Management of Chronic Kidney Disease and its Complications

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Objectives

• Review timing of CKD related complications and referral to specialists for CKD care

• Understand the management of anemia and hyperkalemia in those with CKD

• Review management of various aspects of secondary hyperparathyroidism in CKD
**Albuminuria**

- Random urine albumin:creatinine ratio (UACR) is recommended for all CKD patients
  - Early morning sample is better
  - Normal UACR - <10 mg/g
  - Term microalbuminuria is not recommended (30-300 mg/g) by both ADA and nephrology guidelines
  - 24 hour urinary protein excretion is cumbersome and unreliable
Lower eGFR and higher levels of albuminuria increases the risk of cardiovascular death.
Higher Cardiovascular Disease Burden in Those with CKD

December 31, 2010 point prevalent Medicare enrollees

Source: United States Renal Data System
## KDIGO CKD Classification

### Prognosis of chronic kidney disease by GFR and albuminuria

<table>
<thead>
<tr>
<th>Glomerular filtration rate</th>
<th>Albuminuria normal to mildly increased (ACR &lt; 30 mg/g or &lt; 3 mg/mmol)</th>
<th>Albuminuria moderately increased (ACR 30–299 mg/g or 3–29 mg/mmol)</th>
<th>Albuminuria severely increased (ACR ≥ 300 mg/g or ≥ 30 mg/mmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal or high (&gt; 90 mL/min/1.73m²)</td>
<td>Low risk&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Moderately increased risk</td>
<td>High risk</td>
</tr>
<tr>
<td>Mildly decreased (60–89 mL/min/1.73m²)</td>
<td>Low risk&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Moderately increased risk</td>
<td>High risk</td>
</tr>
<tr>
<td>Mildly to moderately decreased (45–59 mL/min/1.73m²)</td>
<td>Moderately increased risk</td>
<td>High risk</td>
<td>Very high risk</td>
</tr>
<tr>
<td>Moderately to severely decreased (30–44 mL/min/1.73m²)</td>
<td>High risk</td>
<td>Very high risk</td>
<td>Very high risk</td>
</tr>
<tr>
<td>Severely decreased (15–29 mL/min/1.73 m²)</td>
<td>Very high risk</td>
<td>Very high risk</td>
<td>Very high risk</td>
</tr>
<tr>
<td>Kidney failure (&lt; 15 mL/min/1.73 m²)</td>
<td>Very high risk</td>
<td>Very high risk</td>
<td>Very high risk</td>
</tr>
</tbody>
</table>

<sup>a</sup>If no other markers of kidney disease are present and the patient does not have chronic kidney disease

ACR = albumin-creatinine ratio, GFR = glomerular filtration rate
When to refer to Nephrology?

We recommend referral to specialist kidney care services for people with CKD in the following circumstances (1B):

- AKI or abrupt sustained fall in GFR;
- GFR < 30 ml/min/1.73 m² (GFR categories G4-G5)*;
- a consistent finding of significant albuminuria (ACR ≥ 300 mg/g [≥ 30 mg/mmol] or AER ≥ 300 mg/24 hours, approximately equivalent to PCR ≥ 500 mg/g [≥ 50 mg/mmol] or PER ≥ 500 mg/24 hours);
- progression of CKD (see Recommendation 2.1.3 for definition);
- urinary red cell casts, RBC > 20 per high power field sustained and not readily explained;
- CKD and hypertension refractory to treatment with 4 or more antihypertensive agents;
- persistent abnormalities of serum potassium;
- recurrent or extensive nephrolithiasis;
- hereditary kidney disease.
Complications of CKD

- Hypertension
- Hyperlipidemia
- Anemia
- CKD- Mineral and bone disorder: Hyperphosphatemia, vitamin D deficiency
- Metabolic acidosis
- Hyperkalemia
- Vascular access referral
Recent Hypertension Guidelines for CKD

Whelton PK, et al.
2017 High Blood Pressure Clinical Practice Guideline

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA
Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

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**CKD + HTN: Target BP = 130/80 mm Hg**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>SBP: B-R&lt;sup&gt;SR&lt;/sup&gt; DBP: C-EO</td>
<td>1. Adults with hypertension and CKD should be treated to a BP goal of less than 130/80 mm Hg (1-6).</td>
</tr>
<tr>
<td>Ila</td>
<td>B-R</td>
<td>2. In adults with hypertension and CKD (stage 3 or higher or stage 1 or 2 with albuminuria [≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio or the equivalent in the first morning void]), treatment with an ACE inhibitor is reasonable to slow kidney disease progression (3, 7-12).</td>
</tr>
<tr>
<td>Iib</td>
<td>C-EO</td>
<td>3. In adults with hypertension and CKD (stage 3 or higher or stage 1 or 2 with albuminuria [≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio in the first morning void]) (7, 8), treatment with an ARB may be reasonable if an ACE inhibitor is not tolerated.</td>
</tr>
</tbody>
</table>
How do we manage hypertension in CKD

Treatment of hypertension in patients with CKD

BP goal <130/80 mm Hg (Class I)

Albuminuria (≥300 mg/d or ≥300 mg/g creatinine)

Yes → ACE inhibitor (Class IIa)

No → Usual "first-line" medication choices

ACE inhibitor intolerant

Yes → ARB* (Class IIb)

No → ACE inhibitor* (Class IIa)
ACEI & ARBs

- ACEI lowered kidney disease progression, CV events and mortality in CKD

- ARB exerts renal and CV benefits but mortality benefits are unknown

- Combination therapy with ACEI and ARB is not justified

- Despite data supporting RAASI use in CKD, >40% of the CKD population is not on these much-deserved medications
Agents to treat hypertension in CKD

- ACEI or ARB
- Diuretics (loop preferred in those with GFR <30)
- Calcium channel blockers
- Beta-blockers
- Vaso-dilators- Hydralazine or Nitrates or Minoxidil
- Alpha blockers- clonidine
- Resistant HTN: BP >140/90 mm Hg despite using three agents including a diuretic
Management of Resistant Hypertension

Step 1

Exclude other causes of hypertension, including secondary causes, white-coat effect and medication nonadherence +

Ensure low sodium diet (<2400 mg/d)
Maximize lifestyle interventions:
- ≥6 hours uninterrupted sleep
- Overall dietary pattern
- Weight loss
- Exercise

Optimize 3-drug regimen
Ensure adherence to 3 antihypertensive agents of different classes (RAS blocker, CCB, diuretic) at maximum or maximally tolerated doses. Diuretic type must be appropriate for kidney function.

BP not at target

Step 2

Substitute optimally dosed thiazide-like diuretic: ie, chlorthalidone or indapamide* for the prior diuretic.

BP not at target

Step 3

Add mineralocorticoid receptor antagonist (MRA): spironolactone or eplerenone**

BP still not at target

Note: Steps 4-6 are suggestions on the basis of expert opinion only and these steps should be individualized.
Guidelines recommendations for lipid lowering therapy – statins for all CKD patients

• In adults aged >50 years with eGFR <60 ml/min/1.73 m² but not treated with chronic dialysis or kidney transplantation (GFR categories G3a-G5), we recommend treatment with a statin or statin/ezetimibe combination (1A)

• In adults aged >50 years with CKD and eGFR >60 ml/min/1.73m² (GFR categories G1-G2) we recommend treatment with a statin (1B)

**Recommended statin dose in CKD population**

<table>
<thead>
<tr>
<th>Statin</th>
<th>CKD Patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>ND</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>80</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>20</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>10</td>
</tr>
<tr>
<td>Simvastatin/ezetimibe</td>
<td>20/10</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>40</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>40</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>2</td>
</tr>
</tbody>
</table>

* Includes CKD patients with eGFR G3a-G5, Receiving Dialysis or Who Had a Kidney Transplant
Anemia in CKD

![Graph showing anemia prevalence in CKD patients with and without diabetes.](image)
## Box 1. Common Causes of Anemia in CKD

- Relative erythropoietin deficiency
- Iron deficiency
- Blood loss
- Reduced erythrocyte survival duration
- Inflammation
- Infection
- Underlying hematologic disease
- Hyperparathyroidism (dialysis patients)
- Hemolysis
- Nutritional deficits

*Abbreviation: CKD, chronic kidney disease.*
Work-up of anemia in CKD

- Complete blood count (CBC), which should include Hb concentration, red cell indices, white blood cell count differential, and platelet count
- Absolute reticulocyte count
- Serum ferritin level
- Serum transferrin saturation (TSAT)
- Serum vitamin B12 and folate levels
Don’t raise the hemoglobin to normal levels in kidney disease

**TABLE 2**

<table>
<thead>
<tr>
<th>Target hemoglobin</th>
<th>Target ferritin</th>
<th>Target transferrin saturation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic kidney disease</td>
<td>&gt; 10 g/dL</td>
<td>&gt; 100 ng/dL</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>10–11.5 g/dL</td>
<td>200–1,200 ng/dL</td>
</tr>
</tbody>
</table>

Iron therapy

- For people who are not receiving hemodialysis, consider a trial of oral iron before offering intravenous iron therapy.

- If they are intolerant of oral iron or target hemoglobin levels are not reached within three months, offer intravenous iron therapy.

- Offer iron therapy to people with anemia of CKD who are iron deficient and who are receiving ESA therapy.
Erythropoiesis-stimulating agents

- CKD patients who have a hemoglobin <10 g/dL whose iron stores are replete
  - Subcutaneous administration – better
  - Benefits: Reducing transfusion needs and anemia related symptoms
  - Adverse effects: Worsening of hypertension, stroke, clotting of fistula
  - Caution in those with active malignancy
Hyperkalemia with ACEI ARB use

- Assess renal function to define overall risk of hyperkalemia
- Start with low doses and monitor closely
- Discontinue medications that can impair renal potassium excretion, including herbal preparations and over the-counter NSAIDS
- Reduce potassium in diet, avoid salt substitutes containing potassium
- Ensure effective diuretic therapy (loop diuretics should be used if the estimated glomerular filtration rate is < 30 mL/min/1.73 m²)
- Correct metabolic acidosis when present
Initiation of low dose ACEI/ARB

- No hyperkalemia
- No AKI

Check basic metabolic panel in 1-2 weeks

Home BP monitoring/
Office visit in 4 weeks

- Symptomatic hypotension
- SBP <100 mmHg

- Discontinue ACEI/ARB

STEP 1

STEP 2

- No hyperkalemia
  - AKI

Continue to titrate dose based on BP

Recheck BMP in 2 weeks

Follow STEP 2

- Stop ACEI/ARB
  - Consult Nephrology

- Mild hyperkalemia
  - AKI

Reassess diet, diuretics and metabolic acidosis

- Moderate to severe hyperkalemia
  - No AKI

- Mild hyperkalemia
  - No AKI

- Moderate to severe hyperkalemia
  - No AKI

Mild hyperkalemia: potassium levels 5.0-5.5 mEq/L
Moderate to severe hyperkalemia: potassium levels >5.5 mEq/L
Acute Kidney Injury (AKI): >30% rise in serum creatinine
Management of chronic hyperkalemia

- Low potassium diet and diuretics
- Novel agents- Patiromer and ZS-9
CKD-Mineral and Bone Disorder

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

When and what to test?

<table>
<thead>
<tr>
<th>Suggested frequencies of serum calcium, phosphorus, and PTH measurements according to CKD stage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progressive CKD stage 3</strong></td>
</tr>
<tr>
<td>Calcium and phosphorus</td>
</tr>
<tr>
<td>PTH and alkaline phosphatases</td>
</tr>
</tbody>
</table>

Recommended target: Calcium and phosphorus within normal range reported in your laboratory

PTH: 2-9 times the upper limit of the assay used to measure PTH

KDIGO CKD-MBD guidelines. Kidney Int. 76; 2009
How to correct Abnormal PTH Levels

- Correct hyperphosphatemia
- Replete nutritional vitamin D deficiency
- Vitamin D analogue initiation
- Cinacalcet in dialysis patients
## Phosphate Binders Currently Available for Clinical Use

<table>
<thead>
<tr>
<th>Binder type</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum salts (RARELY USED)</td>
<td>Highly effective, inexpensive</td>
<td>Proven toxicity, requires monitoring</td>
</tr>
<tr>
<td>Calcium carbonate and acetate (widely prescribed)</td>
<td>Moderately effective, inexpensive</td>
<td>Hypercalcemia and possible vascular calcification</td>
</tr>
<tr>
<td>Magnesium salts</td>
<td>Moderately effective, free of calcium and aluminum, fairly inexpensive</td>
<td>Gastrointestinal effects, requires monitoring</td>
</tr>
<tr>
<td>Lanthanum carbonate</td>
<td>Highly effective, low pill burden</td>
<td>Expensive, gastrointestinal effects</td>
</tr>
<tr>
<td>Sevelamer hydrochloride and sevelamer carbonate (widely used)</td>
<td>Moderately effective, lipid effects</td>
<td>Expensive, high pill burden, gastrointestinal effects</td>
</tr>
<tr>
<td>Iron based binders (Ferric citrate, Sucroferric oxyhydroxide)</td>
<td>Lower iron requirement along with phosphate binding, lower pill burden</td>
<td>Lack of clinical experience</td>
</tr>
</tbody>
</table>
# How to Treat Vitamin D Deficiency

<table>
<thead>
<tr>
<th>Serum 25 (OH)D (ng/ML)</th>
<th>Definition</th>
<th>Ergocalciferol Dose (Vitamin D&lt;sub&gt;2&lt;/sub&gt;)</th>
<th>Duration (months)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>Severe vitamin D deficiency</td>
<td>50,000 IU/wk orally x 12 wks; then monthly</td>
<td>6 months</td>
<td>Measure 25 (OH) D levels after 6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>500,000 IU as single I.M. dose</td>
<td></td>
<td>Assure patient adherence; measure 25(OH)D at 6 months</td>
</tr>
<tr>
<td>5-15</td>
<td>Mild vitamin D deficiency</td>
<td>50,000 IU/wk x 4 weeks, then 50,000 IU/month orally</td>
<td>6 months</td>
<td>Measure 25(OH)D levels after 6 months</td>
</tr>
<tr>
<td>16-30</td>
<td>Vitamin D insufficiency</td>
<td>50,000 IU/month orally</td>
<td>6 months</td>
<td></td>
</tr>
</tbody>
</table>
Vitamin D Analogues in CKD

- Agents: Calcitriol, Doxercalciferol, Paricalcitol
- Lowers PTH levels
- Hypercalcemia risk
- Large observational study showed survival benefit with newer vitamin D analogues such as Paricalcitol in dialysis
Types of bone disease in CKD

- Osteitis fibrosa: High turnover state
- Adynamic bone disease: Low turnover disease
- Osteomalacia: Bone formation rate is low
- Mixed uremic osteodystrophy
Benefits and Harms of Osteoporosis Medications in Patients With Chronic Kidney Disease
A Systematic Review and Meta-analysis
Lisa M. Wilson, ScM; Casey M. Rebholz, PhD, MPH, MS; Ermias Jirru, MD, MPH; Marisa Chi Liu, MD, MPH; Allen Zhang, BS; Jessica Gayleard, BS; Yue Chu, MSPH; and Karen A. Robinson, PhD

Limitation: Unclear rigor of evidence, possible reporting biases, and scant evidence among patients with stage 3 to 5 CKD.

Conclusion: Effects of osteoporosis medications on BMD, fracture risk, and safety among patients with CKD are not clearly established.

Primary Funding Source: Kidney Disease: Improving Global Outcomes.
Osteoporosis Medications

- CKD stages 1–2 with osteoporosis and/or high risk of fracture, we recommend management as for the general population (1A).

- CKD stage 3 with PTH in the normal range and osteoporosis and/or high risk of fracture, we suggest treatment as for the general population (2B).

- CKD stages 4–5D having biochemical abnormalities of CKD–MBD, and low BMD and/or fragility fractures, we suggest additional investigation with bone biopsy prior to therapy with antiresorptive agents (2C).

KDIGO CKD-MBD guidelines. Kidney Int. 76; 2009
Metabolic acidosis

- Metabolic acidosis is associated with cardiovascular disease, kidney disease progression and death in CKD

- KDIGO guidelines: We suggest that in people with CKD and serum bicarbonate concentrations <22 mmol/l treatment with oral bicarbonate supplementation be given to maintain serum bicarbonate within the normal range, unless contraindicated. (2B)

- Sodium bicarbonate 650 meq PO three-four times daily-safe and effective. Most studies used sodium bicarbonate rather than Bicitra
Protein and salt intake – Guideline recommendations

- We suggest lowering protein intake to 0.8 g/kg/day in adults with diabetes (2C) or without diabetes (2B) and GFR <30 ml/min/1.73 m² (GFR categories G4-G5), with appropriate education.

- We suggest avoiding high protein intake (41.3 g/kg/day) in adults with CKD at risk of progression. (2C)

- We recommend lowering salt intake to <90 mmol (<2 g) per day of sodium (corresponding to 5 g of sodium chloride) in adults, unless contraindicated. (1C)
WEIGHT LOSS – DIETARY OPTIONS

• CKD: A reduction in daily caloric intake by 500 kcal
• Balanced reduction in calorie intake
• Close monitoring for weight loss – avoid malnutrition and preserve muscle mass
• Intensive caloric restriction (<1200 kcal/day) might be avoided
• Counsel to watch-out for high-protein diets

Navaneethan SD et al. CJASN 2009
Glycemic targets in CKD

- Imprecision of HbA1c with CKD

- HbA1c 7-8% to prevent or delay progression of the microvascular complications of diabetes, including DKD

- Do not target HbA1c <7% in those at risk for hypoglycemia

PILL BURDEN IN CKD

We recommend timely referral for planning renal replacement therapy (RRT) in people with progressive CKD in whom the risk of kidney failure within 1 year is 10–20% or higher†, as determined by validated risk prediction tools. (1B)

The kidney failure risk equations were developed in patients with CKD stages G3-G5 referred to nephrologists in Canada, and have now been validated in more than 700,000 individuals spanning 30 + countries worldwide.
KIDNEY FAILURE RISK CALCULATION

If you don't have the information required below talk to your doctor.

Age (Yrs)  Sex  Region

GFR (MI/Min/1.73M2)  Urine Albumin: Creatinine Ratio  Units

[Input fields]

CALCULATE

About this calculator

The kidney failure risk equations were developed in patients with CKD stages G3-G5 referred to nephrologists in Canada, and have now been validated in more than 700,000 individuals spanning 30+ countries worldwide.

The four and eight variable equations accurately predict the 2 and 5 year probability of treated kidney failure (dialysis or transplantation) for a potential patient with CKD Stage 3 to 5. Predicted risks may differ from observed risks in clinical populations with lower and higher observed risks than the study population, and a calibration factor for non-North American
Referral for vascular access

- CKD education
- Vascular access referral

“We recommend timely referral for planning renal replacement therapy in people with progressive CKD in whom the risk of kidney failure within 1 year is 10–20% or higher, as determined by validated risk prediction tools. (1B)”
Conservative kidney care

- Conservative management should be an option in people who choose not to pursue RRT and this should be supported by a comprehensive management program
- Loop diuretics and other medications can be continued
Conclusions

- Statins are indicated for all CKD patients

- BP Target: 130/80 mm Hg and ACEI or ARB first choice

- Don’t target Hb >10-11 g/dl in those with kidney disease

- Metabolic acidosis and hyperphosphatemia should be corrected to improve outcomes

- Refer all CKD patients with EGFR <30 and those with rapid decline in EGFR (>3 ml/min/year)

- Protein intake not to exceed 0.8 g/kg/day depending on their stage of kidney disease
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