Chronic kidney disease

The right clinical information, right where it's needed
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Proteinuria or hematuria, and/or a reduction in the glomerular filtration rate, for more than 3 months' duration.

The most common causes are diabetes mellitus and hypertension.

The majority of people are asymptomatic, and the diagnosis is determined only by laboratory studies.

Glycemic control for diabetic nephropathy and optimization of blood pressure are key in slowing the progression of disease.

Increased risk for cardiovascular disease.
Chronic kidney disease (CKD), also known as chronic renal failure, is defined by either a pathologic abnormality of the kidney, such as hematuria and/or proteinuria, or a reduction in the glomerular filtration rate to <60 mL/minute/1.73 m² for ≥3 months’ duration.[1]

Epidemiology
This is a common condition that is often unrecognized until the most advanced stages. It is estimated that 11% of the adult population worldwide has CKD.[3] [4] [5] The incidence is rising and is thought to be due to an aging population; a higher incidence of diseases such as diabetes and hypertension, which are the most common causes in the adult population;[6] and an increased incidence of glomerular disorders such as focal segmental glomerulosclerosis.[7] 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.[8] [9] 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.[10]

Etiology
The most common cause in the adult population is diabetes.[6] [11] It is estimated that one third of patients with diabetes will develop kidney disease, as defined by macroalbuminuria (>300 mg albumin/24 hours) and/or a reduction in the glomerular filtration rate to <90 mL/minute/1.73 m², within 5 to 10 years after the diagnosis of diabetes.[12] [13]

Hypertension is the second most common cause.[6] [11] Often people are given the diagnosis of hypertensive renal disease if no other identifiable etiology 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.[14]

Pathophysiology
The pathophysiology is complex. Regardless of the method of renal injury (i.e., diabetes, hypertension, or glomerular disorders), once renal damage has occurred, a cascade of events ensues.[15] [16]

- In response to renal injury, there is thought to be an increase in intraglomerular pressure with glomerular hypertrophy, as the kidney attempts to adapt to nephron loss to maintain constant glomerular filtration.
- An increase in glomerular permeability to macromolecules such as transforming growth factor-beta (TGF-beta), fatty acids, proinflammatory 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.
Chronic kidney disease

• All forms of CKD are also associated with tubulointerstitial 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] [2]

• Acute kidney injury is defined by a rise in the serum creatinine of ≥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.
• CKD is defined by evidence of kidney damage based on pathologic diagnosis, abnormalities of radiographic imaging, or laboratory evidence of kidney damage such as hematuria and/or proteinuria or a reduction in the glomerular filtration rate (GFR) to <60 mL/minute/1.73m² for ≥3 months.

CKD is divided into 6 distinct stages based on GFR, as follows:[1]

• Stage 1: kidney damage with normal or increased GFR, ≥90 mL/minute/1.73m²
• Stage 2: kidney damage with mild decrease in GFR, 60 to 89 mL/minute/1.73m²
• Stage 3a: kidney damage with moderate decrease in GFR, 45 to 59 mL/minute/1.73m²
• Stage 3b: kidney damage with moderate decrease in GFR, 30 to 44 mL/minute/1.73m²
• Stage 4: kidney damage with severe decrease in GFR, 15 to 29 mL/minute/1.73m²
• Stage 5: kidney failure (end-stage kidney disease), with GFR <15 mL/minute/1.73m²
Primary prevention

The evidence for the prevention of CKD is lacking as compared with large scale randomized trials for cardiovascular disease. Most trials have focused on modifiable diseases and risk factors that have been associated with CKD, namely diabetes and hypertension. Clinical evidence supports the recommendation for a goal HbA1c <7%, blood pressure 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.[29]

Screening

There are no established screening guidelines for the general population for chronic kidney disease. However, based on expert opinion, there are recommendations to screen those considered high-risk and include all individuals with diabetes and hypertension 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 program.[34]

Patients with risk factors for CKD such as diabetes, hypertension, 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 hematuria and/or proteinuria.

In addition, underlying risk factors associated with disease states should be treated, including optimization of glycemic control in diabetes and achievement of the goal blood pressure of <140/90 mmHg with ACE inhibitors or angiotensin receptor-blocking agents. Consideration can be given to a lower blood pressure goal in those with proteinuria of >500 mg per 24 hours.[35] [36] 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 uremia 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 optimization of glycemic control in diabetes and achievement of the goal blood pressure of <140/90 mmHg with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor-blocking agents. Consideration can be given to a lower blood pressure goal in those with proteinuria of >500 mg per 24 hours.[35] [36] [105] 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 uremia 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.
Case history

Case history #1

A 54-year-old man with a 10-year history of diabetes and hypertension, 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 glycemic 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 exam reveals an obese man with a sitting blood pressure of 158/92 mmHg. The only pertinent physical exam findings are cotton wool patches and microaneurysms bilaterally on fundoscopic exam and pitting, bilateral lower-extremity edema.

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. Edema is a common presentation - as the glomerular filtration rate 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 edema.

Step-by-step diagnostic approach

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

History

Signs and symptoms are often vague, including fatigue (which may be related to the anemia associated with CKD), nausea, and possibly the development of edema. As kidney failure progresses to the more advanced stages of uremia, 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 edema and resultant pulmonary edema with dyspnea and orthopnea. In the most advanced stages of uremia, patients may present with seizures or coma.

Examination

Physical exam findings are often directed toward the discovery of end-organ damage associated with disease states such as diabetes or hypertension, which cause CKD. A fundoscopic eye exam is critical for the diagnosis of diabetic or hypertensive retinopathy as evidence of microvascular damage that has likely occurred in the kidney, resulting in CKD. In men, a rectal exam 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 hypertension, periorbital and peripheral edema, rashes, or arthritis on
musculoskeletal exam for patients with autoimmune disorders. Patients may describe their urine as foamy if significant proteinuria is present, or tea- or cola-colored in the setting of hematuria.

**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 hematuria 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.[30] 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 end-stage renal disease.

**Additional investigations**

A renal biopsy to determine a pathologic 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 hypertension, periorbital and peripheral edema) 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 pathologic lesion.

Imaging of the genitourinary tract may be helpful in the evaluation of a patient with CKD. A plain abdominal x-ray is a nonspecific test that may aid in the detection of calcium-containing kidney stones. Other radiologic tests, such as an abdominal computed tomography (CT), are reserved for evaluation of stone disease and further characterization of renal cystic or mass lesions. Magnetic resonance imaging (MRI) is reserved for renal mass lesions such as renal cell carcinoma.

**Risk factors**

**Strong diabetes mellitus**

- This is the most common cause.[6] [11]
- It is estimated that approximately 30% of people with diabetes will have CKD, as documented by proteinuria and/or a reduction in the glomerular filtration rate (GFR), within 5 to 10 years of diagnosis.[12] [13]
- Glycemic control directly correlates with the development of diabetic nephropathy and the rapidity of progression to end-stage renal disease (ESRD).
- Hyperglycemia 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.[17] These promote collagen production, leading to glomerular sclerosis.[18]
hypertension

• This is the second most common cause of CKD.[6] [11]
• Uncontrolled hypertension is thought to be one of the greatest risk factors for progression to ESRD in other types of chronic kidney disease, such as diabetic kidney disease, and glomerular nephrotic and nephritic syndromes.
• Hypertension is thought to affect both the vasculature and tubulointerstitial components of the kidney, resulting in ischemic 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 aging process causes a decline in the GFR.[3] Typically the GFR declines by 1 mL/minute/1.73 m² per year after the age of 50 years.

childhood kidney disease

• A history of childhood kidney disease is a risk factor for adult chronic kidney disease and ESRD. Children with a medical history of congenital anomalies, glomerular disease, or pyelonephritis with normal kidney function and blood pressure have a four-fold increased risk for ESRD as compared to children without kidney disease.[19]

Weak smoking

• Smoking has been associated as a risk factor for the development and progression of the disease, likely because of accelerated atherosclerosis and vascular disease, as well as exacerbating underlying hypertension.[20]

obesity

• Obesity is an associated risk factor.[21] It may contribute to the development of diabetes, exacerbate poor control of hypertension, contribute to renal ischemia and hypertension with associated sleep apnea, and cause glomerular strain with hypertrophy and glomerulosclerosis.

black or Hispanic ethnicity

• Black or Hispanic people are at higher risk than white people.[22] [23] The mechanism is not known but is thought to be due in part to a higher incidence of diseases such as diabetes and hypertension 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.

family history of chronic kidney disease

• People with a close family member with the disease are at a higher risk themselves of developing chronic kidney disease.[9] The mechanism is thought to be due in part to genetic susceptibility to certain disease states, such as diabetes, hypertension, polycystic kidney disease, Alport syndrome, and possibly glomerular syndromes, such as IgA nephropathy and focal segmental glomerulosclerosis.

autoimmune disorders

• Autoimmune disorders such as systemic lupus erythematosus, rheumatoid arthritis,[24] sarcoidosis, and Sjogren syndrome may cause glomerular or tubulo-interstitial chronic kidney disease.
male sex

- Men are at a higher risk than women.\textsuperscript{[25]}
- 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.\textsuperscript{[26]}

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.\textsuperscript{[27]} \textsuperscript{[28]} NSAIDs and previously phenacetin have been described as causing analgesic nephropathy.

### History & examination factors

#### Key diagnostic factors

**fatigue (common)**

- Anemia is associated with chronic kidney disease due to the lack of erythropoietin produced by the kidney once the glomerular filtration rate (GFR) declines to <50 mL/minute/1.73 m\(^2\).

**edema (common)**

- Periorbital and peripheral edema 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 uremia, 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 pathologic lesion.

#### Other diagnostic factors

**arthralgia (common)**

- If patient has concomitant autoimmune disorder.

**enlarged prostate gland (common)**

- Prostate exam in men should be performed to exclude obstructive uropathy.
foamy-appearing urine (uncommon)
• Indicative of proteinuria.

cola-colored urine (uncommon)
• Indicative of hematuria.

rashes (uncommon)
• Ecchymosis and purpura are signs of hematologic consequences of chronic kidney disease.
• Patient may have concomitant autoimmune disorder (e.g., systemic lupus erythematosus and butterfly rash).

dyspnea (uncommon)
• Associated with pulmonary edema due to reduced urine output in worsening disease.

orthopnea (uncommon)
• Associated with pulmonary edema 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/hypertension. Diabetic and hypertensive patients should be screened for such changes.
## Diagnostic tests

### 1st test to order

<table>
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<th>Test</th>
<th>Result</th>
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<tr>
<td><strong>serum creatinine</strong></td>
<td>Elevated: &gt;1.1 mg/dL in men; &gt;1.2 mg/dL in women</td>
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| • 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 0.8 to 1.4 mg/dL, and in women 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 0.2 mg/dL. |  |
| **urinalysis**           | Hematuria and/or proteinuria                 |
| • Screening test to determine for pathologic markers of kidney damage excreted in the urine. |  |
| **urine microalbumin**   | Microalbuminuria (30 to 300 mg/day)         |
| • Microalbuminuria is a risk factor for the development of progressive CKD and coronary artery disease associated with diabetes and hypertension. Indicated in patients with diabetes and CKD if there was no evidence of proteinuria on urine dipstick.[31] |  |
| **renal ultrasound**     | Small kidney size; presence of obstruction/hydronephrosis/kidney stones |
| • Helps to diagnose chronic kidney disease if kidney atrophy is present and diagnoses obstruction with hydronephrosis or bladder retention. |  |
| **estimation of GFR**    | <60 mL/minute/1.73 m²                       |
| • Determines more accurately, by mathematical equations such as Cockcroft-Gault, the Modification of Diet in Renal Disease Formula, or the CKD EPI equation, the GFR and the severity and stage of CKD.[32]  
• More accurate than serum creatinine alone.  
• Formulas have not been proved to be reliable estimators in patients with a glomerular filtration rate >90 mL/minute/1.73 m².[1] |  |

### Other tests to consider

<table>
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<th>Test</th>
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<tr>
<td><strong>renal biopsy</strong></td>
<td>Variable depending on etiology</td>
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<td>• Helps to determine pathologic 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 pathologic lesions are due to infection (e.g., hepatitis B and C, syphilis,</td>
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<tr>
<td>Test</td>
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<tr>
<td><strong>Chronic kidney disease</strong></td>
<td><strong>Diagnosis</strong></td>
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<td>Provides insight into treatment options based on severity or chronicity of scarring of glomeruli and interstitium.</td>
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<td>plain abdominal radiograph</td>
<td>Nonspecific test that may aid in the detection of calcium-containing kidney stones, as medication and urate stones are not apparent on plain radiography.</td>
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<tr>
<td>abdominal CT</td>
<td>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 &lt;60 mL/minute, as it can cause acute kidney injury.</td>
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<tr>
<td>abdominal MRI</td>
<td>Imaging test that further characterizes 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) &lt;30 mL/minute/1.73m² undergo gadolinium-based studies. If required, then institution of hemodialysis 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 m², and gadolinium-based studies should be avoided or used with caution until further study is performed in this population.[33]</td>
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### Differential diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
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<tr>
<td>Diabetic kidney disease</td>
<td>• History of poorly controlled diabetes for 5 to 10 years. Often with coexisting diabetic retinopathy.</td>
<td>• HbA1c is typically &gt;7%.</td>
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<td>• Diagnostic tests include urinalysis for microalbumin or protein and a serum creatinine for GFR assessment.</td>
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<td>• The quantification of proteinuria is variable over time and will decrease as the GFR declines.</td>
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<td>• Urine microalbumin is helpful to confirm the diagnosis of early diabetic nephropathy prior to the onset of macroalbuminuria.</td>
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<td>• Kidney ultrasound will typically show small, atrophic kidneys only in late stages of the disease, once substantial renal injury occurs.</td>
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<tr>
<td>Hypertensive nephrosclerosis</td>
<td>• History of poorly controlled hypertension for years. More common in black people than white people.</td>
<td>• Diagnostic tests include urinalysis for microalbumin or protein and a serum creatinine for GFR assessment.</td>
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<td>• The urine sediment is described as bland, without formed elements or hematuria. Quantification of proteinuria is &lt;2 g/24 hours.</td>
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<td>• Kidney ultrasound typically reveals small, atrophic kidneys.</td>
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<td>Ischemic nephropathy</td>
<td>• History of long-standing essential hypertension that suddenly is uncontrolled. More common in white people and older people. Often will have a history of atherosclerotic disease such as coronary artery disease or peripheral vascular disease. There is also a history of tobacco abuse and hyperlipidemia.</td>
<td>• The urine sediment is described as bland, without formed elements or hematuria. Quantification of proteinuria is &lt;2 g/24 hours.</td>
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<td>• Kidney ultrasound reveals asymmetric kidney size of ≥2.5 cm with unilateral disease, and duplex scan demonstrates an increase in the resistive index, suggesting obstruction.</td>
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<td>• Angiotensin-converting enzyme (ACE) inhibitor renogram, CT angiogram, magnetic resonance angiogram, or renal</td>
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<tr>
<td>Condition</td>
<td>Differentiating signs / symptoms</td>
<td>Differentiating tests</td>
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<td><strong>Obstructive uropathy</strong></td>
<td>• More common in men and older people. Often due to prostatic enlargement or cancer.</td>
<td>• 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 flow.</td>
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<td>• Typical symptoms include urinary frequency, hesitancy, inability to empty the bladder completely, and decrease in urinary stream.</td>
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<td>• Urinary tract infections may develop.</td>
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<td>• Rectal exam may reveal prostatic enlargement or nodules.</td>
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<td><strong>Nephrotic syndrome</strong></td>
<td>• Often associated with a more sudden onset of hypertension, or acceleration of essential hypertension and development of periorbital and peripheral edema.</td>
<td>• Laboratory evidence may reveal hyperlipidemia and an increase in serum creatinine, and urinalysis has proteinuria as defined at &gt;3.5 g/24 hours.</td>
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<td>• A kidney biopsy is required to determine the pathologic lesion for nephrotic syndrome.</td>
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<td>• Serologic tests for secondary causes of nephrotic syndrome such as antinuclear antibody (ANA) in systemic lupus erythematosus, 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 nephrotic syndrome.</td>
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<td><strong>Glomerulonephritis</strong></td>
<td>• Often associated with a sudden onset of hypertension or acceleration of essential hypertension.</td>
<td>• Laboratory evidence reveals an increased serum creatinine, and urinalysis is significant for hematuria and proteinuria.</td>
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<td>• Patients with autoimmune disorders may have a skin rash or arthritis; postinfectious glomerulonephritis has a recent history of a pharyngeal or cutaneous</td>
<td>• Urine sediment is evaluated for the presence of dysmorphic RBCs and RBC casts, which are diagnostic of glomerulonephritis.</td>
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Chronic kidney disease

Diagnostic classification[1]

- Stage 1: glomerular filtration rate (GFR) >90 mL/minute/1.73 m², and evidence of kidney damage based on pathologic diagnosis, abnormalities of radiographic imaging, or laboratory findings such as hematuria and/or proteinuria
- Stage 2: GFR of 60 to 89 mL/minute/1.73 m²
- Stage 3a: GFR of 45 to 59 mL/minute/1.73 m²
- Stage 3b: GFR of 30 to 44 mL/minute/1.73 m²
- Stage 4: GFR of 15 to 29 mL/minute/1.73 m²
- Stage 5: GFR <15 mL/minute/1.73 m²

Clinical indicators of kidney damage[1]

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

Diagnostic criteria

Serologic tests such as ANA, complement levels, hepatitis B and C antibodies, antineutrophil cytoplasmic antibody, antiglomerular basement antibody, and antistreptolysin O titer are often helpful in confirming the diagnosis of glomerulonephritis.

A kidney biopsy is required to confirm the pathologic lesion of the glomerulonephritis.
Step-by-step treatment approach

All etiologies of chronic kidney disease 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 anemia and secondary hyperparathyroidism may be treated.

CKD is divided into 6 distinct stages based on glomerular filtration rate (GFR), as follows:[1]

- Stage 1: GFR >90 mL/minute/1.73 m², and evidence of kidney damage based on pathologic diagnosis, abnormalities of radiographic imaging, or laboratory findings such as hematuria and/or proteinuria
- Stage 2: GFR of 60-89 mL/minute/1.73 m²
- Stage 3a: GFR of 45-59 mL/minute/1.73 m²
- Stage 3b: GFR of 30-44 mL/minute/1.73 m²
- Stage 4: GFR of 15-29 mL/minute/1.73 m²
- Stage 5: GFR <15 mL/minute/1.73 m².

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 optimizing glycemic control, optimizing blood pressure (BP) with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin-II receptor antagonist, introducing lipid-lowering agents (e.g., statins, ezetimibe),[38] [39] and reducing proteinuria is recommended.[40] [41]

Hypertension is one of the greatest risk factors for the progression of CKD, regardless of etiology. 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.[36] 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.[36] [42] [43] [44] [45] [46] [47] [48] 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.[49] However, this has not been validated in other BP trials in CKD. A combination of antihypertensive agents should be used to meet the target BP goal (except that ACE inhibitors and angiotensin-II receptor antagonists should not be combined within the same regimen).

ACE inhibitors[1][B]Evidence 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 nondiabetic CKD.[51] [52] [53] [2][C]Evidence 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. This emphasizes the importance of these agents as the first-line therapy in the treatment of CKD.[54]

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.[55] The study concluded that there was no difference in deaths from cardiovascular causes, in myocardial infarctions, cerebrovascular accidents, or hospitalizations for congestive heart failure, in the treatment groups. Also, the rates 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 hyperkalemia 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.[56] 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, hyperkalemia, and hypotension in patients taking the drug for 18-24 months. 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 hyperkalemia. 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 m²).

Dyslipidemia 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).[38] For patients ages ≥50 years with CKD stage 3 or 4, ezetimibe can be combined with the statin simvastatin.[39] Statin therapy has been shown to have cardioprotective effects in patients with CKD.[57] [58] [59] [60] 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).[61] 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.[62]

**Stages 1-4 intolerant to first-line therapy**

If a patient is unable to tolerate either an ACE inhibitor or an angiotensin-II receptor antagonist due to adverse effects, then an alternative is warranted. Nondihydropyridine calcium-channel blockers have been demonstrated to have more proteinuric-lowering effects than other antihypertensive agents. Clinical
Chronic kidney disease

Treatment trials in both diabetic and nondiabetic CKD have demonstrated greater protein-lowering effects than other classes of antihypertensive agents.[63] [8][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.

Stage 3a/3b

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

Treatment of anemia with the use of erythropoietin-stimulating agents is recommended for patients with CKD after other causes of anemia 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 hemoglobin (Hb) falls to <10 g/dL and the patient has signs and symptoms of anemia. 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 10-11 g/dL is appropriate, as normalization of Hb has resulted in increased risk for death and cardiovascular disease in this population.[65] [66] In the TREAT study of patients with diabetes with CKD and anemia, treatment with the erythropoietin-stimulating agent darbepoetin 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 hemoglobin fell below 9 g/dL). Interestingly, as in other studies of anemia 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.[67] [68] [69] [70] All patients should have an evaluation of iron stores if erythropoietin therapy is planned. The goal ferritin for those not on hemodialysis is >100 nanograms/mL, while for those on hemodialysis is <200 nanograms/mL. All patients should have a transferrin saturation >20%. Iron replacement can be given orally or parenterally.

For secondary hyperparathyroidism, calcium, phosphorus, and intact parathyroid hormone (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 <30 nanograms/dL. For those with stages 3-5 CKD not on dialysis, it is not routinely recommended to use active vitamin D analogs due to the risk of hypercalcemia and lack of improvement in clinically relevant outcomes.[71] Use of active vitamin D analog therapy in patients with CKD not requiring dialysis is indicated if hyperparathyroidism is progressive or severe.[71] [72] There is emerging evidence that the use of noncalcium-based phosphate binders has a survival advantage over calcium-based phosphate binders in patients with CKD.[73]

Stage 4

Patients need to be educated about renal replacement therapy such as hemodialysis, 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 hemodialysis should be educated on vein preservation with limiting venipuncture and intravenous access to the access arm.[74] 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 anemia and secondary hyperparathyroidism should be continued. It is recommended to check serum calcium and phosphate every 3-6 months, and intact PTH every 6-12 months.[71] 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.[75]

Stage 5 and uremia

Renal replacement therapy may be initiated once patients have stage 5 disease and/or signs of uremia such as weight loss, lack of appetite, nausea, vomiting, acidosis, hyperkalemia, or fluid overload.[1] Those with stage 5 CKD on dialysis, calcium, phosphorus, and intact PTH should be managed with phosphate binding agents, calcimimetics, active vitamin D analogs, or a combination of these therapies, based on serial laboratory assessments of calcium and phosphate every 1-3 months, and PTH every 3-6 months.[71] Calcimimetics (e.g., cinacalcet, etelcalcetide) negatively feedback on the parathyroid glands and do not have the consequences of calcium augmentation.[76] Cinacalcet lowers PTH levels in patients with CKD and secondary hyperparathyroidism both prior to and after the initiation of dialysis, but it is associated with hypocalcemia, and long-term benefits are not known.[77] [78]

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.[79]

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 center 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.[80] [81]

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 uremia in order to delay the initiation of dialysis. Severe protein restriction may result in malnourishment and poorer outcomes.[82] 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

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer.
### Chronic kidney disease

#### Treatment

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<td>1st</td>
<td>angiotensin-converting enzyme (ACE) inhibitor or angiotensin-II receptor antagonist</td>
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</table>

| stages 3-4 without uremia |  |
| 1st | angiotensin-converting enzyme (ACE) inhibitor or angiotensin-II receptor antagonist  |
| plus | statin ± ezetimibe  |
| adjunct | additional antihypertensive therapy  |
| adjunct | education about renal replacement therapy  |
| 2nd | nondihydropyridine calcium-channel blocker  |
| plus | statin ± ezetimibe  |
| adjunct | additional antihypertensive therapy  |
| adjunct | education about renal replacement therapy  |
| with anemia | adjunct erythropoietin-stimulating agent  |
| adjunct | iron  |
| with secondary hyperparathyroidism | plus dietary modification ± phosphate-binding drug  |
| adjunct | ergocalciferol  |
| adjunct | active vitamin D analog  |
| with metabolic acidosis | adjunct oral sodium bicarbonate  |

<p>| stage 5 or with uremia |  |
| with secondary hyperparathyroidism | 1st dialysis  |
| plus | dietary modification ± phosphate-binding drug  |
| adjunct | calcimimetic ± active vitamin D analog  |</p>
<table>
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<tr>
<td>adjunct ergocalciferol</td>
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<tr>
<td>2nd kidney transplant</td>
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Treatment options

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer.
### Acute

**Chronic kidney disease**

**Treatment**

**Acute stages 1-2 without uremia**

1st **angiotensin-converting enzyme (ACE) inhibitor or angiotensin-II receptor antagonist**

**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

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

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

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

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

- **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

- **losartan**: 50 mg orally once daily initially, adjust dose gradually according to response, maximum 100 mg/day
Chronic kidney disease

**Treatment**

### Acute

- **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

- The Joint National Committee (JNC) 8 redefined the target blood pressure (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.[36] 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.[49] However, this has not been validated in other BP trials in CKD.

- Clinical trials in both diabetic and nondiabetic 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,[55] it is sometimes given to patients with nephrotic syndromes and glomerulonephritis to reduce proteinuria.

- Both classes of drug may be associated with hyperkalemia and acute renal failure, more commonly in older people, those with an estimated glomerular filtration rate (GFR) <30 mL/minute/1.73 m², and with use of longer-acting agents. Hyperkalemia and acute renal failure are reversible once medications have been discontinued.

- Doses should be low initially and adjusted gradually according to clinical response.
### Treatment

**Acute**

**plus statin**

Treatment recommended for ALL patients in selected patient group

**Primary options**

- **simvastatin**: 40 mg orally once daily
- **pravastatin**: 40 mg orally once daily
- **rosuvastatin**: 10 mg orally once daily
- **atorvastatin**: 20 mg orally once daily

*Statin therapy has been shown to have cardioprotective effects in patients with CKD.*[57][58][59][60] 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).[61]

- Total cholesterol and low-density lipoprotein (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).[38]

- Statin therapy has been associated with liver dysfunction and myopathy and should be monitored in patients with CKD.4[B]Evidence

**adjunct additional antihypertensive therapy**

Treatment recommended for SOME patients in selected patient group

**Primary options**

- **hydrochlorothiazide**: 12.5 mg orally once daily initially, adjust dose gradually according to response, maximum 50 mg/day
- **OR**
### Treatment

#### Acute

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

- **metoprolol succinate**: 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

- Other classes of antihypertensive agents (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.
Chronic kidney disease

Treatment

**Acute**

» 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.[56] 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, hyperkalemia, and hypotension in patients taking the drug for 18-24 months. 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 hyperkalemia. It also recommends that this combination of drugs be avoided in patients with moderate to severe renal impairment (i.e., GFR <60 mL/minute).

2nd nondihydropyridine calcium-channel blocker

**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

» ACE inhibitors and angiotensin-II receptor antagonists are the superior treatment for patients with chronic kidney disease.

» If these medications need to be discontinued due to adverse effects such as cough, angioedema, hemodynamic decline in renal function, and/or hyperkalemia, then nondihydropyridine calcium-channel blockers have been demonstrated to have more proteinuric-lowering effects than other antihypertensive agents.3(B)Evidence

**plus** statin

Treatment recommended for ALL patients in selected patient group
<table>
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<td><strong>Primary options</strong></td>
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<td>OR</td>
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### Chronic kidney disease

#### Treatment

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|       | OR |                   |
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- **metoprolol succinate**: 25 mg orally (extended-release) once daily initially, adjust dose gradually according to response, maximum 100 mg/day
- **amlodipine**: 5 mg orally once daily initially, adjust dose gradually according to response, maximum 10 mg/day
- **felodipine**: 2.5 mg orally once daily initially, adjust dose gradually according to response, maximum 20 mg/day
- **spironolactone**: 12.5 mg orally once daily initially, adjust dose gradually according to response, maximum 200 mg/day given in 2-4 divided doses
- **aliskiren**: 150 mg orally once daily initially, adjust dose gradually according to response, maximum 300 mg/day
- **hydralazine**: 10 mg orally three to four times daily initially, adjust dose gradually according to response, maximum 300 mg/day
- **minoxidil**: 5 mg orally once daily initially, adjust dose gradually according to response, maximum 40 mg/day
- **clonidine**: 0.1 mg orally (immediate-release) twice daily initially, adjust dose gradually according to response, maximum 0.6 mg/day

- Other classes of antihypertensive agents (e.g., thiazide diuretics, beta-blockers, etc.) should be added when the target BP is not achieved with the use of a nondihydropyridine calcium-channel blocker.
### Chronic kidney disease

#### Treatment

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<td>1st angiotensin-converting enzyme (ACE) inhibitor or angiotensin-II receptor antagonist</td>
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</table>

**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 erbumine**: 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
Chronic kidney disease

Treatment

<table>
<thead>
<tr>
<th>Acute</th>
</tr>
</thead>
<tbody>
<tr>
<td>» irbesartan: 75 mg orally once daily initially, adjust dose gradually according to response, maximum 300 mg/day</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>» telmisartan: 20 mg orally once daily initially, adjust dose gradually according to response, maximum 80 mg/day</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>» eprosartan: 300 mg orally once daily initially, adjust dose gradually according to response, maximum 600 mg/day</td>
</tr>
</tbody>
</table>

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.[36] 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.[49] However, this has not been validated in other BP trials in CKD.

» Clinical trials in both diabetic and nondiabetic 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,[55] it is sometimes given to patients with nephrotic syndromes and glomerulonephritis to reduce proteinuria.

» Both classes of drug may be associated with hyperkalemia and acute renal failure, more commonly in older people, those with an estimated GFR <30 mL/minute/1.73 m², and with use of longer-acting agents. Hyperkalemia and acute renal failure are reversible once medications have been discontinued.

plus statin ± ezetimibe
### Acute

Treatment recommended for **ALL** patients in selected patient group

**Primary options**

- **simvastatin**: 40 mg orally once daily
  
- **pravastatin**: 40 mg orally once daily
  
- **rosuvastatin**: 10 mg orally once daily
  
- **atorvastatin**: 20 mg orally once daily
  
- **ezetimibe/simvastatin**: 10 mg (ezetimibe)/20 mg (simvastatin) orally once daily

> Statin therapy has been shown to have cardioprotective effects in patients with CKD.\[^{[57-60]}\] 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).\[^{[61]}\]

- 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).\[^{[38]}\] For patients ages ≥50 years with CKD stage 3 or 4, ezetimibe can be added to simvastatin.\[^{[39]}\]

- Statin therapy has been associated with liver dysfunction and myopathy and should be monitored in patients with CKD.\[^{[4B]}\]

### Adjunct

**additional antihypertensive therapy**

Treatment recommended for **SOME** patients in selected patient group

**Primary options**
### Acute

- **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 succinate**: 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

» Other classes of antihypertensive agents (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.[56] 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, hyperkalemia, and hypotension in patients taking the drug for 18-24 months. 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 hyperkalemia. It also recommends that this combination of drugs be avoided in patients with moderate to severe renal impairment (i.e., GFR <60 mL/minute).

adjunct education about renal replacement therapy

Treatment recommended for SOME patients in selected patient group

» Patients need to be educated about renal replacement therapy such as hemodialysis, 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 hemodialysis should be educated on vein preservation with limiting venipuncture and intravenous access to the access arm.[74]
### Chronic kidney disease

#### Treatment

<table>
<thead>
<tr>
<th>Acute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney transplantation is indicated once the eGFR is &lt;20 mL/minute and the patient has been evaluated and undergone the required testing process by a transplant team.</td>
</tr>
</tbody>
</table>

#### 2nd non-dihydropyridine calcium-channel blocker

**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

#### ACE inhibitors and angiotensin-II receptor antagonists are the superior treatment for patients with chronic kidney disease.

- If these medications need to be discontinued due to adverse effects such as cough, angioedema, hemodynamic decline in renal function, and/or hyperkalemia, then non-dihydropyridine calcium-channel blockers have been demonstrated to have more proteinuric-lowering effects than other antihypertensive agents.3[B]Evidence

#### plus statin ± ezetimibe

Treatment recommended for ALL patients in selected patient group

**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
### Acute

**Primary options**

- **ezetimibe/simvastatin**: 10 mg (ezetimibe)/20 mg (simvastatin) orally once daily

- Statin therapy has been shown to have cardioprotective effects in patients with CKD.\[57\] [58] [59] [60] In those individuals not on dialysis, 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).\[61\]

- 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).\[38\] For patients ages ≥50 years with CKD stage 3 or 4, ezetimibe can be added to simvastatin.\[39\]

- Statin therapy has been associated with liver dysfunction and myopathy and should be monitored in patients with CKD.\[4\][B]Evidence 

**adjunct**  
**additional antihypertensive therapy**

Treatment recommended for SOME patients in selected patient group

**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 succinate**: 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
### Acute

- **» felodipine**: 2.5 mg orally once daily initially, adjust dose gradually according to response, maximum 20 mg/day
- **» spironolactone**: 12.5 mg orally once daily initially, adjust dose gradually according to response, maximum 200 mg/day given in 2-4 divided doses
- **» aliskiren**: 150 mg orally once daily initially, adjust dose gradually according to response, maximum 300 mg/day

### Secondary options

- **» hydralazine**: 10 mg orally three to four times daily initially, adjust dose gradually according to response, maximum 300 mg/day
- **» minoxidil**: 5 mg orally once daily initially, adjust dose gradually according to response, maximum 40 mg/day
- **» 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

Treatment recommended for SOME patients in selected patient group

- Patients need to be educated about renal replacement therapy such as hemodialysis, 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
**Chronic kidney disease**

**Treatment**

<table>
<thead>
<tr>
<th>Acute</th>
<th>with anemia</th>
<th>adjunct erythropoietin-stimulating agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>patients should undergo chronic kidney disease education for modality choice.</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>All patients who are proceeding with hemodialysis should be educated on vein preservation with limiting venipuncture and intravenous access to the access arm.</td>
<td>Kidney transplantation is indicated once the eGFR is &lt;20 mL/minute and the patient has been evaluated and undergone the required testing process by a transplant team.</td>
<td></td>
</tr>
<tr>
<td>Kidney transplantation is indicated once the eGFR is &lt;20 mL/minute and the patient has been evaluated and undergone the required testing process by a transplant team.</td>
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<td></td>
</tr>
<tr>
<td>Treatment recommended for SOME patients in selected patient group</td>
<td>Treatment recommended for SOME patients in selected patient group</td>
<td></td>
</tr>
<tr>
<td><strong>Primary options</strong></td>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
<tr>
<td>» epoetin alfa: consult specialist for guidance on dose</td>
<td>» darbepoetin alfa: consult specialist for guidance on dose</td>
<td></td>
</tr>
<tr>
<td>» When stage 3a/3b has been reached, identification of comorbidities such as anemia is recommended and treatment begun if required. Treatment of anemia with the use of erythropoietin-stimulating agents is recommended for patients with chronic kidney disease (CKD) after other causes of anemia 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.</td>
<td>» Erythropoietin-stimulating agents are initiated once the hemoglobin (Hb) falls to &lt;10 g/dL and the patient has signs and symptoms of anemia.</td>
<td></td>
</tr>
<tr>
<td>» The target Hb for patients with chronic kidney disease on erythropoietin therapy is 10-11 g/dL, as normalization of Hb has resulted in increased risk for death and cardiovascular disease in this population.</td>
<td>» Erythropoietin-stimulating agents are initiated once the hemoglobin (Hb) falls to &lt;10 g/dL and the patient has signs and symptoms of anemia.</td>
<td></td>
</tr>
<tr>
<td>» Peginesatide was withdrawn from the market in early 2013 due to postmarketing reports of</td>
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<td></td>
</tr>
</tbody>
</table>
### Acute

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Chronic kidney disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>adjunct iron</strong></td>
<td>Treatment recommended for SOME patients in selected patient group</td>
</tr>
</tbody>
</table>

#### 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
  - OR

- **ferumoxytol**: consult specialist for guidance on dose
  - OR

- **ferric carboxymaltose**: consult specialist for guidance on dose

- **All patients should have an evaluation of iron stores if erythropoietin therapy is planned.**
  - The goal ferritin for those not on hemodialysis is >100 nanograms/mL, while for those on hemodialysis is <200 nanograms/mL. All patients should have a transferrin saturation >20%. Iron replacement can be given orally or parenterally. [83]

### with secondary hyperparathyroidism plus dietary modification ± phosphate-binding drug

Treatment recommended for ALL patients in selected patient group

### Primary options
### Acute

<table>
<thead>
<tr>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>» sevelamer</strong>: 800-1600 mg orally three times daily initially, titrate according to serum phosphate level</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td><strong>» calcium acetate</strong>: 1334 mg orally with each meal initially, titrate according to serum phosphate level</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td><strong>» calcium carbonate</strong>: 1-2 g/day orally given in 3-4 divided doses</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td><strong>» lanthanum</strong>: 500-1000 mg orally three times daily initially, titrate according to serum phosphate level</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td><strong>» sucroferric oxyhydroxide</strong>: 500 mg orally three times daily initially, titrate according to serum phosphate level, maximum 3000 mg/day</td>
</tr>
</tbody>
</table>

» 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.

» Phosphate binders should be initiated to normalize phosphorus levels if patients are unable to sufficiently restrict phosphorus in the diet.[71] Calcium-based phosphate binders should be restricted if there is associated hypercalcemia, arterial calcification, suppressed parathyroid hormone (PTH), or adynamic bone disease.[71]

» Calcium, phosphorus, and PTH testing should be performed every 6-12 months for patients with stage 3a/3b CKD and secondary hyperparathyroidism. For patients with stage 4 CKD and secondary hyperparathyroidism, calcium and phosphate should be checked every 3-6 months, and PTH every 6-12 months.[71]

» There is limited evidence that dietary restriction in calcium and phosphorus affects renal osteodystrophy.[84]
## Acute

<table>
<thead>
<tr>
<th>adjunct ergocalciferol</th>
<th>There is emerging evidence that the use of noncalcium-based phosphate binders has a survival advantage over calcium-based phosphate binders in patients with chronic kidney disease.[73]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment recommended for SOME patients in selected patient group</td>
<td></td>
</tr>
<tr>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
<tr>
<td>» <strong>ergocalciferol (vitamin D2)</strong>: dose depends on serum 25-OH vitamin D level; consult specialist for guidance on dose</td>
<td></td>
</tr>
<tr>
<td>» It is recommended to exclude concomitant 25-OH vitamin D deficiency and prescribe 25, dihydroxyvitamin D if &lt;30 nanograms/dL.</td>
<td></td>
</tr>
<tr>
<td>adjunct active vitamin D analog</td>
<td>Treatment recommended for SOME patients in selected patient group</td>
</tr>
<tr>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
<tr>
<td>» <strong>calcitriol</strong>: consult specialist for guidance on dose</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>» <strong>paricalcitol</strong>: consult specialist for guidance on dose</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>» <strong>doxercalciferol</strong>: consult specialist for guidance on dose</td>
<td></td>
</tr>
<tr>
<td>» It is not routinely recommended to use active vitamin D analogs for CKD not requiring dialysis unless hyperparathyroidism is progressive or severe.[71]</td>
<td></td>
</tr>
<tr>
<td>» The optimal PTH level is currently not known.</td>
<td></td>
</tr>
<tr>
<td>with metabolic acidosis adjunct oral sodium bicarbonate</td>
<td>Treatment recommended for SOME patients in selected patient group</td>
</tr>
<tr>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
<tr>
<td>» <strong>sodium bicarbonate</strong>: consult specialist for guidance on dose</td>
<td></td>
</tr>
</tbody>
</table>
| » For patients who develop metabolic acidosis, supplementation with oral sodium bicarbonate to a target serum bicarbonate level of >20
### Acute

<table>
<thead>
<tr>
<th>stage 5 or with uremia</th>
<th>1st dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal replacement therapy is initiated once patients have stage 5 disease and/or signs of uremia such as weight loss, lack of appetite, nausea, vomiting, acidosis, hyperkalemia, or fluid overload. [1]</td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>Continuous cycling peritoneal dialysis is done with a machine at night on a daily basis.</td>
<td></td>
</tr>
<tr>
<td>Continuous ambulatory peritoneal dialysis is done on a daily basis. Patients manually exchange the peritoneal fluid.</td>
<td></td>
</tr>
<tr>
<td>Hemodialysis 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 traversing a dialysis membrane and dialysis solution. Other dialysis options include short daily dialysis and nocturnal dialysis, which are available at some dialysis centers.</td>
<td></td>
</tr>
</tbody>
</table>

**Primary options**

- **sevelamer**: 800-1600 mg orally three times daily initially, titrate according to serum phosphate level

**OR**
### Acute

**calcium acetate**: 1334 mg orally with each meal initially, 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 initially, 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

**For patients with stage 5 CKD on dialysis, calcium, phosphorus, and intact PTH levels should be managed with phosphate binding agents, calcimimetics, active vitamin D analogs, or a combination of these based on serial laboratory assessments.**

**Calcium and phosphorus testing every 1-3 months and PTH testing every 3-6 months should be performed for patients with stage 5 CKD and secondary hyperparathyroidism.[71]**

**Increasing dialytic phosphate removal may be required in cases of persistent hyperphosphatemia.**

### adjunct

**calcimimetic ± active vitamin D analog**

Treatment recommended for SOME patients in selected patient group

### Primary options

**cinacalcet**: 30 mg orally once daily initially, increase dose according to serum PTH level, maximum 180 mg/day

--AND/OR--
### Acute

- **calcitriol**: consult specialist for guidance on dose  
  - or -  
- **paricalcitol**: consult specialist for guidance on dose  
  - or -  
- **doxercalciferol**: consult specialist for guidance on dose

### Secondary options

- **etelcalcetide**: adults: 5 mg intravenously three times weekly at the end of hemodialysis treatment, adjust dose according to PTH level and corrected serum calcium response, maintenance dose ranges from 2.5 to 15 mg three times weekly

  --AND/OR--

- **calcitriol**: consult specialist for guidance on dose  
  - or -  
- **paricalcitol**: consult specialist for guidance on dose  
  - or -  
- **doxercalciferol**: consult specialist for guidance on dose

For those requiring PTH-lowering therapy, calcimimetics (e.g., cinacalcet, etelcalcetide), active vitamin D analogs (e.g., calcitriol, paricalcitol, doxercalciferol), or a combination of a calcimimetic with an active vitamin D analog should be given,[71]

- Etelcalcetide is a second-generation, type II calcimimetic that may be used when treatment with a calcimimetic is indicated but cinacalcet is not a suitable option. It is given intravenously (rather than orally like cinacalcet) and has a longer half-life than cinacalcet.

### ergocalciferol

Treatment recommended for SOME patients in selected patient group

### Primary options

- **ergocalciferol (vitamin D2)**: dose depends on serum 25-OH vitamin D level; consult specialist for guidance on dose

- It is recommended to exclude concomitant 25-OH vitamin D deficiency and prescribe 25, dihydroxyvitamin D if <30 nanograms/dL.
### Acute

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 center 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. Kidneys may be transplanted from deceased or living donors.
Emerging

Novel therapies for CKD

Currently, there are many novel agents that are being investigated to slow progression of CKD. Most studies have focused on diabetic kidney disease; however, there are small clinical trials suggesting benefit of some agents in nondiabetic kidney disease. Antifibrotic agents such as tranilast have been shown to reduce the decline in kidney function and proteinuria; however, there has been concern for adverse hepatic and renal effects when used at higher doses in cardiology trials.[85] Agents targeting glycosaminoglycan metabolism such as sulodexide, inhibitors of advanced glycation end products (AGEs), and anti-inflammatory agents such as pentoxifylline have all demonstrated short-term effects in proteinuria reduction.[85] [86] [87] [88] How these agents will perform in large-scale randomized clinical trials remains to be seen. As of now, there are no novel approved therapies for the treatment of CKD.
Recommendations

Monitoring

Patients with risk factors for CKD, such as diabetes, hypertension, or a family member with CKD, should be evaluated annually with serum creatinine and mathematical formulation for estimation of the glomerular filtration rate in addition to urinalysis for hematuria 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 anemia and bone mineral disorders at least every 6 to 12 months with a hemoglobin, calcium, phosphorus, and intact parathyroid hormone (PTH). For those in stage 4 disease, hemoglobin, calcium, phosphorus should be monitored every 3 to 6 months and intact PTH every 6 to 12 months. For patients in stage 5 CKD, anemia should be evaluated with a monthly hemoglobin, 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, optimization of glycemic control, and blood pressure 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 hemodialysis and peritoneal dialysis are discussed, to determine their option of choice. Also, patients may be evaluated for kidney transplantation and referred to a transplant center 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

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>anemia</td>
<td>long term</td>
<td>high</td>
</tr>
</tbody>
</table>

Anemia of chronic kidney disease is due to a deficiency of erythropoietin as the glomerular filtration rate (GFR) declines.

Anemia is typically identified in stage 3a/3b CKD. Patients should be screened with a complete blood count at least every 6 to 12 months, and an erythropoietin-stimulating agent may be considered once hemoglobin (Hb) falls to <10 g/dL and there are symptoms of anemia. The target Hb is 10 to 11 g/dL.[67] [68] [92]

If the patient is iron-deficient, oral or intravenous supplementation may also be prescribed.[93]

Patients with CKD on erythropoietin-stimulating agents for the treatment of anemia have a higher risk of death and cardiovascular complications if the Hb is normalized >13 g/dL.[66] [94] [95] [96] [97]

<table>
<thead>
<tr>
<th>renal osteodystrophy</th>
<th>long term</th>
<th>high</th>
</tr>
</thead>
</table>

May be caused by an elevation in parathyroid hormone (PTH) as a result of phosphorus retention and hypocalcemia from 1,25 vitamin D deficiency as the GFR declines. Severe hyperparathyroidism and hyperphosphatemia are risk factors for death, cardiovascular disease, and vascular calcification in patients with CKD.[71]

Patients with stage 3 to 5 CKD should be routinely monitored for hyperparathyroidism and treatments based on serial assessments of phosphorus, calcium, and PTH levels, considered together.[71]

25-dihydroxyvitamin D should be monitored and treated if the level is <30 nanograms/L.[98] [99]

<table>
<thead>
<tr>
<th>cardiovascular disease</th>
<th>long term</th>
<th>high</th>
</tr>
</thead>
</table>

CKD is a risk factor for cardiovascular disease, independent of comorbidities such as diabetes, hypertension, and dyslipidemia. 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, optimization of blood pressure and glycemic control, tobacco cessation, and aspirin use.[101] [102]

<table>
<thead>
<tr>
<th>protein malnutrition</th>
<th>variable</th>
<th>medium</th>
</tr>
</thead>
</table>

As the GFR falls, patients develop anorexia, nausea, vomiting, and lack of protein intake. Previously, patients with advanced 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.[100]

<table>
<thead>
<tr>
<th>metabolic acidosis</th>
<th>variable</th>
<th>medium</th>
</tr>
</thead>
</table>

Metabolic acidosis is common in patients with 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...
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 anemia and hyperparathyroidism develop that may contribute to worsening cardiovascular disease and renal osteodystrophy, respectively. There is no cure for CKD. Optimization of glycemic control in people with diabetes has been associated with a reduction in the development of microalbuminuria and macroalbuminuria; however, it has not led to a reduction in progressive CKD. Optimization 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.

Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uremia with retention of phosphate anions</td>
<td>Rarely</td>
<td>Low</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>Medium</td>
<td>Medium</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Variable</td>
<td>Medium</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>Variable</td>
<td>Medium</td>
</tr>
</tbody>
</table>

Hyperkalemia is common in patients with CKD, due to the kidney’s inability to excrete potassium from the diet as the estimated GFR declines. Hyperkalemia is more common in patients with oliguria, resistant or deficient aldosterone state, or coexisting metabolic acidosis. Most patients with hyperkalemia are asymptomatic, but some may present with muscle weakness.

The hallmark for the severity of hyperkalemia is identification of cardiac disturbances on an ECG with peaked T waves, prolongation of the conduction system, sine wave, or asystole. Hyperkalemia associated with cardiac conduction disturbances is a medical emergency and is treated with intravenous calcium; medications 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, hemodialysis.

Pulmonary edema occurs in patients with CKD, especially those with concomitant congestive heart failure. Treatment of fluid overload with loop diuretics is often used to prevent episodes of pulmonary edema and manage peripheral edema. 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 anemia and hyperparathyroidism develop that may contribute to worsening cardiovascular disease and renal osteodystrophy, respectively. There is no cure for CKD. Optimization of glycemic control in people with diabetes has been associated with a reduction in the development of microalbuminuria and macroalbuminuria; however, it has not led to a reduction in progressive CKD. Optimization 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

## International

**ACR appropriateness criteria: renal failure [37]**  
*Published by:* American College of Radiology  
*Last published:* 2013

**KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease [1]**  
*Published by:* Kidney Disease: Improving Global Outcomes  
*Last published:* 2013

## Treatment guidelines

## International

**Preservation of peripheral veins in patients with chronic kidney disease [74]**  
*Published by:* Association for Vascular Access  
*Last published:* 2011

**Shared decision-making in the appropriate initiation of and withdrawal from dialysis, 2nd edition [89]**  
*Published by:* Renal Physicians Association  
*Last published:* 2010

**KDIGO 2017 clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD) [71]**  
*Published by:* Kidney Disease: Improving Global Outcomes (KDIGO)  
*Last published:* 2017

**Clinical practice guideline for the evaluation and management of chronic kidney disease [1]**  
*Published by:* Kidney Disease: Improving Global Outcomes (KDIGO)  
*Last published:* 2013

**Clinical practice guideline for lipid management in chronic kidney disease [38]**  
*Published by:* Kidney Disease: Improving Global Outcomes (KDIGO)  
*Last published:* 2013

**KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease [90]**  
*Published by:* Kidney Disease: Improving Global Outcomes (KDIGO)  
*Last published:* 2012

**KDIGO clinical practice guideline for anemia in chronic kidney disease [68]**  
*Published by:* Kidney Disease: Improving Global Outcomes (KDIGO)  
*Last published:* 2012
Evidence scores

1. Disease progression, mortality, and cardiovascular events: there is medium-quality evidence that, compared with control, ACE inhibitors are more effective at lowering blood pressure in people with chronic renal failure.[50]
   **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.

2. Disease progression and end-stage renal disease (ESRD): there is poor-quality evidence that, compared with control, ACE inhibitors may be more effective at reducing the risk of disease progression and end-stage renal disease (ESRD) in those with chronic renal failure. Very poor-quality evidence has not shown whether ACE inhibitors are more effective at reducing mortality in those with chronic renal failure.[50]
   **Evidence level C:** Poor quality observational (cohort) studies or methodologically flawed randomized controlled trials (RCTs) of <200 participants.

3. 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.[64]
   **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.

4. Disease progression: there is medium-quality evidence that has not shown whether statins are more effective than controls at reducing disease progression or end-stage renal disease (ESRD) in people with chronic renal failure.[50]
   **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.
Key articles


References


87. Rhee SY, Kim YS. The role of advanced glycation end products in diabetic vascular complications. Diabetes Metab J. 2018 Jun;42(3):188-95. Full text Abstract


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