Chronic Kidney Disease

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INTRODUCTION

Chronic kidney disease (CKD) is common in the general population (affecting 10 to 12% of people) and is estimated to affect between 1.3 and 2.9 million Canadians. It is associated with significant morbidity (in particular, an increased risk of cardiovascular disease) and mortality, placing an immense burden on our health care system. Early detection and management can slow progression to kidney failure and reduce the risk of cardiovascular disease.

OBJECTIVES

This module will enable clinicians to:

- Appropriately identify, assess and diagnose patients with a new presentation of CKD.
- Manage patients with CKD, including patient education, monitoring for complications, medication management and referral.
- Engage in shared decision-making and conservatively manage patients with kidney failure (end-stage kidney disease).

Note: In this module, the units for measuring kidney function are:

- eGFR (estimated glomerular filtration rate) – mL/min/1.73 m^2
- urine ACR (albumin-to-creatinine ratio) – mg/mmol

CONTENTS

CASES

Case 1: Meghan, female, age 55

Meghan is a regular patient who has had essential hypertension since her early 40s. She is well controlled on hydrochlorothiazide (HCTZ) 12.5 mg po daily and ramipril 10 mg po daily. She is otherwise well but has been a smoker (about 10/day) since the age of 21. She works full time in retail. You see her about every six months to assess her BP, and her annual eGFR and ACR have been normal.

Her family history is positive for hypertension in her mother, who is still otherwise alive and well. Her father died of a stroke at the age of 76. She has no siblings.

Last year her eGFR was 64 and urine ACR 1.2. At that time, her lipids put her 10-year cardiovascular risk at 9.6%. Her A1C was 5.2%. You did not repeat them this year.

She sees you today for regular follow-up. Her lab work done prior to this visit shows her serum creatinine was 107, eGFR 51, ACR 3.4 and electrolytes normal.

What further information would be helpful?

Part Two

Meghan has had no recent intercurrent illness and drinks on average about six 240 ml (8 oz) glasses of fluid daily. She has not engaged in vigorous exercise and does not take any creatine supplements. She has been adherent to her medication. She occasionally uses NSAIDs (ibuprofen) for knee pain. She last used it about two weeks ago (400 mg TID for about four days) but has not used any other OTC medications. She has been feeling well, without any evidence of swelling and no urinary tract symptoms of any kind. She has no family history of kidney disease.

On examination today her BP is 140/85 (based on an automated BP cuff average) and her BMI is 32, which has been stable. Her cardiovascular and respiratory examinations are unremarkable and there is no evidence of edema.

What would be your approach to Meghan?

Part Three: Three months later

Meghan's follow-up testing reveals an eGFR of 53, ACR 4.1 and A1C 5.3%. Serum potassium and urine routine and microscopy (R&M) are normal, and her lipids are unchanged. BP today is 145/88. There is no change in her physical examination. Meghan has stopped her NSAIDs as advised but has not stopped smoking.

When you share her lab results, Meghan asks what this decrease in her kidney function means and how she can prevent it from getting worse?

How would you respond to Meghan and how would you follow her?

Case 2: Thomas, male, age 68

Thomas is a regular patient of yours. You see him today for his regular quarterly diabetes follow-up—he has had type 2 diabetes for 15 years. He is married with two older children and works as a lighting technician for the local theatre.

Thomas has a previous history of nephrolithiasis 10 years ago which required lithotripsy (calcium oxalate stone). He has had no recurrence since then. He has a history of mild benign prostatic hypertrophy (BPH) that has not required treatment. He has osteoarthritis in his neck for which he occasionally takes over-the-counter naproxen (usually one to two tablets BID about twice a month) as it is really the "only thing that works." His BP has been well controlled (last reading 121/78), A1C is usually 7.0 to 7.5%. He has no known cardiovascular disease. He does have some mild peripheral neuropathy in his feet. He is a non-smoker. He does not monitor his blood sugar at home.

His medications include sitagliptin/metformin (Janumet) 50/1000 mg BID, losartan 50 mg once daily (had a cough on an ACE-inhibitor), atorvastatin 20 mg once daily and sildenafil 100 mg PRN.

Last year his serum creatinine was 112, eGFR 62, urine ACR 1.4. In preparation for this visit, he had his blood work and urine done. Results are as follows:

- Serum creatinine 120, eGFR 56, ACR 28.4
- A1C 7.4%
- Sodium and potassium normal
- Serum cholesterol 2.25, LDL (calculated) 1.35, HDL 0.83, cholesterol/HDL ratio 3.1, triglycerides 0.84

What further information would be useful?

Part Two

Thomas has had no recent illness that would cause dehydration, no vigorous exercise and no supplements. He has had no increase in urinary obstructive symptoms and no swelling anywhere. He has not increased his NSAID use, although he continues to use it a few times a month. He has no pain suggestive of renal colic.

BMI is 28 today (previously 29) and BP 125/72. Normal cardiovascular examination. You note mild reduced sensation in his feet to the ankle. No dorsalis pedis or posterior tibial pulses palpable, but good cap refill. He has no edema.

Urinalysis and microscopy revealed 1+ protein, no blood and no casts. The ACR and eGFR are repeated one month after this visit and are stable at 25.8 and 55 respectively.

What would be your approach to Thomas?

Part Three: Four months later

Blood work done prior to this visit reveals the following: most recent A1C was 7.5%, creatinine 132 (eGFR 48), ACR 129.5. Urine R&M shows 2+ protein. His renal ultrasound showed no evidence of obstructive uropathy. His kidneys appeared normal. He continues to feel well and there is no change in his physical examination.

What would be your next steps?

Case 3: Edward, male, age 81

Edward has been a long-time patient in your practice. He has multiple comorbidities including coronary artery disease (ST-segment elevation MI eight years ago with subsequent coronary stenting), type 2 diabetes, osteoporosis (discovered after a fall four years ago that resulted in a hip fracture), osteoarthritis, hypertension and CKD.

Though frail, he lives in his own home with his wife who is seven years younger and very healthy. She always accompanies Edward to his appointments and shares information with you about his health status.

His medications include ASA 81 mg once daily, metformin 500 mg BID, HCTZ 25 mg daily, atorvastatin 80 mg daily, perindopril 8 mg daily, risedronate 150 mg once a month and nitroglycerin spray PRN (used about three times a week for symptomatic chest pain with minor activity such as climbing one flight of eight steps).

You have been following his kidney function semi-annually and have seen a gradual reduction in his eGFR over the years, but it had been stable at 38 to 40 for the last 18 months. His urine ACR had been normal (< 3.0). However, one month ago, his eGFR decreased to 32, and his urine ACR at that time was 26.

Edward and his wife had noted no new symptoms other than easy fatiguability which has become worse in the last year. You asked him to have the blood work repeated, and today he and his wife have come to see you about the latest results:

- eGFR 29, urine ACR 24
- A1C 7.5%
- Sodium and potassium upper limits of normal
- CBC shows slight anemia (normochromic, normocytic)—Hb of 102 with normal RBC indices
- Urine R&M: 1+ protein only

Today his BP is 138/88, heart rate 64. The rest of his cardiovascular examination is unchanged. His energy level is about the same, and he and his wife deny any other new symptoms. He has some chronic 2+ edema of his ankles and feet.

What would be your approach with Edward and his wife today?

How would you manage Edward going forward if his renal function continued to decline?

INFORMATION SECTION

1. "CKD is defined as abnormalities of kidney structure or function, present for more than three months, with implications for health."[1] The common abnormalities of kidney structure include albuminuria, hematuria or other urine sediment abnormalities and structural kidney defects detected on histology and/or imaging. Abnormalities in kidney function entail decreased GFR (eGFR of < 60).

2. The prevalence of CKD in Canada is on the rise based on recent estimates, a trend that can be attributed to an aging population, and rising rates of hypertension and diabetes.[2]
   a) A recent Canadian study of CKD in primary care found the prevalence is higher in rural versus urban settings (86.2 versus 68.4 respectively per 1,000 individuals), and also higher in those with three or more other chronic diseases (281.7 per 1,000).[3]
   b) Although end-stage renal disease (ESRD) is uncommon (about 1% of those with CKD),[4] annual health care costs even for those not on dialysis are high, estimated at $32 billion,[4] based on extrapolation of recent data from Alberta.[5]
   c) ESRD is three times higher in Indigenous peoples (First Nations, Inuit and Métis) than non-Indigenous (age-standardized rate of 267 versus 99 respectively per 100,000). This is primarily due to higher rates of obesity and diabetes. Furthermore, Indigenous peoples with ESRD have a median age of 54, almost a decade younger than those who are non-Indigenous (median age: 62).[6]

ASSESSMENT (see Appendix 1 for a flowchart on the assessment of patients with CKD)

Who to Test?

3. Screening the general population for CKD is not recommended.[7,8] Instead, a case-finding approach is appropriate, targeting people at high risk or who may be exposed to the risk of acute kidney injury such as:[1]
   - Those with hypertension or diabetes.
   - Those aged 60–75 with cardiovascular disease.
   - First Nations, Inuit and Métis peoples
   - Those undergoing major surgery with a risk of acute kidney injury.[2,7,9]

   Note: Additional risk factors include family history of G5 CKD (see Table 1), hereditary kidney disease (e.g., polycystic kidney disease), multi-system disease with renal involvement (e.g., systemic lupus). These factors, however, present less commonly in family practice.[2]

How to Test

4. Two tests should be ordered in patients at higher risk for CKD: serum creatinine-based eGFR (a measure of kidney function) and urine ACR (protein excreted in urine is a measure of kidney damage/injury).[1,9,10]

5. A diagnosis of CKD can be made when the following results are persistent for a three-month period:
   - eGFR result of < 60, confirmed on repeat testing AND/OR
   - Urine ACR results of ≥ 3, confirmed on one or more repeat tests.[1,9,10]

   a) At least two of three urine ACR tests need to be elevated for the diagnosis of CKD.[1] If the initial urine ACR is very high (> 60), repeat in two to four weeks or sooner based on clinical presentation.
   b) If the initial eGFR is very low (< 30) or represents a significant decline from previous (≥ 5 units), repeat in two to four weeks or sooner based on clinical presentation.[1]

   Note: A 24-hour urine collection should not be ordered. Its use is generally reserved for nephrologists who are assessing patients with advanced CKD.[1]

6. GFR is influenced by several factors including acute illness, hydration, vigorous activity, hormonal entities (puberty, pregnancy, menopause) and vasodilation (e.g., significant sunburn). Creatine supplementation may increase creatinine levels and falsely indicate renal dysfunction. When interpreting eGFR, these factors must be considered.[7] Patients should not be screened for CKD during the presence of an intercurrent illness (e.g., gastroenteritis). In this scenario, their creatinine level may be elevated and likely reflects an acute kidney injury secondary to dehydration as opposed to CKD.

How to Handle Results

7. If test results are negative for CKD, yearly follow-up is recommended, especially in patients with diabetes.[7,9]

8. In patients with results consistent with CKD, its severity can be classified according to eGFR and albuminuria categories. Associated risk of adverse outcomes can then be determined to guide prognosis and management (see Table 1).[10,11]
   Note: These eGFR categories, along with the addition of albuminuria categories, replace the previous stages to classify CKD and are supported by the Canadian Society of Nephrology (CSN).[7]

Table 1. Prognosis of CKD by GFR and Albuminuria Categories

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/ 1.73 m^2) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

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FURTHER ASSESSMENT

9. More useful in primary care is the Kidney Failure Risk Equation (KFRE) Calculator which can help to identify higher-risk patients who may require referral to a nephrologist. Used in those with CKD categories G3 to G5, the calculator provides the two- and five-year probability of kidney failure requiring dialysis or transplant, using a patient's sex, age, ACR and eGFR. An online calculator can be accessed at https://kidneyfailurerisk.com/. Nephrology referral is recommended for those with a ≥ 5% risk over five years.[12]
   Note: Other indications for referral are included in the Management section.

10. Following the diagnosis, further work-up includes a complete medical history, physical exam, and a review of past/current BP, medication (including over-the-counter drugs), dietary history (including the use of any supplements) and weight measurements.

11. Additional blood work includes electrolytes, fasting lipids, A1C and urine R&M to assess for red blood cell casts (nephritis). Serum hemoglobin, calcium, phosphate, albumin and parathyroid hormone (PTH) may be ordered for those with eGFR < 30.[2,11]

12. Reversible causes of acute kidney injury (e.g., frequent NSAID use, intercurrent illness such as viral gastroenteritis, urinary retention due to BPH) should be ruled out in patients with initial abnormal results.[1,7]

13. In addition to initiating a nephrology consultation, order a renal ultrasound if patients with CKD have:
    - eGFR category G4 or G5.
    - Accelerated disease progression: a sustained decrease in eGFR of ≥ 25% and a change in eGFR category (Table 1) within 12 months or a sustained decrease in eGFR of 15 units per year.
    - Hematuria (persistent visible or microscopic).
    - Urinary tract obstruction (e.g., from BPH, nephrolithiasis).
    - Family history of polycystic kidney disease and age > 20.[13]

MANAGEMENT OF CKD

Reduce CVD Risk and Prevent CKD Progression

Lifestyle Modifications

14. Lifestyle advice includes:[2,10,13]
    - Regular exercise: 30 minutes, five times per week.
    - Adequate fluid intake. Fluid restriction is not needed for most patients.
    - Healthy BMI: 18.5–25.
    - Smoking cessation. Continued smoking is associated with a faster decline in GFR and a greater increase in albuminuria compared to quitters and non-smokers. Similarly, smoking cessation slows the decline in kidney function, as compared to active smokers.[14,15]

15. Healthy diet advice will depend on the severity of the CKD. Specific recommendations are variable.
    a) Although a salt intake of < 2 g per day is recommended by the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines,[1] the CSN does not support this recommendation owing to a lack of quality evidence. Among people with renal disease, those with the fewest adverse outcomes had a urinary sodium excretion of 2.7 to 3.3 g/day. The CSN suggests "reducing sodium intake in patients whose estimated intake exceeds these values."[7]
    b) Recommendations related to intake of protein are also varied. National Institute for Health and Care Excellence (NICE) guidelines do not recommend that patients follow a low protein diets (< 0.6 to 0.8/kg/day).[13] However, the KDIGO guidelines "suggest avoiding high protein intake (> 1.3 g/kg/day) in adults with CKD at risk of progression." The CSN makes no strong recommendation as there have been no RCTs performed but adds that diets lower in meat and higher in vegetables (e.g., Mediterranean or DASH diets) lead to reductions in cardiovascular events in the general population.[7]

Blood Pressure Treatment Targets for Patients with CKD and Hypertension

16. Based on Hypertension Canada's 2020 guidelines, target blood pressure for high-risk patients with hypertension (including those with CKD) is < 120/90. This approach is based on the SPRINT trial which showed a reduction in cardiovascular outcomes (NNT=61) and mortality (NNT=90) in those at high cardiovascular risk (> 20%) (see Info point 21) [Grade B Recommendation, Moderate Evidence].[16]
    a) The Ontario Renal Network recommends caution in those patients not included in the SPRINT trial, such as those with diabetes, a high degree of frailty, on more than five medications (polypharmacy), stroke, standing BP < 110 and limited life expectancy. In this case, shared decision-making with careful monitoring for postural hypotension and risk of falls is recommended.[2] Achieving a treatment target of < 140/90 in this scenario is acceptable.[16]
    b) If the patient has diabetes, the recommended target is < 130/80.

17. Use of renin-angiotension system (RAS) blockade—ACE-inhibitors or angiotensin-receptor blockers (ARBs)—in CKD patients with albuminuria who have hypertension or diabetes can help to manage proteinuria and prevent progression to kidney failure.[13,17]
    a) Patients with CKD with an **ACR of > 30** and hypertension should be specifically offered RAS blockade—ACE-inhibitors or ARBs.[13,17] Patients with CKD and hypertension without albuminuria can choose any first-line medication to treat their elevated BP which could include an ACE-inhibitor or ARB.
    b) For those patients with CKD and diabetes, RAS blockade should be offered if their urine **ACR is > 3**. For those who are normotensive (BP already < 130/80), monitor carefully for orthostatic hypotension and hyperkalemia.[16]
    c) Titrate to the maximum tolerated dose to control albuminuria.[10] Thiazide-type diuretics can be added for BP control if required. Long-acting and more potent thiazides such as chlorthalidone are preferred, although a recent controlled cohort study (n=730,225) found no difference in cardiovascular outcomes and an increased risk of

electrolyte abnormalities, particularly hypokalemia, compared to HCTZ (hazard ratio 1.57 (95% CI 1.25–2.01).[18] Loop diuretics should be used where there is evidence of significant volume overload particularly with advanced stages of CKD (G4–5) [Expert Opinion].[16]

18. Within two weeks of starting an ACE-inhibitor or ARB, or when doses are changed, it is important to monitor for increased serum potassium (a rise of up to 0.5 mmol/L can be expected) and reduced eGFR. A rise of up to 25 to 30% in serum creatinine (or concomitant drop in eGFR) is due to changes in renal autoregulation and is not associated with an increased risk of persistent worsening of kidney function.[19] A significant drop (> 25 to 30%) in eGFR or rise in serum creatinine may indicate volume depletion, concurrent NSAID use or underlying renovascular disease that may require further assessment.[10]
    a) Patients with CKD and diabetes are at particular risk of hyperkalemia from RAS blockade. Hyperkalemia may be managed by restricting dietary potassium to increase potassium excretion.[2,17] If there is evidence of fluid overload, furosemide may also reduce potassium in addition to controlling edema.
    b) In some cases, the medication might need to be reduced or stopped until a nephrologist can be consulted.[2,17]

19. The combination of an ACE-inhibitor and ARB is not recommended.[7,10] The risks of acute kidney injury and severe hyperkalemia outweigh any cardiovascular or mortality benefit.[1,7,17]

20. When starting an ACE-inhibitor or ARB at an earlier age (e.g., in those with type 1 diabetes), counsel female patients of childbearing age to stop these medications if they are planning to, or could become pregnant. These agents are associated with congenital malformations.[17]

Lipids

21. Guidelines from KDIGO[20] *recommend* statin therapy for all patients with CKD not requiring dialysis who are age 50 or older without diabetes, and *suggest* statin therapy for patients with CKD who are:
    - Age 18 years or older with diabetes.
    - Age 18 or older with known coronary artery disease, prior stroke or 10-year Framingham risk > 10% [High Evidence for all recommendations].[2]
    a) Population-based studies show an increased cardiovascular risk associated with decreasing eGFR < 60 or urine ACR ≥ 3 that is not explained by the presence of traditional risk factors in these individuals. People with CKD are more likely to experience a cardiovascular event than to progress to ESRD and should be considered high risk for these outcomes.[20]
    b) A Cochrane review[21] comparing statin therapy with placebo in patients who had non-dialysis-dependent CKD found that statin therapy reduced major cardiovascular events and all-cause mortality. Taking baseline risk into account, statin therapy of 1,000 people with CKD for one year might be expected to prevent six major cardiovascular events and five deaths from any cause.[20]

Glycemic Control

22. Diabetes Canada recommends a target A1C of < 7.0% for renal protection in most adults with diabetes [Grade A recommendation, High Evidence]. For some people with early or no kidney disease and a low risk of hypoglycemia, a lower A1C (≤ 6.5%) can be considered for renal protection, weighing the risks and benefits.[7,17] Consideration should be given to extending target A1C above 7.0% (7 to 8.5%) in people with comorbidities or limited life expectancy and risk of hypoglycemia.[7]

23. The American and European Diabetes Associations 2019 update[22] recommends considering the addition of Sodium-glucose cotransporter-2 (SGLT2) inhibitors to metformin (where not contraindicated) in patients with CKD and type 2 diabetes where A1C is not at target to prevent CKD progression, ESRD and renal death. This is based on a recent systematic review and meta-analysis[23] of eight trials (n=77,242) (hazard ratio for these combined outcomes 0.55, 95% CI 0.48–0.64). This benefit is strongest in those with a urine ACR > 300 and can be independent of the individual A1C target.[22]
    a) These medications may be contraindicated in significant renal disease. The exact eGFR cut-off depends on the specific drug. For example, metformin should either not be prescribed or discontinued with an eGFR of < 30 and should be adjusted down to 500 to 1,000 mg a day with an eGFR < 45. Furthermore, there is a greater risk of hypovolemia (20%) in patients taking SGLT2 inhibitors versus those not taking it.[24]

b) For further details on pharmacotherapy in those with type 2 diabetes and CKD, please see Appendix 2. It can assist with decisions about adjusting or avoiding antihyperglycemics based on a patient's eGFR stratum.

Antiplatelets

24. Low dose (81 mg) ASA may be indicated for secondary prevention in CKD patients with established vascular disease: acute coronary syndrome, prior MI or coronary revascularization, prior stroke or TIA, or peripheral vascular disease (only for high-risk patients with a low risk of bleeding).[10]

Minimize Further Renal Injury

25. Both OTC and prescribed medications can be nephrotoxic either directly or due to over accumulation in CKD, causing damage to the kidneys and reducing their function. Reduced kidney function results in a slower elimination of renally excreted medications. This, in turn, increases blood levels of these medications and results in a higher risk of adverse reactions.
    a) Nephrotoxic drugs should be avoided in patients with CKD. A list of medications that can have nephrotoxic effects can be found at: http://www.ckdpathway.ca/Content/pdfs/Other_nephrotoxic_effects_drugs.pdf. Medications that should be avoided or adjusted in patients with CKD can be found at: https://www.ontariorenalnetwork.ca/en/medicationsafety.
    b) When CKD is suspected, baseline renal function should be assessed before prescribing any medications that are nephrotoxic or that require dose adjustment based on renal function.[25]
    c) Dose modifications can be achieved by reducing the dose or increasing the dosing interval.[25]
    d) The Cockcroft-Gault equation is no longer recommended to determine drug dosing as it has not been standardized to body surface area. The US National Kidney Foundation recommends the use of the CKD-EPI equation. An electronic version for ease of calculation can be found at: https://www.kidney.org/professionals/kdoqi/gfr_calculator. In many cases eGFR alone can be used to make medication adjustments (see Appendix 2).

26. When patients with CKD cannot maintain adequate fluid intake during an illness, running the risk of volume depletion, medications that are potentially nephrotoxic or renally excreted must be stopped until the patient has recovered. It is important to provide patients with a Sick Day Medication List. The acronym SADMANS may help with recall:
    S: sulfonylureas
    A: ACE-inhibitors
    D: diuretics
    M: metformin
    A: ARBs
    N: NSAIDs
    S: SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin)[9,10,17]

27. Some drugs, such as thiazide diuretics, have reduced ability to overcome fluid retention in patients with CKD. Loop diuretics can be used when volume overload and/or resistant hypertension becomes an issue in more advanced kidney disease.[1]

Monitor

28. The patient's risk level according to the eGFR and ACR will determine the monitoring frequency for these parameters. Patients with an eGFR of 30 to 59 and/or ACR of 3 to 60 should be monitored every six months for two years, more often with rapid decreases in eGFR and higher albuminuria at baseline (> 30) (see Info point 5).[1,7,13] Once a patient's eGFR has been stable for two years, monitoring can be reduced to annually [Expert Opinion].[1,9] See Appendix 1.

29. Patients with CKD are at higher risk of anemia, and mineral and bone disorders.[11]
    a) There is no evidence to support measurement of hemoglobin in those with an eGFR of 30 to 59 beyond clinical judgment. The CSN recommends screening for anemia in patients with an eGFR < 30 [Expert Opinion].[7,11,13]
    b) Screen for osteoporosis using the same strategy (densitometry) as for the general population, except in patients with an eGFR of < 45 where it is not recommended.[1] In these patients, changes in bone mineral metabolism lead to renal bone disease (e.g., osteomalacia, osteitis fibrosa cystica) increasing overall fracture risk.[11] Fracture risk prediction with bone densitometry is thus inaccurate and may require more complex testing of bone turnover. Expert consultation is suggested.[1,26]

c) Measure serum calcium, phosphate and PTH in patients with eGFR < 30 (G4 or 5) as part of the work-up in preparation for nephrology referral.[13]

Refer

30. Referral to a nephrologist will depend on several factors including eGFR/ACR levels, rapid deterioration in kidney function, inability to achieve BP targets (despite optimal therapy), significant electrolyte disorder, or RBC casts or hematuria suggestive of glomerulonephritis/renal vasculitis.[9] See further details in Appendix 1.

31. A nephrologist can manage complications associated with advanced CKD and potentially prepare patients for dialysis or renal transplant.[2]

32. In addition to the most recent eGFR and ACR, work-up recommendations for a referral include urine R&M, electrolytes, CBC, and serum calcium, phosphate, albumin, PTH (see Info point 29c).[9]

33. Despite a referral, patients with CKD will often be co-managed and still require ongoing preventive care such as vaccinations (e.g., the influenza vaccine and pneumococcal vaccine for those with an eGFR < 30[1]) and cancer screening, as well as management of other medical conditions by their primary care provider.[2]

CONSERVATIVE/NON-DIALYSIS MANAGEMENT OF PATIENTS WITH KIDNEY FAILURE

34. Not all patients who progress to ESRD will benefit from dialysis. This is particularly true for patients who are very elderly with multiple comorbidities and frailty. Starting dialysis in these patients may have a significantly negative impact on quality of life without increasing lifespan.[27]

35. Patients who choose a conservative management approach may experience a variety of symptoms that can impair quality of life.[27] CKD patients living with kidney failure are one of the most symptomatic groups of people living with chronic illnesses. More than half of the patients undergoing dialysis, as well as those who are not, experience fatigue, pruritus and constipation, and more than 40% of them experience anorexia or nausea and pain.[28] The use of a validated scale for symptom assessment such as the Edmonton Symptom Assessment System-revised renal (ESAS-r) is recommended by KDIGO[29] and can be accessed at: https://www.albertahealthservices.ca/frm-20351.pdf. Consider administering this at least every six months in those patients with an eGFR of < 15.[30]

36. See Appendix 3 for the most common symptoms and suggested management. This table is not comprehensive. For those wanting more extensive information on the conservative management of patients with ESRD, the following links may be useful:
    - BC Renal Agency renal symptom assessment and management: http://www.bcrenalagency.ca/health-professionals/clinical-resources/symptom-assessment-and-management
    - Alberta Provincial Conservative Kidney Management Pathway: https://sites.ualberta.ca/~kscrg/ckm-pathway.html

KEY POINTS

- A diagnosis of CKD can be made after a three-month period with:
    - eGFR result of < 60, confirmed on repeat testing AND/ OR
    - Urine ACR results of ≥ 3 on two of three repeat tests.
- Use the Kidney Risk Failure Equation to help identify those patients with a ≥ 5% five-year risk who can benefit from nephrology consultation: https://kidneyfailurerisk.com/.
- Manage cardiovascular risk with:
    - A BP target of < 120/90 in non-diabetic patients without frailty if tolerated and < 130/80 in diabetics
    - Statins in those ≥ 50 years of age or ≥ 18 years of age with either diabetes, CVD or at high risk for CVD.
- Patients with CKD who have hypertension and an ACR > 30 or diabetes with an ACR of > 3 should be offered an ACE-inhibitor or ARB to prevent progression of renal disease.
- Consider the addition of SGLT2 inhibitors to metformin to optimize A1C in patients with CKD and type 2 diabetes to prevent CKD progression, ESRD and renal death where this is not contraindicated by eGFR.
- Identify and adjust/avoid potentially nephrotoxic medications in patients with CKD. See https://www.ontariorenalnetwork.ca/en/medicationsafety) and http://www.ckdpathway.ca/Content/pdfs/Other_nephrotoxic_effects_drugs.pdf.

CASE COMMENTARIES

Case 1: Meghan, female, age 55

What further information would be helpful?

It would be helpful to ask Meghan about the use of NSAIDs or any alternative medicines or supplements such as creatine powder, any vigorous exercise or intercurrent illness, compliance with her medications and any family history of renal disease (Info points 3, 6, 9).

A physical exam would include measurements of weight and BP, and cardiovascular and respiratory exams (Info point 9).

Part Two

What would be your approach to Meghan?

It would be appropriate to repeat urine ACR, serum creatinine and eGFR, A1C, potassium and lipids in three months (Info points 4, 5, 10). She should be counselled about smoking cessation (Info point 14) and advised to stop NSAIDs—ibuprofen, naproxen (Info point 25; Appendix 1).

Part Three: Three months later

How would you respond to Meghan and how would you follow her?

Meghan's risk according to the KFRE is only 0.72% (Info point 9). She would likely appreciate knowing that although her renal function is mildly reduced, there are several steps that can be taken to delay or prevent significant deterioration.

Making healthy lifestyle choices such as smoking cessation, regular exercise in her daily routine and healthy eating can be beneficial (Info points 14, 15; Appendix 1). A referral to a dietitian (if available) may be helpful. She should also be receiving an annual flu immunization (Info point 33). She may find it helpful to review the online resource, Living with Reduced Kidney Function (The Kidney Foundation of Canada). It is available at: https://kidney.ca/Support/Resources/Living-with-Reduced-Kidney-Function.

It would be important to try to get Meghan's BP to target (Info point 16; Appendix 1). There are several reasonable options for doing so: adding another medication such as a calcium-channel blocker (amlodipine), increasing the dose of HCTZ to 25 mg or replacing HCTZ with 12.5 mg of chlorthalidone (Info point 17). Avoiding a high salt diet may be beneficial (Info point 15).

A Sick Day Medication List would help Meghan cope if she has a dehydrating illness (Info point 26; Appendix 1).

Finally, starting a statin today (or bringing her back in a month to do so) would be warranted to reduce her cardiovascular risk (Info point 21; Appendix 1).

Case 2: Thomas, male, age 68

What further information would be useful?

It would be helpful to know about (Info points 6, 9):

- Intercurrent illnesses.
- Use of NSAIDs.
- Vigorous exercise or use of supplements.
- Urinary obstructive symptoms.
- Peripheral edema.
- Pain suggestive of renal colic or hematuria.

A physical exam would include measuring weight and BP, and looking for any signs of edema (Info point 9).

Investigations would include repeat ACR/eGFR within the next month given the significant changes from baseline (Info points 4, 5, 10; Appendix 1). If the ACR and/or eGFR are consistent with CKD, a urine R&M could be ordered.

Part Two

What would be your approach to Thomas?

Thomas's eGFR and ACR put him in category G3a/A2 (Table 1), however his five-year risk based on the KFRE is only 1.27%. He should completely stop the use of NSAIDs (Info point 25; Appendix 1). You could consider maximizing his dose of losartan to 100 mg given his significant proteinuria (ACR 25.3) and diabetes, and monitor BP (Info points 16, 17). It would be important to monitor his eGFR and potassium level about two weeks after any dose increases of his ARB. An eGFR increase of up to 25 to 30% is acceptable (Info point 18). Consider a discussion about more aggressive treatment of his diabetes to reach a target A1C of < 7.0%, although his current management may be appropriate given his age and comorbidities (Info points 22, 23; Appendix 1). For more information, see the PBSG module Type 2 Diabetes (Nov 2019) available at https://members.fmpe.org/. A Sick Day Medication List would be important for when he is ill (Info point 26; Appendix 1). You could also counsel him about sodium intake (Info point 15).

Further investigations could include a renal ultrasound due to his history of nephrolithiasis and BPH. However, as his creatinine is similar to his baseline, obstructive uropathy is unlikely (Info point 12). Measurement of calcium, phosphate, albumin and PTH is not necessary given his eGFR is not < 30 (Info point 10; Appendix 1).

Part Three: Four months later

What would be your next steps?

Based on the KFRE, Thomas's five-year risk is now 5.66%, putting him at intermediate risk. Nephrology consultation would be appropriate, if available (Info points 30–32; Appendix 1). You might also consider altering his medications:

- Increase the dose of his ARB, if not already done (Info point 17c).
- If a decision were made to further reduce his A1C, you could add an SGLT2 medication, such as empagliflozin or canagliflozin (Info points 22, 23). If his eGFR falls below 45, his dose of Janumet would need to be modified (Info point 25; Appendix 2). Weight loss may benefit his diabetes, blood pressure and renal function.

Case 3: Edward, male, age 81

What would be your approach with Edward and his wife today?

A medication review would include compliance and the use of blister packs.

You could strongly consider the following modifications to his medication (Info point 25):

- Discontinuing risedronate and metformin.
- If his edema becomes resistant to the HCTZ, consider replacing it with a small dose of furosemide. Monitor for volume depletion and electrolyte abnormalities. His perindopril could be continued.

You could also consider checking calcium, phosphate, albumin and PTH (Info point 10).

This might be a good time to review/revisit his goals of care. This would help with regard to the need for further investigations and the decision to refer to a nephrologist, if available (Info points 30–32). Nephrology consultation could also help the patient to understand the implications of more aggressive management such as dialysis and support fully informed decision-making.

How would you manage Edward going forward if his renal function continued to decline?

Ongoing preventive care would continue to be appropriate such as the annual flu vaccine and the pneumococcal vaccine if he has not had this already (Info point 33).

It would be reasonable to initiate a discussion of what he might expect with ESRD—the signs/symptoms and how they would be managed (Info point 35; Appendix 3)—particularly if Edward has chosen conservative management. Once you are certain that he and his wife have understood the current situation and appear ready, a deeper conversation around end-of-life care could occur.

We always welcome your input. If you would like to provide feedback on this module, the following link will take you to an electronic survey: **http://members.fmpe.org/modulefeedback**

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Web-based resources cited within the module were active as of August 2020.

You can access this module and all its appendices online. Just go to: https://members.fmpe.org/

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EVIDENCE-BASED MEDICINE: QUICK STATISTICAL CONCEPTS

Experimental event rate (EER): The percentage of people in the treatment group experiencing the outcome (may be a good outcome or a bad outcome).

Comparison event rate (CER): The percentage of people in the comparison group experiencing the outcome.

Relative risk or Risk Ratio (RR): The EER divided by the CER. A measure of the probability (risk) of developing a disease for those exposed to a medication/risk factor compared to those who are not. Hazard ratio (HR) is a similar concept.

Absolute risk reduction (ARR): The absolute percentage of people who benefit out of all those treated.

Number needed to treat (NNT): the number who need to be treated in order for 1 to benefit (It is the inverse of ARR-1/ARR).

- ARRs (and thus NNTs) can be calculated from studies where groups are defined based on whether they have been exposed and the effects of treatment (usually benefits) are assessed over time (i.e., in cohort studies and prospective clinical trials).
- ARRs cannot be calculated from retrospective case-control studies, where groups are defined by outcomes that have already happened.
- In case-control studies, the odds ratio (OR) is used as an estimate of the risk.

LEVELS OF EVIDENCE

Evidence Level	Types of Evidence Included
High Study conclusions are unlikely to be strongly affected by information from future studies.	• Systematic reviews/meta-analyses that include a wide range of well-designed studies (few limitations/risk of bias, directly applicable to target population, summary estimate has a narrow confidence interval) • Large, well-designed, multi-centre RCTs
Moderate Study conclusions might be affected by additional information from future studies.	• Systematic reviews/meta-analyses of studies with more limitations/risk of bias (less well-designed RCTs, cohort, case-control studies; summary estimate has a wide confidence interval) • Single, moderate-sized well-designed RCTs • Well-designed, consistent, controlled but not randomized trials • Large cohort studies
Low Study conclusions could likely be affected by additional information from future studies.	• Small RCTs with a high risk of bias • Controlled or cohort studies with significant limitations/risk of bias, significant variation between study results, or not directly applicable to target population
Very Low Evidence from appropriately sized studies in representative populations is lacking or insufficient.	• Individual case reports or series • One or more studies with very severe limitations/risk of bias

In addition to the categorization above, when the body of evidence on a specific issue is limited, we may cite expert opinion as the highest evidence level (if available).

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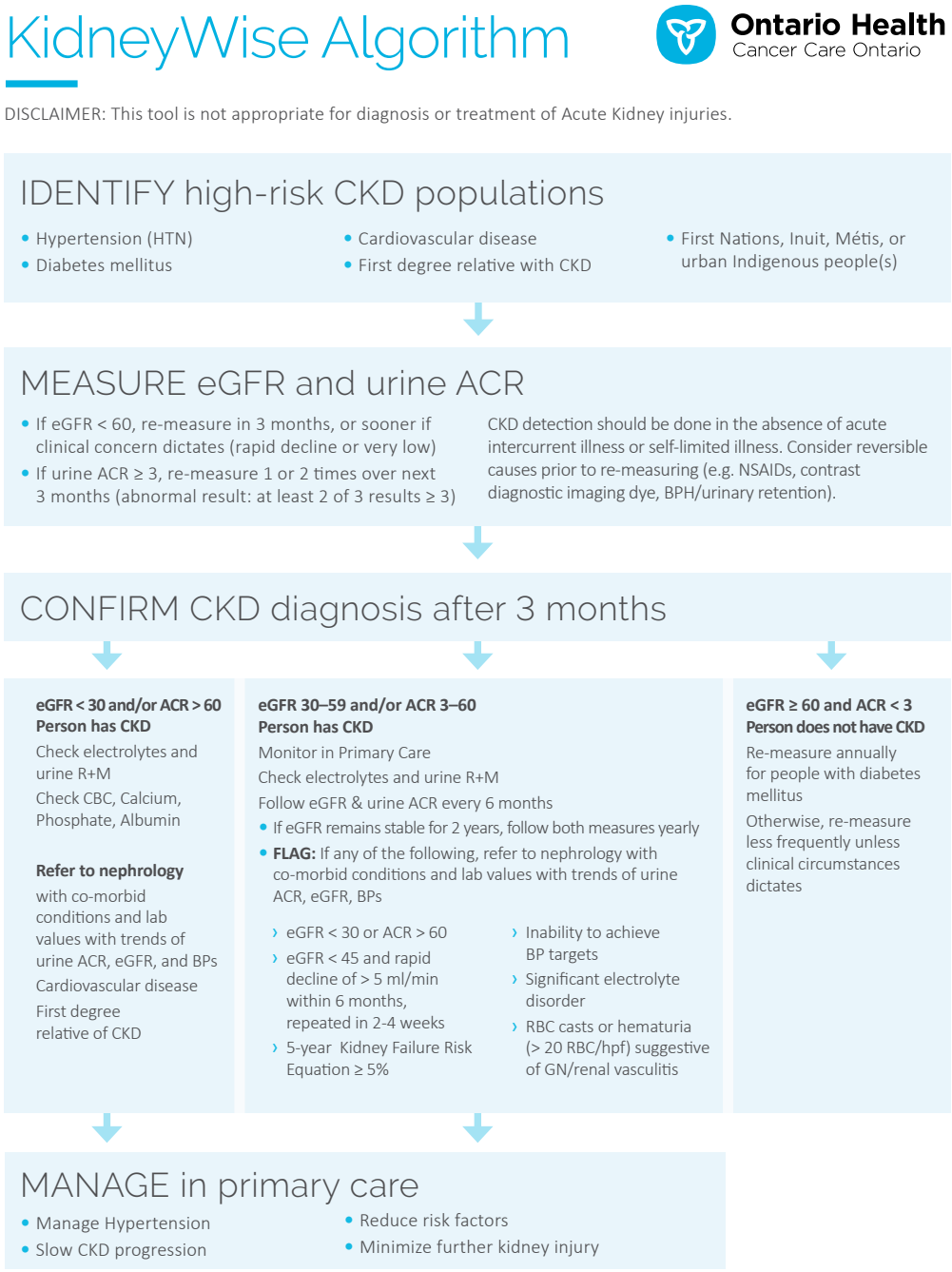
APPENDIX 1. Diagnosis and Management of CKD

Provincial Resources (all are interactive):

- The Chronic Kidney Disease clinical pathway, endorsed by Alberta Health Services and the Universities of Calgary and Alberta, includes diagnosis, management, patient handouts, and a list of nephrotoxic drugs and those that need adjustment in CKD. This can be found at: http://www.ckdpathway.ca/.
- Kidneyfailurerisk.com is endorsed by the University of Manitoba, the Manitoba renal program and the Canadian Primary Care Sentinel Surveillance Network. It is useful for both patients and clinicians, and includes several visual aids to facilitate discussion, a comprehensive handbook for patients and the Kidney Failure Risk Equation (KFRE).
- In addition to the algorithm below, the Ontario Renal Network has large number of tools including a stepwise approach to risk assessment, diagnosis and management, the KFRE, information on medication safety and patient information. This information can be accessed at: https://www.ontariorenalnetwork.ca/en/kidney-care-resources/clinical-tools/primary-care.



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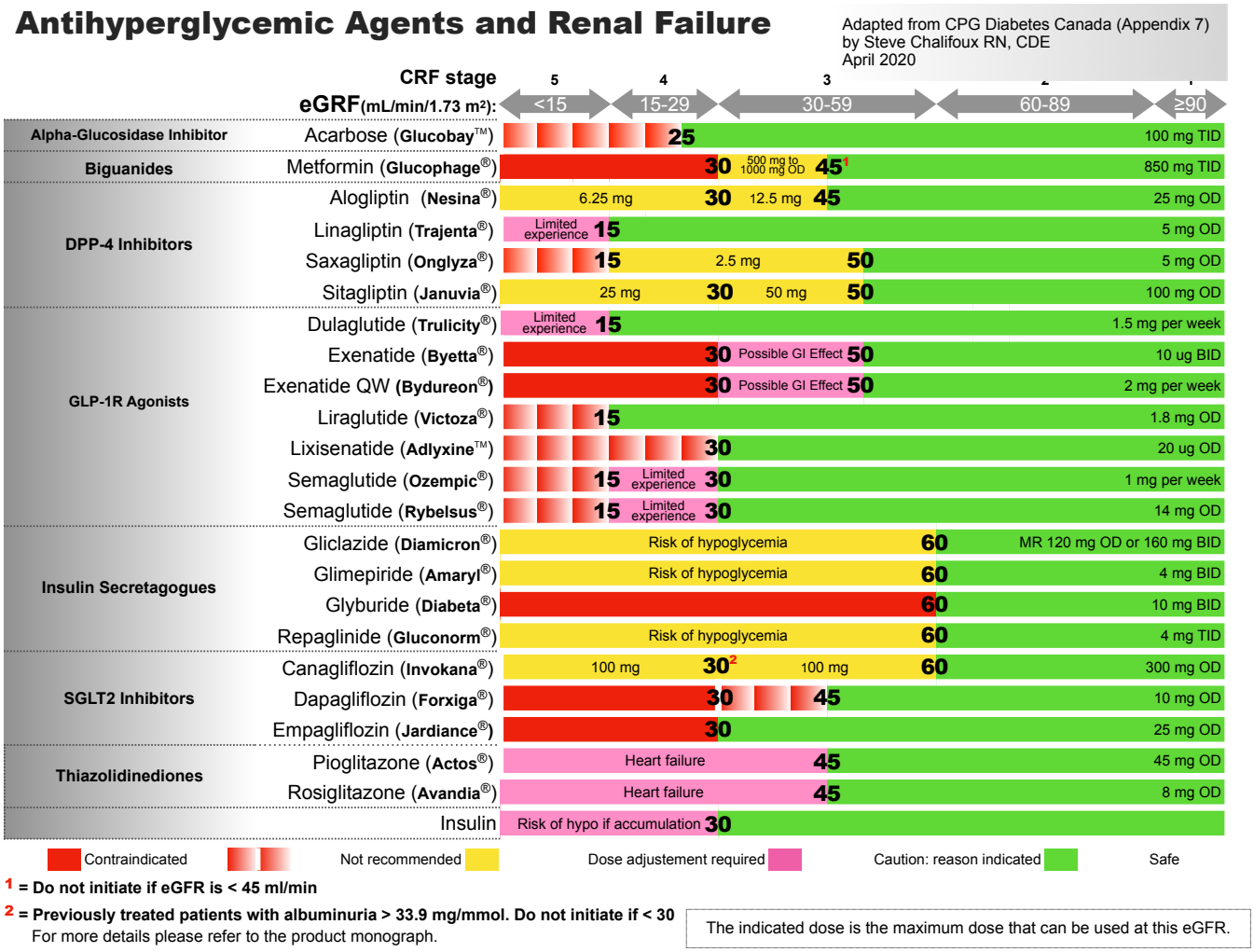
Managing CKD Patients in Primary Care

	Patients with CKD	Patients with CKD & Diabetes
Manage Hypertension	• Target BP < 120/90; • Consider a higher target (< 140/90) in frail individuals, LTC residents, previous stroke, limited life expectancy (< 3 years), polypharmacy (> 5 meds), and standing systolic BP < 110	• Target BP < 130/80 • using RAS inhibition, salt restriction and other anti-hypertensives as required
	• Use caution when treating systolic BP to target; risks may outweigh benefits when diastolic BP < 60	
Slow CKD progression	• **If ACR > 30 and BP not at target,** use an ACEI or ARB as first-line therapy for HTN	• **If ACR > 3,** use an ACEI or ARB as first-line therapy. • If BP already < 130/80, use ACEI or ARB cautiously, monitoring for signs and symptoms of hypotension
Hypertension	• Lipid management: use statin if › Age ≥ 50, or › Age ≥ 18 with known coronary artery disease, prior stroke, or 10-year Framingham risk >10%	• Lipid management: use statin if › Age ≥ 18 • Diabetes management: › Target HbA1c to appropriate level using recommended therapies as per Diabetes Canada guidelines › Treat with SGLT2 inhibitors if type 2 diabetes and eGFR over 30
	• Lifestyle modifications including smoking cessation	
Minimize further kidney injury	• If eGFR <60, avoid nephrotoxins whenever possible (e.g., NSAIDS, IV, intra-arterial contrast) • If contrast necessary, consider oral hydration, withholding diuretics	

Refer to Sick Day Medication List (see Evidence Summary)

APPENDIX 2. Antihyperglycemic Agents and Renal Function



Reproduced with permission from Diabetes Canada. McFarlane P, Cherney D, Gilber RE, Senior P. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Chronic Kidney Disease in Diabetes. Can J Diabetes. 2018;42(Suppl 1):S201-S209. https://guidelines.diabetes.ca/cpg/chapter29. For infographic see the Diabetes Toolbox: http://diabetestoolbox.ca/pdf/Tableau-fr-EN.pdf

APPENDIX 3. End-Stage Renal Disease: Symptoms and Their Management

Symptom	Etiology	Strategy**
Fatigue Insomnia	• Poor sleep—exacerbating conditions (e.g., restless leg syndrome, pain, medications that cause insomnia) • Depression • Uremia, anemia • Treatment burden • Medication side effects • Comorbid conditions (e.g., thyroid disease, diabetes)	• Treat any underlying medical issues first • Anemia: consider erythropoietin • Assess and treat any sleep disorders (see restless leg syndrome below), depression, review medications • Exercise (if possible) • For sleep: avoid sleep aids and benzodiazepines if possible, can cautiously consider mirtazapine 7.5 mg, doxepin 10 mg (monitor for anticholinergic side effects) or zopiclone 3.75–7.5 mg short term • For fatigue, consider: stimulants (methylphenidate 2.5–5 mg am and noon, ↑ 2.5 mg daily based on response)

Pruritis	• Uremia related:
	  ○ Xerosis
	  ○ Anemia
	  ○ Hemodialysis adequacy
	  ○ 2º hyperparathyroidism
	  Check calcium/phosphate/parathyroid hormone
	• Non-uremia related:
	  ○ Allergy, drug reaction, contact dermatitis
	  ○ Liver disease/cholestatic pruritus
	  ○ Malignancy (leukemia, lymphoma)
	  ○ Thyroid disease, uncontrolled diabetes
		• Correct metabolic abnormalities:
		  ○ Dietary phosphate restriction
		  ○ Phosphate binders
		• Vitamin D to decrease parathyroid hormone levels
		• Anemia: correct iron deficiency, erythropoietin
		• Emollient cream, can use topical steroids on localized areas
		• Oral antihistamines:
		  ○ Hydroxyzine (10 mg TID–25 mg QID),
		  ○ Diphenhydramine (25 mg BID–TID)
		• Gabapentin (100–300 mg HS)
		• Doxepin (10–50 mg HS)
		• Ultraviolet B light

Pain	Often multifactorial: • Musculoskeletal (generalized bone and joint pain) • Peripheral neuropathy • Dialysis-related leg cramps • Osteoporotic vertebral fractures	• Similar approach as per the general population using the WHO Analgesic Ladder (available at https://www.who.int/cancer/palliative/painladder/en/) • First-line adjuvant medication for neuropathic pain can include tricyclic antidepressants, gabapentin and pregabalin Note: Avoid duloxetine in dialyzed patients
Anorexia Nausea	• Uremia • Medications: opioids, SSRIs • Constipation • Infection • Gastroparesis (diabetes or opioids)	• If nausea: ondansetron* (4 mg BID–TID) • If gastroparesis: metoclopramide (5 mg BID–QID), haldol (0.5 mg q12 h), domperidone* (5–10 mg po TID) • If anorexia: role of appetite stimulants uncertain. Try mirtazapine (7.5–30 g max), nabilone 0.5–1 mg BID (sedation)

Dyspnea	• Multifactorial and not always fully understood. Consider:
	  ○ Sodium and fluid overload
	  ○ Congestive heart failure
	  ○ Lung disease
		• Treat any underlying causes—correct fluid overload
		• Non-pharmacologic: fan, pursed lipped breathing
		• O_2 if hypoxia
		• Consider opioids (morphine 1 mg s/c q 1–2 h and titrate)

Restless Leg Syndrome (RLS)	• Iron deficiency
	• Neuropathic pain
	• Medication(s)—for example: antipsychotics, metoclopramide, antidepressants (such as SSRIs, mirtazapine, TCAs)
	• Alcohol, caffeine
		• Correct anemia if possible
		• Sleep hygiene
		• Adjust medication
		• Pharmacologic options:
		  ○ Intermittent RLS: levodopa/carbidopa 100/25 mg tablet (½ tab PO HS)
		  ○ Daily RLS: dopamine agonists—ropinirole (0.25 mg PO 2 hours before HS)*
		  ○ If ineffective or RLS with painful neuropathy: gabapentin* (100 mg PO HS), pregabalin* (25mg PO HS)

*Consider risk for QT prolongation, **Collaborative care when managing many of these issues strongly recommended with nephrology or palliative care expertise.

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Sources: 1) Combs SA, Davison SN. Palliative and end-of-life care issues in chronic kidney disease. Current opinion in supportive and palliative care. Mar 2015;9(1):14-19.; **2)** BC Renal Agency. Management of fatigue/insomnia in patients with chronic kidney disease 2017.; **3)** BC Renal Agency. Management of pruritis in patients with chronic kidney disease. 2017.; **4)** BC Renal Agency. Management of restless leg syndrome in patients with chronic kidney disease 2017.;**5)** Conservative Kidney Management. https://http://www.ckmcare.com/InformationRows/PracSymptoms.; **6)** Kidney Supportive Care Research Group (KSCRG). Living well without dialysis. University of Alberta. https://sites.ualberta.ca/~kscrg/ckm-pathway.html