Acute kidney injury (AKI) - previously known as acute renal failure (ARF) - has traditionally been defined as the abrupt loss of kidney function resulting in the retention of urea and other nitrogenous waste products and in the dysregulation of extracellular volume and electrolytes. This can occur in the setting of previously normal renal function or in patients with pre-existing renal disease (acute on chronic kidney disease). More recently it has been recognised that even very small increases in serum creatinine are associated with adverse patient outcomes[1].

It is detected and monitored by serial serum creatinine readings primarily, which rise acutely. Urine output and eGFR fall, and may also be used for detection and monitoring of the condition.

A 2009 report by the UK National Confidential Enquiry into Patient Outcome and Death (NCEPOD), Acute Kidney Injury, adding insult to injury, found serious deficiencies in patients who died with a diagnosis of AKI[2]. They reported that only 50% of patients received good medical care, and made recommendations for improvements. In the wake of this, and because of a lack of consistent guidelines, the UK National Institute for Health and Care Excellence (NICE) produced guidance for AKI published in August 2013[3].

Aetiology[4]

The majority of AKI developing in the community is due to a pre-renal state (90% cases), typically hypotension associated with sepsis and/or fluid depletions (eg, vomiting or diarrhoea). This can be further exacerbated by commonly prescribed drugs (eg, angiotensin-converting enzyme (ACE) inhibitors or non-steroidal anti-inflammatory drugs (NSAIDs)) that impair how the kidneys respond to hypotension[1].

Prerenal

- Volume depletion (eg, haemorrhage, severe vomiting or diarrhoea, burns, inappropriate diuresis).
- Oedematous states: cardiac failure, cirrhosis, nephrotic syndrome.
- Hypotension (eg, cardiogenic shock, sepsis, anaphylaxis).
- Cardiovascular (eg, severe cardiac failure, arrhythmias).
- Renal hypoperfusion: NSAIDs or selective cyclo-oxygenase-2 (COX-2) inhibitors, ACE inhibitors or angiotensin-II receptor antagonists (AIIARAs - commonly called angiotensin receptor blockers (ARBs)), abdominal aortic aneurysm, renal artery stenosis or occlusion, hepatorenal syndrome.

Intrinsic renal problem

- Glomerular disease: glomerulonephritis, thrombosis, haemolytic uraemic syndrome.
- Tubular injury: acute tubular necrosis (ATN) following prolonged ischaemia; nephrotoxins (eg, aminoglycosides, radiocontrast media, myoglobin, cisplatin, heavy metals, light chains in myeloma kidney).
- Acute interstitial nephritis due to drugs (eg, NSAIDs), infection or autoimmune diseases.
- Vascular disease: vasculitis (usually associated with antineutrophil cytoplasmic antibody), cryoglobulinaemia, polyarteritis nodosa, thrombotic microangiopathy, cholesterol emboli, renal artery stenosis, renal vein thrombosis, malignant hypertension.
- Eclampsia.

Postrenal

- Calculus.
- Blood clot.
- Papillary necrosis.
- Urethral stricture.
- Prostatic hypertrophy or malignancy.
- Bladder tumour.
- Radiation fibrosis.
- Pelvic malignancy.
- Retroperitoneal fibrosis.

Epidemiology

Figures are difficult to establish due to the differing definitions used.

It is estimated that 15% of adults admitted to hospital in developed countries develop AKI[5]. It is particularly common in the elderly.

Population incidence in the UK has been found to be 486-630 per million population, depending on definition[6].

The cost to the NHS of AKI in secondary care is estimated to be as high as £630 million per year, which is higher than the combined cost of all lung and skin cancers[8].
It has been estimated that improving standards and care could save 12,000 lives in England and save the NHS £150 million per year\(^7\).

**Risk factors\(^{1, 3}\)**

**In people with acute illness**
The following increase the risks of developing AKI:

- Age ≥65 years.
- Chronic kidney disease (CKD) - particularly if eGFR <60.
- Past history of AKI.
- Co-existing illness - eg, cardiac failure, liver disease or diabetes.
- Neurological impairment or disability, in particular where reliance on a carer may mean reduced access to fluids. Additionally, young age in children for similar reasons.
- Hypovolaemia.
- Symptoms or history of urological obstruction, or a risk factor for it.
- Sepsis.
- Use of iodinated contrast agents within the previous week.
- Current or recent medication with nephrotoxic potential - eg, NSAIDs, ACE inhibitors, ARIRAs, aminoglycosides, diuretics. One study concluded that when two antihypertensive agents (such as diuretics plus an ACE inhibitor or ARIRA) are used concurrently with an NSAID, the risk of AKI was increased\(^8\).
- Deteriorating early warning scores (see use of track and trigger systems in NICE clinical guideline 50: *Acutely ill patients in hospital*\(^9\). Similarly deteriorating paediatric early warning scores in children.
- Patients in the peri-operative period.

**In people having iodinated contrast agents**
The following increase the risk of developing AKI:

- CKD (with an eGFR <40).
- Diabetes if co-existent with CKD.
- Heart failure.
- Age ≥75 years.
- Hypovolaemia.
- Increasing volume of contrast agent.
- Intravenous administration of contrast agent.

**In people having surgery**
The following are associated with increased risk of developing AKI:

- Emergency surgery, particularly in the presence of sepsis or hypovolaemia.
- Intraperitoneal surgery.
- CKD (with eGFR <60 in adults).
- Diabetes.
- Heart failure.
- Age ≥65.
- Nephrotoxic medication.

**Presentation**
The presentation will depend on the underlying cause and severity of AKI. Clinically, AKI is recognised by decreasing urine volume (oliguria or anuria) and a rise in serum creatinine. AKI is associated with at least one of the following\(^1\):

- A rise in serum creatinine of 26 μmol/L or greater within 48 hours.
- 50% or greater increase in serum creatinine (1.5 fold from baseline) within the preceding seven days.
- A fall in urine output to less than 0.5 mL/kg/hour for more than six hours.

**Symptoms**
- Urine output:
  - AKI is usually accompanied by oliguria or anuria. However, polyuria may occur due to either reduced fluid reabsorption by damaged renal tubules, or the osmotic effect of accumulated metabolites.
  - Abrupt anuria suggests an acute obstruction, acute and severe glomerulonephritis, or acute renal artery occlusion.
  - Gradual diminution of urine output may indicate a urethral stricture or bladder outlet obstruction - eg, benign prostatic hyperplasia.
- Nausea, vomiting.
- Dehydration.
- Confusion.

**Signs**
- Hypertension.
- Abdomen: may reveal a large, painless bladder typical of chronic urinary retention.
• Dehydration with postural hypotension and no oedema.
• Fluid overload with raised jugular venous pressure (JVP), pulmonary oedema and peripheral oedema.
• Pallor, rash, bruising: petechiae, purpura and nosebleeds may suggest inflammatory or vascular disease, emboli or disseminated intravascular coagulation.
• Pericardial rub.

Classification and definitions: a work in progress
Over the past few years, international guideline groups have attempted to establish consistent definitions and staging systems for AKI. Initially the RIFLE (Risk, Injury, Failure, Loss, End-stage kidney disease) system was set up in 2004. This was modified by the AKIN (Acute Kidney Injury Network) and further developed in 2012 by KDIGO (Kidney Disease: Improving Global Outcomes)\[10\]. They work on levels of creatinine rise, but use non-SI units. A paediatric version of RIFLE (pRIFLE) is also in use. NICE guidance in 2013 suggests these systems need further development and simplification in order to be useful for clinicians working in the NHS, particularly non-specialists.

Meanwhile NICE recommends that AKI can be detected by using any of the following criteria, in line with pRIFLE, AKIN or KDIGO definitions:

• Rise in serum creatinine of 26+ µmol/L in 48 hours.
• A 50% or greater rise in serum creatinine in the preceding seven days.
• A drop in urine output to 0.5 ml/kg/hour for six hours in adults or eight hours in children and young people.
• In children or young people a fall in eGFR of 25% or more in the preceding seven days.

The stage of AKI affects both management recommendations and prognosis; hence the importance of defining consistent stages. KDIGO defines stage 1, 2 and 3 through increasing rises in creatinine levels and drop in urinary output. For children the pRIFLE, stages 1 (risk), 2 (injury) and 3 (failure), are defined at specific falling levels of eGFR and falling urinary output\[5\].

Assessment and investigations\[10\]
It is important to first identify the cause of AKI, as this will affect management, particularly where there is a potentially treatable cause (for example, obstruction, hypovolaemia, nephrotoxic drugs or glomerulonephritis). Often, however, there are multiple causes and finding the cause will not always dictate specific management.

Cause established by:

History
• Drugs - nephrotoxic drugs, remembering recreational drugs, over-the-counter drugs and herbal remedies.
• Occupational or recreational history - exposure to sewer systems, tropical diseases, rodents.
• Urinary symptoms.
• Past medical history.

Examination
• Signs of infection or sepsis.
• Signs of acute or chronic heart failure.
• Fluid status (dehydration or fluid overload).
• Palpable bladder or abdominal/pelvic mass.
• Features of underlying systemic disease (rashes, arthralgia).

Urinalysis
• Dipstick urine for blood, nitrates, leukocytes, glucose and protein in all patients with suspected AKI. Consider acute nephritis and referral to a nephrologist if there is blood or protein on the dipstick in the absence of urinary infection or trauma due to catheterisation, and no obvious cause for AKI.
• Urine osmolality.

Blood tests
As appropriate to find cause as dictated by history. This could involve:

• FBC, blood film. (Eosinophilia may be present in acute interstitial nephritis, cholesterol embolisation, vasculitis. Thrombocytopenia and red cell fragments suggest thrombotic microangiopathy.)
• U&Es and creatinine.
• Coagulation studies: disseminated intravascular coagulation associated with sepsis.
• Creatine kinase, myoglobinuria: markedly elevated creatine kinase and myoglobinuria suggest rhabdomyolysis.
• C-reactive protein (CRP): nonspecific marker of infection or inflammation.
• Immunology:
  - Serum immunoglobulins, serum protein electrophoresis, Bence Jones' proteinuria: immune paresis, monoclonal band on serum protein electrophoresis, and Bence Jones' proteinuria suggest myeloma.
  - Antinuclear antibody (ANA): ANA positive in systemic lupus erythematosus (SLE) and other autoimmune disorders; anti-double-stranded DNA (anti-dsDNA) antibodies more specific for SLE; anti-dsDNA antibodies; antineutrophil cytoplasmic antibody (ANCA) (associated with systemic vasculitis; classical antineutrophil cytoplasmic antibodies (c-ANCA) and antiproteinase 3 (anti-PR3) antibodies associated with granulomatosis with polyangiitis (Wegener's granulomatosis); protoplasmic-staining antineutrophil cytoplasmic antibodies (p-ANCA) and antiprotease 3 (anti-PR3) antibodies associated with granulomatosis with polyangiitis (Wegener's granulomatosis); protoplasmic-staining antineutrophil cytoplasmic antibodies (p-ANCA) and antimyeloperoxidase (anti-MPO) antibodies present in microscopic polyangiitis; anti-PR3 antibodies, anti-MPO antibodies.
  - Complement concentrations: low in SLE, acute postinfectious glomerulonephritis, cryoglobulinaemia.
  - Antiglomerular basement membrane (anti-GBM) antibodies: present in Goodpasture's syndrome.
  - Antistreptolysin O and anti-DNase B titres: high after streptococcal infection.
**Virology:** hepatitis B and C; HIV: (important implications for infection control within dialysis area).

**New biomarkers:** creatinine is a poor indicator of renal function and there have been many studies trying to find a more sensitive biomarker. These include cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1) and interleukin-18 (IL-18). None has yet been recommended for routine use.

**Ultrasound**
When obstruction is suspected or no cause has been identified.

**Other radiology**
Where appropriate - for example:

- **CXR** (pulmonary oedema).
- Abdominal X-ray if renal calculi are suspected.
- Contrast studies such as intravenous urogram (IVU) and renal angiography should be avoided because of the risk of contrast nephropathy.
- Doppler ultrasound of the renal artery and veins: assessment of possible occlusion of the renal artery and veins.

Which tests are relevant will vary considerably with the individual. Urinalysis is done in all and ultrasound is often indicated.

**Differential diagnosis**

- **CKD:** factors that suggest CKD include:
  - Long duration of symptoms.
  - Nocturia.
  - Absence of acute illness.
  - Anaemia.
  - Hyperphosphataemia, hypocalcaemia (but similar laboratory findings may complicate AKI).
  - Reduced renal size and cortical thickness on renal ultrasound (but renal size is typically preserved in patients with diabetes).

- **Acute on chronic kidney disease.**

**Management**

There is no specific treatment for AKI so management is largely supportive. It consists of treating the cause where possible, monitoring fluid and electrolyte balance closely and optimising haemodynamic status with appropriate fluid therapy.

AKI developing as a result of a pre-renal cause in the community will often respond to fluid replacement and temporary withdrawal of drugs that adversely affect kidney function.

**Stop nephrotoxic drugs where possible**
Nephrotoxic drugs account for some part of the aetiology of AKI in 20-30% of cases. However, because the patient already may be ill when they are started, or because there are other factors, it may be difficult to know exactly how much of the problem they have caused. It makes sense to limit exposure to these drugs as much as possible.

**Monitor creatinine, sodium, potassium, calcium, phosphate, glucose**
Frequency of monitoring should be tailored to the individual and the stage of AKI as appropriate.

Oral potassium and sodium may need restricting, and abnormal levels correcting. Watch for and avoid hyperglycaemia. Insulin therapy may be required in critically ill patients to maintain blood glucose levels. Insulin also has the effect of driving potassium into the cells, thus reducing blood levels, which may be of benefit.

Hypoglycaemia is also a potential risk in AKI, either with or without insulin therapy.

**Identify and treat infection**
Infection is a significant cause of mortality. Therefore, strict sepsis control is essential; avoidance of intravenous lines, bladder catheters and respirators is recommended.

**Optimise fluid balance**
Prompt fluid resuscitation to restore an effective circulating blood volume but avoidance of fluid overload. Accurate measurement of urine output is essential to prevent volume overload or depletion.

**Urgent relief of urinary tract obstruction**
A urologist's advice may be required where there is an obstructive cause. Situations include renal calculi, papillary necrosis, tumours, strictures or prostatic enlargement.

Refer to a nephrologist for specific treatment of underlying intrinsic renal disease where appropriate.
• Acute renal artery thrombosis (of a single functioning kidney) may be treated surgically, or by angioplasty and stenting.
• In rhabdomyolysis with myoglobulinuria, alkaline diuresis may prevent the development of severe renal failure but must be undertaken with care in oliguric patients.
• Acute tubulo-interstitial nephritis may respond to a short course of high-dose corticosteroids, although no controlled trials have been undertaken to support this approach.
• AKI due to crescentic glomerulonephritis may respond to treatment with prednisolone and cyclophosphamide, together with the addition of plasma exchange.
• Haemolytic uraemic syndrome may respond to plasma exchange with fresh frozen plasma.

Identify and treat acute complications
These include:
• Hyperkalaemia.
• Acidosis.
• Pulmonary oedema.
• Bleeding.

Drug options
• There are no drugs which have been shown to limit progression of, or speed up recovery from, AKI.
• Treatment as appropriate for complications.
• Loop diuretics are not routinely used. They may be considered for treatment of fluid overload or oedema while awaiting renal replacement therapy (RRT) or when renal function is recovering.

Referral for RRT
This should be considered if any of the following are not responding to medical management[1]:
• Hyperkalaemia (> 6.5 mmol/L) refractory to medical management.
• Pulmonary oedema refractory to medical management.
• Severe metabolic acidaemia pH ≤7.2 due to kidney failure.
• Progressive renal failure (creatinine ≥300 umol/L and/or rise in serum creatinine of >100 umol/L/day).
• Uraemic complications (periarteritis or uraemic encephalopathy).
• Renal transplant.
• CKD (stage 4 or 5).
• Patients suspected of intrinsic renal disease (vasculitis, primary glomerulonephritis, interstitial nephritis).

This decision should be made on the basis of the overall condition of the patient and should be discussed with the patient and/or relatives in accordance with shared decision-making guidelines.[11] Referral to a nephrologist or critical care specialist should be made immediately if the above criteria are met.

All patients receiving RRT should have an assessment by a dietician and advice about nutritional support. Choice of modality of RRT will be guided by local availability and patient status.

Referral to a nephrologist where indicated[3]
• If the criteria for RRT are met as above.
• When there is uncertainty about cause, management or prognosis.
• Where there is a likely diagnosis that will need specialist treatment (glomerulonephritis, vasculitis, tubulo-interstitial nephritis, myeloma).
• Inadequate response to treatment.
• Complications.
• History of renal transplant or CKD stage 4 or 5.
• Stage 3 AKI according to pRIFLE, AKIN or KDIGO.

Complications
AKI, if unrecognised and allowed to worsen, will result in progressive uraemia (toxic waste accumulation), metabolic acidosis, hyperkalaemia, spontaneous haemorrhage and pulmonary oedema if fluid balance is not carefully monitored. These complications prolong hospitalisation and are associated with increased mortality[1].

Prognosis
• Inpatient mortality varies greatly depending on the severity, setting, and many patient-related factors. In the UK it may be 20-30% or even higher[5].
• Indicators of poor prognosis include older age, multiple organ failure, oliguria, hypotension, number of transfusions and acute on chronic kidney disease. Prognosis is closely related to the underlying cause.
• Patients who need dialysis have a higher mortality but this is a reflection of the condition rather than a result of the treatment.
• The risk of mortality increases with the stage of AKI.
• Patients who have had AKI are at increased risk of developing CKD[12].
• There may be an ongoing requirement for RRT[13].
Prevention

The best treatment of AKI is prevention. NICE guidance of 2013 reflects this, with the emphasis being on identification of patients at risk. Close monitoring of urinary output and creatinine levels for these patients allows early detection. Avoidance of nephrotoxic drugs and iodinated contrast agents in these patients reduces the risk of them developing AKI. All acutely ill patients in hospital should be closely monitored for signs of developing AKI.

At-risk patients who need iodinated contrast agents should be offered intravenous volume expansion with isotonic sodium bicarbonate or 0.9% sodium chloride to reduce the risks of developing AKI.

Further reading & references

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- Renal Association
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- Clinical practice guideline for acute kidney injury; KDIGO (Kidney Disease: Improving Global Outcome), 2012
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