Assessment and management of acute kidney injury

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Abstract

Acute kidney injury (AKI) is a common and dangerous complication of hospital admission, even mild dysfunction being associated with reduced survival. Unfortunately, its recognition is often delayed and its management, frequently suboptimal. A failure to recognize relevant risk factors can expose patients unnecessarily to the danger of AKI. This review presents a structured approach to diagnosis and non-specialist management that should provide a framework for routine clinical care.

Keywords Acute kidney injury; creatinine; medication therapy management; morbidity; mortality; MRCP; renal replacement therapy

Key points

- Acute kidney injury (AKI) is common, dangerous and costly; even mild disease is associated with poor short- and long-term outcomes
- AKI may be preventable — clinicians should be aware of its key risk factors and maintain vigilance for patients with a heightened risk
- Regular monitoring of renal function (at least daily for in-patients) can detect incipient AKI in those at risk and progressive disease in those who have already developed the condition
- Most patients with AKI and those at increased risk of it can be managed with volume and haemodynamic optimization, medicines management, treatment of sepsis and identification and prompt relief of obstruction
- Less common causes are suggested by lack of an initiating insult, blood and protein on urinalysis, delayed renal recovery and the presence of other specific clinical features
- Progressive renal dysfunction, anticipation of complications of AKI and the possibility of a rare diagnosis all highlight the need for early renal or critical care input
- Long-term sequelae of AKI include increased risk of recurrence, chronic kidney disease and vascular disease; these should be managed appropriately

Introduction

Acute kidney injury (AKI) is common, affecting around 1 in 5 emergency admissions in the UK and up to 25% of patients given higher level, including intensive, care. AKI is also dangerous — even mild disease is associated with reduced survival. Mortality rates increase sharply as AKI worsens and can be >50% in septic, multiorgan failure.

Survivors often fail to recover renal function, with many needing long-term dialysis. Long-term survival can be reduced, especially with persisting renal dysfunction; previous AKI is also associated with increased risk of future cardiac and cerebrovascular events. In addition, the condition has significant economic impact as severe disease often requires expensive interventions (e.g. dialysis, critical care), but even modest AKI can increase hospital costs (e.g. from increased hospital length of stay).

Management of AKI is often challenging but even the basics of care can be neglected: systematic failings have been found in the recognition and management of AKI and its complications, with the frequent omission of fluid balance assessment, fluid therapy and regular blood monitoring. Shortcomings in practice may be worst in those who develop AKI during their hospital stay rather than those admitted with it, suggesting insufficient awareness of the condition and individuals at risk of it.[1]

One of the greatest recent challenges has been how these well-documented deficiencies might be addressed. Having historically been a neglected area of research and policy, the findings have galvanized a raft of initiatives including, in the UK alone, the mandated implementation of AKI electronic alerts (e-alerts) in both primary and secondary care settings in England and Wales, and the establishment of the Think Kidneys programme (www.thinkkidneys.nhs.uk/aki/) to improve AKI care. These initiatives are obviously welcome, but definitive evidence of improvements in outcomes remains lacking, for several potential reasons.

First, AKI is not a homogeneous entity; aetiologies vary from prosaic (mostly managed in non-specialist settings) to rare (although clues can be revealed through a structured approach to assessment by non-specialists). In addition, although most AKI occurring across both community and hospital settings is 'ischaemic' in origin, causation can be complex, multifactorial and dependent on an interplay of pre-existing co-morbidity, acute pathology and the intrinsic vulnerability of aged or damaged kidneys. Management of such cases is not necessarily straightforward, and reductive approaches (e.g. 'give fluids', 'stop angiotensin-converting enzyme (ACE) inhibitors') carry the

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potential for unintended consequences (e.g. iatrogenic volume overload, increased risk of cardiac decompensation).

Second, although evidence suggests that patients are not dying with, but because of, AKI, the adverse consequences associated with it could simply reflect an epiphenomenon of an unmeasurable, vulnerable physiological phenotype — another marker of the deteriorating patient — rather than a direct consequence of loss of renal function. This could especially be the case for individuals with less severe AKI, who were not well represented in the pivotal reports on poor AKI care, such as from the National Confidential Enquiry into Patient Outcome and Death (NCEPOD).[1]

Finally, serum creatinine (SCr) is not a rapid marker of renal dysfunction but can take several hours to rise above diagnostic thresholds. In addition, at least for lower stage AKI, the diagnostic SCr (e.g. triggering the first AKI e-alert) can actually be the peak value; the expectation in these cases is that subsequent values will be lower. This can be due to optimal management at the time of diagnosis, but more likely reflects the self-limiting nature of many AKI episodes as the predominant admission pathologies are treated.

The questions facing the non-specialist clinician presented with a patient with AKI, therefore, include:

1. Will this episode of AKI self-limit with the treatment of other, non-renal acute pathologies?
2. If so, am I doing everything I can to encourage renal recovery and avoid further renal damage, without risking adverse unintended consequences?
3. Is this episode of AKI progressing to more severe disease, and could there be a rare cause?
4. After recovery (full or partial), have I done everything necessary to ensure that the long-term risk of further AKI episodes or persisting chronic kidney disease (CKD) is managed appropriately?

This review of AKI in adults aims to provide a structured basis for tackling these complexities. It will not, however, detail the pathophysiology of less common causes of AKI.

Pathophysiology of ischaemic AKI

The commonest aetiology of AKI is ischaemia, for instance, due to hypotension, hypovolaemia, drugs or sepsis. Haemodynamic disturbances trigger a complex interplay of endothelial injury, epithelial injury and immune activation. This leads to an intense, proinflammatory state arising from the ischaemia—reperfusion injury that not only initiates renal injury but extends it even after resolution of the precipitating haemodynamic insult (see also reference 2).

Ischaemic AKI can be represented as one end of a pathophysiological spectrum separated from purely pre-renal disease (an appropriate response to renal hypoperfusion with intense sodium and water retention; see below) by an increasing degree of renal cell injury. There is no set threshold at which renal cell injury occurs, with different parts of the kidney carrying different susceptibilities to hypoperfusion. The outer medulla, for example, is particularly vulnerable to ischaemia, receiving its blood supply downstream of the oxygen-avid loop of Henle. Nevertheless, the initiating insult can be so profound that the pre-renal phase is short-lived and, effectively, irreversible. Conversely, in many cases, timely intervention to restore renal perfusion can mitigate the severity of evolving ischaemic AKI by preventing still-functioning tissue (i.e. areas still in the pre-renal phase) from progressing to overt injury.

After renal injury is established, a variable period of time follows before renal recovery occurs. The gravity of renal dysfunction, the duration of this 'maintenance' phase and the degree of renal recovery vary between individuals. The time course from first insult to renal recovery is usually around 7—21 days but can be more prolonged if the renal insult is severe or subsequent insults occur. An understanding of the natural history of ischaemic AKI is important in appreciating, first, the likely timescales to recovery (important in deciding whether to 'sit tight' or refer for specialist management) and, second, that deviations from expected timescales (particularly coupled with the absence of a clear precipitating insult) might indicate an alternative aetiology (see below).

During the maintenance phase of ischaemic AKI, the loss of renal autoregulation is directly clinically relevant. Under normal circumstances, the glomerular filtration rate (GFR) is tightly maintained over the physiological range of systemic mean arterial pressures (MAPs) through the competing actions of intrinsic renal vasoconstrictive and vasodilatory mechanisms. After renal injury, renal autoregulatory capacity — the ability to buffer the nephron from changes in systemic blood pressure — is disrupted; subtle changes in MAP are transmitted through to the renal microvasculature, risking further injury and delayed recovery if insufficient attention is paid to maintaining renal perfusion (and avoiding 'overshoot' into fluid overload). Volume and haemodynamic management therefore remains a key part of AKI management even after initial resuscitation.

Recovery processes are initiated soon after injury, involving endogenous inhibitors of inflammation, upregulation of various repair genes, actions of various cellular components of the immune system, clearance of debris and tubular regeneration. The received wisdom that survivors of AKI generally recover renal function has been increasingly called into doubt, with subtle pathophysiological changes contributing to longer-term renal attrition. Potential mechanisms contributing to abnormal recovery and repair include non-recoverable loss of the peri-tubular microvasculature, chronic immune system activation leading to the release of proinflammatory cytokines, and cell-cycle arrest in the recovering tubular epithelium.

Risk factors and prevention

Up to 30% of AKI has been said to be preventable through early recognition and simple management of patient risk factors, although this figure is derived from studies of severe AKI. This section is primarily relevant to recognizing the patient at risk of ischaemic AKI, but failure to address these risk factors can also be relevant to those at risk of or with AKI of other aetiologies.

The risk of developing ischaemic AKI is influenced by a variety of factors including pre-existing 'susceptibilities' (e.g. advanced age, CKD) and newer 'exposures' (e.g. sepsis, hypotension, hypovolaemia). Some risk factors both pre-dispose to and trigger AKI, drug therapy (e.g. long-term prescription versus recent initiation of ACE inhibitors) being a particularly prominent example.

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As drugs are such a prominent cause of or contributor to AKI, it is worthwhile noting that some (e.g. aminoglycoside antibiotics, cisplatin, iodinated radiocontrast) can be directly nephrotoxic, whereas others (e.g. ACE inhibitors) are not directly nephrotoxic but reduce GFR through their mechanism of action (affecting glomerular capillary haemodynamics; e.g. ACE inhibitors and related drugs block angiotensin-mediated vasoconstriction of the efferent arteriole). Non-steroidal anti-inflammatory drugs (NSAIDs) can be nephrotoxic and reduce glomerular capillary pressure (by blocking prostaglandin-mediated afferent arteriolar vasodilation).

Thus, clinicians, especially in acute hospital settings or dealing with vulnerable community-based patients, are faced with four questions:

1. What is the AKI risk factor profile for this patient?
2. Can I mitigate it?
3. Can I avoid adding to it?
4. Can I detect incipient AKI if preventive measures fail?

What is the risk factor profile for this patient?

Risk factor profiles for hospital and community populations with acute illness (Table 1) and after surgery (Table 2) have been identified by the National Institute for Health and Care Excellence (NICE; www.nice.org.uk/guidance/cg169). Observational studies have, however, identified a wide range of other risk factors, including atherosclerotic vascular disease, trauma, burns, malignancy including multiple myeloma, cardiopulmonary bypass, smoking, obesity, assisted ventilation, postoperative glycaemic fluctuations, HIV and generic co-morbidity, including a history of hospitalization. Risk factor profiles have been described for various other patient populations as detailed in the latest UK Renal Association Clinical Practice Guideline for AKI (accessible via https://renal.org/guidelines/).

Although risk factor profiling is clearly desirable, there are a range of caveats. For instance, few of the published risk factor profiles have been externally validated, and those that have may not perform as well in similar populations outside the derivation cohort. In addition, risk factor profiles are often indiscriminate and can characterize large proportions of the target population as being 'at risk' — further work is required to understand the weighting that each individual factor brings to the overall level of risk. Furthermore, once a patient has been deemed to be at risk, clinicians face the challenge of contextualizing patient risk according to the clinical scenario — unintended consequences can arise from, for example, inappropriately withholding essential treatments or investigations (e.g. iodinated radiocontrast-enhanced examinations when these might be diagnostic in an acutely unwell patient). Finally, once a patient has been deemed at risk, this needs to be conveyed across the patient journey and adapted according to changing clinical circumstances.

Given these uncertainties, there appears to be no easy solution to AKI risk profiling. Clinical judgement should therefore be exercised by applying these tools (i.e. Tables 1 and 2; see also https://renal.org/guidelines/) in clinical context, noting also the need for vigilance for other well-established susceptibilities such as multiple myeloma and burns.

As one-size-fits-all risk prediction tools, even for disease-specific settings, are unlikely to materialize soon, educational programmes for AKI should include discussion of the complexities and nuances of identifying and managing the at-risk patient, and of the need to seek a more senior opinion, where required.

Can I mitigate the risk factor profile for this patient and can I avoid adding to it?

This is covered in 'Management', below. As noted above, however, the potential complexity of clinical decision-making can require input from experienced practitioners. In the case of drug therapy, for instance, the following may be needed:

- Elderly patients with diabetes may require temporary suspension of an ACE inhibitor during a diarrhoeal illness. The need to restart the drug should be reviewed after the period of increased AKI risk has ended.
- Postoperative patients with pre-existing CKD should avoid NSAIDs.

Assessing the risk of AKI in adults with acute illness (hospital and community settings)

Increased risk is associated with:

- CKD (adults with an eGFR <60 ml/minute/1.73 m^2 are at particular risk)
- Heart failure
- Liver disease
- Diabetes mellitus
- History of AKI
- Neurological or cognitive impairment or disability, which can mean limited access to fluids because of reliance on a carer
- Hypovolaemia/hypotension
- Use of drugs with nephrotoxic potential (e.g. NSAIDs, aminoglycosides) or with the potential to reduce renal function (e.g. ACE inhibitors, angiotensin II receptor antagonists, diuretics) within the past week, especially if hypovolaemic
- Use of iodinated contrast agents within the past week
- Symptoms or history of urological obstruction, or conditions that can lead to obstruction
- Sepsis
- Deteriorating early warning scores
- Age 65 years or over

Source: Adapted from NICE guidance (www.nice.org.uk/guidance/cg169)

Table 1

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Assessing the risk of AKI in adults before surgery

Increased risk is associated with:

- Emergency surgery, especially when the patient has sepsis or hypovolaemia
- Intraperitoneal surgery
- CKD (adults with an eGFR <60 ml/minute/1.73 m^2 are at particular risk)
- Diabetes
- Heart failure
- Age 65 years or over
- Liver disease
- Use of drugs with nephrotoxic potential in the perioperative period (in particular, NSAIDs after surgery) and drugs that can reduce renal function (e.g. ACE inhibitors, angiotensin II receptor antagonists, diuretics)

Source: adapted from NICE guidance (www.nice.org.uk/guidance/cg169)

Table 2

- The initiation of an ACE inhibitor in an elderly patient with CKD and cardiac failure may be entirely justified provided there is close monitoring of renal function.

In the community, 'sick day' guidance offers a route for patient self-management during periods of increased risk, with advice that certain routine drugs with potential to further increase AKI risk be temporarily suspended during acute, intercurrent illness. There is clearly a potential for harm (e.g. through inappropriately low thresholds for drug cessation, failure to restart therapy, decompensation of pre-existing conditions such as hypertension and heart failure, and difficulties with drugs administered via a dosette box). As such, an individualized approach to sick day guidance should be adopted, with clear, written detail provided to the patient of the circumstances requiring drug cessation and the thresholds for seeking medical advice.

Can I detect incipient AKI if preventive measures fail?

Once a patient is deemed higher risk for AKI, renal function should be closely monitored, particularly after exposure to additional insults. Such patients should undergo regular SCr measurements (at least daily in inpatients) until at least 48 hours after the risk factor profile has improved, because of the potential delay in developing a diagnostic increase in SCr. We also recommend that urine output be monitored over periods of higher AKI risk in inpatients, although whether bladder catheterization is undertaken depends on clinical judgement of the balance between risk of infection and the benefits of accurate, hourly surveillance.

Fluid management

Careful fluid management can reduce the risk of AKI. The choice of fluid and electrolyte is guided by decisions on whether fluid is required for 'maintenance' (routine requirements) or 'replacement' (correction of abnormal losses). Guidance on optimal fluid prescribing is given elsewhere in NICE guidance (www.nice.org.uk/guidance/cg174).

Prophylaxis against contrast-induced nephropathy (CIN)[3]

Before using iodinated radiocontrast, baseline renal function should be determined (estimated GFR (eGFR) in stable outpatients, SCr in all others) unless there is such a pressing need for investigation that the risks of delay are deemed to outweigh those of CIN. To the generic risk factors for AKI, noted above, should be added intra-arterial (as opposed to intravenous) contrast administration, and the volume of contrast used. The risk of CIN can be particularly high in acutely unwell patients with sepsis and/or hypotension and in those with combinations of risk factors. In patients deemed to be at increased risk of CIN, risk can be mitigated by:

- use of low- or iso-osmolar agents at the lowest volumes possible to allow diagnosis
- volume expansion with intravenous 0.9% saline or isotonic sodium bicarbonate
  - sodium chloride 0.9% at 1 ml/kg/hour for 12 hours before and after the procedure
  - isotonic sodium bicarbonate at 3 ml/kg/hour for 1 hour before the procedure and 1 ml/kg/hour for 6 hours after it, with careful assessment of volume status before, during and after these regimens to prevent fluid overload.
- withholding of nephrotoxic drugs (e.g. NSAIDs, aminoglycosides) on the day of the investigation
- consideration of withholding ACE inhibitors and related drugs on the day of the investigation, although this is probably unnecessary in stable outpatients
- consideration of omitting metformin for 48 hours after the investigation if the SCr is abnormal or eGFR is <60 ml/minute/1.73 m^2.

There is no clear evidence supporting the routine use of oral or intravenous *N*-acetylcysteine. In addition, renal function should be monitored for up to 72 hours after the procedure in high-risk patients.

Rhabdomyolysis

Filtered myoglobin can cause intratubular cast formation and direct tubular toxicity. The risk of AKI is low if peak serum creatine kinase is <10,000 U/litre. Individuals with greater muscle damage may benefit from an early diuresis and urinary alkalinization to maintain urine pH >6.5, reducing cast formation and mitigating the hyperkalaemia resulting from cell lysis. The optimal combination of intravenous sodium bicarbonate and

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KDIGO classification for the diagnosis and staging of AKI (see AKI guideline at https://renal.org/guidelines/)

AKI is **defined** as any of the following:

- Increase in SCr by ≥26.5 micromol/litre (≥0.3 mg/dl) within 48 hours; *or*
- Increase in SCr to ≥1.5 times baseline, known or presumed to have occurred within the previous 7 days; *or*
- Urine volume <0.5 ml/kg/hour for 6 hours

The severity of AKI is **staged** as follows, using the worst[a] SCr or urine output stage over a given period of time (usually 7 days):

Stage	SCr	Urine output
1	1.5–1.9 times baseline *Or* ≥26.5 micromol/litre (≥0.3 mg/dl) increase within 48 hours	<0.5 ml/kg/hour for 6–12 hours
2	2.0–2.9 times baseline	<0.5 ml/kg/hour for ≥12 hours
3	3.0 times baseline *Or* SCr creatinine[b] to ≥354 micromol/litre (≥4.0 mg/dl) *Or* Initiation of RRT *Or* In patients <18 years of age, decrease in eGFR to <35 ml/minute/1.73 m^2	<0.3 ml/kg/hour for ≥24 hours OR Anuria for ≥12 hours

[a] For example, a doubling of SCr from baseline with a normal urine output would be staged as AKI 2.
[b] By stage 1 diagnostic criteria for SCr.

Table 3

other fluids remains unclear, but a reasonable starting point alternates 500 ml bags of intravenous isotonic sodium bicarbonate with a non-sodium-containing solution such as 5% dextrose, altering the proportions according to urine pH and to maintain an hourly urine output of at least 300 ml/hour. Vigilance for iatrogenic volume overload must be maintained, and further attempts at prophylaxis discontinued if this develops or the patient becomes oliguric.

Definition and staging the severity of AKI

The diagnosis and staging of AKI has been set out by Kidney Disease: Improving Global Outcomes (KDIGO; Table 3). If previous measurements of renal function are not available, frequent (e.g. 12-hourly) monitoring of serum creatinine may reveal a rapid rise, effectively excluding chronic disease. However, prerenal disease (see below) can show a 'wandering baseline', and ischaemic ATN (see also below) on the cusp of recovery may require a longer period of monitoring.

Aetiology and categorization

Pre-renal disease

The kidneys attempt to retain sodium and water as an appropriate response to reduced renal perfusion, with the result that renal excretory capacity is reversibly impaired. Importantly, restoration of renal perfusion at this stage restores renal function as no renal cellular injury has yet occurred. Common causes include decreased effective circulating volume (e.g. volume depletion due to vomiting, volume redistribution due to third-spacing of fluid in peritonitis), drugs (e.g. NSAIDs, ACE inhibitors) and decreased cardiac output.

Intrinsic AKI

This is caused most commonly by tubulo-interstitial injury but also by glomerular or microvascular disease.

Most tubulo-interstitial disease is caused by acute tubular injury, which includes acute tubular necrosis (ATN), apoptosis or sublethal cellular injury – to be consistent with the literature, this entity will be referred to as 'ATN'; it is usually caused by ischaemia, sepsis or, less commonly, nephrotoxins (e.g. aminoglycosides, NSAIDs, radiocontrast media, myoglobin). Tubulo-interstitial disease can also be caused by myeloma cast nephropathy, or an acute allergic interstitial nephritis – a rare, idiosyncratic reaction to certain commonly prescribed drugs (e.g. diuretics, NSAIDs, penicillins, proton pump inhibitors). Urinalysis is usually normal in tubulo-interstitial disease.

Rapidly progressive glomerulonephritis (RPGN) leads to nephritic syndrome, comprising haematuria, proteinuria and AKI. Causes include:

- antiglomerular basement membrane (anti-GBM) antibody disease (Goodpasture's syndrome if lung haemorrhage coexists)
- lupus nephritis
- post-infectious glomerulonephritis
- small vessel vasculitis (granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA)).

Urinalysis is, by definition, always abnormal in RPGN.

Renal biopsy may be avoided in post-infectious glomerulonephritis if there is a typical clinical course, with group A β-haemolytic streptococcal pharyngitis or impetigo (cultures, raised anti-streptolysin O titre), a latent period of about 10 or 21 days, respectively, and low serum complement concentrations. Otherwise, RPGN usually requires histological confirmation.

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Microvascular causes of intrinsic AKI include cholesterol emboli syndrome, haemolytic–uraemic syndrome, malignant hypertension and scleroderma.

Pre-renal disease and ischaemic ATN form a clinical continuum separated by the absence or presence of renal cell injury, respectively. A pre-renal state that is not corrected quickly (through volume replacement or vasopressor therapy) can progress to overt, ischaemic AKI, at which point restoration of renal perfusion will no longer rapidly restore renal excretory capacity. About 75% of all acute renal dysfunction can be attributed to these entities.

Post-renal (obstructive) AKI

Consider this possibility in all patients with AKI especially if there is a history of lower urinary tract symptoms, renal stones, pelvic surgery or possible pelvic or retroperitoneal malignancy – rapid relief can limit damage and quickly restore renal function. It is usually diagnosed by ultrasonography.

Assessment and management

When available, an AKI care bundle should be used to facilitate clinical assessment and management. One example of such a package is described in *Recommended Minimum Requirements of a Care Bundle for Patients with AKI in Hospital* published by the Think Kidneys collaboration between NHS England and the UK Renal Registry (www.thinkkidneys.nhs.uk/aki/wp-content/uploads/sites/2/2015/12/AKI-care-bundle-requirements-FINAL-12.07.16.pdf). In addition, AKI stage 1 can be self-limiting after treatment of any underlying precipitant, such as sepsis. There is therefore a balance to be struck between the rigour of a comprehensive assessment and the pragmatism of a more targeted approach, with the latter contingent on recognizing that a full re-evaluation is needed if the anticipated resolution does not occur or the course appears atypical.

Patients who have not developed AKI but are at risk of it, through either a pre-existing susceptibility or a recent exposure, should undergo relevant clinical assessment. At a minimum, this should comprise a review of the current prescription and regular haemodynamic assessments.

Assessment

History: a relevant history, included in the overall evaluation, includes:

- a review of AKI risk factors, including previous biochemistry suggesting background CKD (check outside laboratory systems too, where relevant)
- a review of possible precipitants, including:
  - reduced fluid intake
  - increased fluid losses or sequestration, including symptoms suggestive of hypovolaemia/hypotension (thirst, postural dizziness, cramps, etc.)
  - a full medication history (prescribed medications, iodinated contrast, over-the-counter agents, herbal remedies, recreational drugs)
  - recent procedures (e.g. vascular intervention raising the possibility of cholesterol embolism)
  - a history of urinary tract symptoms
  - a history suggestive of sepsis
  - symptoms suggesting a rare diagnosis (Table 4).

A history lacking features suggestive of a renal 'hit' (e.g. of volume depletion, hypotension, relevant drug therapy or acute illness) should raise the possibility of obstruction or a rare aetiology.

If renal failure is severe, there may be evidence of the uraemic syndrome on history and examination (e.g. metallic dysgeusia, anorexia, malaise, pruritus, pericardial rub, encephalopathy), although this usually occurs when AKI develops on a background of more indolent, severe, pre-existing CKD.

Clinical examination: this should seek to confirm findings from the history and include:

- evidence of AKI risk factors (e.g. vascular disease, chronic liver disease, diabetic microvascular complications)
- evidence of possible precipitants, including:
  - haemodynamic (including volume) assessment
  - evidence of obstruction (e.g. palpable bladder, enlarged prostate, abdominal or pelvic mass)
  - evidence of sepsis
  - reagent strip urinalysis – preferably before bladder catheterization; urine culture differentiates infection from other causes of haemato-proteinuria (e.g. tumour, catheter trauma, stones) but urine microscopy is required to detect the red cell casts that are pathognomonic of glomerular origin haematuria (e.g as caused by RPGN)
- any signs of a less common cause of AKI (Table 4); these should be specifically sought out if there is no clear precipitant or the AKI episode is following an atypical course

In more detail, examination to assess volume status includes:

- blood pressure measurement including:

Clinical features suggesting a less common diagnosis

Clinical feature	Possible diagnoses
Fever, arthralgias, rashes	Small vessel vasculitis (e.g. GPA, MPA), systemic lupus erythematosus, anti-GBM antibody disease
Haemoptysis	Small vessel vasculitis, anti-GBM antibody disease
Haemolysis, thrombocytopenia	Haemolytic–uraemic syndrome
Hypercalcaemia, hyperuricaemia, bone pain, lytic lesions	Multiple myeloma
Recent vascular intervention ± livedo reticularis, hypo-complementaemia	Cholesterol emboli syndrome
Serum creatine kinase >10,000 U/litre, prolonged severe immobility, crush injury	Rhabdomyolysis
Cirrhosis/fulminant liver failure	Hepatorenal syndrome

Table 4

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  - postural blood pressure (sitting-to-lying if the patient is unable to stand) – a fall >20 mmHg systolic and/or >10 mmHg diastolic suggests volume depletion in the absence of other causes
  - a comparison with premorbid and pre-AKI readings
- pulse rate trends
- capillary refill
- jugular venous pressure
- the presence or absence of a third heart sound, pulmonary or peripheral oedema
- the presence or absence of signs such as reduced skin turgor (over forehead, sternum), furrowed tongue or dry mucous membranes and axilla
- a chart review for serial weights and fluid input–output documentation
- observation of the therapeutic response.

Evidence of improving renal function in response to improved renal perfusion (through fluid and/or vasopressor therapy) can give insights into both volume status and underlying pathology by helping distinguish between pre-renal acute kidney *impairment* and established acute kidney *injury*. However, markers of improved renal function (increased urine output, falling SCr) lag to some degree behind therapeutic intervention, so the immediate goal should be the haemodynamic rather than renal response. This is discussed in more detail under 'Management', but the following points drawn from international AKI guidelines, (as discussed in https://renal.org/guidelines/), should also be noted:

- Static measures of preload (e.g. central venous pressure, pulmonary capillary wedge pressure) are not consistent predictors of the response to volume, especially in critically unwell patients.
- This is because the Frank–Starling relationship, describing the impact of preload on stroke volume, also depends on cardiac contractility and is therefore specific to that individual.
- Only a fluid challenge can determine at which point on the Frank–Starling curve an individual's heart is working.
- This fluid challenge can be administered as a bolus (e.g. 250 ml intravenous crystalloid), although this risks tipping the oliguric/anuric patient into fluid overload.
- An alternative is the passive leg raise, which can help predict fluid responsiveness in critically ill individuals.
- Finally, cyclical alterations in preload induced by mechanical ventilation can suggest whether a given patient's heart is functioning on the steep, initial portion of the Frank–Starling curve (i.e. is potentially volume-responsive; suggested by cyclical variability in arterial pulse pressure of at least 13%) or whether the relationship has plateaued.

Complex volume disturbances (e.g. peripheral oedema in the setting of intravascular volume depletion, extracellular fluid depletion in the setting of cardiac failure) can occur so seek senior advice if required. Discussions of the role of technology in volume assessment and of intra-abdominal pressure monitoring are beyond scope of this review (see above https://renal.org/guidelines/).

Investigations

Check:

- serum biochemistry (including venous bicarbonate, liver function and bone chemistry)
- full blood count
- inflammatory markers
- serum lactate and arterial blood gases if severe sepsis is present (in keeping with standard practice) or hypoperfusion is suspected
- urine culture and microscopy (preferably on the sediment of a freshly collected, freshly centrifuged sample) if haematuria and proteinuria are present
- renal ultrasound scan within 24 hours if obstruction cannot confidently be excluded, and within 6 hours if there is a high index of suspicion or pyonephrosis is suspected. However, if another cause for oliguria (e.g. ischaemic AKI) coexists, and in the very early phases of obstruction when the pelvi-calyceal system is relatively non-compliant, hydronephrosis can be absent – ultrasonography should be repeated some days later if there is a high index of suspicion
- to investigate intrinsic renal disease, a myeloma screen and, in the presence of haematuria and proteinuria, an immunological screen including antinuclear antibody, antineutrophil cytoplasmic antibodies, anti-GBM antibodies and serum complement; anti-streptolysin O titres should be measured if post-infectious acute glomerulonephritis is suspected
- serum creatine kinase levels if rhabdomyolysis is suspected.

Urinary electrolyte measurements, such as fractional excretions of sodium or urea, have been mooted for differentiating pre-renal impairment from overt ATN, but interpretation of the results can be confounded by factors such as diuretic use, and it therefore cannot be recommended. The role of the serum urea:creatinine ratio in making this differentiation is similarly unclear.

Non-specialist management

The five questions a clinician needs to ask when managing a patient with AKI or at high risk of it are as follows.

Have I treated the underlying cause or risk factor(s)?: the physiological status of patients with AKI should be assessed and managed, promptly, after identifying AKI (or recognizing a high risk of it). Most patients with AKI and increased risk of it can be effectively managed with adequate volume replacement and haemodynamic optimization, treatment of sepsis, avoidance or withdrawal of nephrotoxins, review of other potentially deleterious agents (e.g. ACE inhibitors), and identification and prompt relief of obstruction.

Fluid resuscitation should be performed with care through rapid small bolus infusions of fluid, (e.g. in 250 ml aliquots), with close monitoring of the response to minimize the risk of iatrogenic fluid overload, a significant contributor to morbidity and mortality. The individual patient's electrolyte requirements should be carefully assessed, and potassium-containing

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crystalloids, such as Ringer's lactate solution, used with caution if hyperkalaemia is a concern. Relevant NICE guidance is available (www.nice.org.uk/guidance/cg174). Starch-based colloid solutions are now recognized as potentially harmful, increasing the incidence of AKI, the need for renal replacement therapy (RRT) and mortality, so should be avoided. The routine use of 0.9% saline for resuscitation and maintenance therapy should be avoided because of increased risk of complications such as sodium loading and hyperchloraemic metabolic acidosis.

Clinical evidence of hypovolaemia should be the primary drive for further fluid therapy as urine production is delayed in comparison to the haemodynamic response. In addition, oliguria is a predictable and transient response to the hormonal sodium and water retention that occurs in the first 12–24 hours after surgery/trauma.

The other main focus in haemodynamic management is blood pressure; as already described, in health renal autoregulatory processes maintain GFR at a steady level when MAP is generally ≥65 mmHg. This MAP has therefore been suggested as a target for haemodynamic management, but there is still uncertainty about whether higher targets are required (particularly for patients with higher, premorbid blood pressures) and the optimal vasopressor if the patient remains hypotensive once they are volume-replete.

There is currently no specific pharmacological therapy that affects the course or outcomes of ischaemic AKI. Loop diuretics can have a role in alleviating complications (hyperkalaemia, pulmonary oedema) but should not be used to treat the AKI itself.

Is renal perfusion being maintained?: loss of vascular autoregulation in the injured kidney allows fluctuating systemic perfusion to be transmitted directly through to the nephron. Careful maintenance of renal perfusion optimizes the likelihood of renal recovery regardless of the cause of AKI. During the recovery phase, patients can become polyuric and are at higher risk of a negative fluid balance and electrolyte disturbances including hypernatraemia and hypokalaemia.

Am I performing appropriate monitoring?: perform at least daily volume assessment using input–output charting, postural blood pressure recording, clinical examination and daily weights. Physiological severity scoring should supplement bedside observation and inform the need to escalate care. Biochemistry (including calcium, phosphate and venous bicarbonate), haematology and inflammatory markers should be checked at least daily until renal function has returned to baseline or stabilized, and then regularly thereafter, so progressive or recurrent AKI can be detected in a timely fashion.

- Look out for sepsis, one of the leading causes of death in AKI. As well as clinical indicators, regular monitoring of inflammatory markers should be undertaken during the episode.
- Monitor dietary intake as AKI patients are at particular risk of malnutrition. Dietary restrictions (e.g. fluid, potassium, phosphate) may be needed, and dietetic expertise should be sought in these circumstances.

Am I successfully preventing or managing any complications of the AKI?: the kidneys are one of the major excretory pathways for removal of drugs from the body; sudden loss of kidney function can therefore have important implications for the patient's prescribed drug regimen even when agents are not implicated in the AKI itself. Through daily medication review, adjust medication dosages as renal function fluctuates and with the institution of RRT; failure to do this is a significant cause of morbidity. Clinical pharmacists play an important role in mitigating the risk of adverse drug events, and clinical decision support systems – often computerized – have the potential to improve kidney-related prescribing.

Regardless of these modalities, the Renal Drug Handbook[4] and Renal Drug Database (via www.renaldrugdatabase.com; regularly updated but requires subscription) provide valuable guidance on kidney-relevant drug prescribing, including on the implications of different modalities of renal support. The Renal Drug Database provides online calculators of creatinine clearance and eGFR. There are, however, two caveats. First, in patients receiving renal support, removal of creatinine prevents it being a true marker of renal function. Second, in those who are not undergoing RRT, changes in SCr lag behind actual biological change when renal function is altering rapidly.

When medication with the potential for toxic accumulation must be used, doses need to be appropriate to renal function. In addition, blood levels should be monitored when possible, the treatment course should be kept as short as possible, and advice should be sought from a clinical pharmacist or microbiologist.

Prevention of sepsis should include adherence to local infection control practices, removal of redundant urinary or vascular catheters, and changing older central and peripheral vascular access.

In more severe AKI, supplementary nutrition must take into account associated hypercatabolism, the potential loss of nutrients through continuous RRT and electrolyte or volume disturbances; in these circumstances, specialist dietetic input is recommended.

Other complications associated with AKI include hyperkalaemia, pulmonary oedema and acidosis. Their treatment is summarized in Table 5.

Should I contact the renal unit?: patients with severe AKI (stage 3) or with indications for RRT (Table 6) should be given critical care or renal care, the discriminating factor being the level of non-renal organ support required. Current best practice now includes not only absolute indications to commence renal support (e.g. uraemic pericarditis), but also the need to initiate therapy when these complications are anticipated. Early renal specialist contact is needed if a rare diagnosis is possible as this could be treatable.

Finally, if optimal management of renal perfusion pressures and vigorous treatment of the precipitating cause fails to halt progressive AKI, seek expert renal advice; although a rare diagnosis could have been missed, ATN can take weeks to resolve.

Subsequent management

The need for renal biopsy: this should be considered:

- when ATN cannot be diagnosed confidently and pre- and post-renal factors have been excluded
- if there is suspicion of RPGN

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Non-dialytic management of complications of AKI

1.	Hyperkalaemia	Treat as an emergency in the presence of ECG changes or if serum K^+ is >6.5 mmol/litre. Patients should undergo cardiac monitoring (a) **Cardio-protection** **Calcium gluconate IV** 30 ml 10% (preferable) *or* **Calcium chloride IV** 10 ml 10% Use a large vein and give over 5–10 minutes Onset 1–3 minutes; lasts 30–60 minutes Repeat ECG after 5 minutes – consider further dose if changes persist Caution if possible digoxin toxicity – discuss with cardiology (b) **Increase cellular K^+ uptake** **INSULIN – DEXTROSE IV** 10 units Actrapid in 50 ml 50% dextrose via large vein *or* 10 units Actrapid in 100 ml 20% dextrose if concerns about venous access Give over 15 minutes. Onset 10–20 minutes; lasts 2–6 hours Check potassium at a minimum frequency of 60 minutes and 240 minutes after each insulin-dextrose infusion Undetected hypoglycaemia can be fatal – blood glucose *must* be monitored at 15, 30, 60, 90 and 120 minutes after each infusion and then at 3, 4 and 6 hours If potassium is not *maintained* at <6 mmol/litre after three administrations of insulin-dextrose, seek advice from critical care or the renal team *and* **Salbutamol nebulized** (off-licence indication) 20 mg Augments insulin-dextrose – do not use as monotherapy Onset 15–30 minutes; lasts 2 hours. Use 10 mg if ischaemic heart disease; avoid if in presence or high risk of tachyarrhythmia NB. The above measures temporarily reduce serum potassium, but do not reduce total body potassium; hyperkalaemia is likely to recur rapidly if management does not take this into account (c) **Reduce total body potassium** **Intravenous furosemide**: doses of 40–80 mg or higher can be used if volume status and blood pressure allow A hyperkalaemic patient who is oliguric or anuric is likely to require renal replacement therapy NB. Cation exchange resins (e.g. calcium resonium) have no role in acute management of hyperkalaemia
2.	Pulmonary oedema	**High-flow oxygen** and, if available, **non-invasive ventilation**. **Intravenous furosemide**: doses of 40–80 mg or higher can be used, but should not delay more definitive management with renal support if this does not produce a rapid clinical response (evidenced by improved clinical condition with diuresis – remember that the vasodilatory effects of IV furosemide are only temporary). It has no role in 'treating' or preventing AKI per se Intravenous nitrates: can be a useful holding measure but should not delay definitive management with renal support if this is required
3.	Severe metabolic acidosis (pH <7.2)	Give **sodium bicarbonate** 1.26% or 1.4% 200–500 ml IV over 15–60 minutes provided there is no evidence of volume overload. Ionized Ca^{2+} falls with rapid correction and can trigger tetany, seizures and cardiac instability. Correct low ionized Ca^{2+} via a different IV route due to incompatibility of bicarbonate and calcium solutions

IV, intravenous.

Table 5

- if apparent ATN is unusually prolonged; there could be an alternative aetiology or superimposed insult (e.g. antibiotic-related allergic interstitial nephritis).

Renal replacement therapy: a discussion of modality, technology, prescription and delivery is beyond the scope of this article (but see above https://renal.org/guidelines/and reference[5]).

After discharge: patients should be informed of the likely cause of their AKI, in particular whether any drugs were implicated in the episode and whether these are to be restarted.

For patients admitted with AKI or developing it during the course of their inpatient stay, the discharge summary should include a record of AKI detected while in hospital, its maximum stage, the aetiology, the need for renal support (and whether this is continuing) and discharge renal function (if dialysis-independent). Include specific recommendations on the need for immediate, post-discharge monitoring of renal function, and advice on drug therapy that could have been implicated in the episode, including whether to avoid or reintroduce. If causative drugs are to be restarted, renal function and biochemistry should be remeasured within 1–2 weeks after this and after any

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Indications for starting RRT

Indications for renal support:

- Refractory hyperkalaemia (K^+ >6.5 mmol/litre)
- Refractory metabolic acidosis (pH <7.15)
- Refractory fluid overload
- End-organ involvement (pericarditis, encephalopathy, neuropathy, myopathy, uraemic bleeding)
- Certain poisonings (e.g. lithium, toxic alcohols)

Factors to consider in an assessment of the anticipated need/benefit of renal support:

- Current levels and trajectories of biochemical parameters (K^+, pH, urea)
- Uraemic solute burden (increased in tumour lysis syndrome, rhabdomyolysis, hypercatabolic states)
- Requirement for intravascular space to allow administration of therapeutic interventions (e.g. blood products, nutrition)
- Degree and duration of oliguria
- Resolution/persistence of underlying renal insult
- Presence of other organ dysfunction (affecting tolerance of uraemic complications)
- Presence of other electrolyte disturbances (e.g. hypercalcaemia) that could be corrected by renal support

Table 6

subsequent upwards dose titration. Sick day guidance on drug therapy should be detailed. Patients with persistent renal impairment who do not require renal support after hospital discharge should be managed according to local CKD guidelines as they have a higher mortality and a greater likelihood of progression to end-stage renal disease. Survivors of AKI require early review and monitoring of renal function in the event of intercurrent illnesses.

After discharge, nephrology review is recommended as follows:

- within 90 days for those with residual CKD stage G4 at hospital discharge
- within 30 days for those with residual CKD stage G5 (non-dialysis-requiring) at hospital discharge
- within 30 days for those with continuing dialysis requirements at the time of hospital discharge

Renal advice is also suggested if renal function is stable but is 1.5 times baseline or higher, there is evidence of new onset or worsened proteinuria or there is new onset or worsened hypertension. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

An 85-year-old woman presented with a 48-hour history of watery diarrhoea. Her past history included hypertension, treated with a combination of amlodipine and bendroflumethazide, and angina, for which she required occasional sub-lingual glyceryl tri-nitrate spray. On clinical examination, heart rate was 96 beats/minute, blood pressure was 118/56 mmHg (recumbent), jugular venous pressure was at 1 cm above the sternal angle and there were no features suggestive of volume overload.

Investigations

Na+ 143 mmol/litre (137–144)
K+ 5.8 mmol/litre (3.5–4.9)
Cr 195 micromol/litre (60–110) (96, 3 months previously)
Venous bicarbonate 19 mmol/litre (20–28)
C-reactive protein 53 mg/litre (<10)

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What is the most appropriate next step in her management?

A. Bladder catheterization to allow accurate monitoring of urine output
B. Arrange a renal tract ultrasound to be performed within the next 24 hours
C. Obtain a urine sample for a fractional excretion of sodium
D. Resuscitate her with 250 ml IV boluses of a non-potassium containing crystalloid solution
E. Administer Actrapid 10 units in 50 ml 50% dextrose, intravenously, over 15 minutes

Question 2

You are asked to see a 27-year-old man with resolving left lower leg cellulitis and worsening renal function. He had been admitted 5 days previously with cellulitis after minor skin trauma at work. On clinical examination at that time, cellulitis was evident, temperature 37.8°C, heart rate 88 beats/minute, blood pressure 128/85 mmHg. He was treated with flucloxacillin 1g 6-hourly IV paracetamol and prophylactic low-molecular-weight heparin. After 5 days he was improving when the flucloxacillin was converted to oral administration. Urinalysis showed no blood and a trace of protein.

Investigations

Cr 186 micromol/litre (60—110) (108 on admission, 111 on day 2)

What is the most likely diagnosis?

A. Septic acute tubular necrosis
B. Pre-renal impairment
C. Post-infectious glomerulonephritis
D. Rapidly progressive glomerulonephritis due to small vessel vasculitis
E. Acute allergic interstitial nephritis

Question 3

A 75-year-old man, admitted 10 days previously with a community-acquired pneumonia (CURB-65 score 3), appeared ready for discharge. He had been treated with a 5-day course of levofloxacin, IV then oral. Stage 2 acute kidney injury (AKI) was evident on admission but had improved with treatment, careful control of fluid balance and discontinuation of perindopril, taken for long-standing hypertension. Blood pressure had remained stable and was 145/87 at the time of discharge. Urine analysis on admission and subsequently was normal.

Investigations

Cr 160 micromol/litre (60—110) (admission 286, pre-morbid 136)
estimated glomerular filtration rate 39 ml/minute/1.73m^2 (>60) (pre-morbid 47)
Ultrasound renal tract; normal.

What is the best action to take?

A. Contact the renal unit to arrange out-patient review
B. Restart his perindopril with advice to his GP to recheck renal function within the next 2 weeks to ensure that this remains stable
C. Inform his GP of his stage 2 AKI, its likely causes, discharge renal function and recommend re-commencing his angiotensin-converting enzyme inhibitor to optimize blood pressure control, with follow-up monitoring of serum creatinine
D. Inform his GP of the need to avoid renin—angiotensin system antagonists unless there is a clear indication
E. He should not be discharged until his serum creatinine has returned to baseline

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