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Chronic kidney disease: the six red flags

MARK THOMAS MB BS

Treating chronic kidney disease (CKD) is an increasing part of chronic disease management in general practice. Yet many patients remain undiagnosed. Regular monitoring of glomerular filtration rates is important not only to help diagnose patients with CKD, but also to alert GPs to major complications associated with disease.

Key points

- About one in nine adult Australians have chronic kidney disease (CKD) but many patients with the condition are undiagnosed.
- All adults with one or more risk factor for CKD should be screened annually for the disease.
- The severity of CKD is determined by glomerular filtration rate (GFR) and/or the presence of structural kidney disease or urine sediment abnormalities.
- Reduced GFR is a red flag for six major complications in patients with CKD: acute kidney injury risk, resistant hypertension, metabolic abnormalities, adverse drug reactions, accelerated cardiovascular disease and progression to end-stage kidney disease.
- CKD can mostly be managed in general practice if blood pressure, weight, electrolyte levels and diabetes are controlled.
- Referral is indicated if the patient's GFR is less than 30 mL/min or if GFR falls rapidly at any stage.

About one in nine adult Australians have chronic kidney disease (CKD) but many patients with the condition remain undiagnosed.[1] Australian GPs see some 287,000 patients each day, but according to one study, only 17% of patients with CKD were identified by their GP.[2] With widespread reporting of estimated glomerular filtration rate (eGFR), patients with CKD are becoming an increasing part of routine chronic disease management in general practice.

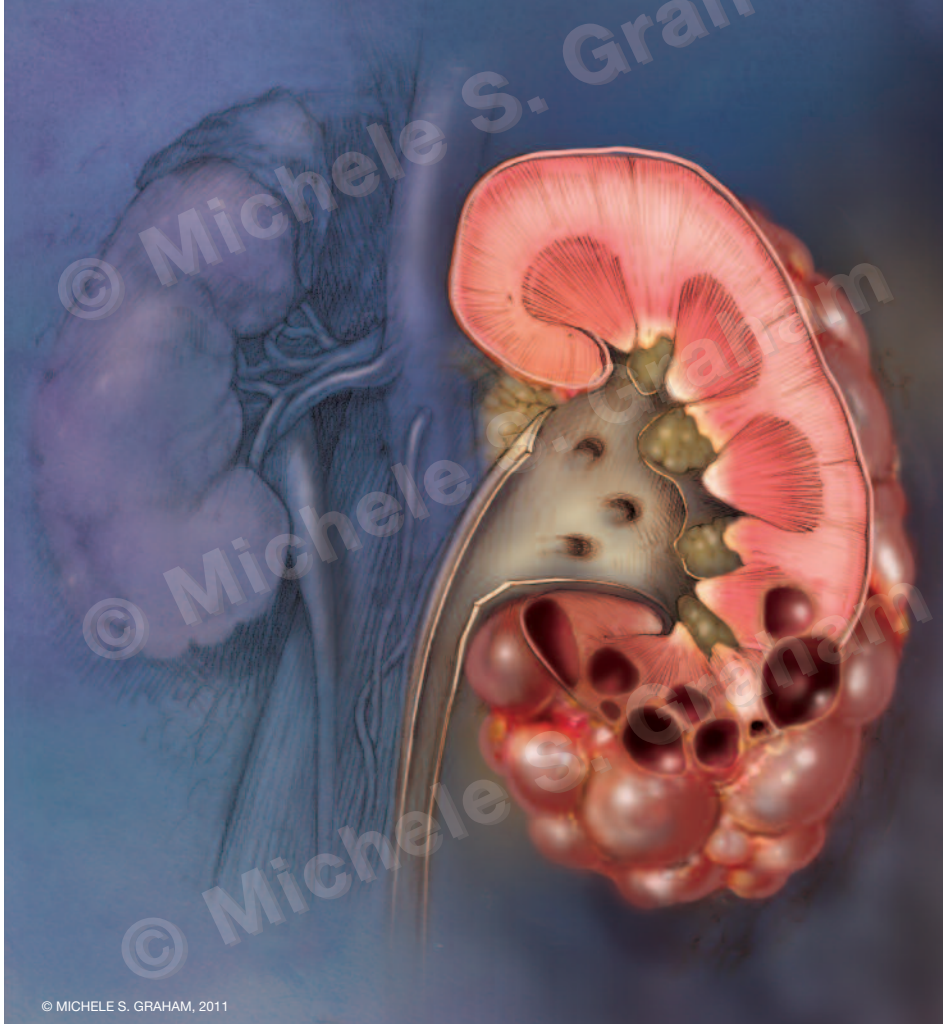
RECOGNISING CKD IN GENERAL PRACTICE

All adults with one or more risk factor for CKD should be screened annually for kidney disease. Risk factors for CKD include modifiable (e.g. diabetes, hypertension, smoking and obesity) and unmodifiable factors (e.g. age 50 years and older, family history of CKD and being of Aboriginal or Torres Strait Island descent).[3] Other recognised at-risk groups for CKD include patients with chronic vascular, lung or liver disease, and those with treated arthritis or malignancy.

What are the screening tests for CKD?

The simplest screening tests for CKD are a measurement of blood pressure, estimation of GFR derived from the serum creatinine, and a spot urine sample to determine the urine albumin–creatinine ratio (ACR), or protein–creatinine ratio if heavy (i.e. urine ACR greater than 200; Nitrogen less then 3.5). If albuminuria is detected, then urine microscopy is necessary to look for accompanying haematuria and to exclude urinary tract infection. An isolated unsustained abnormality in any one of the tests is not diagnostic of CKD. These screening tests can be performed at any time, but are easily included with standard cardiovascular risk factor screening (e.g. of measurement fasting blood glucose levels and lipid levels).

Dr Thomas is a Staff Nephrologist at the Department of Nephrology, Royal Perth Hospital and Clinical Associate Professor at the School of Medicine and Dentistry, University of Western Australia, WA.



How is severity of CKD assessed?

The severity of CKD is graded from stage 1 (mild kidney damage) to stage 5 (end-stage kidney disease; Table 1). The stage is determined by GFR and/or the presence of structural kidney disease (i.e. an abnormal renal ultrasound or biopsy) or urine sediment abnormalities (i.e. nonurological haematuria, proteinuria or casts), provided these abnormalities have been present for at least three months.

How is eGFR calculated?

Serum creatinine is used in various formulae to estimate the GFR, taking into account adjustments for the patient's age (in healthy individuals eGFR falls by about 1 mL/min for every year after the age of 40 years), muscle mass and gender (to reflect the greater creatinine generation associated with the larger muscle mass of men compared with women). The most commonly used formula for estimating GFR is currently the Modification of Diet in Renal Disease (MDRD) equation, which calculates GFR based on serum creatinine, age, race and gender, but not muscle mass. The formula is about to be superseded by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, which uses the same variables but produces a more accurate result.

As a rule of thumb, the age-normal GFR can be estimated using the constant of 140 minus the patient's age in years (see box on page 16). For example, the age-normal GFR for a 50-year-old patient would be 90 mL/min (140–50), or 60 mL/min for an 80-year-old patient (140–80). When assessing CKD in elderly patients, there is some controversy about whether an eGFR of below 90 mL/min/1.73 m^2 constitutes a diagnosis; it can be a cause of concern for an otherwise healthy 80-year-old to be told they have stage 2 to 3 CKD. Current research is contrasting the better prognosis of age-related GFR loss with the worse prognosis of disease-related GFR loss.

How reliable are the formulae?

The formulae for eGFR are fairly accurate when studying the population average GFR. Compared with the gold standard for estimating GFR (i.e. a nuclear medicine isotopic GFR), the MDRD formula differs by a degree of only 2 to 3 mL/min. However, the MDRD equation slightly underestimates true GFR when the value is less than 60 mL/min (i.e. Stage 3 CKD). The more recent CKD-EPI formula provides a more accurate estimate of GFR compared with the MDRD equation, resulting in more people being classified within the stage 2 rather than stage 3 range of CKD.[4]

When using the formulae to assess individual rather than population GFRs, however, wide inaccuracies can occur and discrepancies of up to 50 to 100% above or below the eGFR can result. Such inaccuracies are due to two major, but completely separate, factors: intercurrent illness and extremes of body size or muscle mass.

An unstable serum creatinine invalidates the estimated GFR. Intercurrent illness is a common cause of a temporary rise in serum creatinine, often due to reversible volume depletion. Introduction of an ACE inhibitor, angiotensin II receptor blocker (ARB) or diuretic may cause an increase in serum creatinine of up to 30%, reflecting a reduction in glomerular pressure.

In patients with a stable serum creatinine,

TABLE 1. STAGES OF CHRONIC KIDNEY DISEASE SEVERITY AS DETERMINED BY eGFR

Stage	eGFR definition (mL/min/1.73 m²)
Stage 1	eGFR > 90 with other evidence of kidney disease*
Stage 2	eGFR < 90 with other evidence of kidney disease*
Stage 3	eGFR < 60 (stage 3a: eGFR = 45 to 60; stage 3b: eGFR = 30 to 45)
Stage 4	eGFR < 30
Stage 5	eGFR < 15 (stage 5d on dialysis, stage 5t with transplant)

*Abnormalities on renal ultrasound, or urine sediment (haematuria, proteinuria or casts) or renal biopsy.
ABBREVIATIONS: eGFR = estimated glomerular filtration rate.

RULES OF THUMB FOR MONITORING PATIENTS WITH CHRONIC KIDNEY DISEASE

- Normal GFR for age = 140 – age (years)
- Lean weight (kg; about equivalent to a BMI of 25) = height (cm) – 100
- Expected serum creatinine for women with a normal GFR (μmol/L) = height (cm) – 100
- Expected serum creatinine for men with normal GFR (μmol/L) = height (cm) – 100) x 1.25
- Lean waist (cm) = 50% of height (cm)

ABBREVIATIONS: BMI = body mass index; GFR = glomerular filtration rate.

extremes of body size should be taken into consideration. A tall or muscular person will have a GFR that is higher than that predicted by the formula, while a short or thin person, or an amputee, will have a GFR that is lower than predicted.[5] The eGFR is therefore reported as mL/min/1.73 m² rather than mL/min (i.e. assuming the patient is a standard size). This leaves the onus on the doctor to adjust the eGFR up or down according to the patient's body size, to give a closer estimate of true GFR. However, adjusting for total body surface area may not improve the accuracy of the eGFR in obese patients because their increased weight does not necessarily reflect increased muscle mass (the principal source of creatinine).

Despite these limitations, eGFR remains the most practical tool available for diagnosing CKD.

Recognising hyperfiltration

Inaccuracies in eGFR increase with higher values of the true GFR. The eGFR is therefore reported only to the value of 'greater than 90 mL/min/1.73 m², giving no indication of whether potentially dangerous hyperfiltration (i.e. a GFR above 150 mL/min) may be present. Glomerular hyperfiltration is a recognised complication of obesity and diabetes, and precedes the development of microalbuminuria in patients with hypertension by up to five years.[6]

The clinical clue to the presence of hyperfiltration is an unexpectedly low serum creatinine. A useful rule of thumb for estimating the expected creatinine in women with a normal GFR is the patient's height (cm) minus 100. For example, a woman who is 160 cm tall should have a serum creatinine of about 60 μmol/L (160–100); a serum creatinine of below 45 μmol/L would suggest hyperfiltration in this patient. As men usually have a greater muscle mass for the same height, the expected serum creatinine for men with a normal GFR will usually be about 25% more than that of women. Thus, a 180 cm man should have a serum creatinine of about 100 μmol/L ([180–100] x 1.25); a serum creatinine of below 75 μmol/L would suggest hyperfiltration in this patient.

Correction of hypertension, hyperglycaemia or obesity will usually improve hyperfiltration. The resulting 30% rise and stabilisation in serum creatinine after treatment with an ACE inhibitor or ARB is due to a reduction in hyperfiltration.

When should GFR be measured precisely?

Rarely, it is critical to know a patient's GFR precisely (i.e. measured via a nuclear medicine scan of isotopic GFR). For example, a potential live kidney donor should have a size-unadjusted GFR of greater than 80 mL/min. This will enable their transplant recipient to receive a kidney with a GFR of at least 40 mL/min. In these cases, a scan of isotopic GFR provides a precise measurement at a single point in time. However, because renal function varies frequently (according to blood pressure, volume and medication) there is no substitute for serial creatinine monitoring.

Common causes of chronic low GFR

The major causes of chronic kidney damage in adults after age-related loss of kidney function are diabetic nephropathy, hypertensive/ischaemic nephrosclerosis, primary glomerulonephritis (e.g. immunoglobulin A nephropathy or focal segmental glomerulosclerosis) and congenital/inherited kidney diseases (e.g. polycystic kidney disease or reflux nephropathy).

How does the spot urine albumin–creatinine ratio fit in?

The presence of albuminuria can reflect a raised glomerular haemodynamic pressure as well as established glomerular damage; however, it does not indicate the severity of CKD, which is categorised

by stage according to GFR (Table 1). The severity of albuminuria has recently been classified by the Kidney Disease: Improving Global Outcomes (KDIGO) group as ranging from stage 1 (optimal albuminuria) to stage 3 (macroalbuminuria; Table 2).[4]

The absence of albuminuria or any other abnormality in the urine sediment is a feature of CKD resulting from either vascular causes, such as hypertensive or smoking-related nephrosclerosis, or interstitial disease, such as from cyclosporin use.

Microalbuminuria can occur in poorly controlled hypertension, obesity or in the early phase of diabetic nephropathy. It is useful for diagnosis, for assessing prognosis and for monitoring in these patient groups.

Macroalbuminuria can be seen in many forms of established kidney disease, not just glomerular diseases. As such, macroalbuminuria is called 'nonspecific proteinuria', roughly corresponding to proteinuria of about 0.5 to 2.5 g/day. In contrast, nephrotic-range albuminuria (ACR greater than 300 mg/mmol; about 3 g/day proteinuria) implies glomerular disease. Diagnosis of nephrotic syndrome requires the additional presence of oedema, low serum albumin levels (below 30 g/L) and, usually, a high serum cholesterol level (greater than 6 nmol/L).

There is considerable variation in urine ACR day-to-day, often related to posture and exercise. The convenience of measuring ACR with a single spot urine sample often outweighs the greater reproducibility of the more cumbersome overnight or 24-hour urine collection methods.

The urine protein–creatinine ratio is slightly less sensitive than ACR for measuring the normo–microalbuminuric range, but more robust and reliable for the macronephrotic range. The light chains and gammaglobulin Bence-Jones proteinuria of myeloma are detected with urine protein–creatinine but not ACR.

TABLE 2. ALBUMINURIA AND THE NEW KDIGO STAGING SYSTEM

Stage	Albuminuria (mg albumin/mmol creatinine)
Stage A1	Optimal albuminuria (< 1.0 [men]; < 1.5 [women]) High-normal albuminuria (< 2.5 [men]; < 3.5 [women])
Stage A2	Microalbuminuria (3.5 to 30 or slightly less in women)
Stage A3	Macroalbuminuria (30 to 300) Nephrotic-range (> 300)

N.B. Switch to protein–creatinine ratio if albumin–creatinine ratio is greater than 200 mg/mmol. There is less diurnal variation but less convenience with timed collections.
ABBREVIATIONS: KDIGO = Kidney Disease Improving Global Outcomes.

Why is measuring GFR important?

In patients with CKD, reduced GFR is a red flag for six major complications, with increasing risk as kidney function deteriorates (Figure). These red flags are:

- acute kidney injury risk – in patients with CKD, volume depletion, intercurrent illness, nephrotoxins or obstruction should all be rapidly corrected or avoided altogether, where possible, to prevent acute kidney injury
- resistant hypertension – patients with CKD often require treatment with an average of three antihypertensive agents to achieve blood pressure targets
- metabolic abnormalities – patients with CKD may develop anaemia, hyperkalaemia, metabolic acidosis and mineral–bone disorders (caused by low serum calcium levels, high serum phosphate levels, raised parathyroid hormone levels and cardiovascular calcification)
- adverse drug reactions – patients with CKD should be monitored for drugs that are renally excreted, are nephro - toxic or exacerbate CKD problems
- accelerated cardiovascular disease – patients should be treated aggressively for traditional and nontraditional risk factors
- progression to end-stage kidney disease – when GFR falls below 30 mL/min, patients should be educated about CKD and their treatment options, including arteriovenous fistula formation (with or without a search for a kidney transplant donor) or palliative care pathways.

Based on meta-analyses of 45 cohorts with more than 1.5 million individuals, a GFR of 45 to 60 mL/min confers a two-to threefold greater risk of acute kidney injury, progressive CKD, cardiovascular mortality and all-cause mortality compared with individuals with a GFR of more than 60 mL/min (kidney outcomes) or 90 mL/min (mortality outcomes).[4] The risk for these complications increases further with worsening albuminuria/proteinuria.

THE SIX RED FLAGS OF CKD

Red flag 1: acute kidney injury risk

Patients with CKD are at much higher risk of developing acute-on-CKD after renal insult than patients with normal kidney function. Additional preventive management and closer monitoring are therefore needed in patients with CKD. Prerenal insults, such as volume depletion from gastrointestinal illness or perioperative fasting, can be avoided by the omission of antihypertensive drugs on the day of surgery (especially ACE inhibitors or ARBs; see red flag 3), administering intravenous (IV) saline while the patient is fasting, and monitoring

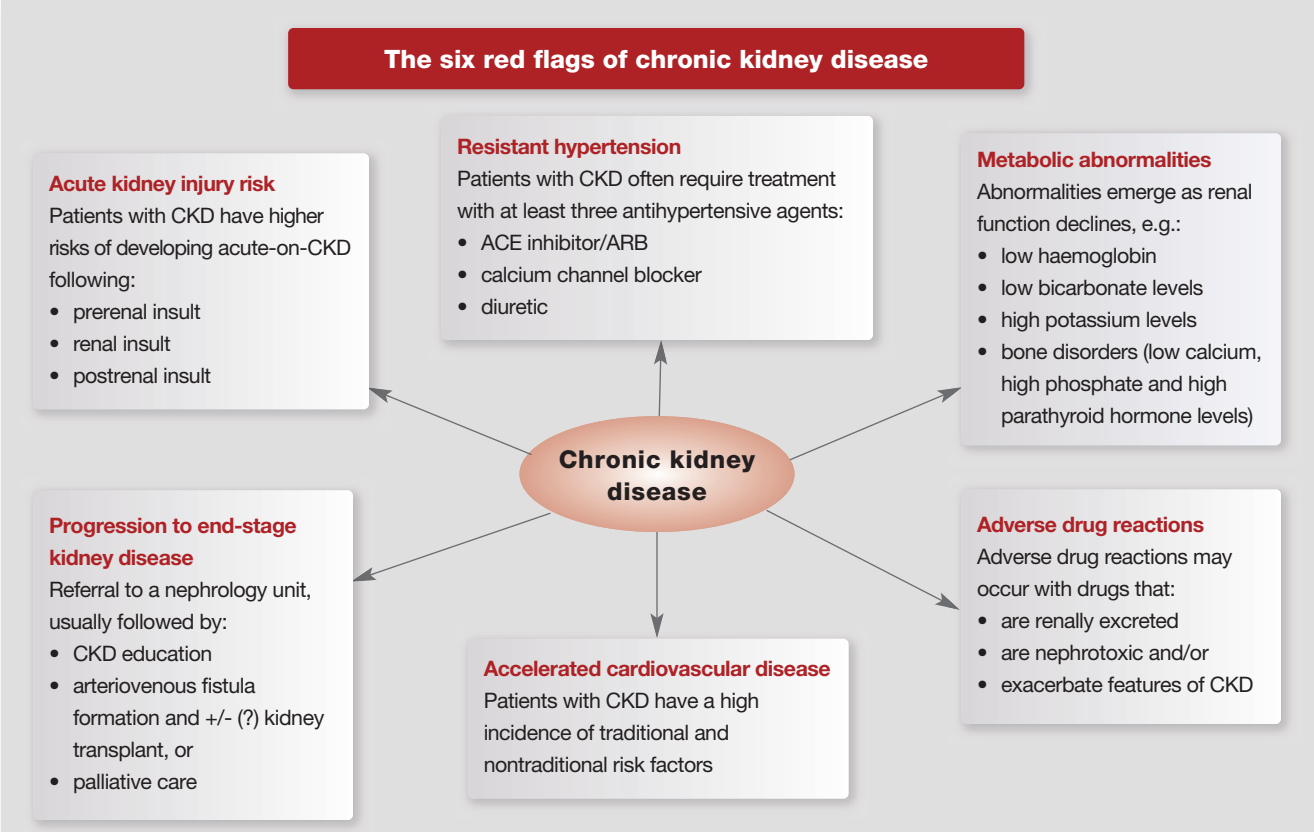


Figure. The six red flags of chronic kidney disease.

blood pressure, fluid balance and body weight. Febrile illnesses or inflammations (e.g. severe gout) can also act as prerenal insults through the mechanism of vasodilatation.

Renal insults from medications (see red flag 4) or IV contrast, as well as postrenal insults from ureteric obstruction (e.g. calculi), require prompt identification and correction, or the patient may otherwise fail to fully recover. Many of these renal insults can be experienced together during hospital admissions, therefore serum creatinine levels should be measured at admission and discharge and repeated at three to four weeks post discharge to assess the degree of recovery.

Red flag 2: resistant hypertension

Patients with CKD are usually hypertensive, often requiring treatment with an average of three antihypertensive agents to achieve systolic blood pressure targets of below 130 mmHg. Notably, these patients are also prone to medication side effects (see red flag 4).

Resistant hypertension is defined as a blood pressure that remains above target levels, despite at least one month of therapy with at least three antihypertensive agents, including a diuretic. As many patients with CKD also have obesity and suboptimal diets, sleep apnoea and/or excess salt intake should be considered if blood pressure remains stubbornly high.

A reduction in systolic blood pressure to below 140 mmHg can slow the rate of progression of CKD by more than 50% (e.g. from an annual loss of GFR of more than 10 mL/min to less than 5 mL/min in patients with CKD versus an annual loss of GFR of 0.5 to 1.0 mL/min in healthy individuals).[7] However, there is a significant danger of acute kidney injury (see red flag 1) if blood pressure is reduced too far or too fast; a useful safety measure is to practice home blood pressure monitoring (lying and standing), especially during periods of dose titration or illness.

The presence of albuminuria (or proteinuria in more advanced cases) acts as an additional and independent marker of cardio–renal risk, as well as being a

prognostic marker for response to antihypertensive therapy. A halving of the urine ACR after initiation of antihypertensive therapy corresponds to a 15 to 50% reduction in risk of progressive kidney disease, but rapid falls in proteinuria (similar to blood pressure) can indicate potentially risky reductions in glomerular perfusion.

Initial therapy

Renin axis blockers (i.e. ACE inhibitors or ARBs) are the best antihypertensive classes for initial therapy based on cardio –renal protection and proteinuria reduction. They provide the best medication adherence and the least risk of inducing new-onset diabetes compared with other antihypertensive drug classes.[7-9] ACE inhibitors and ARBs reduce not only arterial but also intraglomerular pressure, achieved by a reduction in efferent arteriolar tone. Although this outcome is desirable for patients with hypertension and proteinuria who are otherwise healthy, treatment can precipitate acute kidney injury in hypotensive patients who are unwell, especially in patients without proteinuria.[10] This risk, coupled with a risk of high potassium, means patients with CKD should be monitored for their electrolyte levels and spot urine ACR both before beginning treatment with ACE inhibitors or ARBs, and also at one and four weeks after starting treatment.

A rise of up to 30% in the serum creatinine (along with an increase of 0.5 mmol/L in the serum potassium level) is to be expected with treatment, and is a marker of effective cardiovascular risk reduction. Patients should be advised to temporarily stop taking antihypertensive medication when feeling unwell to minimise the risk of acute kidney injury. The active metabolites of ACE inhibitors are renally excreted, requiring that the dose of these agents be reduced in patients with CKD, otherwise disproportionate problems with high potassium levels and cough can become a risk.

Additional therapy

The choice of additional antihypertensive therapies has recently been clarified by two major clinical trials. The ONTARGET trial randomised more than 20,000 patients with known cardiovascular disease or complicated diabetes (mostly without proteinuria) to treatment with an ACE-inhibitor, ARB or both. It showed equivalent cardiac outcomes in all of the treatment arms, but episodes of temporary kidney impairment were more frequent in patients on combined ACE inhibitor/ARB therapy, especially if the patient had borderline low blood pressure or no proteinuria at baseline.

The ACCOMPLISH trial of 11,500 patients with hypertension and at least one other cardiovascular risk factor who were already taking an ACE inhibitor showed that the addition of a calcium channel blocker had significant advantages over the addition of a diuretic.[11] On this basis, calcium channel blockers should be the additional agent of choice after renin axis blockers, unless there are individual contraindications (e.g. ankle oedema or tachycardia).

Diuretics are useful treatment options because of their additional blood pressure-lowering efficacy, control of high potassium (especially when combined with renin axis blockers) and control of low bicarbonate (HCO_3) levels, but they may also precipitate gout, acute kidney injury, hyponatraemia and exercise intolerance in hot weather. Although thiazides become decreasingly effective in patients with a GFR below 30 mL/min, loop diuretics maintain effectiveness at increasing doses. As with ACE inhibitors and ARBs, diuretics should be stopped temporarily when patients with CKD have volume depletion or are fasting.

Renally-excreted antihypertensive drugs should be dose-adjusted downwards as GFR decreases; β-blockers (e.g. sotalol, atenolol and carvedilol) and moxonidine are the main examples of these agents.

Red flag 3: metabolic abnormalities

Characteristic pathology abnormalities emerge as renal function declines. In patients with a GFR of less than 60 mL/min, normocytic anaemia starts to develop, and is exacerbated by deficiencies in iron stores or intercurrent inflammation. Erythropoietin therapy, due to its expense, is funded under the S100 scheme of the PBS when haemoglobin levels are less than 100 g/L and intrinsic renal disease is the primary cause of anaemia, as assessed by a nephrologist. Other causes of anaemia, such as gastrointestinal blood loss, should be excluded or treated before beginning therapy with erythropoietin. The risks of hypertension, myocardial or cerebral thrombosis, or reactivated malignancy in patients undergoing erythropoietin therapy have translated into lower target haemoglobin levels of 110 to 120 g/L for this treatment group.

Metabolic abnormalities, including high potassium, low HCO_3, raised phosphate, low corrected calcium and raised parathyroid hormone levels, can occur in patients when GFR is less than 30 mL/min. Acutely high potassium levels of greater than 6.0 mmol/L can cause muscle weakness and fatal arrhythmias, but stable levels of less than 6.0 mmol/L are often tolerated well, and can respond to simple changes in diet or medication doses.

What to look for

In patients with maintained appetite and weight, metabolic abnormalities caused by dietary excesses should be looked for first. These include:

- high potassium levels – from fruit, fruit juices, nuts, chocolate and bran cereals
- low HCO_3 levels – from meat
- high phosphate levels – from meat, dairy foods, cola drinks, beer and bread.

If the patient shows no dietary excess, abnormalities caused by medications should be looked for next. These include:

- high potassium levels – from ACE inhibitors, ARBs, spironolactone, amiloride, trimethoprim and NSAIDs
- low HCO_3 levels – from acetazolamide (with high chloride)
- high phosphate levels – from calcitriol
- high urea levels – from corticosteroids and excess diuretics.

If dietary and medication causes of metabolic abnormalities have been addressed, then specific therapy can be tailored to each patient's individual pattern of abnormalities, for example:

- fluid overload, and high potassium and low HCO_3 levels – treat with diuretics
- volume depletion, and high potassium and low HCO_3 levels – treat with $NaHCO_3$ (either as bicarbonate of soda powder or mineral water)
- low HCO_3, low calcium and high phosphate levels – treat with calcium carbonate (taken with meals)
- low calcium and low phosphate levels – treat with calcitriol.

When GFR falls below 15 mL/min, symptomatic uraemia can reduce appetite and produce dangerous protein–calorie malnutrition. The patient's body weight should therefore be monitored closely. Other nonspecific uraemic symptoms (e.g. fatigue, nausea, vomiting, itch, bruising, dyspnoea and insomnia) may indicate the need to start dialysis. Specific advice sheets on diet in renal disease are available online at the HERO website for Queensland Health (www.health.qld.gov.au).[12]

Red flag 4: adverse drug reactions

There are three questions to ask about any type of drug therapy in a patient with CKD: Is the drug renally excreted? Is it nephrotoxic? Can it exacerbate any feature of CKD – i.e. nausea, hypertension, high serum potassium, acidosis, bleeding risk?

Failure to appropriately dose reduce renally-excreted drugs can result in toxic symptoms. Examples of renally-excreted drugs (and their corresponding toxic symptoms) are ACE-inhibitors (cough); aminoglycosides, such as gentamicin, colchicine (gastrointestinal illness); digoxin (nausea); metformin (nausea, diarrhoea); methotrexate (marrow suppression); narcotics (nausea, confusion); and (val)aciclovir (hallucinations, confusion).

The risk–benefit ratio of a predictably nephrotoxic drug in a patient with CKD requires careful consideration (see red flag 1). The risk of x-ray contrast for a coronary angiography, for example, can be minimised by prehydration, minimising volume, low-osmolarity media and (controversially) premedication with N-acetylcysteine.

NSAIDs offer rapid relief of acute inflammatory arthritis, but reduce renal perfusion and cause retention of sodium, water and potassium. Their toxicity can be minimised by using the approach of administering the shortest course and lowest effective dose of the drug along with adequate hydration.

Drugs that are both highly nephrotoxic and renally excreted (e.g. gentamicin, amphotericin) are a particularly dangerous combination.

Some nephrotoxicity is idiosyncratic rather than obligatory, making it unpredictable. Such nephrotoxicity usually causes an allergic interstitial nephritis, which may be accompanied by loin pain (e.g. after two to three days of treatment with an NSAID), fever and/or rash and/or eosinophilia (e.g. after two to three weeks of flucloxacillin), or it could be completely silent (e.g. after six to 18 months of treatment with a protein pump inhibitor).

Commonly used drugs that may exacerbate a feature of CKD include:

- metformin, narcotics and digoxin – exacerbating nausea
- NSAIDs, steroids, sympathomimetics (e.g. pseudoephedrine, amphetamines, cocaine), nicotine and ethanol –

exacerbating hypertension
- ACE inhibitors, ARBs, spironolactone, trimethoprim and NSAIDs – exacerbating high potassium levels
- acetazolamide – exacerbating low HCO_3 levels
- aspirin, clopidogrel, warfarin and heparin – exacerbating bleeding/bruising.

Therapeutic dilemmas

Two common therapeutic dilemmas when treating patients with CKD that deserve more detailed discussion are the use of metformin and the treatment of gout.

Metformin

Metformin is the preferred first-line agent for obese patients with type 2 diabetes, but 25% of these patients will have a GFR of below 60 mL/min (approximately 50% of whom are undiagnosed with CKD). Using metformin in the presence of CKD will cause predictable accumulation (with nausea and diarrhoea), as well as the unpredictable risk of lactic acidosis. Metformin not only reduces insulin resistance and hepatic glucose release, but also inhibits hepatic lactate uptake. An episode of acute kidney injury with lactic acidosis is characterised by much more severe lactic acidosis if metformin is continued.

Episodes of lactic acidosis are usually precipitated by a major illness (e.g. cardiogenic shock, ischaemic limbs or septicaemia), often accompanied by acute-on-CKD; however, they are rare, with or without metformin. In Western Australia, the rate of lactic acidosis was calculated at 27 to 58 per 100,000 patient–years, and in the USA it was reported at an upper limit of eight per 100,000 patient– years.[13,14]

Observing the Therapeutic Goods Administration recommendation to cease metformin once GFR is below 30 mL/min and convert to an alternative agent may lead to greater risk of obesity or hypoglycaemia, and potentially worse diabetic complications in the population at highest risk. In the author's experience, and only after an informed discussion with each patient, the two simplest rules to balance the risk–benefit of metformin use are to:
- dose reduce metformin according to the GFR (e.g. initiate treatment with about 1 g/day metformin in patients with a GFR of 50 mL/min, or 500 mg/day metformin in patients with a GFR of 25 mL/min)
- stop metformin immediately if the patient becomes unwell or is at risk of acute kidney injury.

Gout

Episodes of acute gout can generate sufficient inflammation in a patient with CKD to induce acute-on-CKD. However, there are complications with each of the three common effective therapies for treating acute gout (colchicines, NSAIDs and prednisolone) in patients with CKD.

Colchicine is renally excreted and metabolised through the hepatic cytochrome P450 pathway. Short-term treatment with colchicine can induce diarrhoea and vomiting, which can lead to volume depletion and acute kidney injury. NSAIDs can cause acute-on-CKD, especially when combined with volume depletion and treatment with an ACE inhibitor or ARB (the 'triple whammy'). Oral prednisolone (e.g. 15 to 25 mg daily for two to three days) will not cause acute kidney injury, but will cause temporary sodium retention, higher blood pressure and deterioration in diabetic control. Intra-articular corticosteroids are useful for treating monoarticular gout but can still have systemic side effects.

Preventive therapy for recurrent or tophaceous gout can also be problematic. Allopurinol can induce gouty flares if started too early after an acute attack, or if taken in too large an initial dose. Idiosyncratic reactions to allopurinol (e.g. hepatitis, rash and Stevens-Johnson syndrome) are rare and usually appear within one to two months of initiation of treatment. Febuxostat is now available through the Special Access Scheme for patients intolerant to allopurinol.

Prescribing information for allopurinol emphasises the need to dose-reduce allopurinol in patients with CKD due to the potential risk of leucopenia. However, in practice, there are generally no problems with gradual up-titration of allopurinol to the dose required to achieve target uric acid levels of below 0.30 mmol/L – this may be a dose as high as 600 mg in some patients with CKD.

To suppress gouty flares with the initiation of allopurinol, many practitioners use low-dose, long-term colchicine suppression (e.g. one to two tablets/day, for two to three months), but this can be potentially fatal in patients with CKD, and can cause gastrointestinal injury, pancytopenia, areflexic paralysis and rhabdomyolysis. To minimise cumulative colchicine toxicity in patients with CKD, current National Prescribing Services recommendations suggest a minimum of two weeks between treatment for acute attacks.[15]

Many factors can precipitate gout, including injury, alcohol excess, low-dose aspirin and/or diuretics. It is sometimes necessary to defer diuretic therapy of resistant hypertension until gouty flares and uric acid levels are fully suppressed. For an isolated acute attack of gout in a well-hydrated patient with CKD, a short course of NSAIDs or colchicine can be trialled first with close monitoring. Temporary treatment with prednisolone can be used in patients with volume-depletion or NSAID/colchicine intolerance. For recurrent attacks of gout, patients can be treated with very low-dose allopurinol (e.g. 50 mg/day), gradually up-titrated (e.g. by 50 mg every one to two weeks) until the target serum uric acid of less than 0.30 mmol/L is achieved.

Red flag 5: accelerated cardiovascular disease

As GFR falls from 60 to 15 mL/min, the five-year rates of cardiac death rise from

10 to 50%. In patients with end-stage kidney disease, the one-year cardiac death rate rises from 5% in 20-year-old patients to 50% in 80-year-old patients. This strong inverse relation is driven by the high incidence of traditional risk factors (hypertension, obesity, diabetes and smoking), and is further accelerated in the presence of either proteinuria or other abnormalities occurring in patients with CKD (e.g. calcification, inflammation or vitamin D deficiency). It is difficult to dissect the respective contributions each of these risk factors has in observational studies. There is the phenomenon of reverse epidemiology in patients on dialysis, where poorer survival is paradoxically seen with lower blood pressure, lower cholesterol and lower body mass index – presumably due to death rates from multiple comorbidities.

Intervention studies in the CKD population are frequently under-powered or disappointingly negative. Most nephrologists aim to maintain tightly monitored multifactorial cardiovascular intervention when patients are well, judiciously withholding some cardioprotective medications during acute illness, especially ACE inhibitors, ARBs, diuretics and metformin (see red flags 1, 2 and 4). In a post-hoc analysis of the HOT study, 3619 patients with hypertension and a baseline eGFR less than 60 mL/min/1.73 m^2 were randomised to receive either low-dose aspirin or placebo.[16] Aspirin was shown to reduce major cardiovascular events by 9% in patients with a baseline eGFR of 60 mL/min/1.73 m^2 or above, and by 66% in patients with a baseline eGFR less than 45 mL/min/1.73 m^2.

Red flag 6: progression to end-stage kidney disease

Rates of progression of CKD are highly variable. In general, high blood pressure, heavy proteinuria, poor diabetic control, obesity and smoking represent modifiable risk factors for faster progression of CKD, especially when such factors are the sole source of kidney damage (i.e. diabetic nephropathy, obesity-related glomerulo - nephritis and hypertensive nephrosclerosis). Some diseases inevitably progress (e.g. polycystic kidney disease), whereas others often remain stable (e.g. reflux nephropathy).

The course of progression of CKD is often irregular, with patients with intermittent episodes of acute-on-CKD failing to fully recover. As many as 20-fold more patients with CKD die from cardiovascular causes than progress to end-stage kidney disease, but if GFR is less than 15 mL/min, the ratio falls closer to 1:1. Dialysis is now the single largest cause of hospital admissions in Australia. The cost of providing dialysis and transplant services is about $1 billion annually, but could be reduced by up to $400 million with greater use of transplantation and self-care dialysis techniques.[17]

If patients are progressing towards end-stage kidney disease, then referral to a nephrology unit will usually be followed by one or more of:

- education about treatment options, which include dialysis, transplantation or palliative care
- creation of an arteriovenous fistula
- a search for a suitable live kidney donor
- close monitoring for the onset of symptomatic uraemia (see red flag 3), usually when GFR is about 7 to 12 mL/min.

CKD IN ABORIGINAL POPULATIONS IN RURAL AUSTRALIA

Rates of new cases of end-stage kidney disease are five- to 30-fold higher in Aboriginal populations in rural locations than in metropolitan areas. This is due to the accumulation of almost every known lifetime risk factor for CKD in these patients.

Risk factors for CKD are strongly associated with socioeconomic deprivation. Premature babies of smoking mothers are born with fewer nephrons. Forced feeding reduces infant growth mortality, but can result in obesity in teenagers. The release of insulin-like growth factors causes glomerular enlargement, hyperfiltration and proteinuria that presents before the onset of diabetes. Streptococcal skin infections produce superimposed nephritic episodes. Community smoking rates (about 70%) in these populations accelerate intrarenal arteriolosclerosis.

Chronic psychosocial stresses and cortisol release produce hypertension, obesity and insulin resistance, which are compounded by the consumption of cheap, energy-dense foods and drink, and lack of active employment opportunities within these communities. Rapidly progressive diabetic retinopathy and nephropathy may also be evident before age 20 years in these populations.

The dislocation of referral for dialysis in these rural communities is felt by both patients and the community left behind.[18] In the face of these odds, small systematic changes can have profound benefits. Rates of end-stage kidney disease have stabilised over the past decade, and excellent survival rates have been achieved in the Kimberley Aboriginal-controlled satellite dialysis unit. Researchers are currently investigating primary prevention programmes using ACE inhibitors in high-risk individuals, and secondary prevention using polypill compounding.

MANAGING MODERATE-SEVERE CKD IN GENERAL PRACTICE

A South Australian pilot study randomised 66 patients with CKD and serum creatinine levels ranging between 150 and 450 µmol/L (stage 3 to stage 5 CKD) to either standard follow up in a nephrology clinic or to three-monthly GP visits, supported by a level two CKD nurse. Over the following two years, there was no difference in cardio–renal outcomes or hospitalisation rates between the two groups. Superior blood pressure control was achieved in the GP-treated patients compared with the specialist- treated patients (91% at target *v.* 67% at target, respectively) as well as better use of ACE inhibitors, ARBs and statins.[19]

TABLE 3. PRACTICE TIPS FOR MANAGING PATIENTS WITH CKD: RULES AND EXCEPTIONS

Rules	Exceptions
Screening	
Screen for CKD annually in adults aged 50 years or older, who have hypertension or diabetes	Screen all adult Indigenous patients, all obese patients and any patients with a family history of CKD
Measure blood pressure, eGFR and spot urine ACR when the patient is otherwise well and fasting	If the patient is unwell, repeat the investigations when the patient has recovered
Assessment	
Severity of the disease is assessed by the stage of CKD as determined by GFR (stage 1 to 5)	Ignore CKD staging if the patient's serum creatinine levels are unstable
Compare eGFR to the expected age-normal GFR of the patient (140 – age in years)	–
Expect the eGFR to over- or underestimate the true GFR by up to 50 to 100%	Adjust up or down according to body size in the outlier patient
Further investigate with midstream urine samples and renal ultrasound	Omit the ultrasound if the patient has a GFR appropriate for their age as well as normal blood pressure measurements, urine ACR and midstream urine samples
Monitor the patient's blood pressure, weight and ankles at every visit, and test electrolyte levels and urine ACR frequently	Monitor the patient's calcium, phosphate and parathyroid hormone levels only every three to six months, unless the patient is unwell or changing treatment
Management	
Administer IV fluids to the patient while they are fasting	Slow the rate of IV fluids or withhold if the patient is overloaded or has congestive cardiac failure
Avoid inserting an IV cannulae in arteriovenous fistula arm of the patient	–
Treatment	
Use an ACE inhibitor or angiotensin II receptor blocker as first-line antihypertensive therapy	Avoid ACE inhibitors or angiotensin II receptor blockers if the patient has a high potassium level, cough, angio-oedema or is pregnant
Add an '-idipine' calcium channel blocker as the next antihypertensive drug	Avoid calcium channel blockers if the patient has oedema or tachycardia
Add a thiazide diuretic as the third antihypertensive drug	Avoid thiazide diuretics if the patient has a low potassium level, gout or chronic diarrhoea. Use a loop diuretic (e.g. frusemide) if the patient has a GFR below 30 mL/min
Review carefully all the medications that the patient is currently taking	–
Follow up	
Expect accelerated vascular disease in patients with CKD	Stop ACE inhibitors, angiotensin II receptor blockers, diuretics and metformin if the patient is unwell or vomiting
If GFR is falling below 30 mL/min, educate the patient about CKD and proceed to arteriovenous fistula formation and begin searching for a transplant donor for the patient	Discuss a palliative care pathway with the patient if they are unsuitable or unwilling to start renal replacement therapy

ABBREVIATIONS: ACR = albumin–creatinine ratio; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; IV = intravenous.

WHEN TO REFER

If CKD remains stable, with a GFR above 30 mL/min and controlled blood pressure, weight, electrolyte levels and diabetes (if present), then there is little likely to be gained by referral. Many acute changes in serum creatinine either resolve after an acute illness, or represent readjustment to better blood pressure or blood sugar control. In the author's personal experience, there are only three interventions a nephrologist can perform that an interested GP cannot: initiating erythropoietin treatment, starting dialysis, and arranging a kidney transplant. All else is good general medicine in a high-risk patient (Table 3).

Referral to, or at least a telephone discussion with, a specialist should be considered if the patient's GFR is less than 30 mL/min, or at any stage if GFR falls rapidly (a fall of greater than 15 mL/min in less than three months). Clinical clues to glomerulonephritis include proteinuria of greater than 1 g/day (spot urine protein–creatinine ratio or ACR of about 100 mg/mmol) or unexplained haematuria with proteinuria present. Every referral should be accompanied by a full list of current and past pathology results, a medication list and renal ultrasound. MT

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FURTHER READING

A comprehensive booklet on CKD management in general practice is available from Kidney Health Australia with a free summary guide downloadable from the Kidney Health Australia website (www.kidney.org.au). The website also provides helpful patient information.

Kimberley Aboriginal Medical Services Council (www.kamsc.org.au) has useful CKD guidelines. They also provide simple pictorial explanations tailored for Aboriginal patients, which can be beneficial for patients with limited English or literacy.

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