ACUTE KIDNEY INJURY - AN UPDATE

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ABSTRACT

The syndrome of acute kidney injury (AKI) occurs frequently in hospitalised patients, leading to increased morbidity, mortality, and healthcare expenditure. In the context of a precipitating insult, disturbances in both global and microcirculatory renal blood flow, tubular cell damage, and activation of pro-inflammatory pathways lead to impairment of numerous elements of renal function. Classification systems, including the recent 'Kidney Disease: Improving Global Outcomes' (KDIGO) classification, typically define and stage AKI in terms of the magnitude of rise in serum creatinine (SCr) and the presence of oliguria. At present there is no cure for AKI and the key principles of its management include early recognition, haemodynamic optimisation, correction of hypovolaemia, ceasing and avoidance of nephrotoxic medications, and treatment of the underlying cause. Recent data show that the type and volume of fluid therapy can affect renal function and that further guidance is required. In the future it is hoped that novel technologies, including biomarkers and real-time measurement of glomerular filtration rate will allow the earlier identification of patients with AKI, whilst a greater understanding of the pathogenesis of AKI will lead to the identification of new therapeutic targets. Despite SCr usually recovering after an episode of AKI, there is growing recognition that survivors of AKI are at an increased risk of subsequent chronic kidney disease, including end-stage renal failure and premature death.

Keywords: Acute kidney injury (AKI), fluid therapy, AKI biomarkers, AKI e-alert.

INTRODUCTION

Acute kidney injury (AKI) is a frequent complication in hospitalised patients. It is associated with serious short and long-term morbidities, an increased risk of dying, and significant healthcare costs. Even small rises in serum creatinine (SCr) independently predict poor outcome.[1] This review focuses on recent developments in AKI that are of interest to the general physician.

DEFINITION

AKI is a syndrome encompassing many different aetiologies and is characterised by an acute deterioration of renal function. The most common causes are sepsis, volume depletion, haemodynamic instability, and nephrotoxic injury. AKI comprises simultaneous impairment of nitrogenous waste excretion, fluid balance and electrolyte regulation, and acid-base homeostasis, which occur to varying degrees and reversibility according to the magnitude and nature of the insult. Traditional diagnostic tools to diagnose AKI include SCr, blood urea nitrogen, urine output, urine chemistry, urine microscopy, and histology. The need for a standardised definition culminated in the 'Kidney Disease: Improving Global Outcomes' (KDIGO) AKI classification,[2] which evolved from the 'Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease' (RIFLE) and AKI Network criteria (Table 1).[3,4]

Although SCr is readily available in clinical practice, it is affected by muscle mass and fluid status, can change in response to certain drugs without change in renal function, is not reliable in patients with liver disease, and may take 24–36 hours to rise after a definite renal insult. Conversely, patients with advanced chronic kidney disease (CKD) may have a SCr rise as part of natural progression or a relatively small decrease in glomerular filtration rate (GFR), which may bias them towards a diagnosis of AKI. Epidemiological studies have

also shown that some patients have a slow but persistent (creeping) rise in SCr but do not fulfil the criteria for AKI. The term 'acute kidney disease' has been suggested to describe this scenario.[2]

Accurate measurement of urine output is challenging in patients without a urinary catheter and oliguria may be missed, especially outside of critical care areas. Urine output can be manipulated by diuretics and may persist until renal function almost ceases. Importantly, oliguria may be an appropriate response in the setting of hypovolaemia reflecting under-resuscitation rather than kidney injury. The use of weight-based urine output criteria for AKI may be misleading in obesity and result in the overdiagnosis of AKI. The European Renal Best Practice Guidelines (2012) recommend using the ideal weight rather than the true weight when calculating urine output in ml/min/kg to avoid a misdiagnosis of AKI.[5]

There remains debate about the definition of baseline SCr.[2,6] Extending the baseline assessment period to 3, 6, and 12 months prior to hospital admission results in progressively more patients being classified as having AKI, but with decreasing in-hospital mortality.[6] Despite these limitations and potential pitfalls it is recommended to use the KDIGO classification of AKI in clinical practice and research until more specific and sensitive tests are routinely available. The use of formulae to calculate an estimated GFR cannot be recommended in AKI.[2]

EPIDEMIOLOGY

The incidence of AKI is increasing with time[7-9] due to population changes (ageing/comorbidity), changing healthcare behaviours (increasing use of potentially nephrotoxic drugs, contrast media, high-risk interventions), and increased recognition. AKI affects 7-22% of hospital inpatients. Older and critically ill patients are at particular risk. A large, multi-national meta-analysis identified 154 cohorts published between 2004 and 2012, including 3.4 million hospitalised adults that allowed classification according to KDIGO criteria.[10] The pooled incidence of AKI was 22%. The odds of death in the 2.2 million patients for whom data was available was five-times greater for those with AKI than without. The annual incidence in the community may be as high as 1%.[11] The financial burden of AKI is huge as it greatly increases length of stay in the intensive care unit (ICU) and in the hospital, and both in-hospital[12] and post-discharge patient-care costs. The cost of AKI-related inpatient care in England consumes 1% of the entire healthcare budget, and is estimated to be higherthan that of the four most common cancers combined.[13]

EARLY RECOGNITION

The best chance of ameliorating the severity of AKI is through early recognition and intervention. The majority of AKI develops in the context of an acute medical or surgical illness outside renal or critical care units. The UK National Confidential Enquiry into Patient Outcomes and Death (NCEPOD) report in 2009 – 'AKI - adding insult to injury' – was a retrospective case analysis of patients who had died and been coded as having AKI.[14] In only 50% of cases was care considered to be 'good'. In 30% of cases, AKI was deemed to have been both predictable and avoidable. Failures of care included the non-institution of basic measures such as stopping nephrotoxins, prescribing supplemental fluids, and unacceptable delays in recognition. Electronic alert systems use changes in SCr to identify AKI and alert the clinical team with the aim of instituting a review and management plan. A number of studies have suggested that electronic alerts can positively influence physician behaviour and improve outcomes.[15-19] However, a recent randomised controlled trial (RCT) showed no difference in mortality or need for dialysis.[20]

PATHOPHYSIOLOGY

The kidneys receive around 20% of the cardiac output, and renal oxygen extraction is low (approximately 10-15%), yet they are very susceptible to tissue hypoxia, especially during an acute illness. In recent years, the previously held belief that AKI develops due to a global decrease in renal perfusion associated with a state of shock has been called into question.[21,22] For instance, AKI does not necessarily occur in survivors of cardiac arrest despite prolonged periods of hypotension.[23] In sepsis, animal models demonstrated that renal blood flow (RBF) may be reduced, increased, or unchanged, which implies that factors other than RBF play an important role.

Current evidence suggests that the origin of most cases of AKI is multifaceted rather than the result of an individual insult. Several concurrent mechanisms contribute, including regional

variations in perfusion and oxygen consumption, impaired autoregulation, distortion of peritubular and glomerular microcirculation, tubular cell injury, endothelial injury, microvascular thrombosis, and arteriovenous shunting, resulting in the activation of inflammatory processes.[24] AKI is now considered a pro-inflammatory condition. Numerous pro and anti-inflammatory mediators and pathways have been identified, which account for some of the clinical sequelae of AKI and may also serve as therapeutic targets in the future.[25-27]

TREATMENT

The management of AKI is supportive with focus on the optimisation of fluid and haemodynamic status, treatment of the underlying illness, avoidance of further nephrotoxic insults, and renal replacement therapy (RRT) if necessary. There is no cure for AKI. Many pharmacological treatments have been tried with disappointing results. The recent KDIGO expert group appraised and summarised current evidence-based management (Table 2).[2] In cases where the necessary evidence was missing, recommendations were made based on expert opinion.

Avoidance of Nephrotoxic Agents

Nephrotoxic drugs often contribute to the development of AKI during an acute illness. For example, in the UK, angiotensin-converting enzyme (ACE)-inhibitors and angiotensin II receptor blockers are the second most commonly prescribed class of drug and increased prescribing may be responsible for 15% of the increase in admissions for AKI.[28] Non-steroidal anti-inflammatory drugs are easily available and commonly implicated too. Although evidence-based data from RCTs is missing, it makes sense to recommend that during an episode of AKI, drugs with potential for nephrotoxic injury should be avoided or dose adjusted if possible.

Haemodynamic Optimisation

Haemodynamic optimisation uses fluid therapy and vasoactive drugs to achieve cardiac output and perfusion pressures that will restore/maintain adequate oxygen delivery to tissues including the kidneys. Optimisation has three main components:

i) Pre-load optimisation aims to maximise stroke volume (and therefore cardiac output) by augmenting left ventricular end-diastolic volume with intravascular filling. The use of central venous pressure to guide volume expansion is not recommended.[29]

ii) Afterload optimisation aims to ensure adequate perfusion of the kidneys and is especially important in the management of distributive shock, where vasopressors can improve renal haemodynamics.[30]

iii) Contractility optimisation aims to improve oxygen delivery if shock persists, despite pre-load and afterload optimisation. The most commonly used drugs are inotropes.

Table 1: KDIGO definition and classification of acute kidney injury.[2]

Definition	AKI is diagnosed if SCr increases by at least 0.3 mg/dl (26.5 µmol/l) in 48 hours or rises to at least 1.5-fold from baseline within 7 days.	
Stage	SCr rise	Urine output
1	1.5–1.9 × baseline OR ≥0.3 mg/dl (≥26.5 µmol/l) increase	<0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 × baseline	<0.5 ml/kg/h for ≥12 hours
3	3.0 × baseline OR increase in SCr to ≥4.0 mg/dl (≥353.6 µmol/l) OR initiation of renal replacement therapy	<0.3 ml/kg/h for ≥24 hours OR anuria for ≥12 hours

SCr: serum creatinine; KDIGO: Kidney Disease: Improving Global Outcomes; AKI: acute kidney injury.

Table 2: Summary of guidelines for treatment of acute kidney injury from KDIGO.[2]

Do	Do not
Discontinue all nephrotoxic drugs if possible.	Restrict protein intake with the aim of preventing or delaying initiation of RRT.
In the absence of haemorrhagic shock, use isotonic crystalloids rather than colloids as initial management for expansion of intravascular volume.	Use diuretics to prevent or treat AKI, except in the management of volume overload.
Use vasopressors in conjunction with fluids in patients with vasomotor shock with or at risk of AKI.	Use low-dose dopamine, fenoldopam, ANP, or rIGF-1 to prevent or treat AKI.
Consider protocol-based management of haemodynamic and oxygenation parameters in high-risk patients in the perioperative setting or in patients with septic shock.	Use aminoglycosides if a non-nephrotoxic alternative is available (close monitoring of trough levels if unavoidable).
Consider alternatives to radiocontrast procedures.	Use oral fluids, theophylline, fenoldopam, or RRT for prophylaxis of CIN.
In critically ill patients, use insulin therapy targeting plasma glucose 110-149 mg/dl (6.1-8.3 mmol/l).	Use conventional formulations of amphotericin B (lipid preparations are less nephrotoxic).
Achieve a total energy intake of 20-30 kcal/kg/day.	
Provide nutrition preferentially via the enteral route.	
Use lipid formulations of amphotericin B rather than conventional.	
Use intravenous 0.9% saline or isotonic sodium bicarbonate and oral NAC in patients at high risk of CIN.	
Initiate RRT emergently when life-threatening changes in fluid, electrolyte, and acid-base balance exist.	
When considering RRT, consider the presence of conditions that can be modified with RRT, and trends of laboratory tests, rather than single urea and creatinine thresholds.	

AKI: acute kidney injury; ANP: atrial natriuretic peptide; CIN: contrast induced nephropathy; rIGF: recombinant insulin growth factor; RRT: renal replacement therapy; NAC: N-acetylcysteine; KDIGO: Kidney Disease: Improving Global Outcomes.

Fluid Therapy

i) Type of fluid: The optimal type of fluid for prevention and management of AKI is not known. However, there is increasing evidence that starch-based colloids can cause or worsen AKI if given in large volumes and should be avoided in critically ill patients.[31-33] Use of chloride-rich solutions like 0.9% saline is associated with hyperchloraemic metabolic acidosis and an increased risk of AKI.[34] There is some evidence that balanced crystalloid solutions such as Ringer's Lactate, Hartmann's solution, or Plasma-Lyte may have benefits over saline.

Analysis of a large US database of patients undergoing major abdominal surgery showed that patients who received 0.9% saline had a higher unadjusted in-hospital mortality (5.6% versus 2.9%) and need for RRT compared to patients treated with Plasma-Lyte.[35] After correction for confounders, the increased rate of RRT remained significant. Based on animal models the underlying mechanism is believed to be chloride-induced renal vasoconstriction and decrease of renal artery blood flow and GFR.[36-38] It is important to note that all data suggesting that balanced solutions may be superior to 0.9% saline are based on observational studies. An RCT is still awaited.

ii) Volume of fluid: Classically, in volume-depleted patients with intact tubular function, avid retention of sodium is reversible with fluid therapy and oliguria improves. Prolonged volume depletion is harmful to kidney function; fluid administration beyond the resuscitation phase in patients with AKI is not only ineffective but also harmful and associated with reduced chances of renal

recovery and an increased mortality.[39] Fluid overload results in tissue oedema, obstruction of capillary blood flow and lymphatic drainage, impaired diffusion of oxygen, and disturbed cell–cell interactions.[40] Progressive organ dysfunction may result. The effects are pronounced in encapsulated organs such as the kidneys, which cannot accommodate extra volume without an increase in interstitial pressure and compromised organ blood flow. Although both inadequate and overzealous fluid resuscitation are harmful in AKI, there are currently no reliable tools to diagnose euvolaemia. The decision of when to stop fluid therapy is mainly based on the regular clinical assessment of the patient.

Blood Pressure Management

Hypotension and low cardiac output are deleterious for kidney function but the optimal haemodynamic targets for patients with early AKI are unknown. Data in the literature are conflicting. A large Finnish study showed that septic patients who developed AKI within 5 days of ICU admission had a significantly lower mean arterial pressure (MAP) (74 mmHg) compared to septic patients without AKI (MAP: 79mmHg).[41] In contrast, Bourgoin et al.[42] reported that raising MAP to >85 mmHg in patients with shock did not result in an improvement of urine output or SCr. Similarly, an RCT comparing a target MAP of 80-85 mmHg versus 65-70 mmHg in patients with septic shock showed no difference in mortality (although both groups achieved MAPs greater than their target resulting in a less pronounced difference between both groups).[43] Interestingly, patients with chronic hypertension randomised to the high MAP group needed RRT less often. The current recommendation is to tailor MAP targets to the individual. It is reasonable to aim for a higher MAP in patients with chronic hypertension with persistent oliguria or rising SCr.

Exclusion of Obstruction

Ultrasound imaging of the urinary tract is recommended in patients at high risk of obstruction or where there is no obvious cause of AKI.[44] It will also identify important pre-existing anatomical variations, like a single kidney or small kidneys in the case of CKD.

AKI Care Bundles

There has been a trend in critical care towards the use of care 'bundles', which are a structured way of improving the processes of care and patient outcomes through a small set of evidence-based practices that, when performed collectively, improve patient outcomes.[45] Care bundles have been successfully integrated into the management of potentially life-threatening conditions like sepsis or ventilator associated pneumonia. The initial treatment of AKI may benefit from a similar approach but evidence from RCTs is lacking.[46]

Prevention of Contrast-Induced Nephropathy

Iodinated contrast media can cause AKI by several mechanisms including direct tubular toxicity and renal vasoconstriction. It is uncommon in stable patients without risk factors[44] but frequently contributes to AKI in patients with an acute illness or pre-existing CKD, especially if procedures which necessitate high contrast volumes are necessary. Other risk factors are advanced age, diabetes with CKD, heart failure, and concurrent use of nephrotoxic drugs. The only proven effective preventative strategy is to optimise volume status with saline or isotonic sodium bicarbonate before the procedure whilst addressing any treatable components of the acute illness (Table 2).[47] The use of oral N-acetylcysteine is a weak KDIGO recommendation[2] that has been dropped from the recent guideline by the National Institute for Health and Care Excellence UK.[44]

Renal Replacement Therapy

RRT should be considered when the benefits outweigh any potential risks, independent of specific urea and creatinine results, but before the development of any uraemic emergencies.[2] Continuous RRT is recommended for patients who are haemodynamically unstable or have conditions associated with increased intracranial pressure.[2] Peritoneal dialysis is an option but is rarely used in adults in developed countries.[48]

LONG-TERM PROGNOSIS

Several large epidemiological studies have shown that the prognosis of AKI (even with good recovery of SCr) is not entirely benign. Survivors of AKI are at an increased risk of death and CKD including progression to end-stage renal failure, which has a major impact on the patient's life expectancy and contributes to healthcare costs.[49-51] Patients with diabetes, chronic vascular disease, and CKD are particularly at risk. There are several reasons for this, including common comorbidities as well as factors directly related

to repair processes following AKI. A single-centre observational study in Pennsylvania, USA found that patients with AKI were 50% more likely to die and nearly twice as likely to develop CKD following hospital discharge compared with matched controls without AKI.[51] Proteinuria has recently been identified as more common in AKI survivors than controls and is associated with CKD progression.[52] Other studies have found an association between AKI and subsequent risk of coronary events,[53] strokes,[54] fractures,[55] and reduced quality of life.[56] There have been calls for regular follow-ups for patients who survive a hospital admission complicated by AKI in order to improve their long-term prognosis, but the most effective strategy has not yet been identified.[57]

The assessment of residual renal function after an acute illness is challenging. SCr results may be misleading due to changes in muscle mass and metabolism, clearance of excess tissue water, and temporary discontinuation of drugs that affect GFR, such as ACE-inhibitors.[58] This 'pseudo-normalisation' may become apparent only if a repeat SCr is measured after recovery from critical illness. AKI and CKD are complex, interconnected syndromes (Figure 1). Prospective longitudinal studies in AKI survivors are in progress and will be valuable to guide decision making.[59,60]

Self-Management

It is recommended that patients at risk of AKI are informed of the conditions that may cause AKI (i.e. diarrhoea and vomiting) and the drugs to avoid during sick days.[44] This is particularly relevant for patients with CKD.

FUTURE DEVELOPMENTS

There is an ongoing search for more sensitive tests to diagnose AKI before elevations in SCr occur, which may also facilitate the discovery of potential therapies.

Novel Biomarkers

Novel biomarkers of AKI vary in their origin, function, distribution, and time of release following renal injury.[61,62] They can be divided into:

i) Markers of glomerular function: Small molecular weight molecules that are present in the systemic circulation and undergo glomerular filtration (i.e. cystatin C). In the case of reduced GFR their plasma concentration rises.

ii) Markers of tubular function: Molecules that are filtered and undergo tubular reabsorption (i.e. retinol-binding protein) and may appear in the urine in the case of tubular injury.

iii) Markers of tubular injury, damage, or repair: Molecules that are released into urine or plasma as a result of direct renal cell damage, inflammatory activation, or following gene upregulation, i.e. kidney injury molecule-1 (KIM-1), interleukin-18 (IL-18), tissue metalloproteinase-2, and insulin-like growth factor-binding protein 7.

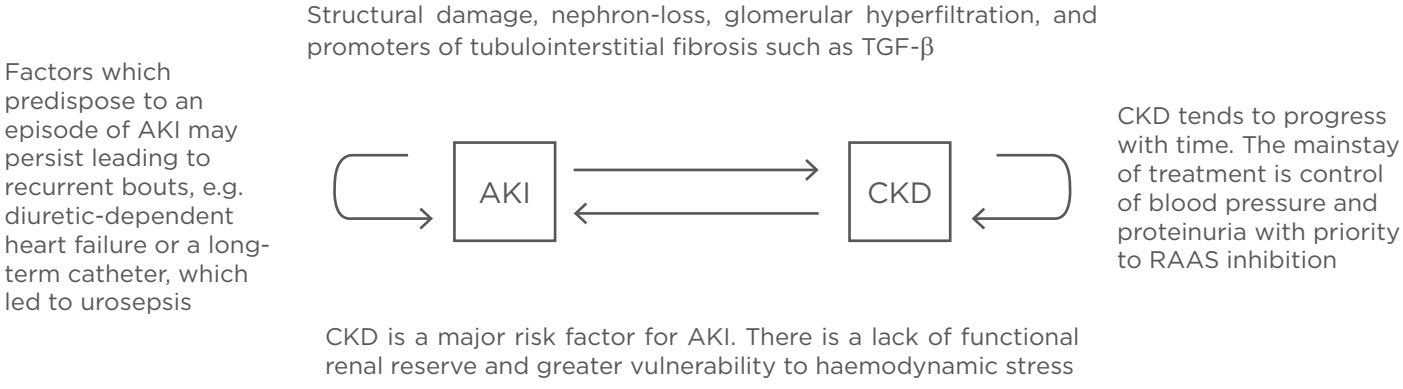

Figure 1: Relationships between acute kidney injury and chronic kidney disease.
Underpinning all these relationships are a large number of potential factors that increase risk for both AKI and CKD e.g. advanced age, hypertension, coronary artery disease, diabetes, heart failure, proteinuria, etc.
AKI: acute kidney injury; CKD: chronic kidney disease; TGF-β: transforming growth factor β; RAAS: rennin angiotensin aldosterone system.

The most-studied biomarkers are neutrophil gelatinase-associated lipocalin, cystatin C, KIM-1, and IL-18. Studies have shown that the use of novel biomarkers in certain situations may indicate the onset of AKI earlier than SCr or urine output, correlate with severity of AKI, and/or prognosticate the need for RRT. However, the results are variable and depend on the case-mix, cause of AKI, clinical setting, associated comorbidities, and timing of biomarker measurements.[63] To date, novel AKI biomarkers have not been integrated into routine clinical practice.

Real-Time GFR Measurement

Knowing the actual GFR would not only define and stage AKI earlier and more accurately, it may also improve clinical management, for instance facilitating correct drug dosing.[62] Some investigators have made progress in real-time GFR techniques. For instance, external whole-tissue radioactivity measured after intravenous injection of Tc-labelled diethylenetriaminepentaacetic acid allowed an accurate, fast, and convenient way to measure total and individual kidney GFR.[64] Several commercial companies are in the process of developing rapid, sensitive, reproducible, and affordable techniques to measure real-time GFR.

Curative Therapies

Novel strategies including mesenchymal stem cell therapy, anti-inflammatory agents, and treatment with alkaline phosphatase are currently being investigated and the results of these studies are awaited.

CONCLUSION

The mainstay of AKI management remains prompt recognition followed by early optimisation of haemodynamics, correction of volume depletion, avoidance of nephrotoxins, and treatment of the underlying cause. The development of new diagnostic tools, including biomarkers and techniques to measure GFR in real time, offers new opportunities and the prospect of diagnosing AKI earlier and more accurately. Until then, strategies to improve AKI care are likely to include a co-ordinated approach to education, electronic alerts, and care bundles. Increasing recognition of the long-term complications confirms that AKI is no longer just an acute illness and deserves long-term follow-up.

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