BMJ Best Practice

Chronic kidney disease

The right clinical information, right where it's needed

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Summary

- Proteinuria or haematuria, and/or a reduction in the GFR for more than 3 months' duration.
- The most common causes are diabetes mellitus (DM) and hypertension (HTN).
- The majority of people are asymptomatic, and the diagnosis is determined only by laboratory studies.
- Glycaemic control for diabetic nephropathy and optimisation of BP are key in slowing the progression of disease.
- Increased risk for cardiovascular disease.

BASICS

Definition

Chronic kidney disease, also known as chronic renal failure, is defined by either a pathological abnormality of the kidney, such as haematuria and/or proteinuria, or a reduction in the GFR to <60 mL/minute/1.73 m^2 for ≥3 months' duration.[1] [2]

Epidemiology

This is a common condition that is often unrecognised until the most advanced stages. It is estimated that 10% of the adult population worldwide has chronic kidney disease.[5] [6] The incidence is rising and is thought to be due to an ageing population; a higher incidence of diseases such as DM and HTN, which are the most common causes in the adult population; and an increased incidence of glomerular disorders such as focal segmental glomerulosclerosis. Black people, Hispanic people, and those with a family member who has a diagnosis of kidney disease have a higher prevalence than the general population. Additionally, individuals with an episode of acute kidney injury are most likely to be at risk for chronic kidney injury and end-stage kidney disease in the future.

Aetiology

The most common cause in the adult population is DM, accounting for approximately 40% of patients on renal replacement therapy (i.e., dialysis, transplant). It is estimated that one third of patients with DM will develop nephropathy, as defined by macroalbuminuria (>300 mg albumin/24 hours) and/or a reduction in the GFR to <90 mL/minute/1.73 m^2, within 5 to 10 years after the diagnosis of diabetes.

HTN is the second most common cause, accounting for one third of patients on renal replacement therapy. Often people are given the diagnosis of hypertensive renal disease if no other identifiable aetiology is evident.

Less frequent causes include cystic disorders of the kidney (polycystic kidney disease), obstructive uropathy, glomerular nephrotic and nephritic syndromes such as focal segmental glomerulosclerosis, membranous nephropathy, lupus nephritis, amyloidosis, and rapidly progressive glomerulonephritis.[7]

Pathophysiology

The pathophysiology is complex. Regardless of the method of renal injury (i.e., DM, HTN, or glomerular disorders), once renal damage has occurred, a cascade of events ensues.[8] [9]

- In response to renal injury, there is thought to be an increase in intra-glomerular pressure with glomerular hypertrophy, as the kidney attempts to adapt to nephron loss to maintain constant glomerular filtration.
- An increase in glomerular permeability to macro-molecules such as transforming growth factor-beta (TGF-beta), fatty acids, pro-inflammatory markers of oxidant stress, and protein may result in toxicity to the mesangial matrix, causing mesangial cell expansion, inflammation, fibrosis, and glomerular scarring.
- Additionally, renal injury results in an increase in angiotensin II production, causing an upregulation of TGF-beta, contributing to collagen synthesis and renal scarring within the glomerulus.

- Both the structural alterations and accompanying biochemical, cellular, and molecular changes seem to account for progressive renal scarring and loss of kidney function.
- All forms of chronic kidney disease are also associated with tubulo-interstitial disease; the exact mechanism of injury is not known, but is thought to be secondary to a reduction in blood supply in addition to an infiltration of lymphocytes and inflammatory mediators that result in interstitial fibrosis and tubular atrophy.

Classification

Clinical classification[1] [3] [4]

- Acute kidney injury is defined by a rise in the serum creatinine of ≥23 micromol/L (≥0.3 mg/dL) from baseline, a 50% increase in serum creatinine from baseline, or a reduction in urine output of <0.5 mL/kg/hour for more than 6 hours that occurs over a period of days to weeks.
- Chronic kidney disease (CKD) is defined by evidence of kidney damage based on pathological diagnosis, abnormalities of radiographic imaging, or laboratory evidence of kidney damage such as haematuria and/or proteinuria or a reduction in the GFR to <60 mL/minute/1.73m^2 for ≥3 months.

  CKD is divided into 6 distinct stages based on GFR, as follows:[4]

  - Stage 1: kidney damage with normal or increased GFR, ≥90 mL/minute/1.73m^2
  - Stage 2: kidney damage with mild decrease in GFR, 60 to 89 mL/minute/1.73m^2
  - Stage 3a: kidney damage with moderate decrease in GFR, 45 to 59 mL/minute/1.73m^2
  - Stage 3b: kidney damage with moderate decrease in GFR, 30 to 44 mL/minute/1.73m^2
  - Stage 4: kidney damage with severe decrease in GFR, 15 to 29 mL/minute/1.73m^2
  - Stage 5: kidney failure (end-stage kidney disease), with GFR <15 mL/minute/1.73m^2

Primary prevention

The evidence for the prevention of CKD is lacking as compared with large scale randomised trials for cardiovascular disease. Most trials have focused on modifiable diseases and risk factors that have been associated with CKD, namely DM and HTN. Clinical evidence supports the recommendation for a goal HbA1c <7%, BP target of <140/90 mmHg, tobacco cessation, and ideal body weight with BMI <27 to prevent the development of CKD. Due to the lack of widespread screening guidelines with serum creatinine or urinary albumin, often patients are diagnosed after CKD has developed.[23]

Screening

There are no established screening guidelines for the general population for chronic kidney disease (CKD). However, based on expert opinion, there are recommendations to screen those considered high-risk and include all individuals with DM and HTN aged <50 years, and all of those aged >50 years, with an annual urinalysis and serum creatinine. Other high-risk populations, such as those with a family history of kidney disease, should also be considered in the screening programme.[28]

Patients with risk factors for CKD such as DM, HTN, or a family member with CKD should be evaluated annually with serum creatinine and mathematical formulation for estimation of the GFR in addition to urinalysis for haematuria and/or proteinuria.

In addition, underlying risk factors associated with disease states should be treated, including optimisation of glycaemic control in DM and achievement of the goal BP of <140/90 mmHg with ACE inhibitors or angiotensin receptor-blocking agents. Consideration can be given to a lower BP goal in those with proteinuria of >500 mg per 24 hours.[29] [30] Although data are limited in the CKD population as compared with the general population, tobacco cessation, weight loss, salt restriction, and optimal lipid management with statin therapy are indicated. Protein restriction should not be recommended until late stage 4 or 5 disease, as a management strategy to control uraemia in order to delay the initiation of dialysis. Severe protein restriction may result in malnourishment and poorer outcomes. Aspirin use has also been beneficial for cardioprotection in those with CKD, although there is a higher risk for minor bleeding than in the general population.

Secondary prevention

Underlying risk factors associated with disease states should be treated, including optimisation of glycaemic control in DM and achievement of the goal BP of <140/90 mmHg with ACE inhibitors or angiotensin receptor-blocking agents. Consideration can be given to a lower BP goal in those with proteinuria of >500 mg per 24 hours.[29] [30] [93] Although data are limited in the chronic kidney disease (CKD) population as compared with the general population, tobacco cessation, weight loss, salt restriction, and optimal lipid management with statin therapy are indicated. Protein restriction should not be recommended until late stage 4 or 5 disease, as a management strategy to control uraemia in order to delay the initiation of dialysis. Severe protein restriction may result in malnourishment and poorer outcomes. Aspirin use has also been beneficial for cardioprotection in those with CKD, although there is a higher risk for minor bleeding than in the general population.

There are no established screening guidelines for the general population for CKD. However, based on expert opinion, there are recommendations to screen those considered high-risk and include all individuals with DM and HTN age <50 years, and all of those age >50 years, with an annual urinalysis and serum creatinine. Other high-risk populations, such as those with a family history of kidney disease, should also be considered in the screening programme.[28]

Case history

Case history #1

A 54-year-old man with a 10-year history of DM and HTN, with complications of diabetic retinopathy and peripheral neuropathy, presents to his primary care physician with complaints of fatigue and weight gain of 4.5 kg over the past 3 months. He denies any changes in his diet or glycaemic control, but does state that he has some intermittent nausea and anorexia. He states that he has noticed that his legs are more swollen at the end of the day but improve with elevation and rest. Physical examination reveals an obese man with a sitting BP of 158/92 mmHg. The only pertinent physical examination findings are cotton wool patches and micro-aneurysms bilaterally on fundoscopic examination and pitting, bilateral lower-extremity oedema.

Other presentations

The disease presents insidiously over months with vague complaints of fatigue, mild reduction in appetite, and, at more advanced stages, nausea and anorexia. Oedema is a common presentation - as the GFR declines, there is an inability to effectively excrete salt and water to remain in metabolic balance with dietary intake. Additionally, proteinuria with a decrease in serum albumin may contribute to the development of peripheral oedema.

Step-by-step diagnostic approach

It is important to note that a significant proportion of people are asymptomatic, and the diagnosis relies on pathological evidence of kidney damage such as haematuria and/or proteinuria, or laboratory evidence of a reduction in the GFR with an elevated serum creatinine.

History

Signs and symptoms are often vague, including fatigue (which may be related to the anaemia associated with CKD), nausea, and possibly the development of oedema. As kidney failure progresses to the more advanced stages of uraemia, patients will often describe anorexia, especially to meat and high-protein foods, nausea, vomiting, pruritus, and overall not feeling well. If patients begin to have a lack of urine production, then there may be an increase in peripheral oedema and resultant pulmonary oedema with dyspnoea and orthopnoea. In the most advanced stages of uraemia, patients may present with seizures or coma.

Examination

Physical examination findings are often directed towards the discovery of end-organ damage associated with disease states such as DM or HTN, which cause chronic kidney disease (CKD). A fundoscopic eye examination is critical for the diagnosis of diabetic or hypertensive retinopathy as evidence of microvascular damage that has probably occurred in the kidney, resulting in CKD. In men, a rectal examination for prostatic enlargement or for the diagnosis of prostate nodules can be helpful in determining a diagnosis of obstructive uropathy. In glomerular nephrotic and nephritic syndromes, the signs and symptoms of CKD may present more acutely with accelerated HTN, peri-orbital and peripheral oedema, rashes, or arthritis on musculoskeletal examination for patients with autoimmune disorders. Patients may describe their urine as foamy if significant proteinuria is present, or tea- or cola-coloured in the setting of haematuria.

Initial investigations

Most people are unaware that they have CKD and are informed only after abnormalities are discovered by blood and/or urine tests. The first diagnostic tests to order are a serum creatinine and GFR, urine microalbumin, urinalysis

to assess for haematuria and proteinuria, and a renal ultrasound to evaluate for kidney size, mass lesions, urinary tract obstruction, and, with a duplex examination, renal arterial blood flow. A urine microalbumin would be indicated in patients with diabetes and CKD if there was no evidence of proteinuria on urine dipstick.

Proteinuria is both a diagnostic and a prognostic variable in the evaluation of patients with CKD.[24] Nephrotic syndrome is defined by a 24-hour urine collection >3.5 g proteinuria. In non-nephrotic syndromes, proteinuria of >1000 mg/day is associated with a more rapid progression to ESRD.

Additional investigations

A renal biopsy to determine a pathological diagnosis is indicated if a glomerular nephrotic or nephritic syndrome is suspected, or in people with diabetes with atypical presentations such as rapidly progressive kidney failure. Nephrotic syndrome may be suggested by proteinuria, and both nephritic and nephrotic syndromes may be suggested by severe presenting symptoms (accelerated HTN, periorbital and peripheral oedema) or with symptoms of underlying autoimmune diseases (rashes or arthritis). Certain infections, such as hepatitis B and C, syphilis, and streptococcal pharyngitis are associated with glomerular disorders. A renal biopsy is essential in these cases to determine the pathological lesion.

Imaging of the genitourinary tract may be helpful in the evaluation of a patient with CKD. Plain abdominal x-ray is a non-specific test that may aid in the detection of calcium-containing kidney stones. Other radiological tests, such as an abdominal CT, are reserved for evaluation of stone disease and further characterisation of renal cystic or mass lesions. MRI is reserved for renal mass lesions such as renal cell carcinoma.

Risk factors

Strong

diabetes mellitus

- This is the most common cause.
- It is estimated that approximately 30% of people with diabetes will have chronic kidney disease (CKD), as documented by proteinuria and/or a reduction in the GFR, within 5 to 10 years of diagnosis.
- Glycaemic control directly correlates with the development of diabetic nephropathy and the rapidity of progression to end-stage renal disease (ESRD).
- Hyperglycaemia results in formation of advanced glycosylated end products. This leads to mesangial oxidative stress, which results in matrix expansion and increased vascular permeability, which in turn attracts inflammatory mediators.[10] These promote collagen production, leading to glomerular sclerosis.[11]

hypertension

- This is the second most common cause and accounts for one third of patients undergoing renal replacement therapy.
- Uncontrolled HTN is thought to be one of the greatest risk factors for progression to ESRD in other types of chronic kidney disease, such as diabetic nephropathy, and glomerular nephrotic and nephritic syndromes.
- HTN is thought to affect both the vasculature and tubulo-interstitial components of the kidney, resulting in ischaemic damage from arterial narrowing. The end result is loss of nephron mass, and atrophy and fibrosis of the tubules and interstitium.

age >50 years

- The ageing process causes a decline in the GFR.[12] Typically the GFR declines by 1 mL/minute/1.73 m^2 per year after the age of 50 years.

Weak

smoking

- Smoking has been associated as a risk factor for the development and progression of the disease, probably because of accelerated atherosclerosis and vascular disease, as well as exacerbating underlying HTN.[13]

obesity

- Obesity is an associated risk factor.[14] It may contribute to the development of DM, exacerbate poor control of HTN, contribute to renal ischaemia and HTN with associated sleep apnoea, and cause glomerular strain with hypertrophy and glomerulosclerosis.

black or Hispanic ethnicity

- Black or Hispanic people are at higher risk than white people.[15] [16] The mechanism is not known, but is thought to be due in part to a higher incidence of diseases such as DM and HTN in these populations. Additionally, in black and Hispanic populations, genetic factors such as apolipoprotein L1 risk variants increase the risk for non-diabetic kidney disease.

FHx of chronic kidney disease

- People with a close family member with the disease are at a higher risk themselves of developing chronic kidney disease.[17] The mechanism is thought to be due in part to genetic susceptibility to certain disease states, such as DM, HTN, polycystic kidney disease, Alport's syndrome, and possibly glomerular syndromes, such as IgA nephropathy and focal segmental glomerulosclerosis.

autoimmune disorders

- Autoimmune disorders such as SLE, rheumatoid arthritis,[18] sarcoidosis, and Sjogren's syndrome may cause glomerular or tubulo-interstitial chronic kidney disease.

male sex

- Men are at a higher risk than women.[19]
- The mechanism of renal injury is not known but is thought to be related to differences in sex hormones that may interact with glomerular and mesangial cells, which have differential attraction of inflammatory mediators and cytokines, resulting in renal injury and scarring.[20]

long-term use of NSAIDs

- Long-term use of anti-inflammatory analgesics for rheumatological disorders and pain control have been associated with the development of chronic kidney disease.[21] [22] NSAIDs and previously phenacetin have been described as causing analgesic nephropathy.

History & examination factors

Key diagnostic factors

presence of risk factors (common)

- Risk factors include age >50 years, male sex, black or Hispanic ethnicity, family history, smoking, obesity, long-term analgesic use, diabetes, HTN, and autoimmune disorders.

fatigue (common)

- Anaemia is associated with chronic kidney disease due to the lack of erythropoietin produced by the kidney once the GFR declines to <50 mL/minute/1.73 m^2.

oedema (common)

- Periorbital and peripheral oedema develop as a result of salt and water retention as the GFR declines.

nausea with/without vomiting (common)

- Thought to be due to an accumulation of toxic waste products in the circulation, such as urea that is not excreted by the kidney. As kidney failure progresses to the more advanced stages of uraemia, patients may report vomiting.

pruritus (common)

- Thought to be due to an accumulation of toxic waste products in the circulation, such as urea that is not excreted by the kidney.

anorexia (common)

- Thought to be due to an accumulation of toxic waste products in the circulation, such as urea that is not excreted by the kidney.

infection-related glomerular disease (uncommon)

- Infections such as hepatitis B and C, syphilis, and streptococcal pharyngitis are associated with glomerular disorders.
- A kidney biopsy is essential in these cases to determine the pathological lesion.

Other diagnostic factors

arthralgia (common)

- If patient has concomitant autoimmune disorder.

enlarged prostate gland (common)

- Prostate examination in men should be performed to exclude obstructive uropathy.

foamy-appearing urine (uncommon)

- Indicative of proteinuria.

cola-coloured urine (uncommon)

- Indicative of haematuria.

rashes (uncommon)

- Ecchymosis and purpura are signs of haematological consequences of chronic kidney disease.
- Patient may have concomitant autoimmune disorder: for example, SLE and butterfly rash.

dyspnoea (uncommon)

- Associated with pulmonary oedema due to reduced urine output in worsening disease.

orthopnoea (uncommon)

- Associated with pulmonary oedema due to reduced urine output in worsening disease.

seizures (uncommon)

- Occurs in advanced-stage disease.
- Thought to be due to an increase in neurotoxins that are not excreted by the kidney.

retinopathy (uncommon)

- Fundoscopy is a key examination in determining presence of diabetic or hypertensive retinopathy, as evidence of microvascular damage, which occurs in uncontrolled diabetes/HTN. Diabetic and hypertensive patients should be screened for such changes.

Diagnostic tests

1st test to order

Test	Result
serum creatinine • Screening test to determine abnormality of the GFR. May be falsely low in conditions of low muscle mass, as in older or malnourished people, or patients with liver failure. • Normal creatinine in men is 70 to 120 micromol/L (0.8 to 1.4 mg/dL), and in women 50 to 97 micromol/L (0.6 to 1.1 mg/dL). However, there is significant variation due to calibration methods between laboratories, with a difference in creatinine measurements of up to 35 micromol/L (0.2 mg/dL).	**elevated: >97 micromol/L (>1.1mg/dL) in men; >105 micromol/L (>1.2 mg/dL) in women**
urinalysis • Screening test to determine for pathological markers of kidney damage excreted in the urine.	**haematuria and/or proteinuria**
urine microalbumin • Microalbuminuria is a risk factor for the development of progressive chronic kidney disease (CKD) and CAD associated with DM and HTN. Indicated in patients with diabetes and CKD if there was no evidence of proteinuria on urine dipstick.[25]	**microalbuminuria (30 to 300 mg/day)**
renal ultrasound • Helps to diagnose chronic kidney disease if kidney atrophy is present and diagnoses obstruction with hydronephrosis or bladder retention.	**small kidney size; presence of obstruction/hydronephrosis; kidney stones**
estimation of GFR • Determines more accurately, by mathematical equations such as Cockcroft-Gault, the Modification of Diet in Renal Disease Formula, or the chronic kidney disease (CKD) EPI equation, the GFR and the severity and stage of CKD.[26] • More accurate than serum creatinine alone. • Formulas have not been proved to be reliable estimators in patients with a GFR >59 mL/minute/1.73 m^2.[1] [2] [National Kidney Disease Education Program: GFR calculators]	**<60 mL/minute/1.73 m^2**

Other tests to consider

Test	Result
renal biopsy • Helps to determine pathological diagnosis of chronic kidney disease in glomerular nephrotic and nephritic syndromes, and in people with diabetes with atypical presentations such as rapidly progressive kidney failure. Also essential in determining whether pathological lesions are due to infection (e.g., hepatitis B and C, syphilis, and streptococcal pharyngitis). Provides insight into treatment options based on severity or chronicity of scarring of glomeruli and interstitium.	**variable depending on aetiology**
plain abdominal radiograph • Non-specific test that may aid in the detection of calcium-containing kidney stones, as medicine and urate stones are not apparent on plain radiography.	**may reveal calcium-containing kidney stones**
abdominal CT • Imaging test that is helpful to determine the presence or absence of kidney stones and confirms obstructive component. It is also helpful to further evaluate cystic lesions or mass lesions in the kidney. Intravenous contrast is contraindicated in high-risk patients, such as those with chronic kidney disease with a reduction in the estimated GFR <60 mL/minute, as it can cause acute kidney injury.	**may reveal kidney stones, renal masses, or cysts**
abdominal MRI • Imaging test that further characterises mass lesions in the kidney, such as renal cell carcinoma. • Gadolinium-based MRI examinations have been associated with nephrogenic systemic fibrosis in patients with kidney disease. It is recommended that no patients with an estimated GFR (eGFR) <30 mL/minute/1.73m^2 undergo gadolinium-based studies. If required, then institution of haemodialysis for gadolinium removal is indicated. The risk of nephrogenic systemic fibrosis is unclear in patients with an eGFR 30 to 60 mL/minute/1.73 m^2, and gadolinium-based studies should be avoided or used with caution until further study is performed in this population.[27]	**may reveal mass lesions in the kidney**

Differential diagnosis

Condition	Differentiating signs / symptoms	Differentiating tests
Diabetic nephropathy	• History of poorly controlled DM for 5 to 10 years. Often with co-existing diabetic retinopathy.	• HbA1c is typically >53 mmol/mol (>7%). • Diagnostic tests include urinalysis for microalbumin or protein and a serum creatinine for GFR assessment. • The quantification of proteinuria is variable over time and will decrease as the GFR declines. • Urine microalbumin is helpful to confirm the diagnosis of early diabetic nephropathy prior to the onset of macroalbuminuria. • Kidney ultrasound will typically show small, atrophic kidneys only in late stages of the disease, once substantial renal injury occurs.
Hypertensive nephrosclerosis	• History of poorly controlled HTN for years. More common in black people than white people.	• Diagnostic tests include urinalysis for microalbumin or protein and a serum creatinine for GFR assessment. • The urine sediment is described as bland without formed elements or haematuria. Quantification of proteinuria is <2 g/24 hours. • Kidney ultrasound typically reveals small, atrophic kidneys.
Ischaemic nephropathy	• History of long-standing essential HTN that is suddenly uncontrolled. More common in white people and older people. • Often will have a history of atherosclerotic disease such as CAD or PVD. There is also a history of tobacco abuse and hyperlipidaemia.	• The urine sediment is described as bland, without formed elements or haematuria. Quantification of proteinuria is <2 g/24 hours. • Kidney ultrasound reveals asymmetrical kidney size of ≥2.5 cm with unilateral disease, and duplex scan demonstrates an increase in the resistive index, suggesting obstruction. • Angiotensin-converting enzyme (ACE) inhibitor renogram, CT angiogram, magnetic resonance angiogram, or renal arteriogram (test of choice) demonstrates luminal narrowing of the renal artery.

Condition	Differentiating signs / symptoms	Differentiating tests
Obstructive uropathy	• More common in men and older people. Often due to prostatic enlargement or cancer. • Typical symptoms include urinary frequency, hesitancy, inability to empty the bladder completely, and decrease in urinary stream. • UTIs may develop. • Rectal examination may reveal prostatic enlargement or nodules.	• Kidney ultrasound is the diagnostic test of choice to document kidney obstruction. It would show hydronephrosis, and there may also be post-void residual volume in those cases when there is obstruction to bladder outflow.
Nephrotic syndrome	• Often associated with a more sudden onset of HTN, or acceleration of essential HTN and development of periorbital and peripheral oedema.	• Laboratory evidence may reveal hyperlipidaemia and an increase in serum creatinine, and urinalysis has proteinuria as defined at >3.5 g/24 hours. • A kidney biopsy is required to determine the pathological lesion for nephrotic syndrome. • Serological tests for secondary causes of nephrotic syndrome such as ANA in SLE, HIV in focal segmental glomerulosclerosis, and hepatitis B and C in membranous nephropathy, and serum protein electrophoresis for amyloidosis, are often helpful in confirming the diagnosis of the nephrotic syndrome.
Glomerulonephritis	• Often associated with a sudden onset of HTN or acceleration of essential HTN. • Patients with autoimmune disorders may have a skin rash or arthritis; post-infectious glomerulonephritis has a recent history of a pharyngeal or cutaneous infection; bloody diarrhoea is associated with haemolytic uraemic syndrome.	• Laboratory evidence reveals an increased serum creatinine, and urinalysis is significant for haematuria and proteinuria. • Urine sediment is evaluated for the presence of dysmorphic RBCs and RBC casts, which are diagnostic of glomerulonephritis. • Serological tests such as ANA, complement levels, hepatitis B and C antibodies, anti-neutrophil cytoplasmic antibody, anti-glomerular basement antibody, and anti-streptolysin O titre are often helpful in confirming the diagnosis of glomerulonephritis. • A kidney biopsy is required to confirm the pathological lesion of the glomerulonephritis.

Diagnostic criteria

Diagnostic classification[4]

- Stage 1: GFR >90 mL/minute/1.73 m^2, and evidence of kidney damage based on pathological diagnosis, abnormalities of radiographic imaging, or laboratory findings such as haematuria and/or proteinuria
- Stage 2: GFR of 60 to 89 mL/minute/1.73 m^2
- Stage 3a: GFR of 45 to 59 mL/minute/1.73m^2
- Stage 3b: GFR of 30 to 44 mL/minute/1.73m^2
- Stage 4: GFR of 15 to 29 mL/minute/1.73 m^2
- Stage 5: GFR <15 mL/minute/1.73 m^2

Clinical indicators of kidney damage[4]

- Microalbuminuria: 30 to 300 mg/g creatinine/day
- Proteinuria: >300 mg proteinuria/day
- Haematuria: >3 RBCs per high power field on more than 2 occasions

Step-by-step treatment approach

All aetiologies of chronic kidney disease (CKD) are progressive. The main goal of treatment is to slow the progressive loss of kidney function and prevent the need for renal replacement therapy or kidney transplantation. The most important factor in treatment is to identify patients early in the course of their disease and classify the stage of CKD (stages 1 to 5) so that risk factor modification can ensue and identification of comorbidities such as anaemia and secondary hyperparathyroidism may be treated.

CKD is divided into 6 distinct stages based on GFR, as follows:[4]

- Stage 1: GFR >90 mL/minute/1.73 m^2, and evidence of kidney damage based on pathological diagnosis, abnormalities of radiographic imaging, or laboratory findings such as haematuria and/or proteinuria
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Stages 1-4 first-line therapy

The major cause of death for patients with CKD is cardiovascular disease. Therefore, treatment of cardiovascular risk factors, such as optimising glycaemic control, optimising BP with an ACE inhibitor or an angiotensin-II receptor antagonist, introducing lipid-lowering agents (e.g., statins, ezetimibe),[31] [32] and reducing proteinuria is recommended.[33] [34]

HTN is one of the greatest risk factors for the progression of CKD, regardless of aetiology. Most patients with CKD will require at least two or three different types of antihypertensive agent to achieve the optimal BP control. The Joint National Committee (JNC) 8 redefined the target BP goal for patients with CKD as <140/90 mmHg, given the evidence from clinical trials that this is associated with the lowest risk of cardiovascular outcomes and mortality.[30] There may also be benefit in strict BP control prior to onset of end-stage renal disease (ESRD) and mortality; however, further investigation into the optimal BP target for these patients needs to be performed.[30] [35] [36] [37] [38] [39] [40] If a patient is noted to have proteinuria of >3 g/day, based on the findings from the Modification of Diet in Renal Disease (MDRD) study, there may be benefit in kidney outcomes if target BP is reduced to <130/80 mmHg.[41] However, this has not been validated in other BP trials in CKD. The combination of antihypertensive agents, except for those acting on the renin-angiotensin system (e.g., ACE inhibitors and angiotensin-II receptor antagonists), should be used to meet the target BP goal.

ACE inhibitors and angiotensin-II receptor antagonists have been shown in numerous clinical trials to slow the progression of CKD and delay the need for renal replacement therapy in both diabetic and non-diabetic CKD.[42] [43] [44] In a meta-analysis of patients with CKD, blockade of the renin angiotensin system with either ACE inhibitors or angiotensin-II receptor antagonists was associated with a reduction in the risk of myocardial infarction, congestive heart failure, and total cardiovascular outcomes when compared with treatment with either placebo or controlled arms with other antihypertensive agents, emphasising the importance of these agents as the first-line therapy in the treatment of CKD.[45]

Although previously thought that a complete blockade of the renin angiotensin system with combination therapy of ACE inhibitors and angiotensin-II receptor antagonists or direct renin inhibitors would delay progression in CKD, clinical trial results have failed to confirm any such benefit. In the ONTARGET trial, individuals were assigned to telmisartan, ramipril, or combination therapy, evaluating the effectiveness of dual therapy on cardiac and renal outcomes.[46] The study concluded that there was no difference in deaths from cardiovascular causes, in myocardial infarctions, cerebrovascular accidents, or hospitalisations for congestive heart failure, in the treatment groups. In addition, the rate of renal outcomes defined as the first time for dialysis, death, or doubling of the serum creatinine were greater in the combination arm as compared with the single-based therapy arms. Thus, there is currently no clinical evidence that supports the use of this combination in the CKD population, and such therapy should not be recommended due to the increased risk of hyperkalaemia and acute kidney injury. Although not recommended for CKD, combination therapy with ACE inhibitors and angiotensin-II receptor antagonists is sometimes used in patients with nephrotic syndromes and glomerulonephritis to reduce proteinuria.

Other classes of antihypertensive agents (e.g., thiazide diuretics, beta-blockers, etc.) can be combined with ACE inhibitors or angiotensin-II receptor antagonists if target BP is not achieved with these first-line agents. Until recently, aliskiren was recommended for use in combination with ACE inhibitors or angiotensin-II receptor antagonists; however, in December 2011, the manufacturer recommended that physicians should no longer prescribe aliskiren-containing products with these two classes of drugs based on the results, and subsequent early termination, of the ALTITUDE trial.[47] The trial assessed the effects of aliskiren in combination with ACE inhibitors or angiotensin-II receptor antagonists in people with type 2 diabetes at high risk for cardiovascular and renal events, and found an increased risk for non-fatal stroke, renal complications, hyperkalaemia, and hypotension in patients taking the drug for 18 to 24 months. In the US, the Food and Drug Administration (FDA) now recommends that the combination of aliskiren with ACE inhibitors or angiotensin-II receptor antagonists is contraindicated in patients with diabetes because of the risk of renal impairment, hypotension, and hyperkalaemia. The FDA also recommends that this combination of drugs be avoided in patients with moderate to severe renal impairment (i.e., GFR <60 mL/minute/1.73 m^2).

Dyslipidaemia is common in patients with CKD. Although specific treatment targets for cholesterol and LDL have been recommended for CKD patients, this 'treat to target' approach has not been well established in clinical trials. As such, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend that CKD patients not on dialysis should start treatment with a statin without the need for routine follow-up to check lipid values, or to change treatment regimen based on set targets (i.e., a 'treat and forget' approach).[31] For patients aged ≥50 years with CKD stage 3 or 4, ezetimibe can be combined with the statin simvastatin.[32] Statin therapy has been shown to have cardioprotective effects in patients with CKD.[48] [49] [50] [51] In those individuals not on dialysis therapy, the use of statins in a large meta-analysis resulted in the reduction of all-cause mortality by 21% (relative risk [RR] 0.79, 95% CI 0.69 to 0.91) and cardiovascular mortality by 23% (RR 0.77, 95% CI 0.69 to 0.87).[52] It was noted that there was no difference in adverse effects for statin users as compared with those in the placebo arms. Despite previous evidence that statins may be renoprotective via anti-inflammatory effects in the kidney, the use of statins in these trials did reduce proteinuria but overall did not improve kidney function. Unfortunately, the beneficial effect of statin use in CKD has not been shown in the dialysis population. In both single investigations and a recent meta-analysis, statin use in patients undergoing dialysis did not improve all-cause mortality or cardiovascular-related deaths.[53]

Stages 1-4 intolerant to first-line therapy

If a patient is unable to tolerate either an ACE inhibitor or angiotensin-II receptor antagonist due to adverse effects, then an alternative is warranted. Non-dihydropyridine calcium-channel blockers have been demonstrated to have more proteinuric-lowering effects than other antihypertensive agents. Clinical trials in both diabetic and non-diabetic CKD have demonstrated greater protein-lowering effects than other classes of antihypertensive agents.[54]

1[B]Evidence

Stage 2

The directed therapy is to continue to modify cardiovascular risk factors, but also estimate the rate of loss of kidney function to determine the eventual need for renal replacement therapy (i.e., dialysis, transplant).

Stage 3a/3b

Identification of comorbidities such as anaemia and secondary hyperparathyroidism is recommended and treatment begun if required.

Treatment of anaemia with the use of erythropoietin-stimulating agents is recommended for patients with CKD after other causes of anaemia such as iron, vitamin B12, folate, or blood loss have been excluded. Patients with CKD frequently have iron deficiency, and iron replacement should be considered as a goal of treatment.

Erythropoietin stimulating therapy may be initiated if the Hb falls to <100 g/L (<10 g/dL) and the patient has symptoms and signs of anaemia. The target Hb for patients with CKD on erythropoietin therapy has changed in the last several years but clinical expert opinion suggests that a target of 100 to 110 g/L (10 to 11 g/dL) is appropriate, as normalisation of Hb has resulted in increased risk for death and cardiovascular disease in this population.[55] [56] In a recent investigation of the TREAT study of patients with diabetes with CKD and anaemia, treatment with the erythropoietin-stimulating agent darbepoietin failed to show a beneficial effect of active treatment on cardiovascular events, death, or end-stage renal disease (ESRD) as compared with those receiving placebo (individuals would receive a rescue dose of medication if the haemoglobin fell to <90g/L [<9 g/dL]). Interestingly, as in other studies of anaemia treatment in CKD, the TREAT investigators demonstrated that individuals in the active treatment arm had an increased risk of stroke (RR 1.92, 95% CI 1.38 to 2.68). In their opinion, the risks of treatment may outweigh the benefits, and discussion between the patient and physician should ensue prior to treatment initiation.[57] [58] [59] [60] All patients should have an assessment of iron stores if erythropoietin therapy is planned. The goal ferritin for those not on haemodialysis is >100 ng/ml, while for those on haemodialysis is <200 ng/ml. All patients should have a transferrin saturation >20%. Iron replacement can be given orally or parentally.

For secondary hyperparathyroidism, calcium, phosphorus, and intact PTH levels should be measured every 6 to 12 months. The calcium and phosphorus levels should be maintained in the normal range with dietary restriction and/or phosphate-binding medications. The optimal PTH level is currently not known. It is recommended to exclude concomitant 25-OH vitamin D deficiency and prescribe 25, dihydroxyvitamin D if <75 nanomol/L (<30 nanograms/mL). If the intact PTH is above the target range of 35 to 70 nanograms/L (35 to 70 picograms/mL), then active vitamin D3 therapy should be considered.[61] [62] [63] There is emerging evidence that the use of non-calcium-based binders has a survival advantage over calcium-based binders in patients with CKD.[64]

Stage 4

Patients need to be educated about renal replacement therapy such as haemodialysis, peritoneal dialysis, and kidney transplantation. Patients should be referred to surgery for dialysis access and/or evaluated for kidney transplantation, based on patient preference for renal replacement modality at this stage. All patients should undergo CKD education for modality choice. Patient preference, family support, underlying comorbid conditions, and proximity to a dialysis facility should be addressed when choosing a modality or consideration for palliative care. All patients who are proceeding with haemodialysis should be educated about vein preservation with limiting venopuncture and intravenous access in the access arm.[65] Kidney transplantation is indicated once the eGFR is <20 mL/minute and the patient has been evaluated and undergone the required testing process by a transplant team.

Treatment of anaemia and secondary hyperparathyroidism should be continued. In stage 4 the target for intact PTH therapy with active vitamin D3 changes to 70 to 110 nanograms/L (70 to 110 picograms/mL), and it is recommended to check calcium, phosphorus, and intact PTH every 3 months.[61] Additionally, for those patients who develop

metabolic acidosis, supplementation with oral sodium bicarbonate to a target serum bicarbonate level of >20 mEq/L has been shown to slow progression of CKD and improve nutritional parameters. Oral sodium bicarbonate is well tolerated in this group.[66]

Stage 5 and uraemia

Renal replacement therapy may be initiated once patients have stage 5 disease or signs of uraemia such as weight loss, lack of appetite, nausea, vomiting, acidosis, hyperkalaemia, or fluid overload.[1] [2] There is no other medical therapy to keep patients alive once they have reached the need for dialysis, other than kidney transplantation. Of note, patients aged over 80 years and those with significant comorbidities, such as advanced congestive heart failure, may do poorly with dialysis and frequently are not considered transplant candidates. For these patients, and for all patients approaching ESRD for that matter, the treating nephrologist should have a discussion with the patient regarding end of life care and palliative care as an additional option.[67]

For those who are considered transplant candidates, transplant confers a significant survival advantage over maintenance dialysis therapy, predominantly due to a decrease in the risk of cardiovascular death. All patients who are on dialysis therapy are potentially eligible for kidney transplantation. A transplant centre including a nephrologist and transplant surgeon will determine the final eligibility and status of the patient for kidney transplantation, after a complete medical history and evaluation.[68] [69]

Other measures

Although data are more limited in the CKD population than in the general population, tobacco cessation and weight loss are recommended. Protein restriction should not be recommended until late stage 4 or 5 disease as a management strategy to control uraemia in order to delay the initiation of dialysis. Severe protein restriction may result in malnourishment and poorer outcomes. Aspirin use has also been beneficial for cardioprotection in those with CKD, although there is a higher risk for minor bleeding than in the general population.

Treatment details overview

Consult your local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing. (see Disclaimer)

Acute (summary)		
Patient group	**Tx line**	**Treatment**
stages 1-2 without uraemia	**1st**	**angiotensin-converting enzyme (ACE) inhibitor or angiotensin-II receptor antagonist**
	plus	**statin**
	adjunct	**additional antihypertensive therapy**
	2nd	**non-dihydropyridine calcium-channel blocker**
	plus	**statin**
	adjunct	**additional antihypertensive therapy**
stages 3-4 without uraemia	**1st**	**angiotensin-converting enzyme (ACE) inhibitor or angiotensin-II receptor antagonist**
	plus	**statin ± ezetimibe**

Acute (summary)			
		adjunct	additional antihypertensive therapy
		adjunct	education about renal replacement therapy
		2nd	non-dihydropyridine calcium-channel blocker
		plus	statin ± ezetimibe
		adjunct	additional antihypertensive therapy
		adjunct	education about renal replacement therapy
	with anaemia	adjunct	erythropoietin-stimulating agent
		adjunct	iron
	with secondary hyperparathyroidism	plus	dietary modification ± phosphate-binding drug
		adjunct	ergocalciferol
		adjunct	active 1,25 vitamin D therapy
	with metabolic acidosis	adjunct	oral sodium bicarbonate
stage 5 or with uraemia		1st	dialysis
		2nd	kidney transplant

Treatment options

Acute

Patient group	Tx line	Treatment
stages 1-2 without uraemia	**1st**	**angiotensin-converting enzyme (ACE) inhibitor or angiotensin-II receptor antagonist**

» The Joint National Committee (JNC) 8 redefined the target BP goal for patients with CKD as <140/90 mmHg, given the evidence from clinical trials that this is associated with the lowest risk of cardiovascular outcomes and mortality.[30] If a patient is noted to have proteinuria of >3 g/day, based on the findings from the Modification of Diet in Renal Disease (MDRD) study, there may be benefit in kidney outcomes if target BP is reduced to <130/80 mmHg.[41] However, this has not been validated in other BP trials in CKD.

» Clinical trials in both diabetic and non-diabetic kidney disease have demonstrated that ACE inhibitors or angiotensin-II receptor antagonists are first-line agents for controlling BP and reducing proteinuria in this population.

» Evidence for the use of ACE inhibitors and angiotensin-II receptor antagonists in combination for CKD is controversial. Although current clinical evidence does not support the routine use of ACE inhibitors and angiotensin-II receptor antagonists in combination for the treatment of CKD,[46] it is sometimes given to patients with nephrotic syndromes and glomerulonephritis to reduce proteinuria.

» Both classes of drug may be associated with hyperkalaemia and acute renal failure, more commonly in older people, those with an estimated GFR <30 mL/minute/1.73 m^2, and with use of longer-acting agents. Hyperkalaemia and acute renal failure are reversible once medications have been discontinued.

» Doses should be low initially and adjusted gradually according to clinical response.

Primary options

» lisinopril: 2.5 to 5 mg orally once daily initially, adjust dose gradually according to response, maximum dose depends on level of impairment

OR

» ramipril: 1.25 mg orally once daily initially, adjust dose gradually according to response, maximum dose depends on level of impairment

OR

Acute

Patient group	Tx line	Treatment
		» enalapril: 2.5 mg orally once daily initially, adjust dose gradually according to response, maximum dose depends on level of impairment **OR** » perindopril: 2 mg orally once daily initially, adjust dose gradually according to response, maximum dose depends on level of impairment **OR** » trandolapril: 0.5 mg orally once daily initially, adjust dose gradually according to response, maximum dose depends on level of impairment **OR** » captopril: 12.5 to 25 mg orally two to three times daily initially, adjust dose gradually according to response, maximum dose depends on level of impairment **OR** » losartan: 50 mg orally once daily initially, adjust dose gradually according to response, maximum 100 mg/day **OR** » irbesartan: 75 mg orally once daily initially, adjust dose gradually according to response, maximum 300 mg/day **OR** » telmisartan: 20 mg orally once daily initially, adjust dose gradually according to response, maximum 80 mg/day **OR** » eprosartan: 300 mg orally once daily initially, adjust dose gradually according to response, maximum 600 mg/day
	plus	**statin** » Statin therapy has been shown to have cardioprotective effects in patients with chronic kidney disease (CKD).[48] [49] [50] [51] In those individuals not on dialysis therapy, the use of statins in a large meta-analysis resulted in the reduction of all-cause mortality by 21% (relative risk [RR] 0.79, 95% CI 0.69 to 0.91) and cardiovascular mortality by 23% (RR 0.77, 95% CI 0.69 to 0.87).[52]

Acute

Patient group	Tx line	Treatment
		» Total cholesterol and LDL treatment targets for patients with CKD have not been well established in clinical trials. As such, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend that CKD patients not on dialysis should be treated with a statin without the need for routine follow-up to check lipid values, or to change medication dose regimens based on set targets (i.e., a 'treat and forget' approach).[31] » Statin therapy has been associated with liver dysfunction and myopathy and should be monitored in patients with CKD. **Primary options** » simvastatin: 40 mg orally once daily **OR** » pravastatin: 40 mg orally once daily **OR** » rosuvastatin: 10 mg orally once daily **OR** » atorvastatin: 20 mg orally once daily
	adjunct	**additional antihypertensive therapy** » Other classes of antihypertensive agent (e.g., thiazide diuretics, beta-blockers, etc.) should be added when the target BP is not achieved with the use of an ACE inhibitor or angiotensin-II receptor antagonist. » Until recently, aliskiren was recommended for use in combination with ACE inhibitors or angiotensin-II receptor antagonists; however, in December 2011 the manufacturer recommended that physicians should no longer prescribe aliskiren-containing products with these two classes of drugs based on the results, and subsequent early termination, of the ALTITUDE trial.[47] The trial was testing the effect of aliskiren (in combination with ACE inhibitors or angiotensin-II receptor antagonists) in people with type 2 diabetes at high risk for cardiovascular and renal events, and found an increased risk for non-fatal stroke, renal complications, hyperkalaemia, and hypotension in patients taking the drug for 18 to 24 months. In the US, the Food and Drug Administration (FDA) now recommends that the combination of aliskiren with ACE inhibitors or angiotensin-II receptor antagonists is contraindicated in patients with diabetes because of the risk of renal impairment, hypotension, and hyperkalaemia. It also recommends that this

Acute

Patient group	Tx line	Treatment

combination of drugs be avoided in patients with moderate to severe renal impairment (i.e., GFR <60 mL/minute).

Primary options

» hydrochlorothiazide: 12.5 mg orally once daily initially, adjust dose gradually according to response, maximum 50 mg/day

OR

» atenolol: 25 mg orally once daily initially, adjust dose gradually according to response, maximum 25-50 mg/day

OR

» metoprolol: 25 mg orally (extended-release) once daily initially, adjust dose gradually according to response, maximum 100 mg/day

OR

» amlodipine: 5 mg orally once daily initially, adjust dose gradually according to response, maximum 10 mg/day

OR

» felodipine: 2.5 mg orally once daily initially, adjust dose gradually according to response, maximum 20 mg/day

OR

» spironolactone: 12.5 mg orally once daily initially, adjust dose gradually according to response, maximum 200 mg/day given in 2-4 divided doses

Secondary options

» hydralazine: 10 mg orally three to four times daily initially, adjust dose gradually according to response, maximum 300 mg/day

OR

» minoxidil: 5 mg orally once daily initially, adjust dose gradually according to response, maximum 40 mg/day

OR

» clonidine: 0.1 mg orally (immediate-release) twice daily initially, adjust dose gradually according to response, maximum 0.6 mg/day

Acute

Patient group	Tx line	Treatment
	2nd	**non-dihydropyridine calcium-channel blocker** » ACE inhibitors and angiotensin-II receptor antagonists are the superior treatment for patients with chronic kidney disease. » If these medicines need to be discontinued due to adverse effects such as cough, angio-oedema, haemodynamic decline in renal function, and/or hyperkalaemia, then non-dihydropyridine calcium-channel blockers have been demonstrated to have more proteinuric-lowering effects than other antihypertensive agents.1[B]Evidence **Primary options** » diltiazem: 120 mg orally (extended-release) once daily initially, adjust dose gradually according to response, maximum 360 mg/day **OR** » verapamil: 120 mg orally (extended-release) once daily initially, adjust dose gradually according to response, maximum 360 mg/day
	plus	**statin** » Statin therapy has been shown to have cardioprotective effects in patients with chronic kidney disease (CKD).[48] [49] [50] [51] In those individuals not on dialysis therapy, the use of statins in a large meta-analysis resulted in the reduction of all-cause mortality by 21% (relative risk [RR] 0.79, 95% CI 0.69 to 0.91) and cardiovascular mortality by 23% (RR 0.77, 95% CI 0.69 to 0.87).[52] » Total cholesterol and LDL treatment targets for patients with CKD have not been well established in clinical trials. As such, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend that CKD patients not on dialysis should be treated with a statin without the need for routine follow-up to check lipid values, or to change medication dose regimens based on set targets (i.e., a 'treat and forget' approach).[31] » Statin therapy has been associated with liver dysfunction and myopathy and should be monitored in patients with CKD. **Primary options** » simvastatin: 40 mg orally once daily **OR**

Acute

Patient group	Tx line	Treatment
		» pravastatin: 40 mg orally once daily
		OR
		» rosuvastatin: 10 mg orally once daily
		OR
		» atorvastatin: 20 mg orally once daily
	adjunct	**additional antihypertensive therapy**
		» Other classes of antihypertensive agent (e.g., thiazide diuretics, beta-blockers, etc.) should be added when the target BP is not achieved with the use of a non-dihydropyridine calcium-channel blocker.
		Primary options
		» hydrochlorothiazide: 12.5 mg orally once daily initially, adjust dose gradually according to response, maximum 50 mg/day
		OR
		» atenolol: 25 mg orally once daily initially, adjust dose gradually according to response, maximum 25-50 mg/day
		OR
		» metoprolol: 25 mg orally (extended-release) once daily initially, adjust dose gradually according to response, maximum 100 mg/day
		OR
		» amlodipine: 5 mg orally once daily initially, adjust dose gradually according to response, maximum 10 mg/day
		OR
		» felodipine: 2.5 mg orally once daily initially, adjust dose gradually according to response, maximum 20 mg/day
		OR
		» spironolactone: 12.5 mg orally once daily initially, adjust dose gradually according to response, maximum 200 mg/day given in 2-4 divided doses
		OR
		» aliskiren: 150 mg orally once daily initially, adjust dose gradually according to response, maximum 300 mg/day

Acute

Patient group	Tx line	Treatment
		Secondary options » hydralazine: 10 mg orally three to four times daily initially, adjust dose gradually according to response, maximum 300 mg/day **OR** » minoxidil: 5 mg orally once daily initially, adjust dose gradually according to response, maximum 40 mg/day **OR** » clonidine: 0.1 mg orally (immediate-release) twice daily initially, adjust dose gradually according to response, maximum 0.6 mg/day
stages 3-4 without uraemia	**1st**	**angiotensin-converting enzyme (ACE) inhibitor or angiotensin-II receptor antagonist** » The Joint National Committee (JNC) 8 redefined the target BP goal for patients with CKD as <140/90 mmHg, given the evidence from clinical trials that this is associated with the lowest risk of cardiovascular outcomes and mortality.[30] If a patient is noted to have proteinuria of >3 g/day, based on the findings from the Modification of Diet in Renal Disease (MDRD) study, there may be benefit in kidney outcomes if target BP is reduced to <130/80 mmHg.[41] However, this has not been validated in other BP trials in CKD. » Clinical trials in both diabetic and non-diabetic kidney disease have demonstrated that ACE inhibitors or angiotensin-II receptor antagonists are first-line agents for controlling BP and reducing proteinuria in this population. » Evidence for the use of ACE inhibitors and angiotensin-II receptor antagonists in combination for CKD is controversial. Although current clinical evidence does not support the routine use of ACE inhibitors and angiotensin-II receptor antagonists in combination for the treatment of CKD,[46] it is sometimes given to patients with nephrotic syndromes and glomerulonephritis to reduce proteinuria. » Both classes of drug may be associated with hyperkalaemia and acute renal failure, more commonly in older people, those with an estimated GFR <30 mL/minute/1.73 m^2, and with use of longer-acting agents. Hyperkalaemia and acute renal failure are reversible once medications have been discontinued.

Acute

Patient group	Tx line	Treatment

Primary options

» lisinopril: 2.5 to 5 mg orally once daily initially, adjust dose gradually according to response, maximum dose depends on level of impairment

OR

» ramipril: 1.25 mg orally once daily initially, adjust dose gradually according to response, maximum dose depends on level of impairment

OR

» enalapril: 2.5 mg orally once daily initially, adjust dose gradually according to response, maximum dose depends on level of impairment

OR

» perindopril: 2 mg orally once daily initially, adjust dose gradually according to response, maximum dose depends on level of impairment

OR

» trandolapril: 0.5 mg orally once daily initially, adjust dose gradually according to response, maximum dose depends on level of impairment

OR

» captopril: 12.5 to 25 mg orally two to three times daily initially, adjust dose gradually according to response, maximum dose depends on level of impairment

OR

» losartan: 50 mg orally once daily initially, adjust dose gradually according to response, maximum 100 mg/day

OR

» irbesartan: 75 mg orally once daily initially, adjust dose gradually according to response, maximum 300 mg/day

OR

» telmisartan: 20 mg orally once daily initially, adjust dose gradually according to response, maximum 80 mg/day

OR

Acute

Patient group	Tx line	Treatment
		» eprosartan: 300 mg orally once daily initially, adjust dose gradually according to response, maximum 600 mg/day
	plus	**statin ± ezetimibe**
		» Statin therapy has been shown to have cardioprotective effects in patients with chronic kidney disease (CKD).[48] [49] [50] [51] In those individuals not on dialysis therapy, the use of statins in a large meta-analysis resulted in the reduction of all-cause mortality by 21% (relative risk [RR] 0.79, 95% CI 0.69 to 0.91) and cardiovascular mortality by 23% (RR 0.77, 95% CI 0.69 to 0.87).[52]
		» Total cholesterol and LDL treatment targets for patients with CKD have not been well established in clinical trials. As such, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend that stage 3 or 4 CKD patients not on dialysis should be treated with a statin without the need for routine follow-up to check lipid values, or to change medication dose regimens based on set targets (i.e., a 'treat and forget' approach).[31] For patients aged ≥50 years with CKD stage 3 or 4, ezetimibe can be added to simvastatin.[32]
		» Statin therapy has been associated with liver dysfunction and myopathy and should be monitored in patients with CKD.
		Primary options
		» simvastatin: 40 mg orally once daily
		OR
		» pravastatin: 40 mg orally once daily
		OR
		» rosuvastatin: 10 mg orally once daily
		OR
		» atorvastatin: 20 mg orally once daily
		OR
		» ezetimibe/simvastatin: 10 mg (ezetimibe)/20 mg (simvastatin) orally once daily
	adjunct	**additional antihypertensive therapy**
		» Other classes of antihypertensive agent (e.g., thiazide diuretics, beta-blockers, etc.) should be added when the target BP is not achieved with the use of an ACE inhibitor or angiotensin-II receptor antagonist.

Acute

Patient group

Tx line

Treatment

» Until recently, aliskiren was recommended for use in combination with ACE inhibitors or angiotensin-II receptor antagonists; however, in December 2011 the manufacturer recommended that physicians should no longer prescribe aliskiren-containing products with these two classes of drugs based on the results, and subsequent early termination, of the ALTITUDE trial.[47] The trial was testing the effect of aliskiren (in combination with ACE inhibitors or angiotensin-II receptor antagonists) in people with type 2 diabetes at high risk for cardiovascular and renal events, and found an increased risk for non-fatal stroke, renal complications, hyperkalaemia, and hypotension in patients taking the drug for 18 to 24 months. In the US, the Food and Drug Administration (FDA) now recommends that the combination of aliskiren with ACE inhibitors or angiotensin-II receptor antagonists is contraindicated in patients with diabetes because of the risk of renal impairment, hypotension, and hyperkalaemia. It also recommends that this combination of drugs be avoided in patients with moderate to severe renal impairment (i.e., GFR <60 mL/minute).

Primary options

» hydrochlorothiazide: 12.5 mg orally once daily initially, adjust dose gradually according to response, maximum 50 mg/day

OR

» atenolol: 25 mg orally once daily initially, adjust dose gradually according to response, maximum 25-50 mg/day

OR

» metoprolol: 25 mg orally (extended-release) once daily initially, adjust dose gradually according to response, maximum 100 mg/day

OR

» amlodipine: 5 mg orally once daily initially, adjust dose gradually according to response, maximum 10 mg/day

OR

» felodipine: 2.5 mg orally once daily initially, adjust dose gradually according to response, maximum 20 mg/day

OR

Acute

Patient group	Tx line	Treatment
		» spironolactone: 12.5 mg orally once daily initially, adjust dose gradually according to response, maximum 200 mg/day given in 2-4 divided doses
		Secondary options
		» hydralazine: 10 mg orally three to four times daily initially, adjust dose gradually according to response, maximum 300 mg/day
		OR
		» minoxidil: 5 mg orally once daily initially, adjust dose gradually according to response, maximum 40 mg/day
		OR
		» clonidine: 0.1 mg orally (immediate-release) twice daily initially, adjust dose gradually according to response, maximum 0.6 mg/day
	adjunct	**education about renal replacement therapy**
		» Patients need to be educated about renal replacement therapy such as haemodialysis, peritoneal dialysis, and kidney transplantation. Patient preference, family support, underlying comorbid conditions, and proximity to a dialysis facility should be addressed when choosing a modality or consideration for palliative care. All patients should undergo chronic kidney disease education for modality choice.
		» Patients should be referred to surgery for dialysis access and/or evaluated for kidney transplantation, based on patient preference for renal replacement modality at stage 4.
		» All patients who are proceeding with haemodialysis should be educated about vein preservation with limiting venopuncture and intravenous access in the access arm.[65]
		» Kidney transplantation is indicated once the eGFR is <20 mL/minute and the patient has been evaluated and undergone the required testing process by a transplant team.
	2nd	**non-dihydropyridine calcium-channel blocker**
		» ACE inhibitors and angiotensin-II receptor antagonists are the superior treatment for patients with chronic kidney disease.
		» If these medicines need to be discontinued due to adverse effects such as cough, angio-oedema, haemodynamic decline in renal function, and/or

Acute

Patient group	Tx line	Treatment
		hyperkalaemia, then non-dihydropyridine calcium-channel blockers have been demonstrated to have more proteinuric-lowering effects than other antihypertensive agents.1[B]Evidence
		Primary options
		» diltiazem: 120 mg orally (extended-release) once daily initially, adjust dose gradually according to response, maximum 360 mg/day
		OR
		» verapamil: 120 mg orally (extended-release) once daily initially, adjust dose gradually according to response, maximum 360 mg/day
	plus	**statin ± ezetimibe**
		» Statin therapy has been shown to have cardioprotective effects in patients with chronic kidney disease (CKD).[48] [49] [50] [51] In those individuals not on dialysis therapy, the use of statins in a large meta-analysis resulted in the reduction of all-cause mortality by 21% (relative risk [RR] 0.79, 95% CI 0.69 to 0.91) and cardiovascular mortality by 23% (RR 0.77, 95% CI 0.69 to 0.87).[52]
		» Total cholesterol and LDL treatment targets for patients with CKD have not been well established in clinical trials. As such, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend that stage 3 or 4 CKD patients not on dialysis should be treated with a statin without the need for routine follow-up to check lipid values, or to change medication dose regimens based on set targets (i.e., a 'treat and forget' approach).[31] For patients aged ≥50 years with CKD stage 3 or 4, ezetimibe can be added to simvastatin.[32]
		» Statin therapy has been associated with liver dysfunction and myopathy and should be monitored in patients with CKD.
		Primary options
		» simvastatin: 40 mg orally once daily
		OR
		» pravastatin: 40 mg orally once daily
		OR
		» rosuvastatin: 10 mg orally once daily
		OR

TREATMENT

Acute

Patient group	Tx line	Treatment
		» atorvastatin: 20 mg orally once daily
		OR
		» ezetimibe/simvastatin: 10 mg (ezetimibe)/20 mg (simvastatin) orally once daily
	adjunct	**additional antihypertensive therapy**
		» Other classes of antihypertensive agent (e.g., thiazide diuretics, beta-blockers, etc.) should be added when the target BP is not achieved with the use of a non-dihydropyridine calcium-channel blocker.
		Primary options
		» hydrochlorothiazide: 12.5 mg orally once daily initially, adjust dose gradually according to response, maximum 50 mg/day
		OR
		» atenolol: 25 mg orally once daily initially, adjust dose gradually according to response, maximum 25-50 mg/day
		OR
		» metoprolol: 25 mg orally (extended-release) once daily initially, adjust dose gradually according to response, maximum 100 mg/day
		OR
		» amlodipine: 5 mg orally once daily initially, adjust dose gradually according to response, maximum 10 mg/day
		OR
		» felodipine: 2.5 mg orally once daily initially, adjust dose gradually according to response, maximum 20 mg/day
		OR
		» spironolactone: 12.5 mg orally once daily initially, adjust dose gradually according to response, maximum 200 mg/day given in 2-4 divided doses
		OR
		» aliskiren: 150 mg orally once daily initially, adjust dose gradually according to response, maximum 300 mg/day
		Secondary options

Acute

Patient group	Tx line	Treatment
		» hydralazine: 10 mg orally three to four times daily initially, adjust dose gradually according to response, maximum 300 mg/day **OR** » minoxidil: 5 mg orally once daily initially, adjust dose gradually according to response, maximum 40 mg/day **OR** » clonidine: 0.1 mg orally (immediate-release) twice daily initially, adjust dose gradually according to response, maximum 0.6 mg/day
	adjunct	**education about renal replacement therapy** » Patients need to be educated about renal replacement therapy such as haemodialysis, peritoneal dialysis, and kidney transplantation. Patient preference, family support, underlying comorbid conditions, and proximity to a dialysis facility should be addressed when choosing a modality or consideration for palliative care. All patients should undergo chronic kidney disease education for modality choice. » Patients should be referred to surgery for dialysis access and/or evaluated for kidney transplantation, based on patient preference for renal replacement modality at stage 4. » All patients who are proceeding with haemodialysis should be educated about vein preservation with limiting venopuncture and intravenous access in the access arm.[65] » Kidney transplantation is indicated once the eGFR is <20 mL/minute and the patient has been evaluated and undergone the required testing process by a transplant team.
with anaemia	adjunct	**erythropoietin-stimulating agent** » When stage 3a/3b has been reached, identification of comorbidities such as anaemia is recommended and treatment begun if required. Treatment of anaemia with the use of erythropoietin-stimulating agents is recommended for patients with chronic kidney disease (CKD) after other causes of anaemia such as iron, vitamin B12, folate, or blood loss have been excluded. Due to the possibility of an increased risk of stroke in those on erythropoietin-stimulating agents, discussion between the patient and physician should ensue prior to treatment initiation.[57] [58] [59] [60]

Acute

Patient group	Tx line	Treatment
		» Erythropoietin-stimulating agents are initiated once the Hb falls to <10 g/dL and the patient has signs and symptoms of anaemia. » The target Hb for patients with chronic kidney disease on erythropoietin therapy is 10 to 11 g/dL, as normalisation of Hb has resulted in increased risk for death and cardiovascular disease in this population.[55] [56] » Peginesatide was withdrawn from the market in early 2013 due to postmarketing reports of serious and fatal hypersensitivity reactions. Therefore, it is no longer recommended. **Primary options** » epoetin alfa: consult specialist for guidance on dose **OR** » darbepoetin alfa: consult specialist for guidance on dose
	adjunct	**iron** » All patients should have an assessment of iron stores if erythropoietin therapy is planned. The goal ferritin for those not on haemodialysis is >100 ng/ml, while for those on haemodialysis is <200 ng/ml. All patients should have a transferrin saturation >20%. Iron replacement can be given orally or parentally.[71] **Primary options** » ferrous sulfate: 60 mg orally once to three times daily Dose refers to elemental iron. **OR** » ferrous gluconate: 60 mg orally once to three times daily Dose refers to elemental iron. **Secondary options** » sodium ferric gluconate complex: consult specialist for guidance on dose **OR** » iron sucrose: consult specialist for guidance on dose

Acute

Patient group	Tx line	Treatment
		OR » ferumoxytol: consult specialist for guidance on dose **OR** » ferric carboxymaltose: consult specialist for guidance on dose
with secondary hyperparathyroidism	**plus**	**dietary modification ± phosphate-binding drug** » When stage 3a/3b has been reached, identification of comorbidities such as secondary hyperparathyroidism is recommended and treatment begun if required. The calcium and phosphorus levels should be maintained in the normal range with dietary restriction and/or phosphate-binding medications. » Calcium, phosphorus, and PTH testing should be performed every 6 to 12 months for patients with stage 3a/3b CKD and secondary hyperparathyroidism, and every 3 months for patients with stage 4 or 5 CKD and secondary hyperparathyroidism. » There is limited evidence that dietary restriction in calcium and phosphorous affects renal osteodystrophy.[70] There is emerging evidence that the use of non-calcium-based binders has a survival advantage over calcium-based binders in patients with chronic kidney disease.[64] **Primary options** » sevelamer: 800-1600 mg orally three times daily, titrate according to serum phosphate level **OR** » calcium acetate: 1334 mg orally with each meal, titrate according to serum phosphate level **OR** » calcium carbonate: 1-2 g/day orally given in 3-4 divided doses **OR** » lanthanum: 500-1000 mg orally three times daily, titrate according to serum phosphate level **OR** » sucroferric oxyhydroxide: 500 mg orally three times daily initially, titrate according to serum phosphate level, maximum 3000 mg/day **OR**

TREATMENT

Acute

Patient group	Tx line	Treatment
		» colestilan: 2-3 g orally three times daily initially, titrate according to serum phosphate level, maximum 15 g/day
	adjunct	**ergocalciferol**
		» When stage 3 has been reached, identification of comorbidities such as secondary hyperparathyroidism is recommended and treatment begun if required. It is recommended to exclude concomitant 25-OH vitamin D deficiency and prescribe 25, dihydroxyvitamin D if <30 nanograms/dL.
		Primary options
		» ergocalciferol: dose depends on serum 25-OH vitamin D level; consult specialist for guidance on dose
	adjunct	**active 1,25 vitamin D therapy**
		» In stage 3a/3b, if the intact PTH is above the target range of 35 to 70 picograms/mL, then active vitamin D3 therapy should be considered.[63]
		» In stage 4, the target for intact PTH therapy with active vitamin D3 changes to 70 to 110 picograms/mL. The optimal PTH level is currently not known.
		Primary options
		» calcitriol: consult specialist for guidance on dose
		OR
		» paricalcitol: consult specialist for guidance on dose
		OR
		» doxercalciferol: consult specialist for guidance on dose
with metabolic acidosis	adjunct	**oral sodium bicarbonate**
		» For patients who develop metabolic acidosis, supplementation with oral sodium bicarbonate to a target serum bicarbonate level of >20 mEq/L has been shown to slow progression of chronic kidney disease and improve nutritional parameters. Oral sodium bicarbonate is well tolerated in this group.[66]
		Primary options
		» sodium bicarbonate: consult specialist for guidance on dose

Acute

Patient group	Tx line	Treatment
stage 5 or with uraemia	**1st**	**dialysis**

» Renal replacement therapy is initiated once patients have stage 5 disease and/or signs of uraemia such as weight loss, lack of appetite, nausea, vomiting, acidosis, hyperkalaemia, or fluid overload.[1] [2]

» Renal replacement therapy in the form of dialysis is designed to remove toxic waste products from the blood, such as urea, and normalise potassium and serum bicarbonate levels, as well as to remove fluid that will accumulate once the kidneys have failed.

» Peritoneal dialysis is performed at home and is available to all patients. A peritoneal dialysis catheter is inserted into the abdomen and dialysis fluid is instilled in order to allow for toxic waste products and fluid to be removed and drained from the body on a daily basis.

» Continuous cycling peritoneal dialysis is done with a machine at night on a daily basis.

» Continuous ambulatory peritoneal dialysis is done on a daily basis. Patients manually exchange the peritoneal fluid.

» Haemodialysis is prescribed 3 times a week for approximately 4 hours each session. The patient's blood is removed from the body through an arteriovenous fistula, an arteriovenous graft, or a dialysis catheter, and then returned after transversing a dialysis membrane and dialysis solution. Other dialysis options include short daily dialysis and nocturnal dialysis, which are available at some dialysis centres.

Primary options

» haemodialysis

OR

» continuous cycling peritoneal dialysis

OR

» continuous ambulatory peritoneal dialysis

2nd **kidney transplant**

» Kidney transplant confers a significant survival advantage over maintenance dialysis therapy, predominantly due to a decrease in the risk of cardiovascular death. All patients who are on dialysis therapy are potentially eligible for kidney transplantation. A transplant centre including a nephrologist and transplant surgeon will determine the final eligibility and status of the patient for kidney

Acute

Patient group	Tx line	Treatment
		transplantation, after a complete medical history and evaluation. Kidneys may be transplanted from deceased or living donors.

FOLLOW UP

Recommendations

Monitoring

Patients with risk factors for chronic kidney disease (CKD), such as DM, HTN, or a family member with CKD, should be evaluated annually with serum creatinine and mathematical formulation for estimation of the GFR in addition to urinalysis for haematuria and/or proteinuria.

For those with established CKD, the rate of progression of CKD should be serially assessed starting in stage 3a/3b disease. Patients should be screened for anaemia and bone mineral disorders at least every 6 to 12 months, with a haemoglobin, calcium, phosphorus, and intact PTH. For those in stage 4 disease, haemoglobin, calcium, phosphorus should be monitored every 3 to 6 months and intact PTH every 6 to 12 months. For patients in stage 5 CKD, anaemia should be evaluated with a monthly haemoglobin, and bone mineral disease with a calcium and phosphorus every 1 to 3 months and an intact PTH every 3 to 6 months. Lipids should be checked annually for all patients with CKD.

Patient instructions

Patients with CKD need to take an active role in managing their disease and monitoring their progression to more advanced stages such as 4 to 5. Dietary therapy such as restriction of potassium, phosphorus and salt, protein, and fluids is typically advocated for stages 3 to 5. Lifestyle changes that would include medical compliance, optimisation of glycaemic control, and BP control are the leading factors that delay progression of CKD and the need for renal replacement therapy. As patients enter stage 4 CKD, it is recommended that they attend educational classes at a CKD clinic where different dialysis modalities such as haemodialysis and peritoneal dialysis are discussed, to determine their option of choice. In addition, patients may be evaluated for kidney transplantation and referred to a transplant centre at this time. Once a patient has been educated and the dialysis modality has been chosen, referral for surgery may be done for dialysis access placement.

Complications

Complications	Timeframe	Likelihood
anaemia	**long term**	**high**
Anaemia of chronic kidney disease (CKD) is due to a deficiency of erythropoietin as the GFR declines. Anaemia is typically identified in stage 3a/3b CKD. Patients should be screened with a FBC at least every 6 to 12 months, and an erythropoietin-stimulating agent may be considered once the Hb falls to <100 g/L (<10 g/dL) and there are symptoms of anaemia. Some have advocated not to treat anaemia except to avoid the need for blood transfusions, given the risks of anaemia treatment in CKD patients. The target Hb is 100 to 110 g/L (10 to 11 g/dL).[57] [73] [74] If the patient is iron-deficient, oral or intravenous supplementation may also be prescribed.[75] Patients with CKD on erythropoietin-stimulating agents for the treatment of anaemia have a higher risk of death and cardiovascular complications if the Hb is normalised >130 g/L (>13 g/dL).[55] [56] [76] [77] [78]		
renal osteodystrophy	**long term**	**high**

Complications	Timeframe	Likelihood

May be caused by an elevation in PTH as a result of phosphorus retention and hypocalcaemia from 1,25 vitamin D deficiency as the GFR declines. Severe hyperparathyroidism and hyperphosphataemia are risk factors for death, cardiovascular disease, and vascular calcification in patients with chronic kidney disease (CKD).[61]

Patients with stage 3a/3b CKD should be screened for hyperparathyroidism with an intact PTH, calcium, and phosphorus at least every 6 to 12 months.[61] [62]

25-dihydroxyvitamin D should be monitored and treated with ergocalciferol or colecalciferol if the level is <30 nanograms/L.[79] [80] Treatment with active 1,25 vitamin D may be indicated if the PTH remains above the normal range. Cinacalcet has been shown to lower PTH levels in patients with CKD and secondary hyperparathyroidism both prior to and after the initiation of dialysis but is associated with hypocalcaemia, and long-term benefits are not known.[81] [82] The optimal target of PTH is not known in CKD patients.

Phosphate binders such as calcium, lanthanum, and sevelamer should be initiated to normalise phosphorus levels if patients are unable to sufficiently restrict phosphorus in the diet.[61] Calcium-based binders should be restricted if there is associated hypercalcaemia, arterial calcification, suppressed PTH, or adynamic bone disease.[62] There is emerging evidence that the use of non-calcium-based binders has a survival advantage over calcium-based binders in patients with CKD.[64]

Those with hyperparathyroidism and elevation of high bone turnover with an increase in alkaline phosphatase may benefit from the use of cinacalcet to decrease intact PTH levels. Based on the EVOLVE trial, the use of cinacalcet did not improve survival in end-stage renal disease patients but did decrease the rate of parathyroidectomy.[83] [84] [85] [86] [87]

cardiovascular disease	**long term**	**high**

Chronic kidney disease (CKD) is a risk factor for cardiovascular disease independent of comorbidities such as DM, HTN, and dyslipidaemia. Cardiovascular disease is the leading cause of death for these patients, and the overwhelming majority of patients with CKD will die prior to reaching the need for renal replacement therapy.

The goal in treatment of cardiovascular disease in patients with CKD is early recognition and risk factor modification, including lipid therapy, optimisation of BP and glycaemic control, tobacco cessation, and aspirin use.[89] [90]

protein malnutrition	**variable**	**medium**

As the GFR falls, patients develop anorexia, nausea, vomiting, and lack of protein intake. Previously, patients with advanced chronic kidney disease (CKD) were placed on low-protein diets, but this recommendation has limitations due to its worsening of malnutrition. It is recommended for patients with CKD to have 0.6 g/kg protein intake daily and those with nephrotic syndrome 0.8 g/kg protein intake daily, to account for protein losses in the urine. If patients are not able to maintain nutrition, then initiation of renal replacement therapy may be warranted.[88]

metabolic acidosis	**variable**	**medium**

Metabolic acidosis is common in patients with chronic kidney disease (CKD), due to the inability of the kidney to excrete acid once the estimated GFR is <50 mL/minute. The anion gap is typically normal, but may be increased in uraemia with retention of phosphate anions. Rarely does the serum bicarbonate level fall below 12 mmol/L (12 mEq/L). Metabolic acidosis may worsen renal osteodystrophy and cause malnutrition, hypercatabolism, and growth retardation.

Treatment involves the administration of sodium bicarbonate 0.5 to 1.0 mmol/kg/day (0.5 to 1.0 mEq/kg/day) for a target serum bicarbonate level >20 mmol/L (>20 mEq/L). Sodium citrate as a bicarbonate source is generally avoided in patients with CKD, as it increases the absorption of aluminium and may contribute to bone disease and dementia.[61] [91] [92]

Complications	Timeframe	Likelihood
hyperkalaemia	**variable**	**medium**
Hyperkalaemia is common in patients with chronic kidney disease, due to the kidney's inability to excrete potassium from the diet as the estimated GFR declines. Hyperkalaemia is more common in patients with oliguria, resistant or deficient aldosterone state, or co-existing metabolic acidosis. Most patients with hyperkalaemia are asymptomatic, but some may present with muscle weakness. The hallmark for the severity of hyperkalaemia is identification of cardiac disturbances on an ECG with peaked T waves, prolongation of the conduction system, sine wave, or asystole. Hyperkalaemia associated with cardiac conduction disturbances is a medical emergency and is treated with intravenous calcium; medicines to shift potassium into the cells, such as insulin and dextrose; beta-agonists and the focused removal of potassium from the body with loop diuretics, if kidney function is intact; sodium polystyrene sulfonate (e.g., Kayexalate™) for GI loss of potassium; and, in severe cases, haemodialysis.		
pulmonary oedema	**variable**	**medium**
Fluid overload occurs in patients with chronic kidney disease (CKD), especially those with concomitant congestive heart failure. Treatment of fluid overload with loop diuretics is often used to prevent episodes of pulmonary oedema and manage peripheral oedema. In some instances, a combination diuretic regimen (e.g., a loop and a thiazide diuretic) provides a more effective diuresis in patients. Failure to maintain fluid balance in those with advanced stages 4 and 5 CKD is an indication to start renal replacement therapy.		

Prognosis

Chronic kidney disease (CKD) is progressive and will eventually lead to end-stage renal disease (ESRD) and the need for renal replacement therapy (i.e., dialysis, transplant). CKD is a strong cardiovascular risk factor, and the majority of patients with CKD will die prior to reaching ESRD. As kidney function declines, complications such as anaemia and hyperparathyroidism develop that may contribute to worsening cardiovascular disease and renal osteodystrophy, respectively. There is no cure for CKD. Optimisation of glycaemic control in people with diabetesas been associated with a reduction in the development of microalbuminuria and macroalbuminuria; however, it has not led to a reduction in progressive CKD.[72] Optimisation of blood pressure control with the use of ACE inhibitors or angiotensin-II receptor antagonist agents and reduction in proteinuria may slow the rate of progression to ESRD and the eventual need for renal replacement therapy.

Diagnostic guidelines

Europe

Chronic kidney disease in adults: assessment and management

Published by: National Institute for Health and Care Excellence **Last published:** 2015

International

Clinical practice guideline for lipid management in chronic kidney disease

Published by: Kidney Disease: Improving Global Outcomes **Last published:** 2013

Summary: Provides evidence-based recommendations for assessing lipid status in patients with chronic kidney disease (including non-dialysis-dependent, dialysis-dependent, kidney transplant recipients, and children).

Clinical practice guideline for the evaluation and management of chronic kidney disease

Published by: Kidney Disease: Improving Global Outcomes **Last published:** 2012

Summary: Provides evidence-based guidance on the evaluation of chronic kidney disease.

Definition and classification of chronic kidney disease

Published by: Kidney Disease: Improving Global Outcomes **Last published:** 2005

Summary: The KDIGO position statement reaffirmed the need for a clear definition of chronic kidney disease (CKD) as stated by the KDOQI guidelines and added that kidney transplant recipients should be considered to have CKD and should be classified in a similar fashion to those who have not undergone transplantation. This group also recommended screening for CKD with testing of creatinine and urinalysis in high-risk groups such as those with DM, HTN, family history of CKD, and/or past or family history of cardiovascular disease, to identify patients in the earlier stages of CKD where risk modification is of the greatest benefit.

North America

ACR appropriateness criteria: renal failure

Published by: American College of Radiology **Last published:** 2013

Summary: Appropriateness criteria of radiological investigations for acute and chronic renal failure.

Detection of chronic kidney disease in patients with or at increased risk of cardiovascular disease

Published by: American Heart Association **Last published:** 2006

Summary: A science advisory from the American Heart Association Kidney and Cardiovascular Disease Council; the Councils on High Blood Pressure Research, Cardiovascular Disease in the Young, and Epidemiology and Prevention; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: developed in collaboration with the National Kidney Foundation.

North America

Clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification

Published by: National Kidney Foundation KDOQI **Last published:** 2002

Summary: Discuss the diagnosis and evaluation of chronic kidney disease.

Oceania

Prevention and management of chronic kidney disease in type 2 diabetes

Published by: Caring for Australasians with Renal Impairment **Last published:** 2010

Summary: Guidelines for the assessment and prevention of chronic kidney disease in individuals with established type 2 diabetes.

Treatment guidelines

Europe

Guideline on water treatment systems, dialysis water and dialysis fluid quality for haemodialysis and related therapies

Published by: Renal Association; Association of Renal Technologists **Last published:** 2016

Summary: This guideline provides recommendations for the delivery of fit for purpose dialysis water and dialysis fluid.

Chronic kidney disease: managing anaemia

Published by: National Institute for Health and Care Excellence **Last published:** 2015

Summary: This guideline provides evidence-based advice on managing anaemia of chronic kidney disease.

Vascular access for haemodialysis

Published by: Renal Association **Last published:** 2015

Summary: This guideline provides recommendations on vascular access in haemodialysis.

CKD - mineral and bone disorders

Published by: Renal Association **Last published:** 2015

Summary: Guideline provides recommendations on the management of bone disease in patients with chronic kidney disease.

Chronic kidney disease in adults: assessment and management

Published by: National Institute for Health and Care Excellence **Last published:** 2015

Europe

When to start dialysis: updated guidance following publication of the Initiating Dialysis Early and Late (IDEAL) study

Published by: European Renal Best Practice Advisory Board **Last published:** 2011

Summary: European guideline on when to start dialysis.

Chronic kidney disease (stage 5): peritoneal dialysis

Published by: National Institute for Health and Care Excellence **Last published:** 2011

Summary: The aim of this guideline is to improve the care of people with stage 5 chronic kidney disease who are to receive dialysis, by making evidence-based recommendations on the role of peritoneal dialysis.

Clinical practice guidelines for the detection, monitoring and care of patients with chronic kidney disease

Published by: Renal Association **Last published:** 2011

Summary: Early chronic kidney disease (CKD) is relatively common, and not all patients require referral to consultant services; however, late referral in established renal failure is associated with poor clinical outcomes and significant costs. These guidelines give recommendations for optimal management of patients with CKD, including identifying those who would benefit from referral.

Cinacalcet for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy

Published by: National Institute for Health and Care Excellence **Last published:** 2007

ESPEN guidelines on enteral nutrition: adult renal failure

Published by: European Society for Parenteral and Enteral Nutrition **Last published:** 2006

Summary: Expert opinion guidelines on the nutrition of patients with acute renal failure. Oral nutrition supplements are recommended for re-feeding depleted conservatively treated patients with chronic renal failure or on dialysis. Oral nutrition supplements have been shown to improve survival of dialysis patients by improving nutrition status.

National service framework for renal services part two: chronic kidney disease, acute renal failure and end of life care

Published by: Department of Health **Last published:** 2005

Summary: There are four key quality requirements for those involved in implementing the renal National Service Framework: prevention and early detection of chronic kidney disease (CKD), minimising progression and consequences of CKD, prompt identification and care of acute renal failure, and end of life care.

Europe

Guidance on home compared with hospital haemodialysis for patients with end-stage renal failure

Published by: National Institute for Health and Care Excellence **Last published:** 2002

Summary: All patients with end-stage renal failure who are suitable for home dialysis should be offered the choice between haemodialysis in their home or in a renal unit. Patients should receive a full assessment of healthcare needs and social and home circumstances before home dialysis is offered.

International

Clinical practice guideline for lipid management in chronic kidney disease

Published by: Kidney Disease: Improving Global Outcomes **Last published:** 2013

Summary: Provides evidence-based recommendations for treating dyslipidaemia in patients with chronic kidney disease (including non-dialysis-dependent, dialysis-dependent, kidney transplant recipients, and children).

Clinical practice guideline for the evaluation and management of chronic kidney disease

Published by: Kidney Disease: Improving Global Outcomes **Last published:** 2012

Summary: Provides evidence-based guidance on the management of chronic kidney disease.

North America

KDOQI clinical practice guideline for diabetes and CKD: 2012 update

Published by: National Kidney Foundation KDOQI **Last published:** 2012

Summary: Guidelines, based on a systematic review of the literature, that update the previous 2007 guidelines and give recommendations on the management of hyperglycaemia, hyperlipidaemia, and albuminuria in patients with diabetes and kidney disease.

Preservation of peripheral veins in patients with chronic kidney disease

Published by: Association for Vascular Access **Last published:** 2011

Summary: A joint position statement from Association for Vascular Access (AVA) and American Society of Diagnostic and Interventional Nephrology (ASDIN).

Shared decision-making in the appropriate initiation of and withdrawal from dialysis, 2nd edition

Published by: Renal Physicians Association **Last published:** 2010

Summary: This guideline provides recommendations for initiating, withholding, and withdrawing dialysis in adult and paediatric patients with AKI, chronic kidney disease, or ESRD.

North America

KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD)

Published by: National Kidney Foundation **Last published:** 2009

Summary: These guidelines contain recommendations on evaluation and treatment of CKD-MBD.

Guidelines for the management of chronic kidney disease

Published by: Canadian Society of Nephrology **Last published:** 2008

Summary: These guidelines describe key aspects of the management of chronic kidney disease, to facilitate shared care for these patients by general practitioners and specialists, including internists, endocrinologists, cardiologists, and nephrologists. Specifically, these guidelines are for the care of patients who are not receiving dialysis.

Detection of chronic kidney disease in patients with or at increased risk of cardiovascular disease

Published by: American Heart Association **Last published:** 2006

Summary: A science advisory from the American Heart Association Kidney and Cardiovascular Disease Council; the Councils on High Blood Pressure Research, Cardiovascular Disease in the Young, and Epidemiology and Prevention; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: developed in collaboration with the National Kidney Foundation.

Oceania

KHA-CARI adaptation of the KDIGO clinical practice guideline for the care of kidney transplant recipients

Published by: Caring for Australasians with Renal Impairment **Last published:** 2012

Summary: These guidelines provide recommendations on the care of kidney transplant recipients.

Prevention and management of chronic kidney disease in type 2 diabetes

Published by: Caring for Australasians with Renal Impairment **Last published:** 2010

Summary: Guidelines for the assessment and prevention of chronic kidney disease in individuals with established type 2 diabetes.

Acceptance onto dialysis

Published by: Caring for Australasians with Renal Impairment **Last published:** 2010

Summary: Recommendations for patients who are to receive dialysis.

Online resources

1. National Kidney Disease Education Program: GFR calculators *(external link)*

Evidence scores

1. Disease progression: there is medium-quality evidence that angiotensin-II receptor antagonists and calcium-channel blockers seem equally effective at reducing disease progression in people with chronic kidney disease.[94]
Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

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