<thead>
<tr>
<th>Reason</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feel very capable of treating kidney-related problems</td>
<td>65% → 10%</td>
</tr>
<tr>
<td>Have found little value in early nephrology consultation</td>
<td>80%</td>
</tr>
<tr>
<td>Fear of “losing” patient</td>
<td>34%</td>
</tr>
<tr>
<td>Financial referral issues</td>
<td>31%</td>
</tr>
<tr>
<td>Long delays to get appointments</td>
<td>25%</td>
</tr>
<tr>
<td>Old patients, comorbidity</td>
<td>20%</td>
</tr>
<tr>
<td>Fear of poor reflection on primary care</td>
<td>2%</td>
</tr>
</tbody>
</table>

*51 of 105 PCPs surveyed delay referral until creatinine clearance is < 50 mL/min.

*65% initially reported that they felt capable of treating these patients: after being asked to review their scores on the analog scale items, only 10% remained confident.
**CKD:** Delayed Referral to Nephrologist

CKD: Reasons for Delayed Referral to Nephrologist

- CKD is under-recognized
- Failure to screen pts at-risk
- Fear of loss of control over pt
- PCPs unaware of incremental benefits of earlier referral
  - Fewer ER visits (pulmonary edema)
  - Significant healthcare cost savings
- Lack of education regarding CKD management

### CKD: Consequences of Delayed Referral

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Time to Referral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;4 mo</td>
</tr>
<tr>
<td>Malnutrition (%)</td>
<td>15.8</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.53</td>
</tr>
<tr>
<td>Hct at Referral (%)</td>
<td>30.7</td>
</tr>
<tr>
<td>Tx with EPO (%)</td>
<td>32</td>
</tr>
<tr>
<td>Received Vascular Access (%)</td>
<td>40.8</td>
</tr>
<tr>
<td>Access Type (AVF; AVG) (%)</td>
<td>14.5; 26.3</td>
</tr>
<tr>
<td>Death Risk ↑ at 1- and 2-Yr (%)</td>
<td>—</td>
</tr>
</tbody>
</table>


Late referral means <4 mo between time of initial Nephrology consultation and dialysis. AVF, arteriovenous fistula; AVG, arteriovenous graft.
**CKD:** Delayed Referral Results in Higher Medical Costs in Early ESRD

**Source:** BA Boissonault for the Niagara Health Quality Coalition, 2003.
Advanced CKD Substantially Impairs Quality of Life

Sickness Impact Profile (SIP)

- Work
- Eating
- Recreation/pastime
- Home management
- Sleep/rest
- Psychosocial
- Physical
- Overall SIP

Note: Higher scores indicate poorer QOL.

Ultimate Goal
Delay CKD Progression

- Diagnose / treat comorbid conditions
- Evaluate / treat CVD
- Iatrogenic risks @ CKD Stage 3
  - protect against further insults (e.g., ARF)

PREVENT & STABILIZE
CKD STAGE 4
— A Clinical Event —
**CKD: ARF Prevention**

**Rationale for Intervention**

- ARF — often preventable
- ARF — produces residual kidney damage, *i.e.*, CKD
- CKD pts — at higher risk for ARF

CKD: Increased Risk for ARF

- ECF volume depletion — fosters ARF
- High-risk groups
  - DM, types 1 and 2
  - Non-DM CKD Stage 3–5 (i.e., GFR <60)*
  - Liver failure
  - Heart failure
  - CV operations
  - Radiocontrast procedures

*Data extrapolated from multiple studies
Avoid Iatrogenic Injury

AVOID NEPHROTOXINS

- NSAIDs, AGs, Amphotericin B
- Radiocontrast
  1. Stop diuretics 3–4 d before procedure
  2. ECF volume expansion (preferably with HCO₃⁻)
  3. N-Acetylcysteine (S_Cr dependent)

Acute Renal Failure: NSAID-Induced Afferent Arteriolar Constriction


$R_{AA}$: afferent arteriolar resistance.
**NSAIDS**

- NSAIDs (COX-1/-2 inhibitors) lower GFR, retain sodium and may cause hyperkalemia
- People with an activated Renin-Angiotensin-Aldosterone system are especially at risk for NSAID-induced ARF
  - Advanced age
  - Hypertension
  - Diabetes
  - Dehydration
  - Concomitant diuretic use
**CKD: Radiocontrast-induced Nephropathy**

- Common complication in CKD and other high risk groups

- Significant morbidity and/or mortality
  - Event-free survival is ↓ by contrast nephropathy
  - In-hospital mortality ↑ by contrast nephropathy

- Preventable, modifiable

An Integrated Model of CIN

Contrast Media

↑PGE
↑ANP
↑Adenosine

↓Blood Flow

Direct Cellular Toxicity

↑Endothelin
↑Vasopressin
↓PGI₂

↓O₂ Delivery

Renal Medullary Hypoxia

↑Osmotic Load Distal Tubule

↑Systemic Hypoxemia
↑Blood Viscosity

↑O₂ Consumption

Contrast Media Nephrotoxicity
CKD: Radiocontrast-induced Nephropathy

- High-risk groups
  - CKD of any cause
  - Advanced age
  - Diabetes
  - Nephrotoxin co-administration
    - NSAID (not aspirin)
    - Diuretics
    - ACEI, ARB
    - Aminoglycosides
    - Cyclosporine, tacrolimus
    - *cis*-platinol

**CKD: Radiocontrast-induced Nephropathy Prevention**

- **Nephrotoxins**
  - Stop diuretics, ACEIs/ARBs, NSAIDs
  - Avoid aminoglycosides, amphotericin B

- **Prophylaxis**
  - Normal saline to expand ECF volume, unless edema is present
  - N-acetylcysteine

- **Preferred contrast media**
  - Non-ionic, low osmolar contrast
  - Iso-osmolar agents, if available

---

# Recommendations for Common Interventions Used to Prevent Contrast-medium-induced Nephropathy

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Details</th>
<th>Evidence</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IV saline therapy</strong></td>
<td>0.9% saline at 1 mL/kg/h for 24 h, start 12 h pre-contrast delivery</td>
<td>Small randomized trials: iv saline vs oral fluids; shorter regimens of iv fluids; and 0.45% saline</td>
<td>Optimal duration of iv therapy not fully established by existing trials</td>
</tr>
<tr>
<td><strong>Contrast Medium</strong></td>
<td>Low osmolality, lowest dose possible</td>
<td>Meta-analysis of many RCTs comparing low to high</td>
<td>Isosmolar contrast may be less risky in high risk pts, more data required</td>
</tr>
<tr>
<td><strong>IV Sodium Bicarbonate</strong></td>
<td>154 mmol/L at 3 cc/kg/h before contrast, then 1 mL/kg/h for 6 hours after</td>
<td>Single RCT showed lower risk of 25% increase of $S_{Cr}$ v 0.9% saline at same rate/duration</td>
<td>Methodologic flaws in trial Not generally recommended, need further trials to confirm efficacy</td>
</tr>
<tr>
<td><strong>N-acetyl cysteine</strong></td>
<td>600 mg po q12 h × 4, starting before contrast delivery</td>
<td>Multiple RCTs Meta-analyses</td>
<td>Inconsistent trial results, optimal dose not clear Recent high-dose study shows benefit in angioplasty</td>
</tr>
</tbody>
</table>
**CKD: Preventing Progression**

- Attain glycemic control in DM
- Attain BP target
- Block RAAS
- Treat anemia of CKD
- Treat associated CVD and dyslipidemia
- Prevent renal osteodystrophy (ROD)
- Prevent ARF and avoid nephrotoxins
- Optimize nutrition

Chronic Kidney Disease (CKD)

- **Generic**
  - Any kidney disorder
  - Does not replace specific disorders
  - CKD, secondary to __________

- **Stratified into Stages by GFR**
  - Complications stratification
  - Morbidity stratification
  - Guides intensity of therapy
CKD Guidelines for Treatment

- National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (NKF KDOQI)
- Based heavily on Evidenced Based Medicine
- Offers opinions that guide treatment
ALL of the above plus:

- Develop clinical action plan for each patient, based on disease stage as defined by the National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI) [B]
- Incorporate self-management behaviors into treatment plan at all stages of CKD [B]

<table>
<thead>
<tr>
<th>Eligible Population</th>
<th>Key Components</th>
<th>Recommendation and Level of Evidence</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>All adults at increased risk for CKD</td>
<td>Screening &amp; Diagnosis</td>
<td>For patients at increased risk for CKD (e.g., diabetes, hypertension, family history of kidney failure, kidney stones, etc.) assess for markers of kidney damage: Measure blood pressure [A] Obtain estimated GFR(^1) (serum creatinine levels should not be used as sole means to assess renal function) Protein-to-creatinine ratio or albumin-to-creatinine ratio (first morning or random spot urine specimen) Urinalysis, fasting lipid profile, electrolytes, BUN</td>
<td>Semi-annual blood pressure monitoring; more frequent monitoring if indicated Monitor GFR every 1-2 years</td>
</tr>
<tr>
<td>Risk Factor</td>
<td>Evaluation and management of comorbid conditions (e.g., diabetes, hypertension, urinary tract)</td>
<td>At each routine health exam</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) If not calculated by lab, refer to the National Kidney Foundation website for GFR calculator (http://www.kidney.org/professionals/tools/)

\(^2\) Reference MQIC guidelines on diabetes, hypertension, hyperlipidemia and obesity (www.mqic.org)

Levels of Evidence for the most significant recommendations: A = randomized controlled trials; B = controlled trials, no randomization; C = observational studies; D = opinion of expert panel

This guideline lists core management steps. It is based on several sources including the 2002 National Kidney Foundation/Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification (www.kidney.org). Individual patient considerations and advances in medical science may supersede or modify these guidelines.

Approved by MQIC Medical Directors 11/06 www.mqic.org
NKF Guidelines address domains of CKD care
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DOMAINS OF CKD CARE

- CV RISK FACTOR MODIFICATION
  - GLYCEMIC CONTROL
  - LIPID CONTROL
  - HTN
- PROTEINURIA REDUCTION
- EVALUATE CKD PROGRESSION
- VAX
- NUTRITIONAL ASSESSMENT
- ANEMIA MGMT
- CKD-MBD MGMT

Periodic eGFR
Decrease CV Disease Risk Factors

Domains of CKD Care

CV Risk Factor Modification
  - Proteinuria Reduction
  - Evaluate CKD Progression
  - VAX
  - Nutritional Assessment
  - Anemia MGMT
  - CKD-MBD MGMT

GLYCEMIC CONTROL

LIPID CONTROL

HTN
Large RCTs that involve CV risk prevention strategies in CKD have not been performed.
Major Cause of Death in CKD
Cardiovascular Disease

Patient population: Participants were recruited through a screening program for high BP that was performed in 14 US communities from 1973 to 1974. All patients had a diastolic BP ≥90 mm Hg. N=5366 (referred care patients).

**CKD: CVD Risks**

- CVD risk $\uparrow$ 1.4–2.05X if $S_{Cr} > 1.4–1.5$ mg/dL
- CVD risk $\uparrow$ 1.5–3.5X with microalbuminuria
- First-year CVD mortality of CKD (3.5%) increases 5-fold (17%) with addition of diabetes
- Annual CVD $\uparrow$10–100X in ESRD

**Cardiovascular Health Study:** “Even Mildly Elevated $S_{Cr}$ Increases CV Disease (CVD) Risk.”

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal $S_{Cr}$</th>
<th>High $S_{Cr}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality (per 1000 pt-yr)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td>13.0</td>
<td>35.8</td>
</tr>
<tr>
<td>Overall</td>
<td>29.5</td>
<td>76.7</td>
</tr>
<tr>
<td><strong>Incident (per 1000 pt-yr)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td>31.8</td>
<td>54.0</td>
</tr>
<tr>
<td>Stroke</td>
<td>11.9</td>
<td>21.1</td>
</tr>
<tr>
<td>CHF</td>
<td>17.0</td>
<td>38.7</td>
</tr>
</tbody>
</table>

**CKD: CVD Comorbidities (1999)**

- **CKD**: Chronic Kidney Disease
- **CVD**: Cardiovascular Disease

---

**Bar Chart**

- **COPD**
- **Diabetes on insulin ‡**
- **Diabetes mellitus §**
- **History of hypertension**
- **Peripheral vascular**
- **CVA/TIA**
- **Cardiac dysrhythmia**
- **Myocardial infarction**
- **Ischemic heart disease**
- **Congestive heart failure**

---

§ Diabetes mellitus as a primary or contributing diagnosis.
‡ Diabetes mellitus that requires insulin treatment, which is a subset of the diabetes category.
CV Mortality in General Population (GP) & Dialysis pts by Ethnicity

Cardiovascular Health Study: “Even Mildly Elevated $S_{Cr}$ Increases CV Disease (CVD) Risk.”

**Rationale for Intervention**

- CV mortality is higher in CKD than general population
  - ~50% of ESRD pts die from CVD
  - Death before CKD Stage 5/ESRD is common
- CVD inherent in CKD
  - CV risk: CKD + 30 y.o. = 75 y.o. non-CKD
  - CKD is “CHD/diabetic equivalent”
  - CKD is pro-inflammatory

Decrease CV Risk Factors

- Strict BP control
- Tight glycemic control
- Use anti-RAAS drugs
- Lipid control
- Correct anemia
Hypertension & CKD

DOMAINS OF CKD CARE

- CV RISK FACTOR MODIFICATION
- PROTEINURIA REDUCTION
- EVALUATE CKD PROGRESSION
- VAX
- NUTRITIONAL ASSESSMENT
- ANEMIA MGMT
- CKD-MBD MGMT

GLYCEMIC CONTROL

LIPID CONTROL

HTN
1.1 Antihypertensive therapy should be used in CKD to:

1.1.a. Lower blood pressure (A);

1.1.b. Reduce the risk of CVD, in pts with or without hypertension (B)

1.1.c. Slow progression of kidney disease, in pts with or without hypertension (A)

1.2 Modifications to antihypertensive therapy should be considered based on the level of proteinuria during treatment (C)

1.3 Antihypertensive therapy should be coordinated with other therapies for CKD as part of a multi-intervention strategy (A).

1.4 If there is a discrepancy between the treatment recommended to slow progression of CKD and to reduce the risk of CVD, individual decision-making should be based on risk stratification (C).
## JNC 7 Reclassification of BP Based on Risk

<table>
<thead>
<tr>
<th>JNC VI</th>
<th>JNC 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP (mm Hg)</td>
<td>BP (mm Hg)</td>
</tr>
<tr>
<td>Optimal</td>
<td>Normal</td>
</tr>
<tr>
<td>&lt;120/80</td>
<td>&lt;120/80</td>
</tr>
<tr>
<td>Normal</td>
<td>120-129/80-84</td>
</tr>
<tr>
<td>Borderline</td>
<td>130-139/85-89</td>
</tr>
</tbody>
</table>

### Hypertension

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Stage 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>140-159/90-99</td>
<td>140-159/90-99</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage 2</th>
<th>Stage 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>160-179/100-109</td>
<td>≥160/100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥180/110</td>
</tr>
</tbody>
</table>

HTN Treatment by JNC 7

HTN w/ No Compelling Indications

Stage 1 HTN (SBP 140-159 or DBP 90–99 mmHg)
- Thiazide diuretic for most
- Consider ACEI, ARB, β-blocker, CCB or combination

Stage 2 HTN (SBP ≥160 or DBP ≥ 100 mmHg)
- 2-drug combo for most
- Usually thiazide + ACEI, ARB, β-blocker, or CCB

C(KD)ompelling Indications

Drug(s) for compelling indications
- Other BP drugs (thiazide + ACEI, ARB, β-blocker, CCB) as needed


Compelling indications: CHF, post-MI, high risk of CAD, DM, CKD, stroke, migraine …
<table>
<thead>
<tr>
<th>Type of Kidney Disease</th>
<th>BP Target (mm Hg)</th>
<th>Preferred Agents for CKD, with or without HTN</th>
<th>Other Agents to Reduce CVD Risk and Reach BP Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic CKD</td>
<td></td>
<td>ACE inhibitor or ARB</td>
<td>Diuretic preferred, then BB or CCB</td>
</tr>
<tr>
<td>Nondiabetic CKD</td>
<td>SBP &lt;125–130</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>UPC ≥200 mg/g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondiabetic CKD</td>
<td>DBP &lt;75–80</td>
<td>None preferred</td>
<td>Diuretic preferred, then ACEI/ARB, BB or CCB</td>
</tr>
<tr>
<td></td>
<td>UPC &lt;200 mg/g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CKD in TX Recipient</td>
<td></td>
<td></td>
<td>CCB, diuretic, BB, ACE inhibitor, ARB</td>
</tr>
</tbody>
</table>

Am J Kidney Dis, May (Suppl.), 2004
HTN Treatment in CKD
Diabetic or Nondiabetic
Hypertension in CKD

- **Rationale for Intervention**
  - Elevated BP worsens CKD
  - GFR declines faster with HTN
    - Rapid decline rate is >4 ml/min/1.73 m²/yr

- **Target BP**
  - <130/80 mmHg if proteinuria <1 g/d
  - <125/75 mmHg if proteinuria >1 g/d
BP Control Prevents CKD Progression

GFR, glomerular filtration rate; HTN, hypertension; MAP, mean arterial pressure.
Hypertension & CKD
Optimal BP Control

- No edema
  - **Limit daily sodium intake**
    - 6 gm NaCl (102 mEq)
    - 2400 mg sodium (104 mEq)
- Diuretics
  - GFR >40 ml/min/1.73 m², HCTZ
  - GFR <40 ml/min/1.73 m², loop agent
- RAAS blockade
  - ACEI
  - ARB
Benefits of BP Therapy

General Population

Adapted from: Kannel WB. JAMA. 1996;275:1571-1576.

RR Ratios:  2.0  3.8  2.0  4.0  2.2  2.6  3.7  3.0

Hypertension and CKD
Multiple Drugs Required

UKPDS (<85 mm Hg, diastolic)
MDRD (<92 mm Hg, MAP)
HOT (<80 mm Hg, diastolic)
AASK (<92 mm Hg, MAP)
RENAAL (<140/90 mm Hg)
IDNT (≤135/85 mm Hg)

Type 2 DM
Nondiabetic Kidney Disease
DM Subgroup Analysis
African Americans, No DM
Type 2 DM Nephropathy
Type 2 DM Nephropathy

MAP = mean arterial pressure.

Glycemic Control

DOMAINS OF CKD CARE

CV RISK FACTOR MODIFICATION
PROTEINURIA REDUCTION
EVALUATE CKD PROGRESSION
VAX
NUTRITIONAL ASSESSMENT
ANEMIA MGMT
CKD-MBD MGMT

GLYCEMIC CONTROL
LIPID CONTROL
HTN
Diabetes (DM) affects more than 170 million people worldwide

- **Number will rise to 370 million by 2030**
- **About 1/3 of affected will eventually develop progressive renal deterioration**
- **Microalbuminuria (MA) develops in 2–5% of pts per year**
Epidemiology of Diabetes

- 19 million persons
  - 0.5 million type 1 DM
  - Remainder, type 2
- Over-representation in ESRD population worldwide
- Over-representation in U.S. ESRD population
- Incidence increasing with rate of obesity
Comorbidities Increase with Increasing BMI

- % of Adults by BMI Category

BMI (kg/m²)

- 18.5-24.9
- 25.0-26.9
- 27.0-29.9
- 30.0-34.9
- ≥35

- Type 2 Diabetes
- Hypertension
- Hypercholesterolemia

Legend:

- Type 2 Diabetes
- Hypertension
- Hypercholesterolemia
Global Estimates and Projections for Incidence of Diabetes Mellitus

NEW ESRD: Incidence from DM

Predictions Regarding T2DM

A. Year 2000 and beyond

- One of three newborns will develop type II diabetes as an adult
- One of two newborns, Hispanic or African American, will develop type II diabetes as an adult

B. Year 2050

A. U.S.: 45–50 million will develop T2DM

C. Implications for CKD and RRT uncertain

Dr. KM Venkat Narayan
“... it appears that there is an emerging pediatric epidemic of type 2 diabetes. If this epidemic cannot be averted, its full public health effect will be felt as affected children become adults and the long-term complications of diabetes develop.”

ESRD: Etiology by 1° Diagnosis

DM 50%
HTN 27%
GN 13%
Other 10%

United States Renal Data System (USRDS) 2000 Annual Data Report • WWW.USRDS.ORG.
First-year mortality rates, by CKD & diabetic status

General Medicare patients age 67 & older; rates adjusted for age, gender, & race, & determined for the first year after the cohort-defining period. Reference population: 1999–2000 cohort.
Natural History of Diabetic Nephropathy

- Insulin resistance syndrome
- Clinical type 2 diabetes
- Functional changes*
- Rising blood pressure
- Structural changes†
- Microalbuminuria
- Proteinuria
- Rising serum creatinine levels
- End-stage renal disease
- Cardiovascular death

Years

-1  2  5  10  20  30
Glomerulus: Site of Hyperfiltration in Diabetes and Obesity
Schematic of Abnormal Kidney

Legend
- Urine
- Protein

Afferent arteriole
Blood flow
Efferent arteriole
Protein leaking from capillary

Tubule  Capillary
Diabetic nodule
Bowman's capsule

Diabetic Kidney Disease (microscopic view)
Diabetic Glomerulosclerosis
Glycemic Control Retards Progression of CKD

![Graph showing relative risk vs. A1C (%) for retinopathy, nephropathy, neuropathy, and microalbuminuria.](image)

- **Retinopathy**
- **Nephropathy**
- **Neuropathy**
- **Microalbuminuria**

*Based on Diabetic Control and Complications Trial data*

Relative Risk

A1C (%)  
6 7 8 9 10 11 12

50% Reduction

Adapted with permission from Skyler JS. *Endocrinol Metab Clin North Am.* 1996;25:243
HbA1c: Delay DN

OHKUBO TRIAL (1995)

- Hypothesis: Development of nephropathy is decreased by intensive insulin therapy

- Primary and secondary prevention study
  - 6-mo F/U intervals for 6 yr

Glycemic Control
## HbA1c: Delay DN

<table>
<thead>
<tr>
<th></th>
<th>MIT</th>
<th>CIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (N)</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>Primary</td>
<td>7.7%</td>
<td>28%</td>
</tr>
<tr>
<td>Secondary</td>
<td>11.5%</td>
<td>32%</td>
</tr>
</tbody>
</table>
HbA1c: Delay DN

REQUIREMENTS

- HbA1C: 6.5%
- FBS: 110 mg/dl
- 2-h PPG: 180 mg/dl

Glycemic Control
HbA1c: Delay DN

EUGLYCEMIA

- Partially reverses glomerular hypertrophy and hyperfiltration
- Type 1 DM — delays onset of microalbuminuria
- Kidney-Pancreas transplant — pancreatic transplant prevents recurrent nephropathy in allograft kidney

HbA1c: Delay DN

HbA$_{1c}$ Predicts CHD in Type 2 Diabetes

CHD mortality (%)

- Low <6%
- Middle 6-7.9%
- High >7.9%

All CHD events (%)

- Low <6%
- Middle 6-7.9%
- High >7.9%

* $P<0.01$ vs lowest tertile
† $P<0.05$ vs lowest tertile

Decline of GFR in DN
Questions?
Chronic Kidney Disease: A Silent Epidemic (Part 2)

Naima Ogletree, MSN, APRN, BC
Nephrology & Hypertension
Henry Ford Health System
Proteinuria Reduction
# CKD: Albuminuria

<table>
<thead>
<tr>
<th></th>
<th>Nontimed Urinary Albumin Sample</th>
<th>Timed Urinary Albumin Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted (µg/ml)</td>
<td>Adjusted by Urine Cr (mg/g)</td>
</tr>
<tr>
<td>Normoalbuminuria</td>
<td>&lt;20</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>20–200</td>
<td>30–300</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>&gt;200</td>
<td>&gt;300</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adjusted by Overnight (µg/min)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24 Hr (mg/24 hr)</td>
</tr>
<tr>
<td>Normoalbuminuria</td>
<td>&lt;20</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>20–200</td>
<td>20–200</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>&gt;200</td>
<td>&gt;200</td>
</tr>
</tbody>
</table>

Proteinuria

Dual Significance

• Proteinuria results from injury to glomerular circulation
  ▪ Increased proteinuria is associated with progressive CKD

• In diabetes and hypertension, proteinuria signifies injury to the systemic circulation
  ▪ Proteinuria is associated with increased CV risk
RAAS, Albuminuria and Atherosclerosis
Steno Hypothesis

American Journal of Kidney Diseases, Vol 47, No 6 (June), 2006: pp 927-946
CKD: Anti-Proteinuric Therapy

**Rationale for Intervention**

- Microalbuminuria — independent CVD risk factor
- In-hospital mortality \(\uparrow\) 3-fold by proteinuria (100 mg pro/g Cr)
- Proteinuria correlates with CKD progression
- Proteinuria may worsen CKD

Albuminuria Decreases Survival
Graded Effect

UPC @ 6 Mo Predicts Kidney & CVD Events
RENAAL Substudy (losartan, no ACEI)

Hazard ratio (95 % C.I.)

- ESRD
- CV events
- CHF

Proteinuria (g)

Less Risk → More Risk →

0.2 0.4 0.6 0.8 1 1.2
BP, Proteinuria and CKD

- Reduction of protein and albuminuria
  - Intermediate goals in slowing CKD
  - Complementary

- Aggressive BP control is primary consideration of “anti-proteinuria”

- Multi-drug regimens required
Renin-Angiotensin System Blockade

- Moderate to high doses of ACEIs / ARBs have been associated with beneficial effects on kidney disease progression in controlled trials.
- Where tested, ACEIs / ARBs have generally similar effects on BP, urine protein excretion, and slowing CKD progression.

Greatest efficacy in proteinuric disorders
ACEIs / ARBs

• Clinicians often avoid / withdraw ACEIs / ARBs in CKD ... fearing hyperkalemia or $\uparrow S_{\text{Cr}}$

• Tolerate ...
  ▪ ... up to 30% increases of $S_{\text{Cr}}$
  ▪ ... $[K]$ of 5.5–5.8 mEq/L
    • Kidney dietitian, not Kayexelate

Alternative to RAAS Blockers

- Non-dihydropyridine CCBs for those who cannot tolerate anti-RAAS agents, especially with proteinuria
  - Diltiazem
  - Verapamil
CKD: Anti-Proteinuric Therapy

- RAAS blockade
  - ARBs preferred in type 2 diabetic nephropathy
  - ACEIs preferred in type 1 diabetic nephropathy
- Quantitate proteinuria q1-2 mo
  - Proteinuria reduction maximized by Week 8 of tx
  - Perform “spot” urine tests to assess efficacy

**RENAAL:** Combined CCB and ARB Reduce Progression to Diabetic Nephropathy


R_{AA}, afferent arteriolar resistance. R_{EA}, efferent arteriolar resistance.
IRMA 2: ARB Prevents Transition from Micro- to Macroalbuminuria

Incidence of Diabetic Nephropathy (%)

Control (n=201)*
Irbesartan 150 mg/d (n=195)*
Irbesartan 300 mg/d (n=194)*

Followup (mo)

RRR=39%
P=.08
RRR=70%
P<.001

IRMA 2: ARB Normalizes Albumin Excretion Rate

# Effect of AngII Receptor Blockade in Type 2 Diabetic Nephropathy

<table>
<thead>
<tr>
<th>Patients:</th>
<th>IDNT†</th>
<th>RENAAL‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1,715 HTN patients with type 2 diabetes and nephropathy</td>
<td>1,513 HTN patients with type 2 diabetes and nephropathy</td>
</tr>
<tr>
<td>Treatment arms:</td>
<td>irbesartan, amlodipine, placebo</td>
<td>losartan, placebo</td>
</tr>
<tr>
<td>Target BP:</td>
<td>135/85 mm Hg</td>
<td>140/90 mm Hg</td>
</tr>
<tr>
<td>Adjunctive therapy:</td>
<td>Permitted except ARBs, ACE inhibitors, or CCBs</td>
<td>Permitted including CCBs; except ARBs or ACE inhibitors</td>
</tr>
<tr>
<td>Primary outcome:</td>
<td>Composite of doubling of SCr, ESRD, or death</td>
<td>Composite of doubling of SCr, ESRD, or death</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>CV events</td>
<td>CV events</td>
</tr>
<tr>
<td>included:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Follow-up:</td>
<td>2.6 years</td>
<td>3.4 years</td>
</tr>
</tbody>
</table>

SCr, serum creatinine; ESRD, end-stage renal disease.
Irbesartan Diabetic Nephropathy Trial

Reduction in Endpoints in Non-Insulin Dependent DM with the Angiotensin II Antagonist Losartan

Diabetes and RAAS Blockade

Type 2 DM

- Brenner et al. (losartan, RENAAL) (N=1513)
- Lewis et al. (irbesartan, IDNT) (N=1715)
- ARBs reduced proteinuria (~35%)
  - reduce rate of GFR decline
  - later onset of ESRD compared to placebo
- Mean delay of ESRD by ~2.3 yr
Lipid Control
Guideline: Lipids in CKD 1–4

1.1. All adults and adolescents with CKD should be evaluated for dyslipidemias. (B)

1.2. For adults and adolescents with CKD, the assessment of dyslipidemias should include a complete fasting lipid profile with total cholesterol, LDL, HDL, and triglycerides. (B)

1.3. For adults and adolescents with Stage 5 CKD, dyslipidemias should be evaluated upon presentation (when the pt is stable), at 2–3 MO after a change in treatment or other conditions known to cause dyslipidemias; and at least annually thereafter. (B)
Dyslipidemia & CKD
Treatment Protocol

Lifestyle Modification ... Always
Dyslipidemia & CKD
Treatment Protocol

Lifestyle Modification ... Always
**CKD: Lipid Therapy**

**Rationale for Intervention**

- CKD progresses faster in dyslipidemia
- Physicians’ Health Study (1982–1996)
  - N=4,483 initially healthy males
  - 14-Yr followup
    - Baseline $S_{Cr} < 1.5 \text{ mg/dL}$
    - HDL $> 40 \text{ mg/dL}: 50\% \downarrow$ risk of reduced GFR
    - Non-HDL-C $> 196 \text{ mg/dL}: 100\% \uparrow$ risk of reduced GFR

# CKD: Lipid Targets

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NCEP ATP III</th>
<th>K/DOQI Revision</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mg/dL)</td>
<td>&lt;130</td>
<td>&lt;100</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>&gt;40</td>
<td>&gt;40</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>&lt;150</td>
<td>&lt;150</td>
</tr>
<tr>
<td>Normal lipids (HD)</td>
<td>20.2%</td>
<td>38.9%</td>
</tr>
<tr>
<td>Normal lipids (PD)</td>
<td>15.1</td>
<td>—</td>
</tr>
</tbody>
</table>

CKD: Dyslipidemia Therapy

- HMG-CoA synthetase inhibitors
- Fibric acid derivatives
  - Use with caution
  - Gemfibrozil preferred
- Cholesterol absorption inhibitor
  - Ezitimibe (Zetia™) — statin-sparing
  - No controlled trials in CKD

Anemia of CKD
Erythropoietin Regulates Red Blood Cell Production

Renal interstitial peritubular cells detect low blood oxygen levels

Erythropoietin (EPO) secreted into the blood

EPO stimulates the proliferation and differentiation of erythroid progenitors into reticulocytes, and prevents apoptosis

More reticulocytes enter circulating blood

Reticulocytes differentiate into erythrocytes, increasing the erythron size

Increased oxygen delivery to tissues

References:
CKD: Anemia Induces LVH

A Mohanran and AS Kliger presentations at NKF Meeting 2003
Association Between Hb and Mortality in CKD Patients

For Every 1-g/dL Decrease in Hb

14% Increase in Relative Risk of Mortality

N=432; mean follow-up 41 months
NKF KDOQI Guideline & CPR 2.1: Hb range

- **Moderately** strong recommendation

  2.1.1 **Lower limit of Hb**
  
  In pts with CKD, the Hb should be $\geq 11$ g/dL

- **2.1.2 Upper limit of Hb**

  In the opinion of the Work Group, there is insufficient evidence to recommend routinely maintaining Hb levels $\geq 13$ g/dL in ESA treated pts.
**CKD: Anemia Therapy**

- **Rationale** for Intervention
  - Anemia worsens with CKD progression
    - Tx regresses LVH/LVMI
    - Tx prevents CHF and hospitalization
    - Tx slows CKD progression?
  - QOL improved by ↑ Hb
    - Cognition
    - Sexual function
    - Exercise tolerance

**CKD: Anemia ↗ as GFR ↘**

RBC Production Response in CKD

![Graph showing RBC Production (mL/Day) vs. EPO Concentration (mU/mL)]

- **Normal**
- **CKD**

EPO Concentration (mU/mL)
EPO Response Blunted as CKD Progresses

Anemia: A Risk Multiplier

Source: Medicare sample (5%), follow up from 1996 to 1997 of enrollees aged ≥65 y.o., adjusted for age, gender and race.
QoL Improves with Higher Hb

- Cognitive function
- Energy/activity
- Sleep and eating behavior
- Satisfaction with health
- Well-being
- Satisfaction

- Exercise capacity
- Functional ability
- Health Status
- Sex Life
- Psychological effect
- Happiness

NKF, KDOQI Clinical Practice Guidelines For anemia of CKD, AJKD, 2001
How Can We Reach Hb Target?

- Efficient erythropoiesis requires both iron and erythropoietin.

- Use of maintenance iron improves patients’ response to EPO therapy, replaces continuous iron losses, and maintains patients’ target Hb/HCT ranges.

- IV iron improves iron and hematologic parameters with health benefits that outweigh the potential adverse effects.

Besarab, A.
IV Iron May Have an Independent Erythropoietic Effect in HD

*P < 0.01 vs baseline.


39 new HD pts (no EPO therapy) with baseline iron deficiency by bone marrow aspiration.

*P < 0.01 vs baseline.
More Rapid Hgb Response With EPO + IV Iron

*Defined as 0.5-g/dL increase in Hgb.
## Available Oral Iron Preparations

<table>
<thead>
<tr>
<th></th>
<th>Strength (mg/tablet)</th>
<th>Elemental Fe (mg/tablet)</th>
<th>No. Tablets to Supply 200 mg Elemental Fe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous sulfate</td>
<td>325</td>
<td>65</td>
<td>3</td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>325</td>
<td>38</td>
<td>5</td>
</tr>
<tr>
<td>Ferrous fumarate</td>
<td>200</td>
<td>66</td>
<td>3</td>
</tr>
<tr>
<td>Iron polysaccharide</td>
<td>150</td>
<td>150</td>
<td>2</td>
</tr>
</tbody>
</table>
Currently Available Erythropoietic Agents

**First generation erythropoietic agents**
- Epoetin beta (Roche)
- Epoetin omega (South America)
- Epoetin delta (in clinical trials, humanized using immortalized)

**Second generation epoetin**
- Darbepoetin alfa (Amgen, Aranesp®)

**Other erythropoietic agents in clinical trials**
- PEG-epoetin beta (CERA Roche)
- Hematide (totally synthetic peptide)
- Fibrogen product. HIF1-alpha inhibitor
CKD: Anemia Therapy

- Begin tx at Hb <11 g/dL (Hct 33%)

Steps (by Nephrology CKD Clinic)

1. Replete iron stores
   - Oral iron salts
   - Iron dextran (INFeD™) or
   - Iron gluconate (Ferrlecit™) or
   - Iron sucrose (Venofer™)

2. Use erythropoietic agent
   - Epoetin-α (Procrit™) or
   - Darbepoetin (Aranesp™)

CKD: Anemia Therapy

- Targets
  - Hb >11 g/dL (Hct 33%)
  - TSAT >20%; Ferritin >100 ng/mL

- EPO level
  - Does not predict marrow response
    - Two-thirds of levels in “normal range”
    - Do not obtain EPO levels

- R/O blood loss and/or iron deficiency

Chronic Kidney Disease—Mineral and Bone Disorder
Definition of CKD-MBD

A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:

- Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism
- Abnormalities in bone turnover, mineralization, volume, linear growth, or strength
- Vascular or other soft tissue calcification
Definition of Renal Osteodystrophy

Renal osteodystrophy is an alteration of bone morphology in pts with CKD. It is one measure of the skeletal component of the systemic disorder of CKD-MBD that is quantifiable by histomorphometry of bone biopsy.

Definition, evaluation, and classification of renal osteodystrophy. KI, April 2006
**CKD:** Metabolic Bone Disease

- Consequence of ↓ renal mass
  - ↓ Vitamin D$_3$
  - ↑ P
  - ↓ Ca$^{2+}$
  - Metabolic acidosis
    - Increased protein catabolism
    - Increased bone lysis / loss

CKD: Metabolic Bone Disease

- **Definition** — any / all metabolic bone disorders associated with CKD
  - 2° hyperparathyroidism
  - Osteoporosis
  - Osteomalacia
  - Adynamic bone disease
  - Mixtures of above

**CKD: Metabolic Bone Disease**

**Rationale for Intervention**

- Multiple aberrations of Ca/P/PTH and bone metabolism accompany GFR decline.

- Hyperphosphatemia is an independent CV risk factor in ESRD (presumed in non-ESRD CKD).

- ESRD pts develop CV calcification (by EBCT) from $\Uparrow$ Ca $\times$ P product.

CKD: Pathophysiology of 2° HPT

Bone Disease

↓ Vit D₃

↓ Ca²⁺

↑ P

↓ PTH

↑ PTH

Systemic Toxicity

CKD
Progression of PTH Gland Hyperplasia in CKD

Decline in receptor density of VDR, CaR

Cells with lower density of VDR proliferate vigorously to form several monoclonal nodules

Normal Diffuse Early nodular Nodular hyperplasia Single nodule

Monoclonal nodules

CKD Progression

VDR = vitamin D receptor; CaR = Ca-Sensing receptor.
**CKD: Renal Osteodystrophy — Ca / P / PTH Axis**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Alteration</th>
<th>GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH</td>
<td>↑</td>
<td>40-70</td>
</tr>
<tr>
<td>P</td>
<td>↑</td>
<td>20-50</td>
</tr>
<tr>
<td>Vitamin D₃</td>
<td>↓</td>
<td>&lt;40</td>
</tr>
<tr>
<td>Bone histology</td>
<td>Variable</td>
<td>—</td>
</tr>
</tbody>
</table>

CKD: ROD PTH Target

K/DOQI PTH Target (pg/mL)

Low bone turnover
Adynamic bone disease

High bone turnover
Bone pain
Cardiovascular disease
Cognitive impairment
**CKD:** ROD Ca Target

- **8.4 mg/dL (K/DOQI Target Ca)**
- **9.5 mg/dL**
- **10.2 mg/dL**

**Stimulus for PTH secretion**
**Stimulus for PT gland enlargement**
**Inadequate skeletal mineralization**
**Vascular/soft tissue calcification**
**Hypertension**
**CKD: ROD P Target**

- K/DOQI Target P (mg/dL)
  - 2.5
  - 3.5
  - 5.5
  - 6.5

- **Malnutrition**
- Inadequate bone mineralization
- **Vascular/soft tissue calcification**
- Cardiovascular disease
- Higher mortality risk
CKD: Renal Osteodystrophy

- **Targets**
  - Ca 8.4–9.5 mg/dL
  - P 2.7–5.5 mg/dL
  - Ca × P <55 mg²/dL²
  - HCO₃ 22–26 mEq/dL
  - PTH <2–3× ULN (100–150 pg/mL)

**CKD:** Renal Osteodystrophy

— ↑ P ↑ Relative Risk of Mortality

![Graph showing relative mortality risk by serum phosphorus quintile](image)


**Statistical Values:**

- 1.39**
- 1.18*
- 1.02
- 0.5
- 1.0
- 1.5
- 2.0

**Serum Phosphorus Quintile (mg/dL):**

- 1.1-4.5
- 4.6-5.5
- 5.6-6.5
- 6.6-7.8
- 7.9-16.9

**Relative Mortality Risk:**

- 1.1-4.5: 1.0
- 4.6-5.5: 1.0
- 5.6-6.5: 1.02
- 6.6-7.8: 1.18*
- 7.9-16.9: 1.39**
Mortality Risk in ESRD
by Serum P and Ca Levels

RR of Death*

Serum P (mg/dL)

N = 40,538

RR = relative risk
*Not adjusted for active vitamin D intake

Prevalence of Calcitriol Deficiency and Anemia in pts With CKD by eGFR

**Design**
- N = 80 CDK
- Anemia defined as Hb <11 g/dL or treatment with ESA
- Calcitriol deficiency defined as calcitriol <30 pg/mL

**Results**
- Prevalence of calcitriol deficiency was greater than prevalence of anemia at all stages of CKD

SHPT Occurs Early in CKD

CKD-Mineral & Bone Disorder
Ca/P/PTH Progression in CKD

*P < 0.05, compared to CrCl > 100 and CrCl 50-59, N = 157
### Recommendations for Early Monitoring of PTH, Ca, and P Metabolism in CKD

**GFR** in mL/min/1.73 m²


<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>GFR Range</th>
<th>Measure PTH</th>
<th>Measure Ca &amp; P</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>30–59</td>
<td>12 MO</td>
<td>12 MO</td>
</tr>
<tr>
<td>4</td>
<td>15–29</td>
<td>3 MO</td>
<td>3 MO</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15 or ESRD</td>
<td>3 MO</td>
<td>1 MO</td>
</tr>
</tbody>
</table>
Stages 3 and 4: Measure serum 25(OH)D in pts with ↑ PTH. If normal, repeat q12 mo.
Normal 25(OH)D ≥30 ng/mL
Insufficiency <25
Deficiency <15 ng/mL

<table>
<thead>
<tr>
<th>Level</th>
<th>Treatment with Vitamin D&lt;sub&gt;2&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 ng/mL</td>
<td>50,000 IU/wk x 12, then q MO x 6</td>
</tr>
<tr>
<td>5–15 ng/mL</td>
<td>50,000 IU/wk x 4, then q MO x 6</td>
</tr>
<tr>
<td>16–29 ng/mL</td>
<td>50,000 IU/MO x 6</td>
</tr>
</tbody>
</table>

(Ergocalciferol, 50,000 IU capsules)

**CKD: Metabolic Bone Disease Tx**

- **Vascular calcification at any site**
  - Avoid Ca-containing P-binders
  - Use sevelamer (not confined to ESRD)

- **Ca > 10.2 mg/dL, stop calcitriol**
  - Switch to non-Ca-containing P-binders (sevelamer)
  - **Limit** elemental Ca in Ca-based binders to 1500 mg/d or sum of total dietary Ca plus elemental Ca to 2000 mg/d

- **P > 5.5 mg/dL**
  - Switch to non-Ca-containing P-binders (sevelamer)
  - Restrict P to 0.8–1.0 g/d if P > 5.5 mg/dL
  - Restrict P to 0.8–1.0 g/d if PTH > 50 pg/mL

High-Turnover Bone Disease Can Result in Soft-Tissue Calcification
Low-Turnover Bone Disease Can Result in Soft-Tissue Calcification

- Calcium
- Magnesium
- Phosphorus

Deposition Into Tissues → Calcification

PTH
**CKD: Renal Osteodystrophy Tx**

- **Ca-based P-binders**
  - Ca acetate (Calphron™, PhosLo™)
    - 667 mg (elemental Ca); 1 capsule tid with meals
  - Ca carbonate (Tums™)
    - 500 mg (elemental Ca); 1 tab tid with meals
  - Ca-based P-binders in CKD Stages 3 and 4 permitted
  - Avoid concurrent Ca-based P-binder and iron salt ingestion
  - Avoid concurrent Ca-based P-binder and levothyroxine ingestion

**CKD: Renal Osteodystrophy Tx**

- **Non-Ca-based binders**
  - Avoid aluminum-based gels
  - **Sevelamer hydrochloride (Renagel™)**
  - Use in CKD Stages 3 and 4
    - 800 mg capsules: 1–2 tid with meals
    - Only FDA-approved for ESRD
  - Alone *or* with Ca-based P-binders

**CKD: Metabolic Acidosis**

- The serum bicarbonate reflects the degree or severity of systemic acidosis. This parameter should be at 22 meq/L or greater, to offset acidosis-driven bone lysis.

- **Bicarbonate therapy**
  - \( \text{NaHCO}_3 \) dose: 0.5–1.0 mEq/kg bw/d
    - 3.87 mEq per 325 mg tablet
    - 7.73 mEq per 650 mg tablet
    - Usual CKD dose 1300 mg TID

---

Acidosis Aggravates Renal Osteodystrophy
Acidosis Treatment

• May occur earlier in diabetic CKD, compared to non-diabetic CKD
  ▪ Type IV RTA

• Treatment same in diabetic and non-diabetic CKD
  ▪ $\text{HCO}_3^- \geq 22 \text{ mEq/L}$
  ▪ $\text{NaHCO}_3$ tablets (0.5–1.0 mEq/kg/day)

Verify acidemia with ABG
Nutritional Assessment
Nutrition Assessment

- Dietician (RD) — integral part of CKD management. Consultation at any CKD stage.
- Utilize RD within 2 wk of initial consultation for dietary assessment and recommendations.
- RD will educate pts on food preparation techniques → increasing compliance with dietary restrictions.
Rationale for RD consult

- Malnutrition evolves during the progression of CKD
- Hypoalbuminemia and vitamin deficiencies are common
- Diet high in biological value must be maintained, while restricting Na, P, K
Food Sources

- **Na**
  - **Na**++ — usually all processed foods (hot dogs, bologna, soups) are high in Na. Be wary of foods that are labeled “low in sodium”. The RD will need to determine ‘how low is low’.

- **K**
  - **K**+ — chief sources are fruits and vegetables and anything that grows below or sits in the ground. Highly colored fruits (i.e., watermelon), deep green vegetables, even dried fruits.

- **P**
  - **P**04 — all high P foods are also in high K foods, unless phosphoric acid is added. Found in dairy products (except butter). Foods prepared with skim milk (i.e., cake mix, biscuits), nuts, dried peas, baked beans, legumes and colas.
Intervention

- **Caloric restriction:**
  - 25 cal/kg of SBW to lose wt
  - 30 cal/kg of SBW to maintain wt
  - 35–40 cal/kg of SBW to gain wt

- **Fluid restriction:**
  - implement only if Na<132 mEq/L and pt is compliant with low Na diet.
  - may be temporary
**CKD: Nutrition**

- **Rationale** for Intervention
  - amino acid loads induce glomerular hyperfiltration
  - protein restriction in small studies retards CKD progression, but **not** in largest RCT, MDRD study
  - obesity (BMI >38 kg/m\(^2\)) — associated with glomerular hyperfiltration

**CKD:** Nutrition — ↑ Protein Intake Associated with ↓ Kidney Function

- **Nurses’ Health Study** (n=1135 females); 11-year followup
  - Median protein intake, 92.3 g/d
  - Each 10-g ↑ in non-dairy protein intake ↓ Cr by 1.21 mL/min
  - Highest quintile ↓ Cr by 4.77 mL/min

**CKD: Nutrition Therapy**

- **Consult** Renal Dietitian at CKD Stage 3

- **Protein restrict @ GFR <25 mL/min/1.73 m²**
  - High biologic protein: 0.6–0.75 g/kg bw
  - Initiate dialysis if ...
    - GFR <15–20 with energy malnutrition from low protein intake
    - 6% wt loss or <90% of IBW in <6 mo

Dietary P Restriction to Control SHPT in CKD

• Commentary:

  “In summary, the available data and the OPINION of the Work Group support the proposal that dietary phosphate restriction should be initiated when blood *PTH levels begin to rise* (Stage 2) and/or when serum *phosphorus levels are elevated* at any stage of CKD.” p S65

• KDOQI Guideline 4. Restriction of Dietary Phosphorus in pts with CKD

  4.1 Dietary phosphorus should be restricted to 800–1000 mg/day when the serum *phosphorus levels are elevated* (4.6 mg/dL) at CKD Stages 3 and 4 (OPINION; p S63)

Vaccinations

DOMAINS OF CKD CARE

CV RISK FACTOR MODIFICATION
- GLYCEMIC CONTROL
- HTN

PROTEINURIA REDUCTION

EVALUATE CKD PROGRESSION

VAX

NUTRITIONAL ASSESSMENT

ANEMIA MGMT

CKD-MBD MGMT
Vaccinations

- CKD pts immunocompromised

- Despite immunodeficiency, CKD pt immunized less frequently against *flu* and *S pneumoniae* than general medical pts
Vaccinations: Recommendations

- Annual influenza A/B
- 23-valent polysaccharide pneumococcal (Pneumovax, PPV23) Q6 years
- HBV vax — give at any CKD stage. Immunization series should be completed by stage 4 since “late” stage 5 vax induces lower Ab titers
Influenza Vax rates Below National Target (Healthy People 2000)

**Dialysis pts**

- HD: 49%
- PD: 39%

**General Population**

- Whites: 60%
- Non Whites: 30%
- 2000: 60%

Odds of Hospitalization & Death are Reduced In Vaccinated HD pts

Gilbertson et al, Kidney Int 2003; 63:738-743
Evaluate Progression of CKD

DOMAINS OF CKD CARE

- CV RISK FACTOR MODIFICATION
  - GLYCEMIC CONTROL
  - LIPID CONTROL
  - HTN
- PROTEINURIA REDUCTION
- EVALUATE CKD PROGRESSION
- VAX
- NUTRITIONAL ASSESSMENT
- ANEMIA MGMT
- CKD-MBD MGMT
Strategies to Improve Vascular Access – Education

**NKF-K/DOQI Guidelines**

- Education when $S_{Cr} > 3$ mg/dl

- Vascular access is necessary to access blood circulation. Refers to fistulas, grafts, and catheters.
Vascular Access

- Preserve arm veins suitable for placement of vascular access, *regardless of arm dominance*.

- Arm veins, especially cephalic veins of the non-dominant arm, should not be used for venipuncture or iv catheters.
Vascular Access

• Dorsum of the hand should be used for iv lines. When venipuncture of the arm veins is necessary, sites should be rotated.

• Avoid subclavian vein cannulation — increases risk of central vein stenosis
DIALYSIS Arteriovenous Fistula

- Surgically connect endogenous artery to endogenous vein (no Gortex, AVG)
- Safest and longest half-life of all accesses
- Least expensive
Brachial artery and cephalic vein anastomosed making brachio-cephalic fistula (dilated cephalic vein segment)

Brachial artery
Basilic vein

Anastomosis of brachial artery to basalic vein (less desirable since basilic vein is too deep, unless vein is moved)

Cephalic vein
Radial artery

Radial artery and cephalic vein are anastomosed. Cephalic vein dilates into a radio-cephalic fistula
Strategies to Improve Vascular Access –
Timing of Access Placement

NKF-K/DOQI Guidelines

- Refer to surgery for primary AVF construction if ...
  - GFR <25 mL/min
  - $S_{Cr} > 4$ mg/dL
  - within 1 yr of anticipated dialysis

- AVF maturation time
  - Okay: >1 month
  - Ideal: 3–4 mo, prior to cannulation
Fistula: Disadvantages

- “Bulge” — unattractive

- Never matures
  - Conversion to AVG, possible
  - Temporary HD catheter may be req’d
Vascular Access: AVG

- Construction timing — 3 to 6 weeks before anticipated need
- When — AVG reserved for pts who are not candidates for an AVF or where AVF failed
- Clot more frequently than AVFs
- Overall half-life 2.5 yr
AV Grafts

Brachio-basilic graft

Radio-cephalic graft

Brachial artery
Basilic vein
Radial artery
Cephalic vein

Brachial artery and basilic vein connected with a graft

Straight graft between radial artery and cephalic vein

Loop graft between radial artery and cephalic vein
Catheters

- Cannulation of large central vein
- Temporary in most cases
- Lower Qb, i.e., less efficient HD
- Requires meticulous care
  - Much higher infection/mortality rates
  - ~50% infection rate at 6 mo
Catheter Locations

Left Subclavian Catheter

Right Internal Jugular Catheter

Right Subclavian Catheter
Majority of Pts Start RRT Without A Permanent Vascular Access

Permanent Access Placed or Attempted Before Start of RRT?

- Yes: 43.9%
- No: 48.2%
- Unsure: 7.9%

Held et al, AJKD 1996, 28 (Suppl. 2):58-78, USRDS DMMS I (1,997 pts incident in 1993)
Vascular Access Used for the First Chronic Hemodialysis

Risk of Infectious Mortality is Increased with Temporary Access

Pts With Temporary Access Have Higher Rate of Hospital Utilization

Vascular Access Survival and Revisions

Gibson et al, J Vasc Surg 2001;34:694-700. Adjusted for age, gender, race, previous access
AVF (USRDS)

Prevalent hemodialysis pts from 2001 CPM data, year represents year in which dialysis was initiated; current access from 2001 CPM survey data; includes only pts for whom an access type is known.
Fistula First Initiative

- A national initiative to expand the number of pts with AVFs, as opposed to catheters or AVGs.
- To date, the initiative has surpassed its target of 40% prevalent pts.
- Year 2010: goal is 50% of all new pts on HD. 66% of continued pts will use fistulas.
Download information

- Updated editions of

  *Chronic Kidney Disease (CKD): Clinical Practice Recommendations For Primary Care Physicians and Healthcare Providers — A Collaborative Approach (Ed 5.0)*

  can be downloaded from:

  Ghsrenal.Com/CKD/Hfhs_CKD_Guidelines_v5.0.pdf
Questions?