Outpatient Management of Chronic Kidney Disease

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In Canada, it is estimated that for every patient receiving some form of renal replacement therapy, there could be 40 patients with chronic kidney disease (CKD). Assuming that the prevalence of CKD in Canada is similar to the US, this amounts to an estimated 600,000 people in Canada who may have CKD. Without evaluation, these patients could develop hastened end-stage renal disease requiring long-term dialysis or kidney transplantation, as well as having unrecognized, potentially modifiable, CV risk. The limited availability of physicians in Canada obliges that the majority of such patients will come to the attention of primary care providers to be evaluated in an outpatient setting. This article is intended to provide a framework of how to evaluate and treat patients with CKD in a primary practice outpatient setting.

Consider reversible etiologies

As with any medical evaluation, start with a thorough history and physical examination. The history should identify:

- drug use (prescription or proprietary medications),
- edema,
- nocturia,
- hematuria,
- polyuria,
- hesitancy,
- BP history,
- family history and
- diabetes history.

Table 1 provides a list of those individuals who should be tested for CKD. Consideration should exclude intercurrent illnesses and volume contraction. Diabetes, hypertension, nephrosclerosis due to age and generalized vascular disease and obstructive uropathy account for the majority of diagnoses of new CKD. Less common secondary causes should be considered, such as:

- vasculitis,
- lupus,
- endocarditis and
- primary renal diseases.

Table 1

People to be tested for kidney disease*

- Hypertensive patients
- Diabetic patients
- Heart failure patients
- Patients with known atherosclerosis (*i.e.*, coronary disease, peripheral arterial disease, stroke)
- Patients with unexplained anemia
- Patients with family history of end-stage renal disease
- First Nations people

* From the Canadian Society of Nephrology Guidelines

Urinalysis

Table 2 provides a list of tests to be ordered to assess renal function. A urinalysis is important for the identification of an active urinary sediment reflected by the presence of red blood cells in the microscopy. Hematuria, when accompanied by proteinuria, in a patient with diminished renal function typically heralds

active glomerular disease and warrants urgent referral to a nephrologist. Isolated hematuria without proteinuria may be glomerular or urologic in origin. Proteinuria found on routine urinalysis indicates glomerular damage. Typically, hypertensive disease shows lower levels of proteinuria (< 1 gm/L) whereas diabetic nephropathy is characterized by higher levels of proteinuria (> 1 gm/L), or nephrotic range levels (> 3 gm/L).

Renal ultrasound

A renal ultrasound should be done if the preliminary assessment confirms the presence of a subnormal glomerular filtration rate (GFR). Renal ultrasound reports should include:

- specific measurement reports of renal sizes,
- echogenicity and
- the presence/absence of hydronephrosis.

Normal kidneys should be roughly 10 cm to 12 cm in length. Small kidneys typically reflect the presence of longstanding renal disease, or renovascular disease. Large kidneys typically reflect diabetes, or infiltrative diseases, such as amyloidosis, HIV-related nephropathy, or myeloma kidney. Hydronephrosis of one kidney should be referred to a urologist for evaluation; hydronephrosis of both kidneys (or a solitary kidney) should be considered a urologic urgency and referred for prompt attention.

Treatment

Knowledge of the GFR is critical for the diagnosis and treatment of kidney disease (Tables 3 and 4). Many laboratories now routinely report the estimated GFR (eGFR) with creatinine levels. This is calculated using the patient's known age, gender and creatinine level and is the best estimate of GFR available for the patient. Once a patient has a GFR < 45 ml/minute/1.73 m^2, they have Stage 3B CKD and are faced with incremental risk of CV morbidity.

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Table 2

Tests to be ordered to assess renal function

- Estimated glomerular filtration rate (GFR) using serum creatinine measurement
- A random urine sample for urinary albumin-to-creatinine ratio or urinary protein-to-creatinine ratio
- A random urinalysis including microscopic examination if dipstick is positive

Table 3

Estimating the GFR

The estimation equation from the Modification of Diet in Renal Disease (MDRD) study has been validated for outpatient use and reflects GFR better than 24-hour urine collections. One advantage is that it does not require the patient's body weight; it is calculated using only age, gender and creatinine level.

Because of the complexity of the equation, online GFR calculators are available if the laboratory does not provide the estimated GFR (eGFR).

- An online calculator is available at: www.mdrd.com
- Downloadable calculators for personal computers and personal digital assistants are available at: www.pcel.info/gfr/
- Single-sheet conversion tables can be printed from the Canadian Society of Nephrology website at: http://csnscn.ca/english/professional%20practice/guidelines/implementationcommittee/

Table 4

Stages of chronic kidney disease (CKD)

Stage	Description	eGFR (ml/minute)	Symptoms
1	Kidney damage with normal or elevated GFR	≥ 90 (avoid MDRD eGFR; Cockcroft-Gault estimate may be better)	None
2	Kidney damage with mildly reduced GFR	60-89 (avoid MDRD eGFR; Cockcroft-Gault estimate may be better)	Typically asymptomatic
3 Category sometimes subdivided as: 3A 3B	Moderately reduced GFR (mild-to-moderate) (moderate-to-severe)	30-59 (either MDRD estimate or Cockcroft-Gault estimates are useful) (45-59) (30-44)	Few symptoms; however, PO4 levels typically rise, PTH rises, LVH and HTN common; Stage 3B elevated CV risk category (CAD risk equivalent state)
4	Severely reduced GFR	15-29 (Cockcroft-Gault clearance estimate unreliable)	Symptomatic renal disease: anemia, anorexia, disturbed sleep behaviour (insomnia with daytime somnolence), pruritis, bruising, edema, weight loss, depression, fatigue
5	ESRD; kidney failure	< 15 (Cockcroft-Gault clearance estimate unreliable)	Azotemia; dialysis access required; consider transplant

For patients with a GFR > 60 ml/minute/1.73 m^2 (Stages 1 or 2 CKD), the MDRD equation may underestimate the true GFR. In these situations, the Cockcroft-Gault formula may be useful, as shown:

For females:

$$\frac{(140\text{-age}) \times \text{weight in kg}}{\text{Serum creatinine}} = \text{Creatinine clearance in ml/minute}$$

(Multiply by 1.2 for males)

The Cockcroft-Gault formula overestimates clearance as renal function declines and should not be relied upon for GFR < 30 ml/minute/1.73 m^2 (Stage 4 and 5 CKD).

PO4: Phosphate
HTN: Hypertension
PTH: Parathyroid hormone
CAD: Coronary artery disease
LVH: Left ventricular hypertrophy
ESRD: End-stage renal disease

Table 5

Goals of therapy in CKD

- Address reversible factors; monitor renal function serially (at least monthly if new or unstable; every 3 months if stable)
- Minimize further injury; avoid exposure to known nephrotoxins (NSAIDs, contrast, aminoglycosides)
- Adjust dosages of, or discontinue, renally-excreted medications (*e.g.*, metformin, glyburide, digoxin)
- Meticulous control of BP and, if diabetic, blood glucose levels
- Intensively treat all identified modifiable CV risks (lipids, tobacco cessation, consideration of antiplatelet therapy if BP is adequately controlled)
- Refer to a nephrologist or CKD team when appropriate. For example, in the presence of:
  - eGFR < 30 ml/minute/1.73 m^2
  - Acute nephritis
  - Rapidly declining GFR > 10%/year
  - Proteinuria > 1 gm q.d.

If the patient's renal impairment is due to the more common causes of CKD, namely diabetes, hypertension, or nephrosclerosis accompanying generalized vascular disease, then the treatment is addressed at meticulously controlling the underlying conditions, avoiding further injury and intensively treating the predisposing risk factors (Table 5).

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BP

Regardless of diabetic status, a decline in renal function is in the range of 4 ml/minute/year to 6 ml/minute/year if BP is controlled to a level of 140/90 mmHg. Renal function can be improved to a decline of about 2 ml/minute/year if BP is controlled to a level < 130/85 mmHg. The current recommendations of the Canadian Hypertension Education Program advise that patients with diabetes or CKD should have BP treatment targeted to systolic < 130 mmHg and diastolic < 80 mmHg.

Generally, the BP regimen should include agents that antagonize the renin-angiotensin system. Stage 3 CKD (eGFR between 30 ml/minute/1.73 m^2 to 59 ml/minute/1.73 m^2) is not a contraindication to using these agents. A recent meta-analysis concluded that ACE inhibitors and ARBs have similar efficacy in reducing proteinuria in CKD patients and that the combination of these agents is more effective than either drug used alone.[1] This conclusion echoes the results of two small prospective trials, one in diabetic nephropathy[2] and one in non-diabetic kidney disease.[3] The use of renin-angiotensin antagonism in combination is extremely attractive for renoprotection, but to date has not been recommended due to concerns of the unknown adverse effect profile. The new agent aliskiren, a direct renin inhibitor, is recently available for therapeutic use.

Take-home message

1. CKD is a progressive disease requiring serial monitoring of serum creatinine levels and eGFR at regular intervals
2. The presence of CKD does not preclude the use of renin-angiotensin drugs, such as ACE inhibitors or ARB agents; in fact, these agents are recommended in the absence of absolute contraindications to slow disease progression
3. CKD Stage 3B (eGFR < 45ml/minute) is a CAD risk-equivalent state requiring more intensive therapy for both BP and lipids than recommendations applied to the general population

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All patients with a GFR < 45 ml/minute/1.73 m^2 have at least Stage 3B CKD, which is a coronary artery disease risk equivalent state. After age 40, this would predictably be seen with creatinine levels > 160 umol/L in men and 130 umol/L in women. At Stage 3B, the "high-risk" treatment recommendations of the Canadian Working Group for Dyslipidemia would apply. Most patients would require the use of statins or ezetimibe to achieve the goals.

Referral to nephrologist

Patients with Stage 4 CKD are more likely to receive recommended evidence-based treatment if their care is coordinated by a multidisciplinary team with a nephrologist rather than by a non-nephrologist. Referral of patients with an eGFR < 30 ml/minute/1.73 m^2 is recommended. Referral is also recommended if the rate of decline of eGFR accelerates beyond a 10% decline per year.

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References
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