BMJ Best Practice

# Acute kidney injury

The right clinical information, right where it's needed

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# Summary

- Commonly associated with sepsis, cardiovascular collapse, CHF, vascular surgery, nephrotoxins (such as antibiotics, intravenous contrast, or other drugs), or urinary outflow obstruction.
- May present with flank pain, haematuria, hypertension or hypotension, oedema, lethargy, uraemia, or decreased urine output; however, often asymptomatic and only diagnosed by laboratory tests.
- An acute increase in serum creatinine is essential for diagnosis. Hyperkalaemia, hyperphosphataemia, metabolic acidosis, and elevated urea nitrogen are common.
- The mainstay of treatment is supportive care, with management of the underlying illness; correction of acid/base, electrolyte, and volume complications; removal and minimisation of nephrotoxins; and relief of any associated obstruction being key.
- Renal replacement therapy with dialysis may be required and is usually well tolerated.
- Failure to treat may be associated with clinical deterioration and death. Outcome is dependent upon the severity of the underlying disease.

BASICS

# Definition

Acute kidney injury (AKI), previously known as acute renal failure (ARF), is an acute decline in the GFR from baseline, with or without oliguria/anuria.[1] The change in terminology emphasises that kidney injury presents as a disease spectrum from mild renal impairment to severe renal failure.[1] [2] [3] A standardised definition is important to facilitate clinical care and research.[4] AKI may be due to various insults such as impaired renal perfusion, exposure to nephrotoxins, outflow obstruction, or intrinsic renal disease. The resulting effects include impaired clearance and regulation of metabolic homeostasis, altered acid/base and electrolyte regulation, and impaired volume regulation.

# Epidemiology

The reported incidences of AKI vary, and are confounded by differences in diagnosis, definition criteria, or hospital discharge coding.[6] [7] In the US, in the hospitalisation discharge diagnoses for kidney disease for 1980 to 2005, the rate of hospitalisation for kidney disease increased, particularly among adults aged >65 years, and primarily because of hospitalisations with diagnoses of acute kidney disease.[6] In the UK, incidence ranges from 172 per million population (pmp) per year to up to 630 pmp per year, depending on the study.[8] Overall incidence among hospitalised patients ranges from 13% to 22%.[3] [9] The overall incidence of AKI in the ICU is higher at 20% to 50% and it is associated with mortality over 50%.[10] Prediction scores have been developed for outcomes of AKI, but have had variable success.[11] [12]

Acute tubular necrosis (ATN) accounts for 45% to 70% of cases of AKI. ATN in ICU patients is caused by sepsis in 35% to 50% of cases. Pre-renal azotaemia, obstruction, glomerulonephritis, vasculitis, acute interstitial nephritis, acute on chronic kidney disease and atheroembolic injury account for most of the remaining.[13] [14]

The incidence of contrast nephropathy varies, and is reported to be the third most common cause of AKI in hospitalised patients. In a study of 7500 patients undergoing percutaneous intervention for CAD, 3.3% of all patients experienced AKI, defined as a rise in serum creatinine of 38 micromols/L (0.5 mg/dL) or more, and 25% of patients, with a baseline creatinine of at least 153 micromols/L (2.0 mg/dL), experienced AKI.[15]

Up to 7% of inpatient cases of AKI require renal replacement therapy.[16] In ICU, the mortality rate exceeds 50% in cases of multi-organ failure.[16] [13] [14] Minor rises in creatinine (≥26.5 micromols/L [0.3 mg/dL]) are associated with an increased risk of hospital mortality, an increased risk of chronic kidney disease, and higher odds of progressing to end-stage renal failure.

# Aetiology

Aetiology of AKI may be multi-factorial, generally classified into pre-renal, intrinsic, and post-renal causes.[17]

- Pre-renal azotaemia can be due to various causes of reduced renal perfusion, such as hypovolaemia, haemorrhage, sepsis, third spacing of fluid (such as in severe pancreatitis), overdiuresis, or other causes of reduced renal perfusion such as heart failure. Hepatorenal syndrome is a form of pre-renal azotaemia not responsive to fluid administration seen in cases of severe liver disease. Renovascular disease, especially with the recent addition of an angiotensin-converting enzyme (ACE) inhibitor to a patient with underlying bilateral renal artery stenosis, is also a consideration, and this sometimes leads to acute tubular necrosis.

- Intrinsic renal failure may be multi-factorial. Acute tubular necrosis, rapidly progressive glomerulonephritis, and interstitial nephritis are the most common aetiologies. Vascular diseases, including haemolytic uraemic syndrome, TTP, scleroderma renal crisis, atheromatous embolisation, and thrombosis, are also causal. Severe ischaemic injury may result in cortical necrosis.

- Post-renal injury results from mechanical obstruction of the urinary outflow tract. Retroperitoneal fibrosis, lymphoma, tumour, prostate hyperplasia, strictures, renal calculi, ascending urinary infection (including pyelonephritis), and urinary retention are common causes.

# Pathophysiology

Pre-renal azotaemia results from impaired renal perfusion and the changes seen are the appropriate physiological responses. The renal response to a lower perfusion pressure is to enhance sodium and water re-absorption. Baroreceptors in the carotid artery and aortic arch respond to lower BP with sympathetic stimulation. This, along with vasoconstriction of the glomerular efferent arteriole and dilation of the afferent arteriole, attempts to maintain glomerular filtration within a relatively narrow range. Decreasing perfusion promotes activation of the renin/angiotensin/aldosterone system. Angiotensin II, a potent vasoconstrictor, stimulates aldosterone release promoting sodium and water resorption at the collecting duct. Low blood volume is also a stimulus to the hypothalamus promoting ADH release and increased tubular water re-absorption, concentrating the urine.

Acute tubular necrosis (ATN) due to ischaemia, the most common form of AKI, is preceded by impaired renal perfusion and tissue hypoxaemia, yielding direct microvascular endothelial injury and tubular ischaemia typically most severe in the early proximal tubule and the outer medullary segments.[18] [19] Hypoxaemia results in increased reactive oxygen species, reduction in available ATP, and cellular dysfunction and death.[20] Additionally, complement system activation, direct neutrophil activation, membrane attack complex activation, cytokines, chemokines, and vasoactive hormones have all been studied and may be contributory.[21] [22] [23] [24] [25] [26] [27] [28] [29] ATN may also result from exposure to drugs, endotoxins, or radiocontrast media. Animal models suggest direct cytotoxic effects of the contrast as well as renal vasoconstriction resulting in impaired medullary blood flow, increased viscosity, and hypoxaemia.[30] [31] [32] [33] [34] [35]

Renal injury associated with obstruction results from increased intratubular pressure yielding tubular ischaemia and atrophy. Evidence also suggests injury results from an influx of monocytes and macrophages. Cytokines, free radicals, proteases, and TNF-beta are released causing tubular injury and fibrosis when obstruction becomes chronic.[36] [37] [38] [39]

There is very preliminary evidence that a genetic predisposition for AKI may exist, especially with apolipoprotein E (APO-E) genes.[40] Genome-wide searches have found other protective candidates, but much more work is needed to validate these findings.[41]

# Classification

## Kidney Disease: Improving Global Outcomes (KDIGO) definition of AKI[1]

Any of the following:

- Increase in serum creatinine by ≥26.5 micromol/L (≥0.3 mg/dL) within 48 hours; or

- Increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume <0.5 mL/kg/hour for 6 hours.

## Classification based on pathophysiology[5]

- Pre-renal: failure due to impaired renal perfusion, with an appropriate renal response.
- Intrinsic: failure due to direct injury to renal parenchyma.
- Post-renal: failure due to obstruction of urinary outflow.

# Primary prevention

Pre-treatment for radiocontrast exposure:

- N-acetylcysteine administration before contrast exposure may offer some protection against contrast-induced nephropathy,[46] [47] [48] [49] although data remain conflicting. One meta-analysis has shown the drug to be of no benefit and that it may, in fact, be harmful.[50] If used, it should be started 24 hours before the procedure and continued for 24 to 48 hours after exposure to contrast, at a dose of 600 mg orally or intravenously every 12 hours. There is, however, no evidence that N-acetylcysteine alters mortality or renal outcomes if given perioperatively when radiocontrast is not used.[49] Some have recommended its use in high-risk patients,[47] although further studies are needed.
- Administration of normal saline at a dose of 1 mL/kg/hour for several hours before and after the contrast is likely to be beneficial in the prevention of contrast nephropathy.[51]
- Probucol may also reduce the risk, according to a study of its use in patients undergoing coronary interventions, but remains experimental.[52] In patients with acute ST-elevation about to undergo coronary intervention, high dose atorvastatin followed by long-term therapy significantly decreased the incidence of contrast-induced nephropathy.[53] [54]
- One meta-analysis has shown that giving sodium bicarbonate does not protect against contrast-induced nephropathy better than saline.[55] However, further meta-analyses suggested that giving sodium bicarbonate may be superior to the sodium chloride alone in the prevention of contrast-induced nephropathy, but another trial again showed no difference.[56] [57] [58]
- Pre-treatment with atrial natriuretic peptide and its continuation for 48 hours has been shown to prevent a rise in creatinine compared with treatment with IV fluids alone .[59] Overall evidence remains lacking.

Treatment during cardiac surgery:

- Sodium nitroprusside has been shown to be associated with improved renal function when given during the rewarming period of non-pulsatile coronary pulmonary bypass in the course of coronary artery bypass grafting surgery.[60]
- One large meta-analysis of 4605 adult patients undergoing cardiac surgery with cardiopulmonary bypass and receiving different forms of therapy, concluded that fenoldopam, atrial natriuretic peptide, and brain natriuretic peptide showed evidence of nephroprotection, although none reduced all-cause mortality.[61] These interventions are hard to justify based on overall evidence.
- Statin therapy has been evaluated as primary prevention of AKI following cardiac surgery, with mixed results. One study analysing the effect of high-dose perioperative atorvastatin in patients undergoing elective coronary artery bypass grafting, valvular heart surgery, or ascending aortic surgery suggested no benefit.[62]
- Levosimendan, a calcium sensitiser used to improved cardiac output, has thus far appeared promising in studies to prevent AKI in patients undergoing cardiac surgery.[63] However, levosimendan is not yet available.
- One meta-analysis has suggested that preoperative intra-aortic balloon pump support for high-risk patients undergoing coronary artery bypass grafting surgery lessens the chance of postoperative AKI.[64]
- Off-pump surgery is probably less risky.[44]

Critically ill patients in ICU setting

- The use of a chloride-sparing intravenous fluid strategy in critically ill patients had been suggested to reduce the incidence of AKI,[65] but other randomised trial data questions this finding.[66]



 

# Case history

## Case history #1

A 65-year-old male smoker with hypertension, dyslipidaemia, and diabetes mellitus presents with chest pain. ECG changes suggest an acute MI. He is taken for an urgent coronary angiogram. Three days later, he is noticed to have developed an elevated serum creatinine, oliguria, and hyperkalaemia.

## Case history #2

A 35-year-old man with a history of congenital valvular heart disease undergoes a dental procedure without appropriate antibiotic prophylaxis. Several weeks later, he presents with fever and respiratory distress. He is intubated, and *Streptococcus viridans* is isolated in all blood cultures drawn at the time of admission. Echo demonstrates a mitral valve vegetation. Laboratory tests reveal a rising serum creatinine and urine output decline. Urine analysis reveals more than 20 WBCs, more than 20 RBCs, and red cell casts. Urine culture is negative. Renal ultrasound is unremarkable. Serum ESR is elevated.

## Other presentations

AKI may develop in the setting of normal urine output and an otherwise asymptomatic patient. Associated laboratory abnormalities including elevated serum creatinine and urea, hyperkalaemia, and anion gap or non-gap metabolic acidosis may be all that are seen. Symptoms such as arthralgias, myalgias, or rash may be seen in cases of vasculitis or glomerulonephritis.

AKI following vascular catheterisation or systemic anticoagulation may result from atheroembolic injury. Abdominal masses, found on examination or by imaging, may be found in otherwise asymptomatic individuals with obstructive nephropathy and renal failure. AKI with allergy symptoms (fever, rash, arthralgia), haematuria, and sterile pyuria suggests interstitial nephritis.

DIAGNOSIS

# Step-by-step diagnostic approach

AKI is diagnosed by an acutely rising urea and creatinine, or sustained oliguria, in line with validated criteria such as the Kidney Disease: Improving Global Outcomes (KDIGO) definition.[1] [3] The KDIGO criteria merges into a single definition features of the RIFLE (Risk, Injury, Failure, Loss of kidney function, and Endstage kidney disease)[67] and Acute Kidney Injury Network (AKIN)[68] criteria.

AKI is diagnosed if any of the following criteria are met:[1]

- Increase in serum creatinine by ≥26.5 micromol/L (≥0.3 mg/dL) within 48 hours; or
- Increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume <0.5 mL/kg/hour for 6 hours.

AKI should then be staged according to severity criteria using KDIGO, RIFLE, or AKIN classifications.[1] [67] [68]

The condition is often asymptomatic and only diagnosed by laboratory tests. General symptoms may include nausea and vomiting. Uraemia and an altered mental status may occur but these are more commonly seen in advanced AKI or in advanced chronic kidney disease.

A history of trauma or predisposing disease (e.g., CHF, chronic kidney disease, diabetes, peripheral vascular disease, and connective tissue diseases such as SLE, scleroderma, and vasculitis) may be present. Several groups have published risk scores for AKI and these have been variably validated by follow-up studies.[45] [69] [70]

## History in pre-renal failure

Patients may have a history of excessive fluid loss from haemorrhage, the GI tract (vomiting, diarrhoea), or sweating. Hospitalised patients may have insufficient replacement fluids to cover ongoing and insensible losses, especially if there is restriction of enteral input.

There may be a history of sepsis, GI surgery, or pancreatitis.

Patients may present with symptoms of hypovolaemia: thirst, dizziness, tachycardia, oliguria, or anuria. Orthopnoea and paroxysmal nocturnal dyspnoea may occur if advanced cardiac failure is present.

## History in intrinsic renal disease

The patient may have a history of rash, haematuria, or oedema with HTN suggesting nephritic syndrome and an acute glomerulonephritis or renal vasculitis. There might have been a recent vascular intervention preceding the AKI leading to cholesterol emboli or contrast-induced injury. A history of myeloproliferative disorder such as multiple myeloma may predispose to AKI, particularly in volume-depleted patients.

A history of all current medicines and any recent radiological examinations should be taken to establish any exposure to potential nephrotoxins.

Allergic interstitial nephritis may be suspected in patients with a history of NSAID use or recent administration of new medicines such as beta-lactam antibiotics.

Pigment-induced AKI, due to rhabdomyolysis, should be suspected in patients presenting with muscle tenderness, seizures, drug abuse or alcohol abuse, excessive exercise, or limb ischaemia (e.g., from crush injury).

Medicines, including aciclovir, methotrexate, triamterene, indinavir, or sulphonamides, can cause tubular obstruction by forming crystals. Over-the-counter medications (OTCs) such as NSAIDs and sympathomimetics are often overlooked,[71] and patients should be specifically queried about their use. Other substances to consider include hallucinogens and "bath salts".[72]

## History in post-renal failure

Post-renal failure is more common in older men with prostatic obstruction. There is often a history of urgency, frequency, or hesitancy.

A history of malignancy, prostatism, nephrolithiasis, or previous surgery may coincide with the diagnosis of obstruction. Obstruction caused by renal calculi or papillary necrosis typically presents with flank pain and haematuria.

## Physical examination

Hypotension, hypertension, pulmonary oedema, or peripheral oedema may be present. There may be asterixis or altered mental status when uraemia is present.

The patient with fluid loss, sepsis, or pancreatitis may have hypotension along with other signs of circulatory collapse.

Patients with glomerular disease typically present with hypertension and oedema, proteinuria, and microscopic haematuria (nephritic syndrome).

The presence of rash, petechiae, or ecchymoses may suggest an underlying systemic condition such as vasculitis or glomerulonephritis.

Patients with acute tubular necrosis may present after haemorrhage, sepsis, drug overdose, surgery, cardiac arrest, or other conditions with hypotension and prolonged renal ischaemia.

An underlying abdominal bruit may support renovascular disease.

The patient with prostatic obstruction may present with abdominal distension from a full bladder.

## Initial tests

Initial work-up should include basic metabolic profile (including urea and creatinine), venous blood gases, FBC, urinalysis and culture, urine chemistries (for fractional excretion of sodium and urea), renal ultrasound (when appropriate by history or examination), CXR, and ECG. Urine osmolality is rarely ordered but, if high, suggests pre-renal azotemia (in the absence of contrast dyes). Urinary eosinophil counts have low sensitivity and specificity for acute interstitial nephritis, but may be of some use in patients with pyuria.[73]

CXR may reveal pulmonary oedema or cardiomegaly.

ECG may demonstrate arrhythmias if hyperkalaemia is present.

Bladder catheterisation is recommended in all cases of AKI, if bladder outlet obstruction cannot be quickly ruled out by ultrasound. It is diagnostic and therapeutic for bladder neck obstruction in addition to providing an assessment of residual urine and a sample for analysis.

A ratio of serum urea to creatinine ratio of 20:1 or higher supports a diagnosis of pre-renal azotaemia, but other causes of elevated urea must be ruled out (such as drug-induced elevations or GI bleeding).

A fractional excretion of sodium (FENa) of <1% supports pre-renal azotaemia but may also be seen in glomerulonephritis, hepatorenal syndrome, and some cases of obstruction and even acute tubular necrosis, as long as tubular function remains intact. The FENa is calculated as follows: (urine sodium x plasma creatinine)/(plasma sodium x urine creatinine) x 100%.

A fractional excretion of urea of <35% supports a diagnosis of pre-renal azotaemia and is helpful if the patient has had diuretic exposure. The fractional excretion of urea is calculated as follows: (urine urea x plasma creatinine)/(plasma urea x urine creatinine) x 100%.

A fluid challenge may be administered with crystalloid or colloid, and is both diagnostic and therapeutic for pre-renal azotaemia if renal function improves rapidly.

High urine osmolality (or an elevated urine specific gravity), seen in pre-renal azotaemia, suggests maintenance of normal tubular function and response to ADH in cases of hypovolaemia. Urine sodium concentration of <20 mmols/L (20 mEq/L) suggests avid sodium retention and would be seen in renal hypoperfusion/pre-renal azotaemia. High urinary sodium is often seen in ATN, but is not exclusive to the diagnosis. Urine osmolality may be very high as the result of radiocontrast dyes and mannitol.

Urinary eosinophils of more than 5% to 7% supports, but is not diagnostic for, interstitial nephritis.

If there is no identified cause of AKI, a renal ultrasound is ordered at onset of work-up to assist in evaluation of obstructive causes as well as in the evaluation of renal architecture and size. It is also useful for diagnosis of underlying chronic kidney disease.

## Subsequent tests

A CT or MR scan may be required to further evaluate cases of obstruction suggested on ultrasound (e.g., possible masses or stones).

Nuclear renal flow scans can evaluate renal perfusion and function, and may be modified using captopril to evaluate for renal artery stenosis, or with furosemide to evaluate for obstruction in cases of mild hydronephrosis, when obvious mechanical obstruction is uncertain.

Further diagnostic tests may be determined by the suspected cause of AKI, such as cystoscopy for cases of suspected ureteral stenosis or serological evaluation (e.g., anti-streptolysin O, ESR, ANA, anti-DNA, complement, anti-glomerular basement membrane, anti-neutrophil cytoplasmic antibodies, acute hepatitis profile, HIV test, and cryoglobulins) if the history suggests autoimmune, vasculitis, infectious, or immune complex disease, or in cases of suspected glomerulonephritis. Novel serum and urinary biomarkers are showing potential as useful indicators for the diagnosis of AKI and as predictors of mortality after AKI.[74] [75] Further studies are still needed.

A renal biopsy may be performed for further evaluation of AKI when the history and physical and other studies suggest systemic disease as aetiology or when the diagnosis is unclear.

Biopsies may confirm acute tubular necrosis, but are rarely done for this condition.

# Risk factors

## Strong

### advanced age

- Advanced age is associated with chronic kidney disease, underlying renal vascular disease, and other comorbid medical conditions that predispose to AKI.

### underlying renal disease

- Associated with increased susceptibility to AKI, particularly contrast-related AKI. Risks increase with increasing severity of CKD.[5]

### malignant hypertension

- Malignant HTN may cause AKI.[5]

### diabetes mellitus

- Incidence rates of AKI of 9% to 38% have been reported in cases of patients with diabetes and chronic kidney disease undergoing contrast exposure.[42]

### myeloproliferative disorders, such as multiple myeloma

- Intratubular precipitation of light chains in times of volume contraction is associated with renal injury, especially in cases of contrast exposure with volume contraction in myeloma patients. Hypercalcaemia predisposes to pre-renal azotaemia.[5] [43]

### connective tissue disease

- May present with AKI (e.g., SLE, scleroderma, anti-neutrophil cytoplasmic antibodies [ANCA]-associated glomerulonephritis, anti-glomerular basement membrane disease).[5]

### sodium-retaining states (e.g., CHF, cirrhosis, nephrotic syndrome)

- Associated with chronic kidney disease, but may present with AKI.[5]

### radiocontrast

- Exposure may cause AKI.[5]

### exposure to nephrotoxins (e.g., aminoglycosides, cancer therapies, NSAIDs, or ACE inhibitors)

- May precede and lead to AKI.[5]

### trauma

- There may be impaired renal perfusion causing pre-renal azotaemia, rhabdomyolysis predisposing to pigment-induced injury, or ischaemia causing acute tubular necrosis.

### haemorrhage

- The resulting impaired renal perfusion supports pre-renal azotaemia as cause of AKI or ischaemia resulting in acute tubular necrosis.

### sepsis

- May result in acute tubular necrosis, infectious glomerulonephritis, pre-renal azotaemia from hypotension, or drug-induced injury from medicines used in treatment. Highest risk with bacteraemia.

### pancreatitis

- There may be severe third spacing of fluid leading to intravascular volume depletion resulting in pre-renal failure.

### drug overdose

- May precede AKI due to rhabdomyolysis and volume depletion.

### surgery

- May precede AKI from pre-renal, intrinsic, or post-renal causes. Cardiothoracic surgery is particularly high risk, although off-pump approaches may limit this risk.[44]

### cardiac arrest

- May precede pre-renal azotaemia or acute tubular necrosis, especially if there is severe and prolonged renal ischaemia.

### recent vascular intervention

- May be associated with atheroembolic injury or contrast-induced AKI.

### excessive fluid loss

- From haemorrhage, vomiting, diarrhoea, or sweating; hospitalised patients may have insufficient replacement fluids.

### nephrolithiasis

- May lead to AKI if significant obstruction is present.

## Weak

### drug abuse

- AKI from nephrotoxicity, ischaemia.

### alcohol abuse

- Suspect pigment-induced AKI if rhabdomyolysis is present (e.g., after prolonged loss of consciousness).

### excessive exercise

- Suspect pigment-induced AKI due to rhabdomyolysis.

### recent blood transfusion

- AKI may be present from intravascular haemolytic transfusion reaction, deposition of immune complexes.

### malignancy

- May lead to post-renal AKI if mass effect is causing outflow obstruction, or AKI may result in association with myeloproliferative disorders or chemotherapy-related toxicities (i.e., tumour lysis). Immune complex glomerulonephritis may result from the malignancy.

### genetic susceptibility

- Some genes may lead to a predisposition to AKI, although there is a dearth of studies.

### use of renin-angiotensin system inhibitors

- Found to be a predictor of risk of postoperative AKI, but may be a marker rather than a mediator of risk. It is unclear whether there is any benefit to stopping agents prior to surgery in high-risk patients.[45]

# History & examination factors

## Key diagnostic factors

### presence of risk factors (common)

- Key factors include advanced age, underlying renal failure, malignant HTN, diabetes mellitus, and exposure to nephrotoxins.

### reduced urine production (common)

- Oliguria and anuria, although not diagnostic, are common in kidney injury but not suggestive of a particular aetiology.

### vomiting (common)

- May precede AKI and suggest pre-renal azotaemia, or be a later manifestation resulting from uraemia.

### dizziness (common)

- Orthostatic symptoms support pre-renal azotaemia.

### orthopnoea (common)

- Symptoms of volume overload may result from impaired salt and volume regulation and decreased urine production.

### paroxysmal nocturnal dyspnoea (common)

- Symptoms of volume overload may result from impaired salt and volume regulation and decreased urine production.

### pulmonary oedema (common)

- Evidence of pulmonary oedema (e.g., rales on examination) suggest volume overload resulting from impaired salt and volume regulation.

### hypotension (common)

- Supports pre-renal azotaemia that may progress to acute tubular necrosis.

### tachycardia (common)

- Supports pre-renal azotaemia.

### orthostatic hypotension (common)

- Orthostatic symptoms support pre-renal azotaemia.

### hypertension (common)

- Suggests intravascular volume expansion.

### peripheral oedema (common)

- May result from impaired renal salt excretion.

### muscle tenderness (uncommon)

- Suspect rhabdomyolysis and pigment-induced AKI.

### limb ischaemia (uncommon)

- Suspect rhabdomyolysis and pigment-induced AKI.

### seizures (uncommon)

- Suspect rhabdomyolysis and pigment-induced AKI.

### prostatic obstructive symptoms (uncommon)

- Post-renal failure more common in older men with prostatic obstruction and symptoms of urgency, frequency, or hesitancy.

### haematuria (uncommon)

- May indicate obstruction caused by renal calculi, papillary necrosis, infection, tumour, or acute glomerulonephritis.

### fever (uncommon)

- If present, suspect interstitial nephritis, systemic disease, infectious complication, or vasculitis.

### rash (uncommon)

- If present, suspect interstitial nephritis, systemic disease, infectious complication, or vasculitis.

### arthralgia/arthritis (uncommon)

- If present, suspect interstitial nephritis, systemic disease, infectious complication, or vasculitis.

### altered mental status (uncommon)

- Although more often seen in chronic renal failure, will also be seen in AKI when uraemia ensues.

### signs of uraemia (uncommon)

- Although more often seen in chronic renal failure, symptoms and signs may be seen in AKI prior to dialysis initiation (e.g., asterixis).

## Other diagnostic factors

### nausea (common)

- May precede AKI and suggest pre-renal azotaemia, or be a later manifestation resulting from uraemia.

### thirst (uncommon)

- Suggests pre-renal azotaemia if normal physiological responses and drives are present in a conscious patient.

### flank pain (uncommon)

- May indicate infection, obstruction caused by renal calculi, or papillary necrosis.

### abdominal distention (uncommon)

- Bladder outlet obstruction may manifest as distention and pain.

### abdominal bruit (uncommon)

- Presence of renal bruits suggests renovascular disease.

### livedo reticularis (uncommon)

- The presence of classic findings for systemic diseases may suggest renal manifestations.

### petechiae (uncommon)

- The presence of classic findings for systemic diseases may suggest renal manifestations.

### ecchymoses (uncommon)

- The presence of classic findings for systemic diseases may suggest renal manifestations.

# Diagnostic tests

## 1st test to order

| Test | Result |
|---|---|
| **basic metabolic profile (including urea and creatinine)**<br>• Often an acutely elevated serum creatinine may be the initial or only sign of decline in renal function. | **acutely elevated serum creatinine, high serum potassium, metabolic acidosis** |
| **ratio of serum urea to creatinine**<br>• Consider other causes of elevated urea (such as drug-induced elevations or GI bleeding) when interpreting results. | **20:1 or higher supports pre-renal azotaemia** |
| **urinalysis**<br>• Collected as clean-catch specimen.<br>• Patients with glomerular disease typically present with proteinuria and microscopic haematuria with HTN and oedema. | **RBCs, WBCs, cellular casts, proteinuria, bacteria, positive nitrite and leukocyte esterase (in cases of infection)** |

| Test | Result |
|---|---|
| **urine culture**<br>• Collected if there is suspicion of infection on initial urinalysis. | **bacterial or fungal growth may occur** |
| **FBC**<br>• Anaemia is suggestive of possible chronic kidney disease, blood loss.<br>• Leukocytosis may support infection.<br>• Thrombocytopenia can be seen in rare disorders such as cryoglobulinaemia, haemolytic uraemic syndrome, or thrombotic thrombocytopenic purpura. | **anaemia, leukocytosis, thrombocytopenia** |
| **fractional excretion of sodium**<br>• May also be seen in glomerulonephritis, hepatorenal syndrome, and some cases of obstruction, as long as tubular function remains intact. Increased levels are also caused by diuretics. | **<1% supports pre-renal azotaemia** |
| **fractional excretion of urea**<br>• Test used if patient has been exposed to diuretics. | **<35% supports pre-renal azotaemia** |
| **urinary eosinophil count**<br>• Urinary eosinophil counts have low sensitivity and specificity for acute interstitial nephritis, but may be of some use in patients with pyuria.[73]<br>• Eosinophiluria may be seen with atheroembolic disease as well. | **>5% to 7% supports a diagnosis of interstitial nephritis** |
| **venous blood gases**<br>• Anion gap acidosis seen in acute and chronic renal failure due to impaired excretion of non-volatile acids.<br>• Assists in further evaluation of acidosis, which is often suggested by the low bicarbonate on the basic metabolic profile. | **diagnostic for metabolic acidosis and certain intoxications** |
| **fluid challenge**<br>• Both diagnostic and therapeutic in pre-renal azotaemia. | **renal function improves rapidly in pre-renal azotaemia** |
| **bladder catheterisation**<br>• Diagnostic and therapeutic for bladder neck obstruction in addition to providing an assessment of residual urine and a sample for analysis. | **significant urine volume released after catheter placement (in cases of bladder outlet obstruction); minimal residual urine after catheter placement (in cases of impaired urine production or higher level obstruction)** |
| **urine osmolality**<br>• Evaluates maintenance of normal tubular function and response to ADH in cases of hypovolaemia. | **high in pre-renal azotaemia (the effect of dyes and mannitol must be excluded); close to serum osmolality in acute tubular necrosis** |
| **urine sodium concentration**<br>• High levels in acute tubular necrosis not exclusive to the diagnosis. | **<20 mmols/L (<20 mEq/L) (suggests avid sodium retention in renal hypoperfusion and pre-renal azotaemia); high level (often with acute tubular necrosis)** |

| Test | Result |
|---|---|
| **renal ultrasound**<br>• Assists in evaluation of post-obstructive causes as well as in the evaluation of renal architecture and size (underlying chronic kidney disease). | **dilated renal calyces (suggesting obstruction), reduced corticomedullary differentiation, or small and sclerotic-appearing kidneys (suggesting chronic kidney disease)** |
| **CXR**<br>• If renal failure is associated with heart failure. | **may show signs of pulmonary oedema and cardiomegaly** |
| **ECG**<br>• May occur with severe hyperkalaemia. | **peaked T waves, increased PR interval, widened QRS, atrial arrest, and deterioration to a sine wave pattern (if severe hyperkalaemia)** |

## Other tests to consider

| Test | Result |
|---|---|
| **ANA**<br>• Elevated titre is supportive of a diagnosis of SLE, which often has renal manifestations. | **normal or elevated** |
| **anti-DNA**<br>• Elevated titre supports the diagnosis of SLE, which often has renal manifestations. | **normal or elevated** |
| **complement (C3, C4, CH50)**<br>• Low complement levels support an active disease process, such as SLE. | **normal or depressed** |
| **anti-glomerular basement membrane**<br>• Elevated titres indicate antibodies to the glomerular basement membrane, which may present in diseases of the kidney (e.g., Goodpasture's and anti-glomerular basement membrane syndrome). | **normal or elevated** |
| **anti-neutrophil cytoplasmic antibodies (ANCA)**<br>• Elevated titres are seen in vasculitic syndromes such as granulomatosis with polyangiitis, eosinophilic polyangiitis, and microscopic polyangiitis. | **normal or elevated titres** |
| **acute hepatitis profile**<br>• The presence of positive serology in active hepatitis C is associated with renal conditions such as membranoproliferative glomerulonephritis and cryoglobulinaemia. | **positive or negative serology** |
| **HIV serology**<br>• HIV-associated nephropathy and certain medicines used in the management of HIV have renal complications. | **positive or negative** |
| **cryoglobulins**<br>• The presence of cryoglobulins support cryoglobulin-associated renal disease, if AKI is present. | **positive or negative serology** |

| Test | Result |
|---|---|
| **ESR**<br>• A normal ESR argues against the presence of inflammatory renal disease or embolic injury. | **normal or elevated** |
| **anti-streptolysin-O antibody**<br>• An elevated titre supports, but does not make a diagnosis of, an infectious glomerulonephritis. | **normal or elevated** |
| **abdominal CT or MR scan**<br>• Sometimes required to further evaluate cases of obstruction suggested on ultrasound. | **image of mass or stone may be present** |
| **nuclear renal flow scan**<br>• May be modified using captopril to evaluate for renal artery stenosis, or furosemide to evaluate for obstruction in cases of hydronephrosis where obvious mechanical obstruction is uncertain. | **normal scan reveals appropriate renal perfusion, tracer uptake, and excretion; impaired tracer excretion (supportive of acute tubular necrosis); poor blood flow (supportive of obstruction of blood supply); normal blood flow and tracer excretion with tracer accumulation in the collecting system (supportive of obstruction of the urine outflow tract)** |
| **cystoscopy**<br>• May be used if obstruction due to stenosis of the ureter is suspected. | **direct visualisation and treatment of ureteral stenosis if present** |
| **renal biopsy**<br>• Biopsy is frequently required to further investigate positive serological studies.<br>• Biopsies also done when the cause of kidney injury is unclear.<br>• May confirm acute tubular necrosis, but not often performed for this diagnosis. | **changes associated with acute tubular necrosis, glomerulonephritis, vasculitis, or other intrinsic renal disease may be present** |

## Emerging tests

| Test | Result |
|---|---|
| **novel serum and urinary biomarkers**<br>• Various novel serum and urinary biomarkers are showing potential as useful indicators for the diagnosis and classification of AKI[76] and as predictors of mortality after AKI,[74] [77] although further studies remain needed.[75] [78] [79] [80] | **results indicative of renal damage** |

# Differential diagnosis

| Condition | Differentiating signs / symptoms | Differentiating tests |
|---|---|---|
| **Chronic kidney disease (CKD)** | • Reduced renal function with elevation of creatinine is chronic (>3 months), although there may be acute on chronic renal disease. | • An acutely elevated serum creatinine is diagnostic of AKI and indicative of reduced clearance.<br>• There are no causes of chronically elevated serum creatinine other than reduced glomerular filtration, except for minor elevations in subjects with increased muscle mass and from certain medicines.<br>• Creatinine elevation over time provides a chronological perspective and assists in differentiating acute from chronic kidney disease.<br>• Twenty-four-hour urine study for creatinine clearance would demonstrate the level of renal function; the use of 131-I iothalamate is the definitive test for this purpose. |
| **Increased muscle mass** | • Any elevation of creatinine is minor and typically non-acute. | • Acutely elevated serum creatinine is diagnostic of AKI.<br>• Minor elevations in creatinine from increased muscle mass may rarely be seen.<br>• Twenty-four-hour urine study for creatinine clearance would demonstrate normal renal function. |
| **Drug side effect** | • Certain medicines such as cimetidine may lead to an elevation of creatinine that is minor and non-acute. | • Discontinuing the medicine should result in normalising of the serum creatinine.<br>• Twenty-four-hour urine study for creatinine clearance should demonstrate normal function. |

# Diagnostic criteria

## Kidney Disease: Improving Global Outcomes (KDIGO) - definition criteria[1]

Any of the following:

- Increase in serum creatinine by ≥26.5 micromol/L (≥0.3 mg/dL) within 48 hours; or
- Increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or

- Urine volume <0.5 mL/kg/hour for 6 hours.

## Kidney Disease: Improving Global Outcomes (KDIGO) - severity criteria[1]

- Stage 1
  - Serum creatinine 1.5 to 1.9 times baseline; or
  - ≥26.5 micromol/L (≥0.3 mg/dL) increase in serum creatinine; or
  - Urine output <0.5 mL/kg body weight for 6 hours
- Stage 2
  - Creatinine increased 2.0 to 2.9 times; or
  - Urine output <0.5 mL/kg for 12 hours
- Stage 3
  - Creatinine increased 3.0 times; or
  - Increase in creatinine to ≥353.6 micromol/L (≥4.0 mg/dL); or
  - Initiation of renal replacement therapy; or
  - Urine output <0.3 mL/kg for 24 hours OR anuria for 12 hours.

## RIFLE (Risk, Injury, Failure, Loss of kidney function, and Endstage kidney disease) consensus criteria[67]

Laboratory test indicates reduced renal clearance.

Severity groups are as follows.

- Indicates risk:
  - Serum creatinine increased 1.5 times; or
  - Urine production of <0.5 mL/kg body weight for 6 hours.
- Indicates injury:
  - Creatinine increased 2.0 times; or
  - Urine production of <0.5 mL/kg for 12 hours.
- Indicates failure:

- Creatinine increased 3.0 times; or
- Urine output <0.3 mL/kg for 24 hours or anuria for 12 hours.

- Indicates loss:
  - Persistent AKI for more than 4 weeks; complete loss of kidney function.
- Indicates ESRD:
  - ESRD (loss >3 months).

## National Institute for Health and Care Excellence: detecting acute kidney injury[3]

Detect AKI, in line with the RIFLE, Acute Kidney Injury Network (AKIN), or KDIGO definitions, by using any of the following criteria:

- A rise in serum creatinine of 26 micromol/L (0.3 mg/dL) or greater within 48 hours; or
- A 50% or greater rise in serum creatinine known or presumed to have occurred within the past 7 days; or
- A fall in urine output to <0.5 mL/kg/hour for more than 6 hours in adults and more than 8 hours in children and young people; or
- A 25% or greater fall in estimated GFR in children and young people within the past 7 days.

# Step-by-step treatment approach

Treatment approaches for AKI vary according to the type of insult. The underlying illnesses require treatment.

General therapy includes intervention in electrolyte and acid/base abnormalities and optimisation of volume status, either by replacing volume in the volume-contracted patient or by fluid removal (either diuresis or renal replacement therapy) in patients with volume overload.

Sodium and volume restriction are generally required along with limiting potassium and phosphorus intake.

Dose adjustment of medications is likely required in all cases and should not be overlooked. Patients with AKI should not be given potentially nephrotoxic drugs unless there is no alternative. Electrolyte and acid-base balance should be monitored and optimised. Early involvement by a nephrologist may be valuable;[81] however, automated electronic alerts to identify AKI have not proved helpful in trials in improving outcomes.[82]

## Pre-renal renal failure

Pre-renal azotaemia is managed with techniques to improve the haemodynamic status of the patient.

The volume-contracted patient requires volume expansion with crystalloid or colloid to restore euvolaemia.

Crystalloid (normal saline or lactated Ringer's) or colloid (considered in cases of significant hypoalbuminaemia) fluids are infused, along with packed RBCs if there is significant anaemia.[5] The use of the semi-synthetic hydroxyethyl starch is not advised, as mortality appears to be increased.[83] Blood transfusion is generally not given if only 1 unit is anticipated. All fluid resuscitation should be performed by one with expertise in the area, with close patient monitoring.

Vasopressors are recommended if hypotension is severe, to augment BP while optimising the patient's volume status. A common goal of vasopressors in this setting is to keep the mean arterial pressure (MAP) >60 mmHg. (MAP is the diastolic pressure plus one third of the pulse pressure, where the pulse pressure is the systolic pressure minus the diastolic pressure.)

If renal hypoperfusion results from impaired cardiac function due to poor left ventricular systolic function, management is often difficult, but requires optimising cardiac output and volume status by use of inotropes, diuretics, or renal replacement therapy as indicated by the clinical scenario along with close following of renal function and urine production during therapy.[5]

Vasopressors and inotropic agents should be used only with appropriate haemodynamic monitoring in place.

Renal replacement therapy may be needed if severe acid/base, electrolyte, or uraemic complications are present while the underlying cardiac or volume issues are treated. The use of diuretics may be helpful to manage volume in patients with ineffective circulating volume and pre-renal AKI. However, they generally cannot avert the need for renal replacement therapy by means of dialysis or filtration, and diuretic-unresponsive volume overload, increased potassium, severe metabolic acidosis, or uraemic symptoms are indications to proceed to renal replacement therapy.[5]

## Intrinsic renal failure

Management of intrinsic renal failure varies according to aetiology.

Volume expansion is required when co-existing pre-renal azotaemia exists.

Generally, patients with volume overload require sodium restriction. The amount of sodium restriction depends on the clinical setting. Volume overload may be managed with diuretics when effective.

Removal of offending drugs, when possible, is necessary in cases of interstitial nephritis or drug-induced AKI.

Acute glomerulonephritis and vasculitis management may also require corticosteroids, cytotoxic agents, or other immune-modifying drugs depending on the specific diagnosis, often determined by renal biopsy and serology studies.

The management of acute glomerulonephritis requires a nephrologist consultation, particularly regarding the use of cytotoxic and immune-modifying agents. Doses and protocols for many of the drugs used vary by centre and are areas of continuing research, and will not be detailed further here. The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for glomerulonephritis can be consulted. [KDIGO clinical practice guideline for glomerulonephritis]

There is no specific therapy for acute tubular necrosis aside from supportive care in maintaining volume status and controlling electrolyte and acid/base abnormalities. Nephrotoxins should be removed or minimised. Renal replacement therapy is generally required if there is severe acidosis, volume expansion refractory to diuretics, hyperkalaemia, or uraemia. These interventions remain a main treatment modality for AKI of all causes.

## Obstructive renal failure

Obstructive renal failure requires relief of the obstruction. Bladder catheter placement should be done in all cases of AKI when bladder outlet obstruction cannot be quickly ruled out by ultrasound.

Urological or surgical assistance for ureteral stenting, urinary diversion, debulking procedures, or other case-specific requirements may become necessary.

Renal replacement therapy may be needed if there is severe acidosis, volume overload unresponsive to diuretics, or electrolyte or uraemic complications while the underlying obstructive issue is being addressed.

## Renal replacement therapy

Various options exist for supporting lost renal function in patients, and selection involves evaluation of the patient's overall condition with haemodynamic and laboratory evaluation.[84] Renal replacement therapy is indicated for refractory severe hyperkalaemia, acidosis, volume overload, or uraemia. Studies to evaluate potential benefits of 'early' dialysis have shown mixed results, with the largest study suggesting no benefit in dialysing before reaching more traditional laboratory values or indications.[85] [86] Determination for need of support and type of therapy to be used is at the recommendation of the nephrologist consultation.

Conventional haemodialysis is often used when the indications for dialysis arise. Other modes of renal replacement include sustained low-efficiency dialysis (SLED), extended daily dialysis (EDD), or continuous renal replacement therapy (CRRT).[87] Arteriovenous and venovenous techniques may be used, although the most frequent is continuous venovenous treatment through a large double lumen catheter placed into the central venous system, such as the internal jugular or femoral vein. Major commonly used modalities include continuous venovenous haemofiltration (CVVH), continuous venovenous haemodialysis (CVVHD), and continuous venovenous haemodiafiltration (CVVHDF).[87] [88] [89] [90]

Use of CRRT is most useful in haemodynamically unstable patients or those in whom aggressive ultrafiltration within the conventional 4- to 6-hour treatment of haemodialysis would not be tolerated. Such patients include septic patients requiring vasopressors, or patients with severe heart failure with volume overload and a BP that would not support conventional haemodialysis. Despite improved haemodynamic stability, studies have shown that CRRT or more intensive/frequent dialysis in critically ill patients with AKI confers no increased benefit to other complications or to mortality.[88] [89] [90]



 

Peritoneal dialysis has generally been thought ineffective in AKI and hypercatabolic states, although studies now suggest equal effectiveness in appropriate subjects. In developing countries, high-volume peritoneal dialysis (HVPD) provides an alternative form of therapy in selected cases.[91] [92]

# Treatment details overview

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

## Acute (summary)

| Patient group | Tx line | Treatment |
|---|---|---|
| **pre-renal azotaemia** | **1st** | **volume expansion and/or RBC transfusion** |
| **with severe hypotension** | **plus** | **vasopressor** |
| **with volume overload** | **adjunct** | **diuretic** |
| **with uraemia, severe metabolic acidosis, hyperkalaemia refractory to medical management, or volume overload unresponsive to diuretics** | **adjunct** | **renal replacement therapy** |
| **intrinsic renal failure** | **1st** | **treatment of underlying condition** |
| **with volume overload** | **adjunct** | **diuretic** |
| **with pre-existing pre-renal azotaemia** | **adjunct** | **volume expansion** |
| **with uraemia, severe metabolic acidosis, hyperkalaemia refractory to medical management, or volume overload unresponsive to diuretics** | **adjunct** | **renal replacement therapy** |
| **obstructive renal failure** | **1st** | **bladder catheterisation** |
| | **2nd** | **relief of obstruction above bladder neck** |
| **with volume overload** | **adjunct** | **diuretic** |
| **with uraemia, severe metabolic acidosis, or hyperkalaemia refractory to medical management, or volume overload unresponsive to diuretics** | **adjunct** | **renal replacement therapy** |

# Treatment options

## Acute

| Patient group | Tx line | Treatment |
|---|---|---|
| **pre-renal azotaemia** | **1st** | **volume expansion and/or RBC transfusion**<br>» The underlying cause of volume contraction or blood loss needs to be treated along with restoring euvolaemia and haemodynamic stability.<br>» Crystalloid (normal saline or lactated Ringer's) is sufficient in most cases for volume expansion. Colloid might be used if there is significant hypoalbuminaemia. The use of the semi-synthetic hydroxyethyl starch is not advised, as mortality appears to be increased.[83]<br>» Volume expansion with normal saline has been demonstrated to be beneficial in reducing the risk of contrast-induced nephropathy. Target doses of normal saline at 1 mL/kg/hour have been demonstrated to have benefit.[51]<br>» As pre-renal azotaemia predisposes the kidney to injury from other means, such as contrast or nephrotoxins, care should be given to minimise exposures and dose-adjust drugs to maximise recovery potential.<br>» Haemorrhage requires blood product replacement. |
| **with severe hypotension** | **plus** | **vasopressor**<br>» Vasopressors are recommended for severe hypotension, often with the goal of keeping mean arterial pressure (MAP) >60 mmHg. (MAP is the diastolic pressure plus one third of the pulse pressure, where the pulse pressure is the systolic pressure minus the diastolic pressure.) All vasopressors should be used only with appropriate haemodynamic monitoring in place.<br>» The underlying cause of hypotension needs to be treated along with restoring euvolaemia and haemodynamic stability.<br>» The septic patient requires haemodynamic support with vasopressors as needed to support MAP and organ perfusion.<br>» Vasopressin is sometimes used as an adjunct to other vasopressors.<br>» If renal hypoperfusion results from impaired cardiac function, management is often difficult but requires optimising cardiac output and volume status. Inotropes, diuretics, or renal replacement therapy may be required. |



 

## Acute

| Patient group | Tx line | Treatment |
|---|---|---|
| | | **Primary options**<br>» dopamine: 1 microgram/kg/min intravenously initially, increase by 5-10 micrograms/kg/min increments until response, maximum 50 micrograms/kg/min<br>**OR**<br>» epinephrine (adrenaline): 1 microgram/min intravenously initially, increase dose according to response, maximum 20 micrograms/min<br>**OR**<br>» norepinephrine (noradrenaline): 1 microgram/min intravenously initially, increase dose according to response, maximum 30 micrograms/min<br>**OR**<br>» phenylephrine: 40-60 micrograms/min intravenously |
| **with volume overload** | **adjunct** | **diuretic**<br>» The use of diuretics may be helpful to manage volume in patients with ineffective circulating volume and pre-renal AKI. However, they generally cannot avert the need for renal replacement therapy (RRT) by means of dialysis or filtration, and diuretic-unresponsive volume overload is an indication to proceed to RRT.<br>» Impaired urine production and volume expansion are commonly seen in cases of AKI.<br>» Loop diuretics (e.g., furosemide) and metolazone may be effective in promoting diuresis, although diuretic resistance is often seen.<br>» Patients also require sodium restriction.<br>» It is important to remove or minimise any nephrotoxins.<br>**Primary options**<br>» furosemide: 20-40 mg intravenously initially, increase by 20 mg/dose increments every 2 hours as necessary until clinical response<br>**Secondary options**<br>» torasemide: 20 mg intravenously once daily initially, increase gradually according to response, maximum 200 mg/day |

## Acute

| Patient group | Tx line | Treatment |
|---|---|---|
| | | **OR**<br>» bumetanide: 0.5 to 1 mg intravenously initially, may repeat in 2-3 hours for up to 2 doses if necessary, maximum 10 mg/day<br>**OR**<br>» metolazone: 5-20 mg orally once daily |
| **with uraemia, severe metabolic acidosis, hyperkalaemia refractory to medical management, or volume overload unresponsive to diuretics** | **adjunct** | **renal replacement therapy**<br>» Nephrologist consultation is required.<br>» Conventional haemodialysis for 4 to 6 hours is used in haemodynamically stable patients.<br>» Other modes of renal replacement include sustained low-efficiency dialysis (SLED), extended daily dialysis (EDD), or continuous renal replacement therapy (CRRT).[87] Major commonly used modalities include continuous venovenous haemofiltration (CVVH), continuous venovenous haemodialysis (CVVHD), and continuous venovenous haemodiafiltration (CVVHDF).<br>» CRRT may be most beneficial in haemodynamically unstable patients (e.g., patients with sepsis, or severe CHF) or those in whom aggressive ultrafiltration within the conventional 4- to 6-hour treatment of haemodialysis would not be tolerated. Data evaluating higher clearance volumes and the addition of a dialysis dose to CVVH have shown improved outcomes.[93] [94] [95]<br>» Despite these promising initial results, studies have shown that intensive dialysis in critically ill patients with AKI confers no increased benefit.[87] [88] [89] [90] [96] |
| **intrinsic renal failure** | **1st** | **treatment of underlying condition**<br>» Management of intrinsic renal failure varies according to aetiology. Nephrotoxic agents should be ceased and the patient referred to a nephrologist if specific treatment, such as dialysis, management of fluids/acid-base status, severe hyperkalaemia, or immunosuppression is required. |
| **with volume overload** | **adjunct** | **diuretic**<br>» The use of diuretics in the management of AKI is primarily for volume control. The use of diuretics cannot avert the need for renal replacement therapy (RRT) by means of dialysis or filtration, but diuretic-unresponsive volume overload is an indication to proceed to RRT. |



 

## Acute

| Patient group | Tx line | Treatment |
|---|---|---|
| | | » Impaired urine production and volume expansion are commonly seen in cases of AKI.<br><br>» Loop diuretics (e.g., furosemide) and metolazone may be effective in promoting diuresis, although diuretic resistance is often seen.<br><br>» Patients also require sodium restriction.<br><br>» It is important to remove or minimise any nephrotoxins.<br><br>**Primary options**<br><br>» furosemide: 20-40 mg intravenously initially, increase by 20 mg/dose increments every 2 hours as necessary until clinical response<br><br>**Secondary options**<br><br>» torasemide: 20 mg intravenously once daily initially, increase gradually according to response, maximum 200 mg/day<br><br>**OR**<br><br>» bumetanide: 0.5 to 1 mg intravenously initially, may repeat in 2-3 hours for up to 2 doses if necessary, maximum 10 mg/day<br><br>**OR**<br><br>» metolazone: 5-20 mg orally once daily |
| **with pre-existing pre-renal azotaemia** | **adjunct** | **volume expansion**<br><br>» Crystalloid (normal saline or lactated Ringer's) is sufficient in most cases for volume expansion. Colloid might be used if there is significant hypoalbuminaemia. The use of the semi-synthetic hydroxyethyl starch is not advised, as mortality appears to be increased.[83]<br><br>» As pre-renal azotaemia predisposes the kidney to injury from other means, such as contrast or nephrotoxins, care should be given to minimise exposures and dose-adjust drugs to maximise recovery potential. |
| **with uraemia, severe metabolic acidosis, hyperkalaemia refractory to medical management, or volume overload unresponsive to diuretics** | **adjunct** | **renal replacement therapy**<br><br>» Nephrologist consultation recommended.<br><br>» Conventional haemodialysis is used in haemodynamically stable patients.<br><br>» Other modes of renal replacement include sustained low-efficiency dialysis (SLED), extended daily dialysis |

## Acute

| Patient group | Tx line | Treatment |
|---|---|---|
| | | (EDD), or continuous renal replacement therapy (CRRT).[87] Major commonly used modalities include continuous venovenous haemofiltration (CVVH), continuous venovenous haemodialysis (CVVHD), and continuous venovenous haemodiafiltration (CVVHDF).<br><br>» CRRT is most beneficial in haemodynamically unstable patients (e.g., patients with sepsis or severe CHF) or those in whom aggressive ultrafiltration within the conventional 4- to 6-hour treatment of haemodialysis would not be tolerated.<br><br>» Initial data evaluating higher clearance volumes and the addition of a dialysis dose to CVVH had suggested improved outcomes.[93] [94] [95]<br><br>» Studies have now shown that more intensive dialysis in critically ill patients with AKI confers no increased benefit.[87] [88] [89] [90] [96] |
| **obstructive renal failure** | **1st** | **bladder catheterisation**<br><br>» Treatment of obstructive renal failure requires mechanical decompression at the level of obstruction.<br><br>» Bladder catheter placement should be done in all cases of AKI if bladder outlet obstruction cannot be quickly ruled out by ultrasound. |
| | **2nd** | **relief of obstruction above bladder neck**<br><br>» If bladder neck obstruction is not the cause of the obstruction, further decompression more proximal in the GU tract, often requiring consultation with a urologist and involving placement of ureteral stents, dilation of strictures, or other necessary procedures may be required.<br><br>» Surgical consultation may be needed if the cause is tumour with mass effect and debulking is required.<br><br>**Primary options**<br><br>» ureteral stenting: if there is a ureteral stricture, stone or extrinsically obstructing mass<br><br>**OR**<br><br>» lithotripsy: stones present at the ureteropelvic junction causing obstruction may require lithotripsy or surgical removal<br><br>**OR** |



 

## Acute

| Patient group | Tx line | Treatment |
|---|---|---|
| | | » exploratory laparotomy: compressing tumours may require surgical removal; may be done following ureteral stenting<br><br>**OR**<br><br>» percutaneous nephrostomy: placement of a catheter into the renal pelvis percutaneously for drainage of urine from a distal obstruction may be done by a urologist, surgeon or interventional radiologist |
| **with volume overload** | **adjunct** | **diuretic**<br><br>» Diuretics should not be used in suspected complete obstruction.<br><br>» The use of diuretics in the management of AKI is primarily for volume control. The use of diuretics cannot avert the need for renal replacement therapy (RRT) by means of dialysis or filtration, but diuretic-unresponsive volume overload is an indication to proceed to RRT.<br><br>» Impaired urine production and volume expansion are commonly seen in cases of AKI.<br><br>» Loop diuretics (e.g., furosemide) and metolazone may be effective in promoting diuresis, although diuretic resistance is often seen.<br><br>» Patients also require sodium restriction.<br><br>» It is important to remove or minimise any nephrotoxins.<br><br>**Primary options**<br><br>» furosemide: 20-40 mg intravenously initially, increase by 20 mg/dose increments every 2 hours as necessary until clinical response<br><br>**Secondary options**<br><br>» torasemide: 20 mg intravenously once daily initially, increase gradually according to response, maximum 200 mg/day<br><br>**OR**<br><br>» bumetanide: 0.5 to 1 mg intravenously initially, may repeat in 2-3 hours for up to 2 doses if necessary, maximum 10 mg/day<br><br>**OR**<br><br>» metolazone: 5-20 mg orally once daily |

## Acute

| Patient group | Tx line | Treatment |
|---|---|---|
| **with uraemia, severe metabolic acidosis, or hyperkalaemia refractory to medical management, or volume overload unresponsive to diuretics** | **adjunct** | **renal replacement therapy**<br>» Nephrologist consultation is recommended.<br><br>» Conventional haemodialysis is used in haemodynamically stable patients. Other modes of renal replacement include sustained low-efficiency dialysis (SLED), extended daily dialysis (EDD), or continuous renal replacement therapy (CRRT) if the patient is haemodynamically unstable despite full support.<br><br>» Renal replacement therapy may be required to manage complications of obstruction while surgical interventions are planned and implemented. |

# Emerging

## Fenoldopam

Studies had suggested that fenoldopam (a rapidly acting intravenous D1 receptor agonist) may reduce the need for renal replacement and reduce mortality in patients with AKI[97] and in patients undergoing cardiovascular surgery.[98] A meta-analysis showed a reduction in AKI, but no effect on renal replacement therapy (RRT) or mortality.[99] Finally, a randomised study of nearly 700 patients with AKI has shown no benefit on outcomes of renal recovery, dialysis requirements, or mortality.[100] Based on the overall evidence, fenoldopam is not recommended as a preventative agent or therapy for AKI.

## Other novel therapeutic agents

The use of other novel therapeutic agents, including atrial natriuretic peptide, theophylline, insulin-like growth factor, epidermal growth factor, free radical oxygen scavengers, antibodies to adhesion molecules, and prostaglandins, has been reviewed. None have been shown to be beneficial in human AKI.[17] However, 2 studies using a prostacyclin analogue and an adenosine A1 receptor blocker have shown them to be somewhat efficacious in myocardial salvage.[101] [102] Further findings to ascertain whether either of these agents is useful clinically are still awaited. Whether statin therapy, administered either pre-intervention or chronically, is protective continues to be debated,[103] [104] [105] but presently appears to be disappointing.[106] [107] [108] Additional therapies which may be of benefit are: controlled hypothermia, ischaemic pre-conditioning, and recombinant alkaline phosphatase infusion.[109] [110] [111] Recombinant erythropoietin and thyroid hormone were also tried to minimise renal injury. However, erythropoietin demonstrated no nephroprotective effect,[112] and treatment with thyroid hormone appears to be associated with worse outcomes than other possible treatments for patients with established AKI; its role in preventing AKI was not adequately investigated.[113] Remote ischaemic pre-conditioning appeared to hold promise to prevent AKI, but the most recent large studies cast doubt on any great value.[114] [115]

# Recommendations

## Monitoring

Follow-up monitoring of patients with AKI will vary.

If recovery of function is complete and a normal GFR is re-established with no evidence of residual renal injury, no renal follow-up is required.

If after AKI, renal function is impaired and the patient is left with residual chronic kidney disease (CKD), a nephrologist follow-up is recommended with interventions based on stage of CKD.[126]

The National Kidney Foundation's KDOQI guidelines for management of CKD and its complications are available for recommended management. Management of chronic intrinsic renal diseases (e.g., glomerulonephritis and vasculitis) requires nephrologist intervention to manage therapies including corticosteroids, cytotoxic drugs, and immune-modifying drugs, and their side effects and toxicities require close observation.

## Patient instructions

Patients who have had an episode of AKI should be seen by a nephrologist before undergoing any diagnostic or therapeutic intervention that carries an increased risk of acute renal injury. NSAIDs should be avoided.

# Complications

| Complications | Timeframe | Likelihood |
|---|---|---|
| **hyperphosphataemia** | **long term** | **high** |
| A late complication usually arising several days after glomerular filtration falls.<br><br>Treatment includes dietary restriction and the administration of phosphate binders, such as calcium acetate, calcium carbonate, sevelamer, or lanthanum carbonate.<br><br>Haemodialysis is effective in phosphorous reduction, and in patients in whom intense renal replacement is undertaken, such as those on continuous renal replacement therapies or daily dialysis regimens, phosphorous replacement may be required. | | |
| **uraemia** | **long term** | **medium** |
| Uraemic toxins accumulate with severe and untreated renal failure, resulting in lethargy, confusion, and obtundation.<br><br>Dialysis is required for management of uraemia. | | |
| **volume overload (pulmonary oedema, peripheral oedema)** | **variable** | **high** |

| Complications | Timeframe | Likelihood |
|---|---|---|
| Impaired volume regulation is common in cases of AKI not occurring from pre-renal azotaemia.<br><br>Volume intake is limited and diuresis maximised with agents such as furosemide.<br><br>Response to diuretics is variable.<br><br>Ultrafiltration (volume removal by renal replacement therapy) may be required. | | |
| **hyperkalaemia** | **variable** | **high** |
| A well-recognised complication of kidney injury, not universally seen.<br><br>Results from impaired excretion of potassium, cell lysis, or tissue breakdown.<br><br>Severe hyperkalaemia may result in classic ECG findings of peaked T waves, increased PR interval, widened QRS, atrial arrest, and deterioration to a sine wave pattern.<br><br>Restrictions on dietary potassium intake should be imposed on all patients and may be sufficient for mild hyperkalaemia.<br><br>Sodium polystyrene sulfonate may be used for moderate to severe cases of hyperkalaemia. However, its effects are not immediate and serum potassium must be rapidly lowered.<br><br>If these initial steps are not sufficient or if hyperkalaemia is severe, medical intervention is mandated and includes cardiac evaluation by ECG.<br><br>If classic changes are present, treatment with IV calcium is required immediately in addition to rapid lowering of serum potassium with insulin, glucose, and beta-agonists. Care should be taken to prevent extravasation when giving calcium salts intravenously, because they are highly toxic to tissues.<br><br>If hyperkalaemia is refractory to medical treatment or if cardiac manifestations are present, haemodialysis is indicated for rapid potassium normalisation. | | |
| **metabolic acidosis** | **variable** | **high** |
| Results from accumulation of non-volatile acids. Oral or intravenous bicarbonate preparations such as sodium bicarbonate or sodium citrate/citric acid may be used to manage metabolic acidosis.<br><br>Management often requires dialysis if severe and if respiratory compensation is unable to maintain pH. | | |
| **chronic progressive kidney disease** | **variable** | **medium** |
| AKI may leave the patient with prolonged renal damage and functional recovery may not return to the baseline.<br><br>Recovery is dependent on the mechanism and severity of the injury and the underlying comorbid medical conditions.<br><br>AKI in children may be associated with chronic renal disease that may progress to ESRD.[124] [125] | | |
| **end-stage renal disease** | **variable** | **medium** |

| Complications | Timeframe | Likelihood |
|---|---|---|
| Severe kidney injury, especially in patients with underlying kidney disease or other comorbid medical conditions, may not recover and chronic renal replacement therapy may be required.[120] | | |

# Prognosis

Recovery for AKI is variable and depends on cause of injury and the severity and duration of AKI.[116]

There is an independent association of AKI with a higher risk of death.[9] [116] [117] In-hospital mortality rates associated with AKI vary from 6% to 80%, and there is increased long-term mortality in those with AKI surviving hospitalisation.[117]

Up to 6% of patients admitted to ICU have AKI requiring renal replacement therapy (RRT).[16] [116] [118] In hospital, when AKI requires dialysis, mortality exceeds 50%, especially in those with multiorgan failure.[13] [16] [118] Mortality rates are high due to death from underlying disease and complications, not just the AKI.

Five-year survival rates in patients with AKI requiring RRT range from 15% to 35% (less than 10% of those patients are dialysis-dependent).[119]

AKI is irreversible in approximately 5% to 7% of adults and as many as 16% of elderly patients.[120] There is controversy as to whether prior AKI is a major risk factor leading to future chronic kidney disease, but increasing evidence of strong association mounts.[121] [122] [123]

# Diagnostic guidelines

## Europe

### Acute kidney injury: prevention, detection and management

**Published by:** National Institute for Health and Care Excellence **Last published:** 2013

**Summary:** Provides detailed evidence-based guidance on detection of AKI.

### Clinical practice guidelines: acute kidney injury

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

**Summary:** Clinical practice guidelines cover aspects of assessing those at risk and preventative treatment, and treatment options for those with established AKI.

## International

### Kidney disease: improving global outcomes (KDIGO) clinical practice guideline for acute kidney injury

**Published by:** International Society of Nephrology **Last published:** 2012

## North America

### ACR appropriateness criteria: renal failure

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

**Summary:** Discusses the use of imaging in the evaluation of renal failure.

# Treatment guidelines

## Europe

### Acute kidney injury: prevention, detection and management

**Published by:** National Institute for Health and Care Excellence **Last published:** 2013

**Summary:** Provides detailed evidence-based guidance on management of AKI.

### British consensus guidelines on intravenous fluid therapy for adult surgical patients

**Published by:** BAPEN; Association for Clinical Biochemistry; Association of Surgeons of Great Britain and Ireland; Society of Academic and Research Surgery; Renal Association/Intensive Care Society **Last published:** 2011

## Europe

### Clinical practice guidelines: acute kidney injury

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

**Summary:** Clinical practice guidelines cover aspects of assessing those at risk and preventative treatment, and treatment options for those with established AKI.

### Clinical practice guidelines: haemodialysis

**Published by:** UK Renal Association **Last published:** 2009

**Summary:** Guidelines for use of haemodialysis, including recommendations on facilities for haemodialysis, equipment, concentrates and water, membranes, dose, frequency and duration, indications of adequacy of dialysis, vascular access, and access to and withdrawal from dialysis.

### ESPEN guidelines on parenteral nutrition: adult renal failure

**Published by:** European Society for Clinical Nutrition and Metabolism **Last published:** 2009

**Summary:** Expert opinion guidelines on the nutrition of patients with AKI. Patients with AKI should be tube fed for nutritional support. Oral nutrition supplements are recommended for re-feeding depleted conservatively treated patients with chronic renal failure or on dialysis. Oral nutrition supplements have been shown to improve survival of dialysis patients by improving nutrition status.

## International

### Kidney disease: improving global outcomes (KDIGO) clinical practice guideline for acute kidney injury

**Published by:** International Society of Nephrology **Last published:** 2012

**Summary:** Evidence-based guidelines for the treatment and care for adults and children at risk of or with AKI, including contrast-induced AKI.

## North America

### KDOQI US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury

**Published by:** The National Kidney Foundation **Last published:** 2013

**Summary:** A group of US experts in adult and paediatric AKI and critical care nephrology organised by the National Kidney Foundation review the recommendations given in the 2012 KDIGO (Kidney Disease: Improving Global Outcomes) clinical practice guideline for AKI, and comment on their relevance in the context of current US clinical practice and concerns.

# Online resources

1. KDIGO clinical practice guideline for glomerulonephritis *(external link)*

## Key articles


- Kidney disease: improving global outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Inter Suppl. 2012;2:1-138. Full text
- Palevsky PM, Liu KD, Brophy PD, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. Am J Kidney Dis. 2013;61:649-672. Full text Abstract
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- Wang HE, Muntner P, Chertow GM, et al. Acute kidney injury and mortality in hospitalized patients. Am J Nephrol. 2012;35:349-355. Full text Abstract
- Gaudry S, Hajage D, Schortgen F, et al. Initiation strategies for renal-replacement therapy in the intensive care unit. N Engl J Med. 2016;375:122-133. Abstract
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