

Chronic kidney disease

Key points

1. The prevalence of chronic kidney disease (CKD) increases with age and is greater in females and some ethnic populations.
2. CKD is classified according to severity from 1 to 5, where 5 is the most advanced and 1 the least.
3. CKD 1–3 is common and may not cause symptoms. It may progress to end-stage renal disease but frequently remains stable for many years.
4. CKD is an important risk factor for cardiovascular disease.
5. As CKD becomes more advanced (stages 4 and 5), virtually all body systems are adversely affected.
6. Clinical signs and symptoms of severe CKD include oedema, anaemia, hypertension, bone pain, nocturia, neurological changes and disordered muscle function.
7. The aims of treatment are to reverse or arrest the process responsible for CKD, relieve symptoms and reduce cardiovascular morbidity and mortality.
8. To prevent further renal damage, adequate control of blood pressure and reduction of proteinuria are essential.
9. Renal anaemia is common when the glomerular filtration rate (GFR) falls below 30 mL/min but can be corrected by erythropoietin in 90–95% of cases.
10. End-stage renal disease is the point at which life can only be sustained by dialysis or transplantation. This may occur soon after presentation or after several years.
11. The need for dialysis therapy is increasing at about 5% per annum with attendant resource implications.
12. There are two principal types of dialysis: haemodialysis and peritoneal dialysis. In both, waste products and metabolites are transferred from the patient's blood across a semipermeable membrane to a dialysis solution.
13. Renal transplantation remains the treatment of choice for end-stage renal disease. However, up to 60% of patients on dialysis programmes are not fit enough to be put on the transplant list.

Definition

Chronic kidney disease (CKD) is defined by a reduction in the glomerular filtration rate (GFR) and/or urinary abnormalities or structural abnormalities of the renal tract. The severity of CKD is classified from 1 to 5 depending upon the level of GFR ([Table 1](#)). It is a common condition affecting up to 10% of the population in Western societies.

Measurement of renal function

MDRD glomerular filtration rate equation

The four-variable equation (MDRD) incorporates age, creatinine, gender and ethnicity.

$$\text{eGFR (mL/min/1.73m}^2\text{)} = 186 \times [\text{serum creatinine } (\mu\text{mol/L})/88.4]^{-1.154} \times [\text{age}]^{-0.203} \times [0.742 \text{ if female}] \times [1.212 \text{ if African-American}]$$

Table 1. Stages of chronic kidney disease.

Stage	Description	eGFR (mL/min)	Potential complications of reduced GFR (in alphabetical order)
1	Kidney damage with normal or ↑ GFR	≥90	<ul style="list-style-type: none">• Anemia, including functional iron deficiency• Blood pressure increases• Calcium absorption decreases• Dyslipidemia /heart failure/volume overload• Hyperkalemia• Hyperparathyroidism• Hyperphosphatemia• Left ventricular hypertrophy• Metabolic acidosis• Malnutrition potential (late)
2	Kidney damage with mild ↓ GFR	60–89	
3	Moderate ↓ GFR	30–59	
4	Severe ↓ GFR	15–29	
5	Kidney failure	<15 or dialysis	

Source: Adapted from Identification, Evaluation and Management of Chronic Kidney Disease (www.health.gov.bc.ca/gpac/pdf/ckd.pdf)

Treatment

The aims of the treatment of CKD can be summarized as follows:

- Reverse or arrest the process causing the renal damage. (this may not be possible)
- Avoid conditions that might worsen renal failure (Box 18.1)
- Treat the secondary complications of CKD (renal anemia and bone disease)
- Relieve symptoms
- Implement regular dialysis treatment and/or transplantation at the most appropriate time.

Box 18.1 Factors that might exacerbate established chronic renal failure

Reduced renal blood flow
Hypotension
Hypertension
Nephrotoxins including drugs
Renal artery disease

Hypertension

Optimum control of blood pressure is one of the most important therapeutic measures since there is a vicious cycle of events whereby hypertension causes damage to the intrarenal vasculature resulting in thickening and hyalinisation of the walls of arterioles and small vessels. This damage effectively reduces renal perfusion, contributing to stimulation of the RAAS. Arteriolar vasoconstriction, sodium and water retention result, which in turn exacerbates the hypertension.

Antihypertensive therapy with certain agents might produce a transient reduction in GFR over the first 3 months of treatment as the systemic and glomerular blood pressure drop; this is mainly seen with ACE inhibitors/angiotensin receptor blockers (ARBs). However, it is possible to ultimately halt or slow the decline in many cases.

Calcium channel blockers

Place

For patients without proteinuria, calcium channel blockers (CCBs) are the agents of choice. They produce vasodilatation principally by reducing Ca^{2+} influx into vascular muscle cells. CCBs also appear to promote sodium excretion in hypertension associated with fluid overload.

Therapeutic options

Both verapamil and diltiazem (non-dihydropyridine CCBs) block conduction across the atrioventricular node and should not be used in conjunction with β -blockers. They are also negative cardiac inotropes. By contrast, dihydropyridines such as nifedipine and amlodipine produce less cardiac depression and differentially dilate afferent arterioles in the kidney. CCBs can produce headache, facial flushing and oedema. The latter can be confused with the symptoms of volume overload but is resistant to diuretics.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

Role in CKD

The role of ACE inhibitors in hypertensive patients with renal insufficiency is complicated, the current evidence base supports the principle that all diabetic patients with micro/macroalbuminuria and CKD should be treated with ACE inhibitors or ARBs regardless of blood pressure. There is also evidence that in non-diabetic patients with proteinuria, the use of these drugs can reduce proteinuria and thus reduce progression of CKD. ACE inhibitors reduce circulating angiotensin II and ARBs block binding to

the angiotensin II receptor, which results in vasodilatation and reduced sodium retention.

Contraindication

These agents can produce a reduction in GFR by preventing the angiotensin II mediated vasoconstriction of the efferent glomerular arteriole. This contributes to the high pressure gradient across the glomerulus, which is responsible for filtration and intra-glomerular hypertension. This problem may only be important in patients with renal vascular disease, particularly those with functionally significant renal artery stenoses where they should be avoided.

Short versus long

For long-term management, it is usually preferable to use an agent with a duration of action that permits once-daily dosing. It has been reported that ACE inhibitors may reduce thirst, which may be useful in those patients who have a tendency to fluid overload as a result of excessive drinking. ACE inhibitors are potassium sparing and therefore serum potassium should be monitored carefully. A low-potassium diet may be necessary.

ARB

ARBs have properties similar to ACE inhibitors with the advantage that, since they do not inhibit the breakdown of kinins such as bradykinin, they do not cause the dry cough associated with the ACE inhibitors.

Diuretics

Choice

Diuretics are of use in patients with salt and volume overload, which is usually indicated by the presence of oedema. This type of hypertension may be particularly difficult to treat. The choice of agent is generally limited to a **loop diuretic**. **Potassium sparing diuretics** are usually contraindicated owing to the risks of developing hyperkalaemia, and **thiazides** become ineffective as renal failure progresses. In combination with ACE inhibitors, spironolactone can significantly reduce proteinuria; however, the combination of these agents clearly raises the risk of significant hyperkalaemia and care must be taken. The combination should be avoided when the eGFR falls to <30 mL/min.

Dosing and monitoring

As loop diuretics need to be filtered to exert an action, progressively higher doses are required as CKD worsens. Doses of more than 250 mg/day of furosemide may be required in advanced renal failure. Patients who do not respond to oral loop diuretic therapy alone may benefit from concomitant administration of metolazone, which acts synergistically to produce a profound diuresis. Alternatively, the loop diuretic may be given intravenously. Care must be taken to avoid hypovolaemia (by monitoring body weight) and electrolyte disturbances such as hypokalaemia and hyponatraemia. Thiazide diuretics, with the notable exception of metolazone, are ineffective at a low GFR and may accumulate, causing an increased incidence of side effects.

B-Blockers

B-Blockers are commonly used in the treatment of hypertension in CKD. They exhibit a range of actions including a reduction of renin production. Consequently, β -blockers have a particular role in the rational therapy of hypertension without fluid overload.

Choice between Bblockers

However, β -blockers can reduce cardiac output, cause peripheral vasoconstriction and exacerbate peripheral vascular disease. It is advisable to use the more cardioselective B-blockers atenolol or metoprolol. Atenolol is excreted renally and consequently should require dosage adjustment in renal failure. In practice, however, atenolol is effective and tolerated well by renal patients at standard doses. However, metoprolol is theoretically a better choice since it is cleared by the liver and needs no dosage adjustment, although small initial doses are advised in renal failure since there may be increased sensitivity to its hypotensive effects.

Management of symptoms associated with CKD

1. Gastro-intestinal symptoms

Therapeutic options

- **Nausea and vomiting** may persist after starting a low protein diet. Metoclopramide is useful to treat this, but sometimes accumulation of the drug and its metabolites may occur, leading to extrapyramidal side effects. Patients should be started on a low dose, which should then be increased slowly. Prochlorperazine or cyclizine may also be useful. The 5-HT₃ antagonists such as ondansetron have also been shown to be effective. The anaemic patient often becomes less nauseated when treated with an erythropoiesis stimulating agent.
- **Constipation** is a common problem in patients with renal disease, partly as a result of fluid restriction and anorexia and partly as a consequence of drug therapy with agents such as phosphate binders. It is particularly important that patients managed with peritoneal dialysis do not become constipated, as this can reduce the efficacy of dialysis. Conventional laxative therapy may be used, such as bulk-forming laxatives or increased dietary fibre for **less severe constipation**.
- Alternatively, a stimulant such as senna with enemas or glycerine suppositories may be used for **severe constipation**. Higher doses of senna, typically 2–4 tablets at night, may be required. It should be noted that certain brands of laxatives that contain ispaghula husk may also contain significant quantities of potassium, and should be avoided in renal failure because of the risk of hyperkalaemia. Sterculia preparations are an effective alternative.

2. Pruritus

Cause

Itching associated with renal failure can be extremely severe, distressing and difficult to treat. It can also be disfiguring as a result of over-enthusiastic scratching. The exact

mechanism responsible for the itching is not clear and several possibilities have been suggested including: xerosis (dry skin), skin micro-precipitation of divalent ions, elevated PTH levels and increased dermal mast cell activity. Generally, however, no underlying cause is found and it is likely that a multifactorial process is responsible.

Management

Sometimes correction of serum phosphate or calcium levels improves the condition, as does parathyroidectomy. Conventionally, oral antihistamines are used to treat pruritus; however, topical versions should not be used owing to the risk of allergy. Non-sedating antihistamines such as loratidine are generally less effective than sedating antihistamines such as chlorphenamine or alimemazine which may be useful, particularly at night. Topical crotamiton lotion and creams may also be useful in some patients. Other non-drug therapies include either warming or cooling the skin using baths, three times weekly, UVB phototherapy and modified electrical acupuncture.

3. Anaemia

Type, options

The normochromic, normocytic anaemia of CKD does not respond to iron or folic acid unless there is a coexisting deficiency. Traditionally, the only treatment available was to give red blood cell transfusions, but this is time-consuming, expensive, an infection risk, may lead to fluid and iron overload and promotes antibody formation, which may give problems if transplantation is subsequently attempted. The introduction of ESAs, initially as recombinant human erythropoietins (epoetin alfa and beta) have transformed the management of renal anaemia.

Rare side effect

Epoetin alfa and beta were thought to be indistinguishable in practical terms, as well as being immunologically and biologically indistinguishable from physiological erythropoietin. However, it has now been recognized that epoetins can be associated with the production of antierythropoietin antibodies leading to a severe anaemia which is unresponsive to exogenous epoetin. This is known as **pure red cell aplasia (PRCA)** and is more commonly associated with epoetin alfa when given by the subcutaneous route.

Route of administration

The subcutaneous route is preferred as it provides equally effective clinical results while using similar or smaller doses (up to 30% less) when given three times a week. Most patients report a dramatically improved quality of life after starting epoetin therapy.

Long acting epoetin

Darbepoetin alfa is a novel erythropoiesis-stimulating protein (NESP) that is a recombinant hyperglycosylated analogue of epoetin which stimulates red blood cell production by the same mechanism as the endogenous hormone. The terminal half-life in man is three times longer than that of epoetin and consequently requires a once weekly or alternate weekly dosing schedule. Recently, a longer acting ESA has been introduced (methoxy polyethylene glycol-epoetin beta, pegzerepoetin alfa). This is a

continuous erythropoietin receptor activator (CERA), which can be used in a once monthly dosing schedule.

Iron and folate supplementation, monitoring

Iron and folate deficiencies must be corrected before therapy is initiated, while patients receiving epoetin generally require concurrent iron supplements because of increased marrow requirements. Supplemental iron is often given intravenously owing to bioavailability problems with oral forms. Maintaining iron stores ensures the effect of epoetin is optimized for minimum cost, as with insufficient iron stores a patient will not respond to treatment with epoetin. Epoetin therapy should aim to achieve a slow rise in the haemoglobin concentration to avoid cardiovascular side effects associated with a rapidly increasing red cell mass, such as hypertension, increased blood viscosity/volume, seizures and clotting of vascular accesses. Blood pressure should be closely monitored.

Dosing, target Hb level

An initial subcutaneous or intravenous epoetin dose of 50 units/kg body-weight three times weekly, increased as necessary in steps of 25 units/kg every 4 weeks, should be given to produce a haemoglobin increase of not more than 2 g/dL per month. The target haemoglobin concentration is commonly 10.5–12.5 g/dL with most aiming for a target around 11.5 g/dL. Once this has been reached, a maintenance dose of epoetin in the region of 33–100 units/kg three times a week or 50–150 units/kg twice weekly should maintain this level. There have been several studies of ESAs which have shown an increased risk of cardiovascular morbidity and overall mortality in people treated to a target >12.5 g/Dl

This has led to more conservative dosing strategies and prompt discontinuation or reduction of dose in patients with Hb >12.5 g/dL. Correcting anaemia usually helps control the symptoms of lethargy and myopathy, and often greatly reduces nausea. Improved appetite on epoetin therapy can, however, increase potassium intake, and may necessitate dietary control.

4. Acidosis

Since the kidney is the main route for excreting H⁺ ions, CKD may result in a metabolic acidosis. This will cause a reduction in serum bicarbonate that may be treated readily with oral doses of sodium bicarbonate of 1–6 g/day. As the dose of bicarbonate is not critical, it is easy to experiment with different dosage forms and strengths to suit individual patients. If acidosis is severe and persistent then dialysis may be required. Correction of acidosis may slow the decline in renal function.

5. Neurological problems

Neurological changes are generally caused by uraemic toxins and improve on the treatment of uraemia by dialysis or diet. Muscle cramps are common and are often treated with quinine sulphate. Restless legs may respond to low doses of clonazepam or co-careldopa.

6. Osteodystrophy

The osteodystrophy of renal failure is due to three factors: hyperphosphataemia, vitamin D deficiency and hyperparathyroidism.

7. Hyperphosphataemia

Difficulty in management of hyperphosphatemia

The management of hyperphosphataemia depends initially upon restricting dietary phosphate. This can be difficult to achieve effectively, even with the aid of a specialist dietician, because phosphate is found in many palatable foods such as dairy products, eggs, chocolate and nuts. Phosphate-binding agents can be used to reduce the absorption of orally ingested phosphate in the gut, by forming insoluble, non-absorbable complexes when taken a few minutes before or with meals.

Traditionally, phosphate-binders were usually salts of a di- or trivalent metallic ion, such as aluminium, calcium or occasionally magnesium.

- Calcium acetate is widely used as a phosphate binder. The capacity of calcium acetate and calcium carbonate to control serum phosphate appears similar. However, phosphate control is achieved using between half and a quarter of the dose of elemental calcium when calcium acetate is used.
- Calcium carbonate has been used as a phosphate binder. Unfortunately, it is less effective as a phosphate binder than aluminium, and sometimes requires doses of up to 10 g daily. Calcium carbonate has advantages, however, in that correction of concurrent hypocalcaemia can be achieved.
- Sevelamer, a hydrophilic but insoluble polymeric compound is used increasingly as a phosphate binder. Sevelamer binds phosphate with an efficacy similar to calcium acetate but with no risk of hypercalcaemia.
- Lanthanum, like sevelamer, is a non-calcium containing phosphate binder; there is therefore no resultant risk of hypercalcaemia but there are gastro-intestinal side effects and the drug is significantly more expensive than the alternatives
- Historically, aluminium hydroxide was widely used as a phosphate binder owing to the avid binding capacity of aluminium ions. However, a small amount of aluminium may be absorbed by patients with CKD owing to poor clearance of this ion, which can produce toxic effects including encephalopathy, osteomalacia, proximal myopathy and anaemia.

Side effects of aluminium hydroxide

Dialysis dementia was a disease observed among haemodialysis patients associated with aluminium deposition in the brain and exacerbated by aluminium in the water supply and the use of aluminium cooking pans. Desferrioxamine (4–6 g in 500 mL of saline 0.9% per week) has been used to treat this condition by removing aluminium from tissues by chelation. The tendency of aluminium to cause constipation is an added disadvantage. Therefore, aluminium as a phosphate binder in CKD should be used with caution.

8. Vitamin D deficiency and hyperparathyroidism

Treatment options

Vitamin D deficiency may be treated with the synthetic vitamin D analogues 1 α -hydroxycholecalciferol (**alfacalcidol**) at 0.25–1 μ g/day or 1,25-dihydroxycholecalciferol (**calcitriol**) at 1–2 μ g/day. The serum calcium level should be monitored, and the dose of alfacalcidol or calcitriol adjusted accordingly. Hyperphosphataemia should be controlled before starting vitamin D therapy since the resulting increase in the serum calcium concentration may result in soft tissue calcification. The rise in 1,25-dihydroxycholecalciferol and calcium levels that result from starting vitamin D therapy usually suppresses the production of PTH by the parathyroids. If vitamin D therapy does not correct PTH levels then **parathyroidectomy**, to remove part or most of the parathyroid glands, may be needed. This surgical procedure was once commonly performed on CKD patients, but is now less frequent owing to effective vitamin D supplementation.

Cinacalcet is a calcimimetic which increases the sensitivity of calcium sensing receptors to extracellular calcium ion, this results in reduced PTH production. The benefit of this treatment is the suppression of PTH without resultant hypercalcaemia. It is recommended for use as an alternative to parathyroidectomy for patients who are not fit enough to undergo this procedure.

Table 18.4 Common therapeutic problems in chronic renal failure with Problem Comment

1. **Drug choice:** Care with choice/dose of all drugs. Care to avoid renotoxic agents pre-dialysis to preserve function. Beware herbal therapies as some contain immune system boosters (reverse immunosuppressant effects) and some are nephrotoxic
2. Drug excretion: CKD will lead to accumulation of drugs and their active metabolites if they are normally excreted by the kidney
3. Dietary restrictions: Restrictions on patient often severe. Fluid allowance includes foods with high water content, for example, gravy, custard, and fruit
4. Hypertension: Frequently requires complex multiple drug regimens. CCBs can cause oedema that might be confused with fluid overload
5. Analgesia: Side-effects are increased. Initiate with low doses and gradually increase. Avoid pethidine as metabolites accumulate. Avoid NSAIDs unless specialist advice available
6. Anaemia: Epoetin requires sufficient iron stores to be effective. Absorption from oral iron supplements may be poor and i.v. iron supplementation might be required. Care required to make sure that epoetin use does not produce hypertension
7. Immunosuppression: Use of live vaccines should be avoided (BCG, MMR, mumps, oral polio, oral typhoid, smallpox, yellow fever)

8. Pruritis (itching): Can be severe. Treat with chlorphenamine; less sedating antihistamines often less effective. Some relief with topical agents, for example, crotamiton
9. Restless legs: Involuntary jerks can prevent sleep. Clonazepam 0.5–1 mg at night may help