Chronic Kidney Disease Management - Summary

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for longer than 3 months, with implications for health. It can be acute or chronic in nature (chronic being greater than 3 months duration) and distinguishing between the two is important since they require different interventions and have different etiologies and outcomes. The goal is early detection and intervention to slow the decline in kidney function.

How do I assess for kidney disease?

Targeted testing is used to identify those who are most at risk of developing CKD and include those with:

- diabetes
- hypertension
- smoking history
- obesity
- established cardiovascular disease
- family history of CKD
- multisystem diseases with kidney involvement (ie. Lupus, rheumatoid arthritis)

Tests used to identify and monitor CKD include

- A blood test for serum creatinine (SCr)
- The SCr is then used to calculate the estimated glomerular filtration rate (eGFR)
- Urine albumin to creatinine ration (ACR) for albuminuria quantification
- Urinalysis for presence of blood

Table 1 Diagnostic criteria for CKD (present for more than 3 months) (3)

Decreased GFR	GFR less than 60 mL/min/1.73m^2 (category G3a-G5)
Markers of kidney damage	Albuminuria Urine sediment abnormalities Electrolyte and other abnormalities due to tubular disorders Abnormalities detected by kidney biopsy Structural abnormalities detected by imagine (ultrasound) History of kidney transplantation

<u>e-GFR</u>

-widely accepted as the best overall indicator of kidney function

-can be unreliable in a number of situations including: acute changes in renal function, patients on dialysis, exceptional dietary intake, extremes in body size, diseases affecting skeletal muscle, paraplegia, amputees

or high muscle mass, children under 18, severe liver disease, drugs interacting with creatinine excretion, pregnancy

Table 2 GFR classification (3)

GFR category	**GFR** (mL/min/1.73 m^2)	**Description**
G1	>90	Normal or high*
G2	60-89	Mildly decreased*
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

*Relative to young adult level. In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD. ☐ Shaded area denotes CKD

<u>Albuminuria</u>

-refers to abnormal loss of albumin in the urine

-albumin is one type of plasma protein found in the urine of patients with CKD

-it is a common marker of kidney diseases associated with diabetes, hypertension, obesity and vascular disease

-albumin to creatinine ratio (ACR) is a single sample preferably on the first early morning void

-albumin excretion rate (AER) can also be used but it is taken with a urine sample over a 24 hour period and on top of it being very inconvenient, missing even a small amount can give inaccurate results

Table 3 Albuminuria categories: Description and range (3)

Category	**AER** (mg/24hours)	**ACR** (mg/mmol)	**Description**
A1	<30 mg/24 hours	<3 mg/mmol	Normal to mildly increased
A2	30-300 mg/24 hours	3-30 mg/mmol	Moderately increased
A3	>300 mg/24 hours	>30 mg/mmol	Severely increased

-in patients with diabetes the threshold for mildly increased albuminuria is lower as an ACR of 2 mg/mmol or greater is considered to mildy increased and CKD management would be initiated at this level (instead of 3 or greater in non-diabetics)

-early detection is important as increasing amount of albuminuria and a reduction in GFR correlate directly with the progression of CKD

-institution of an ACE inhibitor (ACEi) or angiotensin receptor blocker (ARB) can reduce the amount of albuminuria and improve outcomes

Frequency of Monitoring for CKD

-follow up monitoring of CKD is recommended by the CKD KDIGO guidelines from 2012 (see figure below)

-frequency of monitoring is guided by a combination of GFR and Albuminuria measurement

Table 4 Prognosis of CKD and Recommended Frequency of Monitoring Per Year by GFR and Albuminuria Categories (3)

Prognosis of CKD and Recommended Frequency of Monitoring Per Year by GFR and Albuminuria Categories: KDIGO 2012			A1	A2	A3
			<3 mg/mmol	3-30 mg/mmol	>30 mg/mmol
			Normal to mildly increased	Moderately increased	Severely increased
G1	Normal or high	≥90	1 if CKD	1	1
G2	Mildly decreased	60-89	1 if CKD	1	2
G3a	Mildly to moderately decreased	45-59	1	2	3
G3b	Moderately to severely decreased	30-44	2	3	3
G4	Severely decreased	15-29	3	3	4+
G5	Kidney failure	<15	4+	4+	4+

Green: low risk (if no other markers, no CKD), Yellow: moderately increased risk, Orange: high risk, Red: very high risk

How do I treat kidney disease?

The treatment of CKD involves reducing cardiovascular risk factors including and other interventions including:

-reduce albuminuria

-reduction in modifiable lifestyle risk factors (ie. smoking cessation, exercise)

-thrombosis prophylaxis

-cholesterol reduction

-blood pressure control

-controlling diabetes

-dose adjusting renally excreted medications

-avoiding nephrotoxic medications

Reduce Albuminuria

-abnormal loss of protein seen in those with CKD

-it is a surrogate marker of CKD progression

-treatment involves use blockade of renin-angiotensin-aldosterone system (RAAS) with an ACE-I or an ARB

- can be used without issue in every stage of CKD and should not be avoided

-reductions in GFR (reversible 5-30% reduction) and elevations in potassium (K^+) can be seen with initiation of these drugs and needs to be monitored

-thiazides or loop diuretics can be used if potassium remains elevated (5.3-6.2 mmol/L), or patients should be sent to ER for acute hyperkalemia management if potassium is greater than 6.3 mmol/L

Lifestyle Risk Factors

-all patients can benefit

-body mass index (BMI) between 18.5 and 24.9

-at least 150 minutes of moderate to vigorous intensity aerobic activity in bouts of 10 min or more

-smoking cessation

-maintain a healthy diet to maintain normal albumin levels

    -recommendations for salt intake are for less than 1.5 g/day

    -Many CKD patients would benefit from a referral to a dietician where they can seek instruction on diets for reduced potassium, phosphate, sodium and protein

-adequate fluid intake (6-8 glasses or 1.5-2 L per day) is recommended and fluid restriction is not necessary for most patients

Antiplatelet Therapy

-patients with CKD are high risk of developing vascular disease

-low dose ASA can be used for secondary prevention in those with established coronary, cerebral or peripheral vascular disease

    -coronary artery diseases (CAD): acute coronary syndrome (ACS), myocardial infarction (MI), percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG)

    -cerebrovascular diseases (CVD): stroke, transient ischemic attack (TIA)

    -peripheral vascular disease (PVD): patients with PVD receive ASA therapy based on risk of cardiovascular events and risk of bleeding, some may require anticoagulation

Dyslipidemia Therapy

-Total, HDL, and LDL cholesterol and triglyceride levels used to determine if initiation of lipid lowering therapy is required

-routine monitoring of levels *not necessary* for CKD patients since the result will not alter management

-all diabetic and transplant patients should receive a statin unless they have specific contraindications

-all CKD patients that are 50 years of age or older should receive a statin or statin/ezetimibe combination

-CKD patients that are less than 50 years of age should receive a statin if they have coronary artery disease (MI or revascularization), ischemic stroke, Framingham risk score greater than 10%, or albuminuria with an ACR greater than 3 mg/mmol in combination with one of the risk factors previously met.

-statins are contraindicated in patients that:

-have active liver disease

-have high alcohol consumption

-are pregnant

-statins in dialysis dependent patients is still debated, but the KDIGO guidelines suggest not to initiate a statin in these patients but continue therapy if it was initiated before receiving dialysis

Dosing

Table 5 Recommended doses of statins in adults with CKD (6)

Statin	**CKD stage G1-G2**	**CKD stage G3a-G5, including patients on dialysis or with a kidney transplant**
Lovastatin	General population	Not studied
Fluvastatin	General population	80 mg*
Atorvastatin	General population	20 mg†
Rosuvastatin	General population	10 mg‡
Simvastatin/Ezetmibe	General population	20 mg/10 mg§
Pravastatin	General population	40 mg
Simvastatin	General population	40 mg

Data based on *ALERT, †4D, ‡AURORA, §SHARP.

-lower doses than those above may be used in patients of asian decent

-cyclosporine inhibits the metabolism of certain statins resulting in higher blood levels

<u>Blood Pressure Control</u>

-the cornerstone of antihypertensive therapy in CKD is the disruption of the renin-angiotensis-aldosterone system (RAAS)

-ACEi's or ARB's disrupt the RAAS and are important agents in preventing the progression of vascular disease

ACEi's and ARB's

-the **combination** of ACEi's and ARB's is not recommended in patients with CKD

-they can be used safely in patients in ALL stages of CKD and should not be avoided

Diabetic CKD patients

-should receive initial treatment with an ACEi or ARB if they have an ACR ≥ 2 mg/mmol

-if blood pressure is not controlled with monotherapy , the combination of an ACEi or ARB with a dihydropyridine calcium channel blocker (CCB - amlodipine /nifedipine/ felodipine) is preferred over that of a combo with a thiazide diuretic

-addition of a loop diuretic is recommended for patients with extracellular volume overload (peripheral edema)

-the goal blood pressure for the diabetic CKD patient is <130/80 mmHg

Non-Diabetic CKD Patients

-should receive initial treatment with an ACEI or ARB if they have an ACR greater than 30mg/mmol

-a thiazide may be added for additional antihypertensive effect

-a loop diuretic may be added to assist in volume control

-the goal blood pressure for the non-diabetic CKD patient is less than 140/90 mmHg

Renovascular disease Patients

-they should be monitored closely when initiated with an ACEi or ARB as patients with renal artery stenosis (RAS) in a solitary kidney or bilateral disease are at increased risk of acute kidney injury

-these patients are often identified by having high blood pressure that is not easily controlled even while using up to four antihypertensives

-these patients require close monitoring of SCr and should be referred to general practitioner with consideration for a referral to a nephrologist if the SCr rises more than 25%

-RAS can be treated with medical management with angioplasty or stenting

<u>Control diabetes</u>

-diabetic nephropathy is a glomerular disease that results in excessive albumin loss in the urine and causes a progressive decline of GFR

-patients with CKD and diabetes should maintain and hemoglobin A1C (Hgb A1C) less than or equal to 7% to prevent or delay the progression of microvascular complications (retinopathy, nephropathy, neuropathy)

-a select group of patients who may have difficulty maintaining an A1C that low, may target 7-8.5% (ie.multiple co-morbidities, limited life expectancy, excessive coronary artery disease, high risk of hypo or hyper glycemia with unawareness)

-in patients with CKD, Hgb A1C can be falsely low due to reduced cell life span, anemia, altered glycation of Hgb or due to blood transfusions. Results should be interpreted with caution

-Hgb A1C should be measured every 3 months until patients reach target then every 6 months thereafter

-diabetic patients with CKD should receive an ACEi or ARB to reduce the risk of macrovascular disease (CAD, CVD, PVD) and microvascular disease (neuropathy, retinopathy, nephropathy)
-ACEi and ARB reduce albuminuria in CKD patients, and should be instituted when the ACR is > 2 mg/mmol
-ACEi is preferred over an ARB In type 1 diabetics
-all diabetics with established vascular disease should receive antiplatelet therapy

Diabetes drug therapy in those with CKD
-treatment is similar to non-CKD patients but renal dose adjusting may be required

Metformin
-first line therapy in type 2 diabetics
-has been associated with accumulation and lactic acidosis when used in patients with low kidney function
-used with caution in patients with GFR less than 60 ml/min and avoid in patient with GFR less than 30 mL/min
-Metformin may be used in certain circumstances if eGFR is 20-29 mL/min, but requires very close monitoring of serum bicarbonate levels to detect acidosis. Oral sodium bicarbonate may be prescribed to keep the level greater than 22mmol/L
-if Metformin therapy is not effective controlling blood glucose then a second agent individualized to the patient may be added

Sulfonylureas
-reduced kidney function reduces the clearance of sulfonylurea and their active metabolites increasing the CKD patient's risk of hypoglycemia
-Glyburide may start to accumulate at a GFR less than 60 mL/min according to the product monograph and is suggested that its use is contraindicated at a GFR less than 30 mL/min
-Gliclazide may also accumulate but is less affected by reduced kidney function and its use is considered safe until the GFR is less than 15 mL/min

Repaglinide
-is largely unaffected by reduced renal function
-does not require dose reduction, but is recommended to be started at a lower dose and titrated cautiously in those with GFR less than 30 mL/min

Acarbose
-is primarily excreted unchanged by the kidney
-should be discontinued at a GFR of 25 mL/min or below

DPP-4 Inhibitors

Linagliptin

-majority eliminated in the feces unchanged

-can be used in CKD patients, but little experience in ESRD or in dialysis, use with caution at GFR less than 15 mL/min

Saxagliptin

-excreted more than 75% by the kidneys

-requires reduced dosing at GFR less than 50 mL/min and discontinuation at less than 15 mL/min

Sitagliptin

-excreted >80% by the kidneys

-requires reduced dosing at GFR less than 50 mL/min and requires further reductions at less than 30 mL/min

GLP-1 Receptor Agonists

Exenatide

-mostly urinary excretion

-requires reduction in dose at GFR less than 60 mL/min and discontinuation at less than 30 mL/min

Liraglutide

-not readily excreted by the kidney but not recommended with reduced renal function

-use is not recommended at GFR less than 50 mL/min

Thiazolidinediones

Pioglitazone

-no dose adjustments required

-but use is limited by side effects (ie.edema, weight gain, CHF risk, MI risk, fracture risk)

Rosiglitazone

-no dose adjustments required

-but use is limited by side effects (ie. Edema, weight gain, CHF risk, MI risk, fracture risk)

Insulin

-long acting insulin can be added to metformin therapy

-if mealtime boluses necessary then other oral antidiabetic agents should be discontiued

-in type 1 and 2 diabetics insulin regimens should be tailored to get good blood glucose control while avoiding excess hypoglycemia

General Comments:

-during periods of acute illness accompanied by dehydration, vomiting or diarrhea, metformin and sulfonylureas should be held and patients should increase frequency of blood glucose monitoring and insulin doses should be adjusted as required

Renal Dose Adjustments

CKD can cause changes to the pharmacokinetics and pharmacodynamics of many drugs

Clinical judgment is vital when making drug dosing decisions in patients with reduced kidney function

Medication Evaluation

Follow a Stepwise approach

1. Obtain all relevant information
    a. Ensure that all patient information is gathered to determine that the best drug is chosen for the patient
    b. Are there other therapeutic alternatives to the drug in question that may be less nephrotoxic?
2. Estimate the GFR
    a. Calculate CrCl using Cockcroff-Gault and/or reported eGFR
    b. The CKD-EPI equation is the equation used by most laboratories to report estimated GFR
    c. Most references have drug dosing information derived from the Cockcroft-Gault equation; therefore, it should be used when determining dosing regimes
3. Review Medication list
    a. Identify medications that may require renal dosage adjustment
4. Determine the most appropriate dosing regime
    a. Consult references to determine the appropriate dosage adjustment
    b. Drugs may need adjustment in either in dose or interval or both
    c. The risk of toxicity potential should be balanced against the risk of inadequate drug response
5. Monitor for response and adverse effects
    a. Patients should be monitored for drug response and appearance of any adverse side effects indicating toxicity
6. Reassess and adjust dosing regimen as needed
    a. As renal function changes the drug dosing regimen may require further modification

Table 6 Common medications requiring renal dose adjustments

Antimicrobials	• Beta-lactam antibiotics • Intravenous Vancomycin • Macrolides • Ciprofloxacin, levofloxacin • Fluconazole (prolonged therapy) • Antivirals
Cardiac drugs	• Beta blockers • Digoxin • Spironolactone • Fenofibrate
Antidiabetic drugs	• Sulfonylureas • Metformin (monitor closely when GFR less than 30mL/min) • Insulin (more susceptible to hypoglycemia)
Centrally acting drugs	• Benzodiazepines • Opioids • Gabapentin
Anticoagulants	• Low molecular weight heparins • Oral anticoagulants (dabigatran, rivaroxaban, apixaban)
Miscellaneous	• Allopurinol, colchicine • Methotrexate

Avoid Nephrotoxic Medications

-there are medications and combinations of medications that may be expected to cause damage to the kidney

Table 7 Potentially nephrotoxic medications relevant to primary care

Nephrotoxic Medication	**Effects of Medication**
NSAID's & COX-2 Inhibitors	Interstitial nephritis, papillary necrosis
Combination ACEi/ARB, NSAID plus diuretic	Increased risk of acute kidney injury due to changes in blood supply to kidney
Lithium	Renal tubule damage leading to impairment in renal concentrating ability
Tacrolimus, cyclosporine	Acute or chronic changes in renal function primarily due to afferent and efferent arteriolar vasoconstriction
Radio Contrast dye	Risk of acute kidney injury (0-11%), some populations more at risk*
Aminoglycosides	Damage to proximal tubule and secondary injury to the glomerulus
Bisphosphonates	Renal toxicity reported

*GFR<60ml/min, >70 years old, diabetes, dehydration, CHF, large doses of contrast, use of high osmolality agents

How do I monitor and follow up patients?

Home blood pressure monitoring

-2-3 times per week (include a morning and an evening reading) when adding a new antihypertensive

-follow up in 2-3 weeks to determine effectiveness

-ask about symptoms of dizziness or orthostatic hypotension at each encounter

ACE-I and ARB therapy

-SCcr should be checked every 2 weeks after initiation of ACEi/ARB

-rises in SCr up to 25% or increases in K^+ of up to 0.5mmol/L are common

-these parameters should be rechecked in 2-3 weeks to exclude progression

-when used in combo with NSAID's and diuretics, increased monitoring of SCr and K^+ is recommended

Statin Therapy

-no direct evidence that follow up improves outcomes

-ALT and CK monitoring not routinely recommended

Antidiabetic Therapy

-best indicator is self monitoring of glucose

-frequency of daily monitoring should be individualized

-interpretation of HgbA1C should consider inaccuracy of CKD

-HgbA1C should be measured every 3 months when targets not being met, every 6 months when they are met

Avoiding Nephrotoxic Medications

-patients should have medications lists assessed at each visit for potential nephrotoxic medications

-should be reminded about avoiding NSAID's

What should I tell the patient?

-uncontrolled diabetes, hypertension or vascular disease can speed the decline of GFR up to 10-15ml/min per year therefore should be the focus of preventing progression of CKD

-there are no specific symptoms of CKD until kidney function is severely impaired (<15ml/min)

-renal replacement therapy options such as hemodialysis, peritoneal dialysis or transplant are used when patients start to have symptoms of end stage kidney disease (typically a GFR of <10ml/min)

-ACEi , ARB's and statins should only be used in women of childbearing potential if reliable contraception is used

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