Acute Kidney Injury: Management and Prevention

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Until relatively recently, and somewhat to the discredit of nephrology, the management of AKI has been rather a Cinderella subject breeding a nihilistic approach to both the treatment and importance of this common phenomenon. However, overwhelming data demonstrating the high mortality associated with developing AKI, and that AKI predisposes to CKD, have spawned intense interest in AKI and approaches to safely manage patients who develop it. To this end there are now a welter of very good clinical guidelines including 2012 KDIGO [1] NICE [2], intensive care society (www.ics.ac.uk) and the National Confidential Enquiry into patient outcome and death 'Adding Insult to Injury' [3]. The London AKI Network has produced pragmatic and practical guidelines covering the care bundle for the management of patients with AKI which can be modified to suit local practice [4] (http://londonaki.net/clinical/index.html and London AKI app). Imaginative, novel and inspirational approaches are being developed to foster AKI networks harmonising protocols, audit and overall patient care. The challenge for nephrologists is to raise the profile of AKI and implement systems and training that support the prevention and rapid treatment of all patients with AKI.

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Prevention of AKI

Given that there is a notable dearth of effective 'cures' for established AKI, prevention is profoundly important and there is a lot of potential for improvement on current practice. There are three aspects to prevention: (1) identifying patients at increased risk, (2) avoidance of renal insults and (3) prophylactic treatments.

Identifying Patients at Increased Risk of AKI

In terms of identification, it is clear that some patients are at much greater risk. Alerting surgeons, anaesthetists, general practitioners and other specialists to this heightened risk is critical to reducing the incidence of AKI. Some established predisposing risk factors for AKI are shown in Table 6.1.

The trick is having a systematic and robust mechanism for ensuring that all such patients are identified. Some risk factors are more quantifiable than others; nutritional state and vascular disease are not simple metrics, and cardiac and liver disease can be broadly categorised by severity, but perhaps the most accessible risk factors are (a) age, (b) eGFR, (c) proteinuria and (d) previous AKI (KDIGO Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease). Heat maps have been generated showing the risk of AKI based on proteinuria and degree of CKD [5]. A representation of this data is shown in Fig. 6.1 illustrating the profound risk of AKI associated with proteinuria or CKD or both.

Others have developed a more elaborate scoring system to predict AKI following surgery (mostly cardiothoracic surgery) [6]. Easy to use and electronically generated scoring systems need to be developed to flag patients as high, medium or normal risk of AKI. Simple yes/no versions of this can be used in surgical pre-assessment clinic and in emergency rooms.

The UK National Confidential Enquiry into Patient Outcome and Death (NCEPOD) [3] reviewing deaths of

M. Harber (ed.), *Practical Nephrology*,
DOI 10.1007/978-1-4471-5547-8_6, © Springer-Verlag London 2014

Table 6.1 Common risk factors for the development of AKI

Age[a]	
CKD[a]	Risk of AKI proportionate to the degree of renal impairment
Cardiac impairment	Increasingly common precipitant in part due to poor output and inability to compensate for hypotension or hypovolaemia when on renin-angiotensin blockade
Liver disease	Cirrhosis and severe liver impairment are very significant risk factors
Vascular disease	
Sepsis	Significant adverse factor in ~50 % of AKI
Nephrotoxic medication[a]	Toxic medication at inappropriate doses, idiosyncratic reactions
Malnourishment	eGFR will overestimate renal function in the malnourished patient leading to under diagnosis of CKD and delayed diagnosis of AKI
Previous AKI[a]	Recurrent hits even if with apparent full recovery
Cancer	Up to 25 % of patients with cancer have an episode of AKI. Especially high risk: renal, liver or multiple myeloma
Diabetes	If evidence of nephropathy/proteinuria
Proteinuria[a]	Significant risk factor
Major surgery	Emergency > elective, surgical time (e.g. ≥2 h cardiac bypass)
Trauma	
Burns	

[a]Easily identified *and* quantified from notes or initial assessment of the patient. Can be a yes/no check list for elective surgery pre-assessment

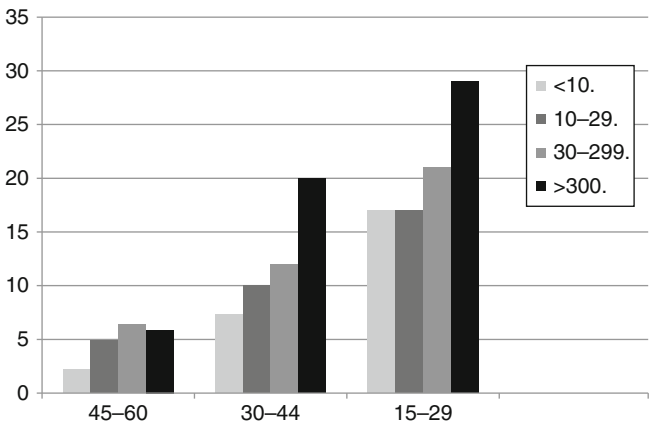

Fig. 6.1 Relative risk of AKI (*y*-axis) in patients with CKD (eGFR (ml/min) on *x*-axis) and/or proteinuria compared to the general population (Reprinted from Levey [5] with permission)

patients with AKI provided a useful and critical focus on the management of AKI. The report made several recommendations, an expedited version of which is shown in Table 6.2. It sets a challenge, but not an unreasonable target, to prevent all avoidable AKI (and better manage the unavoidable).

Table 6.2 Edited recommendations from NCEPOD

1. *All emergency admissions should be assessed for risk of AKI*
2. All acute admissions should receive adequate senior reviews (consultant reviews within 12 h)
3. There should be sufficient critical care and renal beds to allow rapid escalation of care when required
4. *Undergraduate and postgraduate medical training should include the diagnosis, prevention and management of AKI*
As a standard of care, predictable avoidable AKI should not occur

Nephrologists can and should have an important impact in implementing these recommendations through training, audit and support as well as contributing to systems that assess risk and identify AKI.

Avoidance of Renal Insults

Having identified patients at risk, avoiding renal insults seems like a good plan. Strategies for this start with informing patients, their carers and primary care physicians of the importance of good hydration; encouraging them to check that any medication they are prescribed (or buy over the counter, especially NSAIDs) is kidney compatible. We also advise patients at high risk to seek medical assessment early if they become unwell. Patients can be educated on seeking advice on stopping ACEI/ARB, diuretics and NSAIDs if they develop a condition which makes them prone to acute episodes of hypotension such as vomiting and/or diarrhoea. These points need to be well documented in correspondence and reiterated, in particular, at the time of administering the prescription.

In the hospital setting, it may be worth temporarily suspending diuretics and ACEI/ARB on the day of the operation [6, 7] or possibly even when receiving high dose IV contrast in high risk patients. It is worth ensuring that minimum blood pressure limits are set for routine prescription of antihypertensive. Where possible avoiding IV contrast (or giving minimum dose of iso-/low-osmolar contrast) and choosing less nephrotoxic medication (e.g. liposomal amphotericin, non-aminoglycoside antibiotics, non-NSAID analgesia).

For patients at risk of AKI, there are some prophylactic treatments that may reduce the risk of AKI. The most generic and fundamental of these is ensuring that renal perfusion is optimal, i.e. that the patient has a good blood pressure and is euvolaemic and, if necessary, pre-hydrated either orally (with specific instructions, e.g. 'drink a litre of water before coming to hospital') or intravenously. This is worth considering for anyone at risk of AKI undergoing surgery and receiving chemotherapy (ifosfamide, cisplatin, mitomycin) or other potentially toxic medications such as drugs causing crystal nephropathy (acyclovir, indinavir, triamterene, sulphonamides, methotrexate) or others such as foscarnet, cidofovir, ciprofloxacin and salicylates. Drugs such as high-dose

sulphonamides for the treatment of *Pneumocystis jiroveci*, chemotherapeutic agents and antivirals have manufacturer's instructions on fluid administration.

Tumour lysis syndrome is a relatively predictable cause of AKI, and there is usually time to start either allopurinol (xanthine oxidase inhibitor) or rasburicase (recombinant urate oxidase). The risk factors for TLS and prophylaxis are covered in Chap. 30, but both treatments offer significant protection against TLS, rasburicase being more effective and having a very rapid onset of action.

Contrast-induced nephropathy (CIN) typically occurring 48–72 h post intravascular administration is an important and potentially avoidable contributor to hospital-based AKI, tangibly associated with prolonged hospital stay and increased mortality and deserving of special mention. Patient risk factors broadly include renal impairment (CKD of any cause with risk proportionate to severity of renal impairment), reduced renal perfusion (cardiac or liver impairment, sepsis, hypotension), nephrotoxins (medication and endogenous toxins), multiple myeloma and diabetic nephropathy. Dose of contrast and repeated doses are also significant and usually modifiable risk factors. The pathogenesis of CIN is not clear but vasospasm, oxidative injury, direct proximal tubular cell toxicity and vacuolisation have all been implicated.

Prevention is critical and having a system to identify at-risk patients is key (suggested strategies are shown in Table 6.3), and it is important to discuss high-risk patients with your radiologist. Avoidance of radiocontrast where possible may be an outcome, but where unavoidable, then limiting dose of contrast to minimum, using iso-osmolar or low-osmolar nonionic agents and avoiding repeated doses in quick succession, is of proven benefit.

Prophylactic Treatments

The literature on this is hard work; several authors have nobly attempted to organise the data with meta-analyses, and while there is as yet no meta-analysis of the meta-analyses, it is just a question of time. For prophylaxis, normal saline, adenosine receptor antagonists such as theophylline [8] *N*-acetylcysteine (NAC) and sodium bicarbonate have all been studied in the prevention of CIN. In short, the greatest priority seems to be to ensure a good intravascular volume and good renal perfusion with pre-hydration. Multiple studies, usually in the context of coronary angiography, appear to have shown a benefit of sodium bicarbonate over normal saline [9], and a recent meta-analysis demonstrated a significant reduction in AKI following intravenous bicarbonate (OR 0.56 %) but no reduction in the need for dialysis or death once contrast-induced AKI (CI-AKI) had been established [10]. NAC has a very low side effect profile and meta-analyses suggest some modest benefit over saline alone [11] but oral NAC has very poor bioavailability and the merits of NAC remain controversial [12]. Another meta-analysis comparing the combination of NAC and sodium bicarbonate has shown it to be beneficial compared to sodium bicarbonate alone [13], but a more recent large study reported no benefit of urinary and blood alkalisation with sodium bicarbonate over sodium chloride [14].

The prevailing evidence seems to be (mildly) in favour of IV sodium bicarbonate for which there are a variety of regimens, most of which have the advantage of a short run in time of an hour or two thereby avoiding preadmission. There are caveats to using bicarbonate as a universal policy; IV bicarbonate increases serum bicarbonate (this may be hazardous for patients with chronic CO_2 retention) and reduces calcium and potassium which may also be dangerous in patients with low calcium or potassium levels.

A variety of studies have looked at dialysis or filtration immediately post-contrast in an effort to reduce CIN. For a patient without dialysis access, this is a significantly invasive prophylaxis, there are practical difficulties getting immediate dialysis post-contrast, and overall the data shows no significant benefit.

In summary, the literature on prophylaxis for contrast-induced nephrotoxicity is a headache, and the most important elements are to identify patients at risk, minimise and reduce contrast load (without compromising diagnostic sensitivity in a sick patient) and pre-hydrate the patient. Almost certainly more important than which IV fluid is given is the development of an electronic system for identifying those at risk.

Identification of AKI

Whether predicted or not, rapid identification of AKI is likely to be critical in preventing further deterioration. Definitions of AKI are covered in Chap. 5, but in essence rely on a change in creatinine (rise in serum creatinine of ≥1.5 × baseline (within the last week), which is electronically generated data) and urine output <0.5 ml/kg/h for ≥6 h (which usually is not). For most biochemistry units, it is easy to generate an 'AKI alert' when serum creatinine rises ≥x1.5 and even grade the degree of AKI from 1 to 3. While to date there is no evidence that electronic alerts improve outcome, it is self-evident that computers do this sort of thing somewhat better than humans and permit rapid notification of AKI. Alerts can easily grade the degree of AKI, direct requestor to AKI guidelines, recommend renal referral or alert high-dependency outreach teams.

In most countries urine output is not captured electronically and therefore not averaged and flagged if <0.5 ml/kg/h. Urine output as an indicator of AKI also has a few caveats, for instance, a low weight-adjusted urine output may reflect

Table 6.3 Suggested strategies for reducing contrast-induced AKI

Identify risk	Teaching, training and flags on electronic requests
Avoidance	Consider alternative imaging (e.g. MR) or contrast (e.g. CO_2); delay if possible. Avoid concomitant nephrotoxins
Minimise	Use iso-osmolar nonionic contrast, minimum doses and repeated studies
Prophylaxis	IV hydration preferentially sodium bicarbonate 1.26–1.4 % 3 ml/kg/h commencing 1 h before and continuing to 1 ml/kg/h during and for 4 or 6 h post-contrast. Consider bicarbonate and NAC In patients with hypercapnia, hypokalaemia or hypocalcaemia use IV normal saline or NAC instead of IV bicarbonate For hypercapnia, hypokalaemia or hypocalcaemia, use IV normal saline or NAC
Monitor	High-risk patients need a system in place for renal function testing 3 days postexposure

a normal physiological response or obesity, and a high urine output can occur in obstruction, acute tubular disorders and diuretic use despite AKI. However, urine output is a simple and cheap metric. The importance of urine output should be emphasised to medical and nursing staff; a weight-adjusted threshold can be worked out for each patient, e.g. for a 120 kg patient a urine output of ≤60 ml/h should trigger review, and similarly ≤20 ml/h would be the threshold for a 40 kg patient.

Management of Established or Incipient AKI

Stop Toxins

Having identified a patient with AKI, or better still a patient at high risk, early cessation or avoidance of nephrotoxic agents is of paramount importance. Toxins can be divided into exogenous and endogenous (see Table 6.4). Hopefully electronic alerts and prescribing will increasingly flag patients at risk and potentially hazardous medication. In the absence of intelligent IT solutions, clinical vigilance, training and education are critical and particularly important in identifying illicit (such as cocaine) and over-the-counter medication to avoid recurrence.

Exogenous toxins are mostly prescribed or over-the-counter medication, many of which can be predicted to cause or exacerbate renal impairment. For others the nephrotoxicity is idiosyncratic as it may be much less clear whether a valuable medication such as a proton-pump inhibitor, antibiotic, antiepileptic or diuretic should be stopped. Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs), while rarely directly nephrotoxic, have such a profound effect on the kidneys' ability to autoregulate blood flow that it makes sense to consider suspension in AKI or before large surgical procedures. There is a caveat here too as ACEI and ARBs have very substantial benefits in reducing cardiovascular mortality (and reducing proteinuria/renal progression); while it is very sensible to stop these, there needs to be a strategy for reassessing the patient with cardiac failure and timing the reintroduction, if appropriate, of these important drugs.

Aminoglycosides deserve special mention; as cheap and highly effective bactericidal antibiotics, they have great merit and are particularly useful for the initial treatment of a septic patient. However, drugs such as gentamicin, tobramycin and amikacin are associated with significant ototoxicity and nephrotoxicity (~15 %) [15] specifically accumulating at high levels in the proximal convoluted tubule. The bactericidal effect of aminoglycosides is dependent on the peak dose, whereas toxicity is time dependent and correlates with trough levels. Moreover, aminoglycosides are taken up by the megalin receptor which is saturated at high dose. This means that divided doses have the worst of both worlds; once-daily dosing on the other hand achieves higher peaks and less toxicity, and a single initial dose has a low risk of nephrotoxicity. Normograms developed for patients with renal impairment included 36 and 48 h dosing [16]. We need these valuable antibiotics, yet inappropriate usage, dosing and poor monitoring is very common [17]. Table 6.5 suggests some ways in which nephrologists might collaborate with colleagues to reduce the risk of nephrotoxicity from these important drugs.

Endogenous toxins are equally important and need to be treated aggressively. Identification and rapid treatment of the underlying cause is likely to reduce the severity and duration of AKI (see Table 6.5). For severe levels of calcium, urate and oxalate, pre-emptive dialysis is worth considering. Light chain nephropathy deserves special mention as failure to recover from cast nephropathy is associated with a much worse outcome in multiple myeloma. Although there may be a high index of suspicion that a patient has myeloma-related AKI, it often takes several days to achieve a bone marrow and renal biopsy confirming the diagnosis of cast nephropathy. The EuLITE study underway in the UK aims to assess if rapid removal of light chains and/or rapid treatment of the abnormal clone reduces the severity of AKI in myeloma. While awaiting the outcome of this study, it seems common sense for nephrologists to assess these patients as rapidly as possible and consider starting dexamethasone pending haematology review and biopsy.

Treat Sepsis

Sepsis is a contributing factor in roughly 50 % of AKI and associated with a significantly worse outcome. The 'surviving sepsis campaign' (SSC – guidelines recently updated) and proponents of early goal-directed therapy advocate rapid assessment and implementation of treatment care bundles in

Table 6.4 Potential nephrotoxins in AKI

Exogenous	
Medication with direct toxicity	For example, NSAIDs, salicylates[a], aminoglycosides, acyclovir, foscarnet, cidofovir, amphotericin, cisplatin, ifosfamide, lithium[a], calcineurin inhibitors and IV contrast. *All require close renal monitoring especially if renal impairment; consider stopping reducing or avoiding if AKI* *HES (starch-based) colloids*
Medication possibility causing idiosyncratic AKI	For example, penicillins, cephalosporins, co-trimoxazole, quinolones, isoniazid, rifampicin, proton-pump inhibitors, ranitidine or cimetidine, NSAIDs, mesalazine, thiazides and loop diuretics, calcium channel blockers, phenytoin, carbamazepine[b], phenobarbitone[b], allopurinol, azathioprine –*Potentially any drug may cause an interstitial nephritis or AKI; consider stopping if possible and no other explanation for AKI*
Toxins	Ethylene glycol consider inhibition of alcohol dehydrogenase with alcohol or alcohol dehydrogenase inhibitor fomepizole. Rapid injection of antivenom following snake bites. Consider charcoal haemoperfusion[b] for alpha-amanitin mushroom poisoning
Endogenous	
Pigment nephropathy	Rhabdomyolysis (stop cause, remove drug, treat inflammatory myositis, treat malignant hyperpyrexia, consider urgent fasciotomy if compartment syndrome). Intravenous fluids (consider alkaline diuresis). Intravascular haemolysis (treat cause)
Hypercalcaemia	Treat cause; if level 4 mmol/l or ECG changes, consider emergency dialysis
Urate	Tumour lysis syndrome; if not prevented with rasburicase or allopurinol, consider dialysis (especially if dangerous hyperkalaemia)
Oxalate	For enteric hyperoxalosis, where possible treat the underlying cause (e.g. pancreatic insufficiency); for severe acute episodes (high blood levels), consider dialysis
Light chains	Multiple myeloma, light chain nephropathy. If the diagnosis seems likely, then rapid treatment is indicated; if no contra-indication, then consider starting dexamethasone while awaiting bone marrow or renal biopsy
Sepsis	Rapid assessment and empirical treatment of sepsis are critical

[a]Haemodialysis
[b]Charcoal haemoperfusion

Table 6.5 Strategies for reducing aminoglycoside nephrotoxicity

Identify patients at risk and avoid if possible	Elderly, hypotensive, with renal impairment, diabetic, receiving other nephrotoxins, in recent course of aminoglycosides
Review cultures after initial dose	Consider alternative in high-risk patients
Once-daily dosing	Clear evidence of enhanced effect and reduced toxicity
Antibiotic control team	Review choice, dose, monitoring and length of treatment
Appropriate monitoring of levels	This is not done well generally – protocols linking pharmacists, microbiologists and the lab are worth developing
Dose adjustment for renal impairment	The renal drug handbook [18] or e-prescribing tools
Avoid concomitant nephrotoxins	Loop diuretics in high dose, CNIs and any other tubular toxin

the setting of sepsis [19, 20]. The SSC guidelines are extensive and have multiple recommendations, but a more digestible bundle, derived from the original guidelines, known as the sepsis 6 (see Table 6.6) is straightforward and easy to implement and audit (downloadable as a free app ('sepsis 6')).

While these publications were not specifically focused on AKI implementation of 'sepsis six', receipt of goal-directed therapy within an hour is associated with decreased mortality, length of hospital and ICU stay [21]. It seems self-evident that rapid assessment and treatment of severe sepsis should be championed by nephrologists.

Table 6.6 Components of the sepsis six: to be completed within an hour of identifying septic shock or severe sepsis

1. Administer high-flow oxygen
2. Take blood cultures
3. Commence empirical broad-spectrum antibiotics
4. Administer IV fluids
5. Measure serum lactate and obtain full blood count
6. Monitor accurate urine output

Resuscitate Intravascular Volume and Restore Renal Perfusion (Prerenal)

Early and thoughtful restoration of intravascular volume is fundamental to ameliorating AKI. A key part of this is treating the cause of reduced perfusion, for example, emergency PCI for acute coronary syndrome, and treating sepsis or haemorrhage. In a nutshell, beyond correcting the underlying cause, fluid resuscitation can be done badly or well; slow IV filling over an 8–12 h period is rarely appropriate for a patient with acute sepsis or hypotension. Conversely there is increasing evidence that excessive fluid is dangerous not just by precipitating pulmonary oedema but in terms of mortality [22–24].

Assessment of fluid balance is covered in Chap. 1 but is a difficult skill to acquire, and the key to managing the acutely

hypotensive patient is early and frequent assessment of response to filling by an experienced clinician. In the context of sepsis, goal-directed therapy [20] has a large following usually focusing on achieving targets such as mean arterial pressure (MAP), reducing lactate, improving central venous oxygen, maintaining a CVP of 8–12 cm and restoring urine output to >0.5 mg/kg/h. To achieve this, a hypotensive patient with AKI needs to be in a place of safety with experienced nursing and medical staff with haemodynamic monitoring of dynamic changes. Suggestions are to start with 30 ml/kg of crystalloid, though more or less may be required to achieve euvolaemia [19].

Colloid

Starch Solutions

Special consideration must be given to the choice of fluid used in the resuscitation of a haemodynamically compromised patient. Importantly, the use of tetra starch solutions such as hydroxyethyl starch (HES), in the context of sepsis, has been associated with increased adverse outcomes [25]. The multicentre 6S Trial showed increased mortality rates with 6 % HES fluid resuscitation compared to Ringer's acetate [26]. The CHEST study compared HES to isotonic saline and showed no difference in 90-day mortality between resuscitation with 6 % HES and isotonic saline but a greater need for renal replacement therapy in the HES group [27]. HES has now been withdrawn in the UK because of concerns of increased AKI.

A separate meta-analysis of 56 randomised trials found no overall difference in mortality between crystalloids and artificial colloids (modified gelatins, HES, dextran) when used for initial fluid resuscitation [28].

Albumin

A large RCT meta-analysis showed the use of albumin when compared to other fluid solutions in severe sepsis/septic shock was associated with decreased mortality (OR 0.82); and in direct comparison with those patients who received crystalloids, the odds ratio of death was lower (OR 0.78) [29]. Additionally human albumin solution is equally as effective as 0.9 % saline and thus can be used as an alternative or adjunct in fluid resuscitation [30].

Blood

The administration of blood can be indicated in the presence of acute blood loss or symptomatic anaemia and AKI. It is important to remember that although the volume of blood being administered may be relatively small compared to traditional fluid resuscitation regimes with crystalloids, the potassium and oncotic effects may be sufficient to precipitate the need for premature extracorporeal renal replacement therapy in an oligoanuric stage 3 AKI patient. The supernatant potassium concentration [K+] of red blood cell (RBC) units is frequently much higher than normal human plasma potassium levels, especially in units nearing the end of their storage life. Careful fluid balance assessment after each unit of blood and the need for contemporaneous diuretics reduces the likelihood of complications during the transient hyperkalaemia.

Inotropes

In the presence of ongoing hypotension despite appropriate fluid resuscitation, inotropes are required to maintain tissue perfusion (usually aiming for a mean arterial pressure of >65 mmHg) to improve outcome [20].

Norephedrine is the first vasopressor choice in the context of sepsis and hypotension. (The routine use of dopamine over norephedrine as first-line vasopressor support is not recommended as it is less potent and associated with a greater incidence of arrhythmic events and short-term mortality) [31, 32].

Despite its persistence in the 'we must do something' armamentarium, there is also no evidence for the use of low-dose dopamine to encourage renal function. A large randomised trial and meta-analysis compared low-dose dopamine to placebo and found no difference in the peak serum creatinine, need for renal replacement, urine output, time to recovery of normal renal function and survival, and there is reason to believe dopamine may have toxic effects in the sick patient [33, 34].

Perioperative Protocol

Often AKI may be due to the hypotension and/or sepsis associated with an underlying event that requires operative intervention. Insensible losses will be increased and once the patient has been hydrated to euvolaemia, then a rule of thumb for maintenance fluids is UO+ other losses + 500–750 ml per 24 h per London AKI Network guidance, but regular reassessment of EABV is essential as additional fluid challenges may be required. The type of fluid used is also important as hydroxyethyl starch impairs coagulation and platelet function and is associated with increased postoperative bleeding and should be avoided.

Post-renal

The treatment of post-renal causes of AKI is covered in Chap. 30 and essentially amounts to rapid identification and timely resolution of the obstruction. It is worth emphasising that an obstructed infected urinary tract is a medical emergency, and UK guidelines recommend that an ultrasound of the renal tract is performed within 6 h in a septic patient if pyonephrosis is a possibility.

Intrinsic Renal Disease

The management of rapidly progressive glomerulonephritis or interstitial nephritis will, to some extent, depend on cause and is covered in subsequent chapters. The key is rapid renal assessment, diagnosis (haematuria, proteinuria or pyuria being important clues), rapid investigation (several days' wait for an anti-GBM antibody result is not appropriate if Goodpasture's disease is a realistic diagnosis). All patients thought to have intrinsic renal disease need to be built into local care pathways. Service level agreements with immunology departments alerting the nephrologist on call to any positive anti-GBM are straightforward to establish.

As mentioned above, the causes of hypercalcaemia, hyperoxaluria, hyperuricaemia and light chain deposition need to be identified and treated aggressively, and with the first of these three, early dialysis may help reduce the endogenous toxin rapidly.

Myoglobin is less soluble at alkaline pH and a forced alkaline diuresis has been advocated. A recent review of the literature concluded that IV fluids should be given as soon as possible ideally within 6 h of muscle injury and urine output maintained at ≥300 ml/h, but the authors concluded that there is no data to support alkalinising the urine and bicarbonate should only be given if required to manage potassium or acidosis [35]. It is imperative to consider decompressing compartment syndrome, if present, with a fasciotomy.

Crystal-induced AKI

Crystal-induced AKI occurs due to the precipitation of intratubular crystals which result in obstruction and occasionally an inflammatory response. The commonest causes being uric acid nephropathy or drugs, their metabolites or toxins that are poorly soluble in urine [36].

Patients usually have risk factors that need identification such as volume depletion and renal insufficiency, liver disease and metabolic changes in urinary pH. The occurrence of crystal-induced AKI can be prevented or reduced by pre-emptying its occurrence in such at-risk patients with measures such as by premedication hydration, appropriate medication dose reduction and pre- and contemporaneous forced diuresis and urine alkalisation [36].

Guidance for pre-hydration with normal saline and intravenous sodium bicarbonate is well recognised for certain medications which are known to precipitate in acidic or alkaline urine. Intravenous acyclovir is poorly soluble, and pre- and post-hydration aiming for a high urine output is advised. Intravenous bicarbonate may be helpful with high-dose methotrexate.

Once crystal-induced AKI has developed, treatment strategies include stopping or dose reducing the 'offending' medication, alkalinisation/acidification of the urine, consideration of a forced diuresis with furosemide and fluid to achieve a high-volume urine output >75 ml/h and renal placement therapy. The evidence for using furosemide is largely anecdotal, and attempts to alkalise the urine of a patient with established crystal nephropathy can be hazardous; the priority should be ensuring the source is stopped and the patient is euvolaemic and in a place of safety.

Table 6.7 shows some of the well-known crystal-induced AKI medications which respond well to alkalinisation of the urine.

Table 6.7 Alkaline diuresis for drug intoxication

Methotrexate	Urine pH ≥7.5 but haemodialysis if removal of circulating drug metabolite is required (Wall et al. [49])
Sulphonamides	Urine pH ≥7
Salicylate poisoning	Moderately severe (haemodialysis if levels are acutely >120 mg/dl, >100 mg/dl at 6 h and >60 mg/dl chronically (TOXBASE)
Mitomycin	
Cisplatin	

Glycaemic Control

Hyperglycaemia is associated with worse outcome in critically ill patients, and initial studies demonstrated significantly reduced rates of AKI and renal replacement therapy in patients treated with intensive insulin therapy. However, subsequent studies have failed to confirm improved outcomes and intensive insulin arms are associated with increased episodes of significant hypoglycaemia. The current evidence is summarised in the KDIGO AKI guidelines, but in essence the cumulative evidence does not support intensive glycaemic control [1].

Table 6.8 Indications for renal replacement therapy in AKI

Hyperkalaemia	If insoluble with medical treatment
Fluid overload	Pulmonary oedema resistant to diuretics
Severe metabolic acidosis	
Uraemia	Impaired consciousness, pericardial rub
Drug intoxications	Methotrexate, salicylate, lithium, hyperoxalosis (ethylene glycol)
Some electrolyte disturbances	Hypercalcaemia especially if ECG changes and ≥4 mmol/l, tumour lysis syndrome associated with hyperphosphataemia, hypocalcaemia and hyperuricaemia

In all cases the indications are based on degree of abnormality and likelihood of medical correction (i.e. can a good urine output be generated and good mean arterial blood pressure be maintained? If not, then renal replacement needs to be planned sooner rather than later)

Indications for Renal Replacement Therapy

Acute renal replacement therapy is covered in more detail in Chap. 7, but some of the indications for renal replacement therapy are shown in Table 6.8.

To date and perhaps surprisingly, there are no randomised controlled trials showing that continuous renal replacement therapy is superior to intermittent haemodialysis in terms of survival [37]. However, beyond the issue of availability and local expertise, there may be reasons to opt for continuous renal replacement therapy or intermittent haemodialysis preferentially. Continuous renal replacement therapy offers greater haemodynamic stability particularly in the setting of sepsis and hypotension and is probably the therapy of choice in patients with acute brain (with impaired autoregulation or raised intracranial pressure) or cardiac injury. For pragmatic reasons, it is the treatment used in patients with multi-organ failure and is a more measured way of correcting gross electrolyte abnormalities [38–41]. The optimal dose of continuous renal replacement therapy is undecided, but compared to those haemodynamically unstable patients who received an (dialysate and blood) effluent flow of 35 ml or more/kg/min, patients who had 20 ml/kg/min effluent flow had decreased mortality, improved recovery of kidney function and reduced rates of non-renal organ failure [42, 43]. In conjunction with creatinine clearance, an effluent flow of 20 ml/min/kg is a reasonable dose [38].

Haemodynamically stable patients with AKI do not appear to gain any benefit from continuous renal replacement therapy when compared to daily and three ties a week intermittent haemodialysis.

Intermittent haemodialysis may be more accessible, particularly in terms of trained staff, may be preferential for the treatment of some toxic AKI and also permits more rehabilitation between treatments.

There is no consensus on when to start renal replacement in AKI; there are some observational studies advocating an early start, but the data is poor.

From the nephrologist's point of view, the issue is more that of identifying patients who are not going to recover safely with medical therapy and making a robust plan to provide renal replacement therapy in a safe and timely manner.

Finally, nephrologists will be increasingly referred frail patients with significant co-morbidity who have developed AKI due to an intercurrent illness. Frequently the questions are 'does this patient need acute renal replacement therapy?' and 'if renal function did not recover, would they be suitable for long-term dialysis?' These are often very difficult decisions, made at a time when the patient is at their most vulnerable and often made on the basis of sorely limited information. These are really challenging questions and should not be made casually.

BP Control

Often patients with AKI are hypertensive, in particular if they present with an intrinsic renal cause for their AKI. For example, nephritides classically present with hypertension or accelerated hypertension. Accelerated hypertension and its management have been discussed in Chap. 12. Care with capping the blood pressure is required to avoid cerebral hypoperfusion–related strokes and seizures. BP control should be with short-acting IV therapies. Oral medications can be used such as calcium channel blockers and fenoldopam. ACEI and ARBS should be avoided till the creatinine has stabilised post-AKI recovery.

Rehabilitation

Patients with severe AKI may be in hospital for weeks, losing substantial amounts of flesh weight, incurring critical illness neuropathy and becoming depressed. A holistic approach is often an underappreciated yet vital aspect of AKI recovery. Nutrition needs to be considered on a daily basis and nutritional support started early (ideally within 48 h), preferably enteral feeding and aiming for 20–30 kcal/kg/day and protein of 0.8–1 g/kg/day (increasing if on RRT or catabolic) [1].

Mobilisation with physiotherapy support (if required) should be instigated as soon as possible. Stable patients on continuous RRT may benefit from early conversion to intermittent haemodialysis in ICU to permit mobilisation. Getting

Table 6.9 Risk factors for the development of CKD following AKI

Severity of AKI	AKI 3 > 2 > 1. But even AKI-1 is a significant risk factor
Need for renal replacement therapy	Profound risk factor for CKD
Repeated episodes	Particularly in quick succession
Age	Increasing age is a significant risk factor
Complex AKI	Multiple risk factors/insults for AKI seem to increase risk of CKD compared to single cause
Hypoalbuminaemia	Low albumin associated with higher risk
Cause of intrinsic renal disease	Less clear but, for example, delayed treatment of Goodpasture's syndrome has a dire outcome
Time	Duration of AKI

Table 6.10 Suggested inter-hospital transfer criteria (London AKI Network)

Hyperkalaemia	No ECG changes of hyperkalaemia, potassium ≤6 mmol/l (not transient i.e. the result of recent insulin and dextrose administration)
Acidosis	pH ≥7.2, venous bicarbonate 12 mmol/l, lactate ≤4 mmol/l
Cardiovascular	Heart rate ≥50 and ≤120 bpm, systolic blood pressure ≥100 mmHg (sustained), mean arterial pressure ≥65 mmHg, lactate ≤4 mmol/l
Respiratory	Respiratory ≥11 bpm and ≤26 bpm, saturations ≥94 % on not more than 35 % oxygen. If required CPAP then independent of this for ≥24 h
Neurological	Glasgow Coma Scale ≥12

patients into clothes, if possible out of the ward for breaks, and providing talking books, games and clear explanations of projected recovery and future plans are often somewhat neglected aspects of care in patients recovering from serious illness.

Outcomes of AKI

As stated in the introduction, for a long time the seriousness of AKI was underestimated, but it is now clear that AKI is associated with a very high mortality. Roughly 50 % of patients with AKI requiring renal replacement on ICU perish; this rises to nearly 70 % if combined with sepsis. In one multicentre multinational study using the RIFLE categorisation, renal failure was associated with ten times the relative risk of death but even 'risk' and 'injury' had an RR of 2.5 and 5.4, respectively [44]. But even outside the setting of critically ill patients, AKI marks your card. A review of Medicare data from the 1990s showed an average inpatient hospital mortality of roughly 5 % in patients who did not develop AKI, but inpatient mortality was three to six times higher in those with AKI and 90-day mortality was nearly 50 % [45]. The development of AKI significantly increases length of stay and cost of admission. Increasingly recognised are the long-term renal consequences of AKI. A meta-analysis of studies following children with HUS, previously thought to have no long-term consequences, revealed that at 5–10 years 25 % of children had either hypertension, proteinuria or CKD [46]. A meta-analysis in adults dividing AKI into mild, moderate and severe showed a relative risk of subsequent CKD of 2, 3 and 28, respectively [47]. The severity of AKI is thus a key factor and in one study the need for renal replacement therapy conferred a 500-fold increased risk of developing CKD (Table 6.9) compared to no AKI [48].

AKI in the setting of CKD not only is very common but confers a fourfold increased risk of ESRD compared to patients with CKD who do not have an episode of AKI.

Follow-up of AKI

Given the evidence that even apparently reversible AKI has a significant risk of CKD, it seems sensible to ensure some sort of follow-up. The intensity of follow-up and whether it is done by nephrologists or in primary care depend to a large extent on the recovery from AKI (however severe) and the likelihood of recurrence. There are not yet clear guidelines on this but there are formulae to predict the risk of CKD. A practical approach would be to ensure that patients with significant AKI but good recovery have blood pressure, urine dipstick and creatinine annually. Those without complete recovery may need to be seen and assessed as a one-off in an AKI renal clinic, which permits accurate recording of diagnosis, proteinuria and recovery and risk of CKD. Prospective data sets of patients with AKI will be valuable in managing these patients medium term and because of the risks of recurrent AKI and CKD, significant AKI episodes should be recorded in patients problem list.

Transfer Criteria

Many but not all patients with AKI can be managed locally; for those that cannot be managed and need inter-hospital transfer to a renal unit, then transfer should be speedy but clear criteria need to be established regarding patient stability and suitability as death on transfer is not unheard of. The London AKI Network generated the following guidelines (Table 6.10) which are a very useful starting position for negotiation and common sense and which can be modified locally depending on resources.

Summary

AKI is not a benign condition and can have very profound short- and long-term consequences for the patient. There is a huge potential for dramatically improving standards of care and patient experience starting with ongoing audit of AKI management. Nephrologists, through training and teaching, need to up the profile of AKI, promote systems to develop local protocols and AKI networks, implement straightforward guidance and be responsive to early referrals and transfer of appropriate patients.

Tips and Tricks

Given the dearth of decent treatments and the significant mortality and CKD associated with AKI, prevention is critical. Establishing systems (ideally electronic) to rapidly identify patients at risk and alert the patient's practitioner is crucial, and nephrologists should be instrumental in establishing these systems. Where electronic prescribing is not available or unsophisticated, close engagement with pharmacists can be very helpful in limiting unhelpful prescribing elsewhere in the hospital setting.

An element of this is the introduction of electronic prescribing, ideally linked to the patients' eGFR results (accepting that this may not be entirely accurate in AKI) or simply flagging the risk of exacerbating AKI.

Adopting an aggressive approach to sepsis (via the 'sepsis six' or other systems) is simple, likely to save lives and probably reduce sepsis-related AKI.

While yet to be proven in randomised trials, electronic alerts of AKI based on changes in creatinine can be used to flag AKI and/or act as a biomarker to outreach teams of a patient's deterioration and risk.

Establishing an AKI network in local hospitals with agreed protocols, transfer criteria and audits should foster an increased awareness and improved management. Training and teaching campaigns will also be required.

Pathways to facilitate rapid discharge of some patients with recovering AKI into renal clinics, virtual clinics or ambulatory care programmes can reduce length of stay and permit an assessment of who is at risk of CKD in the medium term.

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