Renal Disorders: Chronic Kidney Disease

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Chronic kidney disease (CKD) is estimated to affect approximately 2 million Canadians. It often coexists with cardiovascular disease and diabetes and is recognized as a risk factor for all-cause mortality and cardiovascular disease.

Kidney function is described using the glomerular filtration rate (GFR) or creatinine clearance. Estimates of GFR (eGFR) are calculated and reported using the MDRD formula which includes age, sex and creatinine, with a correction for black race. Alternatively, an estimated creatinine clearance can be calculated using the Cockcroft-Gault equation (see Appendices: Dosage Adjustment in Renal Impairment) or measured using a 24-hour urine collection. Both equations have limitations, especially at the extremes of age and kidney dysfunction, but are more reliable than serum creatinine alone. The eGFRs used to characterize the stages of CKD are listed in Table 1.

Table 1: KDIGO Stages of Chronic Kidney Disease

<table>
<thead>
<tr>
<th>KDIGO Stage</th>
<th>GFR (mL/min/1.73 m²)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>&gt;90</td>
<td>Normal or high</td>
</tr>
<tr>
<td>G2</td>
<td>60–89</td>
<td>Mildly decreased</td>
</tr>
<tr>
<td>G3a</td>
<td>45–59</td>
<td>Mildly to moderately decreased</td>
</tr>
<tr>
<td>G3b</td>
<td>30–44</td>
<td>Moderately to severely decreased</td>
</tr>
<tr>
<td>G4</td>
<td>15–29</td>
<td>Severely decreased</td>
</tr>
<tr>
<td>G5</td>
<td>&lt;15</td>
<td>Kidney failure (add 'D' if treated by dialysis)</td>
</tr>
</tbody>
</table>

Abbreviations: GFR=glomerular filtration rate; KDIGO=Kidney Disease: Improving Global Outcomes

CKD is now defined as the presence of kidney damage for a period greater than 3 months. An estimated or measured GFR of less than 60 mL/min/1.73 m² is considered abnormal for all adults. A value of more than 60 mL/min/1.73 m² is considered abnormal if it is accompanied by abnormalities of urine sediment or of imaging tests, or if the patient has had a kidney biopsy with abnormalities.

Until recently CKD was thought to be progressive, with the patient experiencing a decline in function over time and ultimately requiring dialysis. With the development of new interventions and prevention strategies, patients with CKD, particularly those without proteinuria, may have little progression of their kidney disease. However, they remain at high risk for cardiovascular events and death.

This chapter summaries the management of patients up to, but not including, the introduction of dialysis.

Goals of Therapy

- Slow the progression of CKD
- Manage reversible cardiovascular risk factors
- Treat the complications of CKD

Investigations

- History:
  - Many causes of CKD are hereditary, genetic or associated with other conditions, so a patient and family history is very important. Risk factors for CKD are listed in Table 2. Patients with risk factors, especially cardiovascular disease and diabetes mellitus, should be screened for CKD.
Table 2: Risk Factors for Chronic Kidney Disease

- Atherosclerotic vascular disease
- Autoimmune diseases, such as lupus, rheumatoid arthritis, connective tissue disease and vasculitis
- Chronic urinary tract obstruction from prostatic enlargement, neurogenic bladder, kidney stones
- Chronic viral infections, such as Hepatitis B and C, HIV
- Diabetes mellitus
- Family history of kidney disease
- First Nations people
- Hereditary polycystic kidney disease
- History of acute kidney injury
- Hypertension
- Multiple myeloma
- Pregnancy complications including edema, hypertension, proteinuria
- Recurrent pyelonephritis
- Reduced nephron mass (e.g., congenital single kidney, post nephrectomy, scarring from reflux nephropathy)
- Use of known nephrotoxic drugs (e.g., acetaminophen, NSAIDs including COX-2 inhibitors, lithium, cyclosporine, tacrolimus, contrast dyes)

Physical exam:
- general appearance: in advanced stages of CKD patients develop cachexia or loss of muscle mass. Advanced uremia is often accompanied by a sallow, grayish complexion and so-called "uremic fetor" which is secondary to breakdown of urea in saliva to ammonia
- weight: measure at each visit to assess fluid and nutritional status. Large changes are usually associated with fluid gains or loss
- vitals: lying and standing blood pressures, pulse, jugular venous pressure and the presence of edema
- abdominal exam: palpation for enlarged, cystic kidneys, and auscultation for renal artery bruits at a position approximately 2 cm above and 2 cm lateral to the umbilicus. Among patients with known hypertension, a bruit audible in both systole and diastole is moderately specific for renal artery stenosis.

Laboratory investigations:
- urine tests (Table 3, Table 4)
  - urinalysis: standard urinalysis is recommended as part of the yearly adult assessment to screen for hematuria (Figure 1 - Stepwise Investigation of Hematuria) and should be done in the following patients:
    - any patient at risk for CKD (see Table 2)
    - abnormal creatinine
    - patients with diabetes at the time of diagnosis and yearly thereafter
    - patients with hypertension
  - urine albumin to creatinine ratio (ACR) or urine protein to creatinine ratio (PCR): these tests detect small amounts of proteinuria (<300 mg) not detected by the urinalysis. The level of proteinuria is used to risk stratify patients for cardiovascular and kidney events. Note that urine dipsticks (an alternate test for protein loss) are affected by hydration status
    - 24-hour urine collection: to measure creatinine clearance or confirm the amount of proteinuria
- blood tests (Table 4)
  - CBC, Na, K, Cl, HCO₃, urea, creatinine (calculated eGFR), fasting lipid profile. If diabetes present add HbA₁c. At Stage G3b or higher add albumin, calcium, phosphorus, parathyroid hormone, serum iron, TIBC, ferritin.
- imaging
  - renal ultrasound in patients who have an increased creatinine, proteinuria or abnormal urine sediment to determine renal size and look for anatomic abnormalities, such as a solitary or polycystic kidney
  - abdominal ultrasound: consider if the eGFR <60 mL/min/1.73 m²

Table 3: Categories of Albuminuria and Tests Used to Quantify Them

<table>
<thead>
<tr>
<th>Urine Test</th>
<th>Albuminuria Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>AER (mg/24h)</td>
<td>A₁ (normoalbuminuria)</td>
</tr>
<tr>
<td>&lt;30</td>
<td>30–300</td>
</tr>
</tbody>
</table>
### Urine Test

<table>
<thead>
<tr>
<th>Albuminuria Category</th>
<th>A1 (normoalbuminuria)</th>
<th>A2 (microalbuminuria)</th>
<th>A3 (macroalbuminuria)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PER (mg/24h)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;150</td>
<td>150–500</td>
<td>&gt;500</td>
</tr>
<tr>
<td>ACR (mg/mmol)</td>
<td>&lt;3</td>
<td>3–30</td>
<td>&gt;30</td>
</tr>
<tr>
<td>PCR (mg/mmol)</td>
<td>&lt;15</td>
<td>15–50</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Protein reagent strip</td>
<td>Negative to trace</td>
<td>Trace to +</td>
<td>+ or greater</td>
</tr>
</tbody>
</table>

<sup>a</sup> Includes nephrotic syndrome (defined as albumin excretion >2200 mg/24h or protein excretion >3000 mg/24h).

<sup>b</sup> Requires a 24-hour urine collection.

Abbreviations: ACR=albumin to creatinine ratio; AER=albumin excretion rate; PCR=protein to creatinine ratio; PER=protein excretion rate

### Table 4: Recommended Frequency of Blood and Urine Screening Tests in Chronic Kidney Disease<sup>4</sup>

<table>
<thead>
<tr>
<th>KDIGO Stage</th>
<th>A1 albuminuria</th>
<th>A2 albuminuria</th>
<th>A3 albuminuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>12</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>G2</td>
<td>12</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>G3a</td>
<td>12</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>G3b</td>
<td>6</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>G4</td>
<td>4</td>
<td>4</td>
<td>2–3</td>
</tr>
<tr>
<td>G5</td>
<td>1–3</td>
<td>1–3</td>
<td>1–3</td>
</tr>
</tbody>
</table>

<sup>a</sup> See text for suggested blood tests. Urine tests include ACR (or PCR if indicated) and standard urinalysis. Urine culture and sensitivity only if urine tract infection suspected.

Abbreviations: ACR=albumin to creatinine ratio; KDIGO=Kidney Disease: Improving Global Outcomes; PCR=protein to creatinine ratio

Refer the following patients to a nephrologist:<sup>8</sup>

- acute kidney failure
- eGFR <30 mL/min/1.73 m<sup>2</sup>
- progressive loss of kidney function
- persistent significant proteinuria (present on 2 out of 3 samples)
  - on dipstick or quantified PCR >100 mg/mmol or quantified ACR >60 mg/mmol
- inability to achieve treatment targets or other difficulties in the management of the CKD patient

For patients with a new finding of eGFR between 30 and 60 mL/min/1.73 m<sup>2</sup>, the physician should determine the stability of the patient's eGFR and repeat test within 2–4 weeks, and then in 3–6 months.<sup>1</sup> Consider reversible causes, such as intercurrent illness, volume depletion, medications (NSAIDs, aminoglycosides, iv contrast dye) and obstruction. If the eGFR remains between 30 and 60 mL/min/1.73 m<sup>2</sup> consider referral to a nephrologist.

**Figure 2** - Management of Diabetic Chronic Kidney Disease and **Figure 3** - Management of Nondiabetic Chronic Kidney Disease outline the management guidelines for diabetic and nondiabetic CKD.

### Therapeutic Choices

### Nonpharmacologic Choices<sup>1, 4</sup>
Encourage patients to exercise for 30–60 minutes 4–7 days per week to reduce the possibility of becoming hypertensive or to lower blood pressure in those with hypertension.

Encourage smoking cessation to slow progression of CKD and to reduce the risk of cardiovascular disease (see Psychiatric Disorders: Smoking Cessation).

Alcohol intake should be limited to 2 drinks or less per day and should not exceed 14 standard drinks per week for men and 9 standard drinks per week for women so as not to increase blood pressure.

Patients with CKD and hypertension should follow a low sodium diet: <90 mmol/day Na, or 2 g Na or 5 g NaCl/day.

If serum potassium >5 mmol/L, first consider medications that can be discontinued, such as potassium supplements and potassium-sparing diuretics. If these medications are not present, advise dietary potassium restriction. Note that ACE inhibitors (ACEIs), ARBs and aldosterone antagonists may also contribute to the hyperkalemia; continue these agents if being used to decrease proteinuria and restrict dietary potassium instead (see Fluid and Electrolyte Disorders: Potassium Disturbances).

Dietary protein intake has been the focus of several trials. However, there is a lack of convincing evidence that a long-term protein restricted diet (<0.7 g/kg/day) delays the progression of CKD. Referral to a dietitian to provide a diet that is protein-controlled (0.8–1 g/kg/day) is recommended.

Encourage weight loss if obese (BMI >30 kg/m²) or overweight (BMI 25–29 kg/m²) to lower the risk of CVD.

**Pharmacologic Choices**

**Antihypertensives**

Encourage patients with hypertension to purchase a BP cuff for home monitoring, with review of these measurements at the medical follow-up. The blood pressure target in adult patients with an ACR <3 mg/mmol is ≤140/90 mm Hg. In adult patients with an ACR >3 mg/mmol, the blood pressure target is ≤130/80 mm Hg. Table 5 presents guidelines on the choice of antihypertensive agent in CKD.

**Table 5: Choices of Antihypertensive Medication in Chronic Kidney Disease**

<table>
<thead>
<tr>
<th>Clinical Condition</th>
<th>Antihypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuric CKD (ACR ≥3 mg/mmol)</td>
<td>ACEI or ARB&lt;sup&gt;a&lt;/sup&gt; The combination of an ACEI plus ARB is not recommended</td>
</tr>
<tr>
<td>Nonproteinuric CKD (ACR &lt;3 mg/mmol)</td>
<td>Choose agents based on current hypertension guidelines (see Cardiovascular Disorders: Hypertension). The combination of an ACEI plus ARB is not recommended</td>
</tr>
</tbody>
</table>

<sup>a</sup> See Figure 2 - Management of Diabetic Chronic Kidney Disease and Figure 3 - Management of Nondiabetic Chronic Kidney Disease for additional therapy options.

Abbreviations: ACEI=angiotensin converting enzyme inhibitor; ACR=albumin to creatinine ratio; ARB=angiotensin receptor blocker; CKD=chronic kidney disease

**ACE Inhibitors and Angiotensin Receptor Blockers**

ACEIs and ARBs are the preferred agents for certain types of CKD (Table 5) because they have the following class effects:<sup>10</sup>

- Reduction of blood pressure and intraglomerular pressure: in controlled trials, the beneficial effect of ACEIs and ARBs on the progression of CKD is greater than would be expected based on their antihypertensive effects alone.
- Reduction of proteinuria: ACEIs and ARBs reduce proteinuria more than any other antihypertensive even when the effect of blood pressure reduction on urinary protein excretion has been taken into account.
- Other mechanisms: ACEIs and ARBs reduce intraglomerular pressure, alter the function of mesangial cells and interfere
Increase the ACEI or ARB dose in patients whose BP is above target, and in patients with elevated proteinuria, even if BP is within target (Figure 2 - Management of Diabetic Chronic Kidney Disease, Figure 3 - Management of Nondiabetic Chronic Kidney Disease). Moderate to high doses of ACEIs and ARBs have been associated with beneficial effects on slowing progression of CKD. Begin with low doses and increase at 4–6 week intervals while monitoring for side effects and hypotension.

Measure eGFR and serum K⁺ prior to and 1–2 weeks after initiating or increasing the dose of ACEI or ARB. Repeat ACR or PCR in 4–6 weeks. Suggestions for monitoring and modifying ACEI and ARB therapy are provided in Table 6.

ACEIs/ARBs are contraindicated in pregnancy. Counsel premenopausal females on appropriate contraception (see Sexual Health: Contraception).

Hold ACEI/ARB if patient has severe vomiting, diarrhea or volume depletion.

### Table 6: Monitoring ACEI and ARB Therapy in Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Test</th>
<th>Monitoring Frequency</th>
<th>Action</th>
</tr>
</thead>
</table>
| eGFR   | If eGFR ≥60 mL/min, repeat in 4–12 weeks | Dosage adjustment is based on change in eGFR since previous test. eGFR decreased by 0–15%: no dose change  
eGFR decreased by 15–30%: no dose change, but repeat eGFR in 10–14 days  
eGFR decreased by 30–50%: reduce dose and repeat eGFR every 5–7 days until GFR within 30% of baseline  
eGFR decreased by >50%: discontinue ACEI or ARB and repeat eGFR every 5–7 days until eGFR is within 15% of baseline value |
|        | If eGFR 30–59 mL/min, repeat in 2–4 weeks |                                                                 |
|        | If eGFR <30 mL/min, repeat in ≤2 weeks |                                                                 |
| K⁺     | If eGFR ≥60 mL/min, repeat in 4–12 weeks | If K⁺ 5–6 mmol/L advise dietary potassium restriction             |
|        | If eGFR 30–59 mL/min, repeat in 2–4 weeks | If K⁺ 6–6.5 mmol/L prescribe loop diuretic if tolerated ± cation exchange resin |
|        | If eGFR <30 mL/min, repeat in ≤2 weeks |                                                                 |

Abbreviations: eGFR=estimated glomerular filtration rate; K⁺=serum potassium

### Diabetic Chronic Kidney Disease

Follow the Canadian Diabetes Association guidelines for glycemic targets (see Endocrine and Metabolic Disorders: Diabetes Mellitus). Discontinue metformin when ClCr or eGFR <30 mL/min/1.73 m² due to an increased risk of lactic acidosis. Metformin should also be discontinued when there are acute decreases in kidney function or illnesses/procedures that could lead to acute kidney injury (e.g., nausea/vomiting, dehydration, administration of iv contrast dye) or cause hypoxia (e.g., cardiac or respiratory failure) as these are also risk factors for lactic acidosis.

Patients with CKD are at higher risk of developing hypoglycemia because the ability of the kidney to metabolize insulin is impaired. Patients with eGFR <30 mL/min/1.73 m² should be taught how to recognize and treat hypoglycemia. Gliclazide is the preferred sulfonylurea because, with a shorter half-life and no renally excreted active metabolite, it causes less hypoglycemia. Doses of insulin and some oral diabetes medications may need to be reduced as CKD progresses (Table 7).

### Table 7: Diabetes Medications That Require Dosing Adjustment in Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concern</th>
<th>Stage G3 CKD</th>
<th>Stage G4 CKD</th>
<th>Stage G5 CKD/Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acarbose</td>
<td>No data for patients with creatinine &gt;177 µmol/L</td>
<td>May use</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
</tbody>
</table>
Drug Concern | Stage G3 CKD | Stage G4 CKD | Stage G5 CKD/Dialysis
--- | --- | --- | ---
Chlorpropamide | Decreased drug clearance leading to prolonged hypoglycemia | Reduce dose to 100 mg/day. Avoid if ClCr <50 mL/min. | Avoid; gliclazide is preferred | Avoid; gliclazide is preferred
Exenatide | Decreased clearance and increased side effects in CKD stages 4–5 | May use | Not recommended | Not recommended
Glyburide | Accumulation of renally excreted active metabolite leading to prolonged hypoglycemia | Use with caution | Avoid; gliclazide is preferred | Avoid; gliclazide is preferred
Liraglutide | Gastrointestinal effects: nausea, vomiting, diarrhea | May use | Not recommended | Not recommended
Metformin | Risk of lactic acidosis | Use with caution | Contraindicated | Contraindicated
Nateglinide | Decreased clearance of drug and active metabolites | Use with caution | Use with caution | Avoid if possible
Saxagliptin | Decreased clearance | Reduce dose to 2.5 mg/day | Reduce dose to 2.5 mg/day | Reduce dose to 2.5 mg/day
Sitagliptin | Decreased clearance when ClCr <50 mL/min. Risk of pancreatitis | Reduce dose to 50 mg/day | Reduce dose to 25 mg/day | Reduce dose to 25 mg/day

**Cardiovascular Risk Reduction for Patients with Chronic Kidney Disease**

Both a reduced eGFR and proteinuria confer substantial increases in cardiovascular risk and death. A secondary analysis of the Multiple Risk Factor Intervention Trial found that the presence of microalbuminuria is associated with a 2.5-fold greater risk of cardiovascular events, even after controlling for other cardiovascular risk factors. Additionally, the prognosis associated with a given level of eGFR varies substantially based on the presence and severity of proteinuria. In fact, patients with heavy proteinuria, but without overtly abnormal eGFR, appear to have worse clinical outcomes than those with moderately reduced eGFR without proteinuria.

**If a patient with CKD is >50 years old, treatment with a low-dose statin or statin/ezetimibe combination is recommended irrespective of LDL level [Evidence: SORT A].** Suggested doses for these drugs are presented in Table 8. In an 18–49-year-old patient with CKD, statin treatment is suggested if one or more of the following is present: known coronary disease (MI or coronary revascularization), diabetes mellitus, prior ischemic stroke or estimated 10-year incidence of coronary death or nonfatal MI >10% [Evidence: SORT C].

In adults with CKD and hypertriglyceridemia, therapeutic lifestyle changes are suggested. Treatment with fibrates is not recommended.

**Table 8: Suggested Daily Doses of Lipid-lowering Agents in Chronic Kidney Disease**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>20 mg</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>40 mg</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>40 mg</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>80 mg</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>10 mg</td>
</tr>
<tr>
<td>Simvastatin/Ezetimibe</td>
<td>20 mg/10 mg</td>
</tr>
</tbody>
</table>

No randomized controlled trials have examined the safety or efficacy of ASA for primary or secondary prevention of atherosclerotic events in patients with CKD. Based on decreased mortality in observational studies, ASA therapy is recommended following MI in patients with CKD.

**Drug Therapy Adjustment in Patients with Chronic Kidney Disease**

Dosage adjustment of drugs in renal impairment is described in Appendices: Dosage Adjustment in Renal Impairment.

Very few drugs are absolutely contraindicated in patients with CKD. However, medications that are generally avoided in patients with stages G4–G5 CKD are listed in Table 9.
**Table 9: Medications to be Avoided in Stage G4–G5 Chronic Kidney Disease**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>Increased risk of bleeding with ClCr &lt;25 mL/min.</td>
</tr>
<tr>
<td>Baclofen</td>
<td>Increased neurotoxicity even at very low doses.</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Increased risk of bleeding with ClCr &lt;30 mL/min. In patients with ClCr 15–29 mL/min, 75 mg BID is suggested, but safety has not been established.</td>
</tr>
<tr>
<td>Magnesium-containing medications, e.g., antacids, laxatives</td>
<td>Magnesium accumulation.</td>
</tr>
<tr>
<td>Meperidine (pethidine)</td>
<td>Accumulation of an active metabolite that can lead to seizures.</td>
</tr>
<tr>
<td>Metformin</td>
<td>Risk of lactic acidosis with ClCr &lt;30 mL/min.</td>
</tr>
<tr>
<td>NSAIDs, COX-2 inhibitors and other nephrotoxins</td>
<td>Increased risk of acute kidney injury.</td>
</tr>
<tr>
<td>Phosphorus-containing products (e.g., Fleet Phospho-soda)</td>
<td>Deaths due to hyperphosphatemia and resulting hypocalcemia have been reported and these products can also cause acute phosphate nephropathy.</td>
</tr>
<tr>
<td>Potassium-sparing diuretics and herbals, such as alfalfa, dandelion, noni juice</td>
<td>Risk of hyperkalemia.</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Increased risk of bleeding with ClCr &lt;30 mL/min.</td>
</tr>
<tr>
<td>Sotalol</td>
<td>Risk of accumulation and torsades de pointes.</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>Risk of accumulation secondary to decreased renal catabolism and increased serum levels of retinol-binding protein.</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Limit to no more than 60–100 mg/day as the metabolite (oxalate) can result in kidney stones and deposits of calcium oxalate in soft tissues.</td>
</tr>
</tbody>
</table>

**Complications of Chronic Kidney Disease**

Complications are seen in Stages G3–G5 CKD. These complications include:

- **Hyperkalemia:** refer to Fluid and Electrolyte Disorders: Potassium Disturbances.

- **Metabolic acidosis:** treat with sodium bicarbonate tablets or Shohl’s solution (citric acid/sodium citrate). Start at 0.5 mmol/kg/day in 2–3 divided doses and titrate to achieve a CO₂ level ≥22 mmol/L. Monitor closely since some patients will experience fluid retention and heart failure.

- **Anemia:** Detailed clinical practice guidelines are provided by Kidney Disease: Improving Global Outcomes. See also Blood Disorders: Common Anemias.

- **Mineral metabolism:**
  - Start therapy with a calcium-containing phosphate binder (calcium carbonate or calcium citrate) if a low phosphate diet (800–1000 mg phosphate/day) fails to control hyperphosphatemia and if hypercalcaemia is not present. If hypercalcaemia develops, reduce the dose of calcium-containing phosphate binders. If hyperphosphatemia is still present, the patient may be changed to a non-calcium-containing phosphate binder, such as lanthanum, sevelamer carbonate or sevelamer hydrochloride. The carbonate salt of sevelamer may help to neutralize uremia-induced metabolic acidosis.
  - If serum intact parathyroid hormone (PTH) is >53 pmol/L, consider starting a vitamin D analogue, such as alfalcaldol or calcitriol. These analogues are required since the kidney is less able to activate other forms of vitamin D. Reduce the dose or discontinue therapy if hypercalcaemia or hyperphosphatemia develops or if PTH levels are <10.6 pmol/L. Cinacalcet may also be considered as a second-line agent to reduce PTH in patients receiving dialysis, but this drug is very expensive and not often covered by medication insurance plans. This drug is not recommended for use in predialysis CKD patients due to an increased incidence of hypocalcaemia.
Therapeutic Tips

- Screen individuals at risk for CKD annually with a history and physical exam including BP assessment, calculation of eGFR or ClCr from serum creatinine, urinalysis and spot urine for albumin/creatinine (ACR) or protein/creatinine (PCR) ratio.
- The use of once-daily ACEI or ARB is preferred to enhance patient adherence and prevent fluctuations in daily blood pressure.
- Start ACEIs or ARBs at moderate doses in those patients with normal GFR and titrate up to the maximally tolerated dose.

Algorithms

**Figure 1 - Stepwise Investigation of Hematuria**

- Microscopic hematuria (>2 RBCs on 2 out of 3 specimens)
  - Exclude transient causes such as UTI (confirm any UTI with urine culture)
  - eGFR ≥60 and ACR or PCR <30 mg/mmol?
    - Yes
      - Refer to a urologist
    - No
      - Repeat eGFR from serum creatinine, urea, electrolytes (Na⁺, K⁺, Cl⁻, HCO₃⁻), ACR or PCR at least once within 2 weeks. Order serum ANA, C3, C4.
        - eGFR declines by 20% in 1–30 days or ACR or PCR >300 mg/mmol or ANA >1:80 or complements decreased
          - Yes
            - URGENT referral to a nephrologist. Repeat eGFR and serum electrolytes at least every 1–4 weeks until seen by a nephrologist
          - No
            - Follow patient or refer to a nephrologist

Abbreviations:  ACR=albumin to creatinine ratio; ANA=antinuclear antibody; C3=complement C3; C4=complement C4; PCR=protein to creatinine ratio; RBC=red blood cell; UTI=urinary tract infection

Adapted with permission from the Manitoba Renal Program [www.kidneyhealth.ca](http://www.kidneyhealth.ca) website.

**Figure 2 - Management of Diabetic Chronic Kidney Disease**
Figure 3 - Management of Nondiabetic Chronic Kidney Disease

ACR >3 mg/mmol (on 2 out of 3 specimens)

No

Screen annually

Yes

Start ACEI or ARB
Repeat ACR in 4–6 weeks
Refer to a nephrologist if eGFR <30 or BP <110/70

Increase dose of ACEI or ARB

No

Is ACR <3 mg/mmol or reduced by ≥50%

Yes

Check BP every 3 months. Repeat blood and urine tests regularly (Table 3)

Yes

BP <130/80?

No

Increase dose of ACEI/ARB and/or add thiazide diuretic

BP <130/80 4–6 weeks later?

No

Add CCB and titrate to maximum tolerated dose and if required add other medications such as beta-blocker or alpha-blocker to achieve target.

Consider referral to a specialist if target not achieved when:
- patient is on 4 medications
- patient is on 3 medications but intolerant of others
- eGFR is falling or proteinuria >1 g with good BP and glucose control

Abbreviations: ACR=albumin to creatinine ratio; ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; BP=blood pressure; CCB=calcium channel blocker

Adapted with permission from the Manitoba Renal Program [www.kidneyhealth.ca](http://www.kidneyhealth.ca) website.
ACR or PCR >200 mg/mmol and/or BP >130/80

eGFR <30

Refer to a nephrologist

eGFR ≥30

Follow or refer to a nephrologist and

Start ACEI or ARB (unless BP <110/70) and repeat ACR/PCR in 4–6 weeks

Increase dose of ACEI or ARB No

ACR or PCR normal or reduced ≥50%?

Yes

Check BP every 3 months

Repeat blood and urine tests regularly (Table 3)

Yes

BP <130/80?

No

Increase dose of ACEI/ARB and/or add thiazide diuretic

BP <130/80 4–6 weeks later?

No

Add CCB and titrate to maximum tolerated dose, and if required add other medications such as beta-blocker or alpha-blocker to achieve target.

Consider consulting a nephrologist if target BP not achieved after patient is on 4 medications or, on 3 but intolerant of others.

Abbreviations: ACEI=angiotensin converting enzyme inhibitor; ACR=albumin to creatinine ratio; ARB=angiotensin receptor blocker; CCB=calcium channel blocker; PCR=protein to creatinine ratio

Adapted with permission from the Manitoba Renal Program www.kidneyhealth.ca website.

Drug Table

Table 10: Drugs Used to Treat Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Adult Dose</th>
<th>Adverse Effects</th>
<th>Drug Interactions</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bicarbonate</td>
<td>sodium bicarbonate generics</td>
<td>Start at 0.5 mmol/kg/day in 2–3 divided doses and titrate to achieve an HCO₃⁻ level ≥22 mmol/L 325 mg tablet = 3.8 mmol bicarbonate 500 mg tablet = 5.8 mmol bicarbonate</td>
<td>Bloating, flatulence, increased Na⁺ absorption.</td>
<td>Reduced absorption of medications requiring an acidic gastric pH (e.g., atazanavir, calcium carbonate, iron tablets, itraconazole, ketoconazole).</td>
<td>$</td>
</tr>
<tr>
<td>Class</td>
<td>Drug</td>
<td>Adult Dose</td>
<td>Adverse Effects</td>
<td>Drug Interactions</td>
<td>Cost</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------------------------------</td>
<td>------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>Shohl’s solution (citric acid/sodium citrate) Dicitrate Solution, generics</td>
<td>1 mmol bicarbonate/mL Start at 0.5 mmol/kg/day in 2–3 divided doses and titrate to achieve an HCO₃⁻ level ≥ 22 mmol/L</td>
<td>Bloating, flatulence, increased Na⁺ absorption.</td>
<td>Reduced absorption of medications requiring an acidic gastric pH (e.g., atazanavir, calcium carbonate, iron tablets, itraconazole, ketoconazole).</td>
<td>$</td>
</tr>
<tr>
<td>Calcimimetics</td>
<td>cinacalcet (Sensipar)</td>
<td>Start at 30 mg po daily. Titrating every 2–4 wk to PTH &lt; 53 pmol/L</td>
<td>Diarrhea, nausea, vomiting, hypocalcemia, hypophosphatemia. Not for use in predialysis CKD.</td>
<td>Cinacalcet strongly inhibits CYP2D6 and can increase levels of metoprolol, flecainide, vinblastine, thioridazine and most tricyclic antidepressants.</td>
<td>~$350</td>
</tr>
<tr>
<td>Phosphate Binders</td>
<td>calcium carbonate (Caltrate, Tums, generics)</td>
<td>Start at 250–500 mg elemental Ca²⁺/day TID po with meals. Titrating to achieve a PO₄ level in the normal range Calcium carbonate is 40% elemental calcium</td>
<td>Constipation and nausea are the most common. Others: hypercalcemia.</td>
<td>Oral iron salts, fluoroquinolones, tetracyclines and levothyroxine: absorption reduced. Give 2 h before or 4 h after calcium. H₂-blockers (e.g., ranitidine), proton pump inhibitors and sodium bicarbonate increase gastric pH and reduce dissolution and phosphate binding of calcium carbonate.</td>
<td>$</td>
</tr>
<tr>
<td>Phosphate Binders</td>
<td>calcium citrate (Osteocit, generics)</td>
<td>Start at 300–900 mg elemental Ca²⁺ (1–3 tablets) TID po with meals. Titrating to achieve a PO₄ level in the normal range</td>
<td>Constipation and nausea are the most common. Others: hypercalcemia.</td>
<td>Oral iron salts, fluoroquinolones, tetracyclines and levothyroxine: absorption reduced. Give 2 h before or 4 h after calcium. H₂-blockers (e.g., ranitidine), proton pump inhibitors and sodium bicarbonate increase gastric pH and reduce dissolution and phosphate binding of calcium carbonate. Less dependent on acidic gastric pH for dissolution. May increase absorption of aluminum from aluminum-containing antacids.</td>
<td>$</td>
</tr>
<tr>
<td>Phosphate Binders</td>
<td>lanthanum carbonate (Fosrenol)</td>
<td>Start at 250–500 mg TID po with meals. May be used in combination with other PO₄ binders</td>
<td>Nausea, diarrhea, flatulence. Potential for accumulation of lanthanum due to GI absorption, but long-term clinical consequences unknown.</td>
<td>Reduced absorption of levothyroxine and mycophenolate mofetil. Administer lanthanum 2 h after these drugs.</td>
<td>$$$</td>
</tr>
<tr>
<td>Class</td>
<td>Drug</td>
<td>Adult Dose</td>
<td>Adverse Effects</td>
<td>Drug Interactions</td>
<td>Costa</td>
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</tr>
<tr>
<td>Phosphate</td>
<td>sevelamer</td>
<td>800–2400 mg (1–3 tablets) TID po</td>
<td>Heartburn, bloating, gas.</td>
<td>Cholesterol-lowering drugs may need to be reduced as sevelamer can lower LDL cholesterol by an average of 30%. Reduced absorption of ciprofloxacin, levothyroxine and mycophenolate mofetil. Administer sevelamer 2 h after these drugs.</td>
<td>$$$$$</td>
</tr>
<tr>
<td>Binders</td>
<td>carbonate</td>
<td>with meals.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Renvela</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>sevelamer</td>
<td>800–2400 mg (1–3 tablets) TID po</td>
<td>Heartburn, bloating, gas. If used alone in patients with nondialysis CKD, monitor CO2 levels as can worsen uremic metabolic acidosis.</td>
<td>Cholesterol-lowering drugs may need to be reduced as sevelamer can lower LDL cholesterol by an average of 30%. Reduced absorption of ciprofloxacin, levothyroxine and mycophenolate mofetil. Administer sevelamer 2 h after these drugs.</td>
<td>$$$$$</td>
</tr>
<tr>
<td>Binders</td>
<td>hydrochloride</td>
<td>with meals.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Renagel</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D</td>
<td>alfalcaldol</td>
<td>Start at 0.25 µg po every other</td>
<td>Hypercalcemia, hyperphosphatemia.</td>
<td>Phenytoin, carbamazepine, phenobarbital, thiazide diuretics may reduce levels of alfalcaldol.</td>
<td>$</td>
</tr>
<tr>
<td>Analogues</td>
<td>One-Alpha</td>
<td>day or daily.</td>
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<tr>
<td></td>
<td>calcitriol</td>
<td>Start at 0.25 mg po every other</td>
<td>Hypercalcemia, hyperphosphatemia.</td>
<td>Phenytoin, carbamazepine, phenobarbital, thiazide diuretics may reduce levels of calcitriol.</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>Rocaltrol</td>
<td>day or daily.</td>
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<td></td>
</tr>
</tbody>
</table>

a. Cost of 30-day supply of usual dose of drug, based on 70 kg weight; includes drug cost only.

Abbreviations:  HCO3 =bicarbonate;  PO4 =phosphate;  PTH=parathyroid hormone

Legend:  $ <$40  $ $40–80  $$$ $80–120  $$$$ $120–160  $$$$$ $160–200

**Suggested Readings**


**References**


